

To The Chairman of Scientific Jury
Designated by Order
No. R-109-236/June 01, 2022
By the Rector of the Medical University-Varna

REVIEW

by Prof. Borislav Georgiev Georgiev
Head of the Cardiology Clinic at the National Heart Hospital
Member of the Jury for awarding the scientific and educational degree "PhD",
designated by order No. R-109-236/ June 01, 2022 by the Rector of the Medical
university of Varna

Regarding: Dissertation of Svetoslav Pavlov Dimitrov, MD, PhD student on a self-study basis, Medical University Varna

Topic of the PhD thesis:

„Determinants of quality of life in patients with nonradiographic axial spondyloarthritis: analysis based on main aspects of the disease“

Scientific tutor: Assoc. Prof. Atanas Angelov

The documents presented by Dr. Svetoslav Dimitrov – dissertation, abstract, and additional documents are in accordance with the requirements of the regulation for acquisition educational and scientific degree “PhD” and rules of Medical university of Varna. I do not find any omission in the submitted documentation.

I declare that I have no conflict of interest with the candidate.

All presented materials are precisely arranged and described.

No evidence of plagiarism.

Brief CV data of the applicant

Svetoslav Pavlov Dimitrov, M.D. was born in 1983 in the city of Varna. He graduated with honors from the Fifth High School for Foreign Languages "John the Exarch", Varna in 2002. He graduated with honors from the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna in 2008 and was awarded with the Golden Hippocrates Award and specialization of choice. Since 2008 he has been working as an intern, and since 2009 he has been a resident in rheumatology at the Rheumatology clinic at the University Hospital "St. Marina", Varna. In 2013, after winning a competition, he was appointed as an assistant in Rheumatology at the Department of Cardiology and Rheumatology and since 2017 in the Sector Rheumatology in The Department of the Internal Diseases. In 2013 he acquired the specialty of Rheumatology. In the period of his specialization he attended a number of courses: 09/2011 - ISDC Bone Densitometry Course - Sofia, Bulgaria, 09/2012 - Course in the field of spondyloarthritis at the Charité Hospital, Berlin, 07/2012 - Course in the field of spondyloarthritis in Zagreb, Croatia, 03/2012 - Course in Epidemiology and Medical Statistics at the University of Aberdeen, Scotland, 06/2012 - Course in Musculoskeletal Ultrasonography, 2012-2014 - Online Rheumatology Course for 2 years, led by the European Rheumatism League (EULAR)). Since 2020 he has been a PhD student in the field of internal medicine at the Department of Propaedeutics of Internal Medicine, MU - Varna.

Significance of the topic

The topic of the dissertation is contemporary and relevant.

Quality of life is impaired in all rheumatic diseases. The introduction and application in everyday practice of the ASAS criteria have contributed to the possibility of early diagnosis of patients in the pre-radiographic phase of spondyloarthritis. This early detection of the disease inevitably led to an increased number of patients worldwide and the associated social and economic consequences.

The impact of axial spondyloarthritis on quality of life is even more significant, given the fact that symptoms of the disease by definition start before the 45th anniversary. In the active age stage of the patient, chronically progressive inflammatory joint disease significantly limits various aspects of daily activities.

Axial SpA impairs health-related quality of life (HRQoL). Several studies comparing health-related quality of life in patients with axial spondyloarthritis and the general population have reported a statistically significantly lower HRQoL in patients with spondyloarthritis. In the context of axial spondyloarthritis, the decrease in HRQoL is more significant at the expense of changes in the physical function of patients compared to the psycho-emotional aspects of the disease. The effect of the disease on the physical function of patients is significant. It is also reflected in a number of other aspects of life - in personal and social terms (education, starting a family and career growth).

The expansion of the range of therapeutic agents from the group of anticytokine therapy in spondyloarthritis coincides with the development of the ASAS criteria and again shifts the focus to the problem of quality of life of patients with nr-/r-ax SpA. It has been found that a number of factors are associated with difficulties at work and loss of productivity in the workplace. Unemployment is associated with older patients, social deprivation, long-term illness, functional impairment and depression. Absenteeism is associated with disease activity and depression, while presenteeism is associated with older patients, disease activity, anxiety, and the level of depression.

Patients with nr-ax SpA have a shorter duration of symptoms of the disease and although there are no radiological signs, they are characterized by a significant severity of the disease. Compared with patients with r-axSpA, the levels of disease activity assessed by the patient and the functional changes associated with the disease show similar results.

Analyzes of the two phases of ax SpA -nr-ax SpA and ax SpA, indicate differences related to the duration of symptoms, gender distribution and age of patients. Despite the significantly lower degree of inflammatory activity, as well as relatively preserved axial mobility in patients with nr-ax SpA, the two phases have similarities in terms of disease activity, physical function and quality of life.

A link has been established between ASDAS calculated by CRP and quality of life due to physical function, but a study did not prove a link between quality of life and MCS (Mental composite score). The level of disease activity partly contributes to the deteriorating quality of life, and according to the authors there are other factors that change it.

Different scales for assessing the level of quality of life in patients with axial spondyloarthritis have been used in the literature. Patient-reported data are categorized into two main groups of quality of life assessment tools - generic and specific (Ankylosing Spondylitis Quality of Life - ASQoL). The disease-specific quality of life questionnaire ASQoL has been widely used in a wide range of spondyloarthritis. It is easy for the patient to perceive, involves aspects not only focused on the patient's physical function, and takes short time to complete.

Structure of the dissertation: The scientific work of Dr. Svetoslav Dimitrov is formed on 158 pages according to the requirements and contains an introduction, literature review, aim and objectives, materials and methods, results, discussion, conclusions, contributions, 14 applications and bibliography. The dissertation is illustrated with 35 figures and 40 tables.

The introduction is on 2 pages. **The literature review** is presented in 29 pages and shows very good awareness of the author regarding spondyloarthritis, the clinic, diagnosis, assessment of disease activity, impact of spondyloarthritis on the quality of life of patients and treatment of axial spondyloarthritis.

The author has good awareness on the topic of the dissertation. Based on the literature review, he draws *conclusions*.

1. Thanks to the experts from ASAS, there are clear criteria for the classification of spondyloarthritis. These criteria make early diagnosis possible and the establishment of the disease in its pre-radiological phase.

2. The continuing research activity in the field of modern therapeutic pathogenetic agents is a great success in the field. The use of anticytokine therapy is at the end of a period of time during which the presence of spondyloarthritis is associated with long-term structures.

3. There is a worldwide increase in the data on the nature and course of the early non-radiographic phase of the axial SpA.

4. There is an improvement in the understanding of the main characteristics of the disease-net in this phase and analysis of the predictors for the progression of the progression of the structure.

5. Non-radiographic axial spondyloarthritis is characterized by a brief history of symptoms and at the same time may be associated with significant. Patients with nr-ax SpA are characterized by high levels of clinical and laboratory disease activity. The physical function of patients and the quality of life, related not only to health, but also to other aspects of life, are also strongly affected.

6. In a number of rheumatological centers, magnetic resonance imaging of the sacroiliac joints and spinal cord is no longer a reserve image. Its advantages over conventional radiography and computed tomography allow for early detection of the disease.

7. After the creation of the modern concept for spondyloarthritis, the myth of the prevalence of spondyloarthritis in men was erased, and with this, there is more data on gender differences. This would lead to a reduction in the time required for diagnostic refinement and would provide an opportunity for early diagnosis.

Based on the literature review, he brings out *unsolved tasks and problems*:

1. The predominant part of the data in the literature is related to the radiographic axial spondyloarthritis. At the current stage of the development of rheumatology, there is ongoing collection and analysis of data on the disease course and development of structural changes. Given the low incidence of spondyloarthritis in all its phases, this process is likely to continue in the coming years.

2. The main emphasis in the discussion of nr-ax SpA so far is mainly on the analysis of the criteria for classification and the advantages of the imaging methods, as well as training of rheumatologists in the calculation of images by MRI of the SIJ and spine. A more in-depth analysis of the assessment of the disease activity and physical function of the patients in the early phase of the disease is needed.

3. There is a lack of a comparative number of comparative analyzes of the various aspects of the disease in patients with the imaging and clinical arm of nr-ax SpA, as well as its effect.

4. There is a tendency for progression of nr-ax SpA to r-ax SpA with different probabilities according to the individual authors, which is probably related to a number of predictors of structural progression, which need to be carefully analyzed.

5. In real clinical practice there is a need to accumulate data of the effect of different anticytokine drugs on the ability to control disease activity, preservation of physical function, improvement of the patient's quality of life and prevention of structural damage.

The bibliography contains 202 cited titles, of which 1 is in Cyrillic and 201 in Latin. All citations are written in Latin. A brief analysis of the content of the publication is also left in citations 102 and 106.

Dr. Svetoslav Dimitrov **aims** to examine the quality of life and factors influencing it (including the main aspects of the disease - activity, function and disability measured by patient-reported results, spinal mobility and SIJs status on MRI) in patients with nr-ax SpA from the Bulgarian population. To achieve this aim he sets the following **tasks**:

1. To assess the severity of symptoms by measuring the level of disease activity in patients with nr-ax SpA, including extraaxial manifestations given the heterogeneous phenotypic manifestation of the disease.
2. To assess the degree of inflammation of the sacroiliac joints (SIJs), using the magnetic resonance scoring system for SPARCC activity and to investigate the association between indicators of clinical disease activity and inflammation of magnetic resonance imaging (MRI).
3. To investigate the extent to which the disease creates limitations in physical function through a comparative analysis of patients with nr-ax SpA and healthy individuals.
4. To analyze the changes in the spinal mobility and the status of the musculoskeletal system as a whole (including involvement of peripheral joints, entheses, dactylitis) in the Bulgarian population of patients with nr-ax SpA.
5. To study the health-related quality of life and the risk factors for its deterioration.
6. To investigate the clinical, laboratory and MRI characteristics in men and women and to determine whether there are gender differences in the severity of nr-ax SpA.
7. To study the connection of the individual pharmacological therapies with the clinical and laboratory parameters of the disease process.

Methodical approach: The study was conducted among 202 patients with low back pain for at least 3 months of duration, of which 160 patients with inflammatory lumbar pain (ASAS criteria for IBP) and 42 with no evidence for inflammatory back pain. Participants in the group with inflammatory type of spinal pain are divided into two subgroups – clinical and imaging arm (respectively 62 patients with HLA B27 antigenic carrier + two or more manifestations of spondyloarthritis and 98 patients with MRI data for BME + at least one characteristic of SpA). After conducting all the studies, three groups were formed - patients with nr-ax SpA (imaging arm), nr-ax SpA (clinical arm), and a control group of patients with non-inflammatory condition. The antigenic presence of HLA B27 is observed in 80.6% in the group of patients with the imaging arm, in 100% of the patients in the clinical arm and in 14.6% of the control group. The relative share of patients with nr-ax SpA who do not receive treatment is 36.8% compared to 66.6% of the control group. In the combined group of patients (group A + group B), the patients receiving non-steroidal anti-inflammatory drugs accounted for 48.1% and sulfasalazine for 15%.

Statistical analysis includes descriptive statistics, statistical evaluation and verification of statistical hypotheses (parametric and nonparametric), regression and correlation, which are in line with the hypothesis and the set goals.

Results: The obtained results of Dr. Svetoslav Dimitrov are diligently presented on 44 pages of the dissertation. The results are well illustrated. The obtained results correspond to the aims of the research.

The discussion of the results is presented in 13 pages and the results are analyzed and compared, where possible, with other publications. An algorithm has been proposed for the diagnosis of non-radiographic axial spondyloarthritis in daily clinical practice, which significantly increases the quality of the dissertation.

An insignificant remark is that in the dissertation the author uses the values of some laboratory parameters in Latin, and others in Cyrillic.

The good knowledge of the issues and the depth of the author's knowledge provide an opportunity to identify future additions to the current scientific work. Future analyzes, which would be important in patients with nr-ax SpA, can be considered in several directions:

1. To estimate in the future how many of the patients with nr-ax SpA pass into the phase with structural changes (AS) and how many of them remain in the non-radiographic phase and for how long. What is the probability of progression?
2. How many of the patients in the clinical arm after a certain period of time already have MRI inflammatory changes, ie. pass into the subset of the imaging arm. What is the probability of "conversion"? How does the quality of life of patients change when moving from one group to another?
3. To assess the dynamics of MRI inflammatory changes, to assess whether there is a possibility of "self-abatement" of the disease.
4. How do biological agents already registered in practice for the treatment of nr-ax SpA affect the disease activity, the degree of progression and the possibilities for permanent remission for the disease?

Conclusions: Dr. Svetoslav Dimitrov offers 8 conclusions. They derive directly from the set tasks and from the conducted research.

1. A positive correlation is found between laboratory biomarkers of inflammation and clinical indices for disease assessment and functional impairment in patients with nr-ax SpA.
2. Changes in magnetic resonance imaging of the sacroiliac joints show a strong positive correlation with markers of inflammation and scores for assessing disease activity in patients with nr-ax SpA.
3. Non-radiographic axial spondyloarthritis affects physical function. Functional impairment is higher in patients with extravertebral symptoms - peripheral arthritis or enthesitis.
4. Changes in spinal motility in nr-ax SpA are significantly more pronounced compared to the control group. The nr-ax SpA imaging arm showed a statistically significantly higher degree of axial damage than the clinical arm.
5. The quality of life of patients with nr-ax SpA is lower than in the control group of patients. It correlates positively with laboratory biomarkers for inflammation and indices for assessing disease activity. We did not find a significant difference between the level of quality of life in patients with imaging and clinical arm of nr-ax SpA.
6. We found statistically significantly higher values of acute-phase reactants and ASDAS-CRP in men with nr-ax SpA compared to women. There are no significant differences in the assessment of physical function, quality of life and SPARCC between the sexes.
7. Treatment with NSAIDs and sulfasalazine did not affect disease activity (BASDAI) and physical function (BASFI) in patients with nr-ax SpA.
8. A negative impact of smoking on quality of life (ASQoL) in patients with nr-ax SpA is found.

Contributions: The contributions are 10, divided into two groups - of original nature (5) and of confirmatory nature (5) and are important for clinical practice.

➤ **Contributions of an original nature:**

1. For the first time in Bulgaria patients with non-radiographic axial spondyloarthritis are examined and analyzed - their demographic characteristics, assessment of laboratory and disease activity, physical function, functional deficit and quality of life.
2. For the first time in Bulgaria and one of the few studies in the world that compares the image and clinical arm of patients with non-radiographic axial spondyloarthritis.

3. For the first time in Bulgaria and one of the few studies in the world that compares the two sexes not only in the general group of patients with nr-ax SpA, but also in subgroups.
4. For the first time in Bulgaria the connection of the SPARCC scoring system with the level of general disease activity and quality of life in patients with nr-ax SpA is established.
5. For the first time, a simplified algorithm has been proposed to help the rheumatologist's daily clinical practice, which aims to optimize the possibilities for early diagnosis of SpA in the non-radiographic phase.

➤ **Contributions of a confirmatory nature:**

1. It is confirmed that despite the absence of irreversible structural changes and a short duration of symptoms in nr-ax SpA, the quality of life deteriorates.
2. Approximately the same sexual performance in nr-ax SpA was confirmed, as well as the association of males with higher levels of disease activity.
3. The connection between the acute phase indicators and the level of assessment of the disease activity is confirmed.
4. Higher levels of disease activity according to ASDAS-CRP in patients with extraaxial manifestations have been confirmed.
5. The link between smoking and deteriorating quality of life, as measured by ASQoL, in patients with nr-ax SpA was confirmed.

The abstract is presented in Bulgarian and English and the Bulgarian version contains 92 pages, the English version – 59, and reflects what is written in the dissertation. It is in accordance with the requirements.

Publications: In connection with the dissertation the author presents 4 publications in journals and 3 presentation on scientific forums.

Conclusion: I appreciate the work of Dr. Svetoslav Dimitrov on the topic „*Determinants of quality of life in patients with nonradiographic axial spondyloarthritis: analysis based on main aspects of the disease*“ as interesting in scientific terms and important for clinical practice.

I consider this dissertation meets the requirements for awarding the educational and scientific degree "PhD" according to Academic Staff Development Act in the Republic of Bulgaria and the Rules for the Academic Staff Development at the Medical University of Varna.

Based on the above merits of the dissertation of Dr. Svetoslav Dimitrov, I strongly recommend to the honorable members of the Scientific Jury to vote positively and to award Dr. Svetoslav Pavlov Dimitrov the educational and scientific degree "PhD".

30.06.2022
Sofia



Prof. Borislav Georgiev Georgiev, MD, PhD