Order No. R-492/02.01.2025

To the Rector

Medical University Plovdiv

REVIEW

On the dissertation work of Dr. Emral Seyfiev Kyosebekirov on the topic "Assessment of the volumetric distribution of body fluids and the effect of infusion therapy in intensive care by bioimpedance analysis" for the award of the educational and scientific degree "DOCTOR" in the doctoral program "Anesthesiology and Resuscitation", with scientific supervisor Prof. Dr. Chavdar Stefanov, MD.

Reviewer: Prof. Dr. Viliyan Platikanov, MD, Medical University "Prof. Dr. Paraskev Stoyanov", Varna

Dear members of the Scientific Jury,
At the first meeting of the scientific jury, I was appointed as one of the external members to prepare a review, which I present below.

Biographical and educational data of the dissertation candidate:
Dr. Emral Seyfiev Kosebekirov was born in 1993. He graduated from the Medical University of Plovdiv in 2018. After graduation, he worked at the Central Emergency Center and several hospitals, since 2019 he has been at the St. George Medical University, and since 2021 he has been an employee of the Medical University of Plovdiv.

Evaluation of the dissertation work:
The infusion policy during intensive care is a basic tool of the resuscitator. How much, when, what, at what speed, what balance is needed, how to make an assessment of efficiency and correctness.... these are just some of the questions that the specialist doctor asks himself when determining the infusion therapy of a critically ill patient. While it can and should help, it can also harm him if it is incorrectly structured. It is not in vain that concepts such as liberal and restrictive infusion policy have been defined. What are the benchmarks for determining correctness? There are many, of different types and with different validity. The presence of many benchmarks means that the problem with the accuracy of infusions exists and there is no single one, no single solution that answers all the questions.

Modern technological achievements are widely penetrating all areas of science and practice. Of course, medicine is no exception. Very soon, artificial intelligence will probably determine many of our activities, some of them will take over completely. The reality of practice will be replaced by virtual reality, augmented or mixed one as well. An example is "Orion" by Meta, which is still for entertainment, but the prototype is about to enter serial use. Bioimpedance measurements are relevant at present and are not so much in the future, but are currently increasingly widely used in medicine. Impedance is a type of resistance that is not visible and requires specific measuring instruments. They must be able to measure impedance, inductance, resistance and capacitance and then analyze them. Each of these instruments has an internal impedance measuring circuit that allows it to function. Indicative of innovative movements is the aspiration of KASIM at MU Plovdiv to implement new technologies. I see such an aspiration in the scientific production submitted to me for review. In technical, intellectual and educational terms, this technology is far from medicine, but it can be used in an adapted way and the results can be applied to everyday practice.

I approach the evaluation of the dissertation work with the clear vision that each dissertation is a unique author's performance, for which there are no categorical boundaries and templates, but there are those accepted by the scientific community, proven in the long-term practice of scientific councils, societies and numerous public defenses.

The dissertation work of Dr. Emral Kosebekirov "ASSESSMENT OF THE VOLUME DISTRIBUTION OF BODY FLUIDS AND THE EFFECT OF INFUSION THERAPY IN INTENSIVE CARE THROUGH BIOIMPEDANCE ANALYSIS" is written on 119 standard typewritten pages. It includes 25 tables, 41 figures and 3 appendices. It is written in proper Bulgarian, is difficult to read, and is arranged according to the requirements. There are many abbreviations that are not listed at the beginning of the presentation, but are explained in the text somewhere, which leads to the need for the reader to go back and look for the explanation. Especially in the "Results" section, there are many numbers, placed or not in brackets, not always explained specifically next to them or on the same page. These and other facts determine the difficulties for the reader in following the main idea, along with the surrounding facts, reflections and conclusions.

Contains 9 + 1 sections:

- introduction,

- literature review,

- goals and objectives,

- materials and methods,

- results

- discussion,

- conclusions,

- contributions,

- used literature,

- applications.

Section "introduction" – covers 1 page and includes a very general description of infusion therapy and bioimpedance analysis.

Section "literature review" is written on 33 pages. It includes data from 167 sources, all in Latin. They are arranged correctly and provide a lot of information on the topic. More than 80% of the authors studied are from the last 10 years. The review is divided into 3 main subsections – one each for infusion therapy and bioimpedance analysis. Especially for bioimpedance analysis, there is information about its importance in almost every medical field – nephrology, hepatology, cardiology, perioperative medicine, etc., which I consider positive, in view of the development of the technology and its application in practical medicine. Each of the subsections is further structured into other sub-subsections. The section ends with subsection 2.3, entitled "Conclusion". It synthesizes and summarizes the information from the literature review. The work would only have benefited if in the conclusion the author had analyzed the current developments in the specifics of intensive care medicine in Bulgaria and the application of the bioimpedance methodology in the monitoring complex.

Section "goals and objectives" – 1 page. Based on the author's views and the extensive literature review, a goal has been formulated, closely related to the title of the dissertation, as well as 4 specific tasks for implementation, clear and precise.

Section "materials and methods" - 24 pages. The study was carried out in 2 stages, with a prospective analysis conducted on 94 intensive care patients from KASIM of St. George University Hospital, for the period December 2022 - May 2024. All bioimpedance measurements were performed by the dissertation candidate. Clear inclusion and exclusion criteria were applied. There is no explicitly formulated working hypothesis, but it is evident throughout the entire section. The research methods are described, along with the methods of clinical observation. The Cole-cole diagram is the chosen appropriate model for characterizing biological tissues, respectively the presence of water in them and the associated electrical conductivity, since here the impedance Z is plotted against the frequency, unlike the Nyquist diagram, which gives the results not in the form of a semicircle, but in the form of an arch and the real impedance Z is plotted against the imaginary one. In these specific cases, partial regression equations, so-called sEREs would not make sense, but could affect the general measurement formula. The author has taken this into account and in conditions of uncertainty the results were not reported. Thus, out of the 123 initially screened patients, only 94 were recruited. Bioimpedance measurement was performed at hours 0, 24, 48 and 72 at all study sites. Technically, the procedure is extremely simple, requiring a specific supine position, with the limbs abducted at 45 degrees and 4 electrode stickers. The rest is a matter of hard - soft wear. The device is easily portable. There is no medicine in the measurement itself. The question is in the interpretation of the data and their significance as a guide and criterion for infusion policy. The water balance is calculated according to an incomplete formula, since invisible losses are excluded from the sum, and they can sometimes increase extremely much and confuse the balance. The author has described this, but I did not find a reason for excluding perspiratio insensibilis from the formula. There is also some ambiguity regarding the cumulative balance, since it is generally and by definition determined for 72 hours – the definition can be found in the publication by Javier Neyra et al, Crit Care Med, 2017 – *Cumulative fluid balance and mortality in sepsis patients with or without acute kidney injury and chronic kidney disease*. With clarification, the cumulative period may be different, but this should be indicated, and I see a graph and a study of this indicator at 24 and 48 hours without additions. The determination of the body weight of study participants is not exact. Since its numerical expression is part of a formula, its approximate determination – as much as relatives say or as much as the patient says, especially at 48 or 72 hours in severe illness, such as sepsis, peritonitis, pneumonia or trauma, as are the patients in the study, can lead to erroneous results and erroneous interpretations, respectively erroneous conclusions and conclusions.

Well-standardized and modern statistical methods have been used, which allow for reliable information and relevant conclusions. The author's techno-bias is too pronounced in some places. For example, there are figures titled "scatter plot", and this is simply a methodology and a type of technique for presenting digital data, but it cannot be the title of a figure or diagram.

Section "results" – 28 pages. The results obtained are described, which correspond to the tasks set. The essential results, relating to a comparative analysis of the volemic status upon admission and at the specified time points of measurement, are on 20 pages and are in line with the idea of the dissertation work. The dependencies found are statistically justified. In general, I believe that the results solve the tasks set.

Section "discussion" – 12 pages for analysis of the results. The characteristics of the patients, the admission diagnosis, mortality and hospital stay, indicators for assessing the volemic status upon admission, during the stay and according to the admission diagnosis are discussed. The comparative analysis of the calculated cumulative water balance and the indicators of the volemic status is also discussed. I believe that the author should allocate more space for reasoned reasoning under section 6.5 – Discussion of the volemic status in critical patients. Less than 1 page is devoted to this, and in my opinion, and according to the basis of the study and the title of the dissertation, this is the most important group of patients. The author's statement, namely: "The second disadvantage of BIA in critically ill patients is that there are often significant and insurmountable interferences in conducting the studies." is worthy of respect and congratulations for his ethics and self-criticism, but this means that the methodology, according to him, already has one disadvantage, there is a second, and probably there are others. I would advise him to concentrate on the positive and applicable qualities of bioimpedance analysis in intensive care, which is difficult to do in just a few sentences, namely in section 6.5 on p. 96.

In the "conclusion" section, the author extrapolates that the results obtained from the present study confirm the conclusions of other publications, namely that bioimpedance analysis can be used as a reliable method for assessing body fluids and, accordingly, optimizing infusion therapy. That is, this scientific study confirms other such studies. The section ends with a prepared protocol for a personalized approach to conducting infusion therapy.

The "conclusions" section presents 6 conclusions drawn from the study.

In the "contributions" section, two main groups have been formed, namely scientific-theoretical and scientific-applied ones.

Scientific production - The dissertation candidate has presented 3 published full-text scientific papers.

Critical notes:

1. They are reflected specifically for each section.

2. Some abbreviations in the text cannot be found in the list of abbreviations at the beginning of the dissertation.

3. Single grammatical errors.

4. There are unnecessary writings and applications that provoke thoughts of searching for a side volume.

CONCLUSION The dissertation work of Dr. Kosebekirov on the topic "Assessment of the volumetric distribution of body fluids and the effect of infusion therapy in intensive care by bioimpedance analysis" has the attributes required for acquiring the scientific and educational degree "DOCTOR". Therefore, regardless of my critical remarks, I propose to the esteemed Scientific Jury to vote positively and grant Dr. Emral Seyfiev Kosebekirov the scientific and educational degree "DOCTOR" in the specialty "Anesthesiology and Intensive Care".

Prepared by the review Prof. V. Platikanov

MD 07.02.2025. Varna