

REVIEW

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By order No. P-109-367, dated 08.08.23, of the Rector of Medical University-Varna and by decision of the scientific jury, protocol No 1/11.08.2023, I am appointed to prepare a review:

Subject: defense of a dissertation on the topic:

"APPLICATION OF ECHOCARDIOGRAPHIC METHODS FOR FUZZY STRATIFICATION DETERMINATION OF THE VOLUME OF SURGERY IN PATIENTS WITH ISCHEMIC MITRAL REGURGITATION"

for the acquisition of the educational and scientific degree " **DOCTOR** "
of **Dr. Daniela Stoyanova Panayotova**

Scientific organization: Department of Cardiovascular Surgery and Angiology, Faculty of Medicine, Medical University - Varna

Professional direction **7.1. Medicine**, Scientific specialty "**Cardiology**", doctoral program "**Cardiology**"

Scientific supervisor: Prof. Dr. Svetoslav Georgiev, PhD, Medical University Varna

Scientific consultant: Prof. Dr. Natalia Nikolova, High Marine School "Nikola Vaptsarov"-Varna, and University of Tasmania, Australia

Brief biographical data:

Dr. Daniela Panayotova was born in Pernik. From 1980-1986, she was a student at the Medical Academy-Sofia. After that, she worked successively as a physician in: Department of Internal Diseases, MHAT-Pernik, Clinic of Cardiology, IVth City Hospital, Sofia, Clinic of Cardiology, Military Academy, Sofia, Clinic of Cardiology in IInd City Hospital, Sofia, Department of Cardiology, Adan Hospital, Kuwait, Cardiac Surgery Clinic, UMHAT "St. Marina", Varna. In 1993, she obtained a specialty in Internal Medicine, and in 1998, a specialty in Cardiology. In 2014, she became a Master in Health Management. Her qualification is as an Expert in echocardiography: transthoracic

echocardiography, transesophageal echocardiography, stress echocardiography - 2013. From 2015-2020 she is a chairman, and from 2020 to the present day, a member of the Commission for awarding Expert level in echocardiography: transthoracic echocardiography, transesophageal echocardiography, stress echocardiography at MU-Varna. The teaching activity began in 2016 as a part-time lecturer in cardiology, and since 2018 until now, she is a full-time assistant Professor in the Department of Cardiovascular Surgery and Angiology teaching Internal Diseases to English language students at MU-Varna. In 2020, she was enrolled as a full-time doctoral student in the Doctoral Program in Cardiology at MU-Varna. Dr. Panayotova is a member of several professional organizations in Bulgaria and abroad.

Dr. Panayotova speaks English.

The submitted documentation for the competition for the educational and scientific degree "Doctor", announced by the decision of the Faculty Council of the Faculty of Medicine, MU-Varna, with protocol No. 7/31.07.2023, is in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria/05.05.2018 and the Regulations for the Development of the Academic Staff at the Medical University of Varna/28.01.2021.

Relevance of the topic

Ischemic heart disease (IHD) is one of the most common heart diseases worldwide. It is a frequent cause of death and disability in the world, and for Bulgaria especially, it is one of the most fatal diseases. The clinical course varies and may be asymptomatic for a long time. On the other hand, IHD is the most common cause of sudden death, especially in people over 60 years of age. It is often complicated by secondary or ischemic mitral regurgitation (IMR), which is the result of changes in the mitral valve apparatus rather than changes in the valve itself. The prognosis for patients with IMR is worse than for patients with IHD but without regurgitation and for patients with primary MR. Operative treatment of patients with IHD and IMP also includes mitral valve correction, together with operative revascularization of the coronary vessels. This complicates the course of the operative process, worsens the postoperative period and is a factor for worse prognosis compared to patients in whom only coronary artery bypass surgery was performed. Selection of appropriate patients for combined operative intervention is difficult for the following reasons: 1) Traditionally, classification of patients has been done quantitatively and there is no specific measure of how typical a given patient is for a given group; 2) The groups are not homogeneous and their comparison is significantly complicated. The correct selection of patients in the appropriate group is critical to the success of the operation. The classification methods proposed so far do not reflect the meaning of the so-called "outliers" and,

therefore, it is necessary to search for new algorithms for the reclassification of patients with IHD who will also need valve surgery.

All this makes the problem considered in the current dissertation significant and appropriate for dissertation.

Structure of the dissertation

The dissertation contains 170 standard typewritten pages. The bibliography covers a total of 324 literary sources, of which 5 are in Cyrillic and 319 are in Latin. It is well illustrated with 15 color and black-and-white figures, 32 tables and 42 mathematical formulas, which are quite informable about the problems under consideration and are easy to understand. There are also two appendices to the dissertation with a total volume of 135 pages.

The dissertation is structured as follows:

Introduction – 2 pages

Literature review – 60 pages (35% of the volume of the dissertation);

Aim and tasks – 1 page;

Material and methods – 65 pages (38%);

Results - 20 pages (12%)

Contributions of scientific work - 1 page

Conclusions – 2 pages

List of publications - 1 page

Appendices – 2 issues, 135 pages in total, with specific examples of application of group selection algorithms for a specific operative method and tables for calculating fuzzy means and determining individual probabilities before and after surgery;

References - 18 pages

I may consent that the structure of the development meets the generally accepted requirements, except for the **lack of a structured discussion part**.

Literature review

It is competently written and shows an excellent knowledge of the available information on the issue. The References chapter includes 324 titles, of which 5 are in Cyrillic and 319 are in Latin.

In the first part, a detailed analysis of the problem of ischemic heart disease is made - types, pathogenesis, and risk factors (e.g., diabetes mellitus, etc.). The role of inflammation as a cause and consequence of IHD is examined in particular detail, and the intimate mechanisms of this interrelationship are described.

The second part of the literature review is dedicated to secondary mitral regurgitation (SMR). Several definitions that have been mentioned in the literature are listed. Epidemiological data suggest that MR is the second most common valve lesion after aortic stenosis, with one-third to one-half of cases being with MR. The pathophysiology of SMR development involves left ventricular and left atrial remodeling that potentiates MR, and this, in turn, leads

to even more significant chamber changes and the vicious cycle closes. Different classifications of MR are considered - the traditional one of Carpentier's and some more recent proposals. An overview of the diagnostic methods of SMR is made, with a significant place being allocated to echocardiography in its two variants - transthoracic and transesophageal, as well as the role of stress echocardiography and deformation techniques in the diagnostic algorithm. The advantages of cardiac magnetic resonance and traditional cardiac catheterization are indicated.

Finally, the main methods of treatment of SMR are discussed, as well as the role of imaging methods peri- and postoperatively, in the diagnosis of complications and in determining the prognosis postoperatively.

Special attention is devoted to the statistical methods of patient selection and, particularly, the Fuzzy Bootstrap procedures. The construction of the samples and the algorithms are revealed in details.

The rich literary material is purposefully synthesized, thought out with skill, maturity and criticality. At the end of the literature review, conclusions are drawn and the unresolved problems are well systematized.

As a remark, I can point out that the volume of the overview could be smaller, avoiding some propaedeutic sections when considering the issues of IHD and SMR, as well as simplifying the statistical part with mathematical formulas. Other methods of risk stratification could have been indicated.

Purpose and tasks

The main aim is clearly defined: using appropriate echocardiographic and clinical indicators to improve the quality and to digitize the safety in the individualized choice of surgical treatment (combined CABG surgery plus mitral valve plastic surgery or isolated CABG surgery), as well as in the diagnosis of the medical status (relatively preserved or relatively impaired) of patients with IHD complicated by chronic ischemic mitral regurgitation by application of fuzzy sets.

In connection with the main objectives, 5 specific tasks are also presented, related to the enrichment of the database of patients with IHD and IMR, improvement of the stratification of patients according to the method of operative treatment and according to the severity of the condition using the method of fuzzy algorithms, as well as proving the benefit of annuloplasty in patients with CHD, depending on individual indicators.

Material and methods

The dissertation is based on the retrospective analysis of a total of 169 patients, who represent a sample of those operated on at the Cardiac Surgery Clinic of UMHAT "St. Marina" for the period 2007-2022. All patients had known significant CAD and significant secondary mitral regurgitation. They are divided into two groups: 85 (Group A) had a combined intervention – revascularization + annuloplasty of the MV (APMV + CABG) and 84 (Group B) had only an isolated revascularization (CABG). Inclusion and exclusion criteria are precisely

described. The number of participants examined is relatively large, which is a prerequisite for obtaining practically and statistically significant results.

The materials and methods section is well presented by Dr. Panayotova, and the clinical data for history, objective examination, laboratory tests and X-ray examination were equally performed in both groups. Echocardiography as the main imaging method is given a major role in the dissertation. The main ways of measuring the cardiac dimensions and function of the cardiac chambers and mitral regurgitation are indicated. As an auxiliary modality, transesophageal echocardiography was also used with all the advantages of the method.

The created database divides the patients into two more subgroups depending on the presence of underlying chronic conditions: A1, B1 and A2, B2. For each patient, 20 identifiers, 18 anamnestic and sonographic preoperative parameters, and 13 three-point parameters were recorded at three different time intervals: baseline, early postoperative, and late postoperative up to 54 months.

The obtained data were processed statistically with a very rich set of statistical methods. In fact, the main weight of the dissertation is in the detailed statistical analyses, where the role of the scientific consultant is also evident. The method of fuzzy means was mainly used and different fuzzy algorithms were prepared: main and auxiliary, which separately for the two groups determine the probability of belonging to a certain pear. As a critic, there is some mixing of methods and results sections here. For example, the prepared algorithms and the creation of fuzzy samples are essentially results of applied statistical methods and their place is in Result section.

For comparison, 8 classifiers based on the Bayesian approach were also used. The latter, however, fail to classify patients with the same precision. Of note, other standard biostatistical methods for discrimination, such as discriminant and logistic regression analysis, were not applied to compare with the fuzzy means method. This would enrich the work in a scientific and didactic aspect.

Results

The results are presented sequentially in several sections:

- Examples of the application of both algorithms, basic and auxiliary, to identify patients, which are presented in Appendix 1. The way of determining the degree of belonging of the specific patient to a certain subgroup leads to the individualization of the approach to surgical treatment.
- Creating fuzzy samples for all 57 features. Fuzzy samples without and with outliers were created for each patient group.
- Deductive statistics with fuzzy pseudo-control groups. The pseudo-control group contains the remaining participants to receive only baseline treatment according to the best practices of the treating physician or team. Fuzzy mean values of parameters in experimental and pseudo-control group were calculated.
- Bootstrap tests determine the statistical difference between the two groups.

- Categorization of the differences in a given measure between the target and pseudo-control groups into five categories depending on the statistical significance of the difference between the two groups. This is done through the three methods described. Finally, the categorization is checked by certain 15 rules.
- Evaluation of annuloplasty on IMR using a pseudo-control group. Appendix 2 shows the effects of annuloplasty on the degree of mitral regurgitation and on its RF. The new fuzzy method (MFPCG) is applied 4 times to solve 4 main problems.

Discussion is very short, only within a few sentences at the end of the results and is practically absent. It indicates what is new in the present work compared to previous similar publications.

Conclusions are 4 in total, but they are not defined separately, and they are in accordance with the main aim and the prespecified tasks. Another caveat is that they are dispersed with discussion and with probable directions for future developments unrelated to the present results.

Overall, 6 contributions of original nature, which are of theoretical and scientific-practical value, have been presented. Original contributions relate to the creation of algorithms to identify patients in subgroups, to correctly categorize them with a view to individualizing the treatment approach, as well as to demonstrate the prognostic benefit of annuloplasty in patients with IMR.

The bibliography comprehensively covers the problem of mitral regurgitation and operative behavior in IHD with IMR. It makes a good impression that most of the titles are from the last 5 and 10 years.

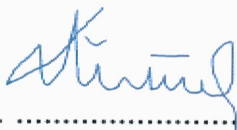
The well-written text, with a mathematically accurate scientific style and good layout, should be noted. The dissertation is well illustrated, including the two appendices that complement the main text of the dissertation

The authoabstract has 51 pages, prepared according to the standards and correctly presents the main problems and results considered in the dissertation work.

In connection with the dissertation, 4 articles were published: 3 in international scientific journals and 1 in Bulgarian in English. Dr. Panayotova is third author on the publications.

In conclusion, I believe that the dissertation work presented by **Dr. Daniela Stoyanova Panyotova** on the topic "**APPLICATION OF ECHOCARDIOGRAPHIC METHODS FOR FUZZY STRATIFICATION DETERMINING THE VOLUME OF SURGERY IN PATIENTS WITH ISCHEMIC MITRAL REGURGITATION**" has all the merits and **MEETS THE REQUIREMENTS** of the Law for development of the academic staff in the Republic of Bulgaria and the Regulations for its application of MU-Varna, **FOR THE AWARD OF THE EDUCATIONAL AND SCIENTIFIC DEGREE "DOCTOR"**, which is why I am convinced to give a **POSITIVE assessment**.

Varna
22.09.2023


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