BMC Gastroenterology

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Hepatitis E virus seroprevalence and infection status among patients with inflammatory bowel disease undergoing advanced therapy: a prospective single-center observational study

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Abstract

Background Hepatitis E virus (HEV) is a significant cause of acute and chronic hepatitis, especially in immunosuppressed individuals. Patients with inflammatory bowel disease (IBD) undergoing advanced therapy may have an elevated risk of persistent HEV infection; however, evidence in this population is limited. This study evaluated HEV seroprevalence and infection status among IBD patients receiving advanced therapy in an endemic European region.

Methods In this prospective observational study, 142 adults with Crohn's disease (CD) or ulcerative colitis (UC) treated with advanced therapy between April 2024 and April 2025 were enrolled. Participants completed a structured questionnaire to assess HEV exposure risks and underwent testing for anti-HEV IgG and IgM antibodies as well as liver enzymes. HEV RNA in blood and stool samples was evaluated by real-time PCR in seropositive individuals.

Results Anti-HEV IgG antibodies were detected in 18.3% of participants, while all tested negative for anti-HEV IgM and HEV RNA, indicating no evidence of active or chronic infection. HEV seropositivity was significantly higher in patients with UC compared to those with CD ($p=0.031$), but was not associated with demographics, disease characteristics, therapy type or duration, aminotransferase elevation, or assessed risk factors.

Conclusions HEV exposure among IBD patients receiving advanced therapy is similar to that observed in the general population, and chronic infection is uncommon. These findings suggest that routine HEV screening may not be necessary in all IBD patients receiving advanced therapy; however, this should be interpreted cautiously.

Keywords Hepatitis E, Inflammatory bowel disease, Biologic therapy

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Background

Hepatitis E virus (HEV) has become a major cause of both acute and chronic viral hepatitis worldwide [1]. As a zoonotic virus primarily transmitted through the enteric route, the precise mechanisms by which HEV crosses the intestinal barrier to access the portal circulation remain poorly understood [2]. Although most HEV infections are asymptomatic or self-limiting, the virus can result in severe disease among immunocompromised individuals, such as those with solid organ transplants, hematologic malignancies, or those receiving immunosuppressive therapy [3]. Chronic HEV infection is of particular concern due to its potential to cause progressive liver injury and cirrhosis [4].

The reported seroprevalence of anti-HEV IgG antibodies across Europe ranges from below 5% to over 20%, depending on geographic region, study design, and diagnostic methodology [5, 6]. In South-East Europe, HEV has been identified in both human and animal populations within the context of the "One Health" approach [7]. Data from Serbia demonstrate that HEV is endemic, with 15% of blood donors testing positive for anti-HEV IgG [8]. Despite this, clinical studies focusing on immunosuppressed populations in this region are limited.

Individuals with inflammatory bowel disease (IBD) represent a distinct at-risk group, due to both alterations in intestinal barrier function and gut–liver axis regulation, as well as the frequent use of immunomodulators and biologic agents that may impair antiviral immunity [9, 10]. Although current IBD guidelines emphasize the importance of monitoring for opportunistic infections in patients receiving immunosuppressive therapies, specific recommendations regarding HEV testing have not yet been established [11, 12].

This study aimed to determine the seroprevalence of anti-HEV IgG in IBD patients receiving advanced therapy, to investigate the association between HEV serostatus and elevated aminotransferase levels over a 12-month follow-up period, and to assess the incidence of chronic HEV infection using both blood and stool PCR testing for HEV RNA. By combining blood tests, molecular methods, and long-term follow-up, the study provides information about the risk of HEV infection in immunosuppressed IBD patients in a European region where HEV is common.

Methods

This observational study was conducted at the Clinic for Gastroenterology and Hepatology, University Clinical Center of Vojvodina, from April 2024 to April 2025. This study was designed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure transparency and completeness in reporting observational research.

The study included patients over 18 years of age with histologically confirmed Crohn's disease (CD) or ulcerative colitis (UC), all of whom had received anti-TNF therapy or tofacitinib for at least six months. A total of 428 patients receiving advanced therapy (anti-TNF, vedolizumab, ustekinumab, tofacitinib) were screened for eligibility. Of these, 286 did not meet the inclusion criteria, primarily due to not receiving anti-TNF therapy or tofacitinib for at least six months. The remaining 142 patients were eligible and consecutively included in the study (Figure S1). The study sample size was determined by the number of eligible patients attending the center during the study period. Approval was obtained from the Ethics Committee of the University Clinical Center Vojvodina, and informed consent was secured from all participants. Data collected from medical records included sex, age, comorbidities (including malignancies), and IBD-related variables such as type of IBD, disease localization and phenotype, age at IBD diagnosis, prior immunomodulatory and biological therapy (including duration and dosage), and extraintestinal manifestations.

All patients completed a structured questionnaire evaluating risk factors for hepatitis E infection (Table S1). The questionnaire addressed consumption of undercooked meat and raw milk, participation in hunting and contact with wild animals, employment in the meat industry, use of well water, connection to the sewage system, travel to rural areas of Asia or Africa within the previous 12 months, residence in collective accommodations or refugee camps, history of blood transfusion or organ/cell transplantation, and employment as a healthcare worker.

Blood sample analyses were conducted at the Center for Laboratory Diagnostics, University Clinical Center of Vojvodina, following established principles of good laboratory practice.

All participants underwent testing for anti-HEV IgG and IgM antibodies, as well as aminotransferase levels, using venous blood samples collected from the cubital vein after an overnight fast of 8–10 h. Serum was separated from whole blood by standard procedures. AST and ALT levels were measured using a spectrophotometric method on the Alinity c automated biochemical analyzer (Abbott, USA) with Abbott reagent kits. IgM and IgG antibodies against HEV were detected using the ELISA method on the Euroimmun I-2P automated analyzer (Euroimmun, Germany) with Euroimmun reagent kits. Participants were followed for 12 months with periodic (every 2–3 months) assessment of liver enzymes.

For participants with positive anti-HEV IgM or IgG antibodies, HEV RNA levels were measured in both

blood and stool samples. Detection of HEV RNA was performed using real-time PCR.

Viral RNA was extracted from blood samples using the GeneRotex 96 automated extractor (Tianlong, China) and the Viral DNA and RNA extraction kit (Tianlong, China). Amplification and detection of RNA were conducted on the Gentier 96 RT-PCR system (Tianlong, China) using the RealStar HEV 15 RT-PCR Kit 2.0 (Altona, Germany).

HEV presence in stool samples (approximately 1 g) was assessed by homogenizing the sample in 1 mL of sterile phosphate-buffered saline (PBS) and applying molecular diagnostic methods. Genomic HEV RNA was extracted from the supernatant of centrifuged, homogenized stool using the *IndiSpin Pathogen Kit* (Indical Bioscience GmbH, Germany) according to the manufacturer's instructions. Prior to extraction, 3 µL of extraction control (Red 500 reactions ref: MDX028, Meridian Bioscience), which also served as an internal control in the subsequent qPCR reaction, was added to each sample (0.2 mL used for extraction). TaqMan-based one-step duplex reverse transcription real-time PCR (RT-qPCR) was performed using the *RNA UltraSense One-Step Quantitative RT-PCR System* (Invitrogen, ThermoFisher Scientific, USA), with primers and probes targeting the highly conserved ORF3 region of the HEV genome and the thermal profile described by Jothikumar et al. (2006). RT-qPCR was conducted in 20 µL reaction volumes containing 5 µL of 5× Reaction Mix, 0.5 µM forward primer HEV-F (5'-GGTGGTTTCTGGGGTGAC-3'), 0.5 µM reverse primer HEV-R (5'-AGGGGTTGGTTGGATGAA-3'), 0.25 µM HEV-P (5'-6-FAM-TGATTCTCAGCCCTTCGC-BHQ1-3'), 0.8 of internal control mix (MDX028, Meridian Bioscience), and 5 µL RNA sample. Thermocycling was performed on the 7500 Fast Real-Time PCR System (Applied Biosystems, ThermoFisher Scientific, USA) with the following conditions: 15 min at 50 °C, 2 min at 95 °C, followed by 45 cycles of 15 s at 95 °C, 20 s at 55 °C, and 35 s at 72 °C.

The primary outcome was HEV seropositivity (anti-HEV IgG). Secondary outcomes included detection of HEV IgM, HEV RNA and liver enzyme abnormalities.

Table 1 Demographic characteristics of study participants. Demographic profile of the study population, including age and sex distribution among patients with Crohn's disease (CD) and ulcerative colitis (UC). Age is presented as mean ± standard deviation (SD) with range. Categorical variables are expressed as number (n) and percentage (%)

Characteristic	Total (*n* = 142)	UC (*n* = 41)	CD (*n* = 101)
Sex, *n* (%)			
Female	66 (46.5)	20 (48.8)	46 (45.5)
Male	76 (53.5)	21 (51.2)	55 (54.5)
Age at inclusion (years) mean ± SD (range)	37.9 ± 13.6 (18–78)		

Variables analyzed included demographic characteristics, disease-related factors, treatment variables, and potential exposure risks. Potential sources of bias include selection bias due to single-center recruitment and recall bias related to questionnaire-based exposure assessment. There were no missing data for the primary or secondary outcome variables.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics, version 28.0. Descriptive statistics summarized the study data. Continuous variables were reported as mean ± standard deviation (SD) for normally distributed data or as median and interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as absolute numbers and percentages. The Shapiro–Wilk test was used to assess normality of continuous variables. Differences between categorical variables were evaluated using the chi-square (χ^2) test. Comparisons of continuous variables were performed using the Mann–Whitney U test for non-normally distributed data. All tests were two-tailed, with statistical significance set at $p < 0.05$.

Results

Demographic characteristics

The study included 142 participants with IBD, of whom 41 had UC and 101 had CD. The gender distribution was balanced across disease types. The mean age at inclusion was 37.9 ± 13.6 years (Table 1).

Inflammatory bowel disease characteristics

The mean age at diagnosis was 29.3 ± 12.3 years. Disease duration ranged from 6 months to 37 years. Bowel resection was performed in 39 participants, all of whom had CD. EIMs were reported in 32 participants (22.5%). All participants received anti-TNF agents during treatment (Table 2).

In most cases (68.3%), CD was diagnosed between the ages of 17 and 40 years. Ileocolonic involvement was the most common localization, observed in 56.4% of cases. In six participants, CD affected both distal and proximal regions of the gastrointestinal tract. The most frequent disease behavior was non-stricturing, non-penetrating, present in 51.5% of CD cases. Perianal disease was observed in one-quarter of participants with CD (Table S2). Among participants with UC, 85.4% had extensive colitis or pancolitis (Table S3).

Risk factors for acquiring hepatitis E infection

The majority of participants (90.8%) reported consumption of undercooked meat. Lack of access to a public sewage system was reported by 21.8% of participants.

Table 2 Inflammatory bowel disease characteristics. Clinical characteristics of patients with inflammatory bowel disease, including age at diagnosis, disease duration, history of bowel resection, presence of extraintestinal manifestations (EIMs), and treatment regimens. Data are presented as mean ± standard deviation (SD) with range or as number (n) and percentage (%). AZA = azathioprine; MTX = methotrexate

Characteristic	Total (*n* = 142)
Age at diagnosis (years), mean ± SD (range)	29.3 ± 12.3 (5–63)
Disease duration (years), mean ± SD (range)	8.8 ± 7.1 (0.5–37)
Bowel resection, *n* (%)	39 (27.5)
EIMs, n (%)	32 (22.5)
Therapy	
Anti-TNF, *n* (%)	142 (100.0)
Vedolizumab, *n* (%)	19 (13.4)
Anti-IL 12/23, *n* (%)	1 (0.7)
Tofacitinib, *n* (%)	2 (1.4)
Azathioprine (AZA), *n* (%)	70 (49.3)
Methotrexate (MTX), *n* (%)	57 (40.1)
Combination therapy (anti-TNF + AZA/MTX), *n* (%)	91 (64.1)

Table 3 Risk factors for acquiring hepatitis E virus (HEV) infection. Self-reported exposure risk factors for HEV infection assessed using a structured questionnaire. Variables include dietary habits, environmental exposures, travel history, and occupational risks. Data are presented as number (n) and percentage (%)

Risk factor	*n*	%
Consumption of undercooked meat	129	90.8
Consumption of raw milk	3	2.1
Hunting	1	0.7
Contact with wild animals	3	2.1
Occupation in a butcher shop	1	0.7
Drinking well water	11	7.7
Access to public sewage system	111	78.2
Travel to endemic regions (Asia or Africa) in the past 12 months	3	2.1
Stay in collective accommodation (prison or refugee camp)	4	2.8
History of blood transfusion	43	30.3
Occupational exposure to patients' blood (healthcare work)	6	4.2

A history of blood transfusion was reported by 30.3% of participants (Table 3).

HEV status

Anti-HEV IgG antibodies were detected in 18.3% of participants (95% CI: 12.3–25.6%). No participants tested positive for anti-HEV IgM antibodies. Additionally, none of the participants with positive anti-HEV IgG antibodies had detectable HEV RNA in blood or stool samples.

HEV seropositivity did not differ significantly between men and women ($\chi^2 = 0.159$, df = 1, $p = 0.690$).

Participants with UC had a significantly higher prevalence of anti-HEV IgG compared to those with CD (29.3% [95% CI: 16–45%] vs. 13.9% [95% CI: 8–22%]; $\chi^2 = 4.628$, df = 1, $p = 0.031$).

Table 4 Treatment duration and hepatitis E virus (HEV) serostatus. Comparison of treatment duration according to anti-HEV IgG serostatus using the Mann–Whitney U test. Mean rank values are presented for each group, along with U statistic, z value, and corresponding p value

Treatment	IGG	Mean Rank	U	z	*p*
Anti-TNF	0	72.86	1350.00	−0.835	0.404
	1	65.42			
Biologic	0	72.27	1419.00	−0.470	0.639
	1	68.08			
AZA	0	73.24	1306.50	-1.140	0.254
	1	63.75			
MTX	0	72.13	1435.50	−0.432	0.666
	1	68.71			
Combined	0	73.26	1304.00	-1.096	0.273
	1	63.65			

No significant associations were observed between HEV seropositivity and patient age at inclusion ($U = 1382.0$, $p = 0.506$), age at diagnosis ($U = 1401.0$, $p = 0.572$), or disease duration ($U = 1432.5$, $p = 0.690$).

Among patients with CD, HEV seropositivity was not associated with age at diagnosis ($\chi^2 = 2.54$, df = 2, $p = 0.280$), disease localization ($\chi^2 = 0.411$, df = 2, $p = 0.814$), disease behavior ($\chi^2 = 0.487$, df = 2, $p = 0.784$), or the presence of perianal disease ($\chi^2 = 2.941$, df = 1, $p = 0.086$). Among patients with UC, HEV seropositivity did not differ according to disease extent ($\chi^2 = 2.632$, df = 2, $p = 0.268$).

Bowel resection was not associated with HEV seropositivity ($\chi^2 = 1.083$, df = 1, $p = 0.298$). Similarly, HEV serological status was not significantly related to the presence of EIMs ($\chi^2 = 1.236$, df = 1, $p = 0.266$).

All participants received anti-TNF therapy. HEV seropositivity was not associated with AZA ($\chi^2 = 0.622$, df = 1, $p = 0.430$), MTX ($\chi^2 = 0.404$, df = 1, $p = 0.525$), or combination therapy ($\chi^2 = 1.450$, df = 1, $p = 0.229$). Treatment duration was also not significantly related to HEV antibody status (Table 4).

Elevated AST and ALT levels were not associated with HEV seropositivity (AST: $\chi^2 = 0.00$, df = 1, $p = 0.990$; ALT: $\chi^2 = 0.10$, df = 1, $p = 0.752$).

No significant associations were observed between HEV seropositivity and patient age at inclusion ($U = 1382.0$, $p = 0.506$), age at diagnosis ($U = 1401.0$, $p = 0.572$), or disease duration ($U = 1432.5$, $p = 0.690$).

None of the risk factors for hepatitis E were significantly related to HEV IgG status (undercooked meat: $\chi^2 = 1.079$, df = 1, $p = 0.299$; public sewage access: $\chi^2 = 0.029$, df = 1, $p = 0.865$; blood transfusion: $\chi^2 = 0.283$, df = 1, $p = 0.595$) (Table 5).

Table 5 Characteristics of study participants according to hepatitis E virus (HEV) serostatus. Comparison of demographic, clinical, laboratory, and exposure-related variables between anti-HEV IgG–negative and anti-HEV IgG–positive participants. Continuous variables are presented as mean ± standard deviation (SD) or as mean ranks where appropriate, and categorical variables as number (n) and percentage (%). Statistical comparisons were performed using chi-square (χ^2) test for categorical variables and Mann–Whitney U test for continuous variables. CD = Crohn's disease; UC = ulcerative colitis; AZA = azathioprine; MTX = methotrexate; EIM = extraintestinal manifestations; AST = aspartate aminotransferase; ALT = alanine aminotransferase

Variable	Total sample (*n* = 142)	anti-HEV IgG negative (*n* = 116)	anti-HEV IgG positive (*n* = 26)	*p*
Demographic characteristics				
Male	76 (53.5%)	63 (82.9%)	13 (17.1%)	0.690
Female	66 (46.5%)	53 (80.3%)	13 (19.7%)	
Age at diagnosis (years)	29.3 ± 12.3	70.58	75.62	0.572
Age at inclusion (years)	37.9 ± 13.6	70.41	76.35	0.506
Disease duration (months)	105.3 ± 85.4	70.85	74.40	0.690
Risk factors for HEV exposure				
Undercooked meat	129 (90.8%)	104 (89.7%)	25 (96.2%)	0.299
Public sewage access	111 (78.2%)	91 (78.4%)	20 (76.9%)	0.865
Blood transfusion	43 (30.3%)	34 (29.3%)	9 (34.6%)	0.595
Liver enzymes				
AST	49 (34.5%)	40 (34.5%)	9 (34.6%)	0.990
ALT	53 (37.3%)	44 (37.9%)	9 (34.6%)	0.752
IBD characteristics				
CD	101 (71.1%)	87 (86.1%)	14 (13.9%)	**.031**
UC	41 (28.9%)	29 (70.7%)	12 (29.3%)	
Bowel resection	39 (27.5%)	34 (29.3%)	5 (19.2%)	0.298
AZA	70 (49.3%)	59 (50.9%)	11 (42.3%)	0.430
MTX	57 (40.1%)	48 (41.4%)	9 (34.6%)	0.525
Combined regime	91 (64.1%)	77 (66.4%)	14 (53.8%)	0.229
EIM	32 (22.5%)	24 (20.7%)	8 (30.8%)	0.266

Discussion

In this study, we evaluated the seroprevalence and clinical significance of HEV infection in IBD patients receiving advanced therapy in Serbia, an endemic European region. Anti-HEV IgG antibodies were detected in 18.3% of participants, while no active or chronic infections were identified by HEV RNA PCR in blood or stool. To our knowledge, data on HEV epidemiology in immunosuppressed IBD patients from this region remain limited. This study provides prospective, region-specific data using both serological and molecular methods, contributing to the existing body of evidence. Moreover, previous studies in IBD populations have been mostly cross-sectional, often limited to serology and blood PCR, without systematic follow-up.

Several European studies have examined the prevalence of HEV infection among patients with IBD, reporting antibody rates comparable to or slightly higher than those observed in the general population. Despite frequent exposure to immunosuppressive therapies, none of these studies identified cases of active or chronic HEV infection or significant liver-related complications. However, the current evidence is limited by small sample sizes, lack of prospective data, and variable study designs, underscoring the need for further research to clarify the epidemiology and clinical implications of HEV infection in this patient population [13–16].

The observed seroprevalence fell within the mid-to-upper range reported in European populations. Meta-analyses indicate that HEV IgG seroprevalence in Europe varies widely, from below 5% to over 20%, depending on regional endemicity and assay type [5, 6]. In Serbia, the seroprevalence among blood donors is estimated to be 15%, suggesting that our cohort of immunosuppressed IBD patients had a comparable exposure risk to the general population [8]. Similar results were obtained in studies from Spain [14] and Germany [13]. In contrast, markedly higher rates have been reported in certain transplant cohorts, confirming that the degree of immunosuppression and local epidemiology influence HEV exposure and persistence [1, 16, 17].

Interestingly, HEV seropositivity in our study was significantly higher in UC patients than in CD patients. This finding should be interpreted cautiously and may reflect sample size limitations or residual confounding rather than a true biological difference. Although all patients received anti-TNF therapy, no association between HEV serostatus and the use of AZA, MTX or combination regimens was found, which is consistent with earlier reports [13, 15]. Biologic therapy alone does not appear to increase HEV acquisition risk; however, profound or combined immunosuppression may favor viral persistence once infection occurs [3, 17].

None of the seropositive participants had detectable HEV RNA in the serum or stool, nor did they show persistent aminotransferase elevation during 12 months of follow-up. This suggests the absence of chronic infection, consistent with previous observations that chronic HEV is uncommon in IBD compared to transplant recipients or patients with hematologic malignancies [2, 17]. Nonetheless, sporadic acute infections may remain clinically silent and underdiagnosed, as most cases are asymptomatic [18, 19]. Given that infliximab, AZA, and MTX can transiently elevate liver enzyme levels [20–22], HEV testing may be useful in patients with unexplained hepatic abnormalities, particularly in endemic regions [11, 12].

No significant correlations were observed between HEV serostatus and known epidemiologic risk factors, such as consumption of undercooked meat, lack of access to public sewage, or prior blood transfusion. This may reflect the high baseline exposure to HEV in the general population, and the limitations of questionnaire-based assessment, such as recall bias and underreporting, are possible [5, 8]. Although parenteral transmission has been described, zoonotic and foodborne routes of transmission remain predominant in Europe [6, 8].

The strengths of this study include the use of both serologic and molecular diagnostics, prospective follow-up, and focus on a well-defined IBD population treated with biologics in an endemic area.

Limitations of the study

This study has several limitations that should be considered when interpreting the findings. First, the single-center design may limit the generalisability of the results to broader IBD populations. Second, the moderate sample size reduces statistical power to detect small differences and may contribute to imprecision in subgroup analyses, including the observed difference between UC and CD patients.

Third, the absence of a matched healthy control group precludes direct comparison with the general population, and therefore conclusions regarding comparable HEV seroprevalence rely on indirect comparisons with previously published data. This may introduce uncertainty in the interpretation of relative exposure risk.

Fourth, exposure data were collected using questionnaire and are subject to recall bias and potential underreporting, which may have attenuated associations between risk factors and HEV serostatus. Additionally, although participants were followed for 12 months, transient or subclinical HEV infections occurring outside sampling time points may not have been detected.

Finally, the observational design does not allow causal inference, and residual confounding from unmeasured variables cannot be excluded. These limitations should be taken into account when interpreting the findings, which are best considered hypothesis-generating.

Taken together, these findings provide additional evidence from an endemic European region that HEV exposure is relatively common but rarely associated with active or chronic infection in IBD patients receiving advanced therapy. These observations are informative and suggest that routine HEV screening may not be necessary in all patients; however, this should be interpreted cautiously given the study design and limitations. These findings should be considered hypothesis-generating and require confirmation in larger, multicenter studies.

Conclusions

The HEV seroprevalence among IBD patients receiving advanced therapy in Serbia was 18.3%, with no evidence of chronic infection. These data emphasize the importance of awareness of HEV as a potential cause of liver enzyme abnormalities in immunosuppressed IBD patients, particularly in endemic areas. Larger multicenter studies with longer follow-up periods and inclusion of healthy controls are needed to clarify the risk determinants and to guide evidence-based screening recommendations.

Abbreviations

HEV	Hepatitis E virus
IBD	Inflammatory bowel disease
CD	Crohn's disease
UC	Ulcerative colitis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-026-04907-1.

Supplementary Material 1: Table S1. Questionnaire on risk factors for hepatitis E virus infection. Table S2. Montreal classification of Crohn's disease. Table S3. Montreal classification of ulcerative colitis.

Supplementary Material 2: Figure S1. STROBE participant flow diagram. Flow diagram showing the number of patients assessed for eligibility, excluded based on predefined inclusion criteria, included in the study, and followed throughout the study period. All eligible participants completed baseline assessment, follow-up, and were included in the final analysis. HEV RNA testing was performed in all seropositive individuals, with no cases of active infection detected.

Acknowledgements

Not applicable.

Authors' contributions

D.D.: design of the study, patient recruitment, writing; J.S.M.: data analysis, writing; T.P.: data interpretation, writing; Ž.S.: literature search, data interpretation; M.K.: data collection, design of the study; V.G.: data collection, data interpretation; M.R.: design of the study, writing. All authors read and approved the final version of the manuscript.

Funding

No specific funding was received.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study protocol obtained approval from the Ethics Committee of the University Clinical Center of Vojvodina (Approval No. 00-322) and adhered to the guidelines of good clinical practice and the Declaration of Helsinki. All participants provided written informed consent before participating in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 6 December 2025 / Accepted: 4 May 2026
Published online: 12 May 2026

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