



The Delay and Costs of Diagnosing Systemic Vasculitis in a Tertiary-Level Clinic

Kirsi Taimen · Anssi Mustonen · Laura Pirilä

Received: October 29, 2020 / Accepted: November 28, 2020 / Published online: December 14, 2020
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ABSTRACT

Introduction: The diagnosis of systemic vasculitis is a challenge because of the heterogeneity of clinical manifestations. The aim of this study is to analyze the diagnostic delay in systemic vasculitis, the total costs during the first year of care, and how the diagnostic delay affects the costs in a tertiary health care facility.

Methods: Patients with a new diagnosis of systemic vasculitis between 2010 and 2018 were identified from hospital records. The diagnostic delay and health care costs were evaluated during the diagnostic period and within 12 months after the first contact with tertiary health care. Vasculitis-related costs were recorded as true costs charged. A total of 317 patients fulfilled the study criteria. The diagnoses were grouped into three clinically relevant groups: IgA vasculitis and other small-vessel vasculitis

($n = 64$), ANCA-associated vasculitis (AAV) ($n = 112$), and large-vessel vasculitis (LVV) ($n = 141$).

Results: The diagnostic delay from the first referral to tertiary-level clinic was shortest in the LVV group and longest in the AAV group. Total costs during the diagnostic period were the highest in the AAV group (median = €6754 [IQR €8812]) and lowest in the LVV group (median = €3123 [IQR €4517]), $p < 0.001$. There was a significant positive correlation between the diagnostic delay and total costs during the diagnostic period and 12 months ($r_s = 0.38$, $p < 0.001$ and $r_s = 0.34$, $p < 0.001$, respectively). In a linear model, the inpatient days and the number of laboratory tests were the strongest predictors ($p < 0.001$) of a higher treatment cost during the diagnostic period.

Conclusions: There is a substantial diagnostic delay that correlates significantly with the costs in tertiary-level health care when diagnosing systemic vasculitis.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40744-020-00266-9>) contains supplementary material, which is available to authorized users.

Keywords: Cost of illness; Delay; Giant cell arteritis; Health care costs; Vasculitis

K. Taimen (✉) · A. Mustonen · L. Pirilä
Division of Medicine, Center for Rheumatology and
Clinical Immunology, Turku University Hospital,
Turku, Finland
e-mail: kirsi.taimen@tyks.fi

K. Taimen · A. Mustonen · L. Pirilä
Department of Internal Medicine, University of
Turku, Turku, Finland

Key Summary Points

Why carry out this study?

The heterogeneous nature of systemic vasculitis presents a diagnostic challenge, which may delay early diagnosis and cause notable expense.

Little is known about the diagnostic delay and economic burden of systemic vasculitis.

What was learned from the study?

This study analyzed the diagnostic delay in systemic vasculitides, their total cost during the first year, and how the diagnosis delay affects the costs.

There is a substantial diagnostic delay that correlates significantly with the higher costs in tertiary-level health care.

The highest costs are due to hospitalization. Faster diagnostic methods could reduce health care costs.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13295819>.

INTRODUCTION

Primary systemic vasculitides are complex and often serious autoimmune disorders characterized by inflammation of the vessel walls. Commonly, they are distinguished by the predominant size of vessels involved [1]. Large-vessel vasculitis (LVV), including giant cell arteritis (GCA), is the most common idiopathic vasculitis. The highest incidence is reported in Scandinavia and the UK ranging from 15 to 44

per 100,000 persons over the age of 50 [2, 3]. The European incidence of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) ranges from 1.3 to 2.0 persons per 100,000 [4], and the incidence of IgA vasculitis (IgAV) has been estimated to be 0.1–14 per 100,000 adults in France [5].

The diagnosis of systemic vasculitis is a challenge because of the rarity and complexity of the clinical presentation [6]. This may lead to delayed treatment causing end-organ damage and increased financial costs of workup investigations involving also non-essential tests. Different studies report great variability in diagnostic delay. In GCA, a systemic review and meta-analysis reported on average a 9-week delay from symptom onset to diagnosis, but the mean delay ranged substantially from 1.2 to 34.7 weeks [6]. In granulomatosis with polyangiitis (GPA), one form of AAV, a Finnish study reported a diagnosis delay of 4 months between the years 1996 and 2000 [7]. More recently, an English AAV study reported a median diagnostic delay of 2.6 months from symptoms to diagnosis [8]. Little is known about the diagnostic delay in IgAV, but likely it is less than in other vasculitides [9]. A recent study reported symptom duration a median of 7 days prior to IgAV diagnosis [10].

There are limited and variable data about the economic burden of systemic vasculitis on healthcare systems [11]. Thorpe et al. reported that in the year 2010 in the USA, patients with systemic vasculitis had about double the annual healthcare expenditures compared to their non-vasculitis counterparts [12]. Babigumira et al. reported that the US patients with a new GCA diagnosis had substantially higher health care costs compared to the patients without GCA; the difference in 1-year cost was \$16,431 (95% CI \$13,821–\$19,041) [13]. In 2017, a French study showed that the cumulative incremental cost during the first 3 years of GCA exceeded €6400 compared to matched controls, representing an adjusted increase of 72% of costs [14]. In GPA, a US study reported that hospitalization is on average \$17,000 higher in cost per admission than in non-GPA patients [15]. Regarding the costs of adult IgAV, there are no reliable studies.

During recent years, the diagnostic methods for vasculitis have improved. In GCA, nowadays ultrasound is the first preferred method [16]. In unclear cases, ^{18}F -fluorodeoxyglucose positron-emission tomography (^{18}F -FDG-PET) with computed tomography (CT) is effective in diagnosing vasculitis and in excluding other diseases with similar symptoms [17, 18]. However, the PET/CT method is expensive (in 2019 the price was €1979 at Turku University Hospital, Turku, Finland), and the data showing the costs of PET/CT to the overall diagnostic costs in vasculitis are scarce.

The aim of this study was to analyze the diagnostic delay in systemic vasculitis in a tertiary health care facility, the total costs during the first year of care, and how the diagnostic delay affects the costs. The secondary aim was to evaluate how PET/CT affects the diagnostic costs.

METHODS

Patient Selection

The retrospective cohort of this study was retrieved from the Hospital District of Southwest Finland covering a population of 470,000 people. Turku University Hospital Centre for clinical informatics and Biobank (= Auria Clinical Informatics, ACI) searched the hospital medical records and identified patients with a new diagnosis of systemic vasculitis (ICD-10 codes D69.0, D89.1, L95.0, L95.8, L95.9, M30.0, M30.1, M30.8, M31.0, M31.3, M31.4, M31.5, M31.6, M31.7, M31.8, M31.9, M35.2, see Supplement 1) between January 2010 and November 2018. Patients had to be 16 years or older and requiring hospitalization for the vasculitis. Since, in some cases, an accurate vasculitis diagnosis is difficult to verify, we required that the diagnosis code for systemic vasculitis was recorded at least three times and, in addition, two clinically experienced rheumatologists (LP, KT) validated each patient's diagnosis based on the American College of Rheumatology 1990 criteria and/or the clinical presentation of the disease [19–22]. The exclusion criterion was an active malignancy requiring active treatment

and follow-up, because it causes a significant amount of confounding costs. Excluded patients had an uncertain or a false vasculitis diagnosis ($n = 89$), an old diagnosis ($n = 18$), concomitant or metastatic malignancy or malignancy-related vasculitis ($n = 14$), a final diagnosis of Goodpasture syndrome ($n = 5$), another disease causing a significant cost ($n = 5$) or technical reasons ($n = 5$).

Defining the Diagnostic Period and Costs

The medical records were manually searched for the date of the first contact with the tertiary health care, being the first date, and the exact date when the vasculitis diagnosis was recorded for the medical files, being the diagnosis date. ACI provided us with the data about the number and costs of inpatient diagnostic examinations, results of the key biological markers, the number of days of hospitalization and total costs. All costs were recorded and reported as true costs, which were charged from the final payer. The patient paid only a nominal fee per outpatient visit or per inpatient day. The fee was equal for all patients and was not affected by the medical treatment received. This study focused only on the direct medical costs related to the hospital services during the diagnostic period and within the first 12 months. The costs comprised of the following: diagnostic procedures, such as laboratory, radiology and pathology examinations; endoscopies related to the diagnostic process; hospitalization; therapy during hospitalization and out-patient visits related to the vasculitis. The costs included the services from the staff, equipment, and the surroundings. Non-medical costs were not included, since they were not paid by the hospital. In order to focus on the vasculitis-based cost, we have excluded the costs from the departments, which are not likely connected to the vasculitis disease. We have excluded costs from anesthesiology, clinical genetics, dental care, hematology, neurosurgery, obstetrics and gynecology, psychiatry, occupational clinics, oncology, orthopedics, pain clinic, physiatry, rehabilitation, thoracic surgery and traumatology as well as costs from physiotherapy, speech therapy,

occupational therapy or nutritional therapy. All costs were in euros. The diagnostic period was defined as the time span between the first date and the diagnosis date and this period was referred to as diagnostic delay in this article. For each patient, we evaluated data during the diagnostic period and within 12 months after the first date, being the 1-year period. Information on patient demographics, key laboratory findings, histopathology, radiology, and disease activity at baseline was retrieved.

The study was reviewed and approved by the Institutional Review Board at the University Hospital of Turku and conducted in accordance with the ethical standards of the Helsinki Declaration.

Statistical analyses

Normally distributed continuous data were expressed as mean (standard deviation, SD) and for skewed distributions, data were expressed as median (interquartile range, IQR), unless stated otherwise. Categorical variables were described with absolute and relative (percentage) frequencies. An independent sample *t* test or Mann–Whitney *U* test was applied to determine the significance of differences for continuous variables as appropriate and a Chi-square or Fischer's exact test for categorical variables. A one-way ANOVA or Kruskal–Wallis test was used to compare multiple groups, and significance values have been adjusted by the Bonferroni correction for the multiple tests. The linear models were used to study how different factors affected the variation in total costs. Diagnostic delay, inpatient days, number of laboratory studies, C-reactive protein (CRP) values, and total costs were log-transformed for linear models due to the skewed distributions. All statistical analyses were calculated using the SPSS Software Package (IBM SPSS Statistics Version 26). *p* values ≤ 0.05 were considered significant.

RESULTS

Study Population and Demographic Characteristics

We identified 450 eligible patients with the new vasculitis diagnosis in the database from 2010 to November 2018. A total of 317 patients fulfilled the study criteria and were included in the study. Demographic characteristics are summarized in Table 1.

Diagnosis and Diagnostic Delay

The most frequent single diagnoses of vasculitis were: GCA, $n = 132$, 41.6% (ICD-10 code M31.5); IgAV $n = 43$, 13.6% (ICD-10 code D69.0) and GPA, $n = 41$, 12.9% (ICD-10 code M31.3). For statistical analysis, the diagnoses were grouped into three clinically relevant groups: IgAV and other small-vessel vasculitis ($n = 64$; ICD-10 codes D69.0, D69.2, D89.1, L95.0, L95.8, L95.9), AAV ($n = 112$; ICD-10 codes M30.0, M30.1, M30.8, M31.0, M31.3, M31.7, M31.8, M31.9) and LVV ($n = 141$; ICD-10 codes M31.4, M31.5, M31.6). The AAV group included three patients with polyarteritis nodosa because it was clinically the most applicable group for those patients.

The diagnostic delay from the first referral to tertiary-level clinic was shortest in the LVV group (median 5 [IQR 13]) days and longest in the AAV group (median 22.5 [IQR 38]) days (Table 1). In our study, 21 patients had a diagnostic delay for 0 days, and 15 of those were LVV patients (10.6% of all LVV patients). In the LVV group, the diagnostic delay was significantly longer in males ($n = 42$) than in females ($n = 99$) with a median of 9.5 (IQR 24) days and 5.0 (IQR 9) days, respectively ($p = 0.034$). In other groups, there was no difference in delay based on the sex. Age had no significant correlation with the diagnostic delay.

Costs and Factors Associated with High Costs

Total costs during the diagnostic period were the highest in the AAV group with a median of

Table 1 Demographics of the patients

Disease group	LVV (<i>n</i> = 141)	AAV (<i>n</i> = 112)	IgAV (<i>n</i> = 64)	<i>p</i> value ^A
Age in years, mean (SD)	73.1 (9.5)	65.6 (13.9)	56.3 (22.1)	< 0.001 ^{a,b,c}
Sex, female, <i>n</i> (%)	99 (70.2)	57 (50.9)	28 (43.8)	< 0.001 ^{a,b}
Maximum CRP ^B , mg/l, mean (SD)	92.3 (81.5)	107.3 (97.5)	62.6 (65.4)	< 0.01 ^{b,c}
Diagnostic delay ^C , days, median (IQR)	5.0 (13)	22.5 (38)	9.5 (25)	< 0.001 ^{a,b,c}
Hospitalization time within the diagnostic period, days, median (IQR)	5.0 (5)	10 (12)	7.0 (12)	< 0.001 ^{a,c}
Hospitalization time within 12 months ^D , days, median (IQR)	7.0 (11)	22.0 (22)	13.5 (22)	< 0.001 ^{a,b}
PET/CT performed within 12 months ^D , <i>n</i>	25	19	3	
Dialysis treatment within 12 months ^D , <i>n</i>	0	7	0	

LVV large-vessel vasculitis, AAV antineutrophil cytoplasmic antibody-associated vasculitis, IgAV IgA vasculitis and other small-vessel vasculitis, CRP C-reactive protein, PET/CT positron-emission tomography/computed tomography

^A *p* value across all the groups. Significant values expressed between the groups: ^aLVV vs. AAV, ^bLVV vs. IgAV, ^cAAV vs. IgAV

^B Highest CRP value available closest to the diagnosis

^C Diagnostic delay: timeline between the first contact to the tertiary health care and the date of vasculitis diagnosis

^D 12 months forward starting from the first contact to the tertiary health care

€6754.5 (range, €549.9–106,416.4) and lowest in the LVV group with a median of €3123.0 (range, €0–28,691.4). Similar trends were seen during the 1-year period, since the highest cost was in the AAV group (Table 2).

There was a statistically significant positive correlation between the diagnostic delay from the first referral to tertiary-level clinic and total costs during the diagnostic period and 12 months ($r_s = 0.38$, $p < 0.001$ and $r_s = 0.34$, $p < 0.001$, respectively). In a linear model, when the effects of other factors were simultaneously controlled, the inpatient days and the number of laboratory tests were the strongest predictors ($p < 0.001$) of a higher treatment cost during the diagnostic period. Sex, diagnosis, a PET/CT study or the CRP value did not have a statistically significant effect on total costs during the diagnostic period, and the R^2 for this model was 0.705. In this model, the diagnostic delay was significant ($p < 0.05$) for total costs. Similar results were seen within the 12-month results. Inpatient days and the number of laboratory tests were the strongest predictors

($p < 0.001$), but the diagnostic delay was no longer a significant factor in this model (Table 3). Age was not a significant factor for costs. Dialysis was a significant contributor to total costs but since there were only seven patients, all with an AAV diagnosis, receiving the dialysis treatment, it was not included in the linear model. For dialysis patients, the median costs for the diagnostic period were €24,651.6 (IQR €18,300.8) and for 12 months, €55,164.3 (IQR €61,629.1). The costs were 3.6 and 3.4 times higher, respectively, than the median of the AAV patients ($p < 0.005$ and $p < 0.001$, respectively).

Impact of PET/CT for the Vasculitis Diagnosis

A linear model including the effects of sex, diagnostic delay, CRP value, the number of laboratory studies, the number of inpatient days, and diagnosis showed that PET/CT had no significant effect on costs within the diagnostic period or within 12 months, $p = 0.081$ and

Table 2 Number and costs of diagnostic studies within the diagnostic period and within the first 12 months

Disease group	LVV (<i>n</i> = 141)	AAV (<i>n</i> = 112)	IgAV (<i>n</i> = 64)	<i>p</i> value ^A
Diagnostic period, days, median (IQR)	5.0 (13)	22.5 (38)	9.5 (25)	< 0.001 ^{a,b,c}
Laboratory tests, <i>n</i> , median (IQR)	34.0 (35)	85.5 (96)	48.0 (56)	< 0.001 ^{a,c}
Laboratory costs, €, median (IQR)	242.5 (432.9)	1024.9 (1049.6)	547.0 (755.3)	< 0.001 ^{a,b,c}
Radiology tests, <i>n</i> , median (IQR)	2.0 (3)	4.0 (4)	1.5 (2)	< 0.001 ^{a,c}
Radiology costs, €, median (IQR)	189.0 (451)	357.0 (657)	76.0 (185)	< 0.001 ^{a,c}
Total costs, €, median (IQR)	3123.0 (4517.3)	6754.5 (8812.9)	3346.1 (6371.5)	< 0.001 ^{a,c}
12-month period				
Laboratory tests, <i>n</i> , median (IQR)	125.0 (82)	312.0 (246)	169.5 (224)	< 0.001 ^{a,b,c}
Laboratory costs, €, median (IQR)	662.0 (651.2)	2764.1 (2193.1)	1590.5 (1867.8)	< 0.001 ^{a,b,c}
Radiology tests, <i>n</i> , median (IQR)	4.0 (5)	10.0 (9)	6.0 (8)	< 0.001 ^{a,b,c}
Radiology costs, €, median (IQR)	520.0 (1206)	1330.1 (2030)	554.5 (1191)	< 0.001 ^{a,c}
Total costs, €, median (IQR)	6605.2 (7681.1)	16,169.5 (19,193.6)	10,049.4 (15,137.8)	< 0.001 ^{a,b,c}

LVV large-vessel vasculitis, AAV antineutrophil cytoplasmic antibody-associated vasculitis, IgAV IgA vasculitis and other small-vessel vasculitis

Diagnostic period: timeline between the first contact with the tertiary health care and the date of vasculitis diagnosis
12 months after the first contact with the tertiary health care

^A *p* value across the all groups. Significant values expressed between the groups: ^aLVV vs. AAV, ^bLVV vs. IgAV, ^cAAV vs. IgAV

p = 0.516, respectively (Table 3). PET/CT was performed for 47 patients. The average waiting time from PET/CT referral to imaging was 7.2 days (range, 1–34 days). PET/CT showed vasculitis findings in 27 patients (59.6%), of which 16 had LVV. On average, patients with diagnostic PET/CT had 16.5 days (range, 0–31 days) of inpatient hospitalization within the diagnostic period. In comparison, the mean diagnostic period hospitalization was 9.4 days in the whole study population.

DISCUSSION

This single-center study showed that there was a substantial diagnostic delay in tertiary-level health care when diagnosing systemic vasculitis. This causes considerable costs for the health care system and may cause low quality-of-life for the patients.

Little is known about the economic burden of systemic vasculitis on health care costs. Trieste et al. [11] failed to do a systemic literature review on this subject based on a paucity of relevant papers. A few summarized articles suggested that disease severity, hospitalization, and costly procedures determine high costs [23, 24]. Our study adds valuable information for the cost of illness (COI) for hospitalized vasculitis patients. Mounie et al. [14] and Babingura et al. [13] both studied the incremental costs of GCA compared to the controls, but they received very distinct results within the first year, €2840 vs. \$16,431, respectively. Mounie et al. [14] speculated that the difference is partly explained by the societal perspective and the differences in health care systems. In our study, we recorded the COI of systemic vasculitis including GCA, and the median costs for GCA patients within 12 months was €6605.2. Italian researchers reported that the COI of GCA, measured as direct health care

Table 3 The background factors on total costs used for the linear model

Factor	Diagnostic period ^a		12-month period ^a	
	Adjusted β (SE) or adjusted mean (SE)	<i>p</i> value	Adjusted β (SE) or adjusted mean (SE)	<i>p</i> value
PET/CT		0.081		0.516
Yes	8.47 (0.09)		9.32 (0.06)	
Gender		0.216		0.314
Male	8.34 (0.06)		9.28 (0.04)	
Diagnosis		0.289		0.324
LVV	8.31 (0.06)		9.33 (0.04)	
AAV	8.43 (0.07)		9.24 (0.05)	
IgAV	8.41 (0.08)		9.31 (0.06)	
CRP ^a	0.04 (0.03)	0.156	− 0.04 (0.02)	< 0.05
Diagnosis delay ^a	0.05 (0.03)	< 0.05	0.02 (0.02)	0.204
Number of laboratory studies ^a	0.17 (0.04)	< 0.001	0.47(0.04)	< 0.001
In-patient days ^a	0.59 (0.04)	< 0.001	0.52 (0.03)	< 0.001

PET/CT positron-emission tomography/computed tomography, *AAV* antineutrophil cytoplasmic antibody-associated vasculitis, *IgAV* IgA vasculitis and other small-vessel vasculitis, *CRP* C-reactive protein, β regression coefficient for a one-unit increase in continuous factors

^a Log-transformed values were used in the linear modeling

expenses, was €2374 per patient-year [25]. This lower cost, compared to our results, reflects the longer observation time with a median of 3.9 years, and only 52% of patients were hospitalized during the observation period. In AAV, a US study from the year 2015 reported that the mean total all-cause and vasculitis-related costs were \$41,400 and \$24,319 during the 12-month follow-up [26]. The costs were significantly higher than the ones we report here during the first 12 months for AAV patients with a median of €16,169. Recently, an Italian group reported a total COI of AAV patients to be €6168 per patient-year during follow-up of 8 years [27]. This emphasizes the need for more studies to gather information from different health care systems. There are no studies concerning costs of adult IgAV, so this needs further investigation. In children, the hospitalization rate in the US in Henoch–Schönlein purpura was 2.4 per

100,000 children, and the hospitalization cost was \$3254 in year 2014 [28].

There are scarce data about the connection between the diagnostic delay and health care costs in systemic vasculitis, and there are no data directly studying this connection. Indirectly, the delay in receiving diagnosis has been shown to have negative effects on outcomes in rheumatic diseases, such as in rheumatoid arthritis [29] and GCA [30], and the disease severity connects to the higher costs [31]. Previous studies have shown that the diagnostic delay in systemic vasculitis is variable [6, 7, 32, 33]. In line with the previous studies, our study shows that the diagnostic delay is shorter in GCA/LVV than in AAV [4, 6]. In our study, we found that the diagnostic delay in a tertiary-level clinic was significantly correlated with total costs within the diagnostic period and 1-year period mostly due to the high costs of hospitalization. In order to reduce the costs

during the diagnostic period and during the first year, it is essential to find ways to shorten the inpatient time. One effective tool could be PET/CT, since it has the ability to confirm the vasculitis diagnosis but also discover other causes, such as infection or malignancy, which may lie behind the vasculitis-like symptoms [17, 18]. PET/CT is an expensive examination, however in our data, it was not a significant contributor for the total costs. Instead, it seems that patients who received PET/CT had longer hospitalization and waiting time, causing notable costs. When performed, PET/CT revealed vasculitis in over half of the patients. Even though expensive, PET/CT may be cost saving if imaging is easily accessible and the diagnostic delay in tertiary care can be shortened.

Overall, the range in delay and costs is wide. Further studies are needed to fully recognize the characteristics of patients with long periods of delay or with high costs.

Limitations and Strengths

Our study had limitations. It was a single-center, retrospective study. The health care utilization patterns and associated costs represented the clinical practice in Finland and may not be generalized to other settings. While this study focused on direct health care costs of systemic vasculitis, it is highly likely that patients are burdened and have high out-of-pocket costs from diagnostic delay. This should be considered in future studies. The strength was that each diagnosis and pivotal dates were validated manually. Based on the registry results alone, the amounts of incorrect diagnoses would have been significant.

CONCLUSIONS

There is a substantial diagnostic delay in tertiary-level health care when diagnosing systemic vasculitis. This delay has a significant positive correlation with the costs.

ACKNOWLEDGEMENTS

The authors wish to thank Juha-Matti Varjonen from Auria Clinical Informatics for helping with data mining and Tero Vahlberg from the University of Turku for statistical knowledge. Robert M. Badeau, M.Sc., Ph.D. of Aura Professional English Language Consulting, Ltd. (auraenglish.com) performed this manuscript's English language checking and proofreading service.

Funding. This study was supported by State Research Funds of Turku University Hospital, Finnish Kidney Foundation (Munuaissäätiö) and Maire Lisko Foundation. The authors are funding the journal's Rapid Service Fee.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. The authors (Kirsi Taimen, Anssi Mustonen, and Laura Pirilä) have declared no conflicts of interest.

Compliance with Ethics Guidelines. The study was reviewed and approved by the Institutional Review Board at the University Hospital of Turku and conducted in accordance with the ethical standards of the Helsinki Declaration.

Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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