




Costs of Hospital-Associated Care for Patients With Juvenile Idiopathic Arthritis in the Dutch Health Care System

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Objective. The aim of this study was to quantify costs of hospital-associated care for juvenile idiopathic arthritis (JIA), provide insights in patient-level variation in costs, and investigate costs over time from the moment of JIA diagnosis. Results were reported for all JIA patients in general and by subtype.

Methods. This study was a single-center, retrospective analysis of prospective data from electronic medical records of children with JIA, ages 0–18 years, between April 1, 2011 and March 31, 2019. Patient characteristics (age, sex, JIA subtype) and hospital-based resource use (consultations, medication, radiology procedures, laboratory testing, surgeries, emergency department [ED] visits, hospital stays) were extracted and analyzed. Unit prices were obtained from Dutch reimbursement lists and pharmaceutical and hospital list prices.

Results. The analysis included 691 patients. The mean total cost of hospital care was €3,784/patient/year, of which €2,103 (55.6%) was attributable to medication. Other costs involved pediatric rheumatologist visits (€633/patient/year [16.7%]), hospital stays (€439/patient/year [11.6%]), other within-hospital specialist visits (€324/patient/year [8.6%]), radiology procedures (€119/patient/year [3.1%]), laboratory tests (€114/patient/year [3.0%]), surgeries (€46/patient/year [1.2%]), and ED visits (€6/patient/year [0.2%]). Mean annual total costs varied between JIA subtypes and between individuals and were the highest for systemic JIA (€7,772/patient/year). Over the treatment course, costs were the highest in the first month after JIA diagnosis.

Conclusion. Hospital care costs of JIA vary substantially between individuals, between subtypes, and over the treatment course. The highest annual costs were for systemic JIA, primarily attributable to medication (i.e., biologics). Costs of other hospital-associated care were comparable regardless of subtype.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood, affecting ~1 in 1,000 children (1,2). The International League of Associations for Rheumatology classification distinguishes 7 categories of JIA, including systemic arthritis, oligoarthritis (which can be subdivided into persistent and extended oligoarthritis), rheumatoid factor (RF) negative polyarthritis, RF positive

polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis (3).

Early recognition and adequate clinical management of JIA is crucial to control inflammation, reduce pain, and prevent irreversible joint damage (4). Treatment of JIA is multifaceted, combining pharmacologic, physical, and occupational therapy with lifestyle modifications and psychosocial support (5). As a consequence, treatment costs are high (6–9). JIA is also associated with

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SIGNIFICANCE & INNOVATIONS

- To the best of our knowledge, this is the first study in the world to quantify costs of hospital-associated care in juvenile idiopathic arthritis (JIA) subtypes while simultaneously providing insights into patient-level variations in costs and trends in costs over the treatment course.
- This study provides high-level evidence that, when implementing personalized treatments, the costs of early, intensive treatment strategies in patients with severe JIA should be offset against its benefits and costs over the long term.

significant long-term issues, including the risk of long-term functional impairment, lower educational attainment (10), higher unemployment rates (10), and a lower quality of life (11–13). Consequently, JIA results in a high burden to the affected individual and to society.

To determine the burden of JIA to society, a first and critical step is to quantify JIA-related hospital-care resource use and associated costs, referred to as “hospital costs” in the remainder of this article. Although a body of evidence presenting hospital costs is available (14), the majority of these studies either do not distinguish between JIA subtypes, focus on 1 specific subtype, or do not consider costs at the individual patient level. Reporting hospital costs separately by JIA subtype is important because these subtypes differ in clinical and laboratory features, disease severity, and in the efficacy, type, and accompanying costs of pharmacologic treatments prescribed (3,15,16). In addition, substantial variation in disease severity and treatment response is observed even between patients with the same subtype (17,18). Thus, JIA is known for its personalized treatment and for its huge variation in treatment lines and sequences with different impact on health outcomes and costs. Therefore, the current study aims to quantify the impact of JIA on hospital costs, provide insights in patient-level variation in costs, and investigate costs over time from the moment of JIA diagnosis. Results were reported for all JIA patients and by JIA subtype.

MATERIALS AND METHODS

Data sources and extraction. This study was a retrospective analysis of prospective data extracted from electronic medical records from the Wilhelmina Children’s Hospital (Utrecht, The Netherlands), using a previously developed research data platform (19). This resulted in a comprehensive data set enabled by linkage of several databases within the hospital through a unique, deidentified patient number. For the current study, data on medication use, radiology procedures, laboratory tests, hospital stays, surgeries, consultations with pediatric rheumatologists and other within-hospital specialists, and emergency

department (ED) visits were extracted for all patients with a diagnosis of JIA between April 1, 2011 and March 31, 2019. As treatment strategies in JIA change rapidly, and because the electronic data was available after April 1, 2011, this date was set as the starting point of the analyses. In addition, as this study focuses on children, only data up until the patient’s 18th birthday were included when they turned 18 before March 31, 2019. Data on within-hospital physician visits (other than pediatric rheumatologist visits) were, however, only available up to December 12, 2018 and thus were included until that point in time.

The use of data from the above-mentioned research data platform was classified by the Institutional Review Board as exempt from the Medical Research Involving Human Subjects Act (14/684). The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki (20). Further, the ethical committee of the faculty of Behavioural, Management and Social Sciences of the University of Twente approved this study (no. 190215).

Data selection. Patients were excluded if they reached the age of 18 years before April 1, 2011, were diagnosed with idiopathic uveitis, were not primarily treated in the Wilhelmina Children’s Hospital (because they, for example, only came for a second opinion), had major comorbidities (such as inflammatory bowel disease) alongside JIA, received treatment as part of a pharmaceutical trial that they would not have received outside the trial setting (regardless of whether this occurred between April 1, 2011 and March 31, 2019), or had a follow-up in <1 year. Resource use and costs were included up to 10 years after JIA diagnosis.

Resource use and costs. Within-hospital resource use and costs were quantified from a payer’s perspective. Resource use was measured from the extracted data. Unit prices were based on 2019 tariffs when available (regardless of the year in which they occurred) or converted to 2019 euros using Dutch consumer price indices (21). Medication costs were derived from Dutch pharmaceutical list prices (<https://www.farmacotherapeutischkompas.nl/>) and multiplied with the frequency of use, accounting for the dose used in each individual patient. All other costs were derived from Dutch reimbursement lists where possible (<https://zorgproducten.nza.nl/>) or, alternatively, from hospital list prices. All within-hospital costs that occurred during the inclusion period and that were assumed to be JIA-related, as decided in consultation with a pediatric rheumatologist, were included. To illustrate this, the costs of hospital stays related to (for example) a sports injury were excluded, whereas the costs of hospital stays related to JIA (for example, for treatment of disease flares or for complications related to JIA treatment, such as infections), were included. A detailed overview of all assumptions made is provided (see Supplementary Table 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24621>).

Analysis. Results were presented for all JIA patients in general and by JIA subtype. Patients with persistent oligoarthritis were further subdivided into antinuclear antibody (ANA) negative oligoarthritis and ANA positive oligoarthritis cohorts. Costs over the period of follow-up were reported as costs/patient/year in the years following JIA diagnosis. In other words, for a patient diagnosed with JIA on April 6, 2012, the first year of follow-up spans the time between April 6, 2012 and April 6, 2013. As a consequence, hospital-related costs immediately after JIA diagnosis were unavailable for patients diagnosed before April 1, 2011. These patients were, however, included in the calculation of hospital-related costs up to 10 years after JIA diagnosis. The analysis was performed in R (version 3.5.3) using the packages *dplyr*, *ggplot2*, *lubridate*, and *plotrix* (22–26). Patients and/or the public were not involved in the design, conduct, reporting, or disseminating of the results of this study.

RESULTS

A total of 691 patients were included in the study, including 447 girls (65%) and 244 (35%) boys, with a median age at diagnosis of 8 years and a median duration of follow-up of 4.9 years. The study excluded 278 patients (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24621>). Table 1 shows a detailed overview of patient characteristics.

The impact of JIA on hospital costs. The overall mean hospital cost of JIA was €3,784/patient/year, of which €2,103 (55.6%) was attributable to medication costs and €1,681 (44.4%) to costs of other hospital-based services. Hospital costs varied substantially between subtypes, with the highest mean costs in systemic JIA (€7,772/patient/year), followed by RF+

polyarticular JIA (€6,906/patient/year). When multiplying the costs per patient with the number of patients in each JIA subgroup, patients with polyarticular RF– JIA ($n = 144$) contributed most to the hospital costs (i.e., 25.4%). A detailed overview, including the distribution of costs of other hospital-based services into sub-categories, is shown in Table 2.

Variation in costs between individual patients. As the mean annual costs presented in Table 2 differed substantially on an individual patient level, the mean annual costs per patient (over their entire follow-up period) were visualized in a histogram, resulting in a strongly right skewed distribution (Figure 1). More specifically, 471 (68.2%) of 691 patients had mean annual costs ranging between €0/patient/year and €2,500/patient/year, and only 11 patients had mean annual costs of €25,300 or higher. Eight of these patients with mean annual costs between ~€31,000 and ~€119,000 were not shown as these were out of range in Figure 1. These costs involved 8 patients with systemic JIA or polyarticular RF+ JIA in which high costs were mainly attributable to medication use (i.e., canakinumab [$n < 5$; the exact number is not provided in order to prevent traceability of the study's results to individual patients] and/or intravenous tocilizumab [$n = 6$]) and to hospital stays.

When considering the histograms for the different types of hospital-based services (including medication), similar right-skewed distributions were observed (see Supplementary Figure 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24621>). The only category in which the distribution was more evenly distributed involved costs of consultations with pediatric rheumatologists. As a fixed cost of €159.94 per consultation was applied in the current analysis (regardless of the duration of the appointment), this figure also represents the distribution of how frequently JIA patients visited a pediatric rheumatologist. Therefore, this data indicates that consultations with pediatric rheumatologists also occurred in patients who, on average, had low JIA-related hospital costs.

Variation of costs over the course of JIA treatment.

Figure 2 shows the mean monthly total hospital costs for JIA treatment over 10 years of follow-up. Each point in the graph represents the mean monthly hospital costs when taking the average over the patients for whom data was available for each of the time periods during the 120 months of follow-up (with 0 representing the moment of JIA diagnosis).

This figure demonstrates that the mean monthly total hospital costs peaked in the month following JIA diagnosis (i.e., €913) and tended to decrease over the course of follow-up. When excluding costs of medication use, this decrease was more pronounced (see Supplementary Figure 3, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24621>),

Table 1. Characteristics of patients included in the analysis*

Total number	691 (100)
Age at JIA diagnosis, median (IQR) years	8.0 (4.0–12.6)
Duration of follow-up, median (IQR) years	4.9 (2.8–7.0)
Male sex	244 (35%)
JIA subtype	
Oligoarticular persistent JIA	294 (42.5)
ANA–	147 (21.3)
ANA+	147 (21.3)
Polyarticular JIA	175 (25.3)
RF–	144 (20.8)
RF+	31 (4.5)
Extended oligoarticular JIA	70 (10.1)
Enthesitis-related JIA	59 (8.5)
Systemic JIA	57 (8.2)
Psoriatic arthritis	29 (4.2)
JIA undifferentiated	7 (1.0)

*Values are the number (%) unless indicated otherwise. ANA = antinuclear antibody; IQR = interquartile range; JIA = juvenile idiopathic arthritis; RF = rheumatoid factor.

Table 2. Overview of mean annual hospital costs per patient*

	No.	Mean annual hospital costs/patient (% of population costs)			Minimum-maximum	Mean annual medication costs/patient (%)	Mean annual costs of other hospital-based services/patient (% of costs of other hospital-based services)			Surgeries	ED visits	
		hospital costs/patient (%)	Mean annual costs of other hospital-based services/patient (%)	Mean annual costs of other hospital-based services/patient (%)			Pediatric rheumatologist visits	Hospital stay	Other within-hospital specialist visits			Radiology procedures
All patients	691	€3,784 (100.0)	€2,103 (55.6)	€0-166,789	€2,103 (55.6)	€1,681 (44.4)	€439 (26.1)	€324 (19.3)	€119 (7.1)	€114 (6.8)	€46 (2.7)	€6 (0.4)
Systemic JIA	57	€7,772 (17.0)	€4,790 (61.6)	€0-166,789	€4,790 (61.6)	€2,981 (38.4)	€1,685 (56.5)	€191 (6.4)	€124 (4.2)	€233 (7.8)	€48 (1.6)	€11 (0.4)
Polyarticular RF+ JIA	31	€6,906 (8.2)	€5,020 (72.7)	€0-51,144	€5,020 (72.7)	€1,886 (27.3)	€458 (24.3)	€252 (13.4)	€187 (9.9)	€168 (8.9)	€2 (0.1)	€8 (0.4)
Psoniatic arthritis	29	€4,945 (5.5)	€3,300 (66.7)	€0-40,264	€3,300 (66.7)	€1,644 (33.3)	€353 (21.5)	€360 (21.9)	€87 (5.3)	€124 (7.5)	€7 (0.4)	€5 (0.3)
Polyarticular RF- JIA	144	€4,592 (25.4)	€2,589 (56.4)	€0-39,687	€2,589 (56.4)	€2,003 (43.6)	€574 (28.7)	€375 (18.7)	€151 (7.5)	€132 (6.6)	€69 (3.5)	€6 (0.3)
Extended oligoarticular JIA	70	€4,477 (12.0)	€2,723 (60.8)	€0-26,827	€2,723 (60.8)	€1,754 (39.2)	€240 (13.7)	€391 (22.3)	€154 (8.8)	€129 (7.4)	€33 (1.9)	€11 (0.6)
Enthesitis-related JIA	59	€4,100 (9.3)	€2,606 (63.6)	€0-24,914	€2,606 (63.6)	€1,494 (36.4)	€199 (13.3)	€226 (15.2)	€205 (13.7)	€121 (8.1)	€16 (1.1)	€17 (1.1)
Oligoarticular ANA+ JIA	147	€2,340 (13.2)	€893 (38.2)	€0-21,349	€893 (38.2)	€1,447 (61.8)	€231 (15.9)	€409 (28.2)	€78 (5.4)	€82 (5.7)	€59 (4.1)	€1 (0.1)
Oligoarticular ANA- JIA	147	€1,653 (9.3)	€588 (35.6)	€0-29,315	€588 (35.6)	€1,065 (64.4)	€160 (15.1)	€259 (24.3)	€83 (7.8)	€59 (5.5)	€40 (3.7)	€4 (0.4)
Undifferentiated JIA	7	€432 (0.1)	€25 (5.8)	€0-2,602	€25 (5.8)	€398 (92.1)	€0 (0.0)	€41 (10.2)	€46 (11.5)	€41 (10.3)	€0 (0.0)	€0 (0.0)

* ANA = antinuclear antibody; ED = emergency department; JIA = juvenile idiopathic arthritis; RF = rheumatoid factor.

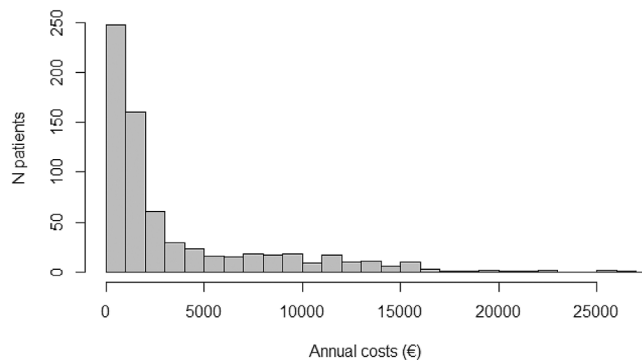


Figure 1. Histogram of the distribution of mean annual total hospital costs (including medication) per patient over the period of follow-up for each individual patient in the database, regardless of juvenile idiopathic arthritis (JIA) subtype. Eight patients (with systemic JIA or polyarticular rheumatoid factor–positive JIA) with average annual costs ranging from ~€31,000 to ~€119,000 are not shown as associated data were out of range of this figure. N = number.

attributable to the fact that costs of medication use peaked after ~25 months of follow-up. When plotting the costs for the other types of hospital-based services over time, results show a peak in costs at the time of JIA diagnosis for costs of hospital stay, consultations with pediatric rheumatologists and other within-hospital specialists, as well as for radiology and laboratory testing (see Supplementary Figure 4, available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24621>). In addition, regardless of the duration of follow-up, the majority of costs were attributable to hospital stays and consultations with pediatric rheumatologists and other within-hospital specialists, whereas costs of laboratory testing, radiology, surgeries, and ED visits only contributed to a minority of these costs.

Finally, our study demonstrates that, although costs of hospital-associated care for JIA treatment may decrease over time, costs of systemic JIA tended to peak after ~25 months of follow-up (attributable to the <5 patients who received canakinumab), which explains the peak in medication costs at this time point (see Supplementary Figure 5, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24621>). The mean monthly total hospital costs specified according to JIA subtype are also shown. A detailed analysis of medication use and their accompanying costs, however, falls outside the scope of the current analysis but has been described in another study (27).

DISCUSSION

The overall mean hospital costs of JIA were €3,784/patient/year, of which 55.6% was attributable to medication use. These costs varied considerably between patients. Systemic JIA patients incurred (on average) the highest annual costs, which were primarily attributable to medication use and secondarily to hospital stays. The majority of the costs for hospital stays for systemic JIA patients occurred within the first month after diagnosis. Costs of other hospital-based services, like specialist consultations, laboratory testing, radiology procedures, ED visits, and surgeries were comparable between JIA subtypes (except for undifferentiated JIA). In contrast to medication costs, costs of other hospital-based services peaked in the first month after JIA diagnosis and decreased over time.

The annual hospital costs reported in this study were relatively low because, in contrast to other cost studies in JIA (6,8,9,28), this study included all patients regardless of their disease state. In line with our results, Minden et al reported that costs

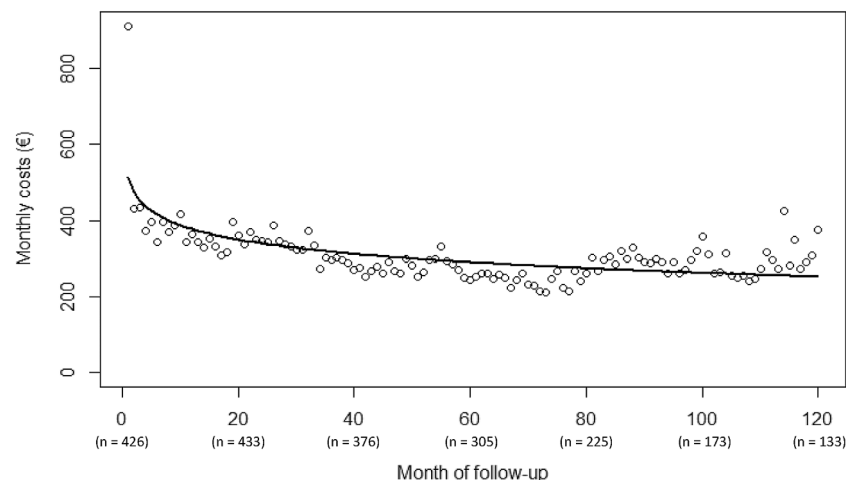


Figure 2. Mean monthly total hospital costs per patient (including medication) over the course of follow-up. Circles represent the mean costs for the set of patients for which data was available during the different months of follow-up during the 120 months. Logistic regression was used to fit a line through the data points. 0 = the moment of juvenile idiopathic arthritis diagnosis.

vary strongly depending on patients' disease state, with patients with active disease having mean annual costs of €5,681 compared with €782 for patients whose disease was in remission (29). When considering medication costs, previous studies found that (if biologics were used) medication costs contributed to almost half of the health care costs of JIA patients (7,30,31), which is in line with the 55.6% found in the current study. However, the rise in use of biologics over time (i.e., 31% in the current study versus 6% in the study by Minden et al [30]) as well as the fluctuations in prices of biologics makes these numbers hard to compare.

In the current study, the maximum duration of follow-up was 8 years (i.e., from 2011 to 2019) but differed between patients. Therefore, this study generally did not capture the entire patient's disease course (i.e., from JIA diagnosis until reaching the age of 18). As a consequence, total costs of JIA treatment on an individual patient level could not be calculated. Costs were therefore expressed as mean costs per patient per year or per month of follow-up. This approach allowed for inclusion of most of the available data in the analysis. In addition, it allowed inclusion of patients who were recently diagnosed with JIA. Despite the relatively short duration of follow-up, the inclusion of these recently diagnosed patients was nevertheless highly desirable and necessary as treatment strategies in JIA and costs for medication are continuously evolving.

The current analysis used fixed cost prices, indicating that price fluctuations over time (e.g., for biologics) were not incorporated. Such an approach was taken because the moment of JIA diagnosis was used as starting point of the analysis. To illustrate this approach, patients were analyzed as being in their first year of follow-up (i.e., the first year following JIA diagnosis), regardless of whether this diagnosis was established in, for example, 2011 or 2018.

Although differences in annual hospital costs between individual patients are (inevitably) caused by differences in disease severity, they are also attributable to the part of the treatment course captured for each patient between April 1, 2011 and March 31, 2019. In other words, for some patients, data may have been available for the first 2 years after JIA diagnosis, whereas for other patients, only a period of inactive disease was captured. In addition, fluctuations in treatment intensity on an individual patient level further increase the variability in annual hospital costs. Consequently, including uncertainty boundaries with regard to patient-level outcomes would have led to extremely large confidence intervals. Furthermore, as the annual hospital costs were strongly right skewed (which is common with cost data), reporting medians would disregard this skewness and thus underestimate the effect of rare cost-intensive cases. Therefore, histograms are preferred in health economic decision-making to visualize patient-level variations in costs (32).

Treatment options for JIA continue to develop, indicating that the costs and health impact of JIA have changed significantly over

the last years, which is especially attributable to the rise in the availability and use of biologics (9). In order to increase the likelihood that patients were comparable at each year of follow-up, the duration of follow-up was limited to 10 years after JIA diagnosis. Also, as the maximum duration of follow-up a patient could reach before his/her 18th birthday depended on the age at JIA diagnosis (e.g., a patient diagnosed at the age of 12 could reach a maximum follow-up of 6 years), the number of patients decreased over time (i.e., from 426 in year 1 to 133 by the end of year 10). A duration of follow-up longer than 10 years would have decreased the reliability of the mean annual costs, as fluctuations in costs over time would then primarily be attributable to the large variation in costs between individual patients.

One strength of the present study is that it is the first patient-level analysis of hospital costs in a large database for different JIA subtypes and over the course of JIA treatment. More specifically, the number of studies that have investigated health care-related resource use and costs in JIA is limited (14), and many of these studies did not distinguish costs between subtypes of JIA, focused on a specific subtype, or did not investigate changes in health care-related costs over the course of JIA treatment.

Another strength of our study is that it is expected to provide an accurate representation of the average costs of all patients with a diagnosis of JIA, regardless of disease or medication state. To illustrate this, this study also included patients that have not received treatment or visited their pediatric rheumatologists for a substantial amount of time. Disease in these patients was most likely in remission, which was associated with considerably lower treatment costs (29).

This study also has some limitations. One limitation is that data on physician visits within the hospital (other than pediatric rheumatologist visits) were only available up to December 12, 2018, indicating that visits during the last 3.5 months of the 96 months database were missing. This is expected to represent an underestimate of costs of other physician visits with €12/patient (i.e., €336/patient instead of €324/patient). However, as the frequency as well as the type of physician visits differed considerably between JIA subtype, between patients, and over the course of follow-up, extrapolating these costs was considered to incur more uncertainty compared to the current underestimation.

Another limitation of the current study is that costs occurring outside the hospital (e.g., including costs of visits to a regional physiotherapist or ophthalmologist) as well as out-of-pocket costs and productivity losses for patients, parents, and caregivers are expected to substantially impact the societal costs of JIA (8,9,14,33), but this was beyond the scope of this retrospective analysis of hospital costs. Nevertheless, it is critical to evaluate these costs. Therefore, the impact of JIA on the overall costs to society is currently investigated in a large multicenter, international prospective collaborative study into management strategies for JIA, conducted in Canada and The Netherlands, named UCAN CAN-DU (<https://www.ucancandu.com/>). The findings of the

current study will be used to optimize the methodology of UCAN CAN-DU.

Our study yields implications for practice and generalizability. We found major differences in hospital-related resource use between patients, which emphasizes that JIA-related treatment costs also need to be analyzed at the individual level. More specifically, future studies should investigate the impact of early, intensive treatment in patients with severe JIA on resource use and costs for the short- and long-term and offset these against health outcomes like the Juvenile Disease Activity Score or the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) measure.

The present study was conducted as a single-center study that is known to be the largest JIA treatment center in The Netherlands. Because patients participating in pharmaceutical-sponsored studies were excluded, this ensures results are highly representative of current practice. The extent to which the results are generalizable to other countries will however depend on differences in costs as well as access to hospital resources. An example of such differences is that in The Netherlands, anakinra is recommended as first-line treatment in systemic JIA patients (34), a medication that is not reimbursed in all countries. Therefore, this generalizability will largely depend on similarities and differences between treatment protocols.

In conclusion, hospital-care associated costs of JIA vary substantially between individual patients and between JIA subtypes. Mean annual costs were the highest for systemic JIA patients and were primarily attributable to medication costs. Costs of other hospital-based services were comparable regardless of JIA subtype. Except for medication use, costs of other hospital-based services decrease after JIA diagnosis. Future studies are required to capture the full impact of JIA to society, including costs associated with JIA-related care as well as productivity losses and out-of-pocket costs.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. IJzerman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kip, Roock, van den Berg, Currie, Marshall, Grazziotin, Twilt, Swart, IJzerman.

Acquisition of data. Kip, Roock, van den Berg, Vastert, Wulffraat, Swart.

Analysis and interpretation of data. Kip, Roock, van den Berg, Currie, Marshall, Grazziotin, Twilt, Yeung, Benseler, Vastert, Wulffraat, Swart, IJzerman.

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