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Probable Lyme carditis in pacemaker candidates with atrioventricular block: Preliminary results from northern Serbia

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ABSTRACT

Objectives: This study aimed to estimate the proportion of patients with newly diagnosed cardiac conduction disorders requiring pacemaker implantation who have serological findings consistent with probable Lyme carditis in endemic northern Serbia.
Methods: Adults presenting with new conduction disorders and scheduled for permanent pacing were enrolled and provided serum at baseline and 4-week follow-up. Anti-*Borrelia* immunoglobulin (Ig)G was assessed using a two-tier algorithm (enzyme-linked immunosorbent assay screening, immunoblot confirmation). Probable Lyme carditis was defined as IgG seroconversion or stable/rising titers; no Lyme carditis was defined as persistent seronegativity or declining titers.
Results: Of 80 enrolled patients, 74 completed follow-up (92.5%; mean age 71.6 years; 68.9% male). Third-degree atrioventricular block was most frequent (56.8%). Probable Lyme carditis was identified in eight of 74 (10.8%) patients. Of 14 patients who were enzyme-linked immunosorbent assay–reactive/borderline, six (42.9%) were immunoblot-negative. Seropositive patients were older (age 76.3 vs 71.1 years); titers were higher in men at 4 weeks. IgG positivity was associated with suspected Lyme carditis (relative risk 6.8 at baseline; 16.2 at 4 weeks). No participant reported a recent tick bite or erythema migrans.
Conclusion: Approximately one in 10 pacemaker candidates showed serological patterns compatible with probable Lyme carditis. Incorporating two-tier paired serology into evaluation of high-grade conduction disorders in endemic settings may improve etiologic diagnosis and inform management.

Introduction

Lyme borreliosis (LB) is a tick-borne disease caused by pathogenic species of the *Borrelia burgdorferi* sensu lato complex, primarily transmitted through the bites of *Borrelia*-infected *Ixodes* ticks [1]. After inoculation into the skin, pathogenic *Borrelia* can cause localized infection, such as erythema migrans, and/or disseminate to affect various systems, leading to manifestations such as neuroborreliosis, Lyme arthritis, chronic atrophic acrodermatitis, or Lyme carditis (LC) [2].

Recent evidence indicates that climate- and environment-related changes are altering tick seasonal activity and geographic distribution in Europe, with consequent increases in LB risk in multiple regions [3,4]. As human exposure increases, clinicians in endemic areas may more frequently encounter disseminated manifestations, including LC and associated high-grade atrioventricular block (AVB), in which early recognition can influence pacing decisions and antimicrobial management [5].

LC occurs when *Borrelia* invades the heart structures, triggering an intense immune response, predominantly involving lympho-

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cytes and macrophages. It most commonly presents as a conduction disorder, particularly AVB [6], although signs and symptoms can vary depending on the specific areas of the heart affected [7]. Despite its sometimes dramatic presentation, LC is typically self-limiting and resolves within several weeks, with or without antibiotic treatment [7,8].

Cardiac involvement in LB is challenging to diagnose due to the time delay between the tick bite and the symptom onset (i.e. from several weeks to 2 months) [2,7]. Nevertheless, accurate diagnosis can significantly influence the decision on whether a pacemaker placement is necessary [9,10]. Timely and effective detection of LC not only ensures appropriate patient management but also offers economic benefits by preventing potentially unnecessary procedures.

Serbia has been considered endemic for LB since the first cases were reported in 1988 [11]. However, none of the LB stages (e.g. erythema migrans, neuroborreliosis, LC, etc.) are subject to mandatory reporting, and standardized case definitions for its various manifestations are absent [12,13]. Consequently, the incidence of LB, overall and at its specific stages, remains unknown in Serbia.

The primary objective of this observational study was to estimate the proportion of patients with serological findings consistent with probable LC and secondarily describing associated clinical and demographic patterns.

Methods

Ethical declaration

This study received approval from the Commission for Scientific Research and Publications of the Institute for Cardiovascular Diseases of Vojvodina (approval date: June 3, 2023.). The research was conducted in adherence to the principles outlined in the Declaration of Helsinki and complied with the Patient Rights Laws of the Republic of Serbia.

Patient recruitment and serum sampling

Patients eligible for the study presented to the Emergency Department of the Institute for Cardiovascular Diseases of Vojvodina with newly diagnosed conduction disorders (see diagnostics tests and case definitions), scheduled for permanent pacemaker implantation. Nonadherent patients, individuals with a history of conduction disturbances, minors, and pregnant women were excluded from participation. To minimize confounding of serologic kinetics, patients who had initiated antibiotic treatment before enrollment were excluded. After the completion of the initial evaluation in the emergency department, informed consent was obtained and a blood sample was collected using BD Vacutainer SST Tubes (BD, Franklin Lakes, NJ, USA).

All enrolled patients received standard care according to their clinical condition and were invited to return after 4 weeks for a second blood draw. Blood samples were allowed to clot at room temperature and were then centrifuged at 2000 $\times$ g for 10 minutes. The resulting serum was separated and stored at -80°C at the Pasteur Institute Novi Sad. When sampling process was completed, all serum samples were thawed in a single batch and processed/assayed on the same day to ensure analytical consistency (see enzyme-linked immunosorbent assay [ELISA] and immunoblot [IB]-based serological analysis). Figure 1 illustrates the patient selection process, timing of serum sampling, and the subsequent serological analyses. After blood sampling, patients were asked whether they had any tick bites, skin lesions, or outdoor activities in the previous 30 days.

In this cross-sectional study, post-implantation follow-up data were not systematically collected. Any antibiotic regimens administered during the index hospitalization and after pacemaker implantation were not recorded in this exploratory protocol. Clinical decisions regarding pacemaker implantation and management were made independently of *Borrelia* serology and were not influenced by the study findings.

Diagnostic tests

All patients enrolled in the study were managed according to standard hospital diagnostic protocols before pacemaker implantation. Upon admission and during the index hospitalization, the following data were collected: (i) demographic characteristics; (ii) clinical data on symptoms and signs; (iii) International Classification of Diseases–coded admission diagnoses; and (iv) in-hospital clinical data used to assess eligibility for study inclusion.

Case definitions

The diagnosis of conduction system disorder was made based on current guidelines on cardiac pacing and cardiac resynchronization therapy [14]. Diagnoses were established before hospitalization based on standard electrocardiography (ECG) and/or 24-hour ECG Holter monitoring or loop recorder recordings.

All subjects in the study group underwent a standard hospital at-rest 12-lead surface ECG recorded on a ECG machine (SCHILLER AG, Baar, Switzerland; Cat No. AT-102) at a paper speed of 25 mm/s and gain of 10 mm/mV. The ECG parameters were measured manually by using a graduated lens to confirm the diagnosis. Standard two-dimensional echocardiography was performed to evaluate cardiac morphology and exclude potential secondary causes of conduction system disturbances.

ELISA and IB-based serological analysis

Serum samples were heat-inactivated at 56°C before seroreactivity detection. Commercial ELISA kits were used for anti-*Borrelia* spp. immunoglobulin (Ig)G reactivity (recomWell *Borrelia* IgG, Mikrogen Diagnostik GmbH, Neuried, Germany, Cat. No. 4204). The kits include OspC and VlsE antigens from *B. burgdorferi* sensu stricto (s.s.), *Borrelia garinii*, and *Borrelia afzelii*. Assays followed the kit instructions and were validated using the provided controls. Results were interpreted qualitatively (positive/negative). Values <20 units/mL were negative and >24 units/mL positive, whereas values between 20 and 24 IU/mL were considered as borderline. Units/mL were calculated from optical density at 450 nm.

All samples that showed reactivity against *Borrelia* antigens were analyzed via IB assay (recomLine *Borrelia* IgG, Mikrogen diagnostik, Germany, Cat. 4273). The second-tier test allowed detection of IgG specific to the proteins p100, VlsE, p58, p41 (flagellin), p39, OspA, four strain-specific OspC proteins (from *B. burgdorferi* s.s., *B. afzelii, B. garinii*, and *Borrelia spielmanii*), and five strain-specific p18 antigens (from *B. burgdorferi* s.s., *B. afzelii, B. garinii, B. spielmanii*, and *B. bavariensis*), using a commercial IB-based assay. First- and second-tier tests were performed and analyzed according to the manufacturer's instructions.

After paired serology results were obtained, enrolled patients were classified into two categories: probable LC and no LC. Probable LC was defined as (i) seroconversion to *Borrelia*-specific IgG (ELISA +, IB+) between the first and second samples or (ii) persistent IgG positivity with a stable or rising IgG level in the second sample. The no LC group included patients who remained IgG-negative in both samples or demonstrated declining IgG levels, that is higher IgG levels in the first compared with the second sample.

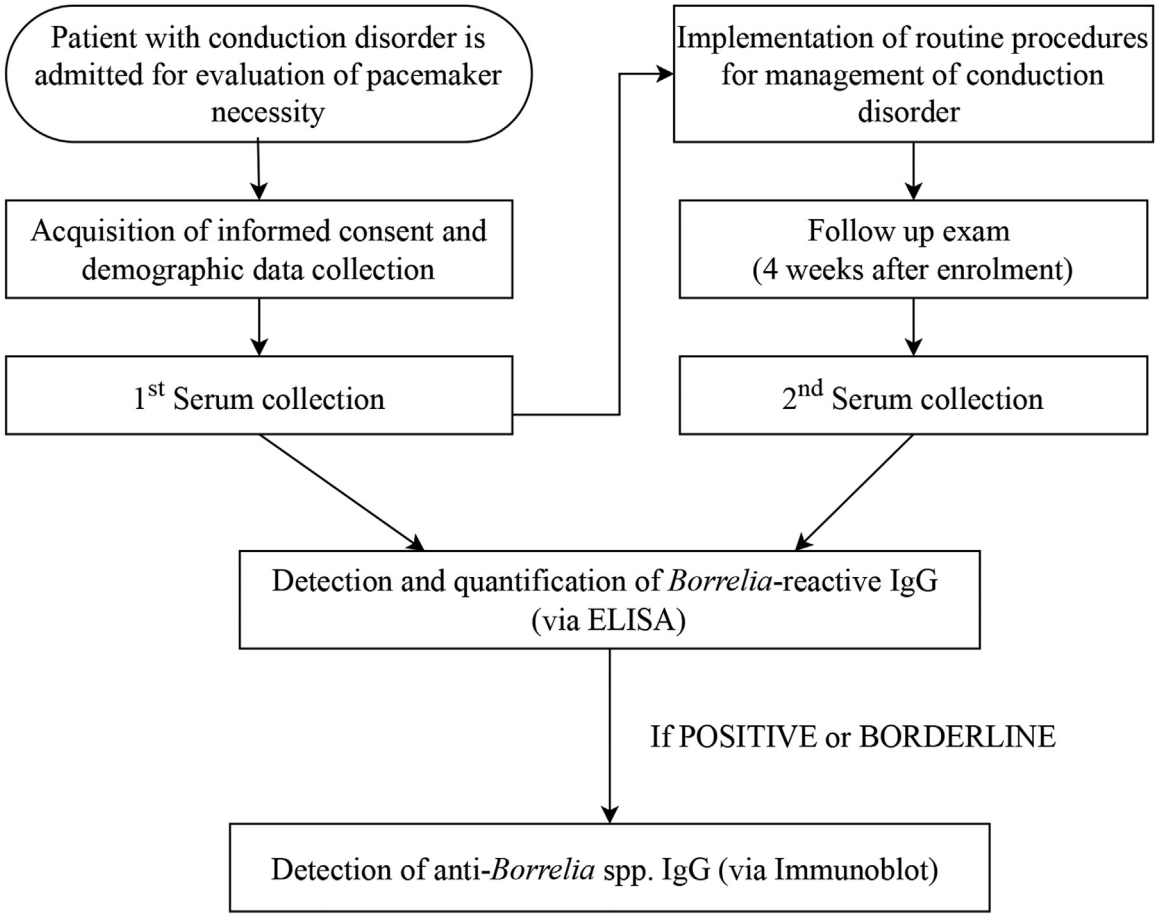

Figure 1. Study flowchart. The flowchart was generated using the open-source software draw.io (https://app.diagrams.net/). ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin.

Statistical analysis

The percentage (%) and 95% confidence interval (CI 95%) calculations, as well as analysis of variance, relative risk (RR) analysis, and Student's *t*-test, were performed using GraphPad Prism v.8.0.1 (GraphPad Software Inc., La Jolla, CA, USA). Statistical significance was considered when $P < 0.05$.

Results

Participant enrollment

During the period from March 13, 2023 to November 25, 2024, informed consent for study participation was obtained from 80 individuals, of whom 74 adhered to follow-up and a second blood sampling (74 of 80; 92.5%).

Demographics of enrolled patients

The examined cohort predominantly consisted of men (51 of 74; 68.92%), whereas women were less frequent ($P = 0.0291$). The mean age of enrolled individuals was 71.62 years (95% CI: 69.36-73.87 years). Although men were, on average, older than women (72.14 years [95% CI: 69.57-74.71] vs 70.54 years [95% CI: 65.84-75.25]), the difference was not statistically significant ($t = 0.6618$, $df = 71$, $P = 0.5103$).

Patients examined in this study reported residence in 27 municipalities, located mainly in the northern province of Vojvodina and the Mačva District (Figure 2). The highest number of patients resided in the municipalities of Novi Sad (20 of 74; 27.02%), Bečej (eight of 74; 10.81%), and Bačka Palanka (five of 74; 6.75%).

The most common diagnosis among the enrolled patients was third-degree AVB (42 of 74; 56.75%), followed by second-degree AVB (16 of 74; 21.62%). Left anterior fascicular block and trifascicular block were each diagnosed in four patients (four of 74; 5.40%). Other conduction disorders, including right fascicular block, bifascicular block, and sick sinus syndrome, were recorded only sporadically.

None of the patients reported recent tick infestation or skin lesions within 30 days of each examination.

*Anti-*Borrelia *spp. antibodies and their association with demographic factors*

Anti-*Borrelia* spp. IgG was detected in 11 (11 of 74; 14.86%) and 10 (10 of 74; 13.51%) samples acquired on the day of enrollment (i.e. sample 1) and 4 weeks later (i.e. sample 2), respectively. Borderline findings were detected during follow-up in four individuals (four of 74; 5.40%). We found no statistically significant difference in the rate of individuals who were seropositive in relation to time of sampling ($P > 0.05$).

Among 14 individuals who yielded positive or borderline reactivity at screening stage (ELISA), specific anti-*Borrelia* IgG was confirmed via IB in eight cases (eight of 74; 10.81%), whereas false-positive ELISA finding occurred in six cases (six of 14; 42.85%) (Figure 3). According to our predefined criteria, eight of 74 (10.8%) patients were classified as having probable LC, whereas 66 of 74 (89.2%) were classified as no LC.

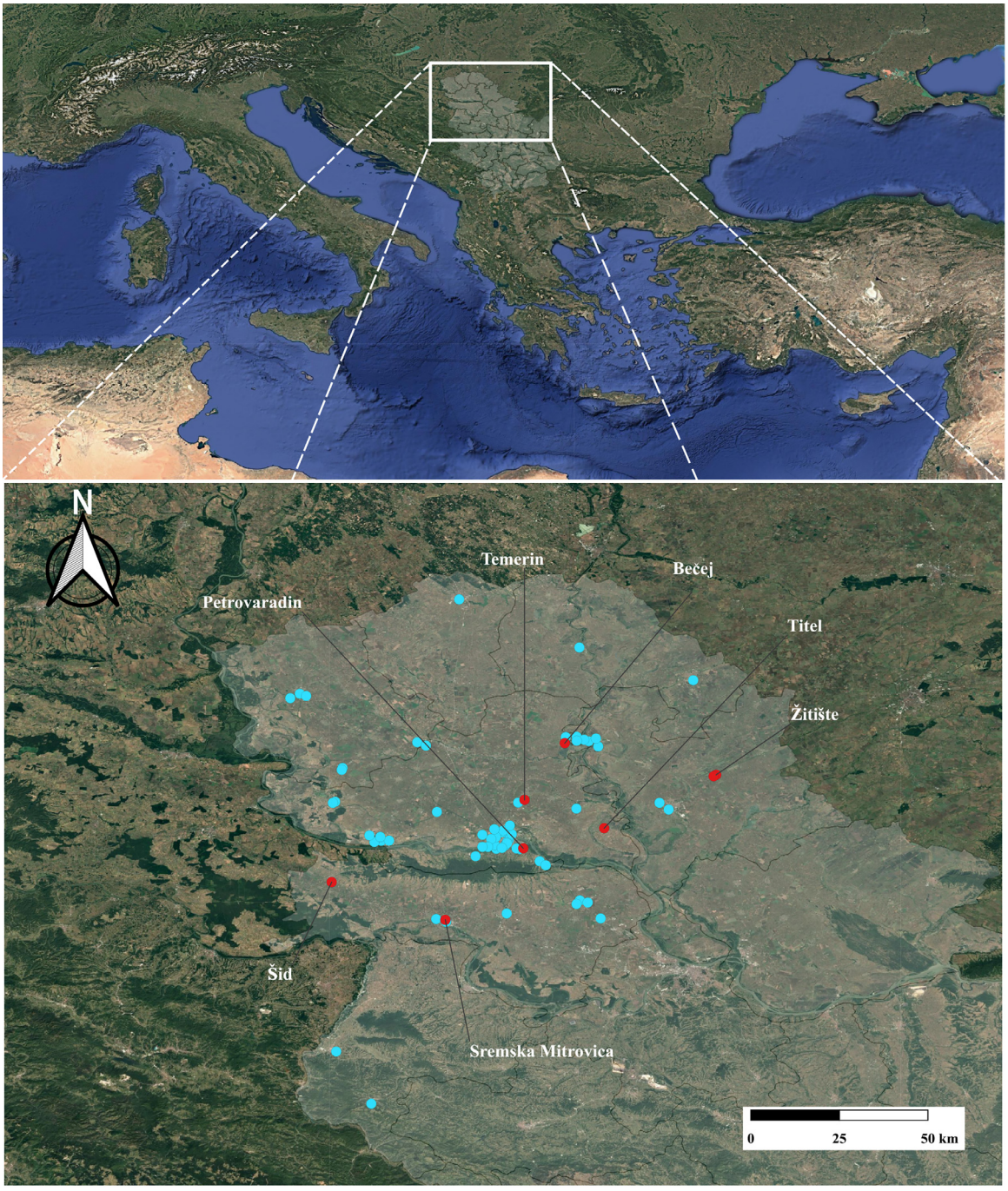

Figure 2. Map of Balkans, Asia Minor, and southeast Europe, highlighting the region of North Serbia. Blue dots represent residences of patients without anti-*Borrelia* spp. immunoglobulin G. Red dots represent residences of patients with anti-*Borrelia* spp. immunoglobulin G (western Blot confirmed). The Serbian shape file for mapping is available at the GADM database of Global Administrative Areas (v4.1, July 2022, https://gadm.org/). The map was generated using QGIS v3.32 (QGIS Development Team, 2023) and Goggle Quick Map Services.

Individuals with anti-*Borrelia* IgG had a significantly higher average age (76.29 years [95% CI: 73.01-79.56]) compared with patients who were seronegative (71.12 years [95% CI: 68.66-73.58]) ($t = 2.839$, $df = 19.12$, $P = 0.0104$) (Figure 4a).

Comparing anti-*Borrelia* IgG titers, men exhibited higher reactivity than women on the day of enrollment (i.e. sample 1) (22.20 IU/mL [95% CI: 13.83-30.57] vs 12.48 IU/mL [95% CI: 10.26-14.70]) and 4 weeks later (i.e. sample 2) (31.53 IU/mL [95% CI: 19.89-43.17] vs 13.35 IU/mL [95% CI: 10.44-16.26]) (Figure 3c). No statistically significant difference was observed between men and women at enrollment ($t = 1.615$, $df = 71$, $P = 0.1107$). However, a statistically significant difference emerged after 4 weeks ($t = 2.175$, $df = 71$, $P = 0.0329$) (Figure 4b).

In addition, patients with elevated anti-*Borrelia* IgG at their initial presentation to the Institute for Cardiovascular Diseases of Vojvodina Emergency Department exhibited a substantially elevated likelihood of suspected LC, corresponding to an almost 7-fold increase in risk (RR = 6.8, $P < 0.001$) (Figure 4c). This association remained robust in samples collected 4 weeks later because individuals who were seropositive demonstrated an approximately 16-fold higher risk of suspected LC compared with their seronegative counterparts (RR = 16.2, $P < 0.0001$) (Figure 4c).

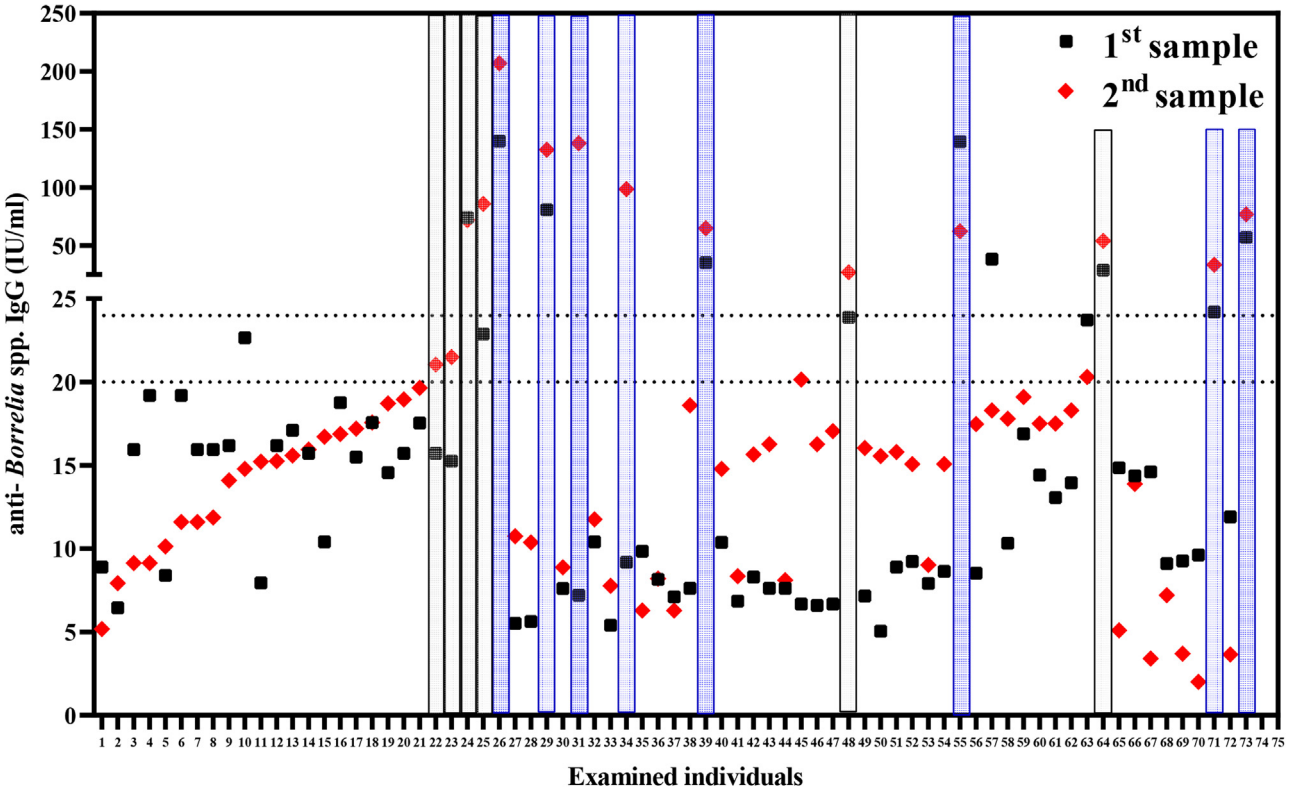

Figure 3. Titer of anti-*Borrelia* spp. IgG in patients with heart conduction disorder. Blue bars mark individuals with a positive western blot reaction (true-positive ELISA finding). Gray bars mark patients with a negative western blot reaction (false-positive ELISA finding). Dotted lines mark upper and lower threshold values for ELISA. ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin.

From an administrative perspective, the highest seropositivity rates were observed in the municipalities of Žitište (two of two; 100%), Šid (one of one; 100%), Titel (one of one; 100%), Temerin (one of two; 50%), Sremska Mitrovica (one of three; 33.33%), Petrovaradin (one of three; 33.33%), and Bečej (one of seven; 14.28%) (Figure 2). Although Novi Sad had the highest number of reported residents, no individuals who were seropositive were identified there (zero of 20; 0%).

Regarding the type of conduction disorder, the highest average reactivity to *Borrelia* antigens on the first examination day (sample 1) was observed in patients with trifascicular block (54.50 IU/mL [95% CI: 0.00-151.1]) and third-degree AVB (18.42 IU/mL [95% CI: 10.76-26.08]). In contrast, the lowest average reactivity was recorded in individuals with first-degree AVB and left anterior fascicular block, at 15.07 IU/mL (95% CI: 6.74-23.39) and 13.94 IU/mL (95% CI: 6.75-21.14), respectively.

A total of 4 weeks later (sample 2), the highest average reactivity was observed in patients with left anterior fascicular block (46.23 IU/mL [95% CI: 0.00-143.7]) and trifascicular block (43.52 IU/mL [95% CI: 0.00-92.28]). In addition, average reactivity levels exceeding the upper cut-off value of 24 IU/mL were recorded in patients with second-degree AVB (27.19 IU/mL [95% CI: 12.42-41.96]), whereas those with third-degree AVB showed slightly lower reactivity (23.71 IU/mL [95% CI: 12.33-35.09]).

No statistically significant differences (F [4,22] = 0.6052, P = 0.6630) in reactivity to *Borrelia* spp. were observed between groups either at baseline (sample 1) or at the 4-week follow-up (sample 2). Among individuals in whom the presence of anti-*Borrelia* IgG was confirmed, complete AVB was the most common diagnosis (five of eight; 62.5%), followed by trifascicular block (two of eight; 25%) and second-degree AVB (one of eight; 12.5%).

Discussion

To assess the prevalence of probable LC, we examined patients with conduction disorders who were scheduled for permanent pacemaker implantation at the regional Institute for Cardiovascular Diseases. The analysis included detection of anti-*Borrelia* IgG and evaluation of IgG titer kinetics over a 4-week follow-up period. Our findings suggest that approximately 10% of these patients may have had LC as a potential underlying cause. This proportion is comparable to reports from the United States (11%) [15] and Poland (12%) [16] but substantially higher than that reported in Sweden (0.12%) [10]. The discrepancy with the Swedish nationwide registry-based analysis [10] should be interpreted with caution because the study designs are not directly comparable. More precisely, the Swedish work estimated population-level incidence and evaluated pacemaker implantation as an outcome at the national level, whereas our study estimates the proportion of serologically probable LC among pacemaker candidates with conduction disorders in a single regional center.

Beyond within-country differences in ascertainment and case definitions, variability in LB epidemiology may also reflect *Borrelia* genospecies composition. In North America, LB is predominantly caused by *Borrelia burgdorferi* s.s., whereas Europe has a more diverse distribution, most commonly *B. afzelii* and *B. garinii* [12,17]. It has been hypothesized that *B. burgdorferi* s.s. may be relatively more cardiotropic than the genospecies prevalent in Europe, although evidence remains limited [10]. Because our study was based on serologic assays, future studies incorporating genospecies-resolved diagnostics would be valuable [10].

In the absence of formal national or regional guidelines for the management of LC, Besant et al. [18] developed the suspicious index in LC, a tool derived from reports of 88 LC cases. We did not

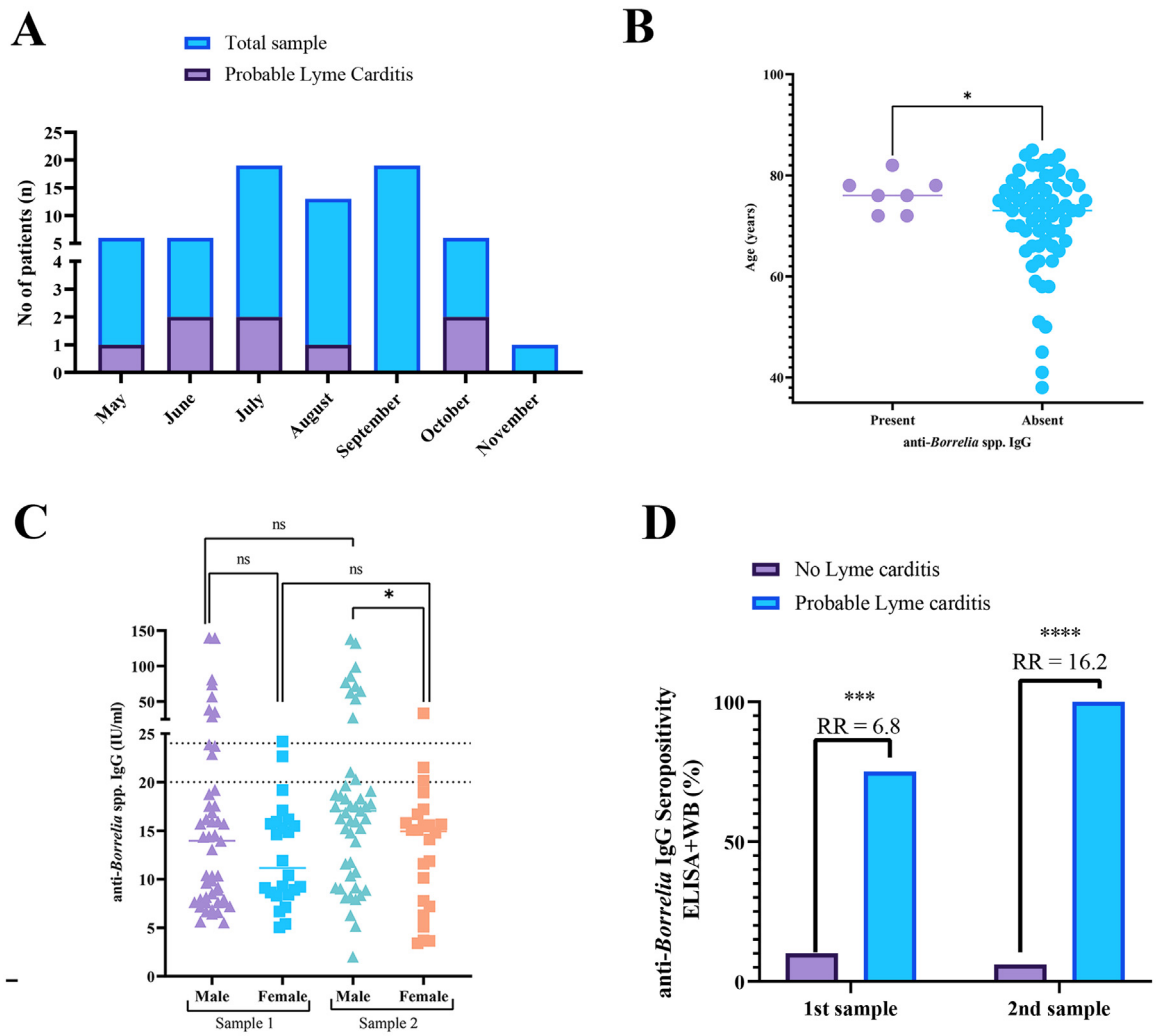

Figure 4. Prevalence of anti-*Borrelia* spp. IgG in individuals with conduction disorders. (a) Age comparison between seropositive (WB-confirmed) and seronegative individuals; (b) gender-based comparison of anti-*Borrelia* IgG titer in sera collected on first examination day (sample 1) and 4 weeks later (sample 2); (c) RR of suspected Lyme carditis by anti-*Borrelia* IgG status at baseline and 4-week follow-up. Patients who were IgG-positive had a higher risk at initial presentation (RR = 6.8) and an even stronger association at follow-up (RR = 16.2).
ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; ns, not significant; RR, relative risk; WB, western blot.
$^{*}P$ <0.05; $^{***}P$ <0.001; $^{****}P$ <0.0001.

apply the suspicious index in LC score in our cohort because several key criteria were inapplicable: all patients were older than 50 years, none reported a tick bite or rash, and the criterion "outdoor activity/living in an endemic area" lacked discriminatory value because the entire northern province of Serbia is considered endemic for LB [13].

In our study, patients suspected of LC were significantly older than those in the non-LC group and in similar age group as patients with rhythm disorders in France [19]. The findings from Poland showed the opposite pattern, with patients with LC being younger than patients without LC [16], whereas reports from Sweden describe patients with LC of similar age to those observed in our cohort [10]. Studies from the United States show greater variability, with one cohort reporting a mean age of 51 years and another reporting a mean age of 75.8 years, highlighting that older age can be used as predictor of LC in hospitalized patients [15]. Although the age of our cohort is similar to that of patients with rhythm disorders elsewhere in Europe [19], the age distribution of enrolled patients represents a limitation of this study because younger adults and adolescents with conduction disorders were not assessed.

With respect to sex, we found that most patients with conduction disorders and probable LC were men (51 of 74 [68.9%] and seven of eight [87.5%], respectively). Although men are more frequently diagnosed with conduction disorders in general [19], a similar male predominance among patients with LC has been consistently reported, with a male-to-female ratio of approximately 3:1 [10].

Our findings are consistent with previous studies from Europe and the United States, in which third-degree AVB, followed by second-degree AVB, predominated in the overall study population and among patients with LC [15,16]. Given the small number of patients in each conduction subgroup and the wide CIs, these findings should be interpreted with caution and regarded as hypothesis-generating. Larger, preferably multicenter, studies would be needed to determine whether specific conduction patterns, such as trifascicular block, carry a higher probability of LC and might, therefore, merit prioritized etiological investigation.

The pronounced variability in seropositivity between municipalities, with clustering of positive cases in some smaller communities and complete absence of seropositive patients from Novi Sad may require additional examination. Although these patterns may partly

reflect the small sample size and random variation, they may also indicate local micro-foci of *Borrelia* transmission related to specific ecological conditions, occupational exposures, or recreational behaviors. Linking clinical data from pacemaker centers with entomological surveillance and population-based seroprevalence surveys could help to identify high-risk areas more precisely and support targeted public health interventions, such as tailored education on tick bite prevention and early recognition of LB manifestations.

This study has several strengths. It was conducted prospectively at a regional pacemaker center with a large catchment area, included systematic paired serology, and applied a standardized two-tier serological algorithm with centralized laboratory analysis. These features reduce analytical variability and increase internal consistency.

A key limitation of this study is that we could not determine whether the detected anti-*Borrelia* IgG antibodies reflected a recent, unrecognized tick bite, or an active infection. Because none of the patients reported a tick bite at baseline or during follow-up, and no skin lesions were documented, we lack direct clinical evidence of active LB in any of the examined patients and our classification of probable LC relies on serology and clinical context.

In addition, sample size was modest and derived from a single tertiary center, which may limit the generalizability of our results because patterns of tick exposure and clinical practice may differ in other regions of Serbia. Second, we did not systematically record or adjust for comorbidities and concomitant medications that might influence susceptibility to conduction disease and the immune response to *Borrelia*.

It remains possible that some of the detected IgG reflected recent exposure that did not progress to clinically manifest disease and was cleared during the early phase of skin colonization. From a diagnostic standpoint, our use of paired sera and a two-tier serological algorithm (ELISA screening, followed by IB confirmation) was designed to maximize specificity for LC in a population with relatively high background exposure to *Borrelia* [12,13,20,21]. By differentiating between seroconversion or stable/rising IgG titers and declining IgG titers over a 4-week interval, we sought to minimize misclassification of patients with remote, past infection that could generate *Borrelia*-reactive IgG [22]. Future studies with longer follow-up intervals before permanent pacemaker implantation may help to better optimize this balance between sensitivity and specificity.

In the context of pacemaker practice, this study provides preliminary findings suggesting that a non-negligible proportion of patients with conduction disorders requiring permanent pacing may have LC as an underlying, potentially reversible cause. In real-world settings, however, the need for urgent pacing in patients with high-grade AV block limits the possibility of postponing device implantation until the etiological workup is completed [23]. From a management perspective, current guidance emphasizes that conduction disturbances attributable to LC are typically reversible and that intravenous ceftriaxone should be initiated after actively assessing for other LB manifestations and excluding alternative causes of cardiac abnormalities [2]. These recommendations underscore the clinical relevance of systematic etiologic evaluation for LC in pacemaker candidates from endemic regions because early recognition may support temporary pacing strategies and reduce potentially avoidable permanent device implantation in selected patients.

In addition, generation of systematic documentation of LC in pacemaker recipients can improve epidemiologic surveillance and ultimately contribute to the development of regional diagnostic and management algorithms in Serbia, as well as in other Balkan countries endemic for LB. This study provides preliminary hypothesis-generating evidence that supports continued prospective enrollment and broader, systematic LC surveillance within Serbian pacemaker centers.

Declaration of competing interest

The authors have no competing interests to declare.

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Author contributions

Dragana Gazibara (D.G.), Verica Simin (V.S.), Ivana Bogdan (I.B.), Aleksandra Milovančev (A.M.), Aleksandar Redžek (A.R.), Dragan Kovačević (D.K.), Pavle Banović (P.B.). Conceptualization: D.G., P.B. Methodology: D.G., V.S., I.B., P.B. Investigation: A.M., A.R., D.K., V.S., I.B. Data curation: D.G., A.M., A.R., D.K., V.S., I.B. Formal analysis: D.G., P.B. Visualization: D.G. Writing – original draft: D.G. Writing – review & editing: D.G., V.S., I.B., A.M., A.R., D.K., P.B. Supervision: P.B. Project administration: D.G., P.B. All authors have read and agreed to the published version of the manuscript.

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