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

THESIS SUMMARY

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The thesis contains 170 pages and is illustrated with 15 colour and black-and-white figures, 32 tables and 42 mathematical formulas. The research is based on patient data from the Cardiac Surgery Clinic at St. Marina University Hospital – Varna for the period 2007 – 2022 and covers 169 patients operated for IHD complicated with severe chronic ischemic mitral regurgitation.

The bibliography includes 324 references, of which 5 are in Bulgarian and 319 are in Latin (English). EndNote x 8 licensed program was used for presenting the bibliography.

The doctoral thesis was discussed and referred for defence by a departmental council of the First Department of Internal Diseases at the Medical University "Prof. Dr. P. Stoyanov" – Varna.

The defence materials are available at the Career Development Center of MU–Varna.

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ABBREVIATIONS

CABG – Coronary-artery bypass grafting

CAD – Coronary artery disease

CSC – Cardiac Surgery Clinic at St. Marina University Hospital – Varna

E/e' ratio – Ratio of the mitral inflow E wave to the tissue Doppler e′ wave in TTE

EF – Ejection Fraction

ERO – Effective Regurgitant Orifice

FMR – Functional Mitral Regurgitation

IHD – Ischemic Heart Disease

IMR – Ischemic Mitral Regurgitation

LA – Left Atrium

LAVi – Left atrial volume index

LV – Left Ventricle

LVEDV – Left Ventricle End-Diastolic Volume

LVEDVi – Left Ventricle End-Diastolic Volume Index

LVESV – Left Ventricular End-Systolic Volume

LVESVi – Left Ventricle End-Systolic Volume Index

MA – Main algorithm

MFPCG – Method of the Fuzzy Pseudo-Control Group

MR – Mitral Regurgitation

MV Repair – Mitral Valve Repair

RF – Regurgitant Fraction

RRA – Restrictive ring annuloplasty

RV – Regurgitant Volume

SMR – Secondary Mitral Regurgitation

TEE – Transesophageal Echocardiography

TTE – Transthoracic echocardiography

VC – Vena Contracta [mm]

2D – Two-dimensional (echocardiography)

3D – Three-dimensional (echocardiography)

I. Introduction

Ischemic heart disease (IHD), also called coronary heart disease (CHD) or coronary artery disease (CAD), is considered one of the most prevalent heart diseases worldwide. When it is further complicated with ischemic mitral regurgitation (IMR), also called secondary mitral regurgitation (SMR), the prognosis of patients is significantly worsened compared to those who have isolated IHD. There are two main approaches when surgical treatment is necessary: 1. Isolated coronary artery bypass graft (CABG); 2. Combined treatment – CABG + MV Repair (Mitral Valve Repair). In patients with moderate to severe IMR, the optimal approach is still debatable. The studies performed so far are with relatively small groups, difficult to compare because they differ in the diagnostic criteria and surgical techniques involved.

The choice of approach is far from straightforward and is associated with specific difficulties:

1. Traditionally, patient classification is performed quantitatively, and there is no specific measure of how typical a patient is for a given group;

2. The groups are not homogeneous, and their comparison is complicated.

Some patients are suitable for a particular procedure, and others are certainly not, but the decision is unclear and ambiguous for the rest.

This impels the core of the current research, which consists in building three fuzzy algorithms that result in the affiliation degree of each patient to a particular fuzzy subgroup. Thus, the approach is individualized to a considerable extent and reduces the risk of incorrect decisions. Medical resources can be more precisely planned for each specific patient.

II. Aim

This study aims to use appropriate echocardiographic and clinical parameters to improve the quality and to digitize the certainty in the individualized choice of surgical treatment (combined CABG + MV Repair or isolated CABG surgery). Additionally, by applying fuzzy sets, it is aimed at the diagnosis of the medical condition (relatively preserved or relatively impaired) of IHD patients complicated by chronic ischemic mitral regurgitation.

III. Tasks

1. To improve the choice of surgical treatment for patients with IHD complicated by IMR by creating a fuzzy classification algorithm in two inhomogeneous groups: CABG and mitral valve repair or isolated CABG.

2. To improve the homogeneity stratification of patients with combined CABG and mitral valve repair by creating a fuzzy classification algorithm in two relatively homogeneous medical status subgroups: relatively preserved or relatively impaired.

3. To improve the homogeneity stratification of patients with isolated CABG by creating a fuzzy algorithm for classification in two relatively homogeneous medical status subgroups: relatively preserved or relatively impaired.

4. To update the existing CSC database of patients with IHD complicated by IMR by adding new patients, expanding it with new medical features, incorporating a computable system of groups' and subgroups' affiliation degrees from the fuzzy classifications measuring the individual typicality of each patient.

5. To provide evidence by the fuzzy pseudo-control group method of the positive impact of annuloplasty on integral medical parameters: we compared fuzzy samples of indications where a patient's typicality is digitized by his/her affiliation degree to the corresponding subgroup.

IV. Material and Methods

IV.1. Selection of patients included in the study:

The research is based on patient data from the Cardiac Surgery Clinic at St. Marina University Hospital – Varna. The patients were operated on for IHD complicated with mitral regurgitation in the period 2007 – 2022. In this thesis, the study is based on a sample of 169 of these patients after using inclusion and exclusion criteria. Of the included patients with IHD and significant chronic IMR treated surgically, 85 had a combined intervention: revascularisation + MV plasty (MV Repair + CABG), and 84 had isolated revascularisation (CABG).

Study inclusion criteria

1. Patients with IHD and coronary pathology proven by coronary angiography for whom surgical revascularisation is indicated according to current recommendations.

2. Evidence of left ventricular dysfunction (segmental or diffuse hypokinesia to akinesia and dyskinesia in TTE) caused by ischemic heart disease and the presence of mitral regurgitation as a result of these changes.

3. Unambiguous echocardiographic evidence of the absence of morphological changes in the mitral valve leaflets would indicate primary mitral regurgitation.

4. Age over 18 years.

5. Life expectancy is not less than 4 years.

6. Informed consent for surgical intervention, signed by the patient after the Heart Team (HT) has explained the nature of the procedure, and data processing for the purposes of the study.

Study exclusion criteria

1. Patients in the first seven days of the acute stage of myocardial infarction.

2. Mitral regurgitation, which occurred in the evolution of acute myocardial infarction due to mechanical complications – rupture of subvalvular structures (papillary muscle, one or more chordae).

3. Low-grade MR, which does not lead to left ventricular cavity obstruction and is without haemodynamic significance.

4. IMR combined with morphological changes in the valve leaflets and subvalvular apparatus, resulting in primary mitral regurgitation in combination with ischemic mitral regurgitation.

5. Patients with coronary, valvular or other cardiac surgery history.

6. Presence of general or cardiac indications assessed as an absolute or relative contraindication to cardiac surgery.

7. Patients with severe comorbidities due to which life expectancy is less than 3 years.

In all patients included in the study, a detailed history of current and past complaints associated with IHD and secondary IMR and of concomitant indications was taken. A thorough examination of the general and local physical status was performed, including careful auscultation of the heart (systolic murmur in IMR was significantly lower than in primary IMR). Standard laboratory tests in the same volume were performed on all patients included in the study. Each patient had several X-ray examinations during the hospital stay.

IV.2. Echocardiographic methods

At least three transthoracic echocardiographic examinations (TTE) were performed in all patients, and transesophageal echocardiography (TEE) was performed preoperatively and immediately postoperatively in most patients.

Echocardiographic evaluation of the study patients focused on the mitral valve leaflets (morphology and functional features), subvalvular apparatus and mitral valve annulus. These examinations determined the degree of mitral regurgitation in each patient using pulse, continuous-wave and colour Doppler imaging. The examinations were performed from parasternal, apical, two-, three- and four-cuff positions. Left ventricular (LV) dimensions, volumes and function, left atrial (LA) dimensions and volumes were studied.

In selecting the patients in the study, we relied on data from published studies showing that the prognosis for patients with IMR is worse than that for patients with mitral regurgitation with another cause (e.g., primary mitral regurgitation – PMR, in which the valve apparatus is affected). This is due to the fact that in these patients, the diagnosis is a myocardial disease of the left ventricle of the heart, and this disease is the leading cause of IMR, which tends to progress.

After a detailed echocardiographic examination, MR was considered to be of ischemic genesis when the following was found: LV remodelling, displacement of one or both papillary muscles (lateral, dorsal and/or apical), tethering of the LV (symmetric or asymmetric), dilatation and remodelling of the mitral valve annulus, and various combinations thereof. As a prerequisite, no primary morphological changes in the mitral valve apparatus were found.

TTE assessment

1. Left ventricular (LV) end-systolic and end-diastolic dimensions from a parasternal position along papillary muscle short-axis level;

2. LV volumes in end-systole (LVESV) and end-diastole (LVEDV) from apical 4-cuff and 2-cuff positions calculated by the Simpson's method;

3. Left atrial (LA) dimensions and volume;

4. Mitral valve leaflets from parasternal and apical positions were examined to exclude morphological changes;

5. Assessment of the presence and type of leaflet tethering;

6. Measurement of the tethering area and tethering height;

7. Measurement of the degree of coaptation – coaptation length (coaptation line);

8. Assessment of the degree of regurgitation by semi-quantitative and quantitative methods:

- VC

- ERO and RV

- RF.

TEE assessment

When transthoracic echocardiography (TTE) imaging is not absolute for classifying valvular heart problems and establishing a surgical strategy, TEE is very useful and can complement it. TEE helps to exclude organic aetiology when evaluating a patient with MR of ischemic origin and provides high image quality due to the proximity of the transducer to the valve, subvalvular apparatus, and the regurgitation jet.

IV.3. Research database

The database of the present research includes the records of 169 patients presenting with IHD requiring surgical revascularisation and significant chronic IMR. These patients could be treated with surgical revascularisation and mitral valve repair (group A: MV Repair + CABG) or isolated surgical revascularisation (group B: CABG). In our study, each group was divided into two relatively homogeneous subgroups:

- ❖ with relatively preserved medical status (A1 and B1) and
- ❖ with relatively deteriorated medical status (A2 and B2).

For each patient, the following parameters were recorded and archived:

- 20 indicators,
- 18 anamnestic and ultrasonographic preoperative parameters, and
- 13 dimensional (triple) parameters.

The 13 tridimensional parameters were measured at three time points: 1) before surgery, 2) soon after surgery (5 to 30 days after surgery), and finally, 3) late after surgery (6 to 54 months after surgery). Therefore, each tridimensional parameter actually represents three different values at different time points. Thus, each patient is described by a 75-dimensional record of the following parameters.

Table 4.1. Number of patients with measured LVEDVi and LVESVi

Subdivision	Preop LVEDVi Preop LVESVi	Early Postop LVEDVi Early Postop LVESVi	Late Postop LVEDVi Late Postop LVESVi
A	87 (100%)	87 (100%)	78 (89.7%)
A_1	34 (100%)	34 (100%)	31 (91.2%)
A_2	53 (100%)	53 (100%)	47 (88.7%)
B	82 (100%)	82 (100%)	73 (89.0%)
B_1	43 (100%)	43 (100%)	41 (93.1%)
B_2	39 (100%)	39 (100%)	32 (82.0%)
Total (%)	169 (100%)	169 (100%)	151 (89.3%)

Table 4.2. Number of patients with measured LAVi

Subdivision	Preop LAVi	Early Postop LAVi	Late Postop LAVi
A	87 (100%)	87 (100%)	78 (89.7%)
A_1	34 (100%)	34 (100%)	31 (91.2%)
A_2	53 (100%)	53 (100%)	47 (88.7%)
B	82 (100%)	82 (100%)	73 (89.0%)
B_1	43 (100%)	43 (100%)	41 (93.1%)
B_2	39 (100%)	39 (100%)	32 (82.0%)
Total (%)	169 (100%)	169 (100%)	151 (89.3%)

Table 4.3. Number of patients with measured VC, Coaptation Length, Tenting Area, Tenting Height, PISAr and EF

Subdivision	Preop_VC Preop Coaptation Length Preop Tenting Area Preop Tenting Height Preop PISAr Preop _EF	Early_Postop_VC Early Postop Coaptation Length Early Postop Tenting Area Early Postop Tenting Height Early Postop PISAr Early Postop EF	Late_Postop_VC Late Postop Coaptation Length Late Postop Tenting Area Late Postop Tenting Height Late Postop PISAr Late Postop EF
A	87 (100%)	87 (100%)	78 (89.7%)
A_1	34 (100%)	34 (100%)	31 (91.2%)
A_2	53 (100%)	53 (100%)	47 (88.7%)
B	81 (98.8%)	81 (98.8%)	73 (89.0%)
B_1	43 (100%)	43 (100%)	41 (93.1%)
B_2	38 (97.4%)	38 (97.4%)	32 (82.0%)
Total (%)	168 (99.4%)	168 (99.4%)	151 (89.3%)

Table 4.4. Number of patients with measured RV

Subdivision	Preop_RV	Early_Postop_RV	Late_Postop_RV
A	87 (100%)	87 (100%)	79 (90.8%)
A_1	34 (100%)	34 (100%)	31 (91.2%)
A_2	53 (100%)	53 (100%)	47 (88.7%)
B	81 (98.8%)	81 (98.8%)	73 (89.0%)
B_1	43 (100%)	43 (100%)	41 (93.1%)
B_2	38 (97.4%)	38 (97.4%)	32 (82.0%)
Total (%)	168 (99.4%)	168 (99.4%)	152 (89.9%)

Table 4.5. Distribution of patients by MR grading

Discrete-valued time series	Preop Real MR	Early Postop Real MR	Late Postop Real MR
0	0	82	48
0-I	0	9	20
I	0	31	48
I-II	29	20	3
II	64	26	22
II-III	26	0	8
III	42	1	1
>III	8	0	1
Unevaluated	0	0	18

IV.4. Algorithms for classification of patients with significant IMR

All 75-measurement records were analysed, and patients were divided into 4 groups: A1, A2, B1, and B2. However, this division does not provide information to what extent each patient is suitable for one of the two main surgical interventions. Some patients are very suitable for the given procedure, and their affiliation degree would be 1. Other patients are unsuitable for that procedure; their affiliation score in the grading would be 0. For the remaining patients, the affiliation grading score would be between 0 and 1. The scoring of patients undergoing isolated revascularisation (CABG) is not clear but ambiguous. The same applies to group A patients undergoing combined surgery. This led to the development of a basic fuzzy classification algorithm that provides the degree of affiliation to groups A and B.

MAIN ALGORITHM (MA) and determining the affiliation degree of patients with IHD complicated with IMR into the respective affiliation groups.

The purpose of this algorithm is to establish the process of identifying the type of surgical treatment for patients with IHD complicated with IMR, which can be either isolated revascularisation (CABG) or revascularisation combined with mitral valve reconstruction (MV Repair + CABG).

From an information point of view, this problem can be defined as a fuzzy division of patients with IHD complicated by IMR into two groups: A (combined treatment) and B (isolated revascularisation). During classification, we need to find the affiliation degree of the patient to the group to which he/she is classified (μ_A или μ_B).

The choice of surgical treatment is formalized using the 6-step Main algorithm (MA) (Fig. 1).

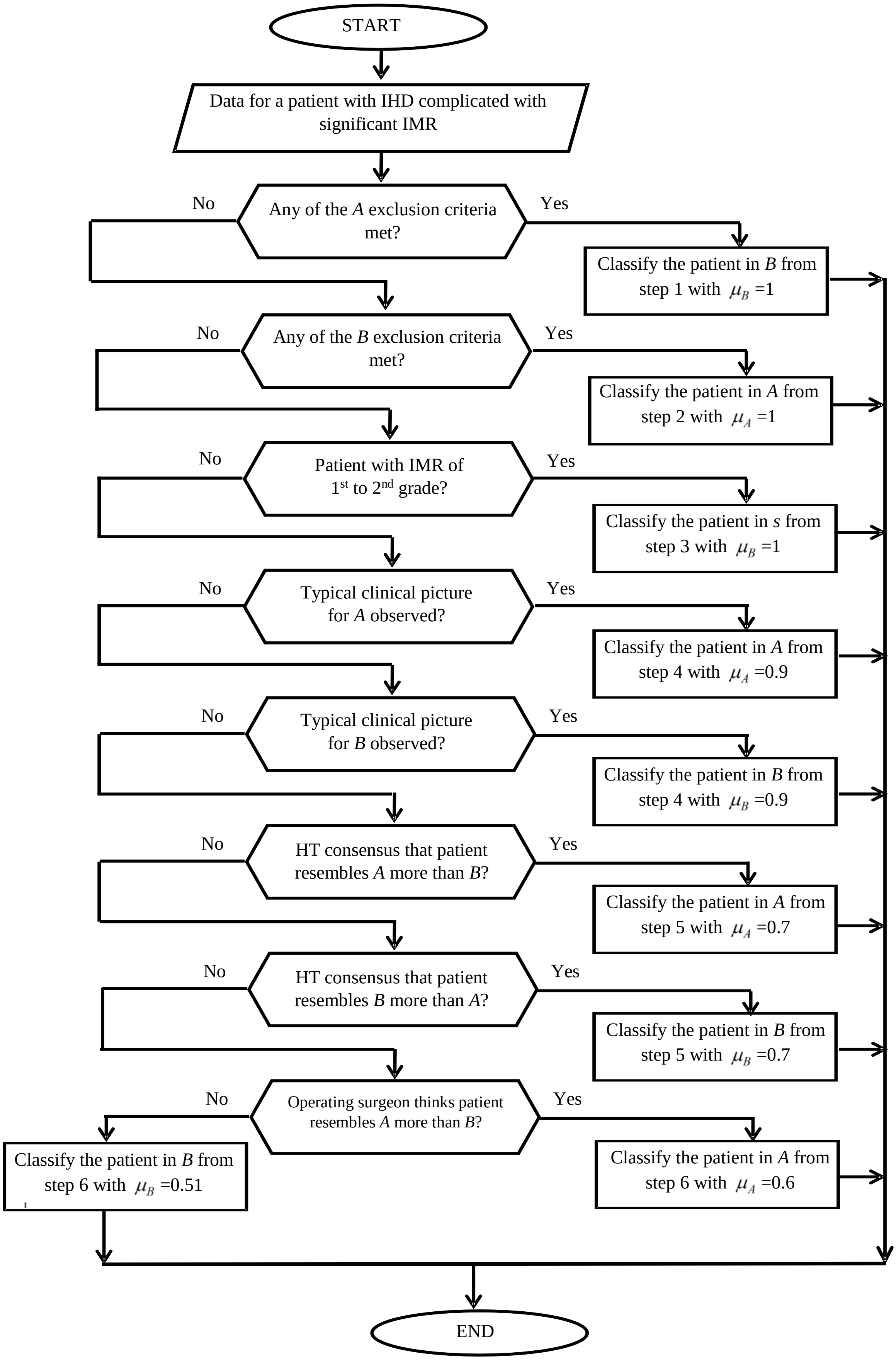

Fig. 1. Basic algorithm for assigning patients to groups A or B

INFORMATION CLASSIFICATION OF GROUP *A* PATIENTS

As outlined above, group A was divided into two relatively homogeneous groups – A_1 and A_2. However, the patients in these subgroups are also not uniformly assigned to their respective subgroups. Subgroup A_1 will include patients with better general and cardiac status. The combined surgical intervention aims to achieve the best possible improvement in the cardiac status (reverse remodelling of cardiac structures) in order to bring the patient back to a normal lifestyle. Subgroup A_2 will include patients with more impaired cardiac and general status. The aim is to implement a combined surgery strategy, including MV Repair, to achieve treatment of heart failure caused by IHD and MR. The expectation for these patients is to stop or slow down the process of remodelling of the left cardiac structures (left ventricle and left atrium) and not so much to achieve their reverse remodelling.

Determining the affiliation degree has significant practical utility. Let patient X be assigned to subgroup A_1 with an affiliation degree of 0.6 and patient Y to be assigned to the same subgroup with an affiliation degree of 1. It does not make sense to assume that the characteristics of these two patients will have equal influence in shaping the characteristics of subgroup A_1. If we model the problem using pure (classical) sets, then the two patients will have equal weight in shaping patient Y will have more weight in shaping the generalized characteristics of subgroup A_1 than those of patient X.

During classification, we need to find the affiliation degree positioning the patient to the subgroup in which he/she is classified, considering that the patient clearly belongs to group A

($\mu_{A_1 \mid A}$ or $\mu_{A_2 \mid A}$).

For this purpose, a 6-step FUZZY AUXILIARY ALGORITHM for A (Auxiliary Algorithm for A – AAA) was created, and the conditional degree of affiliation was determined (Fig. 2).

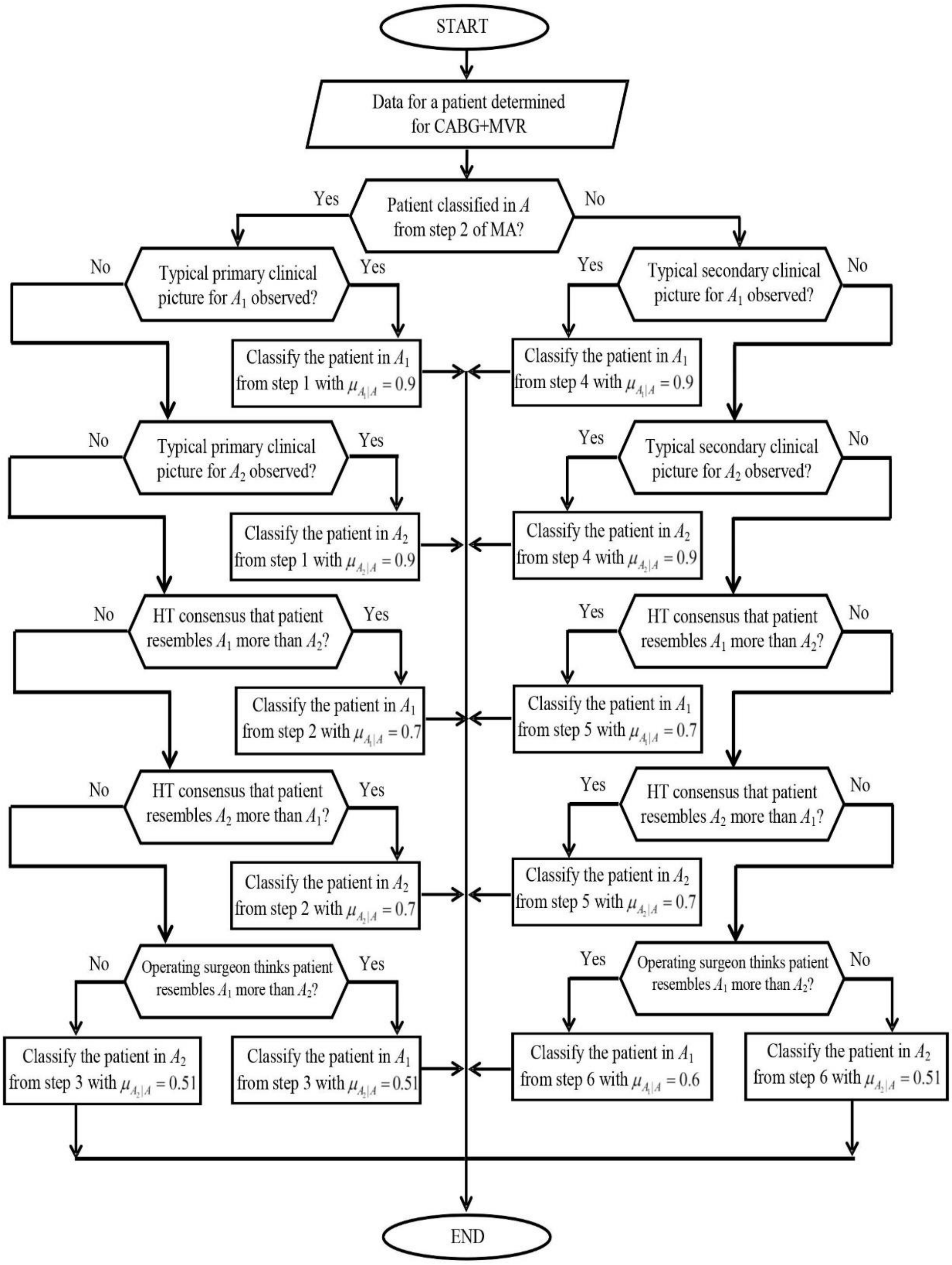

Fig.2. Fuzzy Auxiliary Algorithm for A (AAA) and determining the conditional degree of affiliation

The rationale of AAA is based on the following three medical aspects:

- If ischemic cardiac remodelling is at a relatively early stage, then classification into subgroup A_1 is undebatable.
- If ischemic cardiac remodelling is at a relatively advanced stage, then classification in subgroup A_2 is also undebatable.
- If the patient is classified in group A according to Step 2 of the MA, then he/she has a relatively higher degree of IMR compared to what he/she might have if classified in group A according to steps 4, 5 or 6 of the MA. Therefore, if ischemic cardiac remodelling is advanced, then the patient who is classified in group A according to Step 2 of the MA should be assigned to subgroup A_2, whereas the patient classified in group A according to steps 4, 5, or 6 of the MA should be assigned to subgroup A_1.

INFORMATION CLASSIFICATION OF GROUP *B* PATIENTS

To tackle the problem of how typical a patient is for group B, in addition to determining the subgroup, we need to estimate the affiliation degree for each patient in the relevant subgroup.

Subgroup B_1 would include patients with relatively preserved general heart condition and function, with the expectation that revascularisation (without the additional risks of combined surgery) will lead to a significant improvement in the cardiac condition (with the eventual reverse remodelling of left heart structures), allowing the patient to return to a normal lifestyle. Subgroup B_2 would include patients with relatively deteriorated cardiac and general status. These are patients with a subjectively assessed probable life expectancy of less than 4 years, in whom the aim is to use the least invasive surgical intervention possible to treat IHD and heart failure resulting from IHD complicated by IMR.

At the time of classification, the affiliation degree assigning a patient to a particular subgroup should be assessed, provided the patient clearly belongs to the group ($\mu_{B_1|B}$ or $\mu_{B_2|B}$).

The information task of dividing the patients of group B into two subgroups was formulated using a 7-step auxiliary algorithm for B (Fig. 3).

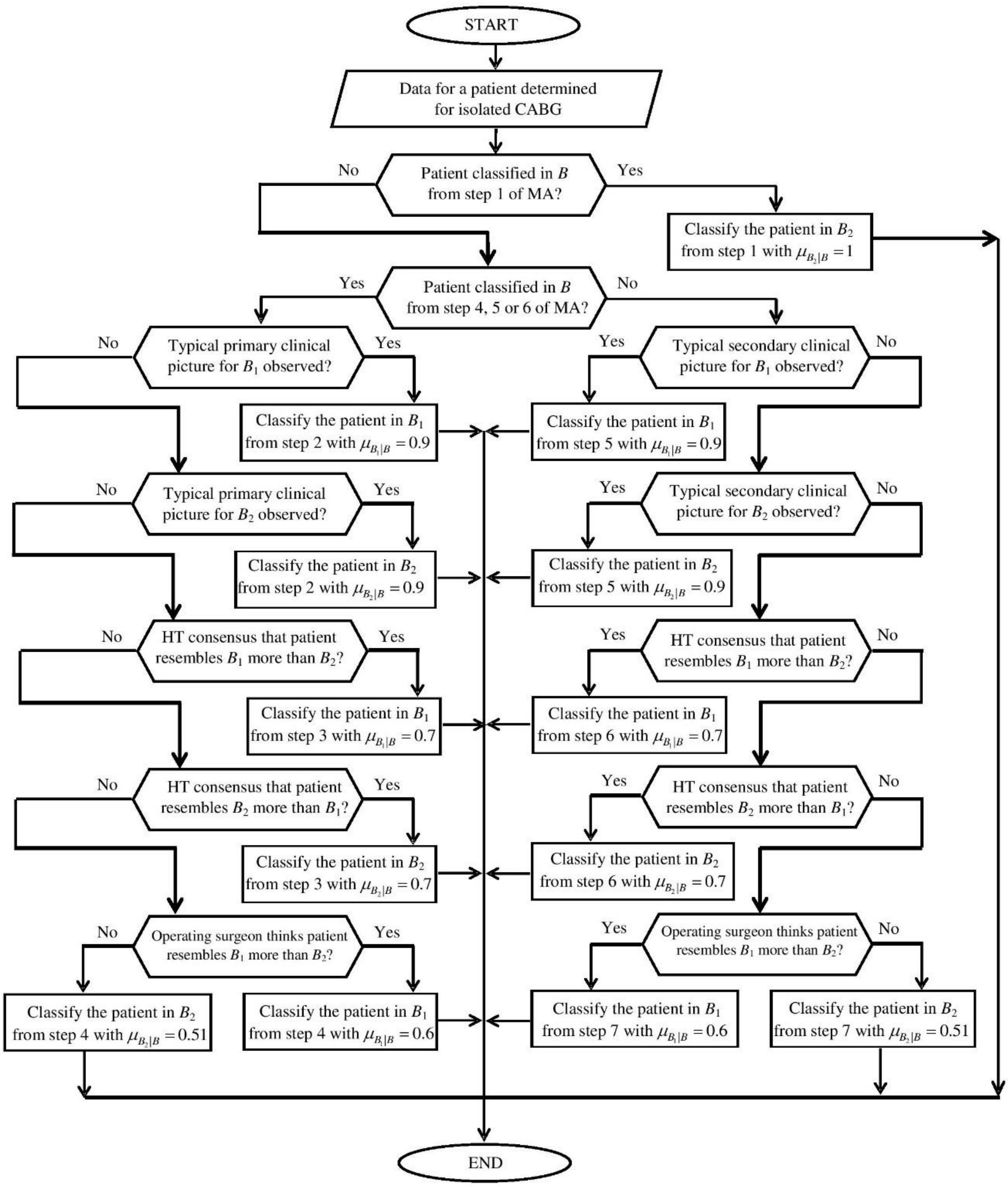

Fig. 3. The information task of dividing the patients of group B into two subgroups was formulated using a 7-step auxiliary algorithm for B

The rationale of AAB is based on the following six medical aspects:

- If the patient is classified to group B according to Step 1 of the MA, then the patient has a severely deteriorated medical condition and classification in subgroup B_2 is undebatable.
- If the ischemic cardiac remodelling is at an early stage, then for a patient classified in group B according to MA steps 3, 4, 5, or 6, the classification in subgroup B_1 is undebatable.
- If the ischemic cardiac remodelling is at a relatively advanced stage, then for a patient classified in group B according to steps 3, 4, 5, or 6 of the MA, the classification in subgroup B_2 is also undebatable.
- If a patient is classified in group B according to steps 4, 5 or 6 of the MA, then there is a significantly higher MR compared to the condition for which the patient is classified in group B according to Step 3 of the MA. Therefore, if ischemic cardiac remodelling is advanced, then a patient classified in group B according to steps 4, 5, or 6 of the MA should be classified in subgroup B_2, whereas a patient classified in group B according to Step 3 of the MA should be classified in subgroup B_1.
- IMR of a patient classified in group B according to steps 4, 5 or 6 of the MA is significantly lower than that of a patient classified in group A according to Step 2 of the MA. In the latter case, however, reduction of MR is one of the goals of the surgical treatment, whereas in the former case, IMR would be treated as a complication of isolated revascularisation. Because of all these considerations, the typical primary profiles for subgroups B_1 and B_2 are similar to those for subgroups A_1 and A_2.
- IMR of a patient classified in group B according to Step 3 of the MA is significantly lower than that of a patient classified in group A according to Steps 4, 5, or 6 of the MA. In the latter case, however, IMR reduction is one of the goals of the surgical treatment, whereas in the former case, IMR would be treated as a complication of isolated revascularisation. Because of all these considerations, the typical secondary profiles for subgroups B_1 and B_2 are similar to those for subgroups A_1 and A_2.

CALCULATING THE AFFILIATION DEGREE TO A SUBGROUP

We use the multiplicative *t-norm* (product t-norm) to compute the affiliation degree of a fuzzy set that is the intersection of two others.

Then the affiliation degree of a patient to the subgroup to which he/she is classified can be calculated using the appropriate formula from the four given below:

$$(4.2)\quad \mu_{A_1} = T_{prod}\left(\mu_A, \mu_{A_1|A}\right) = \mu_A\, \mu_{A_1|A}$$

$$(4.3)\quad \mu_{A_2} = T_{prod}\left(\mu_A, \mu_{A_2|A}\right) = \mu_A\, \mu_{A_2|A}$$

$$(4.4)\quad \mu_{B_1} = T_{prod}\left(\mu_B, \mu_{B_1|B}\right) = \mu_B\, \mu_{B_1|B}$$

$$(4.5)\quad \mu_{B_2} = T_{prod}\left(\mu_B, \mu_{B_2|B}\right) = \mu_B\, \mu_{B_2|B}$$

QUALITY ASSESSMENT OF FUZZY ALGORITHMS

As outlined in the previous sections, the preoperational data was subjected to MA, AAA, and AAB. Patients with subgroup affiliation degrees less than 0.5 were designated as outliers. A low threshold would result in larger but less homogeneous subgroups of patients. A high threshold would result in more homogeneous but smaller subgroups. A threshold of 0.5 is an appropriate compromise between obtaining homogeneous subgroups and obtaining large subgroups.

Any patient classified by Step 6 of MA, Step 6 in AAA, or Step 4 in AAB is an outlier. There is no patient classified by Step 3 of AAA. The only two patients classified by Step 7 of AAB are close to the outliers, with no algorithms able to identify them accurately, although their affiliation rate of 0.51 is very close to the threshold of 0.5.

MA was applied to the total sample of 169 patients. Of these, 87 were classified in group A and 82 in group B. The affiliation degrees to A or B (μ_A or μ_B respectively) were calculated for each patient.

MA classified the 87 patients in group A as follows: 10 were classified in Step 1; none in Step 2; 28 in Step 3; 21 in Step 4; 18 in Step 5; and 5 in Step 6. The average affiliation degree in their corresponding subgroup was:

$$E\mu_A = \frac{1}{87}\left(\sum_{i=1}^{34} \mu_{A_1}^{(A_1,i)} + \sum_{i=1}^{53} \mu_{A_2}^{(A_2,i)}\right) = \frac{34E\mu_{A_1} + 53E\mu_{A_2}}{34+53} = 0.683$$

Of these patients, 16 (6 from subgroup A_1 and 10 from subgroup A_2) were declared outliers because their respective subgroup affiliation rate was less than 0.5

($\mu_{A_1}^{(A_1,i)}$ < 0.5 or $\mu_{A_2}^{(A_2,i)}$ < 0.5). Their average affiliation degree is:

$$E\mu_A^{out} = \frac{1}{16}\left(\sum_{i=29}^{34}\mu_{A_1}^{(A_1,i)} + \sum_{i=44}^{53}\mu_{A_2}^{(A_2,i)}\right) = \frac{6E\mu_{A_1}^{out} + 10E\mu_{A_2}^{out}}{6+10} = 0.446$$

The remaining non-outliers form a fuzzy sample for A of 71 patients with an average affiliation degree calculated as:

$$E\mu_A^{in} = \frac{1}{71}\left(\sum_{i=1}^{28}\mu_{A_1}^{(A_1,i)} + \sum_{i=1}^{43}\mu_{A_2}^{(A_2,i)}\right) = \frac{28E\mu_{A_1}^{in} + 43E\mu_{A_2}^{in}}{28+43} = 0.736$$

MA has classified 82 patients in group B as follows: 10 were classified in Step 1; none in Step 2; 28 in Step 3; 21 in Step 4; 18 in Step 5; 5 in Step 6; and none in Step 7. The average affiliation degree to their subgroup is:

$$E\mu_B = \frac{1}{82}\left(\sum_{i=1}^{43}\mu_{B_1}^{(B_1,i)} + \sum_{i=1}^{39}\mu_{B_2}^{(B_2,i)}\right) = \frac{43E\mu_{B_1} + 39E\mu_{B_2}}{43+39} = 0.700$$

Of these patients, 20 (6 from subgroup B_1 and 14 from subgroup B_2) were declared as outliers because their respective subgroup affiliation rate was less than 0.5 ($\mu_{B_1}^{(B_1,i)}$ < 0.5 or $\mu_{B_2}^{(B_2,i)}$ < 0.5). Their average affiliation degree is:

$$E\mu_B^{out} = \frac{1}{20}\left(\sum_{i=38}^{43}\mu_{B_1}^{(B_1,i)} + \sum_{i=26}^{39}\mu_{B_2}^{(B_2,i)}\right) = \frac{6E\mu_{B_1}^{out} + 14E\mu_{B_2}^{out}}{6+14} = 0.422$$

The remaining non-outliers formed a fuzzy sample of 62 patients for B with an average affiliation degree:

$$E\mu_B^{in} = \frac{1}{62}\left(\sum_{i=1}^{37}\mu_{B_1}^{(B_1,i)} + \sum_{i=1}^{25}\mu_{B_2}^{(B_2,i)}\right) = \frac{37E\mu_{B_1}^{in} + 25E\mu_{B_2}^{in}}{37+25} = 0.790$$

AAA was applied to the sample of 87 patients classified in A. Of these, 34 were classified in A_1 and 53 in A_2. The conditional degrees of A_1 or A_2 ($\mu_{A_1|A}$ or $\mu_{A_2|A}$ respectively) for each patient in group A were calculated using formula (4.2) or formula (4.3).

All 34 patients classified into group A_1 were further tagged with local subgroup indices – (A1,1), (A1,2), ..., (A1,34). The AAA classified the 34 patients into subgroup A_1 as follows: 5 were classified into Step 1; 4 into Step 2; none into Step 3; 14 into Step 4; 10 into Step 5; and 1 into Step 6. The average affiliation degree of subgroup A_1 was 0.660. Of these patients, 6 belonged to subgroup A_1 with an affiliation degree lower than 0.5 (< 0.5) and were defined as outliers, indicated as (A1,29), (A1,30), ..., (A1,34). Their average affiliation degree is:

$$E\mu_{A_1}^{out} = \frac{1}{6}\sum_{i=29}^{34}\mu_{A_1}^{(A_1,i)} = 0.468$$

The remaining non-outliers set up a fuzzy sample of 28 patients for A_1 with an average affiliation degree:

$$E\mu_{A_1}^{in} = \frac{1}{28}\sum_{i=1}^{28}\mu_{A_1}^{(A_1,i)} = 0.701$$

The average affiliation degree to subgroup A_1 is:

$$E\mu_{A_1} = \frac{1}{36}\sum_{i=1}^{36}\mu_{A_1}^{(A_1,i)} = \frac{28E\mu_{A_1}^{in} + 6E\mu_{A_1}^{out}}{28+6} = 0.660$$

All 53 patients classified into group A_2 were further designated by local subgroup indices – (A2,1), (A2,2), ..., (A2,53). The AAA classified 53 patients into subgroup A_2 as follows: 12 were classified into Step 1; 17 into Step 2; none into Step 3; 9 into Step 4; 13 into Step 5, and 2 into Step 6. Of these patients, 10 belonged to subgroup A_2 with an affiliation degree lower than 0.5 (< 0.5) and were defined as outliers, indicated as (A2,44), (A2,45), ... (A2,53). Their average affiliation degree is:

$$E\mu_{A_2}^{out} = \frac{1}{10}\sum_{i=44}^{53}\mu_{A_2}^{(A_2,i)} = 0.435$$

The remaining non-outliers formed a fuzzy A_2 sample of 43 patients with an average affiliation degree:

$$E\mu_{A_2}^{in} = \frac{1}{43}\sum_{i=1}^{43}\mu_{A_2}^{(A_2,i)} = 0.758$$

The average affiliation degree to subgroup A_2 is:

$$E\mu_{A_2} = \frac{1}{53}\sum_{i=1}^{53}\mu_{A_2}^{(A_2,i)} = \frac{43E\mu_{A_2}^{in} + 10E\mu_{A_2}^{out}}{43+10} = 0.697$$

AAB was applied to a sample of 82 patients classified in group B. Of these, 43 were classified in B_1 and 39 in B_2. The conditional affiliation degrees of B_1 or B_2 ($\mu_{B_1|B}$ or $\mu_{B_2|B}$ respectively) for each patient in group B were calculated using (4.4) or (4.5).

The 39 patients classified into subgroup B_2 were further indicated by local subgroup indices – (B2,1), (B2,2), ..., (B2,39). The AAB classified 39 patients into subgroup B_2 as follows: 10 were classified into Step 1; 2 into Step 2; 13 into Step 3; 6 into Step 4; none into Step 5; 6 into Step 6, and 2 into Step 7. Of these patients, 14 belonged to subgroup B_2 with an affiliation degree lower than 0.5 (< 0.5) and were defined as outliers, indicated as (B2,26), (B2,27), ..., (B2,39). Their average affiliation degree is:

$$E\mu_{B_2}^{out} = \frac{1}{11}\sum_{i=26}^{39} \mu_{B_2}^{(B_2,i)} = 0.403$$

The remaining non-outliers formed a fuzzy sample of 25 patients for B_2 with an average affiliation degree:

$$E\mu_{B_2}^{in} = \frac{1}{25}\sum_{i=1}^{25} \mu_{B_2}^{(B_2,i)} = 0.792$$

The average affiliation degree to subgroup B_2 is:

$$E\mu_{B_2} = \frac{1}{39}\sum_{i=1}^{39} \mu_{B_2}^{(B_2,i)} = \frac{25E\mu_{B_2}^{in} + 14E\mu_{B_2}^{out}}{25+14} = 0.653$$

COMPARISON WITH OTHER CLASSIFIERS

We subjected our data to other known classification techniques to demonstrate the advantages of the proposed approaches.

We constructed 8 classifiers defined from C1 to C8. All classifiers are Bayesian classifiers with equal a priori probability classifying patients into one of four categories – A_1, A_2, B_1 or B_2. The patient is considered an A or B outlier when the maximum posterior probability is less than 50%.

The resubstitution errors of these classifiers were calculated using a test sample of 169 patients, distributed as follows – 28 in A_1; 43 in A_2; 37 in B_1 and 23 in B_2, with 16 outliers from group A and 22 outliers from group B.

The comparison used 15 discrete and 12 continuous discrete features from our database. (Table numbering is consistent with that in the doctoral thesis).

Table 4.20. Modified error matrix for C_1

		Classified						
		A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
True (No.)	A_1 (28)	22	3	3	0	0	0	0
	A_2 (43)	8	35	0	0	0	0	0
	B_1 (37)	0	0	35	1	1	0	0
	B_2 (23)	1	2	4	15	0	1	0
	Outliers A (16)	10	4	0	2	0	0	0
	Outliers B (22)	1	0	7	11	2	1	0

Table 4.21. Modified error matrix for C_2

		Classified						
		A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
True (No.)	A_1 (28)	24	2	2	0	0	0	0
	A_2 (43)	8	35	0	0	0	0	0
	B_1 (37)	0	0	35	1	1	0	0
	B_2 (23)	1	2	4	15	0	1	0
	Outliers A (16)	12	2	0	2	0	0	0
	Outliers B (22)	5	0	5	9	3	0	0

Table 4.22. Modified error matrix for C_3

		Classified						
		A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
True (No.)	A_1 (28)	24	2	1	0	1	0	0
	A_2 (43)	7	34	0	1	1	0	0
	B_1 (37)	1	0	34	0	2	0	0
	B_2 (23)	1	2	5	15	0	0	0
	Outliers A (16)	10	4	0	0	2	0	0
	Outliers B (22)	2	0	8	9	3	0	0

Table 4.23. Modified error matrix for C_4

		Classified						
		A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
True (No.)	A_1 (28)	25	2	1	0	0	0	0
	A_2 (43)	9	33	0	0	1	0	0
	B_1 (37)	2	0	33	1	1	0	0
	B_2 (23)	0	2	5	15	0	1	0
	Outliers A (16)	12	2	0	1	1	0	0
	Outliers B (22)	5	0	6	8	2	1	0

Table 4.24. Modified error matrix for C_5

		Classified						
		A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
True (No.)	A_1 (28)	25	1	2	0	0	0	0
	A_2 (43)	6	36	0	0	0	0	1
	B_1 (37)	0	0	35	0	0	0	1
	B_2 (23)	0	1	4	17	0	1	0
	Outliers A (16)	9	4	0	3	0	0	0
	Outliers B (22)	0	0	7	13	0	0	2

Table 4.25. Modified error matrix for C_6

		Classified						
		A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
True (No.)	A_1 (28)	27	0	1	0	0	0	0
	A_2 (43)	6	36	0	0	0	0	1
	B_1 (37)	0	0	34	2	0	0	1
	B_2 (23)	0	0	2	21	0	0	0
	Outliers A (16)	9	3	0	4	0	0	0
	Outliers B (22)	2	0	12	6	0	0	2

Table 4.26. Modified error matrix for C_7

True (No.)	Classified: A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
A_1 (28)	24	2	1	0	1	0	0
A_2 (43)	6	35	0	1	0	0	1
B_1 (37)	2	0	30	4	0	0	1
B_2 (23)	0	1	3	17	1	1	0
Outliers A (16)	9	5	0	2	0	0	0
Outliers B (22)	2	0	7	10	0	1	2

Table 4.27. Modified error matrix for C_8

True (No.)	Classified: A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
A_1 (28)	28	1	2	0	0	0	0
A_2 (43)	7	34	0	1	0	0	1
B_1 (37)	1	0	30	5	0	0	1
B_2 (23)	0	1	3	18	1	0	0
Outliers A (16)	9	3	0	2	1	1	0
Outliers B (22)	1	0	9	9	1	0	2

We have added to the comparison patients' distribution in the four subgroups based on classical (non-fuzzy) sets:

Table 4.28. Modified error matrix for non-fuzzy algorithms

True (No.)	Classified: A_1	A_2	B_1	B_2	Outliers in A	Outliers in B	Rejected
A_1 (28)	28	0	0	0	0	0	0
A_2 (43)	0	43	0	0	0	0	0
B_1 (37)	0	0	37	0	0	0	0
B_2 (23)	0	0	0	23	0	0	0
Outliers A (16)	6	10	0	0	0	0	0
Outliers B (22)	0	0	6	16	0	0	0

To summarise the information from the modified error matrix, we introduce four quality criteria:

1) K1 – the percentage of non-rejected patients out of all patients;

2) K2 – the percentage of correctly classified patients out of non-rejected typical patients;

3) K3 – the percentage of correctly classified outliers in groups A and B out of non-rejected outliers;

4) K4 – the percentage of correctly classified patients (both typical patients and outliers in groups A and B) from non-outliers.

A serious drawback of six of the Bayesian classifiers is the 2.5% of rejected unclassified patients (first row of Table 4.30). Another shortcoming of all Bayesian classifiers is that between 9% and 14% of the typical patients are not correctly classified (K2 in the second row of Table 4.30). A third shortcoming of the Bayesian classifiers is that between 8% and 26% of the rejected patients would not have received the correct treatment (see K4 in the fourth row of Table 4.30).

However, the main problem of the Bayesian classifiers, as well as with fuzzy algorithms, is the extremely poor diagnosis of non-rejected outliers (K3 is between 0% and 5% in the third row of Table 4.30). This creates difficulties in assessing the characteristics of the subgroups. The fuzzy algorithms (last column of Table 4.30) show excellent differentiation of the typical patients and the outliers. Additionally, fuzzy algorithms are the only approach that measures how typical the patients are for their designated subgroup. This measurement can be used as a weighting factor when evaluating the subgroups' characteristics.

Table 4.30. Values of the quality criteria of classifiers C_1 to C_8 and of the fuzzy and non-fuzzy algorithms

	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	*crisp*	*fuzzy*
K_1	100	100	93	93	93	93	93	93	100	100
K_2	86	87	92	90	90	94	92	93	100	100
K_3	3	3	0	4	4	0	4	4	0	100
K_4	94	74	84	96	96	76	88	88	90	100

Bayesian classifiers, in general, differ from fuzzy and non-fuzzy algorithms in another important, albeit non-numerical, aspect. The Heart Team explicitly implements the algorithms and has no calling in the Bayesian classifiers.

V. Results and Application of Fuzzy Stratification Algorithms

V.1. Creating a complete system of examples

This doctoral thesis shows a complete system of examples for all possible combinations of the outputs of the MA, AAA and AAB algorithms. The system contains 49 examples, each showing a specific or fictitious patient classified by MA into one of the A or B groups. If the patient is classified with group A, the classification into subgroups A_1 and A_2 according to Algorithm AAA is presented. If the patient is classified in group B, the classification in subgroups B_1 and B_2 according to Algorithm AAB is presented.

The title of each example includes the classification and the step of the corresponding algorithm. For example, Example 18 is titled "Example for A_4; A1_6", which means that the MA classifies this patient into group A from Step 4. Similarly, Example 37 is indicated as "Example for B_5; B2_4" and means that the MA classifies this particular patient into group B of Step 5. Subsequently, AAB then classifies the same patient into subgroup B_2 of Step 4.

E1.19 Example for A_4; A2_6

We consider patient #169.

First, we apply the MA (main algorithm).

MA STEP 1:

The patient is not in an impaired medical condition and has no comorbidities (64 years old).

The subjectively estimated life expectancy is more than 4 years.

There is no clinically significant heart failure (HF), and the left ventricular ejection fraction (EF%) is 36%, above the criterion value of 25%.

The patient had no established contraindications to ECC support or definite indications for the least invasive procedure possible.

It can be seen that the patient does not meet any of the exclusion criteria for group A. Therefore, the decision is deferred to the next step.

MA STEP 2:

The patient has moderate to high-grade MR (grade 2 to 3), but the RV is 30 mL, and the VC is 4 mm. Therefore, the patient does not meet any significant exclusion criteria for group B. The decision is deferred to the next step.

MA STEP 3:

The patient's regurgitation is greater than moderate (grade 2 to 3); therefore, the patient cannot be excluded from group A, and the decision is deferred to the next step.

MA STEP 4:

We are considering the typicality of the patient's primary profile (shown in parentheses), which is:

a) Moderate to high-grade MR (2nd to 3rd degree);

b) RV is 30 mL (at least 20 mL);

c) VC is 4 mm (at least 4 mm);

d) Tenting area is 2.0 cm^2 (at least 1.5 cm^2);

e) Tenting height 9 mm (at least 9 mm);

f) Coaptation line 3 mm (up to 4 mm);

g) Presence of symmetrical tethering;

h) Subjectively estimated life expectancy over 5 years.

The patient's preoperative condition matched the typical primary profile for group A. Therefore, the patient was classified in group A with a degree of 0.9 $(\mu_A = 0.9)$. The algorithm concludes.

Secondly, we apply AAA (auxiliary algorithm for the subgroups in group A).

STEP 1 of AAA:

The decision is postponed to the next step since the patient is classified in group A from Step 4 of MA.

STEP 2 of AAA:

The decision is deferred to the next step since the patient is classified in Group A of Step 4 of the MA.

STEP 3 from AAA:

The decision is deferred to the next step since the patient is classified in Group A of Step 4 of the MA.

STEP 4 from AAA:

Since the patient is classified in Group A of Step 4 of the MA, then the typicality of his secondary profile is considered, which is:

a) No history of myocardial infarction;

b) EF is 36%;

c) The patient is in relatively good general condition;

d) There are no significant comorbidities that would worsen the prognosis;

e) LVEDVi is 81.43 mL/m^2 B.S.A.;

f) LVESVi is 51.9 mL/m^2 BSA;

g) LAVi is 39 mL/m^2 B.S.A.

Therefore, the patient's profile does not match the typical secondary profile for A_1 under criteria (b), (e) and (f). The patient's profile also does not match the typical secondary profile for subgroup A_2 under criteria (a), (b), (c), (d) and (f). The decision is deferred to the next step.

STEP 5 from AAA:

The Heart Team (HT) cannot take a consensus decision what is the patient's typical secondary profile since the patient's EF is very close to 35% and he/she has a significantly increased LVESVi. This brings the patient closer to subgroup A_2, although he/she is close to subgroup A_1 on other indicators. The decision is deferred to the next step.

STEP 6 from AAA:

The operating surgeon estimates (using his expertise) that the typical secondary profile for subgroup A_2 is closest to the patient's condition. Therefore, the patient is classified into subgroup A_2 with a conditional affiliation degree of 0.51 $\left(\mu_{A_2|A} = 0.51\right)$. The algorithm terminates.

Thirdly, using formula (3), the patient is finally classified into subgroup A_2 with an affiliation degree of 0.459 $\left(\mu_{A_2} = \mu_A \times \mu_{A_2|A} = 0.9 \times 0.51 = 0.459\right)$.

The purpose of creating a complete system of examples is to illustrate the application of the algorithms we have created in a medically understandable way. We believe that in practical terms, such a system will facilitate decision-making about the approach to a complex medical situation such as IHD complicated with significant chronic IMR. Determining the affiliation degree of a particular patient to a particular subgroup will lead to further individualization of the surgical treatment options. Given the relatively small number of studies on IHD complicated with IMR, which often have contradictory conclusions, personalization in the medical approach is probably the most rational and effective treatment solution at this stage.

V.2. Construction of fuzzy samples

The affiliation degrees discussed above are patients' characteristics. Hence they can be assigned to the values of each of the 57 parameters measured for each patient. So, once the affiliation degrees have been identified, we can form different fuzzy samples for each of the 57 medical parameters (20 identifiers are excluded from the original 77) recorded for each patient in the database.

For example, let us analyse the left ventricular end-diastolic volume index (LVEDVi) measured before surgery (preoperatively) for all patients classified in subgroup B_2. We will construct two fuzzy samples – one for 25 patients without outliers whose $\mu_{B_2} \geq 0.5$ (defined

$\chi_{B_2,preop}^{in,LVEDVi}$), and another one for 14 outlier patients whose $\mu_{B_2} < 0.5$ (defined $\chi_{B_2,preop}^{out,LVEDVi}$):

$\chi_{B_2,preop}^{in,LVEDVi}$ ={(101,0.63), (81,0.7), (100,0.7), (81,1), (69,0.63), (96,1), (38,0.51), (45,0.63), (53,0.63), (38,0.63), (56,0.7), (51,1), (82,1), (36,0.7), (59,0.81), (85,1), (52,0.7), (49,0.7), (59,1), (68,1), (80,0.63), (72,0.51), (99,1), (87,1), (78,1)}

$\chi_{B_2,preop}^{out,LVEDVi}$ ={(49,0.49), (74,0.49), (71,0.357), (53,0.2601), (66,0.49), (42,0.49), (101,0.49), (52,0.357), (73,0.49), (74,0.49), (53,0.357), (36,0.2601), (49,0.2601), (48,0.357)}

We have analysed all other parameters in the same way.

To assess the effect of the surgical intervention, we need to compare the following pairs of fuzzy samples: a) for each of the 57 medical parameters (the original 77, excluding 20 identifiers) for subgroups A_1 and B_1; b) for each medical parameter for subgroups A_2 and B_2; c) for each tridimensional parameter measured preoperatively and late postoperatively for the respective subgroup; d) for each tridimensional parameter measured preoperatively and early postoperatively for the respective subgroup.

For example, let us compare the preoperative left atrial volume index (LAVi) values for the two subgroups of patients with relatively preserved medical status. Then:

1. We construct two fuzzy samples for A_1 – one for 28 patients without outliers whose $\mu_{A_1} \geq 0.5$ (defined $\chi_{A_1,preop}^{in,LAVi}$), and another one for 6 outlier patients whose $\mu_{A_1} < 0.5$ (defined $\chi_{A_1,preop}^{out,LAVi}$):

$\chi_{A_1,preop}^{in,LAVi}$ ={ (32, 0.63), (26, 0.9), (29, 0.63), (70, 0.63), (35, 0.81), (30, 0.0.81), (20, 0.63), (26, 0.9), (35, 0.63), (27, 0.63), (42,0.63), (29, 0.63), (40, 0.7), (24, 0.63), (39, 0.63), (34, 0.63), (35, 0.63), (88, 0.7), (37, 0.9), (54, 0.63), (68, 0.63), (38, 0.9), (30, 0.63), (26, 0.63), (39, 0.63), (43, 0.7), (23, 0.9), (32, 0.7) }

$\chi_{A_1,preop}^{out,LAVi}$ ={ (33, 0.36), (43, 0.49), (28, 0.49), (24, 0.49), (58, 0.49), (44, 0.49) }

2. We construct two fuzzy samples for B_1 – one for 37 patients without outliers whose (defined), and another one for 6 patients with outliers whose (defined):

$\chi^{in,LAVi}_{B_1,preop}$ ={ (30, 0.9), (17, 0.81), (33, 0.9), (43, 0.9), (31, 0.63), (28, 0.81), (35, 0.63), (32, 0.9), (26, 0.81), (28, 0.9), (36, 0.9), (38, 0.63), (25, 0.81), (23, 0.9), (20, 0.63), (44, 0.63), (36, 0.63), (27, 0.81), (25, 0.9), (29, 0.9), (35, 0.9), (27, 0.81), (43, 0.63), (22, 0.9), (25, 0.81), (49, 0.63), (28, 0.9), (31, 0.63), (25, 0.63), (40, 0.9), (26, 0.9), (31, 0.9), (21, 0.9), (36, 0.7), (21, 0.7), (39, 0.7), (19, 0.7) }

$\chi^{out,LAVi}_{B_1,preop}$ ={ (46, 0.49), (60, 0.49), (19, 0.49), (44, 0.49), (36, 0.49), (26, 0.357) }

Similarly, let us compare the preoperative left atrial volume index (LAVi) values in the two subgroups of patients with relatively impaired medical status. Then:

3. We construct two fuzzy samples for A_2 – one for 43 patients without outliers who $\mu_{A_2} \geq 0.5$ (defined $\chi^{in,LAVi}_{A_2,preop}$), and another one for 10 outlier patients whose $\mu_{A_2} < 0.5$ (defined $\chi^{out,LAVi}_{A_2,preop}$):

$\chi^{in,LAVi}_{A_2,preop}$ ={ (46, 0.63), (63, 0.7), (80, 0.9), (49, 0.7), (53, 0.81), (44, 0.81), (49, 0.9), (63, 0.9), (38, 0.63), (59, 0.9), (32, 0.7), (58, 0.7), (65, 0.81), (62, 0.81), (45, 0.63), (45, 0.81), (51, 0.63), (37, 0.7), (39, 0.7), (58, 0.9), (48, 0.9), (76, 0.7), (34, 0.63), (51, 0.7), (40, 0.7), (39, 0.7), (36, 0.7), (60, 0.81), (54, 0.7), (47, 0.9), (69, 0.9), (52, 0.7), (41, 0.7), (28, 0.7), (30, 0.9), (26, 0.9), (28, 0.7), (35, 0.63), (49, 0.9), (40, 0.9), (40, 0.7), (38, 0.63), (34, 0.63)}

$\chi^{out,LAVi}_{A_2,preop}$ ={ (27, 0.306), (46, 049), (25, 0.49), (46, 0.306), (42, 0.49), (58, 0.49), (42, 0.49), (32, 0.49), (52, 0.49), (29, 0.49) }

4. We construct two fuzzy samples for B_2 – one for 25 patients without outliers whose $\mu_{B_2} \geq 0.5$ (defined $\chi^{in,LAVi}_{B_2,preop}$), and another for 14 outlier patients whose $\mu_{B_2} < 0.5$ (defined $\chi^{out,LAVi}_{B_2,preop}$):

$\chi^{in,LAVi}_{B_2,preop}$ ={(53,0.63), (32,0.7), (21,0.7), (30,1), (59,0.63), (24,1), (22,0.51), (35,0.63), (25, 0.63), (31, 0.63), (50, 0.7), (40, 1), (48, 1), (38, 0.7), (28, 0.81), (32, 1), (26, 0.7), (19, 0.7), (49, 1), (31, 1), (57, 0.63), (29, 0.51), (41,1), (30,1), (46, 1)}

$\chi_{B_2,preop}^{out,LAVi}$ ={(21, 0.49), (37, 0.49), (36, 0.357), (29, 0.2601), (36, 0.49), (37, 0.49), (36, 0.49), (26, 0.357), (44, 0.49), (30, 0.49), (44, 0.357), (38, 0.2601), (34, 0.2601), (22, 0.357)}

All these fuzzy samples can be constructed as shown above. The same approach is valid for each medical parameter, regardless of whether the parameter is discrete or continuous.

Fuzzy samples are constructed similarly for each medical parameter early postoperatively and late postoperatively.

V.3. Assessment of the effect of annuloplasty in significant IMR with the method of fuzzy pseudo-control groups (MFPCG)

PSEUDO-CONTROL GROUPS

Sometimes the use of a control group is ethically impossible. In such cases, a pseudo-control group can be used to establish the relative impact of one medical procedure versus another. In our study, all participants had similar medical indications, but the latter differed enough so that patients were stratified into two groups. The experimental group (group A) comprised of patients most suitable for the MV Repair procedure in addition to a baseline treatment (CABG). The remaining participants were assigned to a pseudo-control group (group B) and were designated for the baseline treatment (CABG) only according to the treatment team's soundest rationale.

The use of fuzzy samples will be demonstrated by solving the following numerical-medical issue. Let us look for the effect of operative mitral annuloplasty (R), simultaneously with the baseline impact of surgical revascularisation (V), on one of the continuous parameters described in section 4.1.4 (of the thesis). That parameter characterizes the condition of a target population (P) of patients with significant IMR undergoing a combined procedure of annuloplasty and revascularization. Before and after the combined procedure, the parameter values were experimentally measured for patients in the experimental group Ai. The effect of annuloplasty was compared with the effect of the isolated procedure on the same parameter (X), which now characterizes the state of the pseudo-control population (Q) of patients with significant IMR undergoing isolated revascularisation. Before and after the isolated procedure, parameter values were experimentally measured for patients in the pseudo-control group Bi.

Four fuzzy samples were constructed as follows:

- Eo is a fuzzy sample containing the values of X and their experimental group Ai affiliation degrees before the combined surgical intervention.
- PCo is a fuzzy sample containing X values and their pseudo-control group Bi affiliation degrees before the isolated procedure.
- Ee is a fuzzy sample containing the values of X and their experimental group Ai affiliation degrees late after the combined surgical intervention.
- PCe is a fuzzy sample containing X values and their pseudo-control group Bi affiliation degrees late after the isolated procedure.

The effect of the investigated impact R on the selected parameter X will be researched by the Fuzzy Pseudo-Control Group (MFPCG) method. The populations P and Q are tested for homogeneity – both before the procedural impact via the fuzzy samples Eo and PCo and after the impact via the fuzzy samples Ee and PCe. The comparison between the statistical differences found before and after the surgical impact will show the effect of R on X.

CONSTRUCTION OF POPULATIONS DIFFERENCES

For the experimental group, the fuzzy sample numerical characteristics of the distribution of X can be calculated from fuzzy Sample 1 defined as follows: ME – fuzzy sample mean value in the experimental group; MEDE – fuzzy sample median value in the experimental group; VARE – fuzzy sample dispersion variance in the experimental group; IQRE – fuzzy sample interquartile range in the experimental group.

Similarly, for the pseudo-control group, the fuzzy sample numerical characteristics of the X distribution can be calculated from fuzzy Sample 2 defined as follows: MPC – sample fuzzy mean in the pseudo-control group; MEDPC – fuzzy sample median value in the pseudo-control group; VARPC – fuzzy sample dispersion variance in the pseudo-control group; IQRPC – fuzzy sample interquartile range in the pseudo-control group.

The statistical significance of differences between the X populations was determined by 9 fuzzy Bootstrap statistical tests:

Test 1: Fuzzy Bootstrap Kuiper testing for homogeneity of population distributions;

Test 2. Fuzzy two-sided Bootstrap testing for homogeneity of population mean values;

Test 3: Fuzzy one-Sided Bootstrap testing for homogeneity of population mean values;

Test 4. Fuzzy two-sided Bootstrap testing for homogeneity of population median values;

Test 5. Fuzzy one-sided Bootstrap testing for homogeneity of population median values;

Test 6. Fuzzy two-tailed Bootstrap testing for homogeneity of population dispersion (variance-covariance);

Test 7. Fuzzy one-sided Bootstrap testing for homogeneity of population dispersion;

Test 8. Fuzzy two-sided Bootstrap testing for homogeneity of population interquartile ranges;

Test 9. Fuzzy one-sided Bootstrap testing for homogeneity of population interquartile ranges.

Appendix P2 shows the full results of the evaluation of the effect of annuloplasty on two of the most important integral diagnostic parameters summarising IMR and patient status: the RF (regurgitation fraction in %) and the MR (a discrete dimensionless parameter measuring the degree of Mitral Regurgitation on an 8-degree scale). The assessment was obtained by MFPCG.

On the one hand, the effect of annuloplasty was evaluated by MFPCG in patients with relatively preserved medical status, and the values of the two parameters were compared in subgroups A_1 and B_1. Four fuzzy samples for RF and four fuzzy samples for MR were used.

On the other hand, the same effect was evaluated in patients with a relatively deteriorated medical condition by separately comparing the values of MR and RF in subgroups A_2 and B_2. Four new fuzzy samples for MR and four new fuzzy samples for RF were used.

The results are unanimous on the beneficial and significant effect of annuloplasty on the parameters considered, both in patients with relatively preserved medical conditions and in patients with relatively deteriorated medical conditions.

VI. Conclusions

1. The algorithms applied in this research calculate only the maximum value of four possible coefficients that predetermines the classification of a patient to a particular subgroup.

2. If the maximum value of μ is less than 0.5, the patient is considered an outlier and does not participate in the following calculations. Thus, the characteristics of the subgroup can be more adequately estimated.

3. Based on the different affiliation degrees, a different stratification of patients into groups and subgroups can be created, hence a different treatment recommendation.

4. For the purposes of this study, we decided that four subgroups were an appropriate balance between the homogeneity achieved within the subgroups and the size of the resulting subgroup samples.

Other medical teams may decide to stratify patients into more subgroups to improve sample homogeneity. This approach would be adequate when a more significant initial sample is available.

VII. Contribution claims

The following contributions are claimed as a result of the presented research:

1. For patients with IHD complicated by IMR, a 6-step fuzzy algorithm (MA) has been created. For each patient, the algorithm identifies the affiliation degrees to two inhomogeneous groups: A (CABG and mitral valve repair) or B (isolated CABG).

2. Two conditional fuzzy algorithms were created to homogenize groups A and B stratification. If MA has unconditionally classified a patient into group A, the 6-step conditional fuzzy algorithm AAA computes the conditional affiliation degrees of the patient into two homogeneous subgroups by medical status: A_1 (relatively preserved) or A_2 (relatively impaired). If the MA has unconditionally classified a patient into group B, then the 7-step conditional fuzzy algorithm AAA calculates the conditional affiliation degrees of the patient to two homogeneous subgroups by medical status: B_1 (relatively preserved) or B_2 (relatively impaired).

3. The MA, AAA and AAB algorithms are organized into a diagnostic-stratification system that determines the patient's subgroup (A_1, A_2, B_1 or B_2) for each patient with IHD complicated by IMR, and his/her absolute affiliation degree in that subgroup.

4. A complete system of 49 examples for all possible combinations of MA, AAA and AAB algorithms' outputs is created. It illustrates the application of the created fuzzy algorithms in a medically understandable way. In practical terms, such a system facilitates and personalizes the decision-making approach to a complex medical situation such as IHD complicated with significant chronic IMR.

5. The existing CSC database of patients with IHD complicated with IMR has been updated by adding new patients, expanding it with new medical features, incorporating a computable system of affiliation degrees in groups and subgroups, and measuring the individual typicality of each patient.

6. Using the fuzzy pseudo-control group method, the positive influence of annuloplasty on the integral parameters, the regurgitation fraction and the MR rate was statistically proven. The method compares fuzzy samples of indications where a patient's typicality is digitized by his/her affiliation degree to the corresponding subgroup obtained from the diagnostic stratification system.

VIII. Thesis-related publications

The following publications are related to this research:

Panayotov P, Ivanova S, Panayotova D, Nikolova N, Mircheva L, Petrov V, Donchev N, Tenekedjiev K: Algorithms for formal stratification of patients with ischemic mitral regurgitation. Scripta Scientifica Medica: 2018, 50(4): 33-38.

Natalia N, Panayotov P, Panayotova D, Ivanova S, Tenekedjiev K: Using Fuzzy Sets in Surgical Treatment Selection and Homogenizing Stratification of Patients with Significant Chronic Ischemic Mitral Regurgitation. International Journal of Computational Intelligence Systems 2019, 12(2): 1075–1090.

Panayotov P, Slavov M, Panayotova D, Nikolova N. Surgical Treatment of Ischemic Mitral Regurgitation Triggers Reverse Remodeling of Left Heart Chambers. Cardiology [Internet]. 2016;134(2): 254–254.

Panayotov P, Slavov M, Panayotova D, Nikolova N. Left Atrial Reverse Remodeling and Atrial Fibrillation after Combined Surgical Revascularization and Mitral Repair. Cardiology [Internet]. 2016;134(2): 255–255.