

**Written review of the official reviewer on the dissertation work (in the form of a series of articles) of doctoral student Akerke Auanassova on the topic «Systemic vasculitis at the present stage: clinical and laboratory characteristics and optimisation of patient management strategy», submitted for the degree of Doctor of Philosophy (PhD) on speciality 8D10141 «Medicine»**

№	Criteria	Compliance with criteria (underline one of the response options)	Justification of the official reviewer's position (highlight comments in <i>italics</i> )
1.	The dissertation topic (as of the date of its approval) aligns with the directions of scientific development and/or state programs.	1.1 Compliance with priority areas of scientific development or state programs: 1) The dissertation was carried out within the framework of a project or targeted program funded by the state budget (indicate the name and number of the project or program); 2) The dissertation was carried out within the framework of another state program (indicate the name of the program); 3) <b><u>The dissertation corresponds to a priority area of scientific development approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan (indicate the direction).</u></b>	Dissertation work corresponds to the priority direction of science development approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan «Science of Life and Health».
2.	Significance for Science	The work <b><u>makes</u></b> /does not make a significant contribution to science, and its importance is <b><u>well explained</u></b> /not explained	The dissertation research contains important scientific results for modern healthcare and solves both theoretical and applied research tasks. The relevance of the dissertation work is beyond doubt. The types and features of systemic vasculitis most common among the adult population in modern conditions, depending on gender, age and socio-demographic characteristics in the Republic of Kazakhstan (2019-2021), which have not been studied before, were presented. A.T. Auanassova developed and validated a unique survey to assess the

			<p>knowledge and understanding of healthcare professionals (rheumatologists, internists, general practitioners, etc.) regarding diagnosing and managing patients with systemic vasculitis, which can be used in future studies. As a result of the research (online survey) with the participation of respondents from 21 countries (top 5 countries: India, Kazakhstan, Ukraine, Croatia, Turkey) received valuable information on the management of patients with ANCA-associated vasculitis (AAV) during the COVID-19 pandemic. This study helped to gain information about the differences in the perception of AAV in different countries, including current practices and recent management changes. It also provided information on the treatment of COVID-19 in patients with AAV. «Recommendations for the management of systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2)» were developed. The recommendations are meticulously crafted, drawing from the clinical protocols of the Republic of Kazakhstan, the recommendations of EULAR (European League Against Rheumatism), ACR (American College of Rheumatology), the literature data of recent years and the results of the own research. This comprehensive approach, considering the relevance, the amount of work done, and the results obtained, underscores the significant contribution of A.T. Auanasova's dissertation to science.</p>
3.	Principle of Independence	<p>Level of independence:  1) <b>high;</b>  2) medium;  3) low;  4) no independence.</p>	<p>A.T. Auanassova showed high independence and initiative in carrying out scientific tasks. The dissertator personally completed all the planned tasks, including organizing the research and collecting and analyzing initial data, and the relevant conclusions were formed. A.T. Auanasova took an active part in creating, piloting and distributing an international online questionnaire for medical professionals. The author of the dissertation also developed «Recommendations for the management of systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19</p>

			(SARS-CoV-2)». In the vast majority of published articles, the role of the doctoral student as the first author and correspondent is paramount, emphasizing the importance of her contribution.
4.	Principle of Internal Unity	4.1 Justification of the dissertation's relevance: 1) <b>justified;</b> 2) partially justified; 3) not justified.	The relevance of this dissertation research work is due to several factors reflecting current pressing health problems. SV is considered a problem that causes several problems from the point of view of diagnosis and treatment. Diagnosis of SV is a difficult task due to the rarity and complexity of the clinical picture, which can lead to untimely treatment, leading to damage to target organs, disability, mortality and increased financial costs for additional research. Of particular importance is increasing the awareness and literacy of primary care physicians, general practitioners, and rheumatologists regarding the timely diagnosis of systemic vasculitis and improving patients' prognosis. In worldwide studies, the level of disability associated with the diagnosis of SV is about 20-30%. Recent studies have shown that disability still negatively affects 20-40% of patients with SV. Studies that examined the financial consequences of early retirement or disability due to a diagnosis of SV found that income decreased significantly in 5-26% of patients.
		4.2 The content of the dissertation reflects the dissertation topic: 1) <b>reflects;</b> 2) partially reflects; 3) does not reflect.	The published publications thoroughly cover the dissertation research topic, presenting a logical sequence that unveils the features of systemic vasculitis and the critical need for new approaches to its timely diagnosis and management. The doctoral student's work, which includes reviews, a questionnaire, and the results of a retrospective analysis, provides a comprehensive understanding of the set initial goals and objectives of the thesis, making it a significant contribution to the field. The author has achieved his goals and solved the research tasks.
		4.3. The aim and objectives correspond to the dissertation topic: 1) <b>correspond;</b> 2) partially correspond; 3) do not correspond.	The research goals and objectives fully correspond to the stated topic and also reflect the novelty and practical significance of the dissertation research.

		<p>4.4 All sections and statements of the dissertation are logically interconnected:</p> <ol style="list-style-type: none"> <li>1) <b>fully interconnected;</b></li> <li>2) partially interconnected;</li> <li>3) no interconnection.</li> </ol>	<p>The results of the dissertation's author are an integral scientific study, where the research carried out and the scientific data obtained are interconnected and flow from each other, creating a single integral completed work. The author conducted a review aimed at analysing systemic vasculitis at the present stage, newly formed systemic vasculitis after SARS-CoV-2 infection and vaccination, as well as studying the causes and consequences of delayed diagnosis of systemic vasculitis and a retrospective analysis of medical history records of patients with systemic vasculitis at the second stage, i.e. on clinical databases. A critical approach was applied to analysing literature and sources, making it possible to highlight the problem studied objectively. All the data for the study were obtained from reliable sources, and the results published in scientific articles were blindly reviewed by experts from international journals. Next, a survey was conducted to assess medical professionals' knowledge and conclusions about systemic vasculitis.</p>
		<p>4.5 The new solutions (principles, methods) proposed by the author are substantiated and evaluated in comparison with known solutions:</p> <ol style="list-style-type: none"> <li>1) <b>critical analysis is present;</b></li> <li>2) partial analysis;</li> <li>3) the analysis consists of quotes from other authors rather than the author's own opinions;</li> <li>4) no analysis.</li> </ol>	<p>A.T. Auanassova critically analyzed the literature data and the research results, based on which she developed a unique survey and assessed doctors' knowledge and understanding regarding ANCA-associated vasculitis (AAV). The «Recommendations for the management of systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2)» developed by the author are reasoned and evaluated in comparison with world data with a critical analysis.</p>
5.	Principle of Scientific Novelty	<p>5.1 Are the scientific results and statements new?</p> <ol style="list-style-type: none"> <li>1) <b>completely new;</b></li> <li>2) partially new (25-75% are new);</li> <li>3) not new (less than 25% are new).</li> </ol>	<p>The scientific results obtained during the dissertation research and the provisions submitted for defence are new.</p>

		<p>5.2 Are the conclusions of the dissertation new?</p> <p>1) <b>completely new;</b>  2) partially new (25-75% are new);  3) not new (less than 25% are new).</p>	<p>The conclusions of the dissertation research are entirely new and align with the tasks set. The study results demonstrated that COVID-19 infection and COVID-19 vaccines can cause SV, similar to the phenotypes of primary vasculitis. The vasculitis that develops post-COVID-19 (SARS-CoV-2) damages blood vessels of all sizes. It was recommended that they be classified as «Specific vasculitis associated with the virus» in the Chapel Hill Consensus, potentially impacting healthcare strategies.</p> <p>During the assessment of the factors leading to a delay in the diagnosis of SV, it was concluded that the relatively low level of SV and insufficient awareness of general practitioners, as well as the uneven clinical signs of SV, suggest a delay in diagnosis. Increasing the awareness of therapists and providing patients with timely access to rheumatological care ensures the initiation of timely treatment, which leads to a reduction in the damage caused by SV and an improvement in the quality of life.</p> <p>A retrospective study of the demographic, clinical and anamnestic characteristics of patients with SV showed that the patients had comorbid diseases such as diabetes mellitus, iron deficiency anaemia, coronary heart disease, hypertension and diseases of the gastrointestinal tract. In the studied groups, 27.1% of patients have a disability, and the majority of patients have group II disability.</p> <p>As a result of a cross-sectional analysis (online survey) among healthcare professionals, heterogeneity in diagnosis and treatment concerning AAV was revealed. It was found that there is no consensus regarding patient management during COVID-19 (SARS-CoV-2).</p> <p>«Recommendations for the management of systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2)» have been developed. The guidelines have been designed to guide medical professionals providing medical care to patients with autoimmune rheumatological diseases, as well as students and residents of medical universities.</p>
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6.	Justification of the main conclusions	<p>All main conclusions <b>are</b>/are not based on scientifically sound evidence or are sufficiently well substantiated (for qualitative research and fields of study in arts and humanities).</p>	<p>The conclusions and provisions of the thesis are based on a sufficient and comprehensive study using sound methods and a carefully conducted analysis of the results. The scientific apparatus of the dissertation research is built professionally and devoid of logical contradictions. The articles have been published by doctoral student in scientific journals representing evidence-based medicine («Clinical Rheumatology» (Great Britain), «Rheumatology International» (Germany), and «Central Asian Journal of Medical Hypotheses and Ethics» (Kazakhstan).</p>
7.	Main statements submitted for defence	<p>It is necessary to answer the following questions for each statement separately:</p> <p>7.1 Has the statement been proven?  1) <b>proven;</b>  2) rather proven;  3) rather not proven;  4) not proven;  5) it is impossible to verify the proof of the statement in its current form.</p> <p>7.2 Is it trivial?  1) yes;  2) <b>no;</b>  3) it is impossible to verify the triviality of the statement in its current form.</p>	<p><b>The first statement to defend:</b>  SV is most often found in females of reproductive age in the studied population. Takayasu's disease and IgA vasculitis were the most common. The most common clinical symptoms in patients with SV were injuries to the musculoskeletal system, digestive system, skin, peripheral blood vessels, and cardiovascular system.  The position has been proven, is not trivial, is new, has a wide range of applications, and is presented by a publication in the international peer-reviewed journal Rheumatology International.</p> <p><b>The second statement to defend:</b>  The study revealed a heterogeneity in how attending physicians identify and approach the management of ANCA-associated vasculitis (AAV). There is a lack of consensus regarding the diagnosis and treatment of AAV during COVID-19. However, all</p>

		<p>7.3 Is it new?</p> <p>1) <b>yes;</b></p> <p>2) no;</p> <p>3) it is impossible to verify the novelty of the statement in its current form.</p>	<p>respondents agreed on the need to improve their knowledge of AAV during medical training.</p> <p>The position has been proven, is not trivial, is new, has a wide range of applications, and is presented by a publication in the international peer-reviewed journal Clinical Rheumatology.</p> <p><b>The third statement to defend:</b></p> <p>Recommendations have been developed for managing patients with SV during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2), depending on the results of PCR testing.</p> <p>The provision has been proven, is not trivial, is new, has a broad application level, one author's certificate and three implementation certificates have been obtained and is also represented by a publication in the international peer-reviewed journal Central Asian Journal of Medical Hypotheses and Ethics.</p>	
		<p>7.4 Level of applicability:</p> <p>1) narrow;</p> <p>2) medium;</p> <p>3) <b>wide;</b></p> <p>4) it is impossible to verify the level of applicability of the statement in its current form.</p>		
		<p>7.5 Has it been proven in the article?</p> <p>1) <b>yes;</b></p> <p>2) no;</p> <p>3) it is impossible to verify the proof of the statement in the article in its current form.</p>		
8.	Principle of Reliability. Reliability of sources and provided information.	<p>8.1 Is the choice of methodology justified or sufficiently detailed?</p> <p>1) <b>yes;</b></p> <p>2) no.</p>	<p>The choice of research methods is justified and fully corresponds to the tasks set.</p> <p>The dissertation research is based on a broad and detailed methodology described in the articles, which includes the use of competent literature search strategies, a retrospective study (study of data from 162 patients), a study of a series of clinical cases (study of clinical cases of systemic vasculitis in the world practice and the Turkestan region); a cross-sectional study (online survey among specialists healthcare: rheumatologists, general practitioners, etc.).</p>	
		<p>8.2 The results of the dissertation work were obtained using modern methods of scientific research and techniques for data processing and interpretation with the use of computer technologies:</p> <p>1) <b>yes;</b></p> <p>2) no.</p>		<p>A representative sample and correct statistical processing methods using IBM SPSS, version 20 and IBM SPSS Statistics, version 26 statistical data processing programs allowed the doctoral student to interpret the data and formulate reliable conclusions correctly.</p>
		<p>8.3 Theoretical conclusions, models, identified relationships, and patterns are</p>		<p>The theoretical conclusions, identified relationships, and patterns have been proven and confirmed by correct and relevant</p>

		<p>proven and confirmed by experimental research (for fields of study in pedagogical sciences, results are proven based on a pedagogical experiment):</p> <p>1) <b>yes;</b> 2) no.</p>	<p>statistical indicators calculations.</p>
		<p>8.4 Important statements are: <b>confirmed</b> / partially confirmed / not confirmed by references to relevant and reliable scientific literature.</p>	<p>All the author's statements and statements submitted for defence are discussed in detail in the world community through social networks and citations, supported by links to relevant and reliable scientific literature.</p>
		<p>8.5 The literature sources used are: <b>sufficient</b> / not sufficient for the literature review.</p>	<p>The doctoral student studied a sufficient amount of literature, which, according to the published articles, totals 329 sources.</p>
9	Principle of Practical Value	<p>9.1 The dissertation has theoretical significance:</p> <p>1) <b>yes;</b> 2) no.</p>	<p>The theoretical significance of the scientific work is beyond doubt, and the results can be used in the educational process among undergraduate students, interns and residents.</p>
		<p>9.2 The dissertation has practical significance and there is a high likelihood of applying the results in practice:</p> <p>1) <b>yes;</b> 2) no.</p>	<p>The dissertation research is of practical importance as a result of the doctoral student's study, «Recommendations for the management of systemic vasculitis during COVID-19 (SARS-CoV-2) and after vaccination against COVID-19 (SARS-CoV-2)» were developed and included in the clinical and research work of medical organizations (confirmed by the author's certificate and acts of implementation).</p>
		<p>9.3 The proposals for practice are:</p> <p>1) <b>completely new;</b> 2) partially new (25-75% are new); 3) not new (less than 25% are new).</p>	<p>The practice offers are entirely new. As a result of the dissertation research, the doctoral student received 2 Certificates of entry into the state register of Copyrighted objects (Republic of Kazakhstan): «Survey for assessing doctors' understanding of the management of vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) (AAV) in COVID-19», №3 806 1 dated July 21, 2023 and «Recommendations for the management of systemic vasculitis during COVID-19 and after vaccination against COVID-19», №39155 dated September 21, 2023.</p>



10.	Quality of Writing and Formatting	<p>The quality of academic writing:</p> <p>1) <b>high</b>;</p> <p>2) medium;</p> <p>3) below medium;</p> <p>4) low.</p>	<p>The dissertation work is represented by six articles published in international peer-reviewed journals in the Web of Science Core Collection and Scopus databases. The seventh article was published in the journal included in the list of publications recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan. The work is characterized by clear and precise presentation, logical consistency and good presentation style.</p> <p>The quality of academic writing is high.</p>
11.	Comments on the Dissertation	<p>The scientific articles are written at a high level; I have one clarifying question:</p> <p>How can you explain the high level of disability among patients with systemic vasculitis in the study population?</p>	
12.	<p>The scientific level of the doctoral student's articles on the research topic (in case of dissertation defence in the form of a series of articles, the official reviewers comment on the scientific level of each article on the research topic)</p>	<p><b>1. Article: «New-onset systemic vasculitis following SARS-CoV-2 infection and vaccination: the trigger, phenotype, and outcome»</b></p> <p><u>The scientific level:</u> The article studied the effect of COVID-19 and the vaccine against it on systemic vasculitis, as well as the impact of the disease and immunosuppression on the immunogenicity of the COVID-19 vaccine. The doctoral student developed recommendations for managing patients with systemic vasculitis during the COVID-19 pandemic based on this and other articles and recommendations from reputable international communities. These recommendations have been implemented in the practical scientific and methodological work of several medical institutions and HEIs.</p> <p><b>2. Article: «SARS-CoV-2 as a trigger of IgA vasculitis: a clinical case and literature review»</b></p> <p><u>The scientific level:</u> This article thoroughly analyzes and describes documented cases and an own case of IgAV caused by SARS-CoV-2. The cases described in the review indicate a possible link between COVID-19 and IgAV. SARS-CoV-2 has the potential to cause IgAV. IgAV manifests during or after coronavirus infection for several days or months. Healthcare professionals should be informed about the possible link between COVID-19 and IgAV to ensure prompt and effective care for those affected. Early detection and treatment with glucocorticosteroids are crucial, leading to rapid recovery. This article is valuable for practical healthcare and can help rheumatologists and related specialists understand the clinical characteristics of IgAV, involving them in diagnosing and treating this disease.</p> <p><b>3. Article: «Diagnostic delays in systemic vasculitides»</b></p> <p><u>The scientific level:</u> This review article focuses on delays in diagnosing primary vasculitis and its causes. As a result of a comprehensive analysis, possible steps for the early detection and treatment of these diseases were</p>	

presented. These include informing healthcare professionals and the public about vasculitis's signs and symptoms, expanding rheumatologists' staff and facilitating timely referral to a doctor, introducing easily accessible and reliable tests for early detection, and optimizing treatment and diagnostic methods. Such measures can improve overall disease outcomes by ensuring long-term remission, minimal damage, and improved quality of life.

**4. Article: «The impact of the COVID-19 pandemic on patients with systemic vasculitis: a single-centre retrospective study»**

The scientific level: For the first time in the Republic of Kazakhstan, a study was conducted on the types and characteristics of systemic vasculitis, which is the most prevalent among the adult population in contemporary conditions. This study is of great importance for practical healthcare professionals in understanding the impact of systemic vasculitis on the social status of patients. Its results can provide valuable information to improve medical practice and patient care. The research examined these factors based on gender, age, and socio-demographic characteristics. This work is significant in Kazakhstan and globally, as it contributes to advancing scientific knowledge in this field.

**5. Article: «Clinical and anamnestic features of patients with systemic vasculitis: a single-center retrospective study»**

The scientific level: The article contains informative materials about the features of systemic vasculitis in the Republic of Kazakhstan, which have been thoroughly studied and analyzed. The study draws attention to the urgency of the problem by identifying the most frequently affected organs of systemic vasculitis among patients, as well as identifying a high percentage of disability among patients.

**6. Article: «Physicians' perceptions about antineutrophil cytoplasmic antibody-associated vasculitis: an online survey report in the time of the COVID-19 pandemic»**

The scientific level: As part of this study, for the first time, a systemic vasculitis (AAV) survey was conducted among healthcare professionals in the Republic of Kazakhstan and abroad, and physicians' knowledge and understanding regarding the clinical aspects of systemic vasculitis were evaluated. This study helped to gain information about the differences in perception of AAV in different countries, including current practice and recent changes in treatment. It also provided information on the treatment of COVID-19 in patients with AAV. This survey showed that there is still a lack of understanding of standard definitions and a gap between the guidelines and current practice. The article is of high practical importance. The doctoral student received an author's certificate for this questionnaire. The questionnaire can also be used for other nosologies.

**7. Article: «Systemic vasculitis in Kazakhstan: a complex research approach»**

The scientific level: The article presents a comprehensive study aimed at an in-depth understanding of the features of systemic vasculitis. The choice and application of various research methods, including retrospective analysis, analytical methodology and a one-stage cross-examination (online survey), are substantiated. This work is significant in the context of efforts to raise awareness of systemic vasculitis in Kazakhstan and optimize approaches to their treatment. The presented results can significantly impact clinical practice and improve the quality of medical care in this area.

		<p>All articles of the doctoral student are characterized by high scientific novelty, relevance, and the introduction of correct and evidence-based methods. Scientific articles of A.T.Auanassova have great significance for the Republic of Kazakhstan and the international community. They contribute to developing science, health care and educational processes in this area, resolving the actual problem, and forming priorities for adopting effective political decisions.</p>
13.	<p>Official reviewer's decision:</p> <p>1. Award the degree of Doctor of Philosophy (PhD) or Doctor of Profile (in case of defence in a dissertation council at a higher education institution with special status), or petition the Committee to award the doctoral student the degree of Doctor of Philosophy (PhD) or Doctor of Profile (in case of defence in a dissertation council at a higher education institution without special status);</p> <p>2. Send the dissertation for revision if it does not comply with paragraph 4 and/or 6 of the Rules and/or partially complies with the principles (except for the principle of academic integrity) listed in paragraph 5 of the Rules,</p>	<p>The dissertation work of Auanassova Akerke Turebekovna submitted for review on the topic: «Systemic vasculitis at the present stage: clinical and laboratory characteristics and optimisation of patient management strategy» is a completed scientific study, observing the principles of internal unity, practical value, scientific novelty, reliability and academic honesty; It meets the requirements for a dissertation for the degree of Doctor of Philosophy in medicine (PhD) of the Committee for Control in the Field of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, and the applicant Auanassova Akerke Turebekovna deserves to be awarded the degree of Doctor of Philosophy (PhD) in the speciality 8D10141 «Medicine».</p>

<p>and/or there are comments that require correction. In case of defending a dissertation in the form of a series of articles, the dissertation is not sent for revision;</p> <p>3. Deny the awarding of the degree of Doctor of Philosophy (PhD) or Doctor of Profile in case of violation of the principle of academic integrity or non-compliance with the principles of scientific novelty, internal unity, and reliability.</p>	
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**Official reviewer**  
**MD, PhD, Professor,**  
**Head of the Department of Internal Medicine №2,**  
**I. Horbachevsky Ternopil National Medical University**  
**Ternopil Regional Clinical Hospital**  
**Head of Ternopil Regional Internists' Society**



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**Svitlana Smiyan**

