UNIVERSITY OF MEDICINE AND PHARMACY
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Prediction of heart failure decompensation using artificial intelligence

PhD THESIS SUMMARY

PhD Coordinator:
PROF.UNIV.DR. SINESCU CRINA-JULIETA

PhD Student:
PANĂ MARIA-ALEXANDRA (CIUCĂ-PANĂ)

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CONTENT

INTRODUCTION

Heart failure is a plurietiological clinical syndrome, characterized by specific symptoms and/or signs, leading to increased intracardiac pressure and/or signs of low cardiac output at rest and/or during exercise, with a major impact on patients' quality of life from the physically, psychologically and socially point of view [1].

Despite the evolution of diagnostic and therapeutic techniques for heart failure, the associated mortality is still high due to the lack of effective secondary prevention methods of this pathology, a situation which leads to a high incidence of complications and exacerbations [1].

Artificial intelligence is an engineering branch that uses modern concepts in solving complex medical challenges. The implementation of artificial intelligence in the medical sphere should not be seen as a futuristic phenomenon, but rather as a tool capable of saving medical staff time and minimizing human errors. [2-3].

Starting from these needs from current practice I raised the hypothesis of developing effective methods of secondary prevention of heart failure by means of artificial intelligence algorithms. The first study case was build on the hypothesis that voice could be a predictor of chronic heart failure patients' acutizations, while the second research study aimed to evaluate the effectiveness of a virtual cardiac recovery assistant in the secondary prevention of chronic heart failure.

The first study case was a prospective observational type, in which I collected the vocal parameters of each enrolled patient, to whom I associated a NYHA class from I-III. I entered the obtained database into a machine learning algorithm, whose efficiency was tested by voice analysis of a patient who was not part of the initial group.

The second study case was a prospective interventional type, in which I implemented a virtual cardiac recovery assistant. After a period of 3 months, I performed the comparative analysis of the pre-establised parameters of the study group. The results were favorable to telerehabilitation, its benefits being at least equivalent to a classic cardiac rehabilitation program.

The research studies limitations are primarily represented by the small number of enrolled patients, a situation that may lead to an inadequate representation of patients with heart failure. For the same reason, the results obtained are preliminary and require further certification on larger groups of subjects. Also, the need for comprehension, speech and movement of the studied patients led to a limitation of the enrollment of critically il patients, with disabilities or with a low education background.

I.GENERAL PART

1. Prediction of heart failure decompensation using artificial intelligence

Heart failure (HF) is a clinical syndrome characterized by symptoms (dyspnea, fatigue) and/or signs (distension of jugular veins, subcrepitant pulmonary rales, peripheral edema) secondary to some structural or functional pathologies of the heart that lead to increase intracardiac pressure and/or low cardiac output at rest and/or during exercise. [4].

There are currently 26 million people diagnosed with chronic heart failure in the world and the incidence is constantly increasing secondary to the life expectancy improvement and HF diagnostic and treatment techniques. Age-standardized prevalence shows significant geographic variation, thus in 2017, the highest incidence rates of HF were recorded in Central Europe, the Middle East and North Africa, with a value between 1133-1196 reported cases per 100,000 inhabitants, while the lowest rates were seen in Eastern Europe and South-East Asia, of only 498-595 people with HF per 100.000 inhabitants [5].

Economically speaking, heart failure is a burden on health systems worlwide, secondary to the increased costs it generates. In 2012, an extensive study that considered both direct and indirect costs of HF care from 197 countries estimated a total of $108 billion. Out of this amount, 60% represented direct costs ($65 billion) and 40% indirect costs ($43 billion) [6-7].

Artificial intelligence (AI) is defined as computers and advanced technology ability to simulate intelligent human behaviour and critical thinking. The role of AI in the public and private sectors of healthcare is growing rapidly and is sure to have a substantial impact on every aspect of primary care. The purpose of these medical advances is to achieve a mutually beneficial balance between the trained human resource indispensable to the medical act and technology [8].

Widespread implementation of telemedicine and telecardiac rehabilitation services presents the opportunity to combat the certain patient groups access inequality to medical services. Currently, investments in the field of medical technology exceed those in classical medicine. The future is promising, but it is very important to also align ethical standards, manufacturing and government regulations for increased patient protection and minimization of associated risks [9].

II.PERSONAL CONTRIBUTIONS

2. Voice analysis- predictive marker of heart failure decompensation

2.1. Hypothesis and study objectives

Chronic heart failure benefits from impressive current medical advances, however, it still has an ever-increasing incidence and prevalence, especially in industrialized countries. Most of the patients diagnosed with this syndrome go at last once in their life through an episode of disease exacerbation, with lethal potential and need for emergency treatment. The development of artificial intelligence applicability in the medical sphere can prove to be a real help in the primary and secondary prevention of chronic heart failure. Thus, starting from these needs from current medical practice, we raised the hypothesis of using the patients' voice as a parameter for predicting the risk of heart failure decompensation. The current study provides a new perspective on the application of artificial intelligence methods in medicine, using an artificial intelligence software for patients voice analysis.

Accordingly, I formulated the following general objectives of the research study:

1. Creating the profile of the patient with frequent episodes of heart failure decompensation;
2. Creating a database for machine learning of artificial intelligence software;
3. Introducing a new patient into the machine learning algorithm to check its efficiency;

2.2.Material and method

2.2.1. Study type and subject characterization

I carried out a prospective observational study in the Cardiology Department of ''Carol Davila'' University of Medicine and Pharmacy within ''Bagdasar-Arseni'' Emergency Clinical Hospital in Bucharest, by creating a group of patients diagnosed with acute cardiogenic pulmonary edema. In the research study, I included patients aged >18 years old, with an admission diagnostis of acute cardiogenic pulmonary edema, regardless of the known or unknown etiology of heart failure or the precipitating factor of the acute episode. I excluded patients aged <18 years old, with inability to understand and/or comply with the study protocol and/or provide informed consent, patients diagnosed with mutism and/or aphasic patients. The research study population consisted of patients who met the inclusion criteria and did not have any exclusion criteria and who, prior to voluntary enrolment, underwent a detailed study presentation, training and counseling session, The research study presented no potential psychological, physical or legal risk to the enrolled patients and was conducted in accordance with the ethical principles of the Helsinki Declaraction of Human Rights. With the detailed presentation of the research study, each patient signed an informed consent. The current research study was approved by the ethics committee of ’’Carol Davila’’ University of Medicine and Pharmacy in Bucharest, Romania, with protocol code PO-35-F-03, number 17831, dated July 12, 2021.

In establishing the acute cardiogenic pulmonary edema diagnosis, I used the clinical examination at presentation, evaluation of signs of pulmonary and/or systemic congestion, personal pathological history, resting electrocardiogram, heart-lung x-ray, ecocardiography and biological samples. After patient hemodynamic stabilization, I carried out an extensive evaluation to detect the underlying etiology of heart failure and the precipitating factor of the acute episode.

During the hospitalization period, each patient of the study group was recorded twice a day pronouncing two specific key words (the number 33 and the vowel ’’E’’) using a Lenovo P780 mobile phone in an environment with as little background noise as possible. I assigned a NYHA class to each individual voice recording and it helped build the database that I then used as input for the machine learning algorithm. I tested the efficiency of the machine learning algorithm by analyzing the voice of a patient who was not part of the initial group.

2.2.2. Data collection

Patients enrolled in the research study were examined according to the same protocol, to ensure the equivalence of the parameters of the study participants. The collected data were prospectively stored in a database.

Both for the study group and for the patients used to verify the artificial intelligence software’s accuracy, the following parameters were collected: (1) age, (2) sex, (3) environment of origin, (4) financial status, (5) educational level, (6) precipant factor of CAPE, (7) smoking status, (8) NYHA class at discharge, (9) physical activity level, (10) height, (11) weight at admission, (12) weight at discharge, (13) body mass index, (14) average diuresis/24h during the hospitalization period, (15) average water intake/24h during the hospitalization period, (16) presence/absence of atrial fibrillation, (17) presence/absence of esential arterial hypertension, (18) presence/absence of type-2 diabetes miellitus, (19) presence/absence of ischemic heart disease, (20) non-invasive/invasive therapy for ischemic heart disease, (21) ejection fraction of left ventricle, (22)presence/absence of aortic/mitral/tricuspid valvulopathies, (23) presence/absence of pulmonary hypertension, (24) admission NTproBNP value, (25) discharge

NTproBNP value, (26) high-sensitivity Troponin I value, (27) admission presepsin value, (28) blood count, (29) complete lipid profile, (30) creatinine, (31) glomerular filtration rate, (32) uric acid, (33) ionogram, (34) vocal parameters.

2.2.3. Statistical analysis

The data collected from the group of patients enrolled in the study led to the creation of two databases. The first database was created using the Microsoft Office Excel Workbook and contained the parameters numbered 1-32 presented in the previous sub-chapter ''2.2.2. Data collection'', and the second database contained the vocal parameters of the patients. The Microsoft Office Excel Workbook database contained integer, real or boolean variables thata were analyzed and studied individually. Considering the small number of patients enrolled in the study, these data were presented as a case series. The processing of the vocal parameters was carried out by measuring the vocal amplitude at equal distances over a predetermined period of seconds and the continuous signal it emits. I set the signal sampling rate to 48kHz (kilohertz).

2.2.4. Research limitations

The current research study limitations are represented by the small group of patients, framing the results, framing the obtained results as preliminary, with a further need of certification by reserach on large groups of patients. Also, the need for patients to be able to understand and speak led to limiting the enrollment of critically ill, disabled or patients from low-educational backgrounds.

2.3.Results

The study group consisted of 16 patients, 9 male and 7 female. The minimum age was 65 years, the maximum age 91 years, with an average value of 72.68 years. The environment of origin of the studied patients was mostly urban, with a value of 13 patients from the urban environment compared to 3 from the rural environment. I randomly set patients numbered 1-6 and 8-16 to be used in the AI algorithm's machine learning database and patient number 7 to be used for testing its functionality (Table 2.1.)

Table 2.1. Epidemiological data

Patient	Age	Sex	Environment of origin	Financial status	Educational level
1	75 y	F	Urban	Medium	Highschool
2	71 y	F	Urban	Medium	Highschool
3	66 y	F	Rural	Medium	University
4	79 y	F	Urban	Medium	University
5	74 y	F	Rural	Low	University
6	67 y	F	Urban	High	Postgraduate studies
7	66 y	F	Urban	High	Postgraduate studies
8	73 y	M	Urban	Medium	Highschool
9	76 y	M	Urban	Low	Highschool
10	70 y	M	Urban	Low	Highschool
11	65 y	M	Rural	Low	University
12	91 y	M	Urban	High	Highschool
13	70 y	M	Urban	Medium	University
14	75 y	M	Urban	Medium	Highschool
15	78 y	M	Urban	Medium	Highschool
16	67 y	M	Urban	Low	University

I monitored the value of the heart failure specific marker NTproBNP both at admission and at discharge. I interpreted the values starting from the cut-off value of 500 pg/mL. Consequently, the minimum value I observed in the study group was 1207 pg/mL, the maximum value was >30,000 pg/mL, and the mean value was 7,847 pg/mL. During the hospitalization period, NTproBNP values decreaed secondary to treatmen, so on the day of discharge the minimum value I identified was 370 pg/mL, the maximum value 1200 pg/mL and the average value 767.5 pg/mL (Table 2.2.).

Table 2.2. NTproBNP values at admission and discharge

Patient	NTproBNP admission	NTproBNP discharge
1	3480 pg/mL	1200 pg/mL
2	4638 pg/mL	900 pg/mL

3	3664 pg/mL	650pg/mL
4	5200 pg/mL	1105 pg/mL
5	2262 pg/mL	370 pg/mL
6	3797 pg/mL	800pg/mL
7	10.939 pg/mL	589 pg/mL
8	17.545 pg/mL	500pg/mL
9	3131 pg/mL	1000pg/mL
10	>30.000 pg/mL	1200 pg/mL
11	1207 pg/mL	400 pg/mL
12	8987 pg/mL	700pg/mL
13	4277 pg/mL	800 pg/mL
14	15.300 pg/mL	940 pg/mL
15	4325 pg/mL	456 pg/mL
16	6800 pg/mL	670 pg/mL

Echocardiographically, 10 patients had associated heart failure with severe left ventricular systolic dysfunction, 4 patients had moderate left ventricular systolic dysfunction and 2 patients had normal ejection fraction. I observed aortic valvulopathy in 5 cases, mitral valvulopathy in 16 cases and tricuspid valvulopathy in 14 cases (Table 2.3.).

Table 2.3. Echocardiographic patients' characteristics

Patient	LVEF	Valvulopathy_{AO}	Valvulopathy_{MT}	$\text{Valvulopathy}_{TRC}$
1	15%	Metal prostethis	Metal prostethis	Annuloplasty
2	50%	No	Mild regurgitation	No
3	40%	No	Moderate regurgitation	Moderate regurgitation
4	30%	No	Moderate regurgitation	Mild regurgitation
5	20%	No	Moderate regurgitation	Moderate regurgitation
6	40%	No	Moderate regurgitation	Mild regurgitation
7	10%	No	Moderate regurgitation	Moderate regurgitation
8	19%	No	Severe regurgitation	Severe regurgitation
9	35%	Mild regurgitation	Moderate regurgitation	Moderate regurgitation

10	30%	No	Moderate regurgitation	Moderate regurgitation
11	20%	No	Moderate regurgitation	Moderate regurgitation
12	40%	Moderate stenosis	Severe regurgitation	Mild regurgitation
13	25%	No	Mild regurgitation	No
14	25%	Severe stenosis	Metal prostethis	Severe regurgitation
15	50%	Moderate regurgitation	Moderate regurgitation	Moderate regurgitation
16	45%	No	Mild regurgitation	Mild regurgitation

I performed the voice recording of the patients enrolled in the study during their hospitalization, twice a day (morning and evening) using a Lenovo P780 smartphone. Each patients pronounced two predetermined keywords represented by the vowel ''E'' and the number ''33''. I obtained a total of 240 voice recordings that represented the initial database. We assigned each voice recording a class from the top three of the NYHA heart failure Classification System.

In order to introduce it into the artificial intelligence algorithm, I processed the database of vocal parameters by sampling at a rate of 48 kilohertz. Thus, I measured the amplitude of the voice waves at a preset equal distance of points per second alongside the continuous signal. Figure 1 shows the amplitude of the original signal of a recording. In this graphic representation is a female patient who pronounces the number ''33'' (Fig.2.1.).

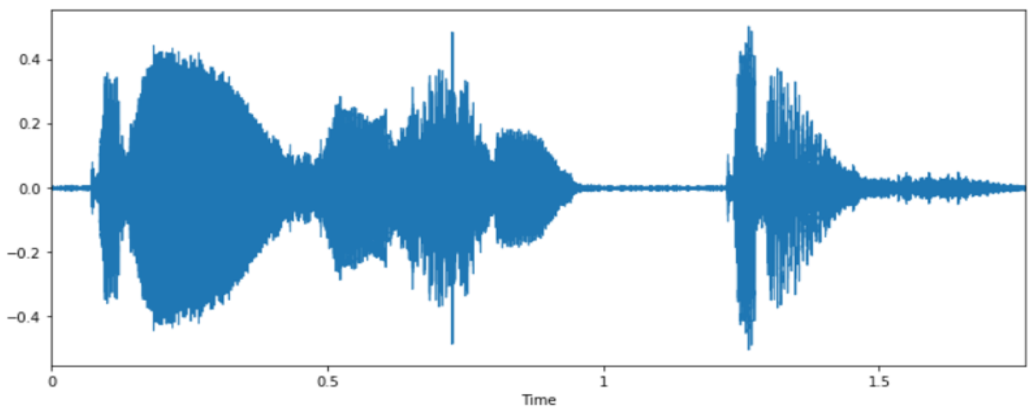


Figure 2.1. The amplitude of the original signal in time

I extracted relevant vocal features from each recording using cepstral coefficients. This stage is necessary in the raw data processing to prepare the input file in the proposed machine learning algorithm (Fig.2.2.).

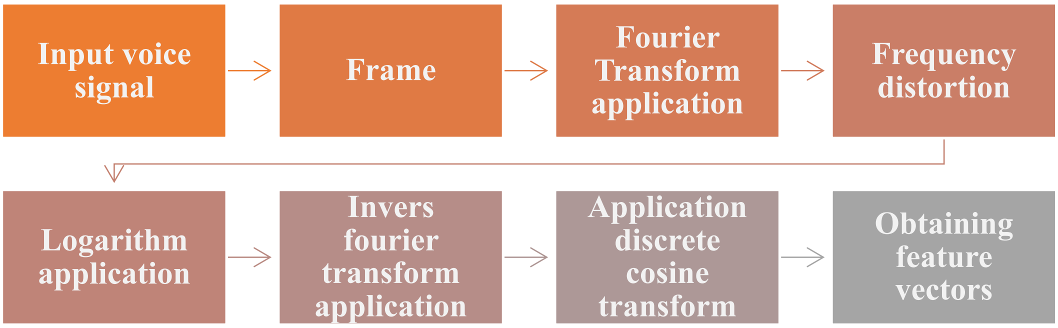


Figure 2.2. Vocal feature extraction stages

The sound processing method shown in Figure 2.3. resulted in obtaining 40 feature vecors. From these we used 20 vectors represented graphically in Figure 2.3.

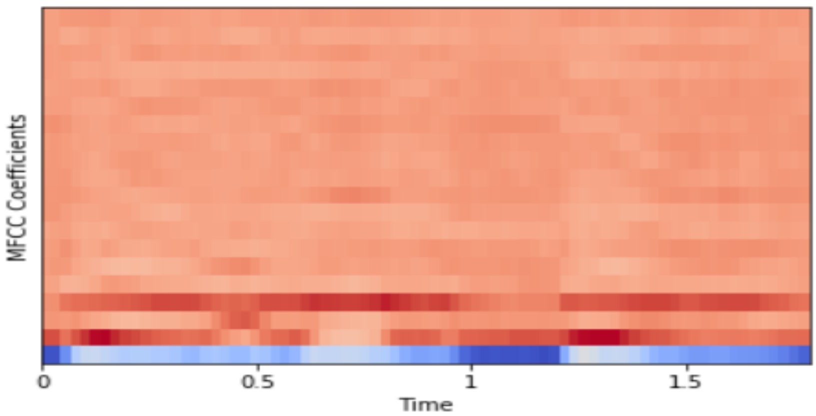


Figure 2.3. Visual representation of the 20 feature vectors

Machine learning algorithms are characterized by the similarity of human nature of data analysis. Several machine learning techniques were used to classify the audio files into one of the first three classes of the NYHA system, namely: Support Vector Mchine, Artificial Neural Networks and K-Nearest Neighbors (KNN). The KNN algorithm was found to be the most relevant as it generated the highest classification accuracy. In addition, the result was supported by the confusion matrix. The three columns in the matrix represent the three classes associated with the audio files (NYHA Class I, NYHA Class II, NYHA Class III). Each element in the diagonal represents the number of correctly classified data and the other elements represent the erroneous ones. The obtained value of 0.945 represents a high accuracy, which was validated by means of the confusion matrix. These two aspects prove that the KNN algorithm is capable of high-precision voice analysis and is reliable for further evelopment (Table 2.4.).

Table 2.4. The methods' score used in the vocal parameters processing

Method	Results
SVM	Accuracy obtained using the radial basis function kernel = 0.709 Accuracy obtained using the linear kernel =0.618 Accuracy obtained using the polynomial kernel =0.527
ANN	Model 1 Maximum value of the loss function obtained during testing = 1.1447 Maximum accuracy obtained during testing= 0.418 Model 2: Maximum value of the loss function obtained during testing = 1.3237 Maximum accuracy obtained during testing = 0.436
KNN	Obtained score = 0.945 Confusion matrix: [[20 0 2] [0 13 0] [1 0 19]]

2.4. Discussions

The aim of the current research study was to demonstrate that the phonation processs suffers during decompensated episodese of heart failure. Thus, the voice can be used as a prognostic and monitoring marker of the clinical status of these patients and can prevent acute episodes through early addressability to outpatient medical services [10].

The patients enrolled in the research study were evaluated throughout the hospitalization period, both in terms of demographic, social, clinical, biological and imaging parameters, as well as in terms of voice evaluation. The average age of the enrolled patients was 72.68 years, with an urban environment of origin and a predominantly average financial status. The educational level assessed in the study group was mostly medium (high school). The obtained data correlates with the data from the specialized literature which states a much higher incidence of HF in patients over 70 years old coming from industrialized areas [11].

Regarding the assessment of the cardiovascular risk factors, there were more men than women in the study group, at least 65 years old and with a hereditary history of cardiovascular disease, but without gender variability. Half of the evaluated patients were smokers and more than half reported moderate or high alcohol consumption per day. We identified an increased body mass index in 12 cases out of 16 analyzed, with values that placed the patients in the category of overweight or obesity. Also, hypertension, dyslipidemia and type-2 diabetes were the most frequent risk factors that we observed in the study group. These three risk factors were evaluated in sedentary patients with increased body mass indexed. Analysis of cardiovascular risk factors is positively associated with data from the Framingham study which states a higher incidence of cardiovascular disease in men than in women, but with a decreasing difference with increasing age. All patients in the study presented cardiovascular risk factors of varying degrees, which according to the previously mentioned study, predisposes them to an increased risk of cardiovascular disease. This result was also confirmed by the fact that all enrolled patients had a history of ischemic heart disease [12].

The precipitating factor of the acute episode assessed in the study group was non-adherence to non-pharmacological and pharmacological treatment, firstly and acute infectious disease, secondary, The mean value of the specific heart failure marker NTproBNP was 7.847 pg/mL at admission, which decreased during the hospitalization period under treatment to a mean value of 767.5 pg/mL. The evaluated patients also had slight increases in the value of HstnI, which outlined an acute myocardial injury diagnosis and not a myocardial infarction one, with a mean value of 136.06 ng/L. In cases of acute heart failure with an infectious precipitating factor, patients associated increased values of Presepsin, the average value being 603.75 pg/mL.

Echocardiographically, most patients had heart failure with severe left ventricular systolic dysfunction.

Regarding the voice parameters, the artificial intelligence algorithm created absorbed the voice parameters extracted from the study group, to which it associated a NYHA class from I-III, according to the indicated clinical status. Voice parameters of the randomly selected patient for testing the algorithm functionality were correctly classified into NYHA class III at admission and NYHA class II at discharge.

Although the group of patients on which the algorithm was tested is small and studies on much larger groups are needed, the positive result of this study provides an opportunity for secondary prevention of heart failure worth considering. The literature states an improvement in the survival of patients with acute heart failure in recent years, with a hope of 85.5% at 1-year. However, the survival of a heart failure patient at 5 and 10 years is 56.7% and 34.9%, respectively. Although statistically, the prognosis of heart failure patients has improved over time, hospitalization and mortality rates remain high [13].

In 2012, the global cost of treating patients with heart failure was estimated at 109 billion dollars, an amount made up of 60% direct costs and 40% indirect costs. This economic assessment noted important variations in the distribution of expenditure betwen low-and middle-income countries and high-income countries. The latter allocated a larger amount of funds to direct costs, while the others to indirect costs. Hospitalization of patients with heart failure generates the highest costs globally, followed by drug therapy, accounting for approximately 43% of the total cost per patient. The rest of the costs are represented by medical procedures, laboratory tests and imaging techniques. In the case of patients with heart failure who associate kidney failure with need for dialysis, the costs increase exponentially, but overall the impact was not that great because the number of these patients was quite low. [14].

2.5.Conclusions

In conclusion, through the current research study I have successfully generated an artificial intelligence algorithm concept capable of using patients' voice in predicting the risk of heart failure decompensation.

Through the data collected in this study, we also managed to outline a profile of the Romanian patient diagnosed with heart failure. By standardizing the obtained data, I can state that the most frequently observed heart failure patient in medical practice is male, over 70 years old, from an urban environment of origin, with an average financial status and educational level, with hereditary antecedents of cardiovascular disease, smoker, moerate etahnol user, sedentary, obese, hypertensive, dyslipidemic and with type-2 diabetes. He most likely associates heart failure with severe systolic dysfunction of ischemic etiology and the frequent case of acute decompensation is represented by non-adherence to non-pharmacological and pharmacological treatment.

The advantages of this algorithm in clinical practice are primarily represented by the decrease in complications associated with heart failure, hospitalization rates and cardiovascular mortality. Also, remote monitoring of heart failure patients and their early referral to outpatient medical services could decrease hospitalization rates and the human resource associated with the medical act. The implementation of such an algorithm on patients' mobile phones means a minimum of effort on their part and an increased efficiency in the management of secondary prevention of heart failure. Also, the ability of the remote monitoring algorithm offers the possibility of minimal evaluation of patients in areas with limited access to medical services. The short-term disadvantage of this algorithm is represented by the need for certification on a larger group of patients, which implies an increased period of time until is actual use in clinical practice. A larger staudy requires economic resources to create the study framework, but much lower resources that those needed to treat patients in the emergency department.

In perspective, this concept would also be able to be implemented in the already existing applications for monitoring vital parameters and cardiovascular risk factors, a situation that will lead to an increase in the detection sensitivity of the parameter through data association and the accuracy of the application through the recommendations offered to patients.

Secondary prevention is the optimal control strategy for heart failure whose incidence and prevalence is extremely difficult to curb. Therefore, the use of artificial intelligence may prove to be a pioneer in chronic disease management technology.

3. vCare virtual assistant- method of secondary prevention of heart failure

3.1.Hypothesis and study objectives

Cardiac rehabilitation is an important component of secondary prevention for patients diagnosed with heart failure, which, despite multiple benefits demonstrated in studies, is rarely prescribed at discharge. Patient participation in cardiac rehabilitation programs is low firstly because of the lack of centers dedicated to this patient segment and secondly because of the pre-established schedule that limits the participation of patients who are professionally active. The virtual assistant concept has existed for many years in the medical research field, but encountered multiple dificulties in evolution and implementation until the time of the COVID-19 pandemic, which demonstrated the need for remote monitoring of cardiac patients. Considering all these aspects from the medical practice, I raised the hypothesis of creating a virtual assistant for heart failure patients that could offer them all the components of a classic cardiac recovery program under the careful monitoring of a multidisciplinary team.

Accordingly, I formulated the following general objectives of the research study:

1. Testing the use, feasibility and effectiveness of the vCare system;
2. Impact evaluation of the vCare system on cardiovascular risk factor reduction, on patients' adherence to the care and rehabilitation plan at home, on the personalization of the treatment and on the promotion of an active life at home.

3.2.Material and method

3.2.1. Study type and subjects characterization

I carried out a prospective interventional study in the Cardiology Department of the ''Carol Davila'' University of Medicine and Pharmacy within ''Bagdasar-Arseni'' Emergency Clinical Hospital in Bucharest by creating a study group of patients diagnosed with chronic heart failure that could benefit from a cardiac rehabilitation program. In the research study I included patients aged ≥ 50 years, with a diagnosis of NYHA class II-IV heart failure, with the ability to interact with digital devices, who had an internet connection at home and a TV with an HDMI port. I excluded patients with unstable angina, systolic blood pressure >200 mmHg, diastolic blood pressure >110 mmHg, with a positive orthostatic hypotension test, severe aortic stenosis, sepsis, life-threatening arrhythmias, acute heart failure, third-degree atrioventricular block, recent pulmonary thrombembolism, phlebitis, persistent ST-segment elevation >2mm, inadequately controlled type-2 diabetes miellitus, motor disability, inadequately controlled thyroid pathology, hypokalemia, hyperkalemia, inability to understand and/or adhere to the study protocol and/or giving informed consent.

The current research study presented no potential psychological, physical or legal risks and was conducted in accordance with the ethical principles of the Helsinki Declaration of Human Rights. Informed consent was signed by each study participant. This research study was approved by the Ethics Committee of the ''Carol Davila'' University of Medicine and Pharmacy in Bucharest, Romania, with protocol code P0-35-F-03, number 36288 dated 21 December, 2021.

It should be noted that this research study was part of a larger study entitled the vCare Project (Virtual Care for Rehabilitation in Elderly Patients), funded by the European Union through the Horizon 2020 Innovation and Research Program, with grant number 769807. In within the framework of the current doctoral thesis, only the study related to the heart failure pathology will be presented.

In establishing the heart failure diagnosis and assessing its severity, I used the objective exmination, medical history, resting electrocardiogram, heart-lung x-ray, cardiac ultrasound, cardio-pulmonary stress test and biological samples. The study group was randomly divided into three subgroups as follows:

- The first study subgroup used the vCare virtual assistant in the cardiac recovery program;
- The second study subgroup performed ambulatory cardiac rehabilitation;
- The third study subgroup performed cardiac rehabilitation at home only with recommendations obtained at discharge.

3.2.2. Virtual assistant components

The vCare virtual assistant was represented by an application pre-installed on a Lenovo Tab M10 Full HD Plus tablet that was given to the patient upon enrollment in the study. This tablet automatically connected with a Xiaomi Mi Band 4 smart watch, a Xiaomi smart weight scale, a Beurer BM85 smart blood pressure monitor, an Astra Orbbec camera and a set top box, the latter also being interconnected with the patient's TV.

This virtual assistant was remotely controlled by a digital platform (entitled Kiola) to which only the medical team had access where the patient's personal and medical data were entered and through which the cardiac recovery program was established, which once activated was found on the patient's tablet.

Depending on the patient's medical needs, the virtual assistant cardiac recovery program was individualized with the following activities:

- Medical education;

- Daily motor activity;
- Aerobic physical activity;
- Resistance training;
- Support for pharmacological therapy;
- Vital parameters control;
- Weight control;
- Smoking reduction;
- Anxiety and depression reduction;

3.2.3. Data collection

For each patient enrolled in the study we collected the following parameters: (1) Age, (2) Sex; (3) Environment of origin; (4) Financial status; (5) Educational level; (6) Smoking status; (7) Height; (8) Weight before cardiac rehabilitation program; (9) Weight after cardiac rehabilitation program; (10) Body mass index before cardiac rehabilitation program; (11) Body mass index after cardiac rehabilitation program; (12) Physical activity level; (13) Presence/absence arterial hypertension; (14)Presence/absence type-2 diabetes miellitus; (15) Total cholesterol value before and after the cardiac recovery program; (16) HDL-cholesterol value before and after the cardiac rehabilitation program; (17) LDL-cholesterol value before and after the cardiac rehabilitation program; (18) Triglyceride value before and after the cardiac recovery program; (19) Cardiopulmonary exercise test parameters before and after the cardiac recovery program (exercise intensity; exercise test duration; maximum heart rate; maximum blood pressure, VO_{2max}); (20) Minnesota Questionnaire Score (21) Fagerstrom Questionnaire Score; (21) Inpatient Anxiety and Depression Questionnaire; (22) Quality of life assessment questionaire (EuroQol-5D); (23) Questionnaire for self-assessment of the state of health (EQ-VAS); (24) User Experience Questionnaire (UEQ); (25) System Usability Scale Questionnaire (SUS); (26) Technology Acceptance Model (TAM); (27) vCare virtual assistant parameters.

3.2.4. Statistical analysis

Through the data collected from the patient groups I created three databases. The first database was created using Microsoft Office Exel Workbook and contained the parameters numbered from 1-19 presented in the previous subchapter 3.2.3. ’’ Data collection’’. This contained integer, real or boolean variables, which have been individually studied and analyzed. The second database was created using SPSS and contained parameters numbered 20-26. The third database was created in the Kiola digital platform and contained the vCare virtual assistant parameters. Each parameter collected was studied and analyzed individually using the programs mentioned above.

3.2.5. Research limitations

Current research study limitations are represented by the small group of enrolled patients, a situation that may lead to an inadequate representation of patients with heart failure who may benefit froma remote cardiac rehabilitation program. Also, using only the tablet version of the virtual assistant may be associated with less efficiency in use than using a mobile phone version. This limitation could have been adressed by the possibility of simultaneous use of both tablet and mobile versions, but due to technical difficulties this solution was not possible.

3.3.Results

The study group consisted of 30 patients, out of which 17 were male and 13 were female, with an average age of 61.53 years ± 9.41 years (Fig.3.1).

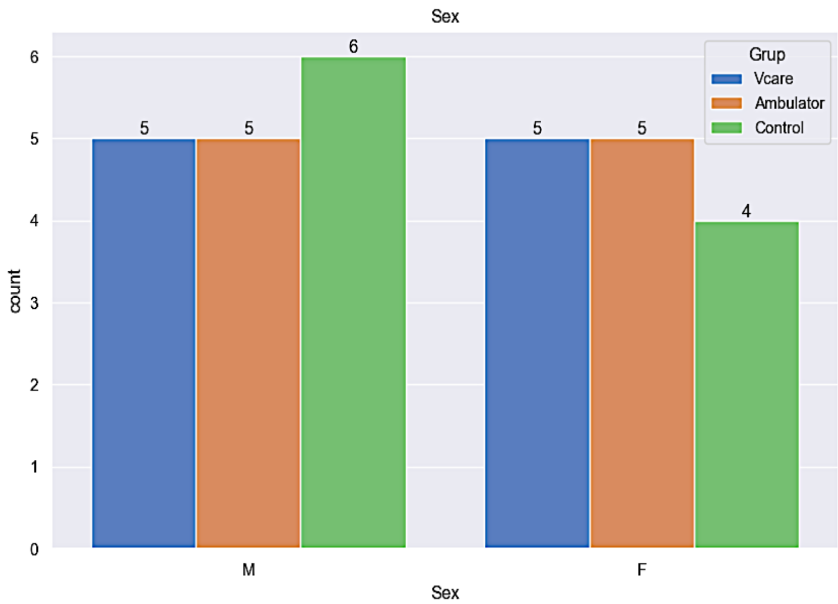


Figure 3.1. Patients distribution according to sex

In Figure 3.2. I performed a comparative analysis of the average value of body mass index (BMI) between the three study subgroups. Analyzing these results, I observed that the most important decrease in BMI was achieved in the experimental subgroup, with a difference of 1.21 kg/m^2, followed by the ambulatory subgroup, where the difference was 0.5 kg/m^2. The patients in the control subgroup presented approximately the same weights before and after the intervention, the average value being even slightly increased by 0.045 kg/m^2 (Fig.3.2.).

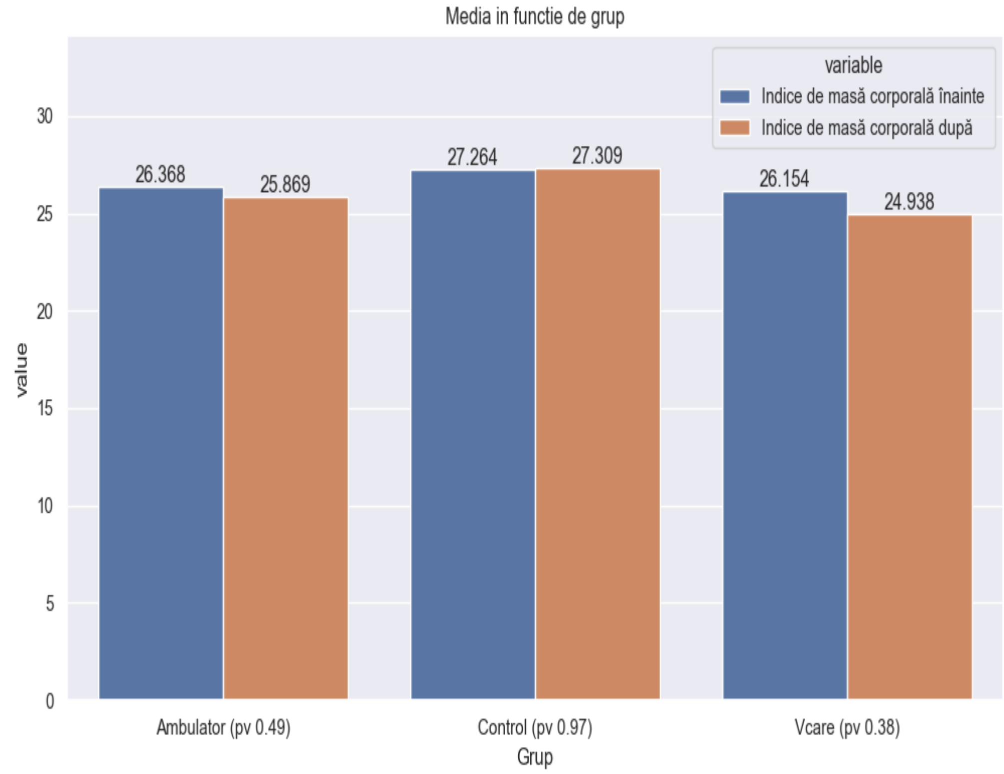
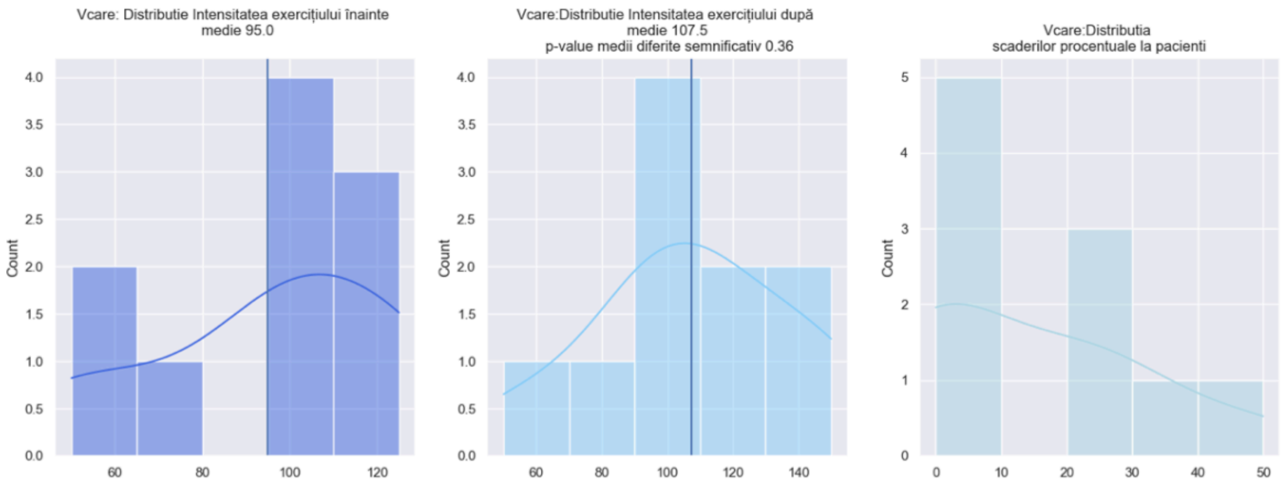


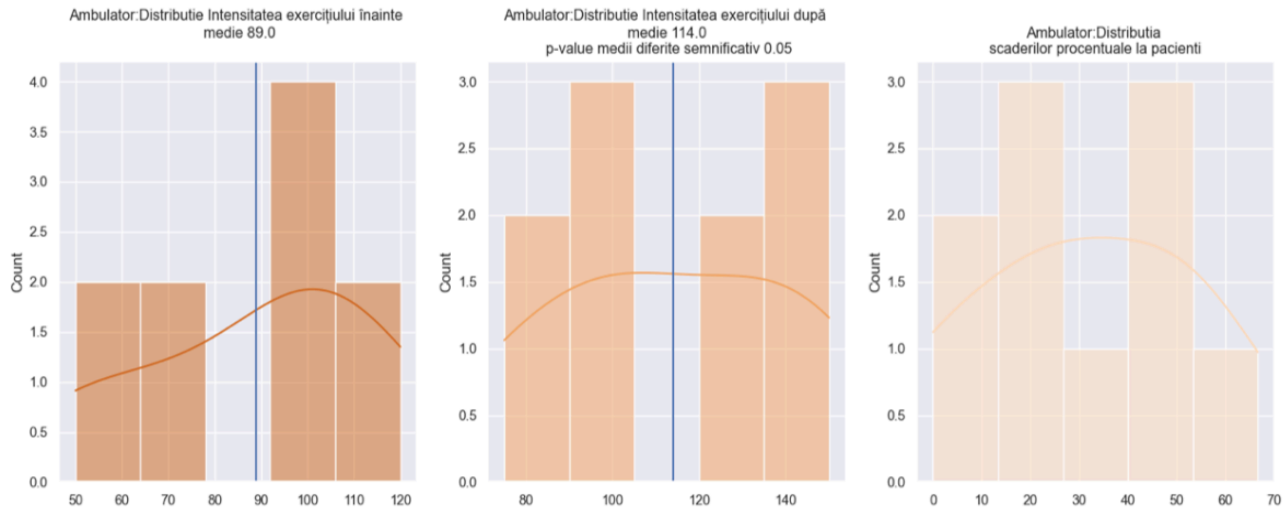
Figure 3.2. BMI comparative analysis before and after the intervention

In the vCare subgroup it can be seen from Figure 3.3.a) that at T0 the average value of the physical exercise intensity was 95W, a value that increased at T1 to 107.5W. In the ambulatory subgroup it can be seen that the initial value of the physical effort intensity was of 89W and increased to 114W after completion of the cardiac recovery program. In the control subgroup, the initial value of the physical effort intensity was 87.5W and decreased after three months to 76.5W. Analyzing all three subgroups I can state that in terms of physical effort intensity, the most important increase was identified in patients who performed ambulatory cardiac rehabilitation, followed by patients who used the vCare virtual assistant. Patients who performed cardiac recovery at home without medical assistance showed a decrease in the physical activity level (Fig.3.3.).

a) **vCare subgroup**



b) **Ambulatory subgroup**



c) **Control subgroup**

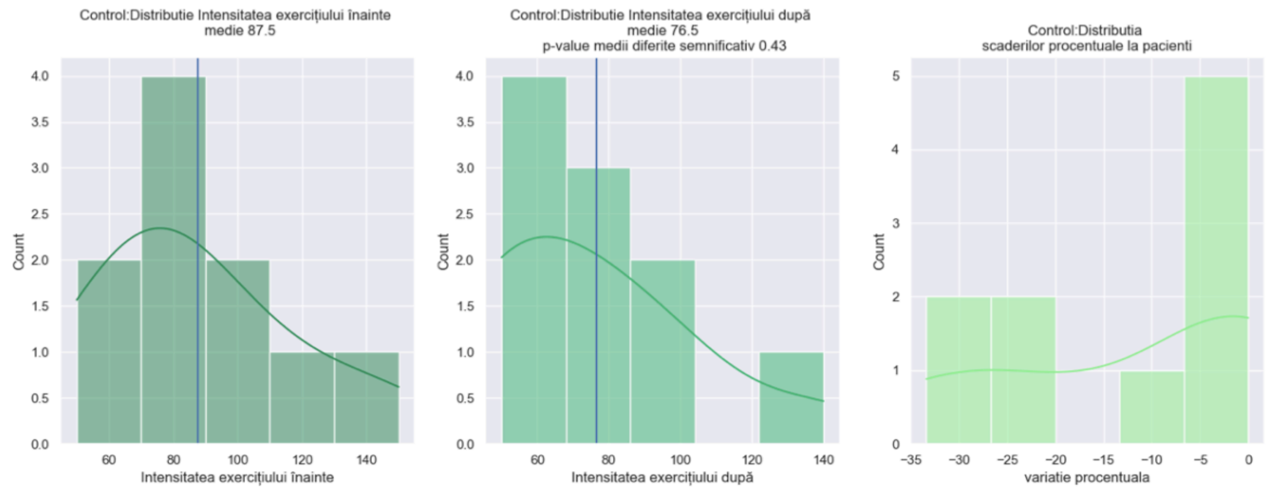


Figure 3.3. Physical effort intensity at the cardiopulmonary exercise test before and after the intervention

In Figure 3.4. are represented the mean values before and after the intervention of the Minnesota Questionnaire score for each subgroup of evaluated patients. It can be observed that in the ambulatory and control subgroups the quality of life before the intervention was the lowest, with a score of 55.9 and respectively 51. The vCare subgroup presented a slightly higher quality of life, with a mean value of 47.3. After the intervention, according to this questionnaire, the quality of life of patients in the ambulatory and vCare subgroups improved considerably, with a decrease of 6.5 points and respectively 5.8 points. In the control group, the quality of life remained aproximately the same, from an average value of 51 to an average value of 51.8 points (Fig.3.4.).

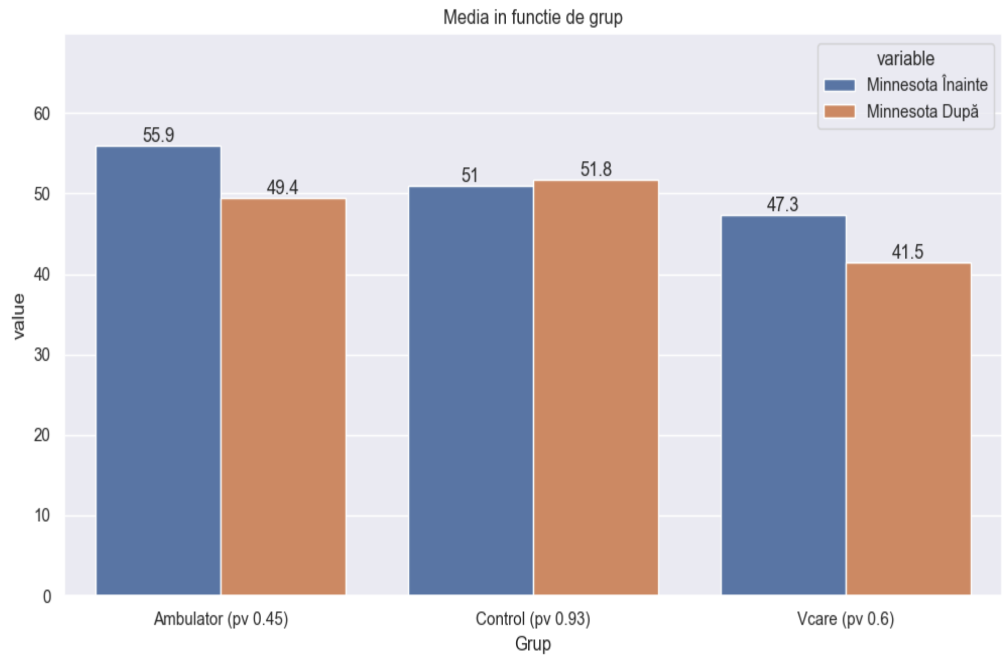
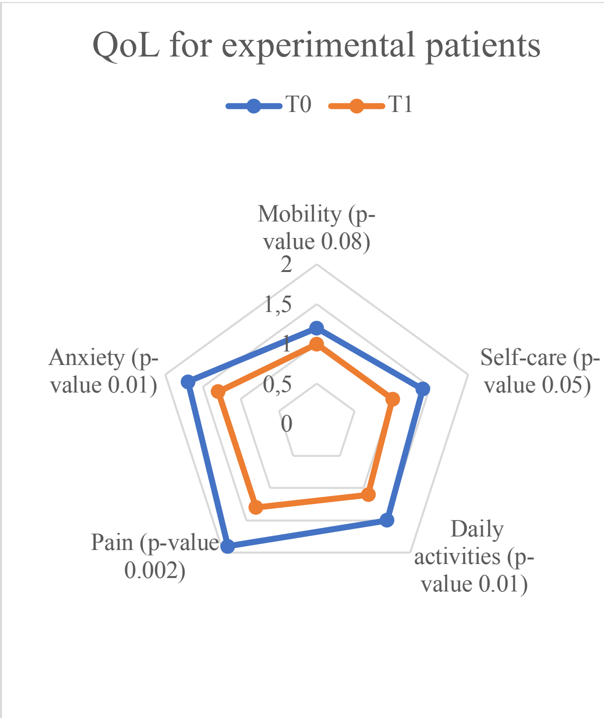


Figure 3.4. Minnesota Questionnaire Score before and after the intervention

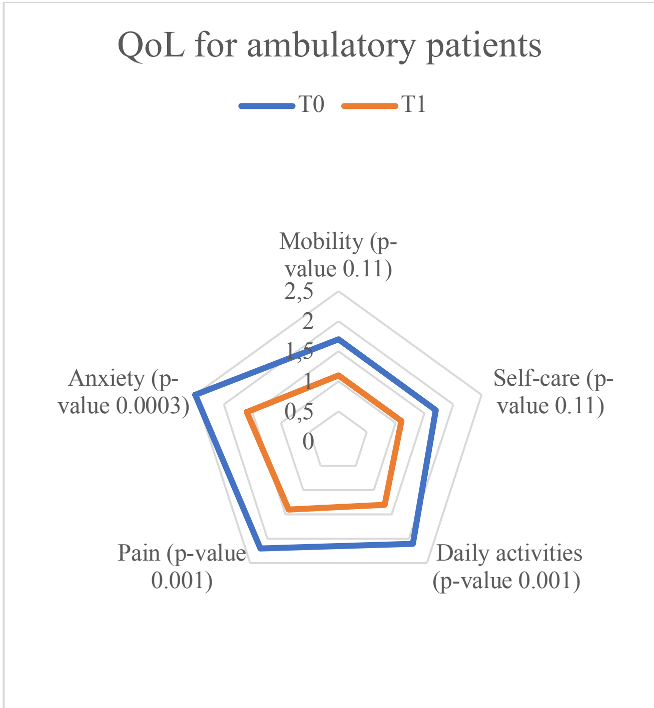
Figure 3.5. a),b),c) show the average values of the parameters evaluated by EuroQol-5D for each subgroup of patients separately. Thus, it can be seen that in the experimental subgroup [Fig.3.5.a)] the patients' quality of life was strongly influenced by pain and anxiety, a situation with an important impact on daily and self-care activities. After the intervention, these parameters improved from a mean initial value of about 4 to a mean value between 2-3. In the ambulatory subgroup, the improvement in quality of life was superior to that in the experimental subgroup, with initial mean values of 3-4 and post-intervention values of 2-3. In

the control subgroup, parameters evaluated in the five dimensions had a score between 3-4, values with a stationary character and at the evaluation from the T1 moment (Fig.3.5.).

a) Experimental subgroup



b) Ambulatory subgroup



c) Control subgroup

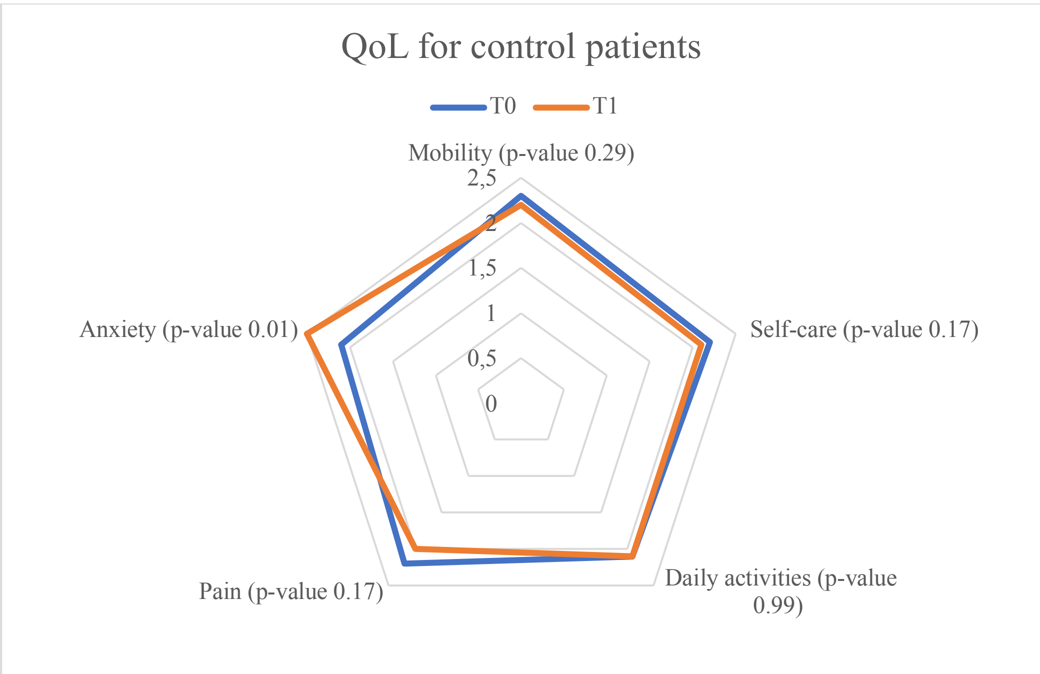


Figure 3.5. Quality of life Questionnaire Score (EuroQol-5D) before and after the intervention

3.4.Discussions

Cardiac recovery programs are a central element of secondary prevention in heart failure patients, due to the multiple benefits they present by reducing associated morbidity, mortality, hospitalization rates and by increasing exercise tolerance and social reintegration. Despite the multiple advantages, there is a persistent gap in the non-pharmacological treatment of heart failure patients caused by the absence of continuity of care after discharge [15].

The research study conducted had as a major obective the evaluation of the effectiveness and use of a virtual assistant (vCare) in the remote cardiac rehabilitation of heart failure patients. Regarding exercise capacity, I can state that in the experimental study subgroup the virtual assistant is at least as effective as a classic cardiac rehabilitation program. The negative results obtained through the comparative analysis of the experimental and control subgroups proved us that telerehabilitation is an extremely effective alternative for patients who cannot access cardiac rehabilitation programs in person. The results obtained are consistent with those in the specialized literature where a considerable improvement in exercise tolerance, maximal oxygen consumption and quality of life was observed through cardiac rehabilitation at home in heart failure patients. In addition, the positive impact of telemonitoring on the physical performance of patients is emphasized. The perception of medical monitoring leads to increased patient adherence to the non-pharmacological recommendations of the medical team [16-17].

Patient perception is an essential element in the medical technology development, due to the fact that designated products' large-scale implementation success is closely related to the impression they give to the user. A very important element that was discovered during the study is represented by patients' motivation and interest to participate, once they met with the opportunity to perform cardiac rehabilitation. I believe that behind this positive attitude is the low availability of such programs in Romania. In a recent study, Nabutovsky I. and collaborators evaluated trough an observational study, the perception, attitude and behaviour of Israeli patients towards telerehabilitation. The study ended with positive results, with 80% of the evaluated patients being very interested in accessing such services. It should be noted that the reslts obtained were not influenced by demographic, social factors or level of technological knowledge [18-19].

In terms of cardiovascular risk factor reduction, vCare virtual assistant has shown effectiveness in reducing high cholesterol levels and nicotine addiction. In this regard, I consider responsible the medical education component integrated in the telerehabilitation program and the constant interrelation of the assistant with the patient. Robotic-assisted medical education is a secondary prevention alternative long discussed in the medical field as a long-term follow-up solution for post-discharge heart failure patients, especially the elder ones [20-21].

The positive impact of remote and ambulatory cardiac recovery programs on anxiety and depression was demonstrated in the experimental and outpatient subgroups, where an improvement in these parameters was observed, compared to the control subgroup that showed a stationary character before and after the intervention. The literature supports this result with multiple evidence of improvements in anxiety and depression levels among heart failure patients undergoing telerehabilitation, along with an overall increase in their quality of life [22].

In addition, EQ-VAS data collected at T0 and T1 suggest a significant improvement in the quality of life of patients who underwent cardiac rehabilitation via vCare virtual assistant. Following the same direction, literature data also suggest equivalence or a slight positive difference on the quality of life of patients enrolled in ambulatory cardiac rehabilitation and telerehabilitation programs, in favor of the latter [23-24].

In a meta-analysis of heart failure patients enrolled in telerehabilitation programs, Cordeiro et al. pointed out that remote cadiac rehabilitation improves social skills, exercise tolerance, sexual activity and heart failure symptoms, being at least as effective as in-person cardiac recovery [25].

The increased desire of the cardiovascular patient to use technology as a way of heart failure management creates a favorable framework for the telerehabilitation development, with future benefits both medical and economical. Considering the unfavorable epidemiological context of cardiovascular diseases, it is necessary to find effective and cheap ways of secondary prevention of heart failure, to avoid overloading the emergency medical system.

Through the results obtained in the current research study, together with those provided by the specialized literature, I believe that the vCare virtual assistant is a viable alternative for heart failure patients to perform remote cardiac rehabilitation, with benefits equivalent to those of cardiac recovery in person, but from the comfort of their own home.

3.5.Conclusions

In conclusion, through the current research study I was able to successfully implement a virtual assistant as a method of performing remote cardiac rehabilitation for heart failure patients and evaluate their perception of use.

I have also evaluated the virtual assistant's impact on cardiovascular risk factor reduction, which was a positive one, because during the system's period of use the enrolled patients showed considerable improvements. The favorable outcome of the evaluation system use and patient perception will prove extremely useful in the near future to system adaptation as precisely as possible to the current need of heart failure patients.

In the long term, the implementation of remote cardiac rehabilitation programs means increasing the efficiency of secondary prevention of heart failure patients due to the flexible participation schedule, elimination of need to travel and enrollment of a much larger number of participants by eliminating geographical barriers.Also, through the intelligent devices associated with the system, a much more effective monitoring of vital parameters would be ensured with the early detection of signs of cardiac decompensation. From a social point of view, heart failure patients who do not have a supportive family framework would benefit from an increased quality of medical care and could be referred to medical services early when they are at risk of decompensation, thus avoiding emergency hospitalizations and certain complications associated with the disease.

The disadvantages of the virtual assistant are primarily represented by the impossibility of enrolling patients at high cardiovascular risk and those with a low educational level. Also, currently there is no legislative framework for the implementation of telerehabilitation services so that they can be compensated by the medical health system, a situation which delays the use of this type of cardiac recovery in heart failure patients.

In perspective, the obtained results may prove useful or future research exploring the effectiveness of the vCare system on larger groups of patients. Also, the current findings can be decisive factors in the development of new legislation to incorporate this system in the non-pharmacological treatment of cardiovascular patients. Furthermure, the vCare system could be considerably improved by making a mobile application, a situation that would facilitate its use.

Cardiac rehabilitation by means of a virtual assistant presents almost equivalent results to those of classical rehabilitation and should be considered as a key element of secondary prevention of patients with heart failure.

4. Personal contributions

Heart failure is a chronic disease with a slow progression over time, but with a very significant impact on the quality of life of the individual and on the society in which he lives, from a medical, social and economic point of view.

In the general part of the current doctoral thesis I highlighted the incidence and increasing prevalence of this pathology, as well as the etiology, associated complications, non-pharmacological and pharmacological treatment. I believe that in many cases of heart failure, lifestyle and external factors play a crucial role in the etiology of the disease. I also believe that these things are difficult to control in an effective way on a large scale, so as to lead in the coming years to an important decrease in the diagnosis of heart failure. Given that we are at a crucial moment, it is imperative that we turn our attention to primary and secondary prevention of heart failure in a way that is both effective and easy to implement on a large scale.

In order to be effective, the methods of primary and secondary prevention of heart failure must be characterized by a minimum human and economic resource, with the possibility of enrolling as many patients as possible and without time and space limitation. Despite the fact that hospitals are overcrowded with heart failure patients, we must not forget about the areas with limited access to adequate medical services, a situation which underestimates the real number of patients in need of adequate therapy.

Technology plays an important role in our daily life and every person regardless of educational or financial status uses remote communication. From this point of view, age no longer represents such a big impediment in the implementation of digital methods of medical treatment.

In the two research studies presented, I aimed to improve the methods of secondary prevention of heart failure by means of artificial intelligence algorithms. Thus, I initially hypothesized the use of voice as a predictor of heart failure exacerbations, as it is a cheap and easy-to-collect parameter. The disadvantage is that it targets patients already diagnosed with heart failure, excluding those who have symptoms but do not yet have a diagnosis because they have not had access to medical services. It is possible that in the future, through the development of technology, this solution can be extended to patients without a medical history, by raising diagnostic suspicion and directing them to a specialist evaluation.

In the second case study presented, considering the poor enrollment of Romanian heart failure patients in cardiac rehabilitation programs, I investigated the possibility of using a virtual assistant as a method to carry out a complete cardiac rehabilitation program, but from the patients' home. Despite the various technical difficulties encountered during the study, I believe that it is an extremely effective way to ensure adequate secondary prevention to as many patients as possible, by using a fairly small human and economic resource, compared to the costs of a classic cardiac rehabilitation program. The preliminary results obtained along with those in the specialized literature place telerehabilitation as at least as effective as in-person cardiac rehabilitation. As I mentioned before, the short-term disadvantage is primarily the lack of adequate legislation for the implementation of this type of service. On the other hand, the COVID-19 pandemic accelerated the development of telemedicine, with the inclusion of certain teleconsultation services in public medical systems, a situation that creates a favorable precedent for telerehabilitation services as well.

The future secondary prevention of heart failure, responsible for the important decrease in complications and associated mortality will certainly include artificial intelligence. Considering the development of various tools for prediction and control of decompensation factors, I consider it appropriate to evaluate the efficiency of each one separately and merge them into a device capable of predicting and monitoring heart failure. By tracking multiple parameters, an increase in instrument sensitivity and specificity and a reduction in associated errors could be achieved.

The perception of cardiovascular patients is favorable to the implementation of digital medical techniques, being eager to use such services. Also, the possibility of individualizing the medical services offered leads to the transition from diagnostic medicine to patient medicine. Each individual patient is unique, despite the common diagnosis they carry, with different needs and outcomes.

Artificial intelligence algorithms are a hot topic in medical research, with impressive results from day to day. Through the unlimited possibility of information they can absorb and process, they are the promise of increased life expectancy for patients with heart failure.

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2. Ștefan-Sebastian Busnatu, **Maria-Alexandra Pană*,** Andreea Elena Lăcraru, Cosmina-Elena Jercălău, Nicolae Păun, Massimo Caprino, Kai Gand, Hannes Schlieter, Sofoklis Kyriazakos, Cătălina Liliana Andrei, Crina-Julieta Sinescu, Patient Perception When Transitioning from Classic to Remote Assisted Cardiac Rehabilitation, *Diagnostics,* 2022, 12, 926. https://doi.org./10.3390/diagnostics12040926;https://www.mdpi.com/1578230; Factor Impact 3.992, (Capitol 4. Asistentul virtual vCare- metodă de prevenție secundară a insuficienței cardiace);
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