REVIEW

By Associate Professor Dr. Tsvetoslav Antonov Georgiev, PhD

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of a dissertation work for the award of the educational and scientific degree

"doctor" on the topic:

"PAIN AS PART OF THE RHEUMATOLOGICAL MANIFESTATIONS OF THE COVID-19 VIRAL INFECTION"

Doctoral Program "Internal Diseases",

Professional direction 7.1. Medicine,

Area of higher education 7. Healthcare and sports

Author of the dissertation: Dr. Simona Bogdanova-Petrova

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Relevance of the topic

COVID-19 is a disease with a pandemic dissemination that is very high contagiousness and has a high risk of permanent disability and mortality. Tissue damage in critically ill patients is mediated by proinflammatory cytokines, similar to a number of autoimmune rheumatic diseases. All these data undoubtedly lead to

changes in the perception of pain, the mood and emotions of the patients - a problem that the PhD student explores in detail in his dissertation work.

In addition, manifestations from the musculoskeletal system are very often present in the clinic of patients with COVID-19, and the most common are pain phenomena - myalgias and arthralgias. In this regard, pain of musculoskeletal origin in COVID-19 is associated with or worsened by the presence of anxiety and depressive symptoms. On the other hand, pain, apart from the presence of inflammation, is significantly affected by the age and gender of the patient.

The presented dissertation work of Dr. Simona Bogdanova-Petrova is dedicated to a current and insufficiently studied problem, which is the genesis of pain as part of the rheumatic spectrum of manifestations of the coronavirus disease. The doctoral student has determined factors predicting the manifestation and severity of musculoskeletal pain in patients with COVID-19, to be applied in clinical practice. The motivation of this dissertation is due to the fact that, both globally and in our country, musculoskeletal pain in SARS-CoV-2 infection is an understudied problem. Its study and characterization would enable the discovery of new diagnostic and prognostic markers of the disease, as well as the assessment of the patient's perception of pain and suffering and its correlation with the severity of the infection.

Volume and structure

The dissertation is written on 166 standard typewritten pages. Contains 55 tables, 21 figures and 9 graphs. The literature reference includes 419 titles. In connection with the dissertation, a total of 2 full-text publications and 9 reports were published in scientific forums in the country and abroad. The two full-text publications were published in the journal Rheumatology, referenced in the world-renowned Scopus database. Two of the attached scientific forum participations with reports were realized during the annual European Congress of Rheumatology and published as reports in the prestigious journal Annals of Rheumatic Diseases.

Literature overview

An in-depth analysis of the world literature on issues related to the issue of musculoskeletal pain in COVID-19 was performed. In the literature review, Dr. Bogdanova-Petrova perfectly combines the broad spectrum of components of the disease process in the context of the subjective sensations of the patients she has studied and not studied by her. This is evidenced by the large number of sources that have been used.

Among the critical notes, I would add the lack of articles by Bulgarian authors among the sources used, apart from the available self-citations. This can be explained by the innovativeness of the topic and the small number of Bulgarian authors actively working in the field of COVID-19 and the connection of the infection with pain, psychological attitudes and rheumatic diseases.

Aim and tasks

The purpose of the dissertation work is precisely and clearly defined. The research in the dissertation work is also subordinate to it. The tasks are five in number, which are precisely formulated and correspond to the set goal. Dr. Simona Bogdanova-Petrova sets herself the task of assessing the severity of the manifestation of myalgias and arthralgias in patients treated in clinical settings with COVID-19, to analyze the anxiety-depressive manifestations in patients treated in clinical settings with COVID-19, to examine the relationship between the severity of pain syndrome and laboratory indicators of inflammation predicting the severity of the course of COVID-19, to assess the relationship between the severity of pain syndrome and the presence of anxiety and depressive symptoms in patients, to analyze the relative severity of both anxiety-depressive symptoms, as well as inflammatory indicators for the presence and expression of pain sensations.

Patients and controls

The PhD candidate has designed a single-center, observational, single-point study that involved 364 patients with proven COVID-19 and new-onset joint-muscle pain during the acute phase of COVID-19 who signed a pre-prepared informed consent. These patients were compared with a control group of 130 patients with chronic inflammatory joint disease pain who were on long-term anti-cytokine drug therapy.

The study was conducted at the Rheumatology Clinic at the "St. Marina" after approval by the Research Ethics Committee at the Medical University - Varna with protocol No. 116/28.04.2022 (KENIMUV), in accordance with the requirements of the Helsinki Declaration, the patients were informed in detail about the goals and methodology of the planned study, about the possible inconveniences during inclusion (traumatic experience when taking blood, additional time for conducting a clinical examination, conversation and providing the available medical documentation).

Materials and methods

In the presented dissertation, the demographic data of the COVID-19 and rheumatic patients, lung involvement (for COVID-19 patients), the degree of inflammation, muscle-joint pain - presence and strength, psychoemotional status - presence and degree have been evaluated using appropriate tools. of anxiety and the level of depression. Validated questionnaires and pain, anxiety, and depression scales were administered to assess sociodemographic and clinical characteristics of COVID-19 patients and controls. With their help, a comprehensive and in-depth study of the key components of pain and diseases in general has been carried out.

Both standard laboratory tests and innovative tests were done. Acute-phase markers of inflammation including: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen were investigated in all study participants, while ferritin, lactate dehydrogenase (LDH), thrombotic biomarkers (D-dimer), as a

specific end product of fibrinolysis have only been studied in patients with coronavirus infection.

Statistical analysis contributes to a significant increase in the quality of the research, giving Dr. Simona Bogdanova-Petrova the opportunity to draw objective and well-founded conclusions from the data she has collected. This contributes to the significance of the doctoral student's dissertation work and applicability in real conditions. I believe that the statistical methods used are suitable for researching the purpose and tasks of the dissertation.

Results

The study of the specified socio-demographic, clinical, laboratory and imaging parameters in the individual groups was carried out in compliance with all the requirements for obtaining reliable results, which is reflected in the published publications. The results are well illustrated in tables and figures. They illustrate the significance of the methods used to assess disease activity.

Of particular interest is the grouping of patients with COVID-19 according to self-assessment tools in the so-called cluster analysis, as its results may find direct application in clinical practice. The analysis for mood disorders and pain intensity can be applied as a screening method for patients in the so-called "risk group" - polymorbid, elderly, with severe disease, ensuring that these patients are referred early and promptly to the appropriate specialist for subsequent psychological or psychiatric treatment. This would help improve the quality of life for these patients.

Discussion

Dr. Simona Bogdanova-Petrova is an extremely well-prepared and analytical doctoral student who has demonstrated great skill in discussing the topic of her dissertation. Her arguments and examples are well-founded and presented with

clarity and she has successfully handled the analysis of complex topics using a comprehensive and creative approach. Her work is an expression of a high level of professionalism and critical thinking, making it a valuable contribution to the academic community.

The discussion emphasizes the available results. The claims are supported by many and most of which, contemporary studies and their results from the available literature. To my knowledge, this is the first time pain, anxiety, and depression levels in Bulgarian patients with COVID-19 have been examined, compared to their levels in chronic inflammatory disease patients, and their correlations with various disease characteristics have been studied.

Conclusions and contributions

The dissertation ends with 9 conclusions presented, which in a generalized form confirm the results of the conducted studies. The contributions are correctly defined and reveal the merits of the dissertation work.

In conclusion, I can summarize that Dr. Simona Bogdanova-Petrova carefully selected her patients, conducted a specific study and analyzed the results, and did an excellent job of discussing them in the context of the available data in the world literature on this problem . The innovative research carried out, the derived results and the apparently current state of the problem give me reason to give a high assessment to the presented dissertation work.

I am voting positively for the awarding of the educational and scientific degree "doctor" to Dr. Simona Bogdanova-Petrova and I recommend to the other respected members of the scientific jury to do the same.

11.05.2023   Signature: ....

/Assoc. Prof. Dr. Tsvetoslav Georgiev, PhD/