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Received: 7 May 2023 | Revised: 28 January 2024 | Accepted: 15 February 2024

DOI: 10.1111/zph.13119

REVIEW

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Discrepancy between IDSA and ESGBOR in Lyme disease: Individual participant meta-analysis in Türkiye

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Abstract

Background: The evidence on the prevalence of Lyme borreliosis (LB) is limited, but there is a suspicion of overdiagnosis of LB in recent years. We reviewed the LB diagnosis and treatment-related data in Türkiye, based on the Infectious Diseases Society of America (IDSA) 2020 and European Society of Clinical Microbiology and Infectious Diseases Study Group for Lyme Borreliosis (ESGBOR) 2018 guidelines. By detecting the disagreements between these two, we outlined the areas to be improved for future guidelines.

Methods: We performed a literature search according to the PRISMA guidelines in PubMed, Ovid-Medline, Web of Science, Turkish Medline, Scopus, CINAHL, ULAKBIM TR Index, Google Scholar and Cochrane Library databases. We included the published cases in a database and evaluated according to IDSA and ESGBOR guidelines. We outlined the reasons for misdiagnoses and inappropriate uses of antibiotics.

Results: We included 42 relevant studies with 84 LB cases reported from Türkiye between 1990 and December 2022. Among 84 cases, the most common clinical findings were nervous system findings ($n=37$, 44.0%), erythema migrans ($n=29$, 34.5%) and ophthalmologic findings ($n=15$, 17.9%). The IDSA 2020 and ESGBOR 2018 guidelines agreed on the diagnosis of 71 (84.5%) cases; there was an agreement that 31 cases (36.9%) were misdiagnosed and 40 cases (47.6%) were correctly diagnosed, and there was disagreement for 13 cases (15.5%). Serum immunoglobulin M (IgM), IgG measurements by ELISA and western blot were widely performed, and they were effective in definitive diagnosis merely when used according to guidelines. Inappropriate use of antibiotics was detected in 42 (50.0%) of cases which were classified in the following categories: incorrect LB diagnosis, inappropriate choice of antibiotic, inappropriate route of drug administration and prolonged antibiotic treatment.

Conclusion: Overdiagnosis and non-adherence to guidelines is a common problem. The discordance between seroprevalence and clinical studies necessitates a consensus over the best clinical approach.

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KEYWORDS
Borrelia burgdorferi, borreliosis, erythema migrans, lyme borreliosis, lyme disease, medical overuse, tick bite, tick-borne diseases

1 | INTRODUCTION

Lyme disease or Lyme borreliosis (LB) is a multi-system infection caused by tick bites infected with *Borrelia burgdorferi* sensu *lato* species. It is the most common infection that is transmitted via tick bites in most of the Northern Hemisphere (Stanek et al., 2012) and affects hundreds of thousands of people living in temperate regions of North America and Eurasia (Lantos et al., 2021).

Even in endemic areas, models predict that people who are bitten by an *Ixodes* spp. tick has a low chance of *B. burgdorferi* (2.5%–4.6%) even if the tick tests positive (des Vignes et al., 2001; Hojgaard et al., 2008; Lantos et al., 2021). Overdiagnosis based on false-positive antibody tests has been previously described in adult (Seriburi et al., 2012) and paediatric (Lantos et al., 2016) practices within endemic areas. On the other hand, even though the USA requires notification of Lyme Disease, it is suspected to be underreported (Henry et al., 2011; Naleway et al., 2002). To prevent errors in diagnosis and treatment, Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases Study Group for Lyme Borreliosis (ESGBOR) have published Clinical Practice Guidelines (CPGs) on LB.

The first LB case in Türkiye was reported in 1990 (Köksal et al., 1990a). LB has been endemic in the forestlands of Türkiye and the infection was commonly observed during the spring and summer seasons (Öztürk, 2019). The IgG seroprevalence of LB in the general population was reported to be between 4 and 14.5% in various cities (Aslan Başbulut et al., 2012; Bucak et al., 2016; Cora et al., 2017). In Samsun, northeastern site of Türkiye, *B. burgdorferi* seroprevalence is 4% (Aslan Başbulut et al., 2012) and in Düzce, which is in northwest region, the seroprevalence is 10.9% among farmers (Kaya et al., 2008). On the contrary, Van, which is among the risky areas in the eastern side of Türkiye, is not endemic to *B. burgdorferi* according to the two-tier antibody testing (Parlak et al., 2015).

Yet, seropositivity does not translate into LB directly, as the true prevalence is estimated to be higher since LB is not a notifiable disease in Türkiye and the disease is little to no known by physicians (Kılıç et al., 2011). Recent metanalysis indicates the prevalence of *B. burgdorferi* in ticks to be 2.8% (0.7–6.5%) for Türkiye, and the most common *B. burgdorferi* infected ticks were reported to be *Haemaphysalis* (50%) and *Ixodes* (30%). *Ixodes* genus had the highest *B. burgdorferi* infection rates (16%) compared to other genera (Ji et al., 2022). Interestingly, a study on ticks in Istanbul found out that only 1.5% of ticks were infected with *B. burgdorferi* (Polat et al., 2021).

Lyme borreliosis incidence varies among countries in Europe. The countries with the highest LB incidence rates of more than 100 cases per 100,000 people per year (PPY) are Belgium, Finland, Netherlands and Switzerland. In contrast, the Czech Republic, Germany, Poland, Scotland, Belarus, Croatia, Denmark, France, Ireland, Portugal, Russia, Slovakia, Sweden and the United Kingdom reported incidence rates of less than 40/100,000 PPY. (Burn et al., 2023)

Impacts

- There is a 15.5% discrepancy in the diagnosis of Lyme borreliosis according to the IDSA and ESCMID guidelines.
- About half of the cases were misdiagnosed, and half of the patients were given inappropriate antibiotic regimens according to the guidelines.
- Neuroborreliosis is the most common manifestation of Lyme borreliosis leading to misdiagnosis.

Lyme disease incidence is 35,000 cases per year in the USA according to Centers for Disease Control and Prevention (Chung et al., 2023), whereas insurance data indicate an incidence of 476,000, which includes asymptomatic and mild cases as well (Kugeler et al., 2021). Furthermore, 85,000 Lyme cases in Europe (Rego et al., 2019), and in another source, more than 200,000 cases per year in western Europe (Marques et al., 2021) are documented each year. However, as Lyme borreliosis is not a notifiable disease in many countries of Europe, including Türkiye, the number is expected to be underestimated (Smith & Takkinen, 2006). Interestingly, however, Turkish media reports a high number of Lyme borreliosis cases, emphasizing the importance of checking if the Turkish cases were correctly identified according to CPGs.

The clinical signs of LB are thought to vary depending on the infectious genospecies in a given region (Ji et al., 2022; Strnad & Rego, 2020). LB in Europe is known to be caused by *B. burgdorferi* sensu stricto, *Borrelia afzelii*, *Borrelia garinii*, *Borrelia bavariensis* and *Borrelia spielmanii* (Stanek et al., 2012), whereas in the USA, it is most commonly caused by *B. burgdorferi* sensu stricto and *Borrelia* mayonii (Pritt et al., 2016). In both cases, the most commonly observed clinical manifestation is erythema migrans (EM). In Europe, this early manifestation is caused by *B. afzelii* generally expands more slowly than in the USA in patients with *B. burgdorferi*-caused EM (Stanek et al., 2011).

B. burgdorferi is most frequently linked to arthritis, *B. garinii* and *B. Bavariensis* to neuroborreliosis (Strle et al., 2006), and *B. afzelii* to a variety of skin disorders such acrodermatitis chronica atrophicans (ACA) or borrelial lymphocytoma (Maraspin et al., 2016). There are distinct variances in clinical presentation and invasiveness within members of the same species. According to Jungnick et al., *B. burgdorferi* species from Europe causes neuroborreliosis more commonly than *B. burgdorferi* from the USA. (Jungnick et al., 2015)

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We aimed to review the LB diagnosis and treatment data in Türkiye, based on IDSA 2020 (Lantos et al., 2021) and ESGBOR 2018 (Dessau et al., 2018) guidelines and by detecting the disagreements between these CPGs we aimed to support areas to be improved for future guidelines.

2 | MATERIALS AND METHODS

2.1 | Data source and strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Liberati et al., 2009) were followed in this meta-analysis.

A systematic literature review was performed using PubMed, Ovid-Medline, Web of Science, Turkish Medline, Scopus, CINAHL, ULAKBIM TR Dizin, Google Scholar and Cochrane Library databases (Table S1). The studies published in a peer-reviewed journal in Turkish or English between 1990 to December 2022 were included. The search criteria were designed and the literature search was performed by two authors (A.B.Y. and E.C.).

2.2 | Selection of cases: inclusion and exclusion criteria

All the reports of LB from Türkiye including retrospective studies, case reports, and case series with suspected Lyme were included. The symptoms, diagnosis criteria, and medications of all given individual cases were recorded. Cases in which tick bites occurred or were diagnosed outside Türkiye were excluded from the study.

Two authors (A.B.Y. and E.C.) screened the abstracts and titles of studies accessed through the above-mentioned search platforms. Bibliographies of relevant articles were also scanned. Selected studies were reviewed (by A.B.Y. and E.C.) for compliance with the inclusion criteria. Full texts of the selected studies were independently evaluated by A.B.Y. and E.C. Data extraction was performed by two authors (A.B.Y. and E.C.), with the extracted information being study characteristics (author, study design, article, year), patient information (age, gender, city, known tick bite experience), specific features of LB (EM, atypical skin lesions), arthritis; eye, cardiac, nervous system findings, chronicity, ACA, serum IgM and IgG levels measured with ELISA and Western Blot, serum antibodies to Borrelia antigens such as IgM OspC, VlsE, p41 and IgG p100, p17/p18 in blood detected by Western Blot, and antibiotic use.

2.3 | Criteria: lyme diagnosis and medical treatment

A structured case definition referring to the IDSA 2020 Clinical Practice Guidelines (Lantos et al., 2021) and ESGBOR 2018 position paper form (Dessau et al., 2018) was used to structure the diagnosis criteria and treatment options. Table 1 highlights the major differences in the two CPGs.

2.4 | Statistical analysis

We used STATA version 17 for statistical analysis (Stata Statistical Software. College Station, TX: StataCorp LP.). Non-normally distributed variables were summarized with the medians and interquartile ranges, normally distributed variables were summarized as means and standard deviations, and categorical variables were shown as frequencies and percentages.

3 | RESULTS

The study selection process (Figure 1) resulted in a total of 84 cases from 42 studies (Table 2). The cases were distributed favouring the west side of Türkiye and were concentrated around Istanbul, Ankara, Hatay and Bolu (Figure 2). Age of patients was distributed with a wide range from 2 to 76 years of age with a mean of 29.2 years (Table 3). History of tick bite was present in 45 (53.6%) of cases. EM, the most specific clinical finding for LB, was observed in 29 (34.5%) cases, whereas skin findings other than EM and ACA were only observed in 14 (16.7%) patients (Table 3). Arthritis (8.3%), carditis (2.4%) and ACA (1.2%) were other important features that strengthened diagnosis (Table 3). A total of 37 patients had nervous system findings, including 8 acute polyneuropathy, 6 facial paralysis, 6 motor and sensory changes and 4 encephalitis cases (Table 4). Approximately 17.9% of the cases had ophthalmologic features, most commonly uveitis (4 patients) and papilledema (3 patients) (Table 4).

Immunoglobulin status specific to LB was the most commonly used method of testing with 72.5% of IgM-positive cases and 69.0% of IgG-positive cases via ELISA. The cases diagnosed with only IgM positivity without IgG positivity were early cases within 6 weeks after the tick bite. About 51.2% of cases had blood IgM and/or IgG positivity that was tested with western blot (Table 3). Another method was two-tier testing, which detected the presence of antibodies to Borrelia antigens such as IgM OspC, VlsE, p41 and IgG p100, p17/p18 in blood and it was used in 6 cases.

Antibiotic use was evaluated according to the IDSA 2020 antibiotic prescription guidelines for LB. Antibiotics were given to LB cases; but 42 patients (50.0%) were given inappropriate antibiotics, mostly due to incorrect diagnosis (34 patients), inappropriate antibiotic choice (5 patients), inappropriate antibiotic choice and inappropriate route of administration (2 patients), and prolonged duration of treatment (1 patient) (Table 5).

Two major guidelines, IDSA 2020 and ESGBOR 2018, were in consensus overdiagnosis of 71 (84.5%) cases, with consensus over misdiagnosis of 31 cases (36.9%) and true diagnosis of 40 cases (47.6%). IDSA and ESGBOR guidelines (Tables 6 and 7) disagreed on the diagnosis of the remaining 13 cases (15.5%). Among the CPG disagreement cases, 11 had incomplete diagnostic workups according

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TABLE 1 Summary of diagnostic criteria for lyme disease by IDSA 2020 and ESGBOR 2018 guidelines.

Features	*IDSA 2020 diagnosis criteria*	*ESGBOR 2018 diagnosis criteria*
Erythema Migrans (EM)	Clinical diagnosis	Clinical diagnosis
Atypical skin lesion (non-EM)	Serum antibodies to *Borrelia burgdorferi*[a]	Serum antibodies to *B. burgdorferi*
Lyme arthritis[b]	Serum antibodies to *B. burgdorferi*	Serum IgG to *B. burgdorferi*
Lyme neuroborreliosis	Serum antibody testing is recommended for patients presented with: • Meningitis • Painful radiculoneuritis • Mononeuropathy multiplex • Acute cranial neuropathies • Spinal cord inflammation with painful radiculitis and tick exposure	• CSF and serum antibody testing on the same day for antibody index • CSF inflammation for shorter duration of clinical disease (<6 weeks)
Lyme carditis, borrelial lymphocytoma, acrodermatitis chronica atrophicans[b]	-	Serum antibodies to *B. burgdorferi*
Disease duration >6 weeks	-	Specific IgG response is a prerequisite, but an isolated IgM response is of no diagnostic relevance.
Long-lasting disease manifestations[c]	-	Only the detection of IgG antibodies to *B. burgdorferi* should be considered diagnostic
Warnings against false-positive diagnosis	• Do not order tests for a low probability of Lyme disease • Do not test asymptomatic patients after *Ixodes* spp. tick bite • Do not screen patients with neurologic symptoms that are unlikely to have Lyme disease: without tick bite history, EM, or more typical symptoms • Do not screen children with developmental, psychiatric, or behavioural disorders routinely in the absence of more specific signs • Do not perform antibody testing on synovial fluid samples in Lyme arthritis	• Do not perform laboratory testing at all and consider other differential diagnoses if LB is unlikely and symptoms do not meet criteria • Do not perform serological testing unless symptoms are indicative of LB • Do not diagnose based on PCR alone

Abbreviations: B, burgdorferi; B, burgdorferi; CNS, Central nervous system; CSF, cerebrospinal fluid; EM, erythema migrans; IgG, Immunoglobulin G; IgM, Immunoglobulin M; LB, Lyme Boreliosis; PNS, Peripheral nervous system.

[a]Followed by a convalescent-phase serum sample if the initial result is negative.

[b]Mentioned in category "remaining disease manifestations" by ESGBOR 2018 criteria.

[c]Examples given by ESGBOR 2018 criteria: Chronic Lyme neuroborreliosis, acrodermatitis chronica atrophicans, or Lyme arthritis.

to ESGBOR, since it recommends CSF serology to be done on the same day with serum antibody testing and calculation of CSF serum index. However, positive serum antibody tests satisfy the IDSA criteria of neuroborreliosis diagnosis. The remaining two cases of disagreement were also on neuroborreliosis diagnosis. The clinical presentation of these two cases did not meet IDSA criteria for serology testing but could be considered neuroborreliosis based on ESGBOR 2018 guideline.

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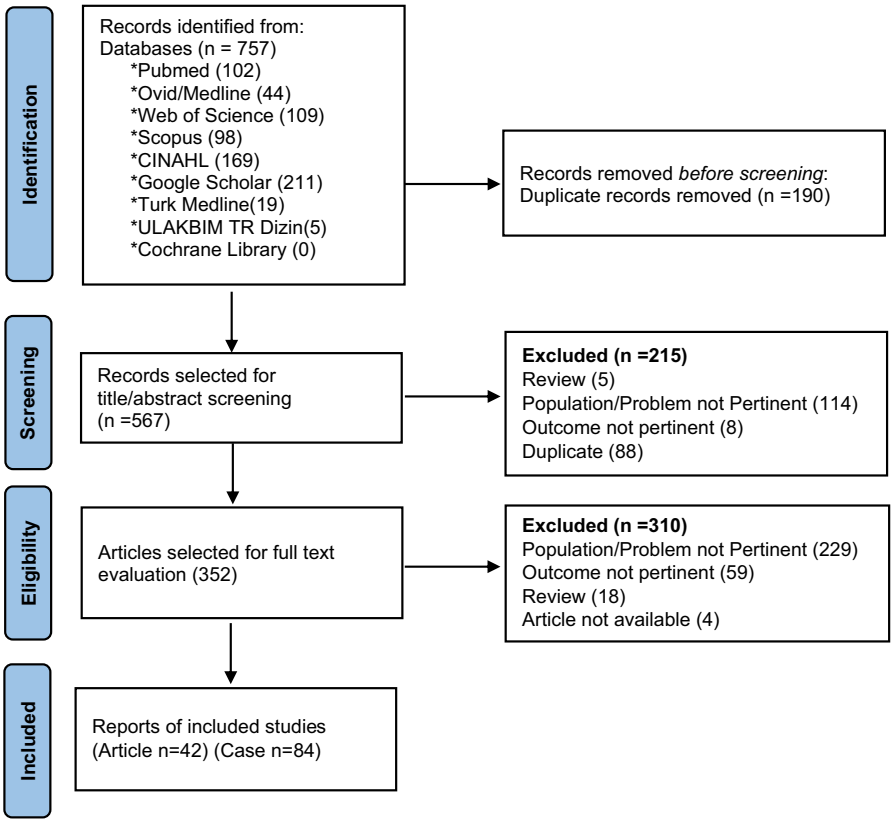


FIGURE 1 Flow diagram of the study selection process according to PRISMA.

4 | DISCUSSION

This study aims to review the LB diagnosis and treatment data in Türkiye, based on IDSA 2020 (Lantos et al., 2021) and ESGBOR 2018 (Dessau et al., 2018) guidelines, and by detecting the disagreements between these CPGs to support areas to be improved for future guidelines.

Despite existing CPGs, diagnosing LB has been a challenge for 44 of 84 cases included in this study. History of tick bite was present in 45 (53.6%) of cases, emphasizing vigilance for specific symptoms in the absence of tick bite. According to the reports from the USA, neurologic manifestations were expected to be seen in 12% of the patients with Lyme borreliosis (Bacon et al., 2008); in Europe, it is known to be between 3 and 15%. (Rauer et al., 2020) The most prevalent neurological symptom of Lyme disease in Europe is painful lymphocytic meningoradiculitis and about 25% of people with meningoradiculitis will only experience pain, which is usually the first symptom. (Koedel et al., 2015) Furthermore, 4% of Lyme neuroborreliosis cases were found to have CNS involvement. (Rauer et al., 2020) In the USA, among Lyme disease patients, facial palsy (9%) and radiculoneuropathy (4%) were the two most typical symptoms of acute Lyme neuroborreliosis. In our study, 45% of neuroborreliosis cases reported CNS involvement, with the most frequently observed clinical manifestations being hemiparesis, cerebellar ataxia/dysdiadochokinesia and meningoencephalitis. The gap between 4% CNS involvement reported in literature and 45% in this study could be caused by publication bias in Turkey considering the small number of published cases or the effects of different *B. burgdorferi* genospecies on nervous system.

Examining each case separately points out to higher prevalence of Neuroborreliosis in Turkey than in Europe. In our cohort, among 44 misdiagnosed cases, 36 cases were diagnosed with neuroborreliosis, possibly due to better recognition with earlier antibiotic initiation and milder neurological symptom progression (Koedel et al., 2015), genospecies variability or publication bias. According to our results, in nearly half (21/44) of the cases, IDSA's list of neuroborreliosis symptoms was absent. In five of the cases, diagnostic procedures were inappropriate because the authors did not prefer ELISA for their diagnostic test but instead used antibodies to Borrelia antigens detected with western blot such as IgM OspC, VlsE, p41 and IgG p100, p17/p18 in blood with two-tier testing. Currently, CPGs do not recommend the routine use of two-tier testing. The use of western blot testing is limited to diagnostic confirmation because of its sensitivity.

Both IDSA and ESCMID guidelines strongly recommend against testing for serology in the absence of concerning neurological findings. However, this study shows that discrepancies among CPGs might also result in inappropriate diagnoses. ESGBOR-2018 requires the testing of both CSF and serum antibody examination on the same day, but it is not essential for the IDSA-2020 criteria. Requirement of CSF:serum index for neuroborreliosis by ESGBOR was another challenge. No neuroborreliosis case has been reported with CSF:serum index in Türkiye. Therefore, it is striking that there were no correctly diagnosed cases of neuroborreliosis in Türkiye. Among misdiagnosed cases for neuroborreliosis, a lack of CSF:serum index was observed in 34 patients (77%).

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TABLE 2 Included articles in analysis.

Article name	Author
Early Localized Lyme Disease in a Paediatric Patient: Case Report	(Baykan et al., 2019)
Lyme Disease Atypically Presenting with a Singular Symptom: Unilateral Chorioretinitis	(Havuz & Güdül Havuz, 2021)
Lyme Disease in the Differential Diagnosis of Rheumatoid Arthritis	(Karadağ et al., 2016)
A Case of Lyme Disease Accompanied by Uveitis and White Dot Syndrome	(Müftüoğlu et al., 2016)
A Presentation of Lyme Disease: Pseudotumor cerebrii	(Şahin et al., 2015)
Acute Cerebellar Ataxia in a Paediatric Case of Lyme Disease and a Review of Literature	(Erol, Saygı, & Alehan, 2013)
Acute Transverse Myelitis in a Child with Lyme Disease and a Review of Literature	(Erol, Kılıçarslan, et al., 2013)
A Lyme Disease Case (Bir Lyme hastalığı olgusu)	(Köksal et al., 1990b)
An Overlooked Disease of Tick Bites: Lyme Disease	(Bulut et al., 2009)
Lyme Disease Presenting as Subacute Transverse Myelitis	(Koc et al., 2009)
Meperidine Induced Seizure in a Patient with Lyme Borreliosis	(Eker et al., 2009)
A Case of Acrodermatitis Chronica Atrophicans Caused by *Borrelia burgdorferi* Infection	(Çalişkan et al., n.d.)
Paediatric Lyme Neuroborreliosis: Different Clinical Presentations of the Same Agent; Single Center Experience	(Celik et al., 2016)
Three Cases of Early Stage Localized Lyme Disease	(Yaldiz et al., 2017)
Treatment of Lyme Neuroborreliosis with Plasmapheresis	(Çelik et al., 2016)
First Report of Three Culture Confirmed Human Lyme Cases in Turkey	(Polat et al., 2010)
A Rare Cause of Peripheral Facial Paralysis in Childhood in Our Country: Lyme Disease	(Özdemir & Gürses, 2017)
Three Cases of Lyme Disease Characterized with Erythema Chronicum Migrans	(Guler & Ural, 2008)
Early Stage Localized Lyme Disease: Case Report	(Tepe et al., 2011)
Facial Granuloma Annulare Associated with *B. burgdorferi* Infection and Seropositivity for P25, P30 and P31 proteins	(Taş et al., 2015)
Lyme Disease and Diffuse Oro-Pharyngeal Ulceration	(Apaydın et al., 1997)
Rheumatoid Arthritis and Lyme Disease: A Case Report	(Borazan et al., 2005)
Bilateral Facial Paralysis Due To Lyme Neuropathy: A Case Report	(Hız et al., 2005)
Bilateral Facial Paralysis Associated with Lyme Disease: Case Report	(Barut et al., 2009)
Neuroborreliosis and Autoimmunity, Guillain Barré Syndrome: Two Case Reports	(Türkoğlu et al., 2016)
The Clinical Characteristics of 12 Cases with Lyme Disease	(Anlar et al., 2003)
Parry–Romberg syndrome: A Possible Association with Borreliosis	(Şahin et al., 2004)
Seronegative Lyme Disease: Report of Two Cases Confirmed with PCR	(Arslan et al., 2011)
Evaluation of 10 Cases of Lyme Disease Presenting with Erythema Migrans in Istanbul, Turkey	(Akın Belli et al., 2015)
Unilateral Sequential Papillophlebitis and Central Retinal Artery Occlusion in a Young Healthy Patient	(Demirok et al., 2015)
Treatment with Doxycycline of Generalized Annular Elastolytic Giant Cell Granuloma Associated with *B. burgdorferi* Infection	(Tas et al., 2015)
Lyme Disease and Myasthenia Gravis	(Evlice & Filiz, 2018)
Lyme hastalığı ve spinal astrositomun birlikte bulunduğu bir olgu	(Akalin et al., 2001)
Transient Complete AV Block due to Lyme Carditis	(Akyol et al., 2003)
A case of acute inflammatory polyneuropathy with atypical features	(Turkoglu et al., 2016)
Differential Diagnosis Approach to Bilateral Peripheral Facial Paralysis: A Case Report	(Akcakaya et al., 2016)
A Case of Early Lyme Disease Diagnosed by Polymerase Chain Reaction	(Kavruk et al., 2012)
Lyme Disease with Unknown Clinical Presentations: A Review of Seven Cases	(Sirmatel et al., 2015)
A Neuroborreliosis Case Presenting with Asymmetric Painful Radiculoneuritis	(Serindag et al., 2018)
Peripheral Retinal Vasculitis Associated with Lyme Disease	(Kılıç et al., 2011)
A Case of Lyme Meningitis with Typical Findings of Meningitis and Encephalitis	(Eroğlu et al., 2002)
Borrelial lymphocytoma cutis successfully treated with intralesional interferon-alpha-2A	(Aydogan et al., 2006)

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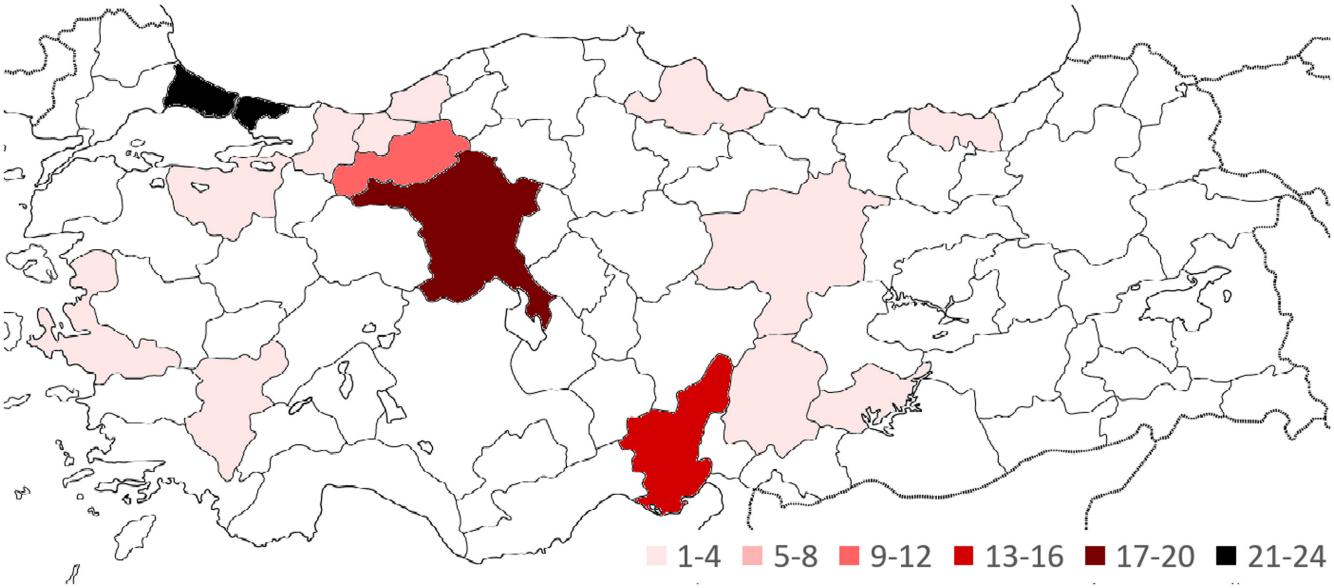


FIGURE 2 Distribution of the LD cases in Turkey.

TABLE 3 General characteristics of cases.

	Cases $n = 84$ (%)
Mean age (sd, min-max)	29.2 (18.2; 2–76)
Age groups ($n = 83$)	
1–15	25 (30.1)
16–30	25 (30.1)
31–45	13 (15.7)
46–60	16 (19.3)
61–76	4 (4.8)
History of tick bite	45 (53.6)
Female gender ($n = 82$)	47 (57.3)
EM	29 (34.5)
Atypical EM	14 (16.7)
Arthritis	7 (8.3)
Ophtalmologic	15 (17.9)
Carditis	2 (2.4)
Neuroborreliosis	36 (42.9)
Acrodermatitis chronica atrophicans	1 (1.2)
Chronicity ($n = 71$)	28 (39.4)
Laboratory findings	
Serum IgM + ($n = 69$) detection with ELISA	50 (72.5)
Serum IgG + ($n = 58$) detection with ELISA	40 (69.0)
Serum IgM and/or IgG detection with Western Blot	43 (51.2)

Abbreviations: CNS, central nervous system; EM, erythema migrans; IgG, Immunoglobulin G; IgM, Immunoglobulin M; max, maximum; min, minimum; N, number; WB_CSF, Western Blot from CSF sampling; yrs, years.

Lack of CSF testing (50%), unnecessary serology testing (50%), lack of ocular findings (27%) and no or negative IgG test for ocular findings (25%) were other significant causes.

Certain manifestations of LB are region-specific. For example, although ACA is described as the most common late disease manifestation (Mullegger, 2004; Steere et al., 2016), it is rare in the US and merely endemic in certain parts of Europe (DiCaudo et al., 1994). *B. afzelii* has been found to be most abundant in biopsied patients with ACA (Brandt et al., 2015; Ogrinc et al., 2021; Rijpkema et al., 1997), but the exact prevalence of *B. afzelii* is not known in Türkiye. In this study, we could only identify one reported case of ACA. The reason for this might be either because Türkiye is not endemic to ACA and its associated genospecies, or it is not well recognized by the physicians, or the widespread use of antibiotic therapy prevented the progression to late disease stage.

This study has demonstrated discrepancies among ESGBOR 2018 and IDSA 2020 guidelines. However, there are common and different genospecies of Borrelia in Europe and the USA, and there are common and different manifestations of Lyme borreliosis. To address this problem, policymakers and scientists on different continents can identify similar manifestations and publish mutual decisions on these symptoms, whereas they can issue different recommendations on geography-specific manifestations. Furthermore, national guidelines focusing on evidence-based local problems should be prepared to eliminate the presented uncertainties in diagnosis and increase adhesion to the CPGs.

4.1 | Laboratory tests

When clinical manifestations raise the suspicion for LB, laboratory tests should be performed according to CPGs. DNA detection tests and antibody tests are available for LB. The sensitivity of Borrelial DNA detection in tissue samples has shown variation among studies, with a mean polymerase chain reaction (PCR) sensitivity of 80% during the first week of the disease, whereas it was merely 20% after a month, while CSF analysis sensitivity was approximated to

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TABLE 4 Reported neurological findings.

Ophthalmologic findings (Total of 15 cases)	Uveitis: 4 Papilledema: 3 Retinal Vasculitis: 2 Chorioretinitis: 2 Blurry vision: 1 Conjunctivitis: 1 Diplopia: 1 Papillophlebitis and central retinal artery occlusion: 1
Neurological Findings (Total of 37 cases)	Central Nervous System Findings Hemiparesis: 5 Meningoencephalitis: 2 Encephalomyeloradiculoneuritis: 1 Meningitis: 1 Cerebellar ataxia/dysdiadochokinesia: 3 Asymmetrical painful radiculoneuritis: 1 Pseudotumor cerebrii: 1 Epilepsy: 1 Lethargy: 2 Somnolence: 1 Peripheral Nervous System Findings Acute polyneuropathy: 8 Facial paralysis: 6 Myasthenia gravis: 1 Transverse myelitis: 2 Parry–Romberg Syndrome: 1 Dysphagia/dysarthria: 2 Numbness: 2

TABLE 5 Inappropriate use of antibiotics according to IDSA guideline 2020 for Lyme disease.

	n = 84 (%)
Inappropriate use of antibiotics	42 (50)
Reasons for inappropriate use	
Incorrect Diagnosis	34
Inappropriate antibiotic choice	5
Inappropriate antibiotic choice + Inappropriate route of administration	2
Prolonged duration of treatment	1

be 40% (Dessau et al., 2018; O'Rourke et al., 2013; van Dam, 2011). PCR is not recommended as part of standard testing as it has low sensitivity in CSF, however, it is used supplementary for skin biopsies or suspected Lyme arthritis cases for aiding diagnosis establishment. Serum antibody testing was widely used in daily clinical practice. Physicians might feel under pressure and conduct serological testing in case of atypical or prolonged disease course when the clinical manifestations are not suspicious for LB according to guidelines. In the Netherlands (Coumou et al., 2014), only a minority (9%) of the patients tested for LB had the relevant clinical manifestation outlined by CPGs. Even though serological testing is very sensitive in individuals with typical extracutaneous symptoms, false-negative antibody testing results are present in the early stages of disease namely the first weeks. Immunodeficient patients may have false-negative antibody test results at any stage of

TABLE 6 Agreement of the cases with IDSA 2020 and ESGBOR 2018.

		ESGBOR 2018		TOTAL
		0	1	
IDSA 2020	0	31	2	33
	1	11	40	51
TOTAL		42	42	84

Note: 1 indicating right diagnosis, 0 indicating wrong according to guidelines.

Abbreviations: ESGBOR, ESCMID study group on Lyme borreliosis; IDSA, Infectious Diseases Society of America.

disease. On the other hand, false-positive serology results without LB have been equally problematic and this phenomenon has been observed due to previous infections, cross-reactive antibodies or autoimmune diseases (Lantos et al., 2021). Therefore, case definitions published in the guidelines should be considered before ordering antibody tests and patients without proper manifestations as detailed in the guidelines should not be tested for LB. Improper testing increases the economic burden of healthcare while causing delays in the correct diagnosis as well as treatment of the patients (Webber et al., 2019).

Furthermore, Indirect Fluorescent Antibody (IFA) and ELISA testing were thought to be highly sensitive and specific for the detection of spirochetes two decades ago (Craft et al., 1984; Magnarelli et al., 1984). In 1984, ELISA was considered the best diagnostic tool (Craft et al., 1984), which has been thought to be not the essential finding but rather a supplementary finding as EM findings, neurologic findings and CSF sampling according to different phenotypes and conditions of LB were considered gold standards to diagnosis. Today, it seems that some physicians might not accommodate recent guidelines and act in concordance with former guidelines which results in unnecessary testing. IDSA does not recommend two-tier testing, whereas ESGBOR finds it helpful to use western blot and ELISA for confirmatory purposes, rather than first line or stand alone. (Aslan Başbulut et al., 2012; Lantos et al., 2021) Steere et al. mention that detection of antibodies to serum Borrelia antigens with western blot is somewhat useful for only false-positive conditions and ELISA-positive cases with suspicion of patients without Lyme but indicates no measurable benefit over ELISA test for first-line use similar to today's CPG (Dessau et al., 2018; Lantos et al., 2021; Steere, 1989). Nowadays the two-tier serology method is widely common, after equivocal and positive ELISA results, western blot confirmation testing is recommended as increases specificity (Jaulhac et al., 2019).

For diagnosis of neuroborreliosis, European guidelines recommend lumbar puncture, whereas American guidelines do not. The lumbar puncture and investigation of cerebrospinal fluid could be determined by several factors that are capability of laboratories, challenges in convincing patients, therefore case-based consideration is necessary.

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TABLE 7 Reasons for misdiagnosis (can be multiple per case) according to IDSA 2020 and ESGBOR 2018 guidelines.

	n = 44 (%)
No CSF: Serum Index for Neuroborreliosis (ESGBOR)	34 (77)
No CSF Testing for neuroborreliosis (ESGBOR)	22 (50)
Serology Testing for Neuroboreliosis without Neurological Symptoms (IDSA)	22 (50)
Ocular Findings/Lymphocytoma	12 (27)
Diagnosis made based on Western Blot (Old guidelines)	11 (25)
No/Negative IgG test for Ocular Findings	11 (25)
No IgG Testing for >6 weeks of disease	8 (18.2)
Diagnosis with Negative/No IgG (ESGBOR) for >6 weeks of symptoms	3 (6.8)
Inappropriate culture	3 (6.8)

Lastly, the condition called chronic Lyme borreliosis presents with persistent nonspecific symptoms after a history of Lyme borreliosis and antimicrobial therapy. While these symptoms can be attributed to other illnesses and syndromes, it is important to act according to CPG for antibiotic therapy to prevent antibiotic overuse (Koedel et al., 2015). The major cause of antibiotic misuse in reviewed studies was incorrect diagnosis (81%). However, eight (19%) of the appropriately diagnosed cases were treated either by inappropriate antibiotics, inappropriate route of administration or inappropriate duration of treatment. This emphasizes the importance of adherence to diagnostic and treatment guidelines.

4.2 | Limitations

This study covers all reported Lyme cases of Türkiye, however, there are several limitations. Firstly, there may be quality differences among publications. Secondly, this article includes a wide range of literature in terms of publication year. This discrepancy in technology, along with differences among various laboratories in different parts of the country, might have led to distant characteristics of testing. Therefore, this study does not account for any false-positive/negative laboratory errors. There is a possibility of publication bias when evaluating case reports and series. Cases selected for publication were mostly symptom-dominant and sometimes extraordinary cases which masks the true prevalence of common milder symptoms like EM.

5 | CONCLUSION

Unnecessary testing for Lyme borreliosis leads to wrong diagnosis of Lyme borreliosis. Incorrect diagnosis causes misuse of healthcare and economic resources, increases antibiotic resistance levels and overestimates the incidence of disease. Reduction of overtesting can be achieved with laboratory ordered only in accordance with an international and national guideline. The determination of which steps to follow from international guidelines and incorporate into national guidelines entails consideration of multiple parameters, including the capabilities of laboratories, challenges in patient persuasion and the practicality of diagnostic tests. This underscores the imperative for a meticulously crafted and context-specific approach to ensure the appropriateness of guidelines for Türkiye.

AUTHOR CONTRIBUTIONS

Project idea: Ö.E.; conceptualization: A.B.Y., E.C; literature search and screening: A.B.Y., E.C.; data extraction: A.B.Y., E.C.; drafted the manuscript: A.B.Y., E.C.; data analysis, generation of figures and tables: A.B.Y.; reviewed the manuscript for intellectual content: A.B.Y., E.C., F.P., Ş.K., F.C., Ö.E. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

We are thankful to Ertaç Nebioğlu for his help with search parameters for the literature search. We also thank Can Ege Yalçın, Ceyda Akartuna, Elif Ozdogan for their contribution to intellectual discussions.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Kuiscid/lyme at https://kuiscid.ku.edu.tr.

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How to cite this article: Yıldız, A. B., Çetin, E., Pınarlık, F., Keske, Ş., Can, F., & Ergönül, Ö. (2024). Discrepancy between IDSA and ESGBOR in Lyme disease: Individual participant meta-analysis in Türkiye. *Zoonoses and Public Health*, *71*, 337–348. https://doi.org/10.1111/zph.13119

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