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Original Article

Significance of parvovirus B19 infection in childhood - collection of demographic data, clinical presentation, diagnostic findings and the impact on patients with hemolytic anemia

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ABSTRACT

Introduction: Parvovirus B19 is a known cause of erythema infectiosum, aplastic crises and severe anemia, especially in patients with hemolytic anemia. The aim of this study was to investigate the clinical and diagnostic parameters of parvovirus B19 infection in children with and without hemolytic anemia and to record the course of case numbers in recent years.

Methods: We retrospectively included all patients diagnosed with acute parvovirus B19 infection at the Department of Pediatrics, Jena University Hospital, Jena, Germany between 2016 and 2024. Diagnosis was confirmed by positive parvovirus B19 IgM serology and/or PCR testing. Both demographic and clinical data as well as diagnostic parameters were collected and analyzed, focusing on differences between children with and without underlying hemolytic anemia.

Results: Among the 40 pediatric patients included in this study, 14 patients were diagnosed with hemolytic anemia. Children with hemolytic anemia suffered from a significantly greater hemoglobin drop and a significantly higher need for transfusion compared to children without hemolytic anemia. A Poisson regression model, adjusted for observation time, was used to compare case rates between 2016 and 2022 and 2023-2024.The model demonstrated a more than fivefold increase in parvovirus B19 cases in 2023-2024 compared to 2016-2022.

Conclusion: Children with hemolytic anemia, such as spherocytosis, are at higher risk of severe anemia and require more frequently transfusions during acute parvovirus B19 infection. The observed increase in cases after 2022 suggests changing epidemiological patterns and highlights the need for careful surveillance and early diagnostic and therapeutic interventions in affected children.

1. Introduction

Parvovirus B19 is a common human infectious agent worldwide. Infection with the single-stranded DNA virus, which was first discovered in 1975 by Cossart, usually occurs via droplet transmission [1,2]. Therefore, most infections arise during childhood when children start attending group facilities such as daycares or schools. In industrialized countries such as Germany the prevalence is particularly high at (pre-) school age whereas children in more tropical regions are often infected at a very early age, often even as infants [3,4]. Antibodies against parvovirus B19 are already detectable in 66.9% of the adolescents (18-19 years) in Germany [5]. However, transmission can also occur transplacental, whereby the virus is passed from the mother to the unborn fetus. It can lead to hydrops fetalis and even to death [6]. In rare cases, infection can also occur via blood products. A seasonal increase in prevalence is observed, particularly in early summer and an epidemic tend to occur approximately every 4-5 years.

Within about a week, viremia occurs and then the clinical presentation of the disease develops. Only about half of all cases show (mostly unspecific) symptoms that can be classified as erythema infectiosum (fifth disease) [7]. The most common symptoms are fever, fatigue, and arthralgia. The development of an exanthema typical for erythema

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infectiosum on the face and the extensor sides of the extremities is much rarer and only occurs around 2 to 3 weeks after infection [8,9]. The highest chance of transmission is before the exanthema breaks out, as the viral load peaks at this time.

The disease is usually self-limited and has no major consequences for immunocompetent patients. After infection, parvovirus B19 multiplies in the red blood cell precursors. Therefore, healthy people may experience a temporary reduction in red blood cell production and numbers. However, in patients with impaired hematopoiesis or reduced blood cell lifespan, acute cytopenia and even aplastic crisis can occur during and shortly after the disease because of the arresting production and the increasing destruction of the red blood cells. Anemia with an accompanying low reticulocyte count is an indication of an aplastic crisis [10]. It is already known that patients with chronic hemolytic anemia are therefore more likely to suffer more severe courses of the disease [11]. Previous studies have shown that a high viral load is associated not only with the onset of aplastic crises but also with an increased risk of transmission, making these children highly infectious [12].

Acute parvovirus B19 infection is detected by a positive serologic parvovirus B19 IgM test and/or parvovirus B19 PCR. It has been shown that the combination of both detection methods provides the most sensitive and reliable method for diagnosis [13]. IgM reaches its maximum increase about 2 to 3 weeks after infection, while the viral load has already decreased considerably by this time. The IgG response starts after 2 weeks and ensures long-term protection [1]. Despite widespread IgM and PCR testing for parvovirus B19 many infections remain undetected due to their asymptomatic nature, and differentiation from other similar viral diseases remains a challenge. Until today, there is no specific treatment. The therapy is primarily limited to treating predominant symptoms, such as the administration of red blood cell concentrates for acute anemia or antipyretics for fever [12]. In recent years, the use of intravenous immunoglobulin has been investigated as a therapeutic option in some cases to support the immune system [14].

Ultimately, parvovirus B19 remains an important viral infectious agent, especially in childhood, with the potential to lead to various clinical manifestations. While the majority of cases are mild, the occurrence of more severe cases or complications requires an immediate and targeted action. Additionally, our study aimed to evaluate whether the hypothesis of increased infection frequency in recent years could be confirmed by the data.

Table 1
Summary of all included patients (n = 40) grouped by diagnostic method, comorbidities and symptoms. Percentages are based on all 40 patients.
"Both" indicates patients tested via IgM serology and PCR. Multiple symptoms per patient were possible.

	n	%
Gender		
male	21	52.5
female	19	47.5
Test		
P19 IgM positive	15	37.5
P19 DNA positive	7	17.5
Both	18	45
Pre-existing hemolytic disorder		
Spherocytosis	12	30
Glucose-6-phosphate dehydrogenase deficiency	1	2.5
Pyruvate kinase deficiency	1	2.5
Symptoms		
Fever	27	67.5
Fatigue	19	47.5
Headache	8	20
Lymphadenopathy	6	15
Head cold	6	15
Cough	6	15
Exanthema	5	12.5
Vomitus	4	10
Absence of appetite	4	10
Arthralgia	3	7.5
No symptoms	5	12.5

P19: Human parvovirus B19.

2. Materials & methods

2.1. Study design and patients

In our retrospective study, we assessed all positive parvovirus B19 tests from the last nine years (2016-2024) at the Department of Pediatrics, Jena University Hospital, Jena, Germany. All patients with an acute infection were included in the study. An acute positive result was defined as the detection of parvovirus B19 DNA by PCR and/or a specific parvovirus B19 IgM signal detected via serology. Not all patients with a positive IgM result underwent PCR testing. Therefore, the absence of a PCR result does not imply a negative PCR. Patients with a positive IgM and a negative PCR were excluded from the study. Patients with isolated IgG titres were excluded from the study, as well as those with potential co-infections such as Epstein-Barr virus or *Mycoplasma pneumoniae*, which were ruled out by laboratory testing.

For quantitative parvovirus B19-PCR viral DNA was extracted from human plasma using the QIAsymphony® DSP Virus/Pathogen Kit on QIAsymphony instrument (Qiagen, Hilden, Germany). Amplification/detection was performed with artus® Parvo B19 RG PCR Kit on Rotor-Gene RealTime PCR platform (Qiagen, Hilden, Germany) and results were reported in international units per milliliter (IU/mL) in accordance with current standardization practices. A cut-off value of $\geq 5 \times 10^1$ was defined as positive.

Specific parvovirus B19 IgG and IgM antibodies were detected in serum samples using the chemiluminescence immunoassays LIAISON® Biotrin Parvovirus B19 IgG Plus and LIAISON® Biotrin Parvovirus B19 IgM Plus on Liaison XL instrument using. IgG-results were reported in IU/mL with results <2.00 considered negative, values from 2.00 - 2.49 as borderline and values ≥2.50 as positive, respectively. IgM-results were reported as index with results <0.90 considered negative, from 0.9 - 1.09 as borderline and ≥1.10 as positive. Alternative infectious causes of positive IgM results were systematically assessed by appropriate serological testing. Participants with any positive serological finding were excluded and only those with negative results for all alternative infections were included in the final analysis. However, unspecific antibody binding cannot be ruled out with absolute certainty. All diagnostic procedures were conducted in accordance with the manufacturer's instructions.

Information on clinical symptoms, administered therapies and the presence of pre-existing hemolytic anemia was collected from the records. Based on these criteria, they were assigned to subgroups. These groups were then compared with particular focus on laboratory parameters that could be affected by the virus or underlying anemia.

In our study, the cut-off value for red blood cell transfusion (RBCT) was a hemoglobin level of 4.5 mmol/L, which corresponds to the guideline applied in our clinic.

2.2. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics, Version 30.0.0.0 (IBM Corp., Armonk, NY). The distribution of continuous variables, including hemoglobin concentration, was assessed using the Shapiro–Wilk test. As the data did not follow normal distribution, group comparisons were performed using the non-parametric Mann–Whitney U test. Categorical variables, such as the presence of hemolytic anemia and administration of red blood cell concentrate transfusion, were analyzed using Fisher's exact test. A significance level of $p < 0.05$ was considered statistically significant. A univariate logistic regression model was used to evaluate the association between IgM levels and the likelihood of receiving transfusion therapy. In addition, a multivariate logistic regression was performed including clinical

Table 2
Demographic data, IgM and PCR results, clinical symptoms and therapy among patients with and without hemolytic anemia.
Children with confirmed parvovirus B19 infection. Includes patients with spherocytosis, glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency.

Patients (n)	Year of diagnosis	Age (years)	IgM (Index)	PCR (IU/ml)	Symptoms	Therapy
1	2016	1	4.2	1.36×10^4	fever, cough, head cold	2 RBCT
2	2016	11	4.9		fever	
3	2016	7		7.49×10^1	fever, fatigue, vomitus	
4	2017	7		4.26×10^2	fever, fatigue, lymphadenopathy	
5	2017	17	21	1.7×10^4	fever, fatigue, headache, vomitus	
6	2017	2	2.6		none	
7	2018	9	2.2		none	
8	2018	1		1.05×10^6	fever, head cold	1 RBCT
9	2018	1	2.0		fever	
10	2018	7		2.61×10^2	none	
11	2019	4	1.9		fever, lymphadenopathy	
12	2020	4	30	3.31×10^4	fever, exanthema, lymphadenopathy	
13	2020	13	1.5		fever, fatigue, headache, loss of appetite, lymphadenopathy	
14	2020	0	2.2		fever, fatigue	
15 Spherocytosis	2021	0	1.3		fatigue	1 RBCT
16 Spherocytosis	2022	6	2.8		none	
17 Spherocytosis	2023	2	>48		fever, fatigue	1 RBCT
18 Spherocytosis	2023	11	>48	2.23×10^5	fever, fatigue, pallor	1 RBCT
19	2023	7	>48	1.59×10^4	fatigue, arthralgia	
20	2023	1	>48	7.14×10^3	fever, fatigue, exanthema	
21 G6PD	2023	5	1.6	5.27×10^8	fatigue, exanthema, pallor	1 RBCT
22	2023	13	23	1.56×10^4	headache	
23	2023	7	3.0		fever, headache, head cold	
24	2024	4	11.7		fatigue, headache, cough	
25 Spherocytosis	2024	15	>48	2.72×10^6	fever, vertigo	3 RBCT
26 Spherocytosis	2024	10	46.6	5.78×10^8	fatigue	
27	2024	6	10.6		exanthema	
28	2024	9	4.3	2.22×10^3	fever, headache, cough, head cold	
29	2024	10	>48	1.277×10^5	none	
30 Spherocytosis	2024	14	41.2	1.48×10^8	fever, headache, vertigo	2 RBCT
31 Spherocytosis	2024	4	>48	1.37×10^6	fever, fatigue	1 RBCT
32 PKD	2024	9		5.4×10^8	fever, fatigue, vomitus	1 RBCT
33	2024	6		6.82×10^2	fever, loss of appetite	
34	2024	3	2.9	1.56×10^3	fever, fatigue, exanthema, lymphadenopathy	
35 Spherocytosis	2024	6	>48	6.36×10^7	fever, fatigue, arthralgia	1 RBCT
36 Spherocytosis	2024	7	>48	6.14×10^7	fever, loss of appetite	1 RBCT
37	2024	14	>48		fever, fatigue, headache	
38 Spherocytosis	2024	10	2.7		fever	
39	2024	8		2.9×10^3	fever, fatigue, vomitus, loss of appetite	
40 Spherocytosis	2024	7	>48	1.64×10^8	fever, cough	3 RBCT

IgM: immunoglobulin M; PCR: polymerase chain reaction; IU: international Units; RBCT: red blood cell transfusion; G6PD: Glucose-6-phosphate-dehydrogenase deficiency; PKD: Pyruvate-kinase deficiency.

parameters such as hemoglobin levels and the presence of hemolytic anemia.

To assess whether the number of parvovirus B19-positive cases significantly increased in the post-COVID-19 years, we conducted a Poisson regression analysis with the number of positive cases as the dependent variable and the observation period (2016–2022 vs. 2023–2024) as the independent variable. The natural logarithm of the number of observation years was included as an offset to account for the different time spans.

3. Results

During the past nine years, 40 children with an acute parvovirus B19 infection were identified. The cohort consisted of 21 boys and 19 girls, with ages ranging from 0 to 17 years and a median age of 4 years. There were 14 cases among ages ranging from 0 to 5 years and 18 cases from 6 to 10 years, supporting the assumption that the majority of children are infected during (pre-) school age. Notably, among the 6-10 year old children, 11 out of 18 patients were already infected at the age of 6 or 7 years, i.e. at the beginning of primary school. In our study, 32 patients (80%) were already infected below the age of 11 years. The remaining 8 patients (20%) were between 11 and 17 years old. Among the children,

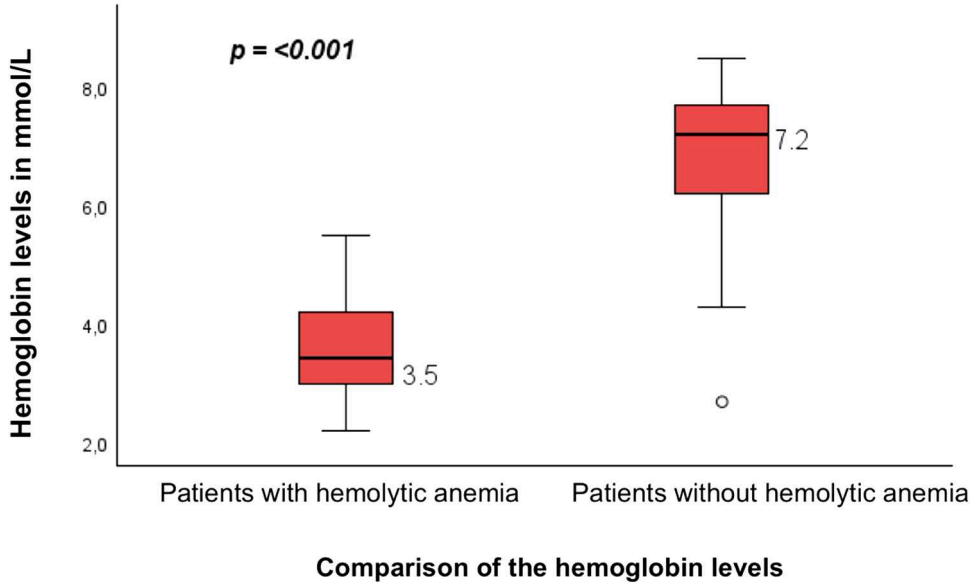

Fig. 1. Hemoglobin levels (mmol/L) in children with and without hemolytic anemia.
Median values are shown with interquartile ranges. A statistically significant difference was found ($p < 0.001$, Mann–Whitney U test). Median hemoglobin levels were 7.2 mmol/L vs 3.5 mmol/L.

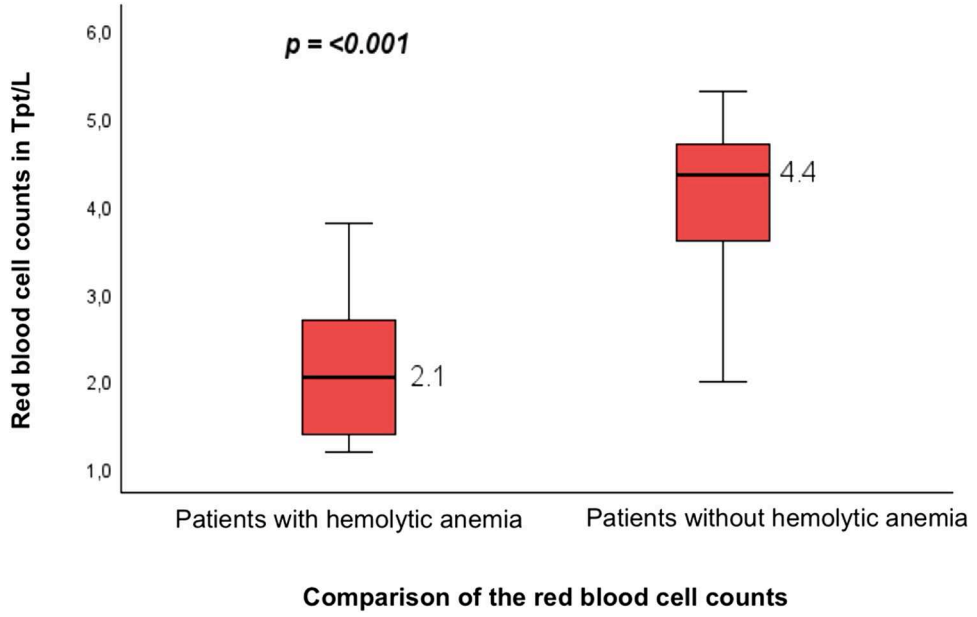

Fig. 2. Red blood cell counts (Tpt/L) in children with and without hemolytic anemia.
Children with hemolytic anemia showed significantly reduced red blod cell counts ($p < 0.001$, Mann-Whitney U test). Median red blood cell count was 4.4 Tpt/L vs. 2.1 Tpt/L.

14 patients were diagnosed with hemolytic anemia, including 12 patients with spherocytosis, one patient with glucose-6-phosphate dehydrogenase deficiency and one patient with pyruvate kinase deficiency (Table 1). The remaining children were otherwise healthy.

Fever was the most common initial symptom, occurring in 67.5% of the cases. Nearly half of the children also experienced fatigue (47.5%). Only five children presented a facial exanthema. Enlarged lymph nodes were noted in 15% of cases and arthralgia occurred in 7.5%. Five children were completely asymptomatic, the virus was detected incidentally (Table 1, 2). In 18 cases, parvovirus B19 infection was proofed with both PCR and serology, in 15 cases only IgM antibodies were detected and in 7 cases only viral DNA was present (Table 1).

All patients underwent at least a complete blood count, and in most cases, the number of neutrophils and reticulocytes was determined. Children with hemolytic anemia showed markedly lower hemoglobin levels than those without hemolytic anemia. This difference was statistically significant (Mann-Whitney-U-Test, $p < 0.001$). These comparisons are demonstrated in the attached graphs (Fig. 1 and 2). For a better overview the numbers of red blood cells are also given.

The administration of red blood cell transfusion differed significantly between the two groups. Of those diagnosed with hemolytic anemia, 11 out of 14 patients (79%) received therapy, in contrast only two out of 26 children without hemolytic anemia (7.7%) were treated accordingly. This association between hemolytic anemia and transfusion therapy was statistically significant (Pearson chi-square test $\chi 2(1) = 13{,}35$; $p < 0{,}001$; Fishers exact test $p < 0.001$).

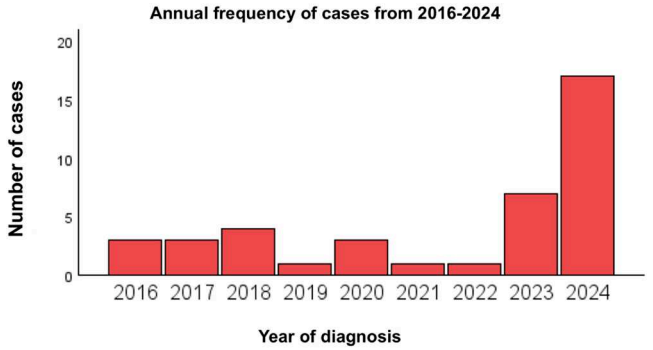

Fig. 3. Annual frequency of confirmed Parvovirus 19 cases in our pediatric hospital from 2016 to 2024.
The figure shows a relatively stable number of cases from 2016 to 2020, followed by a drop in 2021 and 2022 and an increase starting in 2023.

In 2020, three parvovirus B19 cases were recorded, followed by a drop to one case each in 2021 and 2022. However, the number of infections rose to seven in 2023 and further to seventeen in 2024. The median dropped from three in the pre-COVID-19 years (2016-2019) to one during the COVID-19 pandemic (2020-2022) and rose up to 12 in the post-COVID-19 years (2023-2024).

We divided the cohort in two groups, the first for the pre- and pandemic years from 2016 to 2022 ($n = 16$) and the second for the post-COVID-19 years from 2023 to 2024 ($n = 24$). A Poisson regression model revealed a statistically significant increase in parvovirus B19-positive cases in the post-COVID-19 years 2023-2024 compared to the period 2016-2022 (Wald $\chi^2 = 26.4$, $p < 0.001$), adjusted for the number of observation years. The rate ratio indicates that the incidence was approximately 5.3 times higher in the more recent period (Fig. 3).

4. Discussion

In this retrospective study, an acute parvovirus B19 infection was identified in 40 pediatric patients diagnosed at the Department of Pediatrics, Jena University Hospital, Jena, Germany, between January 2016 and December 2024. We compared diagnostic findings, especially in patients with and without hemolytic anemia, and verified an increase in the number of infections in 2023 and 2024. A total of 14 patients was diagnosed with a pre-existing hemolytic anemia. Our findings confirm the already known clinical spectrum of the disease, like fever and fatigue, while also providing new insights into its impact on patients with underlying hemolytic anemia. One of our original research questions - whether parvovirus B19 infections lead to a more severe course in children with hemolytic anemia - was clearly answered by our data.

There was a significant correlation between hemolytic anemia and a more severe course of the infection. The median hemoglobin value was 3.5 mmol/L in patients with hemolytic anemia, while healthy patients had a value of 7.2 mmol/L. This is also reflected in the number of red blood cells, which shows an equally significant result. Therefore, our results are consistent with previous studies which have already described a more severe course of infection in patients with hemolytic anemia [15,16]. A decrease in hemoglobin levels is linked to an elevated risk of anemia and is often accompanied by an increased need for red blood cell transfusions as a therapeutic response to resulting anemia. Of course, children with hemolytic anemia are particularly affected, which was also demonstrated in our study. Of 14 children with hemolytic anemia, 11 children required at least one red blood cell transfusion, compared to just two out of 26 healthy children. The significantly higher transfusion rate among children with hemolytic anemia is in line with the known clinical course of the disease, which mostly includes transfusion [17].

In our study, we also found a significant increase to a total of 24 cases in the post-COVID-19 years (2023 and 2024) coming from one case each year during COVID-19 and three cases in the pre-COVID-19 years (2016-2019). This observation is also supported by other studies from Germany which reported a similar or even higher increase of parvovirus B19 infections [18–21]. High infection rates have recently been detected not only in Germany but also in other countries, such as Denmark, France, the Netherlands, Belgium, and Israel [22–25]. This increase is most likely due to the easing of COVID-19 restrictions following the pandemic [25,26]. Owing to the rise in interpersonal contact, the reopening of social institutions and the lifting of mask mandates and other protective measures as well as the "immunity gap", a higher transmission rate - particularly via droplet infection - became possible [27,28].

Early screening in affected children to detect the virus at an initial stage can be very effective in preventing the spread of the disease. This is particularly important during periods of increased viral circulation. Especially in children with hemolytic anemia an unexplained drop in red blood cells may be an indicator of parvovirus B19 infection and requires immediate diagnostic evaluation [29]. The findings highlight the importance of interpreting serological and molecular markers within a broader clinical context. This is why the combination of PCR and serological diagnostics is important and represents the best approach to identify ongoing infection. This was also the conclusion of another study, which described a combination of both methods as the most sensitive option [13].

Future prospective studies with larger numbers of cases and a control group are necessary to further investigate the casual relationship between parvovirus B19 infection and anemia-related complications. Limitations of this study include its retrospective design and the relatively small sample size as only children with positive PCR tests and/or IgM signals were included. Furthermore, not all laboratory parameters (e.g. LDH, bilirubin, reticulocyte count) were available for all patients, which limits the depth of hematological analysis.

In conclusion, parvovirus B19 infection remains an important differential diagnosis in febrile children with unexplained anemia. Our study reinforces the significance of the infection in patients with hemolytic disorders and supports the use of combined PCR and IgM testing for a reliable diagnosis. Further prospective multicenter studies are needed to assess current epidemiological trends and long-term outcomes, especially in the context of recent international increases in case numbers.

Ethical standard

All procedures were in accordance with the ethical standards of the institutional research committee. The study was approved by the Jena University Hospital Ethics Committee (2025-3700). Informed consent was obtained from all responsible persons.

CRediT authorship contribution statement

Lorraine Lawatsch: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Michael Baier:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Till Milde:** Writing – review & editing, Validation, Supervision. **Bernd Gruhn:** Writing – review & editing, Validation, Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no potential conflict of interest.

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