

TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies

Tauri Türkson 212053YVEM

**Psoriasis treatment costs in Estonia from public
health insurance perspective: a registry-based
cost of illness study**

Master's thesis

Supervisors:

Priit Kruus
MSc

Riina Hallik
MSc, MMS, RN

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TALLINNA TEHNIKAÜLIKOOL
Infotehnoloogia teaduskond

Tauri Türkson 212053YVEM

**Psoriaasi ravikulud Eestis riikliku
ravikindlustuse perspektiivist: registripõhine
haiguskulude uuring**

Magistritöö

Juhendajad:

Priit Kruus
MSc

Riina Hallik
MSc, MMS, RN

Tallinn 2023

Author's declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This work submitted for thesis defence is an original work and has not been presented for examination anywhere else.

Author: Tauri Türkson

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Abstract

Background: Psoriasis is currently an untreatable skin disease that has a prevalence of 2 - 3 % of the total global population. Multiple severity levels of psoriasis can be alleviated through different therapies which reflect in the utilization of different healthcare resources that are paid through national health insurance reimbursement in Estonia. The cost of psoriasis treatment is unknown in Estonia and cannot be assumed as there are no studies published regarding the population in the rest of the Baltic countries as well.

Aim: To quantify the total direct treatment costs per year per patient for diagnoses under the category of L40 to provide comparable data of Estonia for the rest of the world and contribute by laying a foundation for further research on health interventions evaluations regarding psoriasis treatment and care in Estonia.

Methods: A cost of illness method was employed as the type of economical evaluation used for quantitative analysis. Registry data concerning patients who had psoriasis under the category of L40 as a primary or co-morbid diagnosis in at least one treatment bill between 2018 and 2021 was obtained from the Estonian Health Insurance Fund and included in the study. The cost generating components - treatment bills, prescription medical devices, prescription medical devices and benefits for incapacity for work – were assessed from the healthcare payer perspective.

Results: 29 380 psoriasis patients were included in the study, representing about 70% of Estonian psoriasis patients. The mean age of participants was 53,89 and out of all patients 57,14% were females and 42,86% males. The total 4-year average per patient per year treatment cost was 2156,12€. Treatment of patients with comorbidity was on average 51,26% more expensive per patient for the payer compared to patients without any diagnosed comorbidity. No differences between the costs in different years were noticed. The 4-year average percentage of total psoriasis treatment costs from the country's GDP was 0,17% and from the country's total healthcare insurance spending 3,10%.

Conclusions: Psoriasis treatment is a burden to the society and the costs are rising each following year. The treatment costs in Estonia are on par with the costs in other countries, where similar cost of illness studies have been conducted. There are no differences detected in comorbidities with other countries. This cost data can be a valuable input in investigating alternative treatment and care options for psoriasis digital health interventions and remote patient consultations among psoriasis patients are increasing.

This thesis is written in English and is 55 pages long, including 6 chapters, 4 figures, 7 tables, 134 references and 2 appendices. The thesis word count is 16 491.

Keywords: psoriasis, cost of illness, national insurance database, Estonia, psoriasis comorbidities

Annotatsioon

Taust: Psoriaas on praegu ravimata nahahaigus, mille levimus on 2-3% kogu maailma elanikkonnast. Psoriaasi eri raskusastmeid on võimalik leevendada erinevate ravimeetodite abil, mis kajastuvad erinevate tervishoiuressursside kasutamises, mida Eestis makstakse riikliku ravikindlustuse hüvitise kaudu. Psoriaasi ravi maksumus on Eestis teadmata ja seda ei saa oletada, kuna ka ülejäänud Balti riikide elanikkonna kohta ei ole avaldatud taolisi uuringuid.

Eesmärk: Mõõta otsesed ravikulud aastas ühe patsiendi kohta L40 kategooriasse kuuluvate diagnooside puhul, et pakkuda võrreldavaid andmeid Eesti kohta ülejäänud maailmale ja aidata luua alus edasiste uuringute läbi tervishoiusekkumiste hindamiseks seoses psoriaasi ravi ja hooldusega Eestis.

Meetodid: Kvantitatiivse analüüsi puhul kasutati majandusliku hindamise tüübina haiguskulude meetodit. Eesti Haigekassast saadi ja kaasati uuringusse registriandmed patsientide kohta, kellel oli psoriaas kategoorias L40 esmase või kaasuva diagnoosina vähemalt ühel raviarvel ajavahemikul 2018 - 2021. Hinnati kulusid tekitavaid komponente - raviarveid, retseptiravimeid, retseptiravimeid ja töövõimetushüvitisi - tervishoiuteenuse maksja vaatenurgast.

Tulemused: Uuringusse kaasati 29 380 psoriaasipatsienti, mis moodustavad ligikaudu 70% Eesti psoriaasahaigetest. Osalejate keskmine vanus oli 53,89, 57,14% olid naised ja 42,86% mehed. Keskmine 4 aasta keskmine ravikulu patsiendi kohta aastas oli 2156,12 eurot. Kaasuvate haigustega patsientide ravi oli maksjale keskmiselt 51,26% kallim patsiendi kohta võrreldes patsientidega, kellel ei olnud diagnoositud komorbiidsust. Erinevate aastate kulude vahel erinevusi ei täheldatud. Psoriaasi ravikulude osakaal riigi SKPst oli 4 aasta jooksul keskmiselt 0,17% ja riigi ravikindlustuse kogukuludest 3,10%.

Kokkuvõte: Psoriaasi ravi on ühiskonnale koormav ja kulud kasvavad igal järgneval aastal. Eesti ravikulud on samal tasemel kui teistes riikides, kus on tehtud sarnaseid haiguskulude uuringuid. Kaasuvate haiguste osas ei ole tuvastatud erinevusi teiste

riikidega. Need kuluandmed saavad olla väärtuslikuks sisendiks psoriaasi alternatiivsete ravi- ja hooldusvõimaluste uurimisel - näiteks nii digitaalsed tervishoiualased sekkumised kui ka psoriaasipatsientide kaugkonsultatsioonide suurendamine.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 55 leheküljel, 6 peatükki, 4 joonist, 7 tabelit, 134 viidet ja 2 lisa. Magistritöö sõnade arv on 16 491.

Märksõnad: psoriaas, haiguse maksumus, riiklik kindlustuse andmebaas, Eesti, psoriaasi kaasuvad haigused.

List of abbreviations and terms

EHIF	Estonian Health Insurance Fund
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
COI	Cost of illness
WHO	World Health Organization

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1 Introduction

The study lies in the field of dermatology which is a branch of medicine that embraces the research, diagnosis, and management of any health condition concerned with skin, hair, and nails [1]. According to disability-adjusted life years, skin conditions are currently acknowledged as the fourth most significant cause of nonfatal disease burden on a global scale [2] and psoriasis is one of these conditions with a reported prevalence ranging between 0.09% and 11.43% in different countries, making it an important global issue according to the World Health Organization (WHO) [3]. Worldwide, at least 125 million people or on average, 2 - 3 % of the total global population suffer under psoriasis [4] which is a chronic, non-communicable, painful, disfiguring and disabling systemic inflammatory disease negatively impacting patient's quality of life. It can occur at every age and is a lifelong disease without an actual cure [3].

Multiple healthcare resources can be utilized for psoriasis treatment, such as hospital visits, healthcare services, prescription medicines and medical devices. Each of them results in costs which can be measured, but which value varies depending on the severity level [4] or possible comorbidities [5]. These costs inevitably add up, being a huge economic burden both for patients and society [6] [7]. Even the smallest parameters like support from society and family members [8] or distance from the nearest healthcare provider or pharmacy [9] [10] may play an important role in the treatment process and thus reflect in costs to the payer.

In Estonia, there are about 42 000 patients diagnosed with psoriasis [11], which is 3,2% of the country's population. Until now, the cost of psoriasis treatment is unknown in Estonia and there are also no studies published regarding the population in rest of the Baltic countries – Latvia and Lithuania. However, within the last decade, authors in 9 countries - Finland [12], Sweden [13], Germany [14], Switzerland [15], Greece [16], South Korea [17], Taiwan [18] [19], Colombia [20] and United States of America (USA) [21] [22] [23] [24] [25] [26] - have published economic evaluation studies, which assess healthcare costs per year per patient for psoriasis.

The cost of illness (COI) has been chosen as a suitable evaluation technique [27] in order to identify and measure the medical expenses of this disease per person in Estonia. COI

does not assess benefits, effectiveness, quality-adjusted life years or utilities by comparing alternative options but considers various aspects of the disease impact on the health outcomes in the specified location (counties and countries) and population (chosen study subjects). It is used to aid policy decision-making to address the primary interventions [28] and allocate resources according to the set constraints [29]. The cost-generating components which were received from national health insurance institution and analysed in detail are treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work.

The focus is set specifically on psoriasis disease because it is timely and relevant in the context of developing psoriasis care in Estonia as Estonian Health Insurance Fund (EHIF) has an ongoing telemedicine pilot project “Patient monitoring in case of psoriasis and preventing worsening of the disease”. During the project, a service model - where the doctor gets a better overview of the patient's condition, because the patient can remotely send relevant monitoring information and pictures of the skin's condition – will be developed [30]. Combining the results of the pilot project with this cost evaluation study will give valuable input for the next steps in the care of psoriasis patients. Since psoriasis is considered a chronic [31] disease, it fits well with EHIF’s care management program [32], where the prevention of chronic diseases is supported as one of the set goals. Moreover, Estonia does not have clinical guideline for psoriasis treatment, thus the results of this study can be used as an input to implement one. The gathering of background information is especially important when new drugs are introduced in the market [33] [34], signifying the relevance and actuality of the research.

This research covers a gap in the field by providing comparable data of Estonia with the rest of the world. Concurrently, the evaluation of yearly healthcare cost distribution per different cost components will serve as a first step to build a foundation for further research on psoriasis and evaluation of health interventions regarding psoriasis treatment. The central argument of the study would be that psoriasis is a recognized burden for both the patient and the society, and is dependant of multiple factors, including the severity level and diagnosed comorbidity. This study is designed according to the bottom-up approach by referring to the patients’ registry data set, where the aggregated data gives the domain knowledge to solve possible problems and make policy decisions [35], including reimbursement adjustments.

Problem statement

In Estonia a country-specific, or in Baltics, a region-specific overview of direct costs in psoriasis treatment through treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work is missing, preventing to take evidence-based decisions for treatment prioritization policies [36] [37], country benchmarking, budget allocation for reimbursement level adjustments [38] [39] or development of clinical guidelines [40] [41] [42] [43].

Aim

This cost-of-illness study aims to quantify the total direct treatment costs per year per patient for diagnoses under the category of L40 according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [44] in Estonia.

Research questions

- What is the total direct treatment cost per year per patient in Estonia?
- What is the per patient cost difference between patient with comorbidity and without comorbidity among Estonian psoriasis patients?
- How do the different cost components divide within the psoriasis patient treatment cost?

Usefulness of the study

The results of the work could be used in further studies to point out areas where the treatment costs should be reduced or rearranged, taking into consideration also the treatment costs of comorbidities. The potential stakeholders in these actions could be thus either policymakers, health insurance fund, healthcare professionals, researchers or entrepreneurs This study could also potentially help to make clear how much the costs increase due to the disease progression, or severity, per patient. Optimising the treatment methods and moving greater expenses towards preventive care and early detection could thereafter reduce the total healthcare costs in later stages through the avoidance of advanced-stage disease treatment. Consequently, the number of patients who suffer under severe conditions or resultant comorbidities could potentially fall from the shift towards preventive care and early detection [45].

But regarding the benefit to the persons whose data was processed, it will not be evident right after the completion of the analysis as the benefit is dependant of the next steps taken with the conducted research results – either through policy changes, reimbursement adjustments or new treatment implementation.

Structure of the study

This work is structured into 5 sections – introduction, background, methodology, results and discussion. Each section has under it subsections, which are accordingly titled. In background section, the subsections are: cost of illness and conducted cost studies around the world. Methodology covers sections like cost of illness, study design, ethical and philosophical considerations, data source, study subjects, perspective of the costs assessed, data analysis and stratification, sensitivity analysis, and reliability and validity. Results section takes under it sensitivity analysis, comorbidities, health care services, prescription medicines, prescription medical devices, and benefits for incapacity for work. Lastly, the discussion comprises of limitations and further research possibilities, conclusion and acknowledgements.

2 Background

This study concentrates on psoriasis disease, which is categorised under L40 according to ICD-10. Psoriasis is a complex genetic dermatological disorder that results in the development of scaly patches or lesions of skin characterized by flakiness [46]. These patches can be most often found on elbows, knees, scalp, nails and lower back, but may appear also in other body areas [47]. The disease is diagnosed by dermatologist, a specialist in treating skin conditions, based on multiple criteria [48] [49]. For instance, the color, size, scabiness, thickness, itchiness and spread of the patches, the body area and percentage affected [50]. Depending of the assessment results, one of the eight sub-diagnoses, according to ICD-10, may be assigned - psoriasis vulgaris, generalized pustular psoriasis, acrodermatitis continua, pustulosis palmaris et plantaris, guttate psoriasis, arthropathic psoriasis, other psoriasis, or psoriasis, unspecified [51]. For early diagnosis it is important to rule out all other possible health conditions which can exhibit similarities to the illness and impede timely implementation of the suitable treatment method [52].

At present time, there is no known cure for psoriasis and the disease caused situation can be alleviated through different therapies [53] which can either reduce or nearly stop the occurring symptoms [54]. Such treatment options could be either a local or topical therapy via creams and gels applied directly to the skin [55]; phototherapy, where ultraviolet light is used [56]; a full-body or systemic therapy, where the patient is taking certain medicine(s) as a means of treatment [57] [53]; or lastly, the complementary and integrative medicine, where often adjustments in everyday life behaviour are suggested – diet, physical activity, sleep and detachment of possible stressors [58].

Each of those treatment options comes with its own cost. Generally, the systemic therapy is considered to be the most expensive option, especially when biologics are used [59] [6]. Similarly to all other medications, the cost of those is increasing year by year [60], making the treatment more expensive, especially when greater attention in the future will be drawn to new biotechnology drugs that are currently awaiting behind a regulatory approvals [61]. However, even though biologics have shown to be the most effective in treatment, they are not heavily utilized in any country as they are intended only for the most severe cases of psoriasis [62]. Topical therapy, on the other hand, is intended for all severity levels and is the main treatment option for patients who fall into mild severity

level group, as it is the cheapest effective treatment [63]. Phototherapy, however, is the best economical option for patients with moderate psoriasis severity level, as it is more expensive than topical therapy, yet more affordable than biologics [64]. Lastly, complementary, and integrative medicine can be considered with the lowest economic burden as the lifestyle changes often do not incur in increased costs. Different treatment options could be used separately or together – depending on the severity level or comorbidities [65], which determine the chosen treatment approach [66]. Psoriasis severity levels are generally separated into three categories – mild, moderate, and severe – depending on how much body area is affected and what are the comorbidities [4]. However, to date no classification system exists to assign a severity level when diagnosing a patient. Therefore, the assessment is done through questionnaires like PASI (Psoriasis Area Severity Index) [67], DLQI (Dermatology Life Quality Index) [68] or PSSD (Psoriasis Signs and Symptoms Diary) [69], expert’s opinion via the percentage of body area affected, the medicines prescribed and effect to the quality of life [22].

The most common comorbidities among psoriasis patients are different cardiovascular diseases like stroke, coronary artery disease, atrial fibrillation, hypertension or dyslipidemia [70] [71] [72], psoriatic arthritis [73] [31], obesity [74] [75], diabetes [76], mood disorders [77] and mental health diseases [78], mental disorders [79], immune-mediated diseases [80] and eye diseases [81]. Comorbidities make the treatment of psoriasis both more difficult and more expensive, as different conditions are needed to be treated simultaneously. It is common that patient’s primary diagnosis is psoriasis and different comorbidities develop over time. But it may be also vice versa, where named comorbidities are in reality diagnosed before psoriasis and may be a risk factor to develop psoriasis in later life [82].

Several studies have shown that the treatment pathways have changed for patients infected with Covid-19, as additional comorbidities developed [83] [84] [85] [86] [87]. This in turn has resulted in increased healthcare costs [88] [89], but also in decreased productivity and GDP losses [90]. The cost increase referred is on average for all diagnoses and not only for psoriasis. Concerning psoriasis, there have not yet been published many studies which look the correlation between psoriasis and Covid-19. Nevertheless, one Turkish study [91] found no differences in between psoriasis patients diagnosed with Covid-19 and patients without Covid-19 diagnosis in term of treatment differences as the hospitalization, mortality, comorbidities and treatment method differences were not largely different in between groups. Italian study, however,

confirmed that psoriasis patients are among higher risk group to receive Covid-19 diagnosis [92]. No conducted cost studies comparing psoriasis patients with and without Covid-19 were known to the author of this current research.

Cost of illness

COI is known as one of the earliest methodologies of economic evaluation in the healthcare sector, with its history reaching back to the 1960s, first described in detail by Dorothy P. Rice [93] [94]. These studies aim to be descriptive as the intention is to itemize, give value, and summarize the costs of a particular illness or disease by giving an idea of its economic burden according to Tom Jefferson [29]. That is also the reason why these research works are occasionally called as burden of disease (BOD) studies [28]. As a standard practice, the costs identified and measured include both direct and indirect, plus intangible aspects – all either from the payer or patient perspective. For this type of study, two types of costing exist – prevalence or incidence based. The first one takes together the total cost in a selected year, whereas the latter, incidence-based approach, calculates the lifetime costs from the beginning of the initial diagnosis [95].

Conducted cost studies around the world

The estimated healthcare costs per year per patient for psoriasis assessed in the last 10 years worldwide, listed according to geographical distance from Estonia, range from 1,083€ in Finland [12], 3668,81€ in Sweden [13], 4940€ in Germany [14], 3644,53€ in Switzerland [15], 8075,22€ in Greece [16], 151,61€ in South Korea [17], 1350,85€ - 1986,21€ in Taiwan [18] [19], 5857,61€ in Colombia [20] to 23 564,28€ - 28 139,57€ in USA [21] [22] [23] [24] [25]. Among those, according to the Organisation for Economic Cooperation and Development (OECD) report [96], countries closest to Estonia in terms of health expenditure as a share of GDP are Colombia, Greece, and Korea.

Out of the studies conducted in those nine countries, only three studies have explicitly defined their research strategy as a cost of illness on psoriasis – carried out in Colombia, Germany and Switzerland.

In Colombia, which closest to Estonia in terms of healthcare spending from GDP according to OECD, the treatment costs were collected [20] by appointments to different physician specialties, laboratory and imaging costs and medications. The average annual per patient costs were presented separately for males and females – direct medical cost was \$5646 (5857,61€), and \$4365,3 (4528,91€), respectively.

In German cross-sectional study [14] the total average annual healthcare costs of psoriasis per patient amounted to 5543€, including both direct and indirect treatment costs. The direct costs included both out-of-pocket and health insurance expenses. The indirect costs covered absence days from work due to psoriasis. The annual cost of the health insurance for a patient with psoriasis was €4940.

The Swiss retrospective cost-of-illness analysis study [15] noted that costs per patient increase with the degree of disease severity as they were from CHF 1800 (1822,27€) in the mild to CHF 3600 (3644,53€) in the moderate group and between CHF 17 000 (17 210,30€) and CHF 20 000 (20 247,41€) in the severe psoriasis group. The costs are accounted for prescription medicines, healthcare services and are separated by inpatient and outpatient care.

Other studies that have not specified the economic evaluation method but have researched the topic are conducted in South Korea, Taiwan, Greece, Finland and Sweden. In South Korean descriptive cross-sectional study [17] a total annual medical expenditure reported per patient was 209 320 South Korean Won (151,61€), but there was no detailed information stated which cost components were taken into consideration in calculating the average total medical expenditure for one year per person other than both medical and prescription costs of patients with and without (as a comparison group) psoriasis and for patients with mild or moderate to severe psoriasis.

In Taiwanese cross-sectional study [19] the total cost of psoriasis patients' treatment was \$1917,10 (1986,21€), where the calculations were done based on the number and costs of provided dermatology and nondermatology services, which were further detailed into inpatient and outpatient visits. The study also revealed that there was significantly greater utilization of outpatient visits per patient per year than inpatient visits – 24,8 versus 3,7, respectively.

Another Taiwanese study [18] classified patients into moderate to severe and mild psoriasis groups. The total national health insurance' reimbursed treatment costs per year per patient with moderate to severe psoriasis were NT\$41 525 (1350,85€) and for mild psoriasis NT\$14,816 (481,98€).

In Greek's retrospective, observational study [16] a median annual per-patient cost was estimated to be 8075,22€. The cost, however, considers only reimbursed prescription medicines or pharmaceuticals – topical, systemic, and biologic agents. The actual average per patient cost for all reimbursed treatments in Greece should therefore be higher. During the study, it was additionally calculated, that in case of a scenario where a patient of 45

years will be put under psoriasis treatment, considering only prescription medicines, and it will be continued until the rest of his or her life (roughly 30 years), the estimated average cost of it to the payer would be at minimum 240,000€ over the patient's remaining lifetime in 2015 prices.

The Finnish study [12] returned total medication costs 1083€ per year per patient, which considered only the prescription medicines, categorized into topical medications, systemic medications and biologic medications. This indicates that the actual psoriasis treatment costs reimbursed by the country might be higher than reported. Study brought an attention to the fact that even though biologics represented 67% of total medication costs, this treatment option was used only by the 5% of the patients in the data set meaning that a greater sum of medication costs was generated by a small number of patients, who at the same time had severe type of psoriasis. It was also noted that patient receiving more treatment options had higher treatment costs compared to the patients who received less. Lastly, the Swedish study [13] was the most similar to the current work in terms of analysed cost components (costs of inpatient and outpatient care, medications and productivity losses were taken into consideration). For all patients, the mean total healthcare resource utilization costs were estimated at \$3555 (3668,81€) – without the sickness benefit. As the study conducted observed different treatment options, the authors concluded that the economic burden is highly dependent of the chosen treatment method – the most expensive option being biologics.

3 Methodology

Study design

The study design is described according to research “onion” developed by Saunders et al [97], which is made up of 6 layers, from outer to inner – research philosophy, research approach, research strategy, methodological choices, time horizon, and techniques and procedures [98] [99]. For this study, the used research philosophy is positivism because the cost analysis was carried out objectively, without opinions or personal frame of reference. Moreover, the intention was only to observe and state the facts in the end. An inductive approach was used, moving from specific to general. The research strategy is an economic evaluation, a detailed and in-depth investigation of a specific field – healthcare costs and resource utilization in psoriasis treatment in Estonia. As the study focuses strictly on numerical cost data, the study utilises a mono method using quantitative methodology. The longitudinal time horizon was chosen as it enables to see changes over selected period, thus the data for this study is collected for four different years. Registry data for different cost components was obtained from EHIF. The data source is considered primary to which content analysis was carried out according to the COI principles.

The study was conducted according to the validated methodological checklist drafted initially for a study concerning prostate cancer [100] and also used in an Alzheimer’s disease study [101], adjusted specifically for COI research by Molinier et al. The checklist is adapted from the Drummond’s model for assessing economic evaluations [102] [103] and was chosen apart from other recognized checklists [104] [105] [106] as the most recent and compact. The chosen checklists’ methodological questions were continuously assessed while structuring the work to ensure that all the aspects relevant to COI study have been addressed:

1. Was a clear definition of the illness given?
2. Were epidemiological sources carefully described?
3. Were direct/indirect costs sufficiently disaggregated?
4. Were activity data sources carefully described?
5. Were activity data appropriately assessed?
6. Were the sources of all cost values analytically described?
7. Were unit costs appropriately valued?

8. Were the methods adopted carefully explained?
9. Were the major assumptions tested in a sensitivity analysis?
10. Was the presentation of study results consistent with the methodology of the study?

Cost of illness

The intention of this work is to calculate the values of different cost components in different years and compare them with one another and with similar studies published in other countries. For this, a cost of illness (COI) approach, where the method of illness costing is prevalence based, as the total incurred costs of the disease during the selected time period were estimated, is used.

Cost studies are needed for virtually all emerging digital health interventions which need cost data to assess their effectiveness by either comparing traditional, face-to-face visits, with new and novel teleconsultations or telemonitoring solutions [107] or when there is an interest to implement a software-based prescription either into country's healthcare system or reimbursement list, which in long term may reduce the utilization of prescription medicines and thus lower the health insurance spending [108] [109].

Cost generating components assessed during this study were treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work. Treatment bills allow to estimate the healthcare resource utilization by reviewing the healthcare services and cost of comorbidity treatment, whereas prescription medicines and medical devices give an overview of costs related to either systemic or topical therapies. What is more, the information about how much prescription medicines or medical devices were written out by health care professionals and how much was actually bought out by patient's allows to see how much do the patients follow the given treatment, e.g. adherence. In literature, higher adherence has shown to limit the physical manifestations of psoriasis and help improve a patient's quality of life [110], which importance is strongly connected with severity as the more severe the disease, the more important it is to continue treatment without interruption to keep it under control [111]. Benefits for incapacity for work allow to assess another aspect of this disease's economic burden. Mentioned cost components were selected because they are the most readily available information from the national database regarding the treatment cost and the previously mentioned studies have also used similar information of utilized healthcare services and prescriptions to carry out country-specific calculations. In addition to those mentioned

cost components, the results are stratified by psoriasis severity level, comorbidities and socioeconomic variables such as age, gender and insurance status.

The national database data used for the study originates from EHIF (Estonian Health Insurance Fund), the national institution in Estonia which holds and manages healthcare data in addition to organizing health insurance. EHIF finances insured person's medical treatment if health care service provider has entered into contract with EHIF for the respective services. The contract is concluded for five or four years [112]. In addition to contract, the prices of healthcare services - including medical services, procedures, and drugs - are negotiated with partners multiple times a year and adjusted annually per need and available resources [113].

Ethical and philosophical considerations

The study was by approved by the Research Ethics Committee of the University of Tartu on 17.10.2022 through decision 369/M-3 for the study protocol, followed by two other approvals on 19.12.2022 and 20.02.2023 due to the changes in data set parameters. The registry data request was sent to EHIF, from where the pseudonymised and encrypted data set through the secure cloud storage service with temporary access was received. Pseudonymisation enabled the data processor, EHIF, to see non-anonymised data, which triggered the need for ethics committee approval – the research could not have been started if approval by ethics committee would not have been granted. Therefore, the data protection, especially under the light of General Data Protection Regulation (GDPR) [114], which describes data concerning health, had to be taken seriously into account. Additionally, as the data provided is specific, it may be in some cases be possible to link the provided information with an identified person.

One can consider ethical issues also in regard the transparency [115] of the study methods. Therefore, an overview of the steps taken that led to the described results were thoroughly described in this methodology section. Purpose is to not hide any possible misuse or uncertainty and neglect of outliers in the data to deliver an expected and favourable outcome. The results of the study will be thoughtfully interpreted to give an accurate overview. However, there is still a probability that outcome may be misinterpreted due to incomplete information of some cost components and thus incorrect assumptions may be made. Furthermore, there could be a possible bias in data cleaning by the researcher as the analysis preparation could influence the results, when some data points would be either intentionally or unintentionally left out, or in case of decimal point values - “.”

instead of “;” - would be used, depending on the computer’s regional settings. To avoid the possible issues, examples of conducted psoriasis economic evaluation studies are followed for general structure [116].

The last aspect considers how the results of the study will be used in the future for the benefit of Estonian psoriasis patients. The study will be published in the digital collection of the public library of Tallinn University of Technology where it can be read and taken as an input either to further studies or as a reference point to decision-making.

Data source

While conducting the research, various databases were used. For instance, the WHO database of ICD-10 diagnoses [117], Statistics Estonia databases to gather socioeconomic data [118] [119], and EHIF’s publicly available information for certain calculations, such as giving value to zero-bills or calculating the percentage of country’s total healthcare insurance spending [120]. EHIF database represents the entire Estonian population (1.3 million in 2022 [118]) and contains information regarding treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work, which are all identified as cost-generating components. It is also possible to extract socioeconomic variables such as age, gender, place of residence with county accuracy and insurance status from the database [121].

Study subjects

Patients of all ages were included in the retrospective study if they had a primary or co-morbid diagnosis of psoriasis (under the category of L40) according to the ICD-10 coding system in at least one insurance bill submitted to EHIF by a medical service provider’s outpatient, inpatient or emergency departments between 1st of January 2018 and 31st of December 2021. Obtained registry data set consists of the treatment bills of 29 380 persons. Instead of assessing the costs of the last year, or by some certain year as a usual practice in COI studies [29] [101], a longer time period was selected for the registry data set to investigate the possible trend in cost distribution, both by 4-year average and separate years, and also consider the possible impacts of Covid-19 on psoriasis treatment costs, where 2018-2019 would be counted as the pre-Covid period and 2020-2021 as the post-Covid period. Instead of one year per group (pre-Covid and post-Covid), two were taken as a precaution to confirm whether the change of costs could be justified due to Covid-19 or if there are similar, organic changes of costs between the selected years.

Perspective of the costs assessed

This study is conducted from the healthcare payer (national health insurance) perspective to expenses. The cost categories assessed were treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work. Analysing the costs from healthcare payer perspective is also more common among economic evaluation studies as it is more readily available and thus better suitable for comparison [122]. It has been claimed that when adding in patient perspective, the costs may not be fully explored which in turn could affect the overall study quality and reliability [123]. Furthermore, patient's perspective of the expenses was not included due to the lack of information on treatments which were not prescribed by doctor and hence not reimbursed by national health insurance. For instance, out-of-pocket costs are not recorded per patient and thus not traceable.

Data analysis and stratification

Analysis is conducted according to the structure known from COI evaluations. The data set described in detail in Figure 4 (page 54) was requested and obtained from EHIF nationwide database for processing. Columns in different tables concerning treatment bills, comorbidities, healthcare services, prescription medical devices, prescription medical devices and benefits for incapacity for work were linked by matching patients' pseudonyms and the treatment bill numbers. The total costs, mean and standard deviation were calculated as the main characteristics. The costs were presented by years and stratified by different cost components (treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work), comorbidities, disease severities and socioeconomic variables to compare them with other similar studies available and provide a detailed breakdown of the expenses. All expenses in this paper are considered as direct costs and from a payer's perspective.

Patients were stratified by disease severity into groups of mild to moderate and severe as such approach has been used also within other psoriasis cost analysis studies [17] [18] [22]. Into mild group were considered all patients who did not have any systemic treatments and to moderate to severe group patients who had at least one prescription of known systemic or biologic medicines such as methotrexate, acitretin, cyclosporine, apremilast, etanercept, infliximab, adalimumab, certolizumab, secukinumab, ixekizumab, brodalumab, bimekizumab, ustekinumab, guselkumab, tildrakizumab, isankizumab or

deucravacitinib [53]. The categorization is done only through prescription medicine data as no other information was available where severity assessment could be carried out. Per Estonian healthcare system, visits in family medicine are accounted for 0€ on the treatment bill because family medicine centres get their income on the basis of a contract with EHIF. To reflect the costs of those visits, the zero-bills were adjusted for five specialties - family medicine, family nursing, nurse, general medical care and family nurse with additional rights – for which an average cost per visit per year was calculated. The calculations were done by using the total cost of specialty in a given year and dividing it by the number of visits on the same given year, both values originating either from EHIF healthcare statistics [124] or annual reports [120]. Results of the calculation used in further calculations are presented on Table 1 **Error! Reference source not found.** (page **Error! Bookmark not defined.**).

Table 1 Costs per visits in family medicine between 2018 and 2021, in €

	2018	2019	2020	2021
Family medicine	25,63	29,54	33,85	35,53
Family nursing	77,75	83,29	79,13	60,72
Nurse	107,04	110,95	126,34	140,91
General medical care	18,28	20,71	22,63	21,37
Family nurse with additional rights	77,75	83,29	79,13	60,72

For the costs to be comparable in between different years, the cost values were further adjusted per consumer price index [125] according to the respective year using the following formula [126]:

$$\begin{aligned}
 & \textit{Adjusted cost (2023 price)} \\
 & = \textit{Cost (respective year)} \\
 & * \frac{\textit{Consumer Price Index for 2023}}{\textit{Consumer Price Index for respective year}}
 \end{aligned}$$

Such cost adjustment was performed for all cost components. Because the research was conducted early 2023, consumer price index data in the month of February was used for all years as the latest available month for 2023. The data was processed in Microsoft Office Excel 365, the spreadsheet software commonly used for data analysis.

Sensitivity analysis

As a part of this study, a deterministic one-way sensitivity analysis was undertaken to investigate which cost components influence the study outcome the most. The considered cost components were treatment bills, prescription medicines and prescription medical devices, which were substituted to average per patient per year cost calculation one by one, leaving other components' values unchanged. For each parameter its minimum, maximum and median values were substituted. The results of the analysis were visualised through tornado diagram, where the more influential parameters are positioned on the top end of tornado and lower influence parameters on the lower end.

The purpose of a sensitivity analysis within the economic evaluation study is to illustrate and assess the level of confidence of the evaluation results [127]. It is done by taking the key input parameters and varying them to produce a different result which enables to determine how certain parameter values affect the end value [29] and which parameters have the highest influence [128]. The field of healthcare is particularly sensitive to the change of parameters as when transferring evaluation results from initial to new settings as a changed context may result in uncertainty. Sensitivity analysis has three approaches – deterministic, extreme scenario and probabilistic. In deterministic approach one or two parameters are varied at a time, while the remaining parameters stay constant. In 70% of cases, one-way approach as the simplest one is utilized in contrast to two-way approach [129]. Variables are chosen according to assumptions which could affect the outcome the most [130]. However, deterministic one-way sensitivity analysis has been considered to be one of the weakest due to its limitation among other approaches. For instance, the approach assumes that there is no correlation among the parameters, and it fails to offer any insight into the probability of each parameter adopting a particular variable value [131]. What is more, parameter ranges are often chosen randomly, and models do not expose non-linearities which can produce bias in expected costs under different parameter values [132]. In extreme scenario approach, parameters are set into best-case and worst-case scenario. Lastly, in probabilistic approach, all parameters are taken into consideration to determine the pattern in data distribution. Probabilistic sensitivity analysis is considered to be the most complex but also the most precise approach of those. The major limitation of deterministic one-way sensitivity analysis is the fact that it cannot include all possible parameter uncertainties, whereas in extreme scenario cases the

uncertainty tends to exaggerate [129]. In all cases, the parameter values assessed are usually the minimum, maximum and average of the existing data set [133] as they often deliver the highest level of uncertainty [134].

Reliability and validity

Criteria for reliability in this research refers to repeatability of the study in reaching the same results of the analysis. Reliability was assessed through multiple similar calculations which returned the same result, indicating consistency and reproducibility.

Validity can be checked by comparing the results of the data analysis with the results of other psoriasis COI studies, conducted by authors in different countries. The similarity was ensured by using the checklists which have been worked out specifically for COI. The population under research was clearly defined by diagnosis, comorbidities, age range, gender, and place of residence. To avoid sampling and selection bias, 4-year data of all patients who have had a diagnosis under the category of L40 according to ICD-10 in at least one of their treatment bills were included, ensuring that there were enough participants who represent the country's population.

4 Results

The inclusion criteria returned data about 29 380 unique patients, who represent estimately 70% of Estonian psoriasis patients and 2,26% of the Estonian population. These patients totalled in 1 040 703 treatment bills over 4 years (2018-2021). The mean age, over all treatment bills over four years, was 53,89 and the modal age 60. The most dominant age group in a 5-year interval by a number of submitted treatment bills was 60-64, covering 11,78% of all age groups. The same age group had also the highest share of costs of all age groups -12,40%. Out of 29 380 patients in the study's registry data set, 57,14% were females and 42,86% males. More treatment bills were submitted for women than men on every year, on average 28,55% more per year (594 620 for women and 446 082 for men). However, the treatment of male patients was shown to be more expensive than female, on average 35,03% more per year (42,58€ for men and 29,88€ for women on average per patient). Most of the treatment bills (99,7%) submitted were for insured persons.

The total direct treatment cost per year per patient in Estonia is 2156,12€. This is a 4-year average value, when amounted for all treatment bills, where codes under the category of L40 were either a primary or secondary diagnosis in at least one treatment bill submitted for this patient. The total is accounted for all 29 380 patients, where in addition the costs of prescription medicines, prescription medical devices, and benefits for incapacity for work are added, further detailed in Table 2 (page 30). **The different cost components divide within the psoriasis patient treatment cost as following: treatment bills - 68,20%, prescription medicines - 19,52%, prescription medical devices - 0,90% and benefits for incapacity for work - 11,37%.** The trend of costs per patient per year per different cost components has been visualised on Figure 1 (page 31). **Per patient cost difference between patients with comorbidity and without comorbidity among Estonian psoriasis patients is 51,26%.**

By comparing the 2018-2019 as pre-Covid and 2020-2021 as post-Covid period, no notable cost differences between the two groups can be noted in any of the cost components. The 4-year average percentage of total psoriasis treatment costs from the country's Gross Domestic Product (GDP) was 0,17% and from the country's total healthcare insurance spending 3,10%.

Table 2 Psoriasis treatment costs based on EHIF perspective from 2018 to 2021 in Estonia

	2018	2019	2020	2021	4-year average
Total psoriasis treatment costs (including: treatment bills, prescription medicines and prescription medical devices)					
Grand Total, euro (€)	54 755 963,16	61 542 749,56	65 971 580,73	71 117 483,67	63 346 944,28
Per patient, euro (€)	1 863,72	2 094,72	2 245,46	2 420,61	2 156,12
Standard deviation, euro (€)	4 468,93	4 995,30	6 623,16	5 881,99	5 492,35
GDP, euro (€) [119]	35 697 441 326,16	37 489 566 300,58	36 372 368 011,19	41 399 816 605,63	37 739 798 060,89
Grand total's percentage of GDP	0,15%	0,16%	0,18%	0,17%	0,17%
Country's total healthcare insurance spending, euro (€)	1 772 828 462,02	1 923 105 196,60	2 150 671 280,02	2 345 344 175,05	2 047 987 278,42
Grand total's percentage of country's total healthcare insurance spending	3,09%	3,20%	3,07%	3,03%	3,10%
Cost of treatment bills					
Total, euro (€)	37 333 423,66	42 310 952,73	44 741 632,81	48 400 423,85	43 196 608,26
Per patient, euro (€)	1 270,71	1 440,13	1 522,86	1 647,40	1 470,28
Standard deviation, euro (€)	4 031,72	4 371,03	6 187,76	5 256,55	4 961,76
Total's percentage of total costs	68,18%	68,75%	67,82%	68,06%	68,20%
Cost of prescription medicines					
Total, euro (€)	10 793 175,26	11 872 099,39	13 034 497,25	13 747 602,19	12 361 843,53
Per patient, euro (€)	367,37	404,09	443,65	467,93	420,76
Standard deviation, euro (€)	1 211,52	1 471,49	1 694,00	1 807,40	1 546,10
Total's percentage of total costs	19,71%	19,29%	19,76%	19,33%	19,52%
Cost of prescription medical devices					
Total, euro (€)	508 559,60	573 930,66	580 548,60	620 820,62	570 964,87
Per patient, euro (€)	17,30	19,54	19,76	21,13	19,43
Standard deviation, euro (€)	117,49	146,65	124,26	144,14	133,14
Total's percentage of total costs	0,93%	0,93%	0,88%	0,87%	0,90%
Cost of benefits for incapacity for work					
Total, euro (€)	6 120 804,34	6 785 766,92	7 614 902,44	8 348 637,16	7217527,71
Per patient, euro (€)	208,33	230,97	259,19	284,16	245,66
Standard deviation, euro (€)	953,30	1087,99	1067,79	1086,91	1049,00
Total's percentage of total costs	11,18%	11,03%	11,54%	11,74%	11,37%

Total costs (treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work) of patients without any secondary diagnosis, where diagnosis codes under the category of L40 were stated as primary diagnosis

Grand Total	19 861 315,62	21 638 161,09	31 106 707,86	22 717 059,97	23 830 811,13
Per patient	1 063,75	1 158,92	1 666,04	1 216,70	1 276,35
Standard deviation	1 798,53	2 026,96	4 458,47	2 128,81	2 603,19

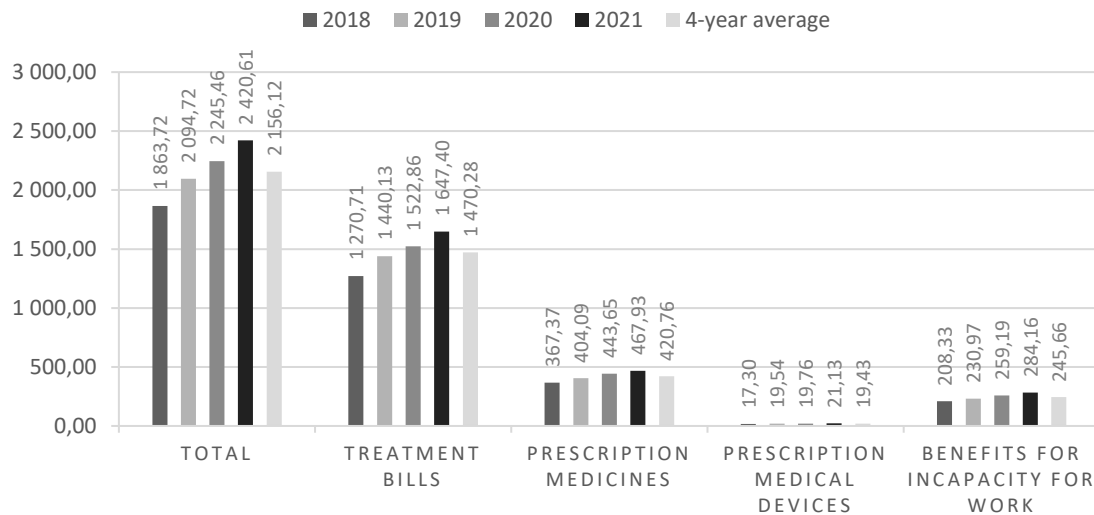


Figure 1 Psoriasis treatment cost components distribution per patient, in €

Sensitivity analysis

The conducted sensitivity analysis considered minimum, maximum and median values of treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work. Analysis shows logically that the treatment bills have the highest influence over the total treatment costs. Prescription medicines have been recorded as the next greatest contributor to costs after treatment bills. Results of the analysis are reflected in Table 3 (page 32), where the base value, against which the sensitivity was calculated, was 1910,46 euros - the actual 4-year average total treatment cost per patient per year. The effects of minimum and maximum values have been represented on a tornado diagram on Figure 2 (page 32).

Table 3 Sensitivity analysis results for varying psoriasis treatment cost components per patient per year on average during 2018-2021

	Minimum	Maximum	Median
Treatment bill component value	0	285 752,32	632,65
Adjusted base value	685,85	286438,17	1318,50
Difference with base value	-32%	13285%	-61%
Prescription medicine component value	0	76 834,05	156,65
Adjusted base value	1735,37	78569,42	1892,02
Difference with base value	-80%	3644%	-88%
Prescription medical device component value	0	3966,68	0
Adjusted base value	2136,69	6103,37	2136,69
Difference with base value	-99%	283%	-99%
Benefits for incapacity for work component value	0	3966,68	0
Adjusted base value	1910,47	5 877,15	1 910,47
Difference with base value	-89%	273%	-89%

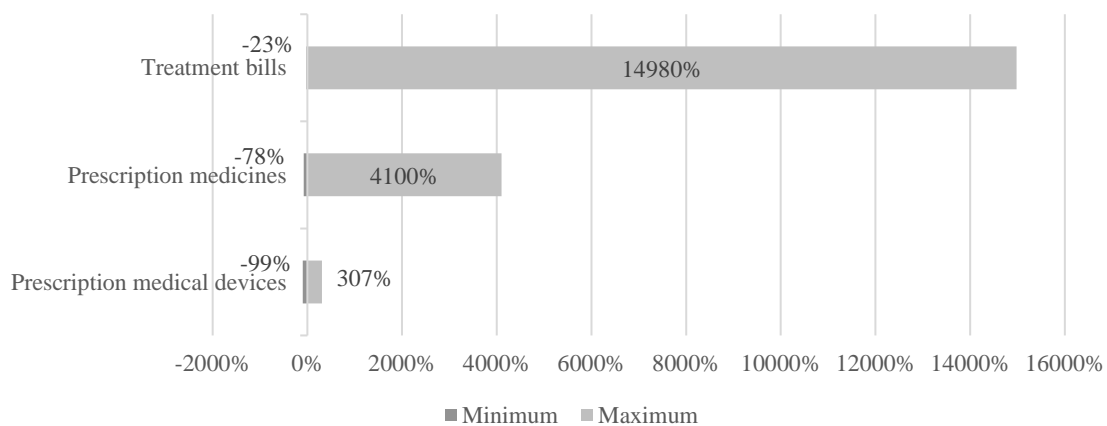


Figure 2 Treatment costs sensitivity to cost components per year per patient on average during 2018-2021

Comorbidities

In total 6764 unique comorbidities out of 776 409 total list from 394 016 different treatment bills were diagnosed for 29 380 patients over a 4-year period. Per 4-year average, the mean value of comorbidities per patient was 13,93, whereas the mode was 7,50. Out of 29 380 patients, there were 69 who did not have a secondary diagnosis. The most occurring of those were related to cardiovascular health, such as hypertensive heart disease without (congestive) heart failure (8,29% of all the secondary diagnoses), essential (primary) hypertension (6,15% of all the secondary diagnoses), atrial fibrillation

and flutter (2,93% of all the secondary diagnoses) and hypertensive heart disease with (congestive) heart failure (2,62% of all the secondary diagnoses). Diagnoses of type 2 diabetes mellitus without complications (1,48%), COVID-19 (1,22%), obesity due to excess calories (0,97%), other psoriatic arthropathies (2,01%), acute upper respiratory infection (1,13%) and primary open-angle glaucoma (0,94%) were also identified among the top 10 most occurring comorbidities – in the brackets percentage of all secondary diagnoses.

The most occurring comorbidities were also with the highest average cost. Namely, the top 5 highest 4-year average costs per patient per year were 2609,66€ for hypertensive heart disease without (congestive) heart failure, 1 559,43€ for atrial fibrillation and flutter, 1 435,10€ for hypertensive heart disease with (congestive) heart failure, 868,32€ for essential (primary) hypertension and 993,59€ for other psoriatic arthropathies.

Health care services

For 1 040 703 treatment bills the data of 5 160 639 health care services were received. Out of them 44 unique health care service groups were determined. Five of the most used service groups were laboratory tests, family physician visits, general examinations and procedures, outpatient visits and lastly, dentistry. Collectively they accounted for 96,86% of all health care services used.

Distinction between the utilization of inpatient and outpatient care can be seen on Figure 3 (page 34), where bed days are representation of inpatient care as no other metric than hospitalization for assessment of inpatient care was available in given data set. The amount of 4-year average bed days was 9556,50 and the amount of outpatient services provided 153 690. The difference in between those is 1508,22% which is referring to notably higher utilization of outpatient care among psoriasis patients. Regarding the per patient costs of inpatient and outpatient care, Table 4 (page 34)**Error! Reference source not found.** details the costs per years. Average 4 year per patient cost was 12 399 € for inpatient and 1453,89 € for outpatient care.

The healthcare service groups are further divided into exact services, which in this registry data set cover 2344 unique services. Surprisingly, the most frequently used service was patient consultation via telephone, which per 4-year average accounted for 5,98% of all services. Next top 9 services were: laboratory test for creatinine, urea, uric acid, accounting for 5,29% of all services; laboratory test for enzymes: ALP, ASAT, ALAT, LDH, CK, GGT, accounting for 5,21% of all services; repeat appointment with a

specialist, accounting for 4,21% of all services; laboratory test for anaemia, cardiac, tumour marker levels, accounting for 3,96% of all services; initial consultation with a specialist, accounting for 3,59% of all services; and laboratory tests for sodium, potassium, calcium; haemogram with five part leukogram; glucose; C-reactive protein, accounting for 3,52%; 3,05%; 2,93% and 2,92% of all services, respectively.

The breakdown of patient visits – either to family physician, family nurse or specialist doctor is detailed in Table 5 (page 35)**Error! Reference source not found..** Rows marked with N/A mark that the data which was unavailable. There has been recorded significantly more specialist visits than family physician visits. Every year, the number of remote, phone or e-mail consultations have grown opposed to face-to-face visits which have steadily declined.

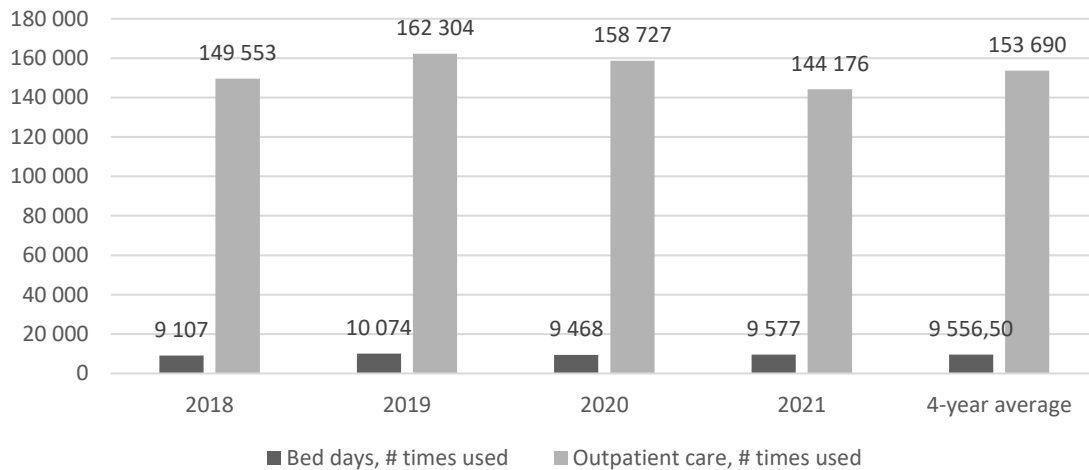


Figure 3 Comparison between utilization of bed days as inpatient care and outpatient care per year among psoriasis patients

Table 4 Cost comparison of psoriasis treatment in inpatient versus outpatient care per patient

	2018	2019	2020	2021	4-year average
Bed days, # patients	3675	3652	3496	3429	3563
Bed days, cost per patient	9 938,38 €	12 011,75 €	13 122,49 €	14 523,40 €	12 399,00 €
Outpatient care, # patients	22056	22030	21412	20323	21455,25
Outpatient care, cost per patient	1 083,75 €	1 410,03 €	1 601,04 €	1 720,73 €	1 453,89 €

Table 5 Appointments utilized by psoriasis patients by number of treatment bills

Healthcare service	2018	2019	2020	2021	4-year average
Family physician's initial appointment	41 976	41 151	29 204	27 610	34 985,25
Family physician's repeat appointment	43 483	43 526	30 614	27 566	36 297,25
Family physician's remote consultation	N/A	N/A	12 660	N/A	3165
Family physician's prophylactic appointment	4966	4718	4507	6183	5093,5
Family physician's consultation via e-mail	1102	1297	2804	3848	2262,75
Family physician's consultation via phone	58 292	62 288	89 061	97 498	76 784,75
Family nurse's consultation	23 720	24 390	19 569	23 581	22 815
Family nurse's care via manual activity	24 877	26 238	20 696	21 238	23 262,25
Family nurse's remote consultation	N/A	N/A	198	695	223,25
Family nurse's consultation via e-mail	610	741	1713	3020	1521
Family nurse's consultation via phone	20 940	24 207	38 812	56 602	35 140,25
Specialist's initial appointment	52 980	51 814	39 397	40 228	46 104,75
Specialist's repeat appointment	54 699	57 124	55 468	49 011	54 075,5
Specialist's remote consultation	N/A	N/A	2444	8617	2765,25

Prescription medicines

Out of 29 380 patients, prescription medicines were prescribed for 29 316 persons. In total, information about 2 063 750 prescriptions were received. Out of them, 710 unique prescription medicines were prescribed to patients over 4 years. The ten most frequently prescribed medicines were either topical treatments to treat psoriasis (mometasone, calcipotriolum+betamethasonum, clobetasol, betamethasonum+acidum salicylicum) or to treat comorbidities such as a range of cardiovascular diseases (metoprolol, rosuvastatin, atorvastatin), diabetes (metformin), insomnia (zopiclone) or digestive tract diseases (omeprazole).

Among prescriptions, there were written seven different systemic or biologic drugs indicated solely for psoriasis treatment (methotrexate, acitretin, adalimumab, cyclosporine, etanercept, ixekizumab and secukinumab – ordered by the number of prescriptions bought out) to 3848 patients who can be considered to suffer under moderate to severe type of psoriasis, representing 13,10% of all psoriasis patients. The costs for moderate to severe type represent 6,83% of all the expenses to prescription medicines and 19,50% of all the treatment costs.

Adherence data is presented in Table 6 (page 36)**Error! Reference source not found..** As per 4-year average, the prescription medicines were prescribed for 26 345,75 patients, but bought out by 26 016,75 patients. This is marking less than 2% difference in between these two cases. Adherence data shows on average 98,75% adherence per patient and 78,18% per prescriptions. The data shows a tendency to buy more prescriptions out as the years go on.

Table 6 Prescribed vs bought out medicines among psoriasis patients

	2018	2019	2020	2021	4-year average
Prescribed medicines					
Number of patients	26 413	26 496	26 339	26 135	26 345,75
Number of prescriptions	488 129	514 428	525 018	536 175	515 937,50
Bought out medicines					
Number of patients	25 931	26 181	26 054	25 901	26 016,75
Number of prescriptions	353 992	405 698	424 232	431 861	403 945,75
Differences					
In number of patients, %	1,84%	1,20%	1,09%	0,90%	1,26%
In number of prescriptions, %	31,86%	23,63%	21,23%	21,55%	24,57%
Adherence					
In number of patients, %	98,18%	98,81%	98,92%	99,10%	98,75%
In number of prescriptions, %	72,52%	78,86%	80,80%	80,54%	78,18%

Prescription medical devices

Out of 29 380 patients, prescription medical devices were prescribed for 6243 persons. In total, information about 67 689 prescriptions were received. Out of them, 70 unique prescription medical devices were prescribed to patients over 4 years. Ten of the most prescribed medical devices were glucometer test strips, disposable needles, lancets, continuous positive airway pressure (CPAP) devices, foot orthoses, ostomy bags, ostomy care products, wrist orthoses, knee orthoses, non-antibacterial wound dressings and drainage bags. Such medical devices indicate the possible diabetes, sleep apnea, digestive, and orthopedic diseases among those patients.

Adherence data is presented on Table 7 (page 37)**Error! Reference source not found..** The percentage of patients per each sampled year who decided not to buy out the prescribed medical devices is rather high – more than a third of those patients did not buy

out the medical devices. Regarding the number of prescriptions itself bought out, then the adherence is disturbingly low – more than half of the written prescriptions were not bought out. On average, there was 71,54% adherence per patient and 47,32% per prescriptions.

Table 7 Prescribed vs bought out medical devices among psoriasis patients

	2018	2019	2020	2021	4-year average
Prescribed medical devices					
Number of patients	3548	3897	4112	4292	3962,25
Number of prescriptions	15 022	16 471	17 520	18 676	16922,25
Bought out medical devices					
Number of patients	2638	2800	2922	3025	2846,25
Number of prescriptions	7400	7931	8178	8443	7988
Differences					
In number of patients, %	29,42%	32,76%	33,84%	34,63%	32,66%
In number of prescriptions, %	67,99%	69,99%	72,71%	75,47%	71,54%
Adherence					
In number of patients, %	74,35%	71,85%	71,06%	70,48%	71,94%
In number of prescriptions, %	49,26%	48,15%	46,68%	45,21%	47,32%

Benefits for incapacity for work

Out of 29 380 patients, benefits for incapacity for work were written for 14 126. In total, information about 82 226 records were received. Out of them, 5 unique types of benefits are distinguished, which were written to patients over 4 years. These are sick leave, continued sick leave, care leave, continued care leave and birth leave. Out of those, the most utilized, based on the reimbursed days count, was continued sick leave with 43,33% utilization, which also had the highest costs amongst all other leave types with 38,20%. The leave from work was given in 4-year average for 221 913,50 days annually with a total 4-year average cost per person per year 245,66 euros.

5 Discussion

The 4-year average total psoriasis patient treatment costs per patient were 2156,12€, accounted for treatment bills, prescription medicines, prescription medical devices and benefits for incapacity for work through the rigorous calculations on EHIF registry data set.

The biggest cost contributor to treatment expenses were treatment bills with a 4-year average per patient cost of 1470,28 euros and 68,20% share of all costs. This was followed up by prescription medicines with a 4-year average per patient cost of 420,76 euros and 19,52% share, followed by benefits for incapacity for work with 245,66 euros and 11,37%. The last component, prescription medical devices had a 4-year average per patient cost of 19,43 euros and share of 0,90%, being the smallest contributor. There were no notably differences of the costs between the analysed years noted, but the data showed the differences between the years gradually decreased as the years went on, approaching to even out. This suggests that there was a minimal effect to overall treatment costs from Covid-19 to financing the psoriasis treatment in Estonia.

The total treatment cost outcome in Estonia is similar to the Taiwanese study [19] with a result of 1986,21€, which took similarly into account both inpatient and outpatient care and dermatology and non-dermatology services. However, opposite to Estonia, the outpatient care costs were higher than inpatient care in Taiwan. Non-dermatology services there can be considered equivalent to the treatment of comorbidities as the psoriasis severity and progression is dependent of multiple factors [82]. By using this equivalency, the cost of treating patients with comorbidity is similarly to Estonia more than half more expensive – difference being 78,65% in Taiwan and 51,26% in Estonia.

Cost-wise, countries which have lower psoriasis costs than Estonia, are South-Korea [17] and Finland [12]. The Finnish study is to date the only accessible COI study on psoriasis in Finland and it is accounting only for prescription medicine costs per patient in the amount of 1083€. In Estonia the prescription medicine costs were 420,76€, making the difference 88,08%. Thus, the actual total psoriasis treatment and care costs in Finland could be considerably higher. The South-Korean study reported the per patient per year cost of treatment to be 151,61€, which took into account the medical and prescription costs of patients. However, it was not further elaborated what exactly was counted under those costs. The treatment of patients with non-psoriasis skin diseases amounted for

79,84€, indicating the difference of 62,02% in between those groups. The psoriasis patient treatment cost difference with Estonia, when considering only the costs of treatment bills and prescription medicine, is 170,31%. Reason, why the healthcare expenditure in South-Korea is lower than other countries, was not identified.

Countries that have higher total psoriasis treatment costs than Estonia, are Greece [16], Sweden [13], Colombia [20], Germany [14] and Switzerland [15]. In terms of the number of different cost components considered in calculations, the study design of Swedish and German study was the most similar to current Estonian study because the scope in terms of different cost components was the widest, taking into consideration also the costs derived from productivity losses or sickness leave. In Swedish study, the average per year per patient outpatient costs were 1963,47€ and inpatient costs 3498,60€. The total medication costs accounted were 2066,67€ and productivity losses 8829,02€. All these values are more expensive in Sweden than in Estonia. In German study, the health insurance costs comprised of topical, systemic and UV therapy's costs, plus inpatient stays, and physician's fees with a total of 4940€. The same cost components in Estonia result in 1891,04€, which gives 89,27% cost difference. Benefits for incapacity for work were considered as indirect costs and counted for 379€ per patient per year. Compared with Estonian 245,66€, the cost difference is 42,69%.

The sensitivity analysis used for this study was a deterministic one-way sensitivity analysis which confirmed that that treatment bills have the highest impact to total treatment cost value per person per year. The greatest influence is understandable and acceptable as treatment bills were the most represented data set in the study and include all kind of healthcare services from both inpatient and outpatient care. The literature also has described the treatment bills as the main cost contributor and therefore the result of this analysis is in line with other cost of illness studies. However, attention should be drawn to the minimum values in the analysis. There are zero-value parameter values in the analysis because in Estonian healthcare system, it is common to submit bills to EHIF with value of 0. Since there was at least one zero-value bill submitted to EHIF, it has been counted in sensitivity analysis as a minimum treatment cost value. Deeper analysis to see the possible uncertainties delivered by number of patients, utilized health care services or patients with and without comorbidity, were not performed due to complexity of the calculations. Within the other earlier referenced COI studies conducted around the world, the sensitivity analysis has not been conducted in any of them which in turn means the lack of comparable data.

The psoriasis patients' comorbidities listed in this study are in line with the psoriasis investigation studies conducted in other countries, although the occurrence rate per country is different. For example, in Columbian study [20] hypertension was reported on 4.8%, musculoskeletal disorders on 7,2%, obesity on 3.6%, and fibromyalgia on 3.6% among study sample patients. Several studies conducted in United States of America have also reported the prevalence of comorbidities among psoriasis patients. The most common has been psoriatic arthritis with 22,1% occurrence from psoriasis population, hyperlipidemia with 27,3% occurrence, hypertension with 23,5%, and diabetes with 9,7% occurrence [21]. Another study reported 33,1% for hyperlipidemia, 18,0% for anxiety, 13,1% for depression and 10,9% for psoriatic arthritis [23]. In Estonian case, the most occurring were cardiovascular diseases (occurrence from 2,62% to 8,29% of all possible comorbidities) and other psoriatic arthropathies (2,01%), but among the top 10 most occurring comorbidities were also obesity and diabetes which are recognized by other authors as a frequent comorbidity. Various cardiovascular diseases are the main comorbidities for patients worldwide [70] [71] [72]. Other similar diseases common in published literature are diabetes [76], obesity [74] [75] and psoriatic arthritis [73] [31]. What is more, the cost of treatment is dependent on the patient comorbidities as it is on average 51,26% more expensive per patient for the payer to treat patients with comorbidities than without - signifying that the comorbidities increase the burden for payer.

Health care services was the most used cost component and thus greatest contributor to expenses. The most utilized health care services among psoriasis patients were laboratory tests, which may be the case for majority of illnesses as under one treatment bill multiple tests are done. Analysis confirmed that more outpatient than inpatient visits were utilised—the difference being 1508,22%. This can be explained by the case that psoriasis patients rarely need an overnight stay in the hospital as the illness is usually self-managed without the need of specialised technology available only in healthcare provider facilities and hospitalization may be necessary mostly in need of some comorbidity treatment. For instance, self-management in this case could comprehend administering prescribed medicines, medical devices or change of lifestyle under complementary and alternative medicine. The data also shows the increase of remote consultations and decrease of more traditional, face-to-face consultations. For instance, from 2018 to 2021 the family physician's initial appointments have decreased by 41,29% whereas consultations by e-mail or phone have grown 110,95% and 50,33%, respectively. In 2018 and 2019 there

was not yet remote consultations utilized – neither for family physician, family nurse or specialist. The increase of remote services from 2020 to 2021 has been 111,31% for family nurse and 111,62% for specialist. No data for family physician on 2021 is available, thus making comparison difficult. Such shift to remote consultations may be the push of Covid-19, as there was a requirement to abstain from face-to-face interactions. This signifies the statement that the use of digital health interventions in psoriasis treatment and care is promising – similarly to other fields where teleconsultation or telemonitoring is already in use [107] [108] [109].

In regards prescription medicines, it became apparent that there is a long list of different medications that are used by patients. Most of them are not directly targeted to psoriasis treatment but rather to treat patient's comorbidities. The next big portion of drugs fall under topical treatments which are generally used to treat psoriasis with a severity level of mild to moderate. Concerning the biologic drugs as for the most severe cases of psoriasis, then they represent 6,83% of all the expenses to prescription medicines and 19,50% of all the treatment costs. This is not in line with the previously referenced studies, where the biologics, even though used by the minority of patients, represented the majority of prescription medicine expenses. This may indicate that either the biological treatments are cheaper in Estonia or the usage of them is not very well spread and only used as the last resort for severe cases of psoriasis. For comparison, although only 5% of patients utilized biologics, they accounted for 67% of the overall medication expenses in Finland [12]. In Sweden, biologics were used by 1,5% of patients and represented 17,43% of total healthcare costs for psoriasis [13]. In a German study, 5% of patients were treated with biologics [14]. In Greece, 12% of the psoriasis patient population received a treatment regimen involving biologics, representing nearly 90% of the expenditure related to psoriasis [16]. In USA, 15.4% of all psoriasis patients were treated with biologics [22]. The information gathered for data analysis also included information of when the prescription was written and when bought out by the patient. It is evident that even though the number of patients to whom prescriptions were written did not increase drastically year-by-year, the number of prescriptions was. The rise in adherence to purchasing prescribed medications year after year could potentially be attributed to the growing awareness among patients, as they recognize the effectiveness of the prescribed treatments in providing relief from their suffering.

For prescription medical devices, most of the medical devices prescribed can be associated with diabetes, which is well known comorbidity of psoriasis [76]. Concerning the adherence rate of buying out prescription medical devices, opposed to prescription medicines, a steady decrease over the years can be noted. This could be explained either through the changes in the cost-of-living, where the prices of medical devices have increased or that persons are looking towards complementary and alternative medicines to seek alleviation to the disease. But as the information about out-of-pocket expenses is not available, this assumption cannot be confirmed. Among already conducted economic evaluation studies described in the background section of this study, none investigated the costs of medical devices, making this study unique in the field.

In cost calculations, the inclusion of work incapacity benefits is a significant factor as it is covered by the payer (EHIF) when individuals are unable to work due to their illness.. Interestingly, the percentage of psoriasis patients who were granted leave from work was less than half of all participants in the study, amounting to 48,08%. This observation could suggest that either psoriasis predominantly manifests with mild severity and does not hinder work, or individuals choose not to claim work incapacity benefits for various reasons. For example, they may fear job loss, anticipate reduced income due to missed work days, or worry about potential stigmatization by colleagues or society for taking time off due to their illness. The Estonian average cost per person per year is 245,66€ which is comparable with two other economic evaluation studies on psoriasis patients. To begin with, German researchers calculated this cost to be 379€ [14], which is 42,69% percent higher than Estonian results. In USA, however, per patient per year reported costs were \$655 (600,07€) [23], which is 83,81% higher than Estonian work-loss-related costs. The results of this work can be used by different stakeholders – either by policymakers national health insurance fund (in Estonian case EHIF) to make decisions for healthcare prioritization or budget allocation, by healthcare professionals for clinical decisions, by scientists for further research or by entrepreneurs and the private sector to develop treatment approaches which are less expensive for the payer. Since the overview of the costs incurred during psoriasis treatment has been non-existent so far, the research can be considered highly relevant.

Limitations and further research possibilities

Carried-out cost of illness analysis have also some limitations. Firstly, the quality of the data from the EHIF database is collection dependent which means that any human errors

that may have been made when for instance, diagnose coding took place, cannot be excluded. Secondly, only the costs of the treatment bills, prescription medicines and prescription medical devices submitted to EHIF were considered when calculating the treatment costs. This means that over-the-counter medicines, medical devices and out-of-pocket treatments, including complementary and integrative medicine, where the patient is treating her- or himself with alternative approaches not prescribed by the healthcare professional were not accounted for as information is recorded in national databases and thus not publicly available per person. Indicating that the actual treatment costs per patient in Estonia could be significantly higher while addressing patient perspective as well. Thirdly, the study did not measure indirect costs, such as being absent from work, travel time or time spent by caregivers giving the same indication that different perspective would rise the total cost of illness for Estonia. This perspective aspect however should be researched further by other researchers, adding patient and or general societal perspective into the current EHIF based approach. Additionally, further research could look at aspects like the assessment of indirect costs related to psoriasis treatment and the investigation of alternative treatment approaches together with their costs to decide for the most optimal and cost-effective treatment for patients suffering under psoriasis, depending on the severity level and comorbidities. These would give the whole overview of psoriasis treatment costs in Estonia per patient per year, as with this study, only half of the expenses, this is, direct costs, are covered.

6 Conclusion

The aim of the thesis was achieved because the total direct treatment costs per year per patient for diagnoses under the category of L40 according to the ICD-10 [44] in Estonia were quantified. Moreover, the preliminary set three research questions were answered - the total direct treatment cost per year per patient in Estonia is 2156,12€ and per patient cost difference between patients with comorbidity and without comorbidity among Estonian psoriasis patients is 51,26%. The different cost components divide within the psoriasis patient treatment cost as following: treatment bills - 68,20%, prescription medicines - 19,52%, prescription medical devices - 0,90% and benefits for incapacity for work - 11,37%. The key takeaway is that the cost of treatment is rising every year and so

do the number of psoriasis patients. As the treatment approaches themselves are also tending to get more expensive over time, it is crucial to find more cost-effective solutions to treat psoriasis patients. This research contextualizes into previous research in the field by offering a comparative data of Estonia to assess the burden of psoriasis in further studies with the most recent information.

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Appendix 1 – Supplemental material

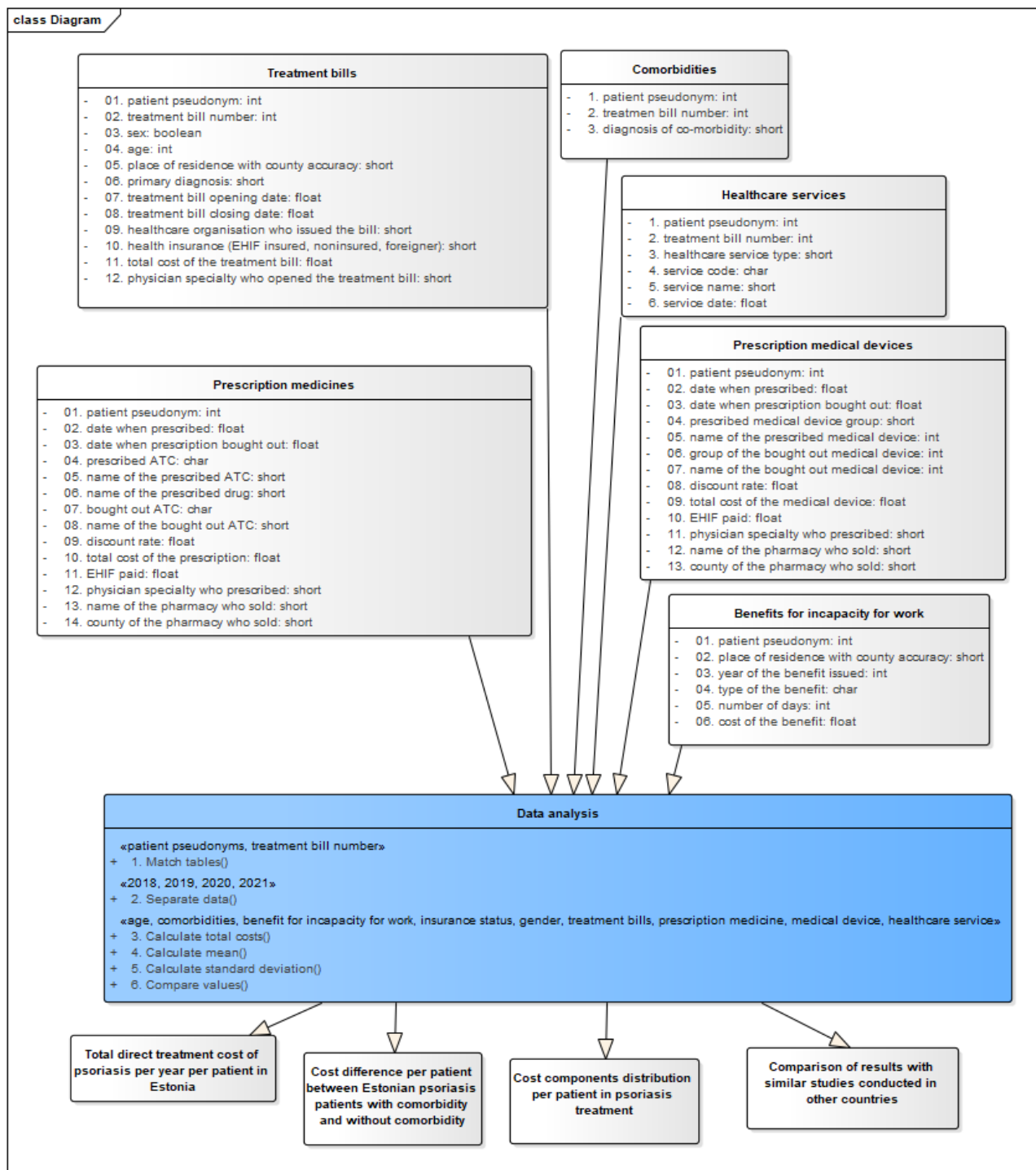


Figure 4 Data set used for data analysis, diagram made with Enterprise Architect

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