ABSTRACT

Dissertation for the degree of Doctor of Philosophy (PhD) in the educational program **"8D10102 - Medicine**" by Yulduz Madikhanovna Khaidarova

on the topic: "Differential Diagnosis of Early Seronegative Spondyloarthritis in Brucellosis-Endemic Settings"

Relevance of the research topic

Spondyloarthritis (SpA) is a heterogeneous group of chronic inflammatory diseases of the musculoskeletal system (MSK), united by common genetic, immunological, and clinical features and characterized by predominant involvement of the axial skeleton (sacroiliac joints and spine), entheses, peripheral joints, and extra-articular manifestations involving the eyes, skin, and gastrointestinal tract [1]. These diseases impose a significant burden on healthcare systems and lead to reduced quality of life, predominantly among patients of working age [2]. SpA is widely distributed worldwide and generally has an early onset, most commonly during the third decade of life [3]. Despite improvements in diagnostic approaches, delayed verification of the disease remains a relevant problem. According to various studies, the mean diagnostic delay ranges from 6 to 10 years and may reach 13 years in some cases [4,5]. In recent years, the introduction of the ASAS classification criteria (2009, 2011) has improved the detection of early forms of SpA. However, these criteria have several limitations, including insufficient specificity, dependence on MRI availability, and variability in the interpretation of results [6–8]. In addition, the ASAS criteria do not fully account for the characteristics of endemic regions where infectious diseases involving the MSK system are prevalent [9].

In the Republic of Kazakhstan, which is a brucellosis-endemic region [10], the problem of differential diagnosis between SpA and chronic brucellosis (ChB) is of particular relevance. Chronic brucellosis is a systemic infectious disease with a polymorphic clinical presentation, in which MSK involvement is one of the major manifestations [11]. Clinical manifestations of ChB include arthritis, sacroiliitis, enthesitis, and back pain, which may mimic SpA and lead to diagnostic errors [12,13]. Moreover, in endemic regions, these diseases may frequently present with similar clinical manifestations, substantially complicating their differential diagnosis [14].

Thus, the similarity of clinical manifestations, limited diagnostic capabilities, and the high prevalence of brucellosis in endemic regions necessitate the development of new approaches to the differential diagnosis of SpA and ChB with MSK involvement.

Aim of the research

Based on the above considerations, the aim of this dissertation was to develop an algorithm for the differential diagnosis of early SpA and ChB with MSK involvement based on a comparative analysis of clinical, laboratory, and instrumental findings in a brucellosis-endemic setting.

Objectives of the research

1. To assess the clinical, laboratory, and instrumental characteristics of patients with seronegative SpA and ChB with MSK involvement and, through comparative analysis, identify common and major distinguishing features.
2. To investigate the cross-applicability of existing criteria used for the diagnosis of SpA and ChB with MSK involvement.
3. To identify predictors that allow differential diagnosis between SpA and the ChB phenotype meeting the ASAS classification criteria.
4. To develop and validate a differential diagnostic scoring system and an algorithm for the early diagnosis of SpA in a brucellosis-endemic setting.
5. To assess healthcare professionals' awareness of the diagnosis of SpA in a brucellosis-endemic setting.

Study population

The study included two main clinical groups and a model validation group:

- patients with a confirmed diagnosis of **SpA** – 150 patients;
- patients with a confirmed diagnosis of **ChB with MSK involvement** – 189 patients;

- model validation group: 30 patients with a confirmed diagnosis of **SpA** and 32 patients with **ChB with MSK involvement**.

In addition, a sociological survey was conducted among 128 physicians (initial survey in 2021) and 135 physicians (repeat survey in August 2026 after implementation of the algorithm and differential diagnostic scoring system for SpA and ChB) from various specialties involved in the diagnosis and management of patients with MSK diseases.

Subject of the research

Demographic, clinical, laboratory-instrumental, and epidemiological characteristics of SpA and ChB with MSK involvement.

Study design

The study was designed as a cross-sectional comparative analytical study with retrospective and prospective data collection and was conducted in four stages.

Stage 1. A retrospective (n=113) and prospective (n=37) analysis of early clinical, laboratory, and instrumental characteristics of patients with SpA was performed.

Stage 2. A prospective study of the clinical, laboratory, and instrumental characteristics of patients with ChB with MSK involvement (n=189) who sought consultation with a rheumatologist was conducted.

Stage 3. A comparative analysis of the obtained data was performed, diagnostically significant features were identified, and a statistical differential diagnostic model was developed, followed by the development of a diagnostic scoring system and an algorithm for the early detection of SpA in a brucellosis-endemic setting.

Stage 4. External validation of the developed diagnostic scoring system was performed in a prospectively recruited group of patients with early SpA (n=30) and ChB with MSK involvement (n=32), and an online calculator was developed for practical use by physicians.

Scientific novelty of the research

1. For the first time, it was established that, in conditions of high brucellosis endemicity, the use of the ASAS classification criteria and the standard case definition of brucellosis has diagnostic limitations associated with a high risk of misclassification of SpA and ChB with MSK involvement.
2. For the first time, a comparative analysis of the clinical, laboratory, and instrumental manifestations of SpA and ChB with MSK involvement was performed in a brucellosis-endemic setting, and significant differential diagnostic features enabling distinction between these diseases at early stages were identified.
3. For the first time, a differential diagnostic scoring system was developed and validated, and an algorithm for the early differential diagnosis of SpA in a brucellosis-endemic setting was developed based on significant clinical and laboratory diagnostic criteria.
4. Based on the sociological survey, data were obtained for the first time indicating low physician awareness of the problem of differential diagnosis between SpA and ChB with MSK involvement, supporting the feasibility of implementing the developed differential diagnostic scoring system and algorithm in healthcare practice in brucellosis-endemic regions.

Methodology of the dissertation research

The methodology of the dissertation research was based on a combination of complementary clinical, analytical, laboratory, instrumental, sociological, and statistical methods. The study included retrospective analysis of archived paper medical records and electronic medical records from the DAMUMED database, clinical examination of patients, laboratory diagnostic methods including assessment of inflammatory activity, serological diagnosis of brucellosis and HLA-B27 determination, instrumental investigations (radiography and MRI), physician surveys, and statistical methods including univariate and multivariable analyses, assessment of diagnostic characteristics, ROC analysis, and development of a diagnostic model.

Theoretical significance of the research

1. The findings contribute to expanding knowledge of the clinical characteristics of seronegative SpA and ChB with MSK involvement and allow assessment of the validity of the diagnostic criteria used.

2. Based on the comparative analysis, the diagnostic significance of individual clinical and laboratory features was clarified, providing a scientific basis for optimizing the differential diagnosis of these diseases and developing an appropriate differential diagnostic scoring system.

Practical significance of the research

The findings can be used in clinical practice by rheumatologists, infectious disease specialists, and primary healthcare physicians to improve the accuracy of early SpA diagnosis and the diagnosis of ChB presenting with sacroiliitis, spondylitis, spondylodiscitis, spondyloarthritis, and arthritis. The developed diagnostic scoring system and algorithm can optimize patient referral pathways and reduce the risk of diagnostic errors in a brucellosis-endemic setting.

A differential diagnostic online calculator has been developed and implemented in the clinical and diagnostic departments of healthcare organizations. It is intended for convenient use by physicians during the initial assessment of patients with MSK involvement in a brucellosis-endemic area.

Link to the online calculator: https://rheumatologist.site-expert.kz/calc/

Key Statements Submitted for Defense

1. Patients with ChB involving the musculoskeletal system (MSK) and patients with SpA demonstrate a high degree of similarity in clinical manifestations. This reduces the specificity of the standard ASAS criteria and the brucellosis case definition criteria in areas endemic for brucellosis, resulting in cross-fulfillment of the criteria and an increased risk of diagnostic errors and inappropriate patient management (up to 27.5% in ChB and up to 10% in SpA).
2. Based on a comparative analysis of the clinical, anamnestic, laboratory, and instrumental manifestations of SpA and ChB, statistically significant clinical differential diagnostic features associated with inflammatory back pain and articular syndromes were identified. These features enable accurate diagnosis of SpA and the osteoarticular form of ChB in adult patients at an early stage of the disease using readily available routine clinical and laboratory parameters, without the need for expensive or difficult-to-access diagnostic methods.
3. A predictive algorithm incorporating a differential diagnostic scoring system was developed and validated for the early verification of SpA based on a combination of statistically significant clinical and laboratory features. The algorithm was adapted to settings endemic for brucellosis, thereby improving diagnostic accuracy and, consequently, reducing the likelihood of diagnostic errors.
4. The identified low level of awareness among physicians of various specialties, regardless of length of professional experience, regarding the differential diagnosis of SpA and ChB supports the need for targeted implementation of the developed diagnostic algorithm and educational programs within the system of continuing medical education for healthcare professionals working in brucellosis-endemic regions.

CONCLUSIONS

1. Despite the typical rheumatological presentation, some patients with SpA exhibited symptoms potentially similar to chronic brucellosis (low-grade fever, weakness, sweating, lymphadenopathy, etc. – in 18.0% of patients). Furthermore, 37.3% of patients with SpA had a positive epidemiological history of brucellosis but negative serological tests for Brucella spp. Chronic rheumatic fever with damage to the joints is a multisystem disease with predominant involvement of the joints (arthralgia - 91.0%, polyarthritis of the small joints of the hands - 63.3% of all polyarthritis), periarticular structures (bursitis - 16.4%, tendinitis - 12.2%), nervous (damage to the PNS - 22.7%) and autonomic systems (dysfunction - 66.1%). Despite the presence of manifestations common with SpA (sacroiliitis - 34.4%, predominantly unilateral - 21.5%), ChB demonstrates distinctive features: the prevalence of polyarthritis (50.0% vs. 19.2% in SpA), the mechanical nature of back pain (78.8% vs. 9.1%), pronounced asthenovegetative syndrome (34.9%), systemic infectious manifestations (74.0%), positive RF (24.3% vs. 8.0%) and a good clinical response to fluoroquinolones (71.4% vs. 12.7%).
2. An assessment of the applicability of the ASAS classification criteria (2009, 2011) in patients with inflammatory back pain and joint syndrome showed that in 27.5% (52 of 189) the clinical criteria in patients with chronic brucellosis fully correspond to the ASAS criteria, and in 26% (49 of 189) they partially correspond, which indicates a significant clinical and diagnostic overlap

between these diseases. An assessment of the compliance of patients with a reliable diagnosis of SpA with the standard case definition of chronic brucellosis showed that 10% had a combination of clinical symptoms characteristic of brucellosis (infectious syndrome, symptoms of autonomic dysfunction and astheno-neurotic syndrome), and a positive epidemiological history was established in 37.3% of patients with SpA, which determines a high risk of diagnostic errors.The study results demonstrated that patients with chronic brucellosis may clinically develop an ASAS-positive phenotype, leading to a reduction in the specificity of the ASAS criteria to 72.5% for the diagnosis of spondyloarthritis in brucellosis-endemic regions.

3. Based on a univariate analysis, key differential diagnostic features were established that make it possible to distinguish between spondyloarthritis (SpA) and chronic brucellosis (ChB) in endemic regions: for SpA, the most significant markers are: inflammatory back pain (91.9% versus 21.2% in ChB), bilateral sacroiliitis (89.9% versus 12.9%), HLA-B27 positivity (72.1% versus 24.3%), good response to NSAIDs (99.3%), enthesitis (22.0% vs. 10.0%), dactylitis (12.7% vs. 1.6%), and family history of SpA (46.7%); for ChB, the most significant are: positive epidemiological history (80.4% vs. 37.3%), infectious syndrome (74.0% vs. 18.0%), nervous system damage (autonomic dysfunction - 66.1%, asthenoneurosis - 34.9%), and good response to antibacterial therapy (71.4% vs. 12.7%). Based on multivariate analysis between the SpA group (n=150) and the overall chronic brucellosis group (n=189), four factors associated with the diagnosis of SpA were identified: inflammatory back pain, morning stiffness, age under 45 years, and HLA-B27 positivity. Two factors associated with chronic brucellosis were also identified: positive epidemiological history and myalgia.According to the results of multivariate analysis between the SpA group (n=150) and the ASAS-positive chronic brucellosis group (n=52), peripheral arthritis and enthesitis were identified as independent predictors of SpA, whereas signs related to infectious and neurasthenic syndromes were associated with chronic brucellosis.

4. 4.The developed differential diagnostic scoring scale, based primarily on clinical signs (with a syndromic combination of infectious, autonomic, and asthenoneurotic manifestations of chronic respiratory disease), demonstrated high diagnostic efficiency during external validation (AUC=0.95; sensitivity 93%; specificity 91%).

5. The study demonstrated that more than half of the doctors used Difficulties exist in the differential diagnosis of SpA and ChB, and these difficulties are not related to experience or specialty, indicating the systemic nature of the problem. The data obtained substantiate the need to develop and implement accessible differential diagnostic algorithms and educational programs for primary care physicians and specialists in endemic regions.

Approbation of the dissertation

The main provisions and results of the dissertation research were presented and discussed at a department meeting on June 1, 2026. In addition, the author participated in 9 international and scientific-practical conferences and congresses related to the dissertation topic, including oral and poster presentations devoted to the early diagnosis and differential diagnosis of SpA and ChB in an endemic setting.

Publications related to the dissertation

A total of **13 scientific articles** have been published on the topic of the dissertation:

- 3 articles in journals recommended by the Science and Higher Education Quality Assurance Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan;
- 2 articles in international peer-reviewed scientific journals with an impact factor according to Journal Citation Reports or indexed in the Web of Science Core Collection, Science Citation Index Expanded, or with a CiteScore percentile of at least 25 in the Scopus database;
- 1 article in a journal with a CiteScore percentile below 25 in the Scopus database;
- 3 articles in other international and Kazakhstani journals;
- 4 publications in proceedings of international conferences held abroad.

Three certificates of registration in the State Register of Rights to Copyright-Protected Objects were obtained (Certificate No. 69550 dated April 3, 2026; No. 69551 dated April 3, 2026; No. 71710 dated May 12, 2026).

Methodological recommendations for physicians were developed and published:

Khaidarova Y.M., Kurmanova G.M. *Clinical and Laboratory Features and an Algorithm for the Early Differential Diagnosis of Spondyloarthritis and Chronic Brucellosis with Musculoskeletal Involvement in Endemic Regions: Methodological Recommendations.* Almaty: Al-Farabi Kazakh National University, 2026. 66 p. ISBN 978-601-382-429-1.

Implementation of the research findings

The differential diagnostic scoring system and online calculator have been implemented in clinical practice at Municipal Polyclinic No. 5, Almaty; **JANUIA Medical Center**, Taraz; **ASMED Turgut Ozal** Polyclinic, Almaty; and the City Rheumatology Center, Almaty.

Personal contribution of the doctoral student

The doctoral student independently conducted an analysis of domestic and international scientific literature on the problems of early diagnosis and differential diagnosis of SpA and ChB.

The author formulated the aim, objectives, study design, and methodology. The author directly participated in the formation of patient groups, collection of clinical material, analysis of medical documentation, clinical examination of patients with ChB with MSK involvement, interpretation of laboratory and instrumental findings, and administration of the healthcare professional survey.

The doctoral student independently performed the systematization and statistical processing of the obtained data, conducted univariate and multivariable analyses, identified diagnostically significant predictors of SpA and ChB, and developed the diagnostic model, differential diagnostic scoring system, and algorithm for the early diagnosis of SpA in a brucellosis-endemic setting. The author participated in the development and implementation of the online calculator for practical application of the developed scoring system.

Preparation of publications, presentations, materials for approbation, presentation of research findings, and writing of the dissertation were performed with the direct participation of the doctoral student.

Volume and structure of the dissertation

The dissertation is presented on **211 pages** of computer-typed text and consists of an introduction, literature review, description of the materials and methods of the research, original research findings, discussion of the results, conclusions, practical recommendations, a reference list comprising **355 sources**, and **7 appendices**. The dissertation contains **13 figures and 68 tables**.