

Healthcare Resource Utilisation of Severe Uncontrolled T2low and Non-T2low Asthma in Finland During 2018-2021

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Purpose: Patients with asthma and low levels of type 2 inflammatory biomarkers (T2 low) have limited effective treatment options. Such biomarkers include eg blood eosinophils (b-eos) and fractional exhaled nitric oxide (FeNO). The healthcare resource utilisation (HCRU) of severe uncontrolled T2 low asthma remains unexplored. Thus, this study aimed to estimate the HCRU of T2 low and non-T2 low severe uncontrolled asthma patients using real-world data in Finland.

Patients and Methods: Adult patients with an asthma diagnosis during baseline (2012–2017) at the pulmonary department of Turku University Hospital were included and followed during 2018–2021, or until death. Total HCRU costs and respiratory-related HCRU costs were evaluated. The main drivers for the HCRU and costs were assessed with gamma and negative binomial regression models.

Results: Of the severe uncontrolled asthma patients with T2 status available, 40% (N=66) were identified with T2 low and 60% (N=103) with non-T2 low asthma. The average cumulative cost per patient was similar in patients with T2 low compared with non-T2 low, with all-cause costs cumulating in four years of follow-up to 37,524€ (95% CI: 27,160, 47,888) in T2 low compared to 34,712€ (25,484, 43,940) in non-T2 low. The corresponding average cumulative respiratory-related costs were 5178€ (3150, 7205) in T2 low compared to 5209€ (4104, 6313) in non-T2 low. Regression modelling identified no differences between the T2-status groups when assessing all-cause healthcare costs per patient-year (PPY). On the other hand, the regression modelling predicted more inpatient days PPY for severe uncontrolled patients with T2 low status compared to the patients with non-T2 low status.

Conclusion: Patients with uncontrolled severe T2 low asthma use equal healthcare resources as corresponding non-T2 low patients. This study brought new insights into the HCRU of severe uncontrolled asthma patients per T2 status, which has not previously been investigated.

Keywords: severe uncontrolled asthma, phenotypes, healthcare resource utilisation, economic burden, real-world evidence

Introduction

The global prevalence of asthma has been estimated to be 4.4%, with a range between 2.2% in low-income countries and 10.2% in high-income countries.¹ In Finland, the prevalence has been estimated to be around 10% and has increased in recent decades.²

Asthma has a high economic burden on healthcare, mainly driven by poor control of asthma symptoms and exacerbation events.³ A review from 2017,⁴ indicated that the healthcare resource utilisation (HCRU) of mild, moderate, and, severe asthma varied between countries, with a mean asthma-related cost per patient per year in Europe of 1790€, and in the US of 2900€.

Severe asthma is defined as asthma that is uncontrolled, despite adherence with maximally optimised high-dose inhaled corticosteroids with a second controller and management of contributory factors, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.⁵

In the Nordic countries, the prevalence of severe asthma among asthmatic patients has been estimated to be 3.5–9.5%.^{6–8} Patients with severe asthma have a higher risk of exacerbation events,⁹ which is the main driver for asthma-related HCRU costs.¹⁰ Several studies have estimated the economic burden of severe asthma in Europe. A Spanish study from 2018,¹¹ estimated the mean annual direct cost per patient to be 7472€, and in a French cohort study from 2018,¹² the mean annual asthma-related cost per patient was estimated to be 8222€. Another study from France, analysing the Medical Claims Database from 2012 until 2015 showed that patients with severe asthma were more frequently hospitalised, and consulted by a general practitioner and private respiratory physicians compared with non-severe asthma controls. A Swedish cohort study from 2020,¹⁰ estimated the mean annual asthma-related costs per patient as 6500€, of which approximately 2400€ and 4100€ were direct and indirect costs, respectively. The main drivers for direct costs were hospitalisations followed by drugs: approximately 1000€, and 800€, respectively.

Patients with severe asthma are classified into two major phenotypes: patients with low levels of type 2 inflammation (T2 low) and patients with high levels of type 2 inflammation (T2 high).¹³ T2 high is defined by elevated biomarkers, such as blood eosinophils (b-eos), fractional exhaled nitric oxide (FeNO), and serum immunoglobulin E (IgE). These biomarkers are measured to determine the active inflammatory pathways and inform the selection of the most appropriate biologic treatment (eg, omalizumab, mepolizumab, benralizumab, dupilumab, or tezepelumab). Previous studies have analysed the economic burden in patients with T2 low and T2 high asthma, defined as high and low b-eos levels. A Spanish real-world observational study from 2020,¹⁴ showed that severe asthmatic patients with high b-eos (≥ 300 cells/ μ L) had poorer lung function, poorer treatment adherence, and a greater mean number of exacerbations compared to patients with low b-eos (< 300 cells/ μ L). The study reported higher healthcare costs for the patients with high b-eos compared to low b-eos, 4230€ and 3065€, respectively. A Finnish study from 2020,¹⁵ also analysed severe asthmatic patients with high b-eos (≥ 300 cells/ μ L) and showed that these patients had a 1.4 to 1.7-fold increase in all-cause and asthma-related outpatient visits and inpatient days. A study from Japan from 2023,¹⁶ analysing severe asthma patients stratified by the T2 biomarkers b-eos and total IgE, showed no statistical difference in asthma-related exacerbations or medicine costs.

Severe uncontrolled asthma patients with T2 low asthma have limited effective treatment options. However, the HCRU costs of severe uncontrolled T2 low asthma defined with more than one inflammatory biomarker remain unexplored. Thus, this study aimed to estimate the HCRU of T2 low and non-T2 low severe uncontrolled asthma patients using real-world data in Finland.

Materials and Methods

Study Design

This was an observational, register-based study utilising data from the Turku University Hospital data lake including all speciality care contacts, diagnoses, procedures, spirometry, asthma control test results, FeNO concentration, other laboratory measures including b-eos and IgE, and date of death. The study design and patient population have been described in detail elsewhere.¹⁷ All patients with an asthma diagnosis (ICD-10 code J45.X and J46) and a visit to the pulmonary department between 1.1.2012 and 31.12.2017 (baseline period) were included and followed from 1.1.2018 until 31.12.2021 or death. Data on drug purchases of ATC class R* (respiratory system), A10* (diabetes), C* (cardiovascular system), H02* (systemically used corticosteroids), J* (anti-infectives for systemic use), N06A* (anti-depressants), M05* (drugs for the treatment of bone diseases) were obtained from the Social Insurance Institution of Finland and linked to the Auria data (permission number THL/2385/14.02.00/2021).

Patient Population

This study included a patient population with severe uncontrolled asthma with T2 low and non-T2 inflammatory biomarkers. To define the severity of asthma, drug purchase data from the first inhaled corticosteroid (ICS) during the baseline period was used. Asthma patients were defined as having severe asthma if they had daily use of fluticasone

propionate $\geq 800\mu\text{g}$ or equivalent complemented with at least one other controlled (Leukotriene Receptor Antagonists (LTRA), Long-Acting Beta-Agonist (LABA), Long-Acting Muscarinic Antagonists (LAMA), or biologic asthma medication) during the same time window as the ICS analyses.

Patient with an asthma control test (ACT) result of <20 , or having an emergency room (ER) visit or hospitalisation for asthma with acute asthma (ICD-10: J46), or asthma as a main diagnosis (J45.x), or a respiratory infection as a main diagnosis + asthma (J45.x) as a side diagnosis were defined as having uncontrolled asthma.

To define the T2 low asthma population, patients with at least two measures of b-eos and one measure of FeNO available during the baseline period were included in the analyses. The patients included in the T2 low population were required to have all available measures below the set threshold of b-eos <300 cells/ μL and FeNO below 25 ppb. The patients with at least one measure above these set thresholds were considered non-T2 low patients.

Healthcare Resource Utilisation

All-cause and respiratory-related HCRU were assessed to describe both the overall and the incremental HCRU costs associated with the T2 low and the non-T2low subpopulations. The HCRU costs were computed from the speciality care data which included visits, operations and procedures, laboratory measurements, imaging, and open-care medication purchases. The respiratory-related speciality care visits were defined as speciality care visits and procedures with ICD-10 J* as the main diagnosis. The prices were derived from Turku University Hospital's list of pricing for 2021.

Statistical Analysis

Where applicable, differences between populations were tested using relevant statistical tests (two-sided *t*-test for normally distributed continuous variables, Kruskal–Wallis test for non-normally distributed continuous variables, and Chi-squared test for categorical variables). The results were plotted with 95% confidence intervals over time. P-values less than 0.05 were considered statistically significant.

For the HCRU costs, the total costs were estimated per patient (dividing the total by the number of patients) and per patient-year (PPY) (dividing total per total follow-up time) and were reported overall and by subpopulations of T2 low and non-T2 low. The 95% confidence intervals for the point estimates were computed by bootstrapping over patients. The missing prices were imputed with the median price of the cost type.

The cumulative total HCRU was assessed as mean cumulative costs estimated by a mean cumulative function. The mean cumulative functions were fitted for the all-cause costs and respiratory-related costs. The results were plotted with 95% confidence intervals over time.

The main drivers for the HCRU were assessed with regression models. Different combinations of dependent and independent variables were tested. The results have been reported for the models that used the total costs PPY and the inpatient days PPY as the dependent variables. The total PPY costs are non-negative, non-normal, and continuous data, and thus, a gamma regression model with a log link was used. The inpatient days per patient-year are positive, overdispersed count data, and hence a negative binomial model with a log link was used. The models were tested using different sets of the following baseline covariates as model variables: T2low status, Age, Sex, Age * sex interaction term, and Charlson comorbidity index (CCI).¹⁸

All analyses were performed using R-4.0.3.¹⁹

Results

In the patient cohort, 1986 patients were identified with severe asthma, where 637 (32%) patients had uncontrolled severe asthma. Of these patients, 468 (73%) patients were excluded from this study due to the T2 type being undefinable due to too few measurements of b-eos and FeNO. Thus, of the severe uncontrolled asthma patients with T2 status available, 66 (39%) patients were identified with T2 low and 103 (61%) patients with non-T2 low asthma. Patients with T2 low asthma were more frequently female and younger compared to the non-T2 low patients. In addition to higher levels of T2 biomarkers, also nasal polyposis was more frequent among subjects with non-T2 low asthma. Both T2 low and non-T2 low asthma patients had poor asthma control according to the ACT result, but there was no difference between the groups (Table 1). None of the subjects in this final cohort of severe uncontrolled asthma patients were on biologics.

Table 1 Patient Characteristics of T2 Low and Non-T2 Low Severe Uncontrolled Asthma Patients at Baseline

	Non-T2low	T2low	p-value
N	103	66	-
Male	39 (38%)	11 (17%)	0.003
Age, median (IQR)	56 (46, 66)	48 (39, 55)	<0.001
Co-existing COPD	8 (7.8%)	8 (12%)	0.3
Nasal polyps	14 (14%)	0 (0%)	0.002
Smoking (ever)	14 (14%)	6 (10%)	0.4
Smoking (Missing)	< 5 (< 4.9%)	6 (9.1%)	-
BMI kg/m ²	-	-	0.057
BMI < 18.5	< 5 (< 4.9%)	< 5 (< 7.6%)	-
BMI ≥ 18.5 to < 25	21 (21%)	22 (37%)	-
BMI ≥ 25 to < 30	39 (39%)	13 (22%)	-
BMI ≥ 30	37 (37%)	24 (40%)	-
BMI (Missing)	< 5 (< 4.9%)	6 (9.1%)	-
Blood eosinophils, max., median (IQR) cells/μL	540 (375, 954)	165 (100, 230)	<0.001
FeNO, max., median (IQR) ppb	24 (14, 50)	12 (9, 17)	<0.001
IgE, max., median (IQR) kU/l	222 (53, 427)	24 (10, 77)	<0.001
IgE (Missing)	23 (22.3%)	16 (24.2%)	-
Asthma control test, min, median (IQR) points	12.0 (8.0, 15.0)	11.0 (8.0, 14.0)	0.3

Abbreviations: BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; FeNO, Fractional exhaled Nitric Oxide; IgE, Immunoglobulin E; IQR, Interquartile range; kU/l, Kilo Units per Litre; ppb, parts per billion.

Total all-cause HCRU costs were similar in the T2 low and non-T2 low patients, even if the average cost was slightly higher in T2 low patients (Figure 1). When assessing the contribution of outpatient visits, emergency room visits, and hospitalisation on the total HCRU-related costs, outpatient visits were the main cost drivers (Figure 2). Although PPY costs for both outpatient visits and hospitalisations seemed higher in T2 low patients vs non-T2 low, the differences were not significant.

The respiratory-related (ICD-10 J-codes) costs accounted for 15–16% of the overall HCRU-related costs, indicating a significant comorbidity burden among the included severe uncontrolled patient groups. The remaining 84–85% of the all-cause HCRU costs came from a variety of different diseases and disorders. Among the most common was hypertension (20–30%), dorsalgia (15–20%), sleep disorder (15%), obesity (10–15%), gastro-oesophageal reflux disease (10–12%), atopic dermatitis (10–12%), disorders of lipoprotein metabolism and other lipidaemia's (8–10%), depressive episodes (7–10%), and anxiety disorder (4–10%).

Medication-related costs were lower in T2 low than non-T2 low patients: 1585€ (95% CI: 1222, 2027) compared to 2500€ (1758, 3495), but the difference was not statistically significant. The main proportion (67%) of drug costs were more specifically related to drugs for obstructive airway diseases (R03) without a significant difference. The costs split by ATC categories of interest are presented in Figure 3. One patient was on immunoglobulin replacement treatment included in the J* category (anti-infectives for systemic use).

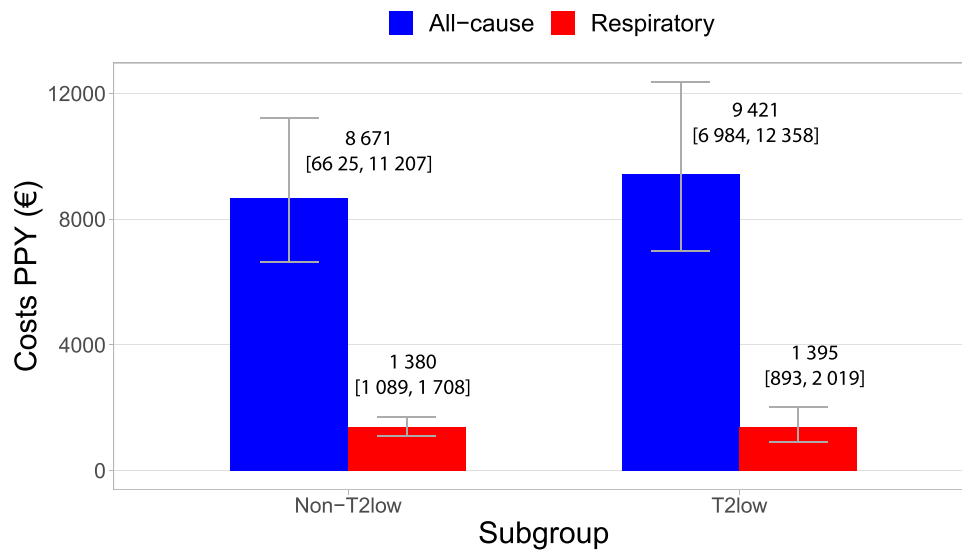


Figure 1 Healthcare resource utilisation related all-cause and respiratory related costs per patient-year (PPY, mean and 95% CI) during follow-up.

The average cumulative cost per patient was similar in patients with T2 low compared to non-T2 low, with all-cause costs cumulating in four years of follow-up to 37,524€ (27,160, 47,888) in T2 low compared to 34,712€ (25,484, 43,940) in non-T2 low (Figure 4). The corresponding average cumulative respiratory-related costs were also similar in T2 low and non-T2 low groups being 5178€ (3150, 7205) and 5209€ (4104, 6313), respectively.

Regression modelling identified no differences between the T2-status groups when assessing all-cause healthcare costs PPY. On the other hand, the regression modelling predicted more inpatient days PPY for severe uncontrolled patients with T2 low status compared to the patients with non-T2 low status (Table 2).

Discussion

The main finding in this study was that the total all-cause HCRU costs were similar in the severe uncontrolled T2 low and non-T2 low patients. The all-cause HCRU costs of the patients in our study are 8 to 9-fold higher than what has been reported in the Finnish background population of 1160€ PPY (indexed to 2023 price from 2011 average cost of 916€

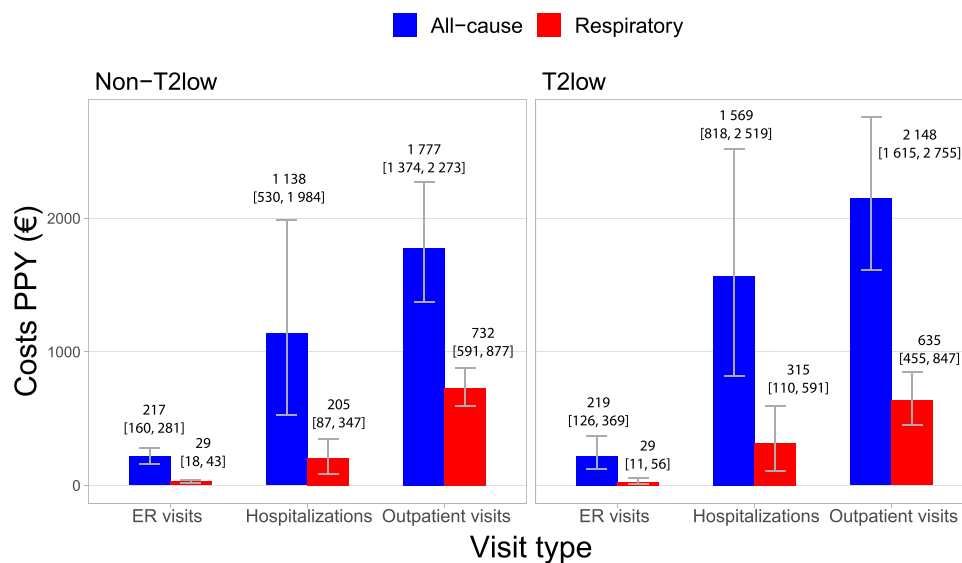


Figure 2 Healthcare resource utilisation related all-cause (blue) and respiratory (red) costs per patient-year (PPY, mean and 95% CI) during follow-up in non-T2 low (left) and T2 low patients (right). Costs stratified into emergency room (ER), hospitalizations, and outpatient visit related costs.

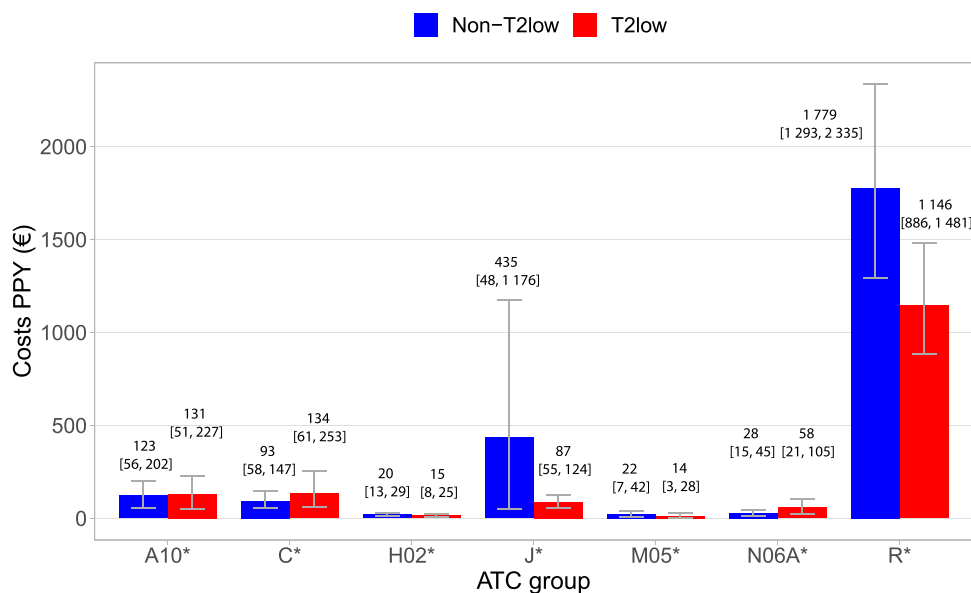


Figure 3 Medication costs per patient-year (PPY, mean and 95% CI) per ATC classes of interest during follow-up in severe uncontrolled T2 low (red) vs non-T2 low patients (blue). A10* (diabetes), C* (cardiovascular system), H02* (systemically used corticosteroids), J* (anti-infectives for systemic use), M05* (drugs for treatment of bone diseases), N06A* (antidepressants), R* (respiratory system, including medication for upper and lower airways).

PPY) for somatic speciality care for patients of similar age 41–64 years.²⁰ This indicates that severe uncontrolled asthmatic patients have a significant comorbidity burden, with respiratory-related costs contributing 15–16% of overall total HCRU costs. The remaining 85% of all-cause HCRU cost came from a variety of diseases and disorders, mainly related to hypertension, dorsalgia and sleep disorders. Similar comorbidities have been found in previous studies from real-world clinical settings.^{5–7}

The total annual HCRU cost estimates in this study are in line with other European cost studies.^{8,9} The respiratory-related annual HCRU and medication costs per patient were estimated to be around 1390€ in this study for both T2 low and non-T2 low. These estimates are somewhat lower compared to a Swedish cohort study from 2020,¹⁰ estimating the mean annual asthma-related HCRU costs per patient to be 2400€. The main difference is that we reported lower hospitalisation costs compared to the Swedish study.

Our findings showed that exacerbations leading to hospitalisation periods had similar hospitalisation costs between T2low and non-T2low. This is in line with a recently published study from Japan,¹¹ also indicating similar asthma-related exacerbation events and medicine costs for T2 low (low b-eos, and low IgE) and non-T2 low patients. It can be speculated that as the treatment potential with corticosteroids is different between T2low and non-T2low, hospitalisations may be a good measure of severe exacerbations in the T2low endotype. A previous study¹⁷ from the same data set as this study concluded that the T2 low endotype was stable during follow-up in three-quarters of patients with b-eos <300 cells/ μ L, and T2 low patients are as severely ill as non-T2low but have limited treatment options at the moment. This study also highlights that patients with persistently low T2 inflammatory markers of b-eos and FeNO should be considered for other treatment options apart from corticosteroids.¹⁷

In this cohort of patients with severe uncontrolled asthma, none of the patients had biologic treatment. The main reason for this is that the inclusion period of this study was when biological treatments for severe uncontrolled asthma were not yet widely available and that some patients may not have had contact with speciality care or not met the local reimbursement criteria (high-dose ICS and minimum of 4 exacerbations per year). A further potential reason for this is that those patients on biological treatments were well-controlled and therefore did not meet the inclusion criteria for this study. Another potential reason is that in Finland, there is no clear cost-effectiveness proven for biologics for all subgroups of patients with severe uncontrolled asthma. Thus, it is important to provide data on patients not on biologics for background purposes and to compare with T2 high and T2 low severe asthma patients not on biologics. The real-life evidence on the economic burden between T2 high and T2 low severe asthma patients cannot be fully compared when

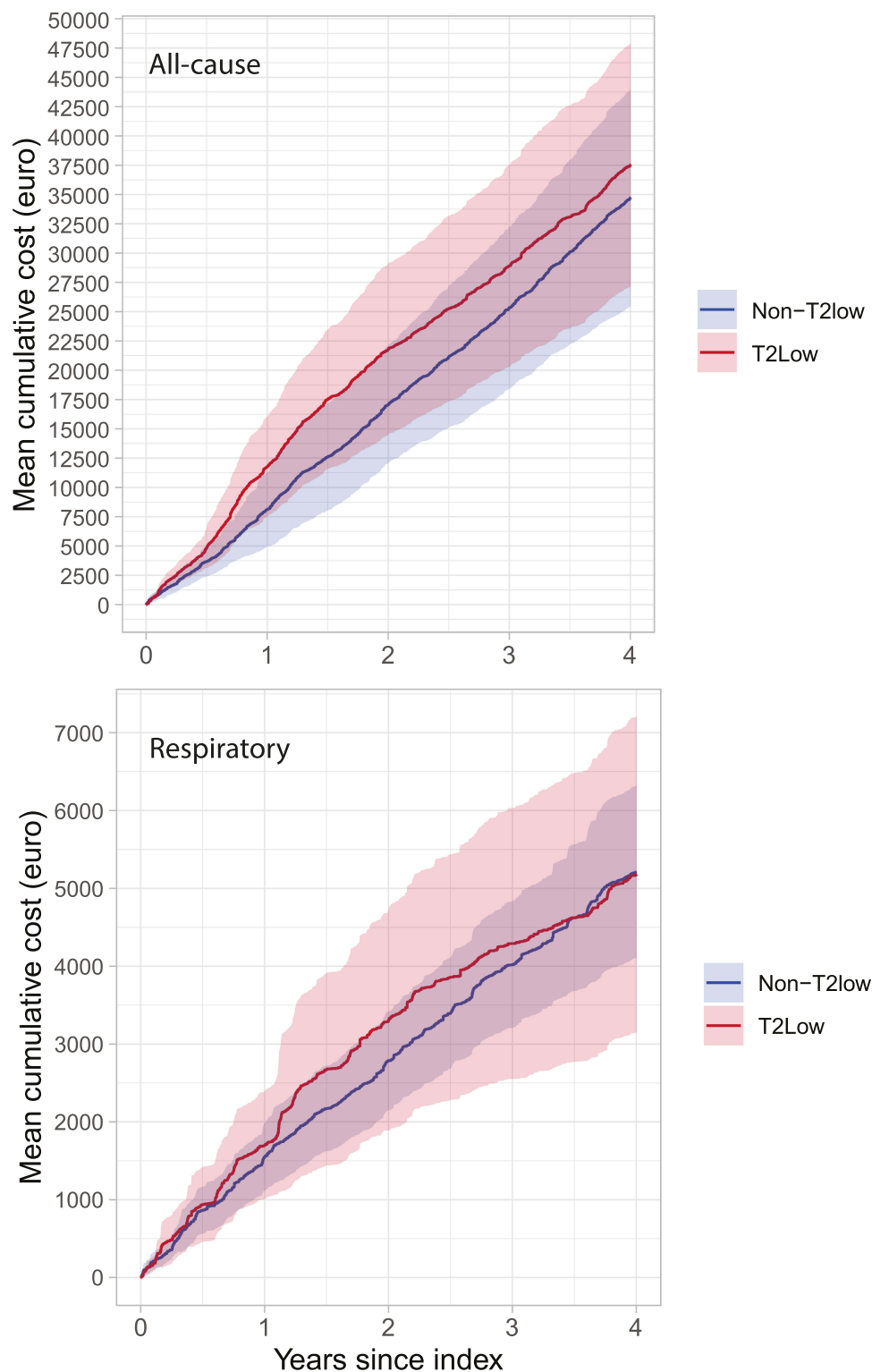


Figure 4 Mean cumulative function (mean and 95% CI) of all-cause healthcare costs during follow-up in severe uncontrolled T2 low vs non-T2 low patients.

not all subgroups of T2 high severe uncontrolled asthma are not eligible for biological treatments in several countries, including Finland and Sweden, due to reimbursement restrictions.

In contrast to our findings of no statistically significant difference in HCRU costs between T2 low and non-T2 low, studies analysing patients solely on their b-eos levels^{14,15} showed higher HCRU costs for increased eos levels. Further,

Table 2 Regression Model of the Association of Patient Characteristics and T2 Status on Healthcare Resource Utilisation

Variable	Level	Total Costs Per Patient Year (gamma Regression With Log Link)				Inpatient Days Per Patient Year (negative binomial regression with log link)			
		β	exp (β)	95% CI (for exp (β))	P-value	β	exp (β)	95% CI (for exp (β))	P-value
T2 low Reference: non-T2 low		0.34	1.4	0.96–2.05	0.069	0.77	2.16	1.42–3.32	<0.001
Charlson Comorbidity Index Reference: 1	2	0.29	1.34	0.71–2.8	0.397	–0.08	0.92	0.44–2.05	0.825
	3	0.62	1.86	1.12–3.32	0.022	0.97	2.64	1.55–4.66	<0.001
	4	1.85	6.36	2.44–23.81	0.001	2.07	7.92	3.06–27.11	<0.001
	5+	1.63	5.1	1.68–25.28	0.012	0.99	2.69	0.88–12.06	0.113
Age at index (years)		0.01	1.01	1.00–1.03	0.144	0.02	1.02	1.01–1.04	0.003
Sex Reference: Female	Male	0.30	1.35	0.32–5.93	0.674	1.46	4.31	1.13–17.29	0.053
Age at index * Sex (interaction term)		–0.01	0.99	0.97–1.02	0.553	–0.03	0.97	0.95–1.00	0.032
Intercept		8.24	3789.54	1669.03–9045.29	<0.001	–0.47	0.63	0.25–1.57	0.304

the Spanish study from 2020,¹⁴ showed that HCRU costs were statistically associated with age, lung function (FEV₁), higher eosinophil levels, and the number of exacerbation events. These studies^{14,15} included severe asthma patients with both controlled and uncontrolled asthma. Patients with severe uncontrolled asthma have by definition poorer control of asthma symptoms, which negatively impacts the patient's health status²¹ and HCRU costs.²² In a general asthma population, higher levels of b-eos are associated with poorer asthma control and higher severity.^{23,24} In our study, the population of interest was patients with severe uncontrolled asthma, and among this population, the HCRU costs did not differ by T2 status. This is also shown in the regression modelling indicating T2 status is not associated with total HCRU costs.

On the other hand, our findings indicate that T2 low patients spend more inpatient days after an exacerbation leading to hospitalisation, and lower medication-related costs, compared to the non-T2 low patients. This indicates that patients with T2 low asthma have limited effective treatment options, even though their economic burden on healthcare equals the economic burden from non-type 2 asthma patients. Our finding highlights that the economic burden on the healthcare system from patients with severe uncontrolled asthma is equally high, regardless of inflammatory biomarker status. These findings are important to several decision-makers when planning interventions and medications for patients with severe uncontrolled asthma.

Strengths and Limitations

The main strength of this study is being one of the first studies to evaluate HCRU among a well-defined population of severe uncontrolled T2 low and non-T2 low asthma patients from real-world clinical practice with detailed biomarker and HCRU data. Nonetheless, several limitations of this study should be noted that relate to the study setting. First, it was not possible to define the T2 status for all the severe uncontrolled patients in the speciality care clinic due to lack of registered T2 biomarker data. Thus, the patients with available biomarker data may have more HCRU compared to patients without available biomarker data. Second, asthma patients managed only in primary care were not included in this study, thus solely the speciality care HCRU costs were available. Third, the exacerbations in our patients may be more severe than in the total asthma population since hospitalisation or ER-visit were required in the definition. We chose not to use OCS-treated exacerbations in the definition since detailed use of OCS could not be assessed based on OCS purchases as patients may purchase it in amounts enough for several courses to be used on demand. Thus, even though the total purchases of OCS were captured, the use of separate courses cannot be captured in the data. However, the responsiveness to corticosteroids is likely lower in T2 low patients, suggesting that hospitalisations can be a relevant measure of severe exacerbations in this group. Fourth, it should be noted that the small number of patients limits the statistical power of the analysis. For example, there may have been true differences in the total HCRU between the patient subgroups, but with this sample size, it was not possible to detect those differences. Furthermore, some effects may not have been seen due to confounding, ie, not all patient characteristics were accounted for.

Conclusion

This study showed that patients with uncontrolled severe T2 low asthma use as much HCRU as corresponding non-T2 low patients, but presently with limited treatment options. This data brought new insights into the HCRU of severe uncontrolled asthma patients per T2 status, which has not previously been investigated.

Data Sharing Statement

All data and study materials are kept in an audited square analysis environment of Findata the central permission authority, access to data is only for those named in the permission. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: <https://astrazenecagroup.trials.pharmacm.com/ST/Submission/Disclosure>.

Ethics Approval and Consent to Participate

The study permission was granted by the central permission authority in Finland, Findata. Permission number THL/2385/14.02.00/2021 (2021/244). No ethical approval or consent was required due to the retrospective registry-based design of the study.

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Author Contributions

All authors contributed to the conception and design of the study. MIL, SK, and JA retrieved and analysed data; JP, AV, LL and HK critically reviewed Results and contributed to interpretation of data analysis. JP wrote the first draft of the manuscript; all authors participated in manuscript writing and editing with a significant intellectual contribution. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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.

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Disclosure

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