Analyzing the Health Status of Heart Failure Patients based on Telemonitoring Data using Machine Learning

Master's Thesis in Medical Engineering

submitted
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Übersicht

Herzinsuffizienz (HF) ist ein komplexes Syndrom, das durch eine schnelle oder schleichende Verschlechterung zu einer kardialen Dekompensation führen kann. Telemonitoring unterstützt Patienten durch sensorbasierte Technologien und durch telemedizinische Mitbetreuung. Ein vielversprechender Ansatz ist es, durch die täglich Aufzeichnung und Bewertung von Telemonitoringdaten eine kardiale Dekompensation frühzeitig zu detektieren.

In dieser Arbeit wurde die Analyse des fortschreitenden Gesundheitszustandes von HF-Patienten für eine automatische Vorhersage untersucht. Die subjektiven Symptomwahrnehmungen von 48 HF-Patienten wurde erfragt. Interviews mit fünf Experten verifizierten und erweiterten leitliniendefinierte Parameter durch evidenz- und erfahrungsbasiertes Wissen. Der Telemonitoringdatensatz der ProHerz App wurde mit statistischen Methoden und maschinellen Lernverfahren auf Dekompensationsmuster analysiert. Der verwendete Datensatz umfasst tägliche Vitalparametermessungen und Gesundheitszustandsdaten von 64 HF-Patienten.

Relevante Symptome und Zeichen, die eine kardiale Dekompensation erkennbar machen, wurden durch die Symptomabfrage und die Experteninterviews identifiziert. Die Patientenbefragung zeigte, dass das Symptomvorkommen chronische und akute HF unterscheidet. Die Experten betonten die Wichtigkeit, den Verlauf der HF durch regelmäßig aufgezeichnete Werte zu erfassen. Nur durch eine Vielzahl von Parametern und Symptomen kann der Gesundheitszustand zuverlässig eingeschätzt werden. Erst durch qualitative und quantitative Werte kann die Komplexität der HF erfasst werden. Die Experten waren sich einig, dass Telemonitoring die Versorgungsqualität von HF-Patienten verbessert. Bei der Datenanalyse wurden schwache Korrelationen zwischen Vitaldaten und Daten zum Gesundheitszustand erkannt. Eine Verbesserung des Gesundheitszustandes konnte anhand der Vitalparameter über den Zeitraum des Telemonitorings gezeigt werden. Relevante Parameter und deren Trends waren verringerter Blutdruck und Körpergewicht und gesteigerte Blutsauerstoffsättigung.

In der Arbeit wurde gezeigt, dass die telemedizinische Erfassung von Vitaldaten und die Aufzeichnung von Symptomen in einem Symptomtagebuch die Einschätzung des Gesundheitszustandes verbessern. Anhand der im Datensatz vorhandenen diskreten Vitaldaten konnte der Gesundheitszustand nicht zuverlässig vohergesagt werden. Um in Zukunft ein Frühwarnsystem etablieren zu können, muss der Datensatz qualitativ hochwertige Informationen zu HF-Ereignissen enthalten. Personalisierte und präzise automatische Vorhersagen können durch Zeitreihenanalysen ermöglicht werden.

Abstract

Heart failure (HF) is a complex syndrome that can lead to cardiac decompensation through rapid or gradual deterioration. Telemonitoring assists patients through sensor-based technologies and telemedical care. A promising approach is to detect cardiac decompensation early through daily recording and assessment of telemonitoring data.

In this work, the analysis of the progressive health status of HF patients was investigated for automatic prediction. The subjective symptom perceptions of 48 HF patients were collected. Interviews with five cardiology experts verified and expanded guideline-defined parameters with evidence- and experience-based knowledge. The telemonitoring dataset of the ProHerz app was analyzed for decompensation patterns using statistical methods and machine learning. The dataset used included daily vital sign measurements, questionnaire results, and health status data from 64 HF patients.

Relevant symptoms and signs indicative of cardiac decompensation were identified through the symptom questionnaire and expert interviews. The patient survey showed that symptom occurrence distinguished chronic and acute HF. The experts emphasized the importance of monitoring the progression of HF through regularly recorded values. Only through a multitude of parameters and symptoms can the state of health be reliably assessed. Only through qualitative and quantitative values can the complexity of the HF be captured. The experts agreed that telemonitoring improves the quality of care for HF patients. Data analysis identified weak correlations between vital signs and health status data. Improvement in health status was shown by vital signs over the period of telemonitoring. Relevant parameters and their trends were decreased blood pressure and body weight and increased blood oxygen saturation.

The work demonstrated that telemedical monitoring of vital signs and recording of symptoms in a symptom diary improved the assessment of health status. Based on the discrete vital signs available in the dataset, health status could not be reliably predicted. To establish an early warning system in the future, the dataset must contain high-quality information on HF events. Personalized and accurate automatic predictions can be enabled by time series analysis.

Contents

Chapter 1

Introduction

According to the Federal Statistical Office, cardiovascular diseases were the most common cause of death in Germany in 2020 [Bun20]. Among cardiovascular disease deaths, heart failure (HF) (ICD-10: I50) was in third place with a proportion of 10.3 % (34855 died). Looking at the billing data across health insurance companies, there are an estimated 2.5 million heart failure patients in Germany [Hol18]. With 455680 inpatient hospital treatments, heart failure is, thus, the most frequent single diagnosis of patients treated as full inpatients in Germany [Bun16]. The frequency of illness and the total number of hospitalizations of patients with heart failure have been rising continuously for years. An data analysis of 7 million statutorily insured patients shows that around 16 % of heart failure patients died within two years [BÄK19]. In advanced heart failure, mortality is up to 50 % within one year [Loe08]. Mortality increases with the severity and age of the disease [Stö21]. The annual prevalence for heart failure is 6.9 % for those aged 65 to 69 years. It increased to a value of 24.3 % for those aged 80 to 84 years and to 47.2 % for those over 95 years [BÄK19][Kad14].

The annual therapy costs for chronic heart failure amounted to 7.4 billion euros in 2020 [Bun22]. In 2021, heart failure patients were hospitalized approximately two times per year and spent on average of 9.2 days in hospital [Stö21]. 24 % of patients need to be hospitalized again in the first 30 days after discharge from hospital [Kru09].

Data show that heart failure is an enormous burden for both patients and the health care system. Therefore, it is imperative to detect deterioration in the health status of heart failure patients at an early stage to prevent cardiac decompensation and associated hospitalization.

According to guidelines, the current care of heart failure patients recommends regular monitoring to detect changes in the clinical and psychosocial situation and to adjust treatment if necessary [BÄK19]. However, literature shows that patients often have difficulties in constantly monitoring their health status, recognizing symptoms early and knowing when to contact the doctor [Set14].

Telemonitoring offers the opportunity to support these patients with easy-to-use mobile and sensor-based technology for the home environment. In addition, telemonitoring has been shown to significantly reduce rehospitalization rates and mortality in patients with chronic heart failure, thereby reducing health care costs [Ebn09].

Telemonitoring apps, such as the ProHerz app or the Tidda Herz app, provide digital and individualized care for heart failure patients. So far, recommendations for action and therapy in these applications have been based on defined guidelines and the experience of physicians and heart failure nurses [BÄK19][McD21]. However, the literature shows that machine learning (ML) can predict heart failure events with reasonable accuracy and in some cases well before clinical diagnosis [Sha20][Wu10]. The use of advanced machine learning techniques of digital health applications aims to increase and accelerate the objectivity of physicians' health assessments.

The aim of this work is, therefore, to analyze the progressive health status of heart failure patients in order to detect cardiac decompensation using machine learning techniques. The work is divided into three parts and includes the objective and subjective assessment of the disease. Based on the literature, relevant parameters are determined from the literature that assess the state of health and make impending decompensation recognizable at an early stage. In the first part, the subjective perception of symptoms will be analyzed and included in the evaluation using patient surveys. Furthermore, expert interviews will be conducted in the second part to verify and extend the guideline-defined parameters with evidence-based knowledge. Overall, the goal is to identify the most important symptoms and parameters to monitor. In a final step, the knowledge gained will be used to analyze a data set containing telemonitoring data of heart failure patients for decompensation patterns using machine learning techniques. The aim is to find out whether correlations between the measured vital parameters and the health status questionnaire data exist and whether health status classification can be implemented on the telemonitoring data. The data used for the analysis was acquired in a previous study by ProCarement GmbH, which includes daily measurements of vital signs and questionnaire data from 64 patients.

The thesis is structured as follows: Chapter 2 gives the medical background to heart failure and clarifies other important medical terms. Chapter 3 describes the background of telemonitoring in heart failure and presents the digital health application ProHerz by ProCarement GmbH. Chapter 4 presents related work on the research areas. Chapter 5 presents the analysis of symptoms and parameters of heart failure and is divided into the collection, analysis and discussion of the patient survey and the expert interviews. The analysis of the telemonitoring data set is presented in Chapter 6, describing the data set and the preparation for further analysis. The analysis consists of the descriptive data analysis and the explorative data analysis with subsequent discussion. The overall results are discussed in Chapter 7. Finally, a conclusion is drawn in Chapter 8 and an outlook on further research is given.

Chapter 2

Medical Background

2.1 Definition of Heart Failure

Heart failure is a complex clinical syndrome in which the heart is no longer able to supply the body and its organs with an adequate amount of blood due to pumping failure or impaired ventricular filling [BÄK19]. The undersupply of the organism with oxygen and nutrients leads to reduced physical capacity, fluid retention in the body and a restriction of the organ function and skeletal muscles [Ste14][Hei22][BÄK19]. The organism tries to counterbalance the weak cardiac output by means of compensatory mechanisms. The release of hormones causes an increase in blood pressure (BP), a constriction of blood vessels and an increase in the total blood volume. If the weak performance of the heart is compensated for over a longer period of time, heart muscles structure changes. In order to achieve better pumping power and be able to eject more blood, the muscle fibres of the heart stretch and thicken. The body tolerates these changes over a long period of time. In this phase, symptoms are only perceived as a reduction in performance capacity during increased stress. If the body is no longer able to compensate for the reduced cardiac output through the body's own counter-mechanisms, this is called decompensation of the heart [Led10][Her20].

According to the European Society of Cardiology (ESC), heart failure is resulting in increased intercardiac pressure and/or inadequate cardiac output at rest and/or during exercise due to a structural and/or functional disorder of the heart [McD21]. Heart failure is further defined by the presence of clinical symptoms and signs, such as dyspnea, ankle swelling, fatigue, increased jugular venous pressure, pulmonary crackles and peripheral oedema [McD21].

Multiple comorbidities often accompany chronic heart failure, and their symptoms are similar. This makes diagnostic differentiation difficult [Kah11].

2.2 Terminology of Heart Failure

Heart failure can be classified and terminologically named according to different criteria. Decisive for the terminology of heart failure can be the temporal course, the cardiac output, the location of the particularly affected chamber, the pathophysiology with the ejection capacity of the heart or the severity.

Classification According to the Time Course

Looking at the course over time, a distinction can be made between chronic and acute heart failure. Chronic heart failure develops over a longer period of time, which can last from a few months to years. Acute heart failure, occurs within hours or a few days. It may be triggered by a sudden event, such as acute coronary syndrome, hypertensive crisis, tachycardic or bradycardic arrhythmias or myocarditis, or it may develop from chronic heart failure. In acute heart failure, cardiogenic shock occurs. This is life-threatening and requires immediate medical treatment [Her20][McD21].

In this thesis, the term “acute decompensation” is always used in the context of chronic heart failure. Acute decompensation refers to a worsening of the health condition in diagnosed chronic heart failure. Acute decompensation requires therapy adjustment or hospitalization and leads to a poorer prognosis overall.

Classification According to Cardiac Output

Cardiac output is described as the product of stroke volume and heart rate. It is influenced by venous return, peripheral vascular tone and neuronal factors. In heart failure, a distinction is made between a “low-output failure” and a “high-output failure”. Heart failure, in which the cardiac output is reduced and thus the peripheral oxygen supply to the organs is decreased, is called “low output failure”. One speaks of “high-output failure” when the cardiac output is normal or increased, but the heart is unable to cover the oxygen demand of the organs [Her20][Led10].

Classification According to the Location of the Particularly Affected Ventricle

Depending on the area of the heart in which the heart failure appears, a topographical distinction is made between left heart failure, right heart failure or global heart failure.

Left-sided heart failure can appear as “forward failure” due to a reduced pumping capacity of the left half of the heart with a reduced supply to the peripheral organs. However, it can also occur as “backward failure” due to a filling disorder of the heart with a backflow of blood into the blood vessels of the lungs. The pressure that builds up there presses the liquid blood components into the lung tissue. Water retention develops. These are the reason for shortness of breath, reduced performance, pulmonary rales, cough and cyanosis. Chronic left heart failure often develops into right heart failure.

In right heart failure, the function of the right ventricle, which pumps deoxygenated blood to the lungs, is weakened. More oxygen-poor blood flows in from the systemic circulation than the right ventricle can transport towards the lungs. The blood backs up into the body’s veins. The venous pressure increases so much that the liquid components of the blood are pushed into the surrounding tissue, causing water retention. Leg oedema, ascites, rapid weight gain, congestion of the neck veins, loss of appetite, indigestion and pleural effusions are typical symptoms. If the pumping capacity of both parts of the heart is reduced, this is called global heart failure or biventricular heart failure. Symptoms of left and right heart failure can be seen [Ste14][Led10].

Classification According to Pathophysiology with the Ejection Fraction of the Heart

Depending on the functional disorder present in left heart failure, it is divided into heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF) and heart failure with midrange ejection fraction (HFmrEF) [McD21]. The ejection fraction is defined as the ratio of stroke volume to end-diastolic ventricular volume. In a healthy heart, the ejection fraction is greater than 60 %. The ejection fraction in HFrEF is less than 40 %, whereas in HFpEF it is at least 50 %. A value between 40 and 49 % is referred to as heart failure with midrange ejection fraction (HFmEF).

HFrEF (systolic heart failure), so-called “forward failure”, is characterised by a pumping dysfunction and reduced contractility of the left ventricle of the heart, so that the ventricle is no longer emptied sufficiently [BÄK19][Ste14].

HFpEF (diastolic heart failure), the so-called “backward failure”, can be described by a filling disorder of the left ventricle with normal ejection fraction. Myocardial stiffness increases with wall thickness. Due to the reduced relaxation of the ventricle, the chamber can no longer fill completely with blood [Her20][Hop11][Led10]. Therapeutically, the subdivision of heart failure according to functional disturbance, including the ejection fraction (EF) of the heart chambers, is most important. Moreover, most studies on heart failure use this classification.

2.3 Classification by Severity of Chronic Heart Failure

The New York Heart Association (NYHA) has established a classification system for determining the severity of chronic heart failure. This system has been used since 1928 and is well established. The classification into the four different NYHA stages (see Table 2.1) is symptom-oriented and refers exclusively to the patient’s performance. It gives no indication of the causes of the cardiac disorder. The NYHA stage becomes higher the more a patient’s exercise capacity decreases. Depending on the progress of the disease or the success of the therapy, a relatively rapid change between the stages is possible. In this staging, there is a high correlation with mortality [New94][BÄK19].

Table 2.1: New York Heart Association Functional Classification [New94].

Class	**Patient Symptoms**
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

The ABCD grouping, of the American Heart Associaton (AHA) and the American College of Cardiology (ACC) involves the development and progression of heart failure (see Table 2.2) [Hei22].

Table 2.2: ABCD classification system for heart failure [Hei22].

Class	Patient Symptoms
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

2.4 Disease Progression of Chronic Heart Failure

In the course of chronic heart failure with reduced left ventricular ejection fraction, there is a progressive deterioration in health-related quality of life, the functional quality of the heart and other organs, and thus a shortening of life expectancy, see Figure 2.1. A drop in the progression curve indicates acute decompensation of the heart and leads to inpatient treatment. Every hospital admission due to acute decompensation leads to a worse prognosis for the patient. With inpatient treatment, there is initially an improvement in cardiac function. However, by the time the patient is discharged from hospital, cardiac function has stabilized at a lower level. The time until a renewed, unplanned readmission to hospital is shortened with each visit. The curve of the disease course of chronic heart failure represents the quality of life or the functional capacity in the course. Each patient can be assigned to one of the four disease stages, early heart failure, stable chronic heart failure, unstable/advanced heart failure, end-stage heart failure [Böh14][McM12].

2.5 Clinical Profiles of Acute Decompensation

The clinical profiles of acute decompensation are guided by the presence or absence of signs of hypoperfusion (cold vs. warm) and signs of congestion (wet vs. dry). The combination of both signs leads to a classification of patients into four groups: The "warm-wet" type denotes well-perfused and congested patients. This is most common in acute decompensation. Hypoperfused and congested patients are labelled "cold-wet". "Cold-dry" is found

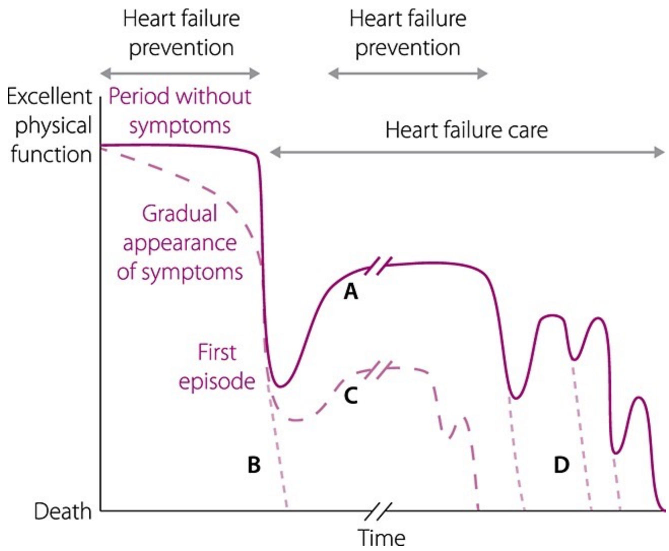


Figure 2.1: Typical progression of acute heart failure, showing a range of clinical courses [Cow14].
A: good recovery after first episode followed by stable period of variable length
B: first episode not survived
C: poor recovery after first episode followed by deterioration
D: ongoing deterioration with intermittent crises and unpredictable death point

in hypoperfused patients without congestion. The "warm-dry" type refers to compensated, well-perfused patients without signs of congestion. These profiles can be seen in Figure 2.2. Patterns of decompensation differed according to the clinical profile. The classification is described in the guidelines and determines the medication therapy [Pon16].

2.6 Causes and Risk Factors of Heart Failure

A wide range of causes are responsible for the development of chronic heart failure. Most frequently, with 70-90 % of cases, arterial hypertension and coronary heart disease or a combination thereof are the triggering factors [BÄK19]. About two-thirds of cases are due to coronary heart disease. The narrowing of the coronary arteries means that the heart muscle is no longer supplied with sufficient oxygen-rich blood. This reduces the pumping capacity of the heart. Persistent hypertension leads to a filling disorder of the heart as the heart muscle thickens and loses elasticity. In a pre-damaged heart, hypertension can trigger acute heart

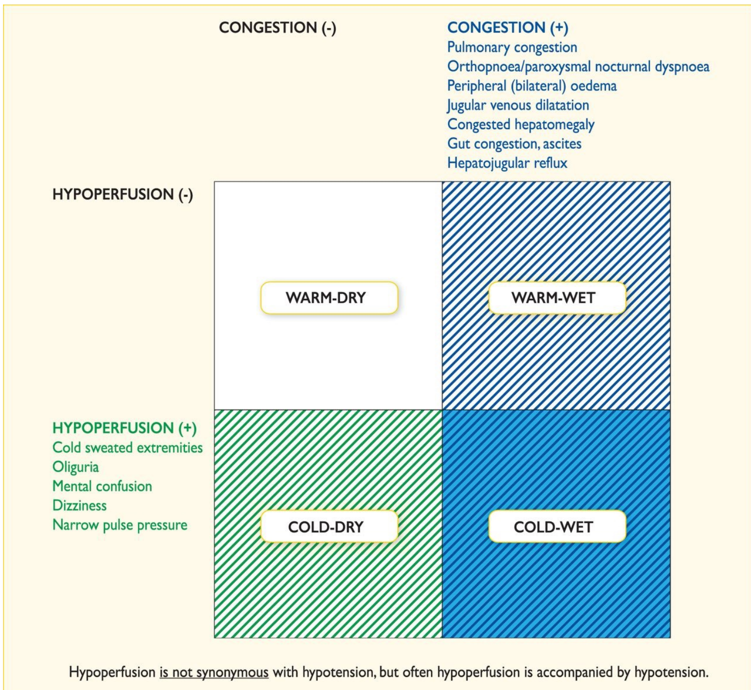


Figure 2.2: Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion [Pon16].

failure or suddenly exacerbate an existing heart failure [Pon16]. Hoppe also cites the level of heart rate as a determining factor of heart failure, as its incidence increases in relation to heart rate [Hop11]. Another trigger for heart failure can be a heart attack. Due to the lack of oxygen supply to part of the heart muscle, this part dies and is replaced by scar tissue. The lack of elasticity of this tissue leads to heart failure. In addition, valvular or pericardial diseases can be responsible for the occurrence of heart failure, as they impair the pumping capacity of the heart. A triggering factor for heart failure can also be inflammation of the heart muscle (myocarditis) [BÄK19]. Studies show that the risk of developing heart failure is also increased by an elevated blood sugar level, as occurs in the metabolic disease diabetes mellitus. Diabetes mellitus permanently damages the function of the heart [Jam18]. Heart failure can also be attributed to other diseases, such as non-ischaemic cardiomyopathy or arrhythmias. In about 2-3 % of cases, chronic heart failure is due to alcohol or drug abuse. However, heart failure can also be caused by drugs that are mainly used in cancer therapy. Other risk factors for the development of heart failure can be renal insufficiency, obesity, elevated cholesterol levels, lack of exercise or also smoking [BÄK19].

Chapter 3

Fundamentals

3.1 Telemonitoring for Heart Failure

Heart failure, as described in the Medical Background, is a complex disease pattern that requires close patient care. Inadequate care leads to increased mortality and hospital admissions [Köh19]. With a remote monitoring system, signs and symptoms are regularly documented and evaluated. Telemonitoring of heart failure patients can help to detect cardiac decompensation at an early stage and to initiate appropriate treatment and care in a timely manner. This improves the quality of care [Pre20][Köh19]. In 2016, the European Society of Cardiology guidelines for the diagnosis and management of chronic heart failure patients recommended remote patient monitoring for the first time [Pon16]. In the following, European studies on telemonitoring of heart failure patients are presented and the effects on the German health care system are described.

TIM-HF2 Study to Demonstrate the Effectiveness of Telemonitoring in Heart Failure

In the Telemedical Interventional Management in Heart Failure II (TIM-HF2) study, which was conducted by the Center for Cardiovascular Telemedicine of the Charité in Berlin from 2013 to 2018 with 1538 heart failure patients with reduced left ventricular ejection fraction, multiple positive effects of telemonitoring were shown [Koe18]. The care of the patients with NYHA class II or III consisted of a combination of outpatient care by specialists or general practitioners and co-care by one of 200 telemedicine centers. The project was carried out by the head of the study, Prof. Dr. Friedrich Köhler, in cooperation with various partners and two large health insurance companies and was funded by the Federal Ministry of Education and Research. The telemedically supervised patients received a scale, a blood pressure monitor, an electrocardiogram (ECG) device with a finger clip for recording blood oxygen saturation and a tablet. On the tablet, the study participants entered data themselves to assess their state of health. The tablet was used to transmit vital signs and data from short clinical questionnaires to the telemedical service center on a daily basis. The data were checked and evaluated almost 24 hours a day, 7 days a week by doctors and by nurses trained in internal medicine and cardiology. If the limit was exceeded, an intervention was initiated and therapy could be adjusted at an early stage. In addition, the patients were trained at home. Compared to the conventional treatment of heart failure patients, daily monitoring of patients with telemedical, non-invasive home monitoring devices leads to a reduction in the length of stay in hospital (17.8 days compared to 24.2 days), to an improved quality of life and to an increased life expectancy. Out of 100 patients, 8 patients died in one year among the patients with telemedical co-management, while about 11 patients died in the control group. Thus, the overall mortality was 30 % lower. With regard to unplanned hospital admissions, patients who received telemedical care were also treated in hospital for a significantly shorter time (3.8 days compared to 5.6 days per year). In the intervention group, a cost saving of 1758 euros per patient year was achieved. It was also shown that structural care deficits in rural areas are compensated for by telemedicine and that the overall quality of care is improved [Spe22].

Further Studies on Telemonitoring in Heart Failure

The European MEMS-HF study, confirming the results of the previous US CHAMPION study, also showed that the prognosis of NYHA class III heart failure patients could be significantly improved by implanting a CardioMEMS™HF pressure sensor in the pulmonary artery and connected telemedical care [Ang21]. The personalized, proactive care of patients has many advantages and leads overall to improved guideline- and needs-based care.

A rise in blood pressure, especially in the pulmonary artery, is an early sign of impending decompensation. If this increase in pressure is detected early, it can be counteracted with an adapted medication. The study showed that an increase in arterial pressure in the pulmonary artery occurs days to weeks before the onset of noticeable symptoms. The prospective study involved 234 heart failure patients regardless of left ventricular ejection fraction. The CardioMEMS™HF sensor is a battery-free device that is inserted into the pulmonary artery.

Heart rate, pulmonary artery (PA) pressure and mean systolic and diastolic PA pressures are recorded. Once a day, the implanted pressure sensor transmitted the 18-second pulmonary artery pressure history from the patients to an online tool. The data was viewed and assessed by physicians. Medications were adjusted with the aim of reducing the pressure load. In addition, patients were trained and guided by telephone. Clinical successes were that hospital admissions were reduced by over 60 % compared to the previous year and annual mortality was relatively low at less than 14 %. About 40 % of patients had their heart failure symptoms relieved. A highly significant decrease in N-terminal pro-B-type natriuretic peptide (NT-proBNP), which serves as a heart failure marker, was recorded. The subjectively perceived health status of the patients was better the greater the reduction in pressure in the pulmonary artery. An improved quality of life of the patients was objectively proven by means of the Kansas City Cardiomyopathy Questionnaire (KCCQ12). The lead investigator, Christiane Angermann, clarifies that the benefit of the CardioMEMS™HF system crucially depends on the downstream therapy adjustment. Not only the telemedical transmission of the values, but also the extent to which the care team uses the system to optimize treatment and the extent to which the trained patients use the health knowledge to implement treatment recommendations in a timely manner is crucial for success [Güd20][Ang21].

The two studies show that telemonitoring of heart failure patients offers great potential for improving the quality of care. However, telemonitoring can only support therapy. Specialized medical staff must continue to monitor and adjust therapy based on the transmitted values and data.

The randomised PASSPORT-HF study, led by Prof. Stefan Störk from Würzburg, is designed to compare implant-based follow-up with intensified standard care [Stö22]. To this end, the application of the CardioMEMS™HF system in the German health care system will be reviewed. The first results of the study are expected in 2024. Prof. Störk is coordinating the observation of 554 heart failure patients with NYHA class III who were hospitalized at least once for heart failure in the last year before the start of the study. If the study is successful, the services and remuneration for telemedical care will be transferred to standard care in Germany.

Telemonitoring as a Standard Service for Heart Failure

Based on the study results, the Federal Joint Committee decided in December 2020 to include telemonitoring in heart failure in the "Richtlinie Methoden vertragsärztliche Versorgung" as a recognized method for heart failure patients from NYHA class II. The decision came into force on 31.03.2021. From January 1, 2022, the services for telemonitoring in heart failure for primary care physicians as well as for the telemedicine center (TMC) were also integrated into the uniform assessment scale. Germany is the first European country in which telemonitoring is reimbursed as a standard service for heart failure [Spe22][Pro20].

Care Structure for Telemonitoring

The telemedical care of heart failure patients, also called "remote patient management", is to be designed as a holistic, outpatient care concept. The concept comprises three pillars: a guideline-based therapy by the general practitioner, cardiologist and/or the specialist in the TMC, training of the patients at home and telemonitoring [Pre20].

Telemedicine centers are currently being set up in many places in Germany. A TMC must be staffed with specialist doctors and nurses around the clock every day. All data, findings and important doctor's letters of the patients are stored in an electronic patient file. The transmitted vital data and values are evaluated on the basis of individual threshold values. All medical actors involved must be in close contact with each other. In the event of a deterioration in values, therapy is adjusted by the primary care physician, who is informed by the TMC . Only in cardiac emergencies do specialists in the telemedical center initiate escalation measures, such as hospitalization. The TMC's nurses and doctors, trained in internal medicine and cardiology, also take care of the patients' technical equipment, device function data and data management. The German Society of Cardiology demands that the structures and processes of a telemedicine center must be aligned with the legal and normative requirements and that these must be ensured by a quality management system [Hel22][Köh19].

Up to now, however, telemedical co-care of heart failure patients in telemedical centers is not yet guaranteed throughout Germany. The conditions are so demanding in terms of finances and personnel that it is difficult to transfer them to standard care. At present, about 500 patients can be cared for simultaneously in the existing telemedicine centers. However, since in Germany about 200000 patients could receive telemedical care due to the severity of the diagnosed heart failure, the need for telemedical centers is about 400. Currently, a

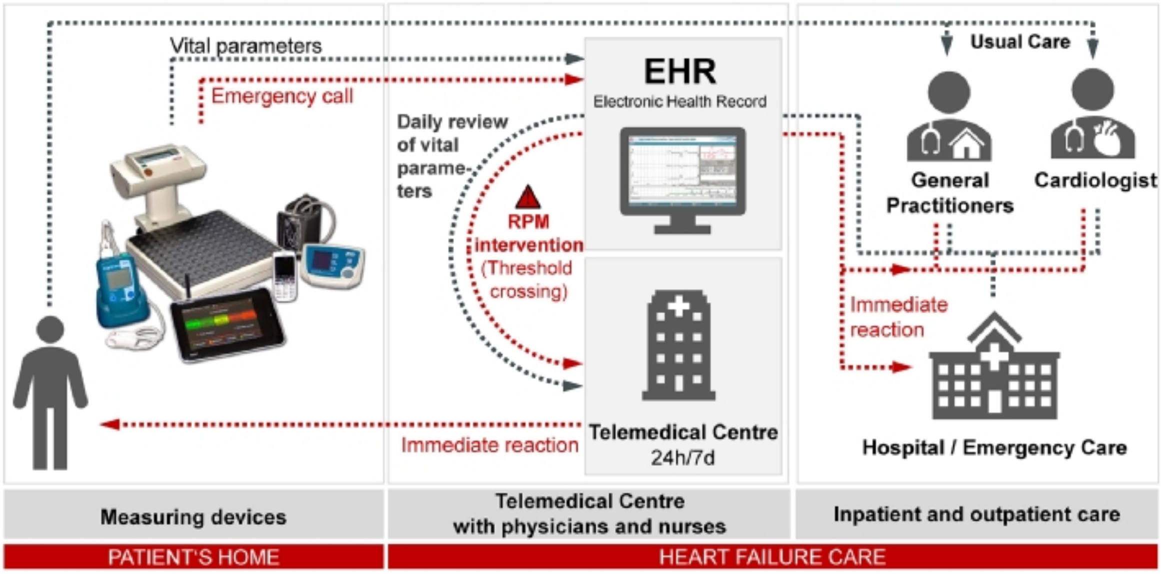


Figure 3.1: Telemedicine center concept for heart failure patients [Pre20].

research project (Telemed5000) is examining whether a reduction to a number of 30-40 is possible by using decision support systems with artificial intelligence. A system solution is to be used that utilizes the possibilities of artificial intelligence, such as deep learning or the Internet of Things, in order to make the management of large numbers of patients technically possible. Self-learning algorithms are to support medical staff in their decisions and thus reduce the workload. The care capacity per TMC is thus to be increased to up to 5000 patients. Telemed5000 builds on the five-year TIM-HF2 study [Köh][TEL].

3.2 ProCarement a Digital Health Start-Up

The start-up company ProCarement GmbH[1], founded in 2019 and based in Forchheim, aims to redesign care systems based on digital technology and thus improve the quality of care. Patient-centered applications are intended to make life with illnesses easier and simplify everyday treatment. Experts from various fields, such as medicine, informatics, software development, medical technology and health economics, are working together to develop and implement new, hybrid care pathways. In the following, the telemonitoring application ProHerz and its vital signs are presented.

[1] https://procarement.com/

3.2.1 ProHerz App a Telemonitoring System for Heart Failure

The ProHerz app is a software application by ProCarement GmbH that supports patients and medical stakeholders in improving the quality of care for heart failure. The app can be downloaded from the App Store[2] and the Google Play Store[3]. The digital health application, which is certified as a medical device of risk class 1 according to the Medical Device Directive, supports heart failure patients (ICD-10: I50) in the regular monitoring of their state of health and trains them in understanding and dealing with the disease by knowledge transfer. In the app, the values of the measurements of relevant vital parameters are continuously recorded, documented and archived. Blood pressure, heart rate, oxygen saturation of the blood, body weight and temperature are measured daily. The values are recorded and entered via Bluetooth-capable, certified measuring devices. Only the values of the analogue temperature measurement have to be entered manually into the app by the patient. The data is transmitted to the CareCenter operated by ProCarement GmbH. Each measured value is displayed in a detailed overview. On the one hand, the current values are briefly explained, on the other hand, the temporal course of the measured values is graphically displayed optionally over one week, three months or one year and compared with the normal values deposited by the national care guideline. Deviating values are visualized by a traffic light system that is easy for the patient to understand. If deviating patterns indicating a deterioration in health are detected, the patient is automatically informed and instructed to contact the doctor. In this way, the patient is involved in the medical decision-making process and therapy can be adjusted at an early stage. Monitoring is supervised by qualified medical professionals who are also in personal contact with the patient. All data and medical documents of a patient are stored in a personal medical record, a so-called document safe, and can be easily shared with other health care providers. Adherence is increased with a digital medication plan that reminds the patient to take their medication. Doctor appointments can be managed using the app's digital calendar. The app offers the patient the expansion of personal health literacy by imparting disease-specific knowledge. With this health coaching adapted to the patient, users additionally find pop-up notifications on diagnosis and therapy. Furthermore, the patient's state of health and psychological well-being are analyzed via regularly evaluated, validated questionnaires. The observation of these subjective, patient-related benchmarks and the

[2]https://apps.apple.com/de/app/proherz/id1540759669
[3]https://play.google.com/store/apps/details?id=procarement.proherzhl=degl=US

inclusion of concomitant diseases complement the system and complete the therapy support provided by the ProHerz app. The aim is to increase the patients' state of health, quality of life and life expectancy. In addition, the goal is to better coordinate the care of patients by simplifying the coordination of all medical actors. Avoidable hospital stays and multiple examinations are to be reduced, thereby lowering costs in the health care system [Gmbc].

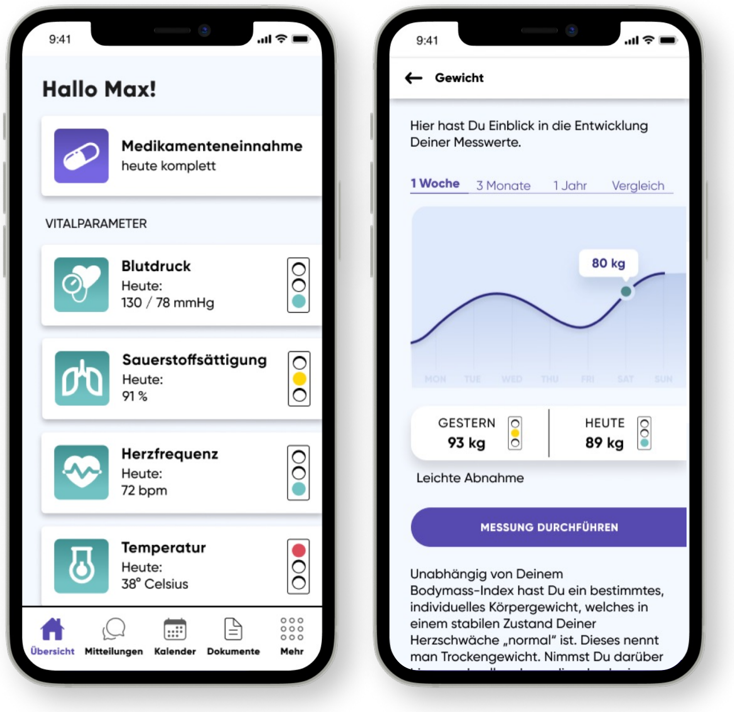


Figure 3.2: User view of the ProHerz app [Gmbc].

3.2.2 Vital Parameters of the ProHerz App

Five vital signs, heart rate, blood pressure, blood oxygen saturation, body weight and body temperature are recorded in the ProHerz app. According to experts, these are relevant vital signs that can be used to assess the health of heart failure patients. With wearable sensors, the vital signs can be easily recorded in a domestic setting by the patients themselves and transmitted to the ProHerz app. In the following, the five vital signs are presented and their significance in relation to the assessment of the health status of heart failure patients is described. The measured vital signs can indicate a worsening of the heart failure status via their deviations in the course. Rapid response and adjustment of therapeutic measures can counteract decompensation of the heart and, in the worst case, prevent hospitalization. As shown in the systematic review "Algorithms used in telemonitoring programs for patients with chronic heart failure" by Brons et al., no uniform thresholds for vital signs can be found in different systems [Bro18]. Threshold values differ from system to system. Similarly, the various heart failure management guidelines do not specify thresholds consistently or at all [McD21]. Threshold values are intended to guide decisions about treatment adjustment. In the following, the threshold values of the five vital signs used in the ProHerz app, which are transferred to a color coding, are shown. In the ProHerz app, recommendations for action are also given on the basis of these threshold values. All information on the threshold values of the vital parameters can be found in the Table 3.1 [Gmbc].

Table 3.1: Threshold values of vital signs for color code in the ProHerz app, adapted from ProCarement GmbH [Gmbc].

Color code	**Heart rate (bpm)**	**Systolic blood pressure (mmHg)**	**Diastolic blood pressure (mmHg)**	**Weight change (kg or %)**	**Oxygen saturation (%)**	**Body temperature (°C)**
Red	> 124	≥ 180	≥ 110	$>$ + 1.4 kg in 24 h $>$ + 2.0 kg in 72 h $>$ + 2.5 kg in 7 d	< 91 %	> 38.5
Yellow	101 - 124	140 -179	90 - 109	$>$ + 1 kg	91 - 94 %	37.5 - 38.4
Green	60 -100	110 - 139	70 - 89	- 0.1 kg bis - 4 kg relative to dry weight	95 - 100 %	35.5 - 37.4
Yellow	50 - 59	100 - 109	60 - 69	- 4 kg bis - 10 % relative to normal weight		34.5 - 35.4
Red	< 50	< 100	< 60	$\leq$ - 10 % of normal weight		< 34.5

Heart Rate / Pulse

The heart rate indicates the number of heart beats per minute (bpm). Pulse (lat. pulsus - the push) is described as the expansion of arterial vessels, which occurs due to the expulsion of blood from the heart [Zin12]. As a rule, heart rate and pulse agree or differ only slightly. In a measurement, the pulse measured at rest is considered the basic value. The resting pulse can vary greatly depending on age, gender, condition, and physiological and psychological factors. The pulse and, in particular, deviations from the norm can provide conclusions about a person's state of health and are thus an important component in the medical monitoring of a patient. In heart failure patients, both a heart rate that is persistently too high (> 100 bpm - tachycardia) and a heart rate that is persistently too low (< 60 bpm - bradycardia) can be symptomatic [Zin12][McD21]. If the course of heart rate values shows deviations from the patient's normal value, therapy adjustment with beta blockers or digitalis glycosides (antiarrhythmic drugs) must be made to counteract cardiac decompensation. The greater the deviation from normal values, the faster the adjustment of medication must be made with a higher dosage [BÄK19][Pon19].

Blood Pressure

Blood pressure is the force that blood exerts on the walls of the arteries. Blood pressure is directly dependent on vascular resistance and cardiac output. A distinction is made between systolic and diastolic pressure. Systolic blood pressure describes the maximum pressure value that occurs as the heart presses blood into the arterial vessels of the systemic circulation. Diastolic blood pressure indicates the minimum pressure value that exists during the filling phase of the heart with blood from the lungs. Values are expressed in units of millimeter of mercury (mmHg) and are usually measured on the upper arm [War07]. If blood pressure values deviate from average values, this represents a cardiovascular risk. When blood pressure is high, the heart has to work harder because it has to counteract increased resistance in the blood vessels. Adaptation of the heart muscle occurs in the form of hypertrophy. The enlargement of the heart muscle leads to an increased oxygen demand of the heart muscle tissue. It can no longer be ensured that the tissue is sufficiently supplied with oxygen. When blood pressure is too low, also called arterial hypotension, the body's organs and the brain are not supplied with enough oxygenated blood [Org21]. In heart failure patients, even small deviations in pressure can lead to a deterioration in health. Keeping an eye on the course of blood pressure levels over the long term and adjusting therapy accordingly is crucial in patient care [Oh20][Jos09].

Body Weight

In heart failure, short-term, large, and unexpected weight gain is an important predictor of worsening health. Tissue fluid retention is usually responsible [McD21]. Water retention indicates worsening heart failure and requires a therapeutic adjustment in diuretic dosage [Far16].

Decreased weight may also indicate worsening health and therefore requires clarification with the treating physician [McD21].

Blood Oxygen Saturation

Oxygen saturation indicates the percentage of oxygen in the blood. It describes what percentage of the red blood pigment hemoglobin is loaded with oxygen molecules [Haf22]. The value provides information about the functioning of the lungs and the effectiveness of oxygen transport in the blood. In a healthy person, the standard values of arterial oxygen saturation should be 95-100 %. The efficiency of the body depends on a sufficiently large oxygen supply. Decreased blood oxygen saturation can result in various symptoms such as low exercise capacity, shortness of breath, fatigue, cyanosis, and even fainting [BÄK19]. Body cells need sufficient oxygen to maintain their function and structure. Brain and heart muscle cells in particular are susceptible to a lack of oxygen and die quickly if they are undersupplied. For heart failure patients, it is important to identify the causes of insufficient oxygen saturation (hypoxygenation) and to counteract them with targeted interventions [Haf22].

Body Temperature

In healthy humans, the core body temperature is largely constant. It is approximately between 35.5 and 37.4 degrees Celsius. Body temperature is an important measure that provides information about the state of health. An increase in core body temperature, noted as a deviation from normal, is a sign of infection, inflammation, or other non-infectious disease. As described in the literature, infections, particularly of a respiratory nature, are more common triggers for hospitalizations in heart failure patients. Respiratory diseases are also associated with a significantly increased risk of in-hospital mortality in heart failure patients [BÄK19]. It is important to detect this early by measuring body temperature and to treat it.

Chapter 4

Related Work

In this chapter, the literature is reviewed for the analysis of the health status of heart failure patients based on telemonitoring data using machine learning. Telemonitoring provides the opportunity to collect a lot of medical data. The amount and complexity of available data requires the use of machine learning algorithms to exploit the full potential of the data and to analyze it automatically and efficiently. Section 4.1 addresses work that highlights relevant parameters to capture health status in heart failure patients in clinical settings and telemonitoring systems. Section 4.2 presents work using predictive models for heart failure early warning systems.

4.1 Relevance of Symptoms and Signs to Assess Health Status in Heart Failure

The guidelines specify that the health status of patients with chronic heart failure should be recorded regularly in a follow-up. The following parameters should be checked and documented: NYHA class, body weight and hydration status, blood pressure, heart rhythm and rate, electrolyte balance and renal function, medication, daily functioning, psychosocial status, quality of life and adherence [BÄK19]. Regular monitoring is important to adjust therapy when clinical and psychosocial symptoms worsen. Novel telemonitoring systems that capture biosignals using sensors offer the possibility to continuously analyze health status by documenting the progression of parameters, thereby improving the overall quality of care [Gmbc][Gmbd][Gmbb][Gmbe]. The literature review by Senarath et al. compares studies that address the acquisition of biosignals for early detection of cardiac decompensation in telemonitoring systems [Sen21]. In the review daily measurements of body weight, blood pressure, heart rate, respiratory rate, and bioimpedance were identified as relevant physiological parameters. These variables used in telemonitoring systems were evaluated for their relevance and reliability to predict cardiac decompensation. As an outcome, it was found that reliable assessment of heart failure status is only well achieved by combining a variety of parameters. In German-speaking countries, there are other telemonitoring systems besides the ProHerz app that provide applications specifically for heart failure and patient health management. In the following, three applications are presented and compared with regard to the inclusion of vital signs and other symptoms to determine health status. The telemedicine platforms described are all CE-marked Class I medical devices under the Medical Device Directive.

Tidda Herz is a health app that uses a smartwatch to record the user's heart rate, blood pressure, blood oxygen saturation, sleep length and quality, and activity level [Gmbd]. In addition, a 1-lead ECG is recorded via a patch monitor using the smartphone. Heart failure-specific symptoms to assess the patient's well-being are queried in app conversations. Patient-reported outcomes are recorded via text or voice conversation based on clinically validated quality-of-life protocols. Tidda Herz is supported by AI-based voice and chatbot technology that uses guideline-based information and expert knowledge. Tidda Herz combines app conversation with real-time monitoring of values and continuously informs experienced clinicians about the patient's health status via a dashboard system.

The iATROS telemedicine platform uses mobile measuring devices to record the blood pressure, ECG, pulse, blood sugar and weight of chronic heart failure patients [Gmbb]. In addition, questions about the patient's health status and compliance with therapy are recorded on a regular basis. Scientifically established scores are used to determine risks related to heart attack, stroke, cardiovascular disease and diabetes. The app combines individual patient care by experienced physician-cardiologists with data-based diagnostics.

The telemedicine platform sekTOR-HF of Curafida GmbH is part of the innovation fund project of the same name [Gmbe][Tel]. The study, which runs from 2021 to the end of 2023, collects vital signs data and questionnaires and links medical staff with patients. The vital signs data collected are: body weight, temperature, blood oxygen saturation, pulse, blood pressure and ECG recordings. Weight is determined with a body scale. A pulse oximeter measures oxygen saturation and pulse. The Cosinuss in-ear sensor records temperature, oxygen saturation, pulse and change in blood pressure. The ECG is recorded via a recorder with an attachable triangular chest adapter. In addition, the app records information about current health status. The type and form of health status recording is not described in more detail in the study design.

The telemonitoring applications differ in individual vital parameters and the query for identifying symptoms. Overall, based on the guideline recommendations, the work of Senarath et al. and the health apps presented, it can be concluded that a variety of parameters are necessary for a reliable and meaningful assessment of the health status of heart failure patients.

4.2 Predictive Models for Heart Failure Early Warning Systems

Decision support systems have been used in the medical field since the 1970s [Sho75]. These systems provide early indication of deteriorating health, identify high-risk patients from large amounts of telemedically collected data, and suggest therapeutic interventions [Gen17]. Machine learning can improve risk stratification when analyzing complex patient data by incorporating a variety of variables. This can increase the objectivity of physicians' assessment of health status and accelerate the prediction of acute deterioration. Especially in heart failure, the use of machine learning techniques improves risk prediction of cardiac decompensation [Gen17][Lev06]. By risk prediction in chronic heart failure, we mean deterioration of health, acute cardiac decompensation, hospital readmissions, or death. In the following, current systems and studies in the field of heart failure with decision support systems using machine learning algorithms are presented. Early warning systems and their algorithms are described that use clinical data, data from telemonitored implants, and noninvasive telemonitoring data. Important contents and findings for this work are the information scope of the data sets, the analysis methods used and the results obtained, which are described in the cited literature.

Heart Failure Early Warning System Based on Clinically Collected Data

The Seattle Heart Failure Model, is a field-proven, validated risk score that calculates mortality risk based on clinical characteristics, treatment modalities, and various laboratory parameters [Lev06]. In this process, 1-, 2-, and 3-year survival rates can be reliably determined using machine learning algorithms. The total area under the receiver operating characteristic curve (AUCROC) is 73 % [Gon21]. The patent US20110119078A1 (A) from 2011 describes an algorithm for risk assessment of acute heart failure in the clinical setting and is similar to the Seattle Heart Failure Model.

Heart Failure Early Warning Systems Based on Invasive Telemonitoring Data

The HeartLogic Index is a proprietary machine learning algorithm that uses data from the Boston Scientific Cardiac Resynchronization defibrillator [Ave22][Gmba]. The defibrillator is an implant. It derives the parameters, heart sounds, thoracic impedance, respiratory rate, respiratory volume, heart rate and motion activity from the implanted defibrillator. The index provides information about a worsening of the heart failure. At a defined threshold, an alarm is triggered that predicts the risk of hospitalization with a sensitivity of 70 % and a positive predictive value of 11.3 % [Ave22][Gmba]. The HeartLogic Index can detect cardiac decompensations with a median of 34 days in advance, allowing appropriate therapy adjustments to be made early [Boe17].

The patented implantable CardioMEMS sensor (see Section 3.1), which monitors pulmonary artery (PA) hemodynamic pressure in heart failure patients, can detect an increase in pressure early [Ang20][Abr20]. The sensor was protected by the patent US20140330143A1 (A) in 2014. Once the PA pressure rises above a threshold for at least three days, an alarm is triggered. The patient and the attending physician are automatically notified of the increased risk. The threshold values are optimized for the patient and are regularly adjusted to the patient's pressure status. The treatment algorithm effectively identifies patients at risk, making it suitable for efficiently monitoring and managing even large numbers of patients. The CardioMEMS system monitors heart failure patients in real time and is a reliable predictor of cardiac deterioration. An increase in pulmonary arterial pressure can be detected before the onset of heart failure and before vital signs such as weight, symptoms, and blood pressure can indicate it. Kobrossi et al. showed that the HeratLogic Index correlates with CardioMEMS pressure sensor values [Kob20]. Both are suitable tools for automatic and early detection of cardiac decompensation based on invasive telemonitoring data.

Heart Failure Early Warning Systems Based on Noninvasive Telemonitoring Data

In 2012, Seto et al. presented an expert system for automatic risk warning and self-care measures for heart failure patients [Set12]. The patient monitoring model is a threshold-based alerting algorithm and is based on telemonitoring data.

Koehler et al. implemented a rule-based algorithm in the Fontane project of the TIM-HF2 study [Koe18][Pol10]. The baseline model achieved an AUCROC of 73 %. Patients at risk were identified based on their daily transmitted vital signs and prioritized in the system for therapy adjustment.

A predictive model for decompensation prevention was presented by Larburu et al. 2018 [Lar18]. The study compared different machine learning methods. Heart failure-related hospitalizations could be predicted with an AUC value of 67 % using telemonitoring data. The data set used included telemonitoring data on body weight, heart rate, blood pressure, blood oxygen saturation, and heart failure-specific symptoms. In addition, health status was assessed via questionnaires. Clinical data and information on heart failure-specific events, such as hospitalizations and interventions, were also included in the data set. The aim of the work was to reduce the number of false alarms of the decompensation prediction model per patient per year. A Naive Bayes classifier using the Bernoulli distribution succeeded in reducing the number of false alarms per patient per year from 28.64 to 7.8.

Another machine learning algorithm for early detection of cardiac decompensation is the HeartPredict algorithm [Bou21]. The data set of a large European heart failure telemonitoring study, OSICAT was used for the evaluation [Ben14]. The data set contained sociodemographic data and time series data of body weight and symptoms. Different machine learning models were compared. The best result was provided by a balanced random forests model, which predicted heart failure-specific events with a 72 % sensitivity and a 94 % specificity and with an AUCROC of 80 %. HeartPredict also achieved better risk prediction results than simple thresholds, such as those defined in guidelines. Cardiac decompensation could be detected with more than 50 % probability three days before occurrence.

Preliminary results have already been published on the ongoing Telemed5000 study (see Section 3.1), showing that the use of deep learning can increase the accuracy of decision support systems [Gon21]. Based on the TIM-HF2 data set, deep neural networks were developed to increase the capacity of telemedicine centers. The data set used contains information on heart failure-related hospitalizations and deaths in addition to daily telemonitoring data. The models used achieved an AUCROC of 84 %. This deep learning approach improved the basic rule-based model implemented in the Fontane project by 11 %. The Telemed5000 research project aims to further improve the efficiency of risk assessment by using recurrent neural networks as time series analysis. In addition, patient-specific data analyses will be used to adapt and improve the models to each patient. The study will be taken further by testing whether patient voice can be used to make statements about body water content. Machine learning algorithms will be used to detect overhydration resulting in cardiac decompensation through voice measure detection.

As described above, the prediction algorithms presented are efficient tools for remote monitoring of heart failure patients, providing early warning of impending cardiac decompensation and thus having the potential to improve patients' quality of life, reduce hospitalizations, and lower health care costs.

4.3 Research Goals

The aim of this master thesis is to analyze the progressive health status of heart failure patients based on telemonitoring data to detect cardiac decompensation using machine learning techniques. The following main research question will be answered:

- Can we predict cardiac decompensation based on telemonitoring data using machine learning?

From the main research question, two additional research questions are formed that address the predictability of cardiac decompensation from different perspectives. The following research questions will be answered:

- What parameters are relevant for early prediction of decompensation in heart failure patients?
- Is there a relationship between vital signs measured daily and the health status of heart failure patients?

The first research question aims to identify relevant symptoms and signs that can predict cardiac decompensation. For this purpose, patient questionnaires on symptom perception in heart failure and expert interviews with cardiologists were conducted. Analysis of the telemonitoring data set will be used to determine and assess the relationship of telemedically recorded vital signs and health status. These three methods will answer the main research question.

Chapter 5

Symptom and Parameter Analysis of Heart Failure

Guidelines for the care of patients with chronic heart failure and cardiology literature identify disease-specific symptoms and signs. A large number of different parameters can be found to assess the health status of heart failure patients. The aim of this part of the paper is to elaborate and evaluate the importance and relevance of the symptoms and signs defined by the guidelines. The subjective perception of the patients as well as expert knowledge will be included. Using an online questionnaire, the symptoms of heart failure perceived by the patients are queried and these are evaluated qualitatively and quantitatively. Through expert interviews, the guideline-defined parameters will be verified by evidence- and experience-based knowledge and differentiated in their importance. Both the patient survey and the expert interviews aim to identify patterns in the course of vital signs and symptoms that precede cardiac decompensation. The methodology and results of the patient survey and expert interviews are presented below.

5.1 Patient Questionnaire

An online questionnaire was developed to capture patients' subjective perceptions of heart failure-specific symptoms. The list of symptoms was compiled based on the literature and in consultation with the medical supervisors. The questionnaire is divided into three parts. The first part collects the demographic data of the study participants. The symptom questionnaire of the second part is divided into two time periods. The first period asks about the symptoms of acute heart failure. This period refers to an acute worsening, a decompensation, which has led to hospitalization, for example. The second period covers symptoms during the stable heart failure phase. For both time periods, the participants could select from a list of typical symptoms those that they had experienced and that they had noticed. For each of the selected symptoms, the frequency, severity and burden were asked on a four-point Likert scale. The frequency of occurrence of a symptom was to be rated as hardly ever, rarely, frequently or very frequently. The severity was rated as mild, moderate, severe, very severe. The classification for the stress could be given as not at all, a little, moderately and strongly. In the third part of the questionnaire, further questions were asked about health knowledge and dealing with the disease heart failure. Appendix B lists the questions asked in the patient questionnaire.

5.1.1 Data Acquisition

The patient questionnaire was made available to participants via the online survey software Unipark between April and August 2022. Participants were recruited through various channels. Direct contact with heart failure patients was given via ProCarement GmbH to users of the ProHerz app. These ProHerz patients were notified via email with a flyer in the patient information system. In addition, further participants were recruited via flyers in cardiological practices in Erlangen and Forchheim, in cardiac sports groups, via social media, as well as via the email distribution list of the "Herz-Kreislauf-Initiative Erlangen" [4]. All participants have a diagnosed heart failure and are over 18 years of age. The questionnaire was conducted anonymously and includes information and consent to a privacy statement.

5.1.2 Study Population

A total of 48 participants, 17 female (35 %), 31 male (65 %), and 0 diverse, answered the questionnaire. Table 5.1 gives an overview of the demographic data of all participants. A proportion of 8.5 % of the participants reported being smokers.

In Table 5.2 the collected data on the medical background of the study participants are presented. 42 participants were users of the ProHerz app.

[4] https://www.hki-erlangen.de/

Table 5.1: Demographic and anthropometric data of the participants. *SD*: standard deviation.

Data		**Mean ± SD**
Age	[years]	66 ± 11
Height	[cm]	174 ± 11
Weight	[kg]	89 ± 23
BMI	[kg/m^2]	29 ± 6

Table 5.2: Medical data of the participants. *n*: describes the absolute number.

Condition Parameters		**Prevalence %**	**n**
Physical performance	NYHA I	22.9 %	11
	NYHA II	52.1 %	25
	NYHA III	25.0 %	12
	NYHA IV	0.0 %	0
Cardiac output	HFrEF (reduced)	22.9 %	11
	HFpEF (not reduced)	52.1 %	25
	Not specified	25.0 %	12
Aetiology of heart failure and comorbidities	Asthma	4.2 %	2
	Hypertension	42.8 %	21
	COPD (chronic obstructive pulmonary disease)	14.6 %	7
	Depression	8.3 %	4
	Diabetes mellitus	22.9 %	11
	Valvular heart disease	35.4 %	17
	Peripheral arterial disease	12.5 %	6
	Atrial fibrillation/flutter (cardiac arrhythmia)	50.0 %	24
	Chronic kidney disease	6.3 %	3
	Coronary heart disease	54.1 %	26
	Sleep-related breathing disorders (sleep apnoea)	25.0 %	12

5.1.3 Results

The results of the symptom query of the patient questionnaires are summarized in the Figure 5.1. The percentage occurrence of the questioned symptoms in acute heart failure and chronic heart failure is shown. The values refer to the entire study population. All queried symptoms were named by the study participants. As shown in Figure 5.1, more symptoms occurred in the acute phase than in the stable phase of heart failure. The incidence of symptoms was increased by 50.9 % in the acute phase. Figure 5.2 shows the percentage by which the individual symptoms were perceived more in the acute decompensation phase.

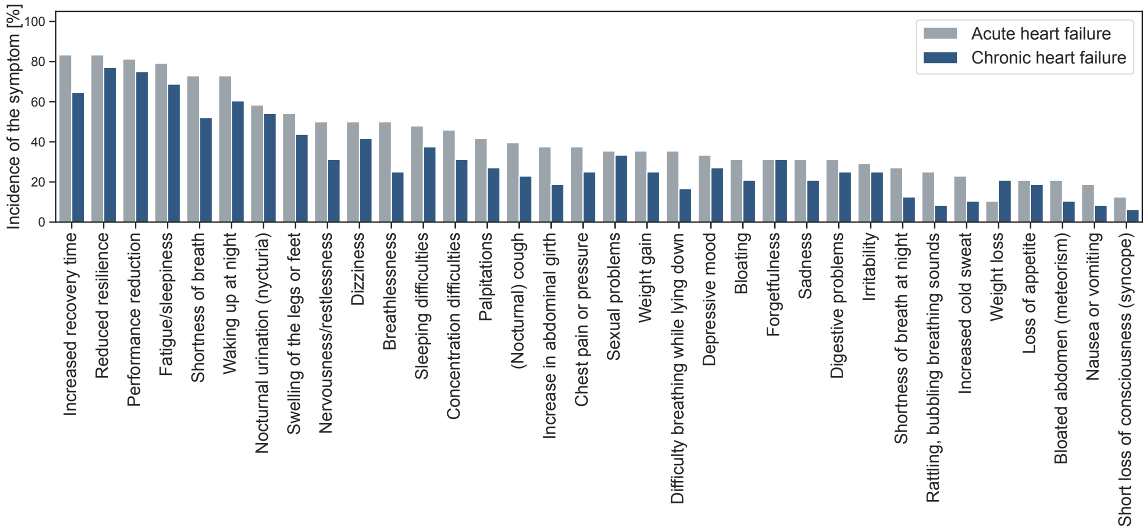


Figure 5.1: Incidence of symptoms in acute heart failure and chronic heart failure.

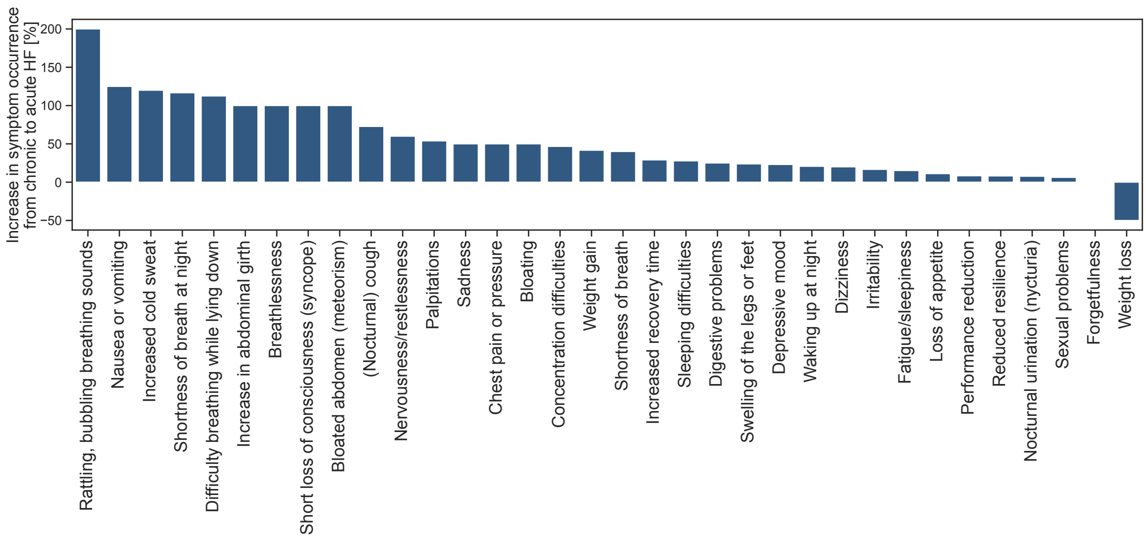


Figure 5.2: Increase in symptom occurrence from the stable phase to the acute phase of heart failure in percent.

The percentage increase from stable to acute heart failure is greatest for the following symptoms: *Rattling, bubbling breath sounds* (200 %), *nausea or vomiting* (125 %), *increased cold sweat* (120 %), *shortness of breath during the night* (116 %), *increase in abdominal girth* (100 %), *shortness of breath* (100 %), *brief loss of consciousness (syncope)* (100 %) and *bloated abdomen (meteorism)* (100 %).

In the evaluation of the patient questionnaire, the increase of these symptoms is particularly relevant for an imminent decompensation. The symptoms always occurred in combination. In the stable phase, the patients stated on average that they noticed 11 symptoms at the same time. In the acute phase, the average value of simultaneously perceived symptoms was 14.

In the acute phase, the most commonly reported symptoms were *increased recovery time after physical activity*, *decreased exercise capacity*, *decreased performance*, *fatigue/sleepiness*, *shortness of breath*, *waking up at night* and *nocturia*. In the stable phase, the same symptoms as above were mentioned most frequently. The order of symptom occurrence differs slightly. *Decreased resilience*, *decreased performance*, *fatigue/sleepiness*, *increased recovery time after physical activity*, *waking up at night*, *nocturia* and *shortness of breath* are the most frequently mentioned symptoms.

If we differentiate the study group by gender in the acute phase of heart failure, we can see that women noticed more symptoms than men. Women experienced 35.6 % more symptoms. The most common symptoms were named in the same way by women and men (see Figure 5.3).

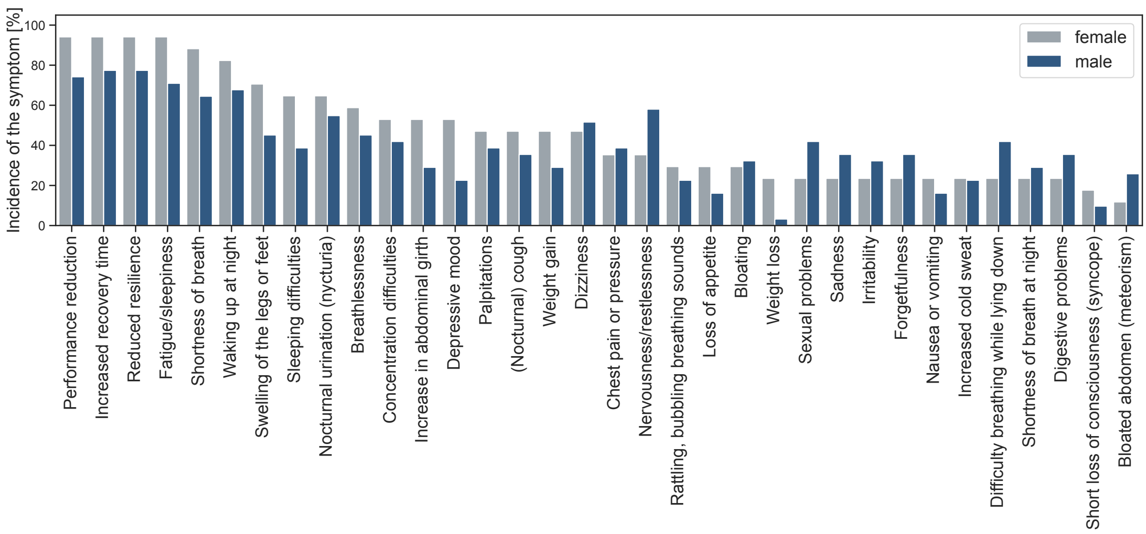


Figure 5.3: Incidence of symptoms in acute heart failure differentiated by gender.

According to physical performance, the study participants are assigned to three different NYHA classes. 21.3 % belong to NYHA class I, 53.2 % are in NYHA class II and 25.5 % of the study participants are assigned to NYHA class III. Looking at the occurrence of symptoms in relation to the NYHA classes, it is noticeable that with increasing NYHA class, the number of symptoms increases in both the stable and acute heart failure phases. While the study participants in NYHA classes I and II hardly complained about breathing problems in the stable phase, they perceived a reduction in performance and physical capacity. In both phases, almost all patients in NYHA class III described the same symptoms. The symptoms most frequently mentioned by this group were: *Shortness of breath*, *decrease in performance*, *increased recovery time after physical activities*, *fatigue/sleepiness*, *waking up at night*, *decreased exercise capacity*. In addition, mental health problems and dizziness were reported by over 50 % of NYHA class III patients.

The results related to cardiac output only include the study participants who provided information on their cardiac output. 21 participants are patients with reduced ejection fraction (HFrEF). 10 participants did not have pump dysfunction (HFpEF). In the stable phase of heart failure, it can be seen that the HFrEF patients had 43.2 % more symptoms. This was particularly noticeable in the symptom group, reduced performance. In the acute heart failure phase, there was hardly any difference in the number of symptoms occurring. The patients with preserved ejection fraction reported more breathing difficulties, also during the night, and more depressive moods than the HFrEF patients in the acute phase.

The differences in symptom query results between ProHerz app users and other patients were not analyzed due to the small group of non-ProHerz app users.

In the patient questionnaire, 39 individual symptoms were queried. In the further evaluation, the individual symptoms were combined into groups with the same problem. The symptom groups and the associated symptoms are described in Table 5.3. The symptom *dizziness* cannot be assigned to any other symptom group and therefore forms its own group. The symptom group *reduction in performance* was mentioned most frequently. The symptom groups, *dizziness*, *sleep problems* and *breathing problems* were perceived with similar frequency during the acute phase of heart failure. *Water retention*, *heart problems* and *psychological problems* occurred with similar frequency during both phases. *Digestive problems* was the symptom group with the lowest incidence. The data on the percentage of occurrence are shown in Table 5.4. In addition, the most frequently mentioned symptoms in the symptom groups are listed in Table 5.4. These symptoms are the most relevant symptoms for the holistic assessment of the health status of heart failure patients and predictors of impending decompensation.

Table 5.3: Definition of the symptom groups with the associated symptoms.

Symptom group	**Symptoms**
Breathing problems	Shortness of breath
	Coughing
	Breathlessness
	Rattling, bubbling breathing sounds
Decreased performance	Decrease in performance
	Fatigue/sleepiness
	Decreased resilience
	Problems with sexual interest or activity
	Increased recovery time after physical activities
Heart problems	Chest pain or pressure
	Palpitations
Water retention	Swelling of the legs or feet
	Increase in abdominal girth
	Meteorism
	Weight gain
Digestive problems	Digestive problems
	Nausea/vomiting
	Bloating
	Loss of appetite
Sleep problems	Nocturia
	Difficulty breathing when lying down
	Breathlessness during the night
	Sleeping difficulties
	Waking up at night
Psychological problems	Sadness
	Nervousness/restlessness
	Depressive mood
	Forgetfulness
	Irritability
	Concentration difficulties
Dizziness	Dizziness

Almost all study participants reported in the further question section that they can perceive and assess heart failure-specific symptoms well to very well. Only one participant reported difficulties in assessing symptoms. Through the use of the ProHerz app and informative talks with the doctor, health literacy and the associated ability to perceive symptoms improved

Table 5.4: Results summarized by symptom groups.

Symptom group	**Phase chronic heart failure**	**Phase acute heart failure**	**Most mentioned symptom of symptom group**
Decreased performance	63.8 %	72.5 %	Decreased resilience
Dizziness	41.7 %	50.0 %	Dizziness
Sleep problems	36.3 %	48.3 %	Waking up at night
Breathing problems	27.1 %	46.9 %	Shortness of breath
Heart problems	26.0 %	39.6 %	Palpitations
Water retention	24.5 %	37.0 %	Swelling of the legs or feet
Psychological problems	26.0 %	36.8 %	Nervousness/restlessness
Digestive problems	18.2 %	25.5 %	Digestive problems

in almost all (95.9 %) study participants. 41.6 % of the study participants stated at the time of the survey that they did not record and document their symptoms. 83.3 % of the study participants could imagine that a symptom diary could help them assess their state of health.

5.1.4 Discussion

Heart failure patients often suffer from a large number of symptoms. The symptoms often do not occur in isolation, but in combination. As the results show, an increased occurrence of symptoms with increased frequency of occurrence, increased severity and increased stress is a clear pattern of decompensation. If there is an increase in symptoms, therapy must be adjusted. Special attention should be paid to all symptoms of heart failure that are asked for in the patient questionnaire. In the National Health Care Guideline, the symptoms that can be decisive for an impending decompensation are described as follows: Shortness of breath on low physical exertion, fatigue, peripheral oedema, cough and weight or abdominal girth gain (ascites) [BÄK19]. The National Health Care Guideline makes it clear that individual symptoms are non-specific. The linkage of symptoms and findings define acute decompensated heart failure and make it clear [BÄK19].

On the basis of the patient questionnaires, it was possible to find out that some symptoms occur more frequently than others. However, all of the heart failure-specific symptoms asked are relevant and cannot be differentiated according to importance. The occurrence of symptoms varies from patient to patient and depends on the functional and/or structural disorder of the heart [All07]. It is not the occurrence of individual symptoms that is decisive for the early recognition of impending decompensation, but the worsening of the symptoms. For this purpose, it is important to recognize the course of symptoms and their worsening, to interpret them and to act accordingly [All07][BÄK19].

When evaluating the patient questionnaires separately according to gender, it was recognized that women had 35.6 % more symptoms in the acute phase than men. The most frequent symptoms that occurred in the acute phase did not differ between men and women. The study by Haedtke et al. also describes that women report more symptoms than men in the acute phase of heart failure. It is recommended to consider gender differences in symptom recording and therapy [Hae19].

The evaluation of the patient questionnaires shows that the number of perceived symptoms increases with increasing NYHA class. This is consistent with the definition of the NYHA classification [New94]. The more and the more severe symptoms patients perceive, the more likely they are to be burdened by depressive symptoms. This relationship is also evident in patients with NYHA class III in the evaluation of the questionnaires.

The literature describes that patients with preserved ejection fraction (HFpEF) are more likely to be older and twice as likely to be women [Lee09][Sim20]. The study population shows a different distribution. More women are HFrEF patients. This makes it difficult to classify and interpret the results in the literature. An increase in respiratory problems was seen in HFpEF patients. This can be attributed to the fact that these patients have more frequent respiratory diseases [Lee09][Sim20]. It can also be seen that patients with HFrEF described more psychological upset.

In order to identify the most relevant symptoms, the symptoms must be grouped together. Although the evaluation of the individual symptoms reflects the most frequently mentioned symptoms, these symptoms do not represent the diverse symptomatology of heart failure. By grouping symptoms of the same problem, the most relevant symptoms can be identified. In this way, the entire range of symptoms is captured by a few, meaningful individual symptoms. The most relevant symptoms from the symptom groups that we identified in our study are: *decreased resilience*, *waking up at night*, *shortness of breath*, *palpitations*, *swelling of the legs or feet* and *nervousness/restlessness*. These symptoms were identified as predictors of impending decompensation.

The majority of the study population are users of the ProHerz app. These patients are trained through the use of telemonitoring with disease knowledge units. Almost all study participants stated that they were able to assess symptoms well. The results from the evaluation of the patient questionnaire are therefore reliable. However, the significance of the study is limited by the small number of participants. In contrast to the statement of the study participants that they can perceive and recognize symptoms well, other findings can be found in the literature. It is reported that patients with heart failure have difficulties recognizing a worsening of symptoms, interpreting and managing them [Lee18][Rie18]. The importance of symptom perception in heart failure has been described in the literature. It combines a functioning self-sufficiency with an adapted self-sufficiency management [San21].

The prospective community study by Fabbri et al. describes that higher health literacy among heart failure patients is associated with a lower risk of hospitalization and death [Fab18]. 95.9 % of participants reported that their disease-specific knowledge improved as a result of using the ProHerz app or informative talks with their doctor. If one relates this statement of the study participants to the study results of Fabbri et al. it can be assumed that the number of hospital admissions and mortality will decrease.

It can be difficult for patients to keep track of the multiple symptoms, recognize deterioration, interpret it correctly and act accordingly. With advancing age, co-morbidities and the slow or gradual progression of symptoms, deterioration is difficult for patients to perceive. Positive influences on symptom recognition include living with other people, a higher level of education, a sudden worsening of symptoms, a longer history of illness and a higher number of hospitalizations [Lee18]. When heart failure patients are poor at perceiving and interpreting their symptoms, there may be a delay in choosing the right treatment and therapeutic interventions [Mos08][Jur09]. Lee et al. describe in their study that inadequate symptom management leads to increased hospital admissions and mortality [Lee18]. Analysis of the survey showed that over 40 % of study participants did not record and document symptoms of heart failure. However, over 80 % of respondents said they believed a symptom diary could help them assess their health. The literature describes the benefits of symptom diaries for heart failure patients. Symptom diaries are intended to be used specifically to support self-monitoring and to engage in exchange with caring health care professionals. In symptom diaries, symptom patterns of deterioration can be made visible over time. The use of a symptom diary can reduce mortality, hospitalization and medical costs [Lee18].

5.2 Expert Interviews

The aim of the qualitative interviews is to collect, bundle and qualitatively classify the knowledge and empirical values from the clinical practice of the experts in conversation. The findings from the expert interviews should help to understand clinical algorithms for the assessment of the health status of heart failure patients and to work out the relevance. Particular emphasis will be placed on the early detection of decompensation and preceding patterns. The findings will then be adapted and made usable for telemonitoring.

The interviews are semi-structured guided interviews. This ensures that all relevant aspects are asked and answered in the course of the interview. The interview guidelines for the present expert interviews were drawn up on the basis of the literature research. The interview guide is divided into four parts, information on the background of the experts, questions on relevant symptoms and signs of chronic and acute heart failure, questions on patients' health literacy, questions on telemonitoring. The complete interview guide can be found in the Appendix C.

5.2.1 Data Acquisition

The five interviews took place between July and August 2022. The length of each interview was approximately 30 minutes. The interviews took place online via a licensed, secure, video conferencing software. With the consent of the interview participants, a video with audio track was digitally recorded. A test run of the interview was conducted in advance with a Heart Failure Nurse from ProCarement's CareCenter to check the length of the interview, the comprehensibility and meaningfulness of the questions and their order. Contact was made with selected experts via ProCarement GmbH. In addition, one expert was interviewed who is not associated with ProCarement GmbH.

5.2.2 Study Population

Table 5.5 contains information and data on the five experts. Four of the experts are familiar with telemonitoring systems in heart failure. These experts have experience through exchanges with patients who use a telemonitoring system.

Table 5.5: Characteristics of the expert interview participants.

Cardiology work experience	**Professional qualification**	**Current field of activity**
11 years	Health care and nursing assistant, Heart Failure Nurse	Care manager, care of patients of a telemonitoring app
12 years	Specialist in cardiology and angiology	Staff Senior Physician for cardiology and angiology at the hospital
22 years	Specialist in internal medicine and cardiology	Specialist in internal medicine in a cardiology and sports medicine practice
22 years	Specialist in cardiology and intensive care medicine	Senior physician for general and interventional cardiology/angiology in the clinic
32 years	Specialist in internal medicine and cardiology	Specialist in cardiology in a joint internal medicine practice

5.2.3 Thematic Analysis

Based on the literature, the guiding questions for the interviews were formulated. The interviews were transcribed. For the evaluation of the expert interviews, a thematic analysis for qualitative data was carried out following Braun and Clarke [Bra06]. According to the two authors, "thematic analysis is a method for identifying, analyzing and presenting patterns (themes) in data" [Bra06]. This allows large amounts of data to be meaningfully summarized and important features to be extracted. Similarities and differences in the responses are recognized and classified thematically. In Table 5.6 the phases of the thematic data analysis are shown. According to these six phases, the data analysis was carried out with the help of Excel and a color-differentiated structuring and filtering.

Table 5.6: Phases of thematic analysis adapted from Braun and Clarke [Bra06].

Phase		Description oft he process
1	Transcription	Writing of the spoken word, familiarization with data
2	Coding	Generating initial codes, coding interesting features in a systematic fashion across the entire data set
3	Searching for themes	Sorting and compilation of the codes on potential themes
4	Reviewing themes	Checking and adapting the found themes, generating a thematic map of the analysis
5	Defining und naming themes	Finding meaningful themes, Identify important aspects within the themes
6	Producing the report	Relating back of the analysis to the research question and literature, producing a scholarly report of the analysis

5.2.4 Results

The three themes, *Progress diagnostics*, *Acute decompensation*, and *Telemonitoring*, and their subthemes were identified. The overall result is presented as a thematic map by showing the relationships between the themes and how they are linked to each other, see Figure 5.4. The themes and their subthemes are presented in detail below.

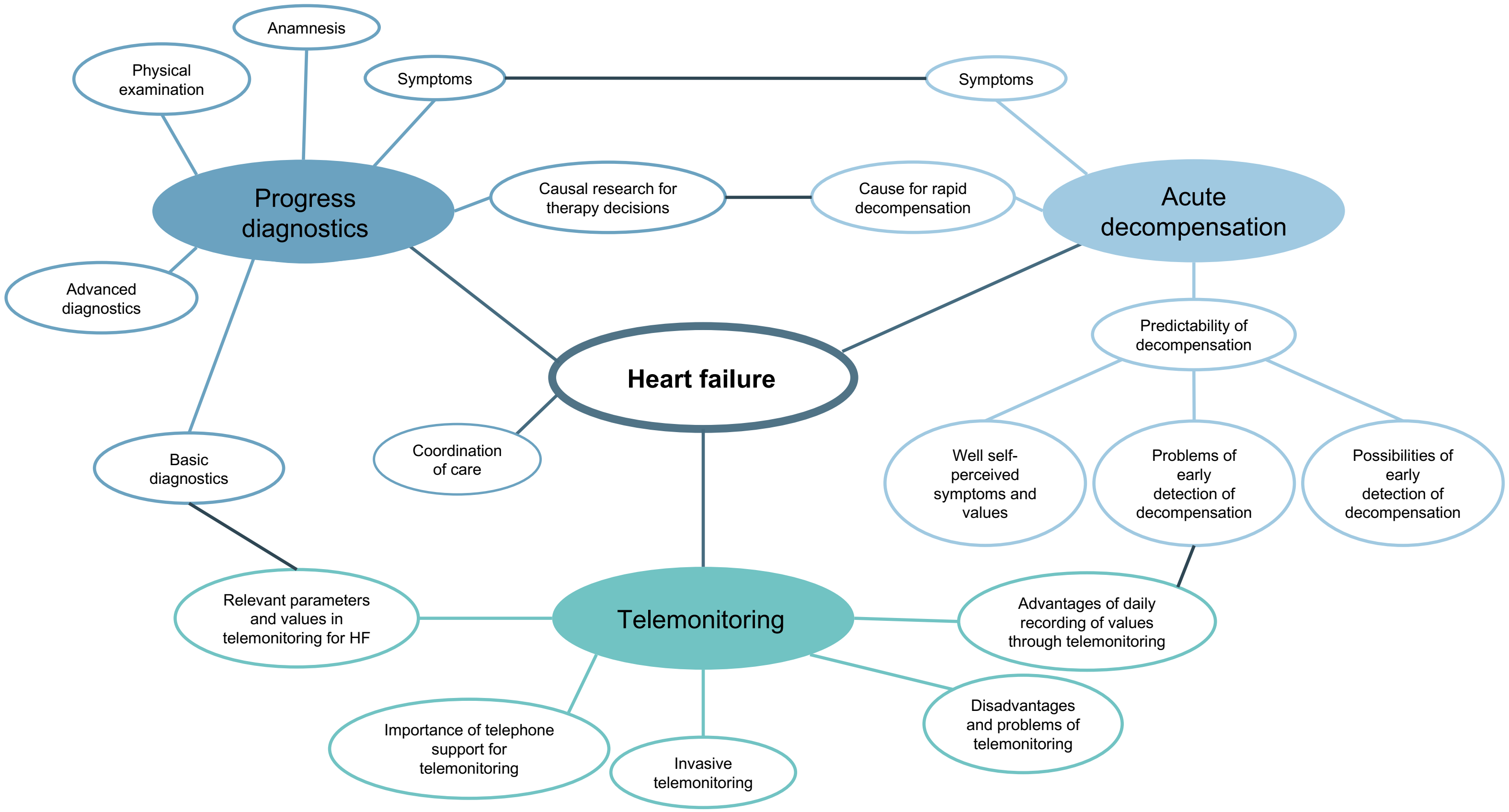


Figure 5.4: Final thematic map of the expert interview results, showing the three main themes (colored filled ovals) and subthemes (non-filled ovals) and their relationships.

Progression Diagnostic

The aim of progress diagnostics is to regularly check and document the progression of the confirmed, diagnosed chronic heart failure in order to adjust the therapy according to the state of health. The theme *Progress diagnostics* is divided into the six subthemes, *Anamnesis*, *Queried symptoms during the routine examination*, *Physical examination*, *Basic diagnostics*, *Further diagnostics* and *Cause research for therapy decisions* (see Figure 5.5).

The experts described that the progression diagnostic procedure is similar to that recommended by the heart failure guidelines.

> Expert: “Der Patient kommt ja letztlich zu mir und klagt über gewisse Symptome. Sprich, er kommt zu mir und klagt über Kurzatmigkeit oder geschwollene Beine oder Schmerzen auf der Brust, rasche Erschöpfbarkeit, solche Dinge. Also neben den ganz banalen anamnestischen Daten wird man lege artis dann körperliche Untersuchungen durchführen. Sprich, ich würde ihn abhören, guck ihn insgesamt an, hat er dicke Beine, was machen die Lippen. Wenn ich ihn abhöre, was höre ich für Herzgeräusche, höre ich was an der Lunge. Das Nächste sind dann langsam die ersten technischen Untersuchungen, sprich EKG, Herzultraschall, und last but not least Laborwerte.” (The patient ultimately comes to me and complains about certain symptoms. In other words, he comes to me complaining of shortness of breath or swollen legs or chest pain, rapid exhaustion, things like that. So in addition to the very banal anamnestic data, one will then perform lege artis physical examinations. I would listen to him, look at him overall, does he have thick legs, how are his lips. When I listen to him, what heart sounds do I hear, do I hear anything in the lungs. The next step is the first technical examinations, i.e. ECG, heart ultrasound, and last but not least laboratory values.)

A large number of symptoms were mentioned by the experts. In Figure 5.5 under *Queried symptoms during routine examination* these are listed and sorted by frequency of mention from top to bottom. Breathlessness as a symptom was mentioned by all experts.

> Expert: “Atemnot ist natürlich das Hauptsymptom.” (Breathlessness is of course the main symptom.)

> Expert: “Wichtig ist bei Herzinsuffizienz ist die Luftnot, erstmal. Das Hauptsymptom ist, dass die Patienten schlecht Luft bekommen und sie sich schlecht

> belasten können." (The important thing in heart failure is shortness of breath, first of all. The main symptom is that the patient has difficulty breathing and straining.)

Oedema as a significant symptom of heart failure was also listed by all experts.

> Expert: "Was aber natürlich auch noch dazu gehört ist, den Ödemstatus zu erheben. Also sprich, ich würde dem auf die Füße gucken, in erster Linie mal schauen, ob der Patient eben geschwollene Füße hat. Und ich würde ihn auch aktiv natürlich befragen, ob das schlimmer geworden ist. Ob ihm die Hausschuhe besser passen oder schlechter passen." (But of course, it is also necessary to determine the oedema status. In other words, I would look at the patient's feet, first to see whether he has swollen feet. And I would also actively ask him, of course, if it has gotten worse. Whether the slippers fit better or worse.)

After the symptom query, the patient can be assigned to an NYHA class. The physical examination for simple diagnostics includes listening to the heart and lungs to detect the occurrence of e.g. a third heart sound or fluid retention in the lungs. Experts agree that the parameters body weight, blood pressure, heart rhythm and rate, oxygen saturation and the ECG should be recorded, checked and documented at every follow-up. Further diagnostics help to differentiate heart failure from other diseases if the symptoms are similar.

> Expert: "Das haben wir natürlich auch häufig, dass die Patienten gleichzeitig eine chronische, obstruktive Lungenerkrankung haben. Dann kann man schwer unterscheiden, wo kommt die Atemnot her, ist es jetzt eher die Lunge oder ist es eher das Herz. Da hilft uns dann wieder der BNP-Wert." (Of course, we often have patients with chronic obstructive pulmonary disease at the same time. Then it is difficult to distinguish where the shortness of breath comes from, whether it is the lungs or the heart. The BNP value then helps us again.)

In addition, further examinations such as laboratory tests, echocardiography, heart ultrasound and/or a chest X-ray can be performed for more precise clarification. In order to be able to make the right therapeutic decisions, it is crucial to clarify the causes of the heart failure. Causes frequently mentioned by experts included coronary heart disease, hypertension, arrhythmias, valve disease, alcohol and nicotine abuse.

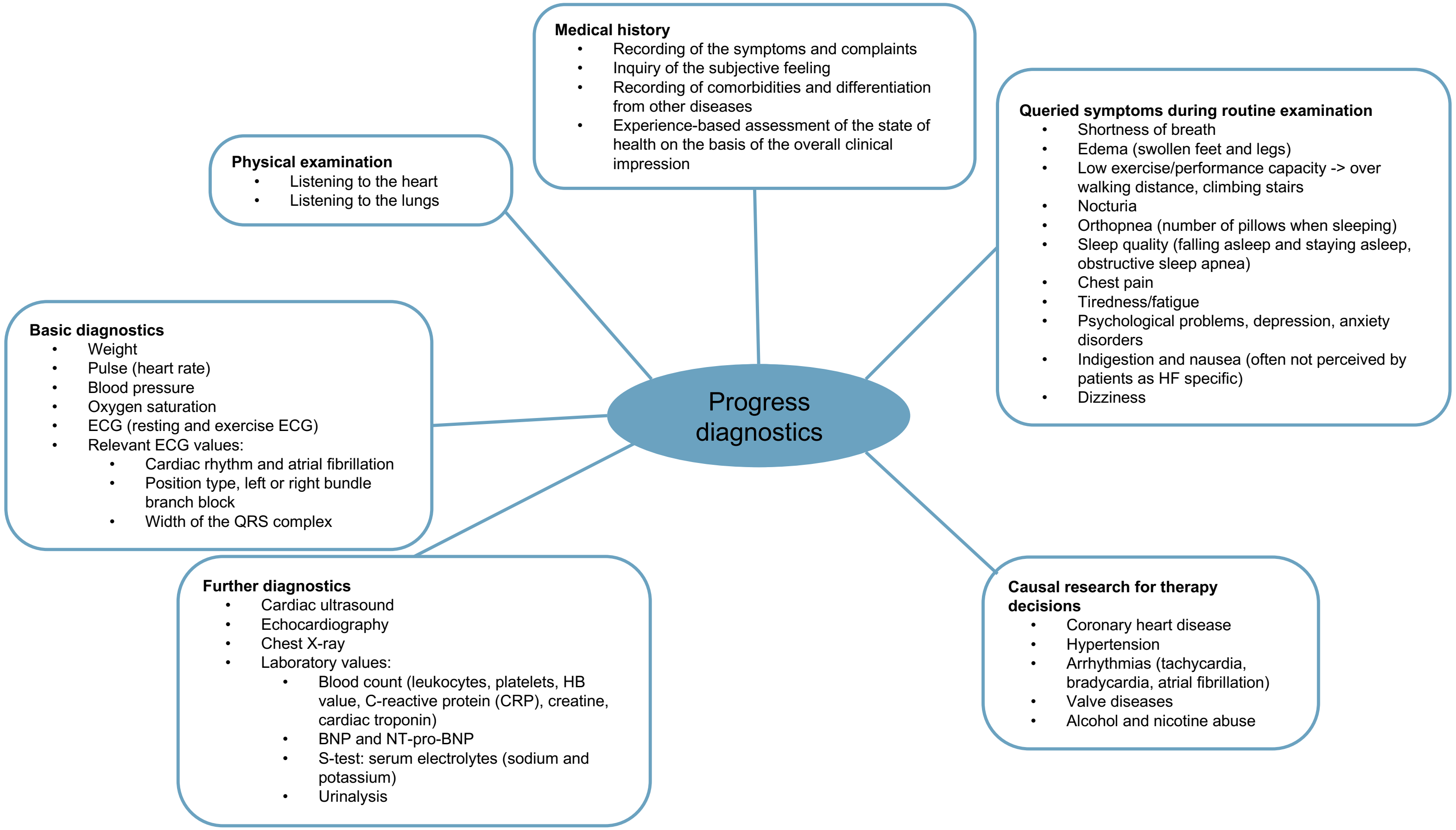


Figure 5.5: Thematic map of the expert interview results on the theme *Progress diagnostics* and related subthemes.

Acute Decompensation

The theme *Acute decompensation* is divided into three subthemes, *Symptoms and signs of acute decompensation*, *Causes of rapid decompensation* and *Predictability of decompensation* (see Figure 5.6).

The experts described that when the symptoms and signs of heart failure worsen significantly, it is called acute decompensation of the heart. In Figure 5.6 under *Symptoms and signs of acute decompensation* the typical features are listed and ordered by importance from top to bottom. The occurrence of several symptoms at the same time, increased frequency, increased intensity and increased stress, is a pattern that can be found and indicates acute decompensation.

As causes of rapid decompensation the interview participants named non-adherence to drug therapy, arrhythmias, blood pressure increase and infections. The experts described that a small impulse can quickly turn chronic heart failure into acute decompensation, as patients already have a poor baseline health status.

> Expert: "Dann hat der Patient vielleicht vergessen die Medikamente einzunehmen. Dann geht es ruckzuck. [...] Oder bei einer Tachyarrhythmie. Wenn die zu schnell werden von der Herzfrequenz. Dann kann das auch relativ rasch gehen. Wenn die Herzleistung eh schon eingeschränkt ist und er wird plötzlich tachyarrhythmisch, dann kann das auch innerhalb von Stunden gehen, dass er dekompensiert." (Then the patient may have forgotten to take the medication. Then it goes in a rush. [...] Or with a tachyarrhythmia. When the heart rate becomes too fast. Then it can happen relatively quickly. If the cardiac output is already limited and he suddenly becomes tachyarrhythmic, then it can also happen within hours that he decompensates.)

For heart failure patients, a specialist cardiological follow-up examination is conducted approximately once every six months, depending on the severity and state of health.

The subtheme *Predictability of decompensation* can be divided into three areas. In order to detect decompensation early, it is important that symptoms are noticed by the patient. Experts said that patients are good at recognizing symptoms themselves, such as decreased exercise capacity, oedema and shortness of breath. In Figure 5.6 under *Well self-perceived symptoms and values*, further symptoms and values mentioned by the experts are listed, which, according to their assessment, patients can perceive well.

As a problem of early recognition of decompensation, the interviewees described that patients can perceive and interpret symptoms differently. The patients' health literacy is partly poor. The temporal development of decompensation depends on the cause. A latent deterioration over a longer period of time is sometimes poorly registered by the patients.

> Expert: "Wenn es halt so ein schleichender Prozess ist, ist es auch schwierig zu erkennen. [...] Dann wird es halt jeden Tag ein bisschen schlechter und die Atmung wird ein bisschen schlechter. Eine Verschlechterung kann aber auch so plötzlich und ohne vorherige Warnsignale eintreten, dass eine rechtzeitige Therapieanpassung nicht möglich ist." (If it is such a gradual process, it is also difficult to recognize. [...] Then it just gets a little worse every day and the breathing gets a little worse. But a deterioration can also occur so suddenly and without prior warning signals that a timely adjustment of therapy is not possible.)

> Expert: "Und beim Vorhofflimmern pumpt der Vorhof nicht mehr, weil er so schnell schlägt, dass es keine Pumpe mehr ist und dann werden die Patienten plötzlich schlechter." (And in atrial fibrillation, the atrium stops pumping because it's beating so fast that it's not a pump anymore, and then patients suddenly get worse.)

Help is then sought too late. In addition, the symptoms of heart failure are so complex or overlaid with comorbidities that patients sometimes misinterpret them. Symptoms are attributed to other diseases or suppressed.

> Expert: "Es wir natürlich auch viel negiert. Also die Atemnot wird halt auf andere Sachen geschoben." (Of course, a lot of things are negated. The shortness of breath is simply blamed on other things.)

The long interval between follow-up visits means that a deterioration in health is only noticed by the doctor in charge with a time delay.

The experts described that there are ways to detect deterioration. The B-type natriuretic peptide (BNP) and NT-pro-BNP provide information about the presence of cardiac decompensation. More important for early detection is deterioration in the course of vital signs. Oedema, especially in the feet and legs, were cited by experts as a significant and easily recognizable symptom.

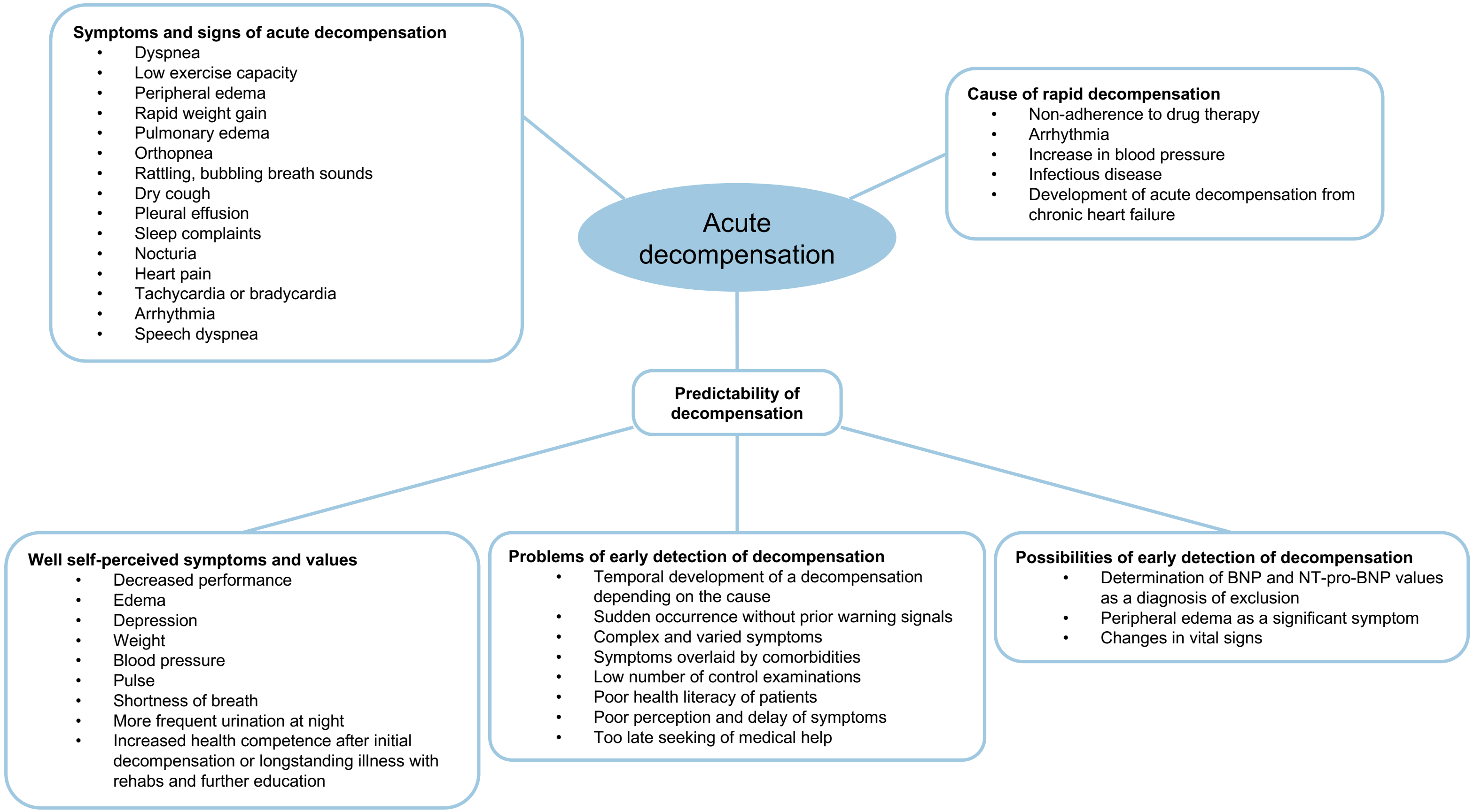


Figure 5.6: Thematic map of the expert interview results on the theme *Acute decompensation* and related subthemes.

Telemonitoring

The *Telemonitoring* theme follows on from the two previous themes (see Figure 5.7).

In order to identify the symptoms and signs of heart failure relevant for telemonitoring, the experts were given the task of designing their own system for the daily, home-based monitoring of heart failure patients. Figure 5.8 lists the parameters mentioned and the number of mentions and thus the importance. All experts considered the daily control of weight, blood pressure and heart rate as relevant parameters.

> Expert: "Also was jeden Tag gemacht werden sollte, meiner Ansicht nach, ist Blutdruck, Puls und das Gewicht." (So what should be done every day, in my opinion, is blood pressure, pulse and the weight.)

In addition to recording the objective values, some experts also mentioned the importance of asking about the subjectively perceived symptoms. These are to be recorded via simple questions and asked in adapted time periods. The symptom questionnaire is intended to supplement the values and the course of the values and to make it easier to assess the state of health.

> Expert: "Ist die Belastbarkeit schlechter geworden? Ist die Gehstrecke weniger geworden? Haben die Unterschenkel von der Dicke zugenommen? Haben Sie das Gefühl, dass Sie mehr atmen?" (Has the resilience become worse? Has the walking distance become less? Have your lower legs increased in thickness? Do you feel that you breathe more?)

The experts particularly emphasized the importance of telephone support for telemonitoring in addition to the recording of values. Through personal contact, symptoms can be recorded and medically assessed by asking specific questions. During the conversation with the patient, the psychological situation and the condition of the respiration can often also be determined. Special medical events can be asked about during the conversation and may have to be included in the therapy recommendations.

> Expert: "Ein wichtiger Punkt ist auch die menschliche Komponente. Dass es nicht alleine auf Telemonitoring ankommt, auf diese Messwerte-Überwachung, sondern auch auf den menschlichen Part. Dass die Leute einfach froh sind, dass sie, wenn sie nicht in der Klinik sind, trotzdem so einen menschlichen Kontakt

> zu medizinischem Fachpersonal haben und darüber sind sowohl die Patienten dankbar, als auch, das hätte ich anfangs gar nicht gedacht, die Angehörigen." (An important point is also the human component. That it's not just telemonitoring that matters, this monitoring of measured values, but also the human part. That people are simply happy that, when they're not in the hospital, they still have such human contact with medical professionals, and both the patients and, I wouldn't have thought at first, the relatives are grateful for that.)

Some experts mentioned that invasive monitoring to record pulmonary arterial pressure by means of an implantable sensor or monitoring via implanted pacemaker systems or implantable cardioverter defibrillators (ICD) are also well suited. Transthoracic impedance measurement, which describes the patient's state of compensation, is also conceivable.

The experts described the advantage of telemonitoring as the possibility of early detection of deterioration through the recording and evaluation of progress values. Based on daily measurements, patterns and trends can be identified and provide information about the patient's state of health. Hospital admissions could thus be prevented. In addition, it seems possible to the experts to increase the intervals of the follow-up checks. According to the experts, the improvement of the patients' state of health can be promoted by telemonitoring. The experts reported from their experiences that patients and relatives experience security through telemonitoring and feel cared for and looked after. Another advantage mentioned is that patients receive support in scheduling doctor's visits and motivation and support for the right choice of doctor and therapy. The experts considered the disadvantage of telemonitoring to be that the assessment of symptoms is done by the patients themselves and not by trained medical staff. Thus, the lack of on-site contact could lead to misjudgments. The interviewees saw problems with adherence, the daily time required and the difficulty in operating the technical devices, especially for older people.

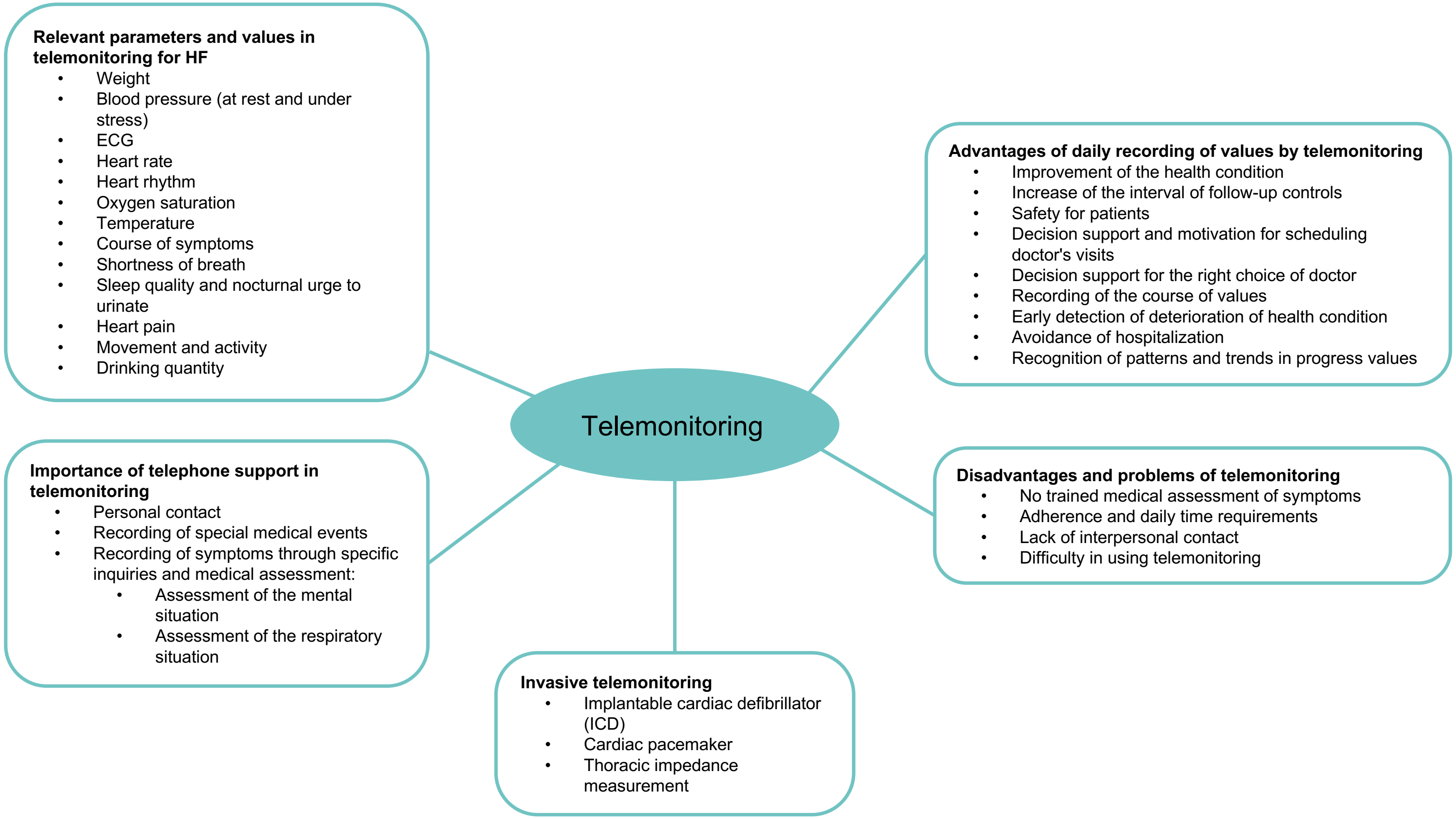


Figure 5.7: Thematic map of the expert interview results on the theme *Telemonitoring* and related subthemes.

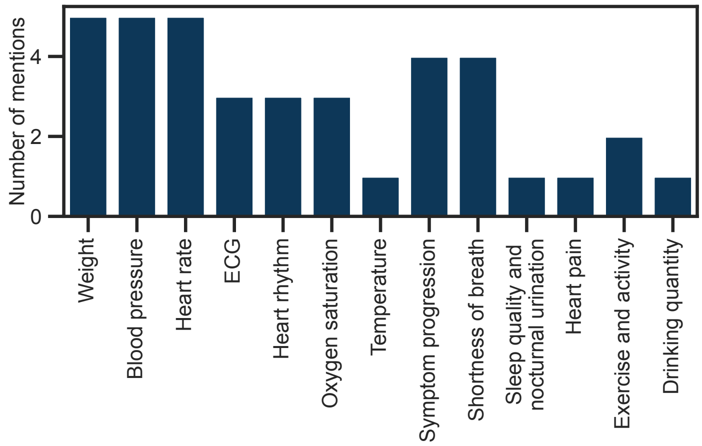


Figure 5.8: Relevant parameters and values in telemonitoring for heart failure mentioned by the five experts.

5.2.5 Discussion

The aim of the interviews is to qualitatively record experience-based expert knowledge on the topic of heart failure and the recognition of cardiac decompensation. The experts' statements provide knowledge and empirical values from clinical practice and should help to correctly assess the health status of heart failure patients. The diagnostic procedure in routine examinations and in acute decompensation is shown, and the relevant symptoms and signs are identified in both cases. The aim of the discussion is how the knowledge gained can be used for telemonitoring.

The results of the expert interviews are limited by the small number of participants. Nevertheless, the experts represent a broad spectrum of this medical field due to their years of professional experience and work in different cardiological fields of activity. The interviewees were motivated and contributed with high professional competence to an informative exchange.

The theme *Progress diagnostics* is about recording the current state of health of patients suffering from chronic heart failure. The experts' statements showed that a holistic view of the patient is particularly important for assessing the patient's state of health. The visual diagnosis is supported by physical examinations, the questioning of symptoms, and the determination of vital signs. If the findings are unclear, further diagnostics are initiated, and the causes and comorbidities are determined. The procedure described by the experts shows that follow-up checks are implemented according to the guidelines [AMK19]. Experts described being able to assess and evaluate the complex clinical picture of heart failure well through years of practical and clinical experience. Often, the patient's state of health can already be well assessed by "simply looking", listening, and asking about important symptoms. The recording of vital signs supports and secures the classification of the state of health.

Because a classical anamnesis is not possible with telemonitoring, the assessment of the stage of the disease must be made by means of easily detectable signs and symptoms. By daily transmission of the relevant values recorded at home, the patient's condition can be assessed, evaluated and the therapy adjusted. Both Senarath et al., and Köhler et al. describe the importance of daily recording of vital signs [Sen21][Köh19]. Experts reported that patients come to the practice about once every six months for a specialist cardiological follow-up examination. The recording of values by the doctor, therefore, takes place only rarely. The course of values over an interval of half a year is not very meaningful and does not capture rapid changes in the syndrome. The experts explicitly emphasized that a deterioration can be assessed promptly and specifically through the changes in the relevant vital parameters and symptoms. Values recorded every six months, on the other hand, have little significance. Decompensation can occur suddenly or over a period of several weeks and can take place outside the follow-up intervals. Routine examinations are important, but they only help to identify decompensation early in rare cases. The cardiology professionals described that patients often find it challenging to interpret heart failure-specific symptoms correctly and to act accordingly. This difficulty is also presented in the literature by Lee et al. and Riegel et al. [Lee18][Rie18]. The experts noted that patients sometimes recognize symptoms too late and thus have to seek intensive care. Telemedicine offers the possibility to record and assess relevant vital parameters on a daily basis. This means that therapy can be adjusted at an early stage. Cardiac decompensation requiring hospitalization can thus be prevented, the experts described. All experts emphasized the importance of observing the vital signs of the patients in the course of their treatment. This can also be proven from the literature [Köh19][Sen21].

The experts described typical patterns before decompensation in general terms, see Figure 5.6 under *Symptoms and signs of acute decompensation*. They did not address the types of decompensation classes as defined in the guidelines. The guidelines distinguish the types of decompensation by the presence or absence of signs of congestion and hypoperfusion. Acute decompensations are divided into the clinical profiles: "warm-wet", "cold-wet" and “cold-dry”. Each decompensation type shows different specific symptoms and signs [Pon16]. The extent to which signs of congestion and hypoperfusion can also provide information for early recognition of decompensation in the values recorded by telemonitoring must be examined.

The first two themes, *Progress diagnostics* and *Acute decompensation* describe the algorithms used in clinical practice to classify the health status of heart failure patients and to recognize decompensation based on the most important symptoms and signs. The experts wished to have the same parameters for a telemonitoring system that they had previously defined as relevant, see Figure 5.7. With the help of telemonitoring, the requirement to record vital signs and symptoms daily and to document the course in the home environment can be fulfilled. The experts agreed that a telemonitoring system could improve the quality of care for heart failure patients. The results of the expert interviews on improved quality of care through telemonitoring are in line with the guidelines [AMK19][McD21][Hei22], the presented studies from the fundamentals [Koe18][Ang21][Stö22], the presented telemedicine platforms in the related work [Gmbd][Gmbb][Gmbe], and the statements of Senerath et al. [Sen21].

Furthermore, the experts explained that the use of artificial intelligence could be helpful for the early detection of deterioration. Decision support systems and early warning systems are applications that hold great potential according to the experts. Complex evaluations of large data sets are possible quickly and precisely. With the help of artificial intelligence, resources and costs could be saved in the care of heart failure patients, the experts assumed. This expert statement can be confirmed by already implemented predictive models, see Chapter 4.2 [Pre][Gon21].

Chapter 6

Telemonitoring Data Analysis

Telemonitoring can be used to document and analyze the progressive health status of heart failure patients [Koe18]. Machine learning will be used to investigate and evaluate correlations between health status, measured vital signs, and questionnaire data. The goal is to analyze the telemonitoring data for decompensation patterns in order to detect deterioration in health status at an early stage. The data set used for analysis is described below. In addition, the preprocessing steps, statistical techniques and machine learning algorithms, are described. Different approaches to analyze the health status of heart failure patients are presented, compared and discussed. The first approach evaluates the relationship between vital signs and questionnaire results. The second approach analyzes the association between vital signs and health data from the CARNA data set. The third approach examines the progression of vital signs over the CARNA study period. In each of the subsections, the methods used, the evaluations, and the results of the different approaches are described. Finally, the results are discussed.

6.1 Data Set

The data set used in this work was provided by ProCarement GmbH. It includes telemonitoring data from users of the ProHerz app and data from the CARNA study. The two data sets include the same patients. All patients have diagnosed chronic heart failure. The content of the two data sets is described below.

6.1.1 ProHerz Data Set

The ProHerz data set includes telemonitoring data of heart failure patients, as already described in Section 3.2. The telemonitoring data set contains measurement points of daily measured vital signs, regularly queried validated questionnaires, information on medication intake as well as demographic and medical data of the patients. Data collection took place from April 2021 to March 2022.

The ProHerz data set is a patient self-recorded telemonitoring data set. Patients were educated at the beginning of the study about the correct use of the sensors and how to answer the questionnaires responsibly. Data recording took place in the home environment without professional or medical supervision. Patients were asked to perform daily vital sign measurements and to document medication intake. The regular and conscientious transmission of the data and the completed questionnaires was not equally successful for all patients, which is why some of the patient data records are incomplete.

Vital Parameter Data

The ProHerz telemonitoring data set contains daily measurements of blood pressure, heart rate, blood oxygen saturation, body weight and temperature (see Section 3.2.2). The measurements were collected with CE certified devices from Beurer GmbH. The corresponding devices were provided to the patients by ProCarement GmbH. Values of blood pressure, weight, heart rate, and oxygen saturation were transmitted directly to the ProHerz app via Bluetooth-enabled measuring devices. Only body temperature was measured using an analog thermometer. The temperature values had to be entered manually into the ProHerz app. The measuring devices from Beurer GmbH used to collect the vital signs were:

- Blood pressure monitor BM 54 Bluetooth®, Article number: 65512
- Diagnostic scale BF 720, Article number: 74938
- Pulsoxymeter PO 60, Article number: 45420
- Thermometer FT 09, Article number: 79109

Questionnaire Data

The evaluation of the vital signs data is supplemented by responses to several standardized questionnaires that provide information about the patient's general state of health, daytime sleepiness, general quality of life, and depressive symptomatology. Patients were regularly prompted to complete questionnaires via the app. The data from the questionnaires are part of the ProHerz data set provided. The five questionnaires queried in the ProHerz app are presented below, along with a general description of their analysis.

The *Kansas City Cardiomyopathy Questionnaire* (KCCQ12) is a standardized procedure that uses twelve questions to assess the quality of life of patients with chronic heart failure [Fal05]. The questions are divided into four categories related to physical performance (questions 1-3), frequency of symptoms (questions 4-7), quality of life (questions 8-9), and social limitations (questions 10-12) over the previous two weeks. Responses are entered on a Likert scale. The average score for each category is calculated. The total score is summarized as the average of all four categories. The questionnaire score ranges from 0 to 100, with a low score indicating poor health.

The questionnaire on the *health status of the EuroQol Group (5-level EQ-5D version) (EQ-5D-5L)* can be used to obtain information on the general quality of life on the day of the query via the standardized procedure. In the first part, the questionnaire describes the state of health based on the five dimensions, mobility, self-care, activities of daily living, pain/discomfort, and anxiety/depression. Each dimension is scored on a scale with five response options ranging from ”no problems” to ”extreme problems.” Each dimension is assigned a value. For the evaluation of the questionnaire, the numerical values of the dimensions can be combined to a five-digit number. By combining the answer options, 3125 (55) different health states can be mapped. The health states are transformed into a one-dimensional quality of life index between 0 and 1 using a special algorithm. Here, an index value of 0 describes a very poor health state and an index value of 1 describes the best possible health state. Another evaluation method of the questionnaire is the *Level Sum Score (LSS)*. Here, the answers of the five questions are summed. The score 5 is the best possible result and describes the best possible state of health. The worst possible result is the summed score of 25, which indicates the worst health status.

In the second part of the EQ-5D-5L, the patient estimates his or her current health status on a *visual analog scale (VAS)*. Here, a value of 0 indicates the worst possible health status, while a value of 100 describes the best possible health status [Fou19][Dev20].

The *Epworth Sleepiness Scale (ESS)* is a questionnaire used as a standardized method to assess the risk of daytime sleepiness. The questionnaire uses eight questions to determine patients’ subjective assessment of their likelihood of dozing off or falling asleep in given situations. The questions refer to a normal life in the recent past. The rating is done in an ascending scale with values from 0 to 3. For evaluation, the results are added to a value. The higher the total value determined, the higher the daytime sleepiness of the respondent or average tendency to sleep in daily life. For example, a value of 16 or above indicates a severe sleep disorder with a high health risk [Joh91][Sau07].

The *Whooley Questions for Depression Screening Questionnaire (2FT)*, consisting of two questions, is a standardized procedure to assess the risk of a mental/psychological illness within the previous month. If both questions are answered "yes", this is a serious indication of a mental health problem [Who97].

To better assess mental health symptomatology, a positive response to one or both of the Whooley Questions is followed by the *Mental Health Questionnaire II-Becks Depression Inventory 2 (BDI)*. It is a standardized procedure to assess the severity of depression. In the questionnaire, four statements are given for each of 21 symptoms of depression. From these, the patient selects the statement that is most true for him or her in the past two weeks. The statements are coded with numbers from 0 to 3. The degree of impairment increases from unimpaired at a value of 0 to maximum impairment at a value of 3. For evaluation, the individual values are summed across the symptom areas to form an overall value. A maximum of 63 points can be achieved. A high total score of 29 points or more indicates severely depressive symptoms, whereas a low total score of up to 8 points provides no indication of depression [Her08][Win10].

Medication Intake Data

In the digital medication plan, patients entered the information on taking medication in the ProHerz app. Daily medication intake was documented with the time, medication name, active ingredient, dose, and type of intake, and additional patient comments were stored. The data on medication intake included heart failure-specific medications as well as medications for the treatment of other diseases and dietary supplements.

6.1.2 CARNA Data Set

The CARNA study data set includes data used to evaluate the effectiveness of the ProHerz smartphone application [Rei21]. The data set includes data on health status, quality of life, health literacy, self-care behaviors, and patient participation in medical decision-making. The mentioned evaluation criteria were collected at the beginning and end of the CARNA study period. The interval between each of the two assessments was three months. Enrollment of patients in the study began in April 2021.

6.2 Methods and Evaluation

This section presents the preprocessing of the data, the statistical methods used, the ML-based regression and their evaluations.

6.2.1 Data Preparation

In a first step, the data exported from the ProHerz app and from the CARNA study were made accessible and transformed into a suitable file format for the following data analysis. The raw data set is inconsistent because, for example, measurements are not available for every day, medication intakes were not documented, or patients do not fill out questionnaires. The data set additionally contains data from test subjects that cannot be used for the analysis. Only valid participants were used in the data analysis. Valid participants are patients who participated in both examinations as part of the CARNA study and regularly collected data using the ProHerz app.

Telemonitoring data were not collected in a medically controlled setting. They were self-recorded and transmitted data from patients in the home environment. During preprocessing, false measurements were detected and removed. Outlier detection was performed. Measurements greater than three times the standard deviation were considered spurious and excluded from the data set.

The methodological steps of preprocessing the vital signs and questionnaire data for further analysis are presented below. A z-score normalization of the vital signs was performed. The normalized feature distributions have a mean of zero and a standard deviation of one [Vir20].

The telemonitoring data set provided contains the answers to the individual questions of the five questionnaires. For the analysis of the data set, the scores of the questionnaires were calculated from the individual responses as described in the literature (see Section 6.1). The specific algorithm used to calculate the quality of life index in the EQ-5D-5L questionnaire is a proprietary algorithm of EuroQol Group, which is not published. Therefore, to evaluate the EQ-5D-5L questionnaire, the one-dimensional level sum score was calculated across the five dimensions. Likewise, the value of the VAS scale is used. In order to combine the two parts of the questionnaire, the values of the Level Sum Score and the VAS Score were averaged and summed up to one value in this paper. The calculated total score lies in a range between 0 and 100, with a value of 0 denoting the best possible health status, while a value of 100 describes the worst possible health status.

In order to use the medication intake data for further analysis, some preprocessing steps had to be performed. Medication information had been written down independently by the patients. The information on drug name, active ingredients and dosage noted in free text fields had to be corrected, sorted and standardized. Heart failure-specific medications were identified and filtered out.

Final Data Set

The final data set includes the data of the 64 valid patients. 21 (32.8 %) of the participants were female and 43 (67.2 %) male. The mean age was 61.8 years at the baseline examination, and the mean body mass index (BMI) was 30.4 kg/m^2. Most patients were assigned to intermediate heart failure severity (NYHA II or III). Table 6.1 provides an overview of the patients' demographic and medical data.

Table 6.1: Demographic and medical data of the final data set, which includes 64 patients. SD : standard deviation, n : absolute number.

Data	**Mean ± SD or [%]**	**n**	**[Min, Max]**
Age [years]	61.8 ± 10.7		[32.0, 78.0]
BMI [kg/m^2]	30.4 ± 5.5		[18.6, 46.0]
Male	67.2 %	43	
Smoker	21.9 %	14	
NYHA Class I	1.6 %	1	
II	40.6 %	26	
III	54.7 %	35	
IV	3.1 %	2	

In addition to chronic heart failure, the patients suffered from an average of six other diagnosed diseases. With 68.8 % hypertension (ICD-10: I10) was the most frequently mentioned further diagnosis of the patients. Other frequently mentioned diagnoses were atrial flutter and fibrillation (ICD-10: I48) with 56.2 %, diabetes mellitus (ICD-10: E11) with 34.4 % and disorder of lipid metabolism (ICD-10: E78) with 31.3 %.

ProHerz telemonitoring data include patients' records during the CARNA study period and additional data beyond the study period. The duration of telemonitoring recordings averaged 172 days per patient. Among these, the longest recording period for a patient was 307 days and the shortest was 51 days. In total, the data set includes 59650 documented measurement points. On average, 916 vital sign measurements were taken and recorded by a patient. In addition, the data set includes 1017 completed questionnaires. During the recording period, an average of 17 questionnaires were answered per patient. The data set also includes information on medication intake. In total, the intake of 94908 medications was documented. On average, 1517 medication intake events were recorded per patient using the ProHerz app.

Figure 6.1 shows the course of the measured vital signs and the calculated questionnaire scores on the days of recording for one patient of the data set.

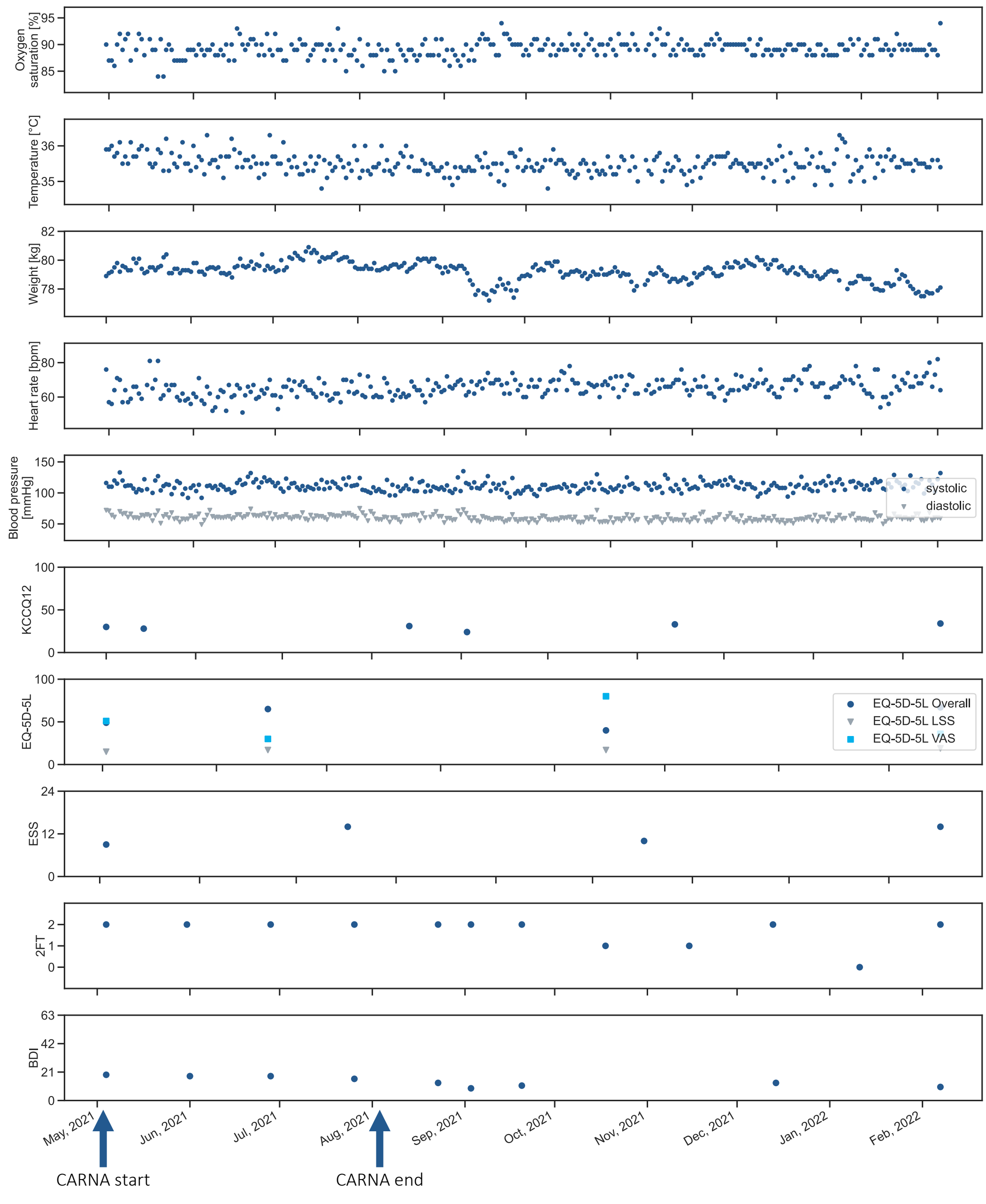


Figure 6.1: Course of the measured vital signs and the calculated questionnaire scores over the recording period for one patient of the data set and date of the CARNA start and end examination.

6.2.2 Statistical Methods

The statistical methods for evaluating correlations between two or more variables are described below. The significance level of $\alpha = 0.05$ was set for all tests. Because of the exploratory data analysis, no multicomparison correction of the significance level was applied [Gel12][Arm14]. The following notation is used to indicate statistical significance in graphs and tables: ns: not significant, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Linear Regression

Linear regression is a statistical method that describes the relationship between two variables [Kut05]. It represents the bivariate linear relationship between an independent variable and a dependent variable. The independent variable is also called the regressor or predictor. The dependence of the two variables is described by a straight line. The method is used under the assumption that there is a linear relationship between the variables. Linear regression can be applied to predict trends in the data. Multiple linear regression, compared to bivariate linear regression, is used to examine the dependence of a dependent variable on several independent variables. Both simple and multiple linear regression calculate the regression equation with the regression coefficient β. The slope β of the regression line describes the trend of the characteristic relationship, an upward trend for $\beta > 0$, a downward trend for $\beta < 0$, or no trend for $\beta = 0$. The coefficient of determination r^2 of the linear regression describes how well the variance of the dependent variable can be explained by the predictor. In addition, the $adjusted\, r^2$ value describes as modified version of the r^2 value. This describes the model accuracy, adjusted for the number of terms in the model. Since the r^2 value tends to estimate the result of the regression too well, the $adjusted\, r^2$ value is additionally used for the evaluation. The r^2 and the $adjusted\, r^2$ can take values in the range between 0 and 1. With an r^2 of 0, the model does not describe the variation in the mean of the dependent variable. A higher r^2 value indicates a better fit of the model to the data being predicted. At a value of 1, all variation in the dependent variable is described by the mean. The p-value of the regression analysis describes the test of the null hypothesis. The null hypothesis makes the assumption that the coefficient is zero. The p-value indicates the significance of the relationship [Kut05]. The analysis is performed using the Python package pingouin [Val18].

Stepwise Backward Multiple Linear Regression

To find the best combination of multiple predictors for optimal prediction of multiple linear regression, a stepwise backward multiple linear regression (SBMLR) was performed. This regression builds a predictive model in which the predictor variables are selected in an automatic, iterative process. Initially, all independent variables are z-normalized and put into backward elimination. Step by step, the least significant regressor is removed from the model until all variables have a p-value below the significance level $\alpha = 0.05$. This analysis finds the best-fitting model for predicting a dependent variable by multiple, selected regressors. Just as in the linear regression method, the regression coefficients β, the p-value, the r^2 value, and the $adjusted\, r^2$ value are output and can be used for evaluation [Hoc76].

Correlation Analysis

Before the statistical analysis of the correlations, the Shapiro-Wilk test is used to test the individual features for the assumption of a normal distribution. If the two features are normally distributed, Pearson correlation is used for the analysis. If the features are not normally distributed, the correlation is calculated using Spearman. The correlation coefficients r of the two methods are in the range of [-1, 1]. A positive sign of the coefficient describes a positive correlation. A correlation coefficient of $r > 0.5$ or $r < -0.5$ defines a high correlation between the data. Smaller values of the coefficient indicate weak to non-existent correlation of the feature data [Muk12]. The Scipy package was used to implement the statistical tests [Vir20].

6.2.3 ML-Based Regression

Machine learning models can identify patterns and correlations in large data sets. The algorithms are trained so that the models make the best decisions and predictions. A distinction is made between classification, which assigns features to a discrete class, and regression, which predicts continuous values [Bis06].

For the analysis of the machine learning based regression, a standard machine learning pipeline was used. The pipeline is composed of a scaling step, feature selection, and regression.

For prediction, three different machine learning based regression models were trained on different feature data: k-nearest neighbors regressor, DecisionTreeRegressor, Support-

VectorRegressor. The different regression models were evaluated using outer five fold cross validation (CV). Within each fold of cross-validation, hyperparameters were optimized using an inner fivefold CV with grid search. The coefficient of determination r^2 was chosen as the target parameter optimization parameter. For each regressor and outer CV fold, the hyperparameter combination that yielded the highest r^2 value was selected. The model was then trained on the entire training data of the respective fold. For evaluation, the model was trained on the test data to calculate the r^2 metric. All machine learning algorithms were implemented and evaluated using the BioPsyKit [Ric21] and scikit-learn [Ped11] libraries.

The feature scaling method is chosen within the hyperparameter tuning. The options are the standard scaler or the MinMaxScaler. The features have a mean of 0 and a standard deviation of 1 after scaling with the StandardScaler. Features transformed with the MinMaxScaler are mapped to the range between 0 and 1. In addition, feature selection is performed to reduce the dimensionality of the feature space. In the context of this work, SelectKBest and recursive feature elimination (RFE) are used. SelectKBest selects the features according to the k highest F-values of the regression task. In RFE, the importance of each feature, using an external estimator, is determined. Recursively, the least important feature is removed until the feature space reaches the predefined size [Ped11].

Nearest Neighbors Regression

For the prediction of continuous data points, neighbour-based regression can be used. In comparison to discrete variables the label is calculated based on the means of the nearest neighbors. The scikit-learn implementation that was used for this thesis prediction is based on the k nearest neighbors of the data point. k is, hereby, defined as an integer value which can be freely chosen. In the basic implementation all k nearest neighbors use uniform weights and thus contribute equally to the prediction. This is implemented into the coding pipeline by using the parameter $\mathrm{weights} = \mathrm{'uniform'}$. Because it might be advantageous to weight data points in close distance more than faraway points, a calculation of weights proportional to the inverse of the distance can be applied. Therefore the parameter $\mathrm{weights} = \mathrm{'distance'}$ is used [Ped11][Cov67][Bra16].

Decision Tree Regression

Decision Trees are non-parametric supervised methods which can be used for both classification and regression problems. Its goal is the creation of a learning model which is able to predict target variables. Decision trees follow the divide-and-conquer principle by learning simple decision rules. Each tree is composed of nodes which encode the binary decisions. The top node of a tree is called root. It represents the input. The bottom nodes are the leaves, which predict the labels or values. During the classification process an instance follows a unique path downwards corresponding to the decision rules until it reaches a leaf of the tree. For implementation the scikit-learn class DecisionTreeRegressor was used. The parameters were set per default as defined in the DecisionTreeRegressor class. The maximum depth of the tree was defined as two or four, which was optimized in the hyperparameter tuning [Ped11][Bre17].

Support Vector Regression

For classification and regression problems a support vector machine can be used. It constructs the optimal linear decision boundaries into a high dimensional space. This best linear decision boundary separates two different classes optimally and also receives good prediction results for unseen data by maximizing the margin. The margin is hereby defined as the distance between the linear decision boundary and its nearest points of each class. The parameter C is the penalty value which can be adapted in the scikit-learn implementation of the SupportVectorRegressor. A large value for C leads to a small margin and overfitting of the data. A small value for C leads to a larger margin. In the hyperparameter tuning the optimal value for C is chosen. The kernel was set to linear or radial basis function [Ped11][Gun98].

6.3 Analysis of Health Status Data

The data set used does not include information on heart failure-related events that provide information on the current health status of patients. Heart failure-related events refer to acute cardiac decompensations, therapy adjustments, hospitalizations, or deaths. Therefore, it is not possible to analyze the telemonitoring data for heart failure-related events or to develop models to predict an event. The data set contains other parameters that can provide information about patient health status.

Data on patient health status can be derived from the five validated questionnaires. However, the questionnaires were answered at irregular intervals and not by all patients to the same extent. Additional data on the health status of all patients were collected at the beginning and end of the 3-month CARNA study period. The NYHA status of the patients was classified by cardiologists. The 6-minute walk test, which is a meaningful measure of physical health, was used to assess patients' exercise capacity below the anaerobic threshold. Medication intake data could also have provided information about the patients' health status. Because the data were not clearly and consistently recorded and the data set did not contain robust records of treatment adjustments, they could not be used for analysis. The following sections describe the various approaches to analyzing the telemonitoring data set. Three research approaches are presented. These are examined using different health status data and adapted methods

6.3.1 Relationship between Vital Parameters and Questionnaire Results

Standardized questionnaires were used to record various dimensions of the health status of the study participants. In this part of the data analysis, the calculated questionnaire scores were used as a quantitative value for health status. The analysis was intended to show whether a relationship between the recorded vital signs and the questionnaire scores could be detected. To find this out, different methods were applied, which should show correlations of the different parameters. In each case, the calculated questionnaire scores were assigned the daily vital signs. If no questionnaire scores were available, the measured vital signs for that day were not used for the analysis.

Since all available scores were described by more than 30 vital sign data, a normal distribution according to the central limit theorem was assumed in the further analysis [Kwa17].

To describe the dependence of questionnaire scores on vital signs, linear regression was calculated across all patients for each combination. The linear regression gives the relationship in terms of the p-value, the r^2 value, and the $adjusted\, r^2$ value. Another approach to determine the correlation between the two parameters is the Pearson correlation. The correlation coefficient and the significance level provide information about the relationship.

Since the methods described so far only show a direct and simple correlation between individual vital parameters and the individual questionnaire results, multiple regression methods were used for further analysis. This makes it possible to describe complex correlations. The correlation analysis of the questionnaire results should be extended by combinations of the vital signs. By using stepwise backward multiple linear regression, a suitable combination of vital signs was identified. This combination of regressors should best predict the questionnaire outcome. Initially, all measured vital signs in the SBMLR served as predictors. Successively, the least significant vital signs were removed. The SBMLR results provide information on the optimal composition of predictors. The p-value, r^2 value, and $adjusted\, r^2$ value were used for the assessment.

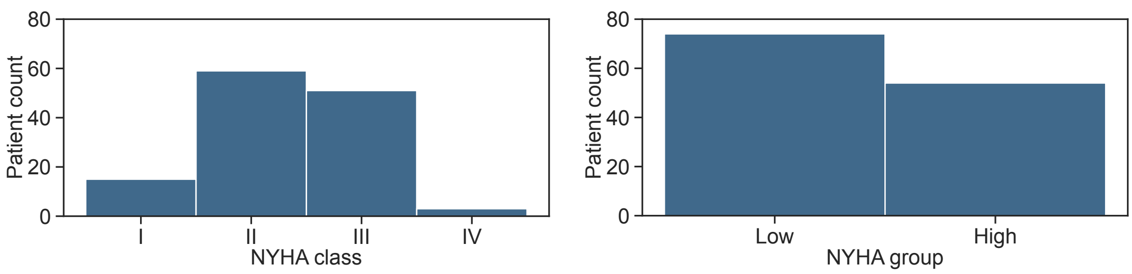
In addition, the prediction of the questionnaire results was investigated using machine learning methods. ML-based regression was applied to estimate the continuous questionnaire results. The six vital signs served as features here. The cross-validation aimed to find the model that best represented and predicted the questionnaire results. The r^2 value provides information about the accuracy of the model. In the cross-validation, the train-test split was performed using the patient identification. This ensures that vital signs of a patient are present in either the training or test data set.

The questionnaires map health status over a defined period of time, as described in Section 6.1. For further analysis, vital sign measurements from each day were averaged over the questionnaire-specific time period. The mean values of the vital signs were calculated for each patient. The four approaches described above were performed again with the calculated mean values. This approach maps the correlation over the questionnaire period. This methodology of averaging was chosen to be able to assign a vital sign result to each questionnaire result. Different numbers of vital sign measurements over the questionnaire interval were compensated for by calculating the mean. Since no exact time specifications are defined for the ESS, a 14-day period was chosen in the analysis. The EQ-5D-5L questionnaire refers only to the current day of processing. Therefore, it does not appear in the analysis of the mean values.

6.3.2 Relationship between Vital Signs and Health Data from the CARNA Data Set

In this part of the analysis, data from the CARNA data set were used to classify patients' health status. NYHA class and distance of the 6-minute walk test were used as quantitative values of health status. These values were collected at the beginning and at the end of the CARNA study. Both values were included in the analysis. The purpose of the analysis was to see if there was a relationship between the recorded vital signs and the health data. To find out, different correlation analysis methods were used.

For the analysis of NYHA status, patients were divided into two classes, *Low NYHA* (corresponding to NYHA I and II) and *High NYHA* (corresponding to NYHA III and IV). This allowed the differences in the number of patients in each NYHA class to be equalized (see Figure 6.2). Grouping allowed meaningful statistical analysis to be performed. The *Low NYHA* group included 74 patients. The *High NYHA* group included 54 patients. Vital signs were averaged over a 14-day period and assigned to the NYHA group. The averaged value of the vital signs represented the health status better than the one-time recorded value of that day. To examine the differences in the groups, a t-test was performed for each averaged vital sign for analysis.



(a) Number of patients grouped by NYHA class (b) Number of patients grouped by *Low NYHA* and *High NYHA*

Figure 6.2: Distribution of patients according to the NYHA classification.

To analyze the distance of the 6-minute walk test in correlation with the measured vital parameters, linear regression, Pearson correlation, and stepwise backward multiple linear regression were performed as in the first part of the data analysis (see Section 6.3.1). Vital signs obtained for the day were assigned to the 6-minute walk test. If vital signs were not available for the day of testing, the data were not included in the analysis. The daily vital signs of all patients were used as predictors to estimate the dependent variable, distance. The range of values of the distance of the 6-minute walk test was from 15.0 to 822.5 meters. Figure 6.3 shows the distribution of distances of all patients.

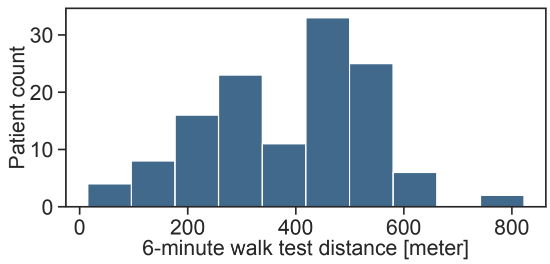


Figure 6.3: Histogram for the distribution of the distance of the 6-minute walk test with number of patients (in meters).

6.3.3 Course of Vital Signs over the CARNA Study Period

The positive effect of the ProHerz app was already described in the report of the CARNA study. The positive effects were shown on the basis of the parameters health status, quality of life, patient self-care and health literacy. The question is whether an improvement can also be determined on the basis of the vital signs recorded in telemonitoring. In this context, the vital signs of the entire study population will be analyzed during the CARNA study period.

Two different approaches were used to examine the data. The first approach used a linear regression over the course of the vital signs. A linear regression line was fitted between the vital signs and the study period for each patient. In each case, the straight lines describe the trend of the vital signs. The regression coefficient β was analyzed for the evaluation. A negative coefficient describes a decrease of the value over time. For the evaluation, the mean value of the regression coefficient β was calculated over all patients. This mean value describes the trend of the vital signs of all patients. Furthermore, the number of positive and negative regression coefficients β was analyzed for the evaluation.

The second approach compared vital signs at the beginning and end of the CARNA study period using a paired t-test. For each patient, the mean of each vital sign was calculated over a 14-day period.

In addition, we aimed to investigate how the progression of vital signs correlated with the change in NYHA class. 32 patients improved their health status, as determined by NYHA class, during the CARNA study period. They could be classified into a lower NYHA class. For 32 patients, the NYHA class remained the same.

The two approaches to analyze the progression of vital signs were performed for both groups of patients and the results were compared.

6.4 Results

This chapter presents the results of the approaches described in Section 6.3.

6.4.1 Relationship between Vital Signs and Questionnaire Results

The main results of the analysis of the relationship between vital parameters and questionnaire results are presented below. In the appendix the whole results of the analysis are shown in detail, see Appendix D.

The significant results of the linear regression and Pearson correlation are shown in Table 6.2. In addition, the number of data points is provided in the table. The two methods, linear regression and Pearson correlation, use the same vital sign data for the analysis. Accordingly, the number of data points does not differ. Significant predictors of the KCCQ12 score are oxygen saturation and diastolic blood pressure. A significant relationship was found between the EQ-5D-5L LSS score and the vital signs oxygen saturation and diastolic blood pressure. The EQ-5D-5L overall score and the ESS Score showed a linear relationship with oxygen saturation. Heart rate and diastolic blood pressure could be found as significant predictors for the BDI score. The most data points available for analysis are for the 2FT score with over 335 data points. No significant p-values are found for the 2FT score. This shows that there is no linear relationship between the individual vital signs on the day of the questionnaire and the 2FT score.

The stepwise backward multiple linear regression SBMLR identifies the appropriate combination of vital signs to predict the different questionnaires. The remaining predictors are correspondingly significant. Because only questionnaire results in which all six vital signs were collected on the recording day were considered, the number of data available for analysis was reduced. SBMLR results for all questionnaires are summarized in Table 6.3.

Table 6.2: Results of linear regression and Pearson correlation with vital signs as the predictor and questionnaire scores as the dependent variable.
$dep.\,var.$: dependent variable, β: regression coefficient, $adj.$: adjusted, p: p-value

		Linear Regression		**Pearson**		**Data**
Predictor	**Dep. var.**	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**size**
Oxygen saturation	KCCQ12	2.293	0.059	0.253	0.000***	191
Diastolic BP	KCCQ12	0.263	0.019	0.156	0.031*	190
Oxygen saturation	EQ-5D-5L LSS	-0.300	0.034	-0.199	0.012*	159
Diastolic BP	EQ-5D-5L LSS	-0.061	0.034	-0.200	0.013*	154
Oxygen saturation	EQ-5D-5L Overall	-1.358	0.026	-0.181	0.023*	159
Oxygen saturation	ESS	-0.302	0.024	-0.173	0.031*	156
Heart rate	BDI	0.262	0.137	0.392	0.004**	53
Diastolic BP	BDI	0.279	0.132	0.386	0.006**	50

Table 6.3: Results of stepwise backward multiple linear regression with vital signs as the predictors and questionnaire scores as the dependent variable.
$dep.\,var.$: dependent variable, β: regression coefficient, $adj.$: adjusted, p: p-value

Predictors	**Dep. Var.**	$\boldsymbol{\beta}$	**adj. r^2**	**p**	**Data size**
Oxygen saturation	KCCQ12	2.189	0.089	0.002**	162
Systolic blood pressure	KCCQ12	0.318	0.089	0.016*	162
Oxygen saturation	EQ-5D-5L LSS	-0.288	0.055	0.027*	134
Diastolic blood pressure	EQ-5D-5L LSS	-0.054	0.055	0.033*	134
Heart rate	BDI	0.266	0.294	0.003**	45
Systolic blood pressure	BDI	0.224	0.294	0.021*	45

The combination of two of the initial six vital signs is significant for the KCCQ12 score. With the two vital signs oxygen saturation and diastolic blood pressure, an $adjusted\ r^2$ value of 0.089 was obtained. For the EQ-5D-5L LSS score, the number of predictors reduced to two. Again, the combination of the two vital signs oxygen saturation and diastolic blood pressure resulted in a significant association with an $adjusted\ r^2$ value of 0.055. For the evaluation of the BDI score, the number of data points decreased to 45. With SBMLR, the combination of heart rate and diastolic blood pressure remained as a significant combination. The $adjusted\ r^2$ value was 0.294. No combination of vital signs allowed significant results to be obtained for the evaluation of the 2FT and ESS scores.

In the following, the results of the correlation analysis of the vital signs averaged over the questionnaire interval are presented (see Table 6.4). Here, the results and significant vital signs of the individual questionnaires differ only slightly from the results of the individual days. Also for the KCCQ12, the two averaged vital signs oxygen saturation and diastolic blood pressure are significant. In contrast to the analysis of the daily data, no significant correlations were found for the averaged parameters for the ESS score. The opposite is true for the correlation analysis of the 2FT score. Whereas no significant correlations were found in the daily updated data, the mean heart rate significantly describes the 2FT score ($p = 0.041$, $adj.\ r^2 = 0.009$, and $r = 0.108$). The averaged heart rate and averaged diastolic blood pressure significantly describe the BDI score with $p = 0.012$ and $p = 0.041$, respectively.

Table 6.4: Results of linear regression and Pearson correlation with mean vital signs as the predictor and questionnaire scores as the dependent variable.
$dep.\ var.$: dependent variable, β: regression coefficient, $adj.$: adjusted, p: p-value

Predictor	**Dep. var.**	**Linear Regression** $\boldsymbol{\beta}$	**adj. r^2**	**Pearson r**	**p**	**Data size**
Mean oxygen saturation	KCCQ12	2.321	0.046	0.224	0.001**	204
Mean diastolic BP	KCCQ12	0.361	0.030	0.186	0.007**	205
Mean heart rate	2FT	0.007	0.009	0.108	0.041*	359
Mean heart rate	BDI	0.314	0.095	0.333	0.012*	56
Mean diastolic BP	BDI	0.255	0.058	0.274	0.041*	56

The SBMLR results of the vital signs averaged over the questionnaire interval are presented below (see Table 6.5). As with the diurnal data, the same combination of vital signs from the averaged values of oxygen saturation and diastolic blood pressure reach significant results for KCCQ12 ($adj.\ r^2 = 0.084$). For the SBMLR of the 2FT, the combination of the averaged values of oxygen saturation and temperature is significant and reaches $adj.\ r^2 = 0.021$. For the other scores, there are either only significant results from individual parameters or no significant results.

ML-based regression using the six vital signs as predictors and the questionnaire results as dependent variables performed very poorly, with consistently negative r^2 values. Table 6.6 shows the results of ML-based regression, the best-performing pipeline, and the size of the feature vector for all questionnaires. A negative r^2 value indicates that the prediction of the model is worse than random guessing. The negative r^2 values describe the very low explained variance of the questionnaire results.

Also for the ML-based regression with the vital signs averaged over the questionnaire period, no model was found that provided a satisfactory result. The mean r^2 values across the five folds were negative for all questionnaires, see Table 6.7.

Table 6.5: Results of stepwise backward multiple linear regression with mean vital signs as the predictors and questionnaire scores as the dependent variable.
$dep. var.$: dependent variable, β: regression coefficient, $adj.$: adjusted, p: p-value

Predictors	**Dep. Var.**	β	**adj. r²**	**p**	**Data size**
Mean oxygen saturation	KCCQ12	2.353	0.084	0.001**	196
Mean diastolic blood pressure	KCCQ12	0.357	0.084	0.008**	196
Mean oxygen saturation	2FT	-0.052	0.021	0.015*	351
Mean temperature	2FT	0.173	0.021	0.023*	351

Table 6.6: Results of the ML-based regression of the questionnaire scores with vital parameters as feature vectors.

Prediction	**Mean r²**	**Std r²**	**Data size**	**Best performing pipeline**
KCCQ12	-0,097	0,083	162	StandardScaler, SelectKBest, SVR
EQ-5D-5L LSS	-0,137	0,047	134	StandardScaler, RFE, SVR
EQ-5D-5L VAS	-0,096	0,054	134	StandardScaler, SelectKBest, SVR
EQ-5D-5L Overall	-0,135	0,052	134	StandardScaler, SelectKBest, SVR
ESS	-0,056	0,019	139	MinMaxScaler, RFE, SVR
2FT	-0,019	0,018	307	MinMaxScaler, SelectKBest, SVR
BDI	-0,489	0,159	45	StandardScaler, SelectKBest, SVR

Table 6.7: Results of the ML-based regression of the questionnaire scores with mean vital parameters as feature vectors.

Prediction	**Mean r²**	**Std r²**	**Data size**	**Best performing pipeline**
KCCQ12	-0,125	0,114	196	StandardScaler, SelectKBest, SVR
ESS	-0,093	0,056	158	StandardScaler, SelectKBest, SVR
2FT	-0,016	0,042	351	StandardScaler, RFE, SVR
BDI	-0,480	0,381	56	MinMaxScaler, RFE, SVR

6.4.2 Relationship between Vital Signs and Health Data from the CARNA Data Set

The results of the association between the NYHA group and vital signs averaged over 14 days can be summarized as follows. Only mean blood oxygen saturation showed a significant difference within *Low NYHA* and *High NYHA* ($p = 0.001$, $Hedges'\,g = 0.687$). All other vital signs showed no significant differences. Figure 6.4 shows the mean vital signs grouped by NYHA group. Patients in the *High NYHA* group were older on average than patients in the *Low NYHA* group ($p = 0.014$, $Hedges'\,g = -0.433$).

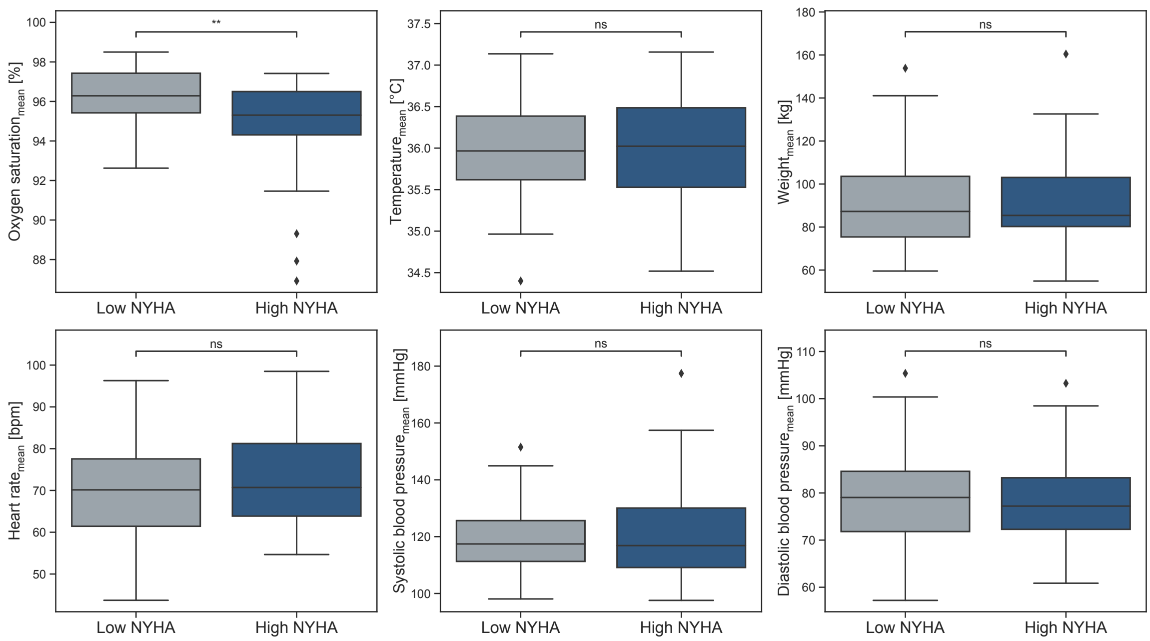


Figure 6.4: Vital parameter differences between the *Low NYHA* and *High NYHA* patient group.

For the linear correlation analysis of the 6-minute walk test distance, between 102 - 119 different vital sign data of all patients were considered. Table 6.8 shows the results of linear regression, Pearson correlation, and number of measurements. Only oxygen saturation and heart rate are significant predictors of correlation with distance. For oxygen saturation, the p-value, Pearson coefficient, and $adjusted\, r^2$ value are $p = 0.010$, $adjusted\, r^2 = 0.047$, and $r = 0.235$, respectively. For heart rate, the calculated values are $p = 0.021$, $adjusted\, r^2 = 0.036$, and $r = -0.212$.

Using SBMLR, a combination of four vital signs was found to predict distance with an $adjusted\ r^2$ value of 0.224, see Table 6.9. The combination of the best predictors is oxygen saturation, heart rate, systolic blood pressure, and diastolic blood pressure.

In addition, age, BMI, and height were shown to be significant predictors of walking distance. Further walking distance was associated with lower age, lower BMI, and greater height.

Table 6.8: Results of linear regression and Pearson correlation with vital signs as the predictor and 6-minute walk test (6mWT) distance as the dependent variable.
β: regression coefficient, $adj.$: adjusted, p: p-value

	Linear Regression		**Pearson**		
Predictor	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**Data size**
Oxygen saturation	15.447	0.047	0.235	0.010*	119
Weight	-0.294	-0.008	-0.044	0.657	102
Heart rate	-2.571	0.037	-0.212	0.021*	117
Diastolic blood pressure	1.379	0.005	0.117	0.217	114
Systolic blood pressure	-1.428	0.015	-0.154	0.101	115

Table 6.9: Results of stepwise backward multiple linear regression with mean vital signs as the predictors and 6mWT distance as the dependent variable.
β: regression coefficient, $adj.$: adjusted, p: p-value

Predictors	$\boldsymbol{\beta}$	**adj. r^2**	**p**	**Data size**
Oxygen saturation	17.339	0.224	0.005**	87
Heart rate	-2.887	0.224	0.013*	87
Diastolic blood pressure	3.293	0.224	0.021*	87
Systolic blood pressure	-4.706	0.224	0.000***	87

6.4.3 Course of Vital Signs over the CARNA Study Period

Linear regression coefficient analysis shows the trend of vital signs over time. The results are summarized in Table 6.10. Here, the value *Mean coefficient* describes the mean value of the regression coefficients over all patients. The value *Mean of sign of coefficient* describes the number of positive and negative regression coefficients β and presents it as the mean of the sign of the regression coefficient over all patients.

Table 6.10: Results of linear regression over the course of vital signs. *mean coefficient*: mean of regression coefficients β over all patients, *mean of sign of coefficient*: mean distribution of sign of regression coefficient β over all patients (Mean $\pm$ standard deviation)

Vital parameter	**Mean coefficient β**	**Mean of sign of coefficient**
Oxygen saturation	0.007 ± 0.016	0.531 ± 0.854
Temperature	0.001 ± 0.006	0.016 ± 1.008
Weight	-0.008 ± 0.024	-0.094 ± 1.003
Heart rate	0.026 ± 0.108	0.250 ± 0.976
Diastolic blood pressure	-0.038 ± 0.088	-0.469 ± 0.890
Systolic blood pressure	-0.035 ± 0.117	-0.344 ± 0.946

It can be seen from the linear regression coefficients that both systolic and diastolic blood pressure and body weight decreased over the CARNA study period. Heart rate and blood oxygen saturation increased, while body temperature remained nearly the same.

The paired t-test can also be used to read and evaluate the trend in vital signs. Figure 6.5 shows the results of the statistical evaluation procedure.

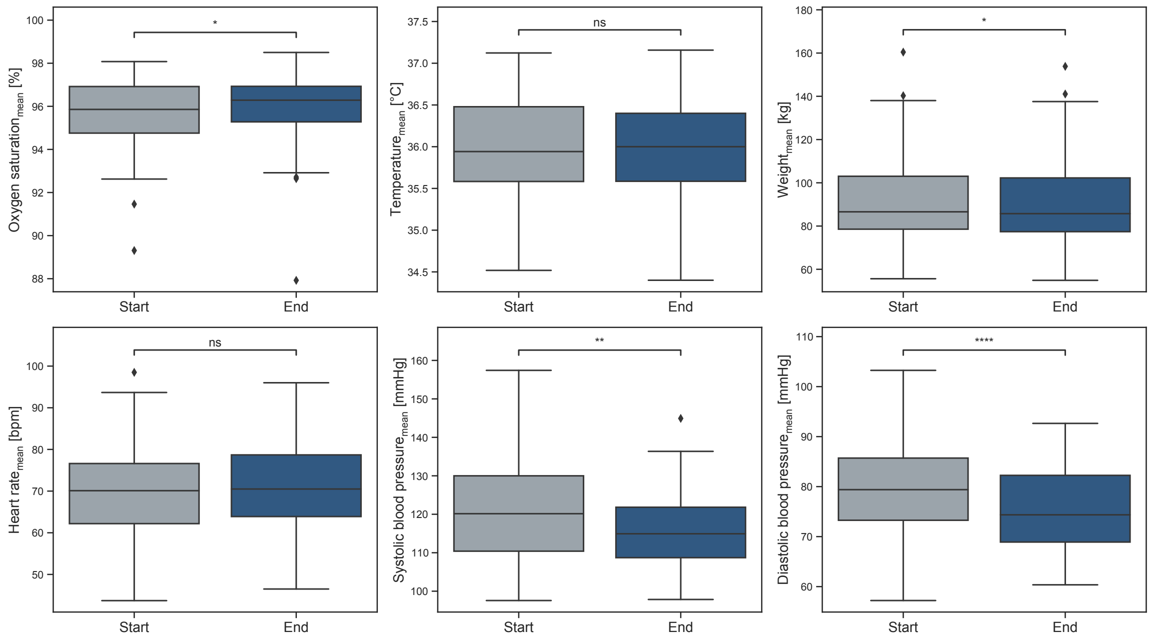


Figure 6.5: Vital parameter differences between the start and the end of the CARNA study period.

Over the study period, blood pressure values fell strongly significant. The mean systolic blood pressure value dropped from 120.7 to 116.4 mmHg ($p = 0.003$, $Hedges'\,g = -0.350$). Mean diastolic blood pressure value decreased from 79.5 to 75.2 mmHg ($p = 0.000$, $Hedges'\,g = -0.489$). A significant reduction was also seen in body weight. The mean weight at the beginning was 91.1 kg, whereas it was 90.5 kg at the end ($p = 0.020$, $Hedges'\,g = -0.029$). Mean blood oxygen saturation increased significantly from 95.6 % to 95.9 % ($p = 0.018$, $Hedges'\,g = 0.191$). No significant changes were recorded in the heart rate and body temperature variables.

Analysis of the linear regression coefficients grouped by patients with and without change in NYHA class showed that the patients with improved NYHA class had a greater change in vital signs. Vital signs changed in the group of patients with improved NYHA class in the same way as in the analysis of the whole population, as described above. However, a much stronger trend is seen in the coefficients of the regression line. All results grouped by patient group are shown in Table 6.11.

Table 6.11: Results of linear regression over the course of vital signs grouped by patients with and without change in NYHA class. *mean coefficient*: mean of regression coefficients β over all patients, *mean of sign of coefficient*: mean distribution of sign of regression coefficient β over all patients (Mean ± standard deviation)

	NYHA no change		**NYHA change**	
Vital parameter	**Mean Coefficient β**	**Mean of sign**	**Mean Coefficient β**	**Mean of sign**
Oxygen saturation	0.007 ± 0.016	0.500 ± 0.880	0.007 ± 0.016	0.562 ± 0.840
Temperature	0.000 ± 0.007	0.097 ± 1.012	0.001 ± 0.005	-0.062 ± 1.014
Weight	0.000 ± 0.020	0.188 ± 0.998	-0.015 ± 0.025	-0.375 ± 0.942
Heart rate	0.037 ± 0.127	0.375 ± 0.942	0.016 ± 0.085	0.125 ± 1.008
Systolic BP	-0.007 ± 0.107	-0.188 ± 0.998	-0.064 ± 0.121	-0.500 ± 0.880
Diastolic BP	-0.011 ± 0.097	-0.188 ± 0.998	-0.065 ± 0.070	-0.750 ± 0.672

Also with the second approach to compare vital signs at the beginning and at the end of the study period, a difference between the patient groups can be seen. While no significant changes were seen in the patients with NYHA class remaining the same, significant changes in vital signs were seen in the patient group with improved NYHA class (see Figure 6.6). Mean blood pressures improved from 122.5 / 80.2 mmHg to 115.8 / 74.6 mmHg ($p = 0.002$, $Hedges'\,g = -0.477$ (systolic) / $p = 0.000$, $Hedges'\,g = -0.612$ (diastolic)). Weight decreased significantly by the mean value of 1.2 kg ($p = 0.010$, $Hedges'\, g = -0.055$).

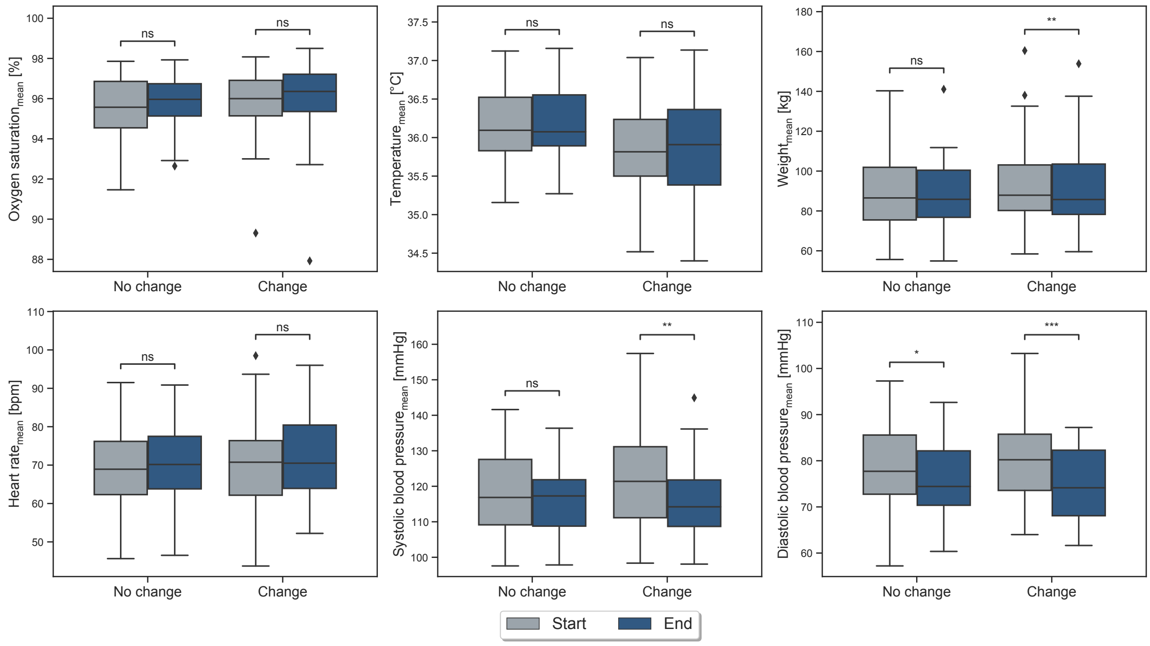


Figure 6.6: Vital parameter differences between the start and the end of the CARNA study period, grouped by patients with no change (*no change*) and patients with change in the NYHA class over the CARNA study period (*change*).

6.5 Discussion

The aim of the analysis of the telemonitoring data set was to find correlations between health status, the measured vital signs, and questionnaire data. In this section, the presented results of the three approaches are evaluated and discussed. Subsequently, additional parameters for the assessment of health status and the development of an early warning system are presented and discussed.

6.5.1 Relationship between Vital Signs and Questionnaire Results

To show a correlation between the recorded vital signs and the questionnaire results, a correlation analysis was performed. With the correlation analysis some significant dependencies could be found. These correlations are discussed and evaluated below.

In the analysis of the general quality of life questionnaire for heart failure patients (KCCQ12), the significant results showed that with higher oxygen saturation and higher diastolic blood pressure, the KCCQ12 score is higher and thus can be described by a linear relationship. The higher the KCCQ12 score, the higher the quality of life is classified. However, only 5.9 % and 1.9 % of the variability of the KCCQ12 score in the data set can be explained. With multiple predictors and the combination of the two vital signs, 8.9 % of the variability can be described. Analysis of the vital sign mean scores also yields similar correlation coefficients and variabilities for the two parameters.

Similar results are obtained from the analysis of the EQ-5D-5L LSS score, general quality of life questionnaire. Again, similar correlations are shown. A decreased value of oxygen saturation and a lower diastolic blood pressure indicate a worse quality of life index. The $adjusted\ r^2$ value and Pearson coefficient, however, show only a weak correlation. The correlation between oxygen saturation and questionnaire scores can be explained logically. High values of blood oxygen saturation are generally associated with normal performance in medicine. Low blood pressure values are generally an indicator of a healthy heart. However, according to the results listed, an elevated diastolic blood pressure value indicates a better quality of life. Medically, this cannot be explained.

Although most of the data points for the mental health questionnaire (2FT) consisting of two questions were available, no correlations between the questionnaire scores and vital parameters could be found in the analysis. Thus, the outcome of the 2FT score cannot be described or predicted by the vital signs.

The correlation analysis of the BDI, to the mental health of the patients, showed the best results. The heart rate and diastolic blood pressure indicate a moderate linear relationship with the BDI score. The Pearson coefficient considered is 0.392 and 0.386. Vital signs can explain 13.7 % and 13.2 % of the variability of the BDI score in the data set.

From a medical point of view, the elevation of both parameters indicate increased stress and mental strain and thus decreased cardiac health [Tae09]. By increasing the parameters, higher BDI and thus poorer mental health status can be predicted based on the analysis. The results with the highest correlation were obtained by the smallest number of data points. Only 53 data points were available for analysis of the BDI score. In addition to the moderate correlations, the results have little significance due to the small number of measurement points.

The significance of the results as a whole is limited by various influencing factors. For example, the number of questionnaires answered varied from patient to patient. In the analysis performed, all available questionnaire results were included. Patients who answered questionnaires more frequently were consequently weighted more heavily in the analysis, which can lead to a bias in the results. Patient body weight as a dependent variable never correlates with questionnaire results. Neither heavier nor lighter patient weight indicates a better quality of life index. The absolute values of weight used are not suitable for prediction. It can be assumed that the change in body weight could influence the results of the questionnaires. Severe deterioration in health status is often accompanied by rapid weight gain in heart failure patients [BÄK19].

No temporal changes in vital signs of individual patients were considered in the analysis. These could provide information about improvement or deterioration in health status and changes in questionnaire scores. The five questionnaires ask questions about many symptoms, different life domains, performance impairments, and physical and psychological dispositions. The questionnaire scores thus represent health status in a complex manner. The vital signs recorded cannot describe this complexity.

In conclusion, the discrete vital signs are not suitable for describing and predicting a relationship to health status derived from the questionnaires.

6.5.2 Relationship between Vital Signs and Health Data from the CARNA Data Set

Vital signs were expected to differ in their expression according to NYHA class. In order to predict the health status of heart failure patients, which is represented in this model by the NYHA groupings, *Low NYHA* and *High NYHA*, the collected averaged vital signs are not sufficient. Only oxygen saturation showed a significant association with NYHA grouping. Higher blood oxygen saturation was associated with the *Low NYHA* group. Individual vital signs are an insufficient predictor of NYHA classification. The lack of association may be explained by the fact that NYHA classes are defined on the basis of heart failure symptomatology. The assumption that NYHA classification and vital signs correlate could not be confirmed. Limiting factors for the inconclusive results could be, on the one hand, the small study population and, on the other hand, the uneven distribution of NYHA classes within the groups, see Figure 6.2(a). The *High NYHA* group contained mainly NYHA class III patients, whereas the *Low NYHA* group was composed of NYHA classes I and II patients.

Physical performance assessed by the walking distance of the 6-minute walk test showed a linear relationship to oxygen saturation and heart rate. Multiple linear regression of the four vital signs, oxygen saturation, heart rate, systolic and diastolic blood pressure can predict walking distance. These results show that with the collection of vital signs, prediction of 6-minute walk distance is possible to some extent. As described in the literature, walking distance can be used as a predictor of the health status of heart failure patients [Gia19]. Thus, the above vital signs could also be sufficient predictors of the health status of heart failure patients.

6.5.3 Course of Vital Signs over the CARNA Study Period

The analysis of the vital signs over the course shows that both approaches reflect the trends of the vital sign changes to the same extent. However, the first approach with the analysis of the regression coefficients can only show the trends. By using the second approach with the pairwise t-test, it is also possible to describe the significance of the differences.

A decrease in systolic and diastolic blood pressure over the CARNA study period can be considered a positive effect of telemonitoring on health status. The load on the heart is thus reduced and the risk of secondary diseases triggered by hypertension decreases [Org21].

The proven reduction in body weight by an average of 0.6 kg over the CARNA study period also has a positive effect on the patients' state of health. Increasing blood oxygen saturation indicates improved functional capacity of the heart and lungs, indicating greater exercise capacity and resilience. That no significant improvement is seen in the mean heart rate cannot be related to the results already listed. That body temperature showed no change on average over the study period was to be assumed.

The results grouped by patients and their changes in NYHA class over the study period showed that patients with improved NYHA class had significantly greater changes in vital signs. In particular, body weight dropped significantly over the course of the study. Blood pressure levels also decreased significantly compared to the patient group without NYHA class change. That the patient group without NYHA class change did not show significant improvements in vital signs was to be assumed and was confirmed by the analysis.

All of the vital sign changes shown contribute to the improvement in health status. The risk for cardiac decompensation is thus reduced. In the report of the CARNA study, the improvement in health status, quality of life, patient self-care, and health literacy was demonstrated [Rei21]. This positive effect of the ProHerz app was additionally proven by the evaluation of the vital signs.

Chapter 7

Discussion

The aim of this work was to analyze the progressive health status of heart failure patients in order to detect cardiac decompensation at an early stage using machine learning techniques. In the following, the results of the patient survey and expert interviews and the results of the telemonitoring data analysis are combined and discussed. The synthesis of the three parts of the paper highlights additional parameters for health status assessment and may enable the development of a reliable early warning system.

Recommendations and ideas are presented to make future prediction of decompensations possible within the ProHerz app. These suggestions for improvement emerged from the work. In answering the research questions, other important parameters were identified that are not yet part of the ProHerz telemonitoring application. Suggestions are made for future data collection within the ProHerz app that may help improve health status analysis.

During the patient survey, expert interviews, and literature review, in addition to the values recorded by the ProHerz app, important characteristics were identified that can improve the assessment of health status, see Table 5.4 and Figures 5.5, 5.6, and 5.7. The complex syndrome of heart failure can only be assessed based on a large number of symptoms and signs [AMK19][McD21][Hei22][Sen21].

The following are examples of relevant parameters that can be recorded telemedically and that could expand the health application. All examples have evolved from the research topics and have been found to be relevant. Equivalent approaches can be found in the literature, reinforcing the importance and significance. With the help of a symptom diary, changes in symptomatology can be detected and recorded in a simple, targeted and patient-specific manner, see also [Lee18]. The identified symptom groups, see Table 5.4, map the symptomatology holistically and provide information about worsening as frequency, severity, and distress increase. In addition, regular records of voice and breathing can detect water accumulation in the lungs and analyze breathing rate, see also [Ami22]. Recording an electrocardiogram allows changes in cardiac activity to be detected. Interesting values that can be read from the ECG are, for example, the detection of atrial fibrillation or cardiac arrhythmias [AMK19]. Records of daily activities and exercise can motivate and lead to an improvement in resilience in everyday life. In addition, daily records can identify worsening as activity decreases, see also [Wal97]. Analysis of sleep, with values for sleep quality, sleep length, and nocturnal urination, can also provide other important parameters, see also [Red05]. Smartwatches provide an easy way to record ECGs, daily activities, and sleep in the domestic setting. Data from smartwatch recordings provide medically meaningful results [Hav19]. Consistent and complete documentation of medication intake can be used to assess adherence and therapy adjustments, see also [Boy14]. It is relatively easy to record all these values in the home environment. Analysis of these other values can help detect deterioration in health further in advance and act as an early warning system.

More advanced results developed from data analysis of the ProHerz telemonitoring data set are presented below. The more data available, the more accurately models can learn information from telemonitoring data. The models can thus lead to better predictability of decompensations. More data can be obtained over a larger number of patients and over a longer admission period. The quality of the data can be increased with more regular recordings. A larger data set is more likely to include data on patient deteriorations and acute cardiac events, such as decompensations, hospitalizations, or deaths. This information must be noted in the form of labels in the data set. Important information that should be included in the data set to implement an early warning system is:

- Cardiac decompensation
- Hospitalizations as a result of heart failure
- Deaths
- Reference values after hospital discharge
- Regular NYHA classification by a physician
- Transmission of clinical data from follow-up controls
- Therapy adjustments

Chapter 8

Conclusion and Outlook

The aim of this work was to analyze the health status of heart failure patients based on telemonitoring data using machine learning algorithms. Deterioration in health status indicates impending cardiac decompensation. Early detection of cardiac decompensation should help reduce mortality in patients with chronic heart failure, prevent hospitalizations, and reduce medical costs. Several predictive models for early warning systems have been described in the literature. Koehler et al., Larburu et al., and Gontarska et al. presented models that successfully predict heart failure-specific events based on noninvasive telemonitoring data, thereby reducing rehospitalizations [Koe18][Lar18][Gon21].

Since heart failure is a very complex clinical syndrome, the research topic of reliably assessing health status and thus predicting decompensation at an early stage was considered from different angles. To identify relevant parameters, heart failure patients were surveyed and expert interviews were conducted with cardiologists.

Through the patient survey, it became clear that subjectively perceived symptoms serve as a distinction between stable chronic heart failure and acute heart failure. The symptom groups decreased performance, dizziness, sleep problems, breathing problems, heart problems, water retention, psychological problems and digestive problems were identified. These represent the symptomatology of heart failure in a holistic and descriptive way. The most relevant symptoms of the symptom groups serve as predictors of health status. The most relevant symptoms identified were: decreased resilience, dizziness, waking up at night, shortness of breath, palpitations, swelling of legs or feet, nervousness/restlessness, digestive problems.

When these symptoms increase in frequency, severity, and distress, they provide information about a deterioration in health. Thus, the progression of symptoms is a meaningful indicator of the progression of heart failure. The main outcome of the patient survey is that recording and evaluating symptoms in a symptom diary can improve the assessment of health status and make deterioration visible at an early stage. Implementing a symptom diary in the ProHerz app is beneficial.

To identify relevant parameters, heart failure patients were questioned and expert interviews were conducted with cardiologists. Patient surveys allowed subjectively perceived symptoms to be included in the analysis to distinguish stable chronic heart failure from acute heart failure. Symptom groups were defined to capture the symptomatology of heart failure in a holistic and descriptive manner. The most relevant symptoms in the symptom groups serve as predictors of health status. As these symptoms increase in frequency, severity and distress, they provide information about deterioration.

The expert interviews allowed valuable evidence- and experience-based knowledge to be included in the analysis for assessing the health status of heart failure patients. The experts emphasized the importance of recording the progression of the disease through regularly recorded values. Telemonitoring is an important tool for early detection of deterioration. With the relevant data regularly recorded in telemonitoring, the state of health can be assessed more holistically than is possible with a six-monthly follow-up check. The experts made it clear that no universally valid patterns for imminent decompensation can be described, since acute deterioration in heart failure can vary greatly from patient to patient. The two methods produced complementary results. It became clear that only by using a variety of parameters and symptoms can the health status be reliably and meaningfully assessed. Only by linking qualitative characteristics and quantitative values can the complexity of heart failure be captured. Only the progression of vital signs in combination with the progression of symptoms can predict deterioration early and with certainty.

Telemonitoring data were analyzed using statistical methods and machine learning techniques for the research topic, early detection of decompensation. The data set used in the work, the ProHerz app from ProCarement GmbH, did not contain information on decompensations, hospitalizations, or deaths. Because the data set contained information on patients' health status in the form of questionnaire results, NYHA classifications, and the walking distance of the 6-minute walk test, the research objective was related to this health information.

Only weak or no correlations were found between the discrete vital signs data and the recorded questionnaire scores using correlation analysis. The analysis showed that vital signs did not differ among NYHA classes. Vital signs cannot be used to predict NYHA class. The walking distance determined in the 6-minute walk test can be estimated by using the vital signs as predictors. The improvement of the health status could be shown over the course of the vital parameters. Relevant parameters and their trends were lower blood pressure, decreased body weight, and increased blood oxygen saturation. Although it was shown that trends in the vital signs recorded by telemedicine can provide information about the state of health, this correlation is not sufficient to reliably predict the state of health.

The results of the patient survey, the expert interviews, and the exploratory data analysis make it clear that time series analysis could provide important information for assessing health status. A combination of multiple vital signs values could reveal progressive deterioration over time. Single values or the combination of values at single, specific time points do not serve as predictors of health status. In clinical practice, many different symptoms and signs are recorded diagnostically to assess the progressive health status of chronic heart failure. Diagnostic methods include laboratory tests, cardiac ultrasound, ECG, chest radiograph, and echocardiography. The five vital signs recorded in the home setting, heart rate, blood pressure, oxygen saturation, body weight, and body temperature, have limited value. Nevertheless, analysis of noninvasive telemonitoring data, as previously described, is a promising approach to reliably assess the health status of patients with chronic heart failure. The findings of this work could help to implement an early warning system for deteriorating health status in the ProHerz app after further research. In the future, personalized thresholds that are also adjusted over time and progression could provide better predictions. In addition, time series analyses could provide accurate and personalized health status predictions. Decompensations could thus be detected and assessed far in advance using machine learning techniques. Alarms for risk assessment and recommendations for therapy adjustments could thus be automated.

Appendix A

Patents

System and Method for Heart Failure Prediction

Publication Number	US20110119078A1
Date of Publication	May 19, 2011
Inventors	Gadi Cotter, Chapel Hill, Beth Davison Weatherley
Assignee	Momentum Research, Inc., Durham, NC (US)
Abstract	A method for monitoring a health status of a human subject includes the capturing of medical data concerning the health of the subject at defined intervals using a questionnaire. The questionnaire provides a standard script for data capture. Part of the captured data is constrained to a Likert scale while other data is on a visual analog scale. The captured data further includes an assessment by a physician of health symptoms of the subject. The captured data is input into a computer, provided to an algorithm that is configured to assess a risk of acute heart failure. The risk of acute heart failure is computed using the algorithm and the captured data from a plurality of the defined intervals. In one method, the health status of the subject as being either improved or worsening is output to the physician as a function of a value of the computed risk. In another method, a survival function outcome for the subject is predicted using the output of the algorithm.

Method and System for Treating Cardiovascular Disease

Publication Number	US20140330143A1
Date of Publication	November 6, 2014
Inventors	Jason Kroh, Erik Moore, Tamara Scholz, Adriane Durey, Jason White, Khin Khin Lay-Khan
Assignee	CardioMEMS, INC., Atlanta, GA (US)
Abstract	A system and method for treating congestive heart failure in a patient, including: implanting at least one pressure sensor in a desired location within the patient; providing an ex-vivo interrogation system and monitoring system that can be configured to optionally affect at least one of: selectively energizing the at one pressure sensor, receiving a return or output signal from the at one pressure sensor, processing the return signal, and displaying processed data derived from the at least one pressure sensor to a physician. The system and method also includes deriving diagnostic and treatment information from the processed data and sending diagnostic and treatment information to the patient.

Appendix B

Patient Questionnaire - Heart Failure Symptoms

A. Prominent Symptoms Prior to Decompensation

1. How do you notice that your heart failure health is deteriorating? What is the first/most noticeable symptom you observe when heart failure worsens?

B. Symptom Query

The symptom query is divided into two time periods.

- Period 1: symptoms in acute heart failure (i.e., before your last hospitalization, before decompensation, before severe deterioration).
- Period 2: Symptoms in stable chronic heart failure (i.e. everyday symptoms)

Please rate the following symptoms during the indicated time period.
The complete symptom list and query can be seen in Figure B.1.

Did you have the following symptoms during the specified period?	I did not have this symptom.	IF YES. How often did the symptom occur?				IF YES. How severe did the symptom occur?				IF YES. How distressing was the symptom?			
		hardly	rarely	more often	very often	slightly	moderately	strongly	very strongly	not at all	a little	moderately	strong
Physical Symptoms													
Shortness of breath		1	2	3	4	1	2	3	4	1	2	3	4
Difficulty breathing while lying down		1	2	3	4	1	2	3	4	1	2	3	4
Difficulty breathing during the night		1	2	3	4	1	2	3	4	1	2	3	4
(Nocturnal) cough		1	2	3	4	1	2	3	4	1	2	3	4
Breathlessness		1	2	3	4	1	2	3	4	1	2	3	4
Rattling, bubbling sounds when breathing		1	2	3	4	1	2	3	4	1	2	3	4
Decreased performance		1	2	3	4	1	2	3	4	1	2	3	4
Fatigue/ drowsiness		1	2	3	4	1	2	3	4	1	2	3	4
Difficulty sleeping		1	2	3	4	1	2	3	4	1	2	3	4
Waking up at night		1	2	3	4	1	2	3	4	1	2	3	4
Decreased resilience		1	2	3	4	1	2	3	4	1	2	3	4
Increased recovery time after physical activity		1	2	3	4	1	2	3	4	1	2	3	4
Chest pain or pressure		1	2	3	4	1	2	3	4	1	2	3	4
Palpitations		1	2	3	4	1	2	3	4	1	2	3	4
Swelling of legs or feet		1	2	3	4	1	2	3	4	1	2	3	4
Increase in abdominal girth		1	2	3	4	1	2	3	4	1	2	3	4
Problems with sexual interest or activity		1	2	3	4	1	2	3	4	1	2	3	4
Dizziness		1	2	3	4	1	2	3	4	1	2	3	4
Increased cold sweat		1	2	3	4	1	2	3	4	1	2	3	4
Brief loss of consciousness (syncope)		1	2	3	4	1	2	3	4	1	2	3	4
Feeling of fullness		1	2	3	4	1	2	3	4	1	2	3	4
Flatulence (meteorism)		1	2	3	4	1	2	3	4	1	2	3	4
Digestive problems		1	2	3	4	1	2	3	4	1	2	3	4
Weight gain		1	2	3	4	1	2	3	4	1	2	3	4
Weight loss		1	2	3	4	1	2	3	4	1	2	3	4
Nausea or vomiting		1	2	3	4	1	2	3	4	1	2	3	4
Loss of appetite		1	2	3	4	1	2	3	4	1	2	3	4
Nighttime urination (nocturia)		1	2	3	4	1	2	3	4	1	2	3	4
Psychological Symptoms													
Sadness		1	2	3	4	1	2	3	4	1	2	3	4
Nervousness/restlessness		1	2	3	4	1	2	3	4	1	2	3	4
Depressed mood		1	2	3	4	1	2	3	4	1	2	3	4
Forgetfulness		1	2	3	4	1	2	3	4	1	2	3	4
Irritability		1	2	3	4	1	2	3	4	1	2	3	4
Difficulty concentrating		1	2	3	4	1	2	3	4	1	2	3	4
Other Symptoms													
Other symptoms... Which?		1	2	3	4	1	2	3	4	1	2	3	4

Figure B.1: Query of heart failure-specific symptoms by occurrence, frequency, severity, and burden.

C. Future - Symptom Diary

1. Can you imagine an app-based symptom diary helping you assess your health?
   A symptom diary could use an app to record symptoms that occur daily and ask about frequency, severity, and burden.
2. How do you currently keep track of your daily symptoms?
3. Do you have difficulty recognizing disease-specific symptoms?
4. For ProHerz app users: Has your ability to recognize symptoms improved as a result of using the ProHerz app?
   For other patients: Has your ability to recognize symptoms improved through educational discussions (e.g., with your doctor)?

Appendix C

Interview Guide - Expert Interviews

Questionnaire for a qualitative interview to identify relevant symptoms and signs of heart failure through evidence- and experience-based expert knowledge

A. Expert Background Information

1. How many years have you worked in the field of cardiology?
2. What degree, title, rank do you have?
3. Where is your current area of practice?
4. Do you have any continuing education in heart failure?

B. Symptoms and Signs of Chronic Heart Failure

1. Which and how many values do you look at when a patient comes to you for a routine checkup?
2. In addition to the standardized characteristics, do you see other relevant values that can provide information about the health status of a heart failure patient, such as out-of-hospital parameters (related to exercise, sleep, ...).

The following questions refer to acute decompensation of heart failure, meaning rapid deterioration of cardiac output.

3. Are there any characteristics by which you can reliably assess the health status of acute decompensated heart failure? If so, which ones?

4. Do you see any typical patterns by which you can determine impending decompensation?
5. How much in advance can you predict an impending acute decompensation?
6. How often does a patient with heart failure visit your practice? At what interval do you see your patients?

C. Physician-Patient Relationship

1. Who normally recognizes worsening heart failure first - patient or physician?
2. How would you rate your patients' ability to recognize symptoms independently and early? Which?
3. Which symptoms are patients unable to assess at all or very poorly?
4. Which symptoms can patients recognize particularly well in return?

D. Telemonitoring

Thought experiment - telemonitoring for heart failure patients: Imagine a system that helps heart failure patients in their daily lives. The system records key patient vital signs on a daily basis and could detect early deterioration in health. Such an app could be used to track symptoms and possibly transmit readings directly via Bluetooth-connected devices.

1. What values/parameters do you think are useful and relevant to include/collect in such telemonitoring to reliably assess patients' health status?
2. What symptoms do you think would be possible to include/assess via a telemonitoring system?
3. To assess which symptoms is it necessary to see the patient on site?
4. To what extent and at what point can telemonitoring systems facilitate/support regular physician visits?
5. Where do you see the potential for AI in the care of heart failure patients? Where can AI enrich the care of heart failure patients? Where can AI enrich you in your care of heart failure patients?

Appendix D

Additional Tables

Results - Telemonitoring Data Analysis - Relationship between Vital Signs and Questionnaire Results

Table D.1: Results of linear regression and Pearson correlation with vital signs as the predictor and KCCQ12 score as the dependent variable.
β: regression coefficient, $adj.$: adjusted, p: p-value

	Linear Regression		**Pearson**		
Predictor	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**Data size**
Oxygen saturation	2.293	0.059	0.253	0.000***	191
Temperature	-2.624	0.000	-0.073	0.305	199
Weight	0.005	-0.005	0.005	0.943	200
Heart rate	-0.008	-0.005	-0.005	0.941	193
Diastolic blood pressure	0.263	0.019	0.156	0.031*	190
Systolic blood pressure	0.046	-0.004	0.037	0.610	191

Table D.2: Results of linear regression and Pearson correlation with vital signs as the predictor and EQ-5D-5L scores as the dependent variable.
$dep.\,var.$: dependent variable, β: regression coefficient, $adj.$: adjusted, p: p-value

		Linear Regression		**Pearson**		**Data**
Predictor	**Dep. var.**	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**size**
Oxygen saturation	LSS	-0.300	0.034	-0.199	0.012*	159
Temperature	LSS	0.334	-0.003	0.060	0.459	155
Weight	LSS	0.008	-0.004	0.049	0.544	158
Heart rate	LSS	0.003	-0.006	0.010	0.896	157
Diastolic blood pressure	LSS	-0.061	0.034	-0.200	0.013*	154
Systolic blood pressure	LSS	-0.020	0.001	-0.088	0.276	154
Oxygen saturation	VAS	1.207	0.013	0.139	0.081	159
Temperature	VAS	-1.056	-0.005	-0.033	0.683	155
Weight	VAS	0.021	-0.006	0.023	0.779	158
Heart rate	VAS	0.035	-0.006	0.022	0.788	157
Diastolic blood pressure	VAS	-0.069	-0.005	-0.041	0.615	154
Systolic blood pressure	VAS	-0.075	-0.003	-0.059	0.467	154
Oxygen saturation	Overall	-1.358	0.026	-0.181	0.023*	159
Temperature	Overall	1.363	-0.004	0.049	0.543	155
Weight	Overall	0.008	-0.006	0.010	0.902	158
Heart rate	Overall	-0.012	-0.006	-0.009	0.911	157
Diastolic blood pressure	Overall	-0.118	-0.000	-0.080	0.324	154
Systolic blood pressure	Overall	-0.013	-0.006	-0.011	0.888	154

Table D.3: Results of linear regression and Pearson correlation with vital signs as the predictor and ESS score as the dependent variable.
β: regression coefficient, $adj.$: adjusted, p: p-value

	Linear Regression		**Pearson**		
Predictor	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**Data size**
Oxygen saturation	-0.302	0.024	-0.173	0.031*	156
Temperature	-0.022	-0.006	-0.004	0.963	164
Weight	0.010	-0.003	0.058	0.461	162
Heart rate	-0.017	-0.003	-0.058	0.464	161
Diastolic blood pressure	0.003	-0.006	0.008	0.921	160
Systolic blood pressure	-0.002	-0.006	-0.009	0.913	160

Table D.4: Results of linear regression and Pearson correlation with vital signs as the predictor and 2FT score as the dependent variable.
β: regression coefficient, $adj.$: adjusted, p: p-value

	Linear Regression		**Pearson**		
Predictor	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**Data size**
Oxygen saturation	-0.014	-0.001	-0.044	0.419	346
Temperature	0.068	0.000	0.057	0.287	348
Weight	0.002	0.001	0.066	0.223	348
Heart rate	0.004	0.002	0.067	0.210	350
Diastolic blood pressure	-0.001	-0.003	-0.008	0.881	335
Systolic blood pressure	-0.003	-0.001	-0.049	0.371	339

Table D.5: Results of linear regression and Pearson correlation with vital signs as the predictor and BDI score as the dependent variable.
β: regression coefficient, $adj.$: adjusted, p: p-value

	Linear Regression		**Pearson**		
Predictor	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**Data size**
Oxygen saturation	0.719	0.034	0.230	0.100	52
Temperature	4.415	0.051	0.265	0.062	50
Weight	-0.055	-0.009	-0.102	0.467	53
Heart rate	0.262	0.137	0.392	0.004**	53
Diastolic blood pressure	0.279	0.132	0.386	0.006**	50
Systolic blood pressure	0.137	0.014	0.184	0.197	51

Table D.6: Results of linear regression and Pearson correlation with mean vital signs as the predictor and questionnaire scores as the dependent variable.
$dep.\,var.$: dependent variable, β: regression coefficient, $adj.$: adjusted, p: p-value

		Linear Regression		**Pearson**		**Data**
Predictor	**Dep. var.**	$\boldsymbol{\beta}$	**adj. r^2**	**r**	**p**	**size**
Mean oxygen saturation	KCCQ12	2.321	0.046	0.224	0.001**	204
Mean temperature	KCCQ12	-3.977	0.006	-0.104	0.137	205
Mean weight	KCCQ12	0.011	-0.005	0.012	0.865	209
Mean heart rate	KCCQ12	-0.093	-0.002	-0.052	0.459	207
Mean diastolic BP	KCCQ12	0.361	0.030	0.186	0.007**	205
Mean systolic BP	KCCQ12	0.014	-0.005	0.011	0.881	205
Mean oxygen saturation	ESS	-0.218	0.006	-0.112	0.154	164
Mean temperature	ESS	-0.487	-0.001	-0.069	0.377	166
Mean weight	ESS	0.010	-0.003	0.058	0.457	166
Mean heart rate	ESS	-0.035	0.005	-0.103	0.183	167
Mean diastolic BP	ESS	-0.005	-0.006	-0.013	0.868	166
Mean systolic BP	ESS	-0.000	-0.006	-0.001	0.987	166
Mean oxygen saturation	2FT	-0.040	0.007	-0.101	0.057	356
Mean temperature	2FT	0.143	0.008	0.103	0.051	358
Mean weight	2FT	0.002	0.001	0.058	0.270	360
Mean heart rate	2FT	0.007	0.009	0.108	0.041*	359
Mean diastolic BP	2FT	0.003	-0.001	0.042	0.430	360
Mean systolic BP	2FT	-0.004	0.002	-0.071	0.180	360
Mean oxygen saturation	BDI	0.750	0.031	0.220	0.104	56
Mean temperature	BDI	3.105	0.008	0.163	0.231	56
Mean weight	BDI	-0.076	0.001	-0.138	0.309	56
Mean heart rate	BDI	0.314	0.095	0.333	0.012*	56
Mean diastolic BP	BDI	0.255	0.058	0.274	0.041*	56
Mean systolic BP	BDI	-0.087	-0.006	-0.109	0.423	56

Appendix E

Acronyms

2FT Whooley Questions for Depression Screening Questionnaire

6mWT 6-minute walk test

ACC American College of Cardiology

AHA American Heart Associaton

AUCROC area under the receiver operating characteristic curve

BDI Mental Health Questionnaire II-Becks Depression Inventory 2

BMI body mass index

BNP B-type natriuretic peptide

BP blood pressure

bpm beats per minute

CV cross validation

ECG electrocardiogram

EF ejection fraction

EQ-5D-5L health status of the EuroQol Group (5-level EQ-5D version)

ESC European Society of Cardiology

ESS Epworth Sleepiness Scale

HF heart failure

HFmrEF heart failure with midrange ejection fraction

HFpEF heart failure with preserved ejection fraction

HFrEF heart failure with reduced ejection fraction

ICD implantable cardioverter defibrillators

ICD-10 International Classification of Diseases

KCCQ12 Kansas City Cardiomyopathy Questionnaire

LSS Level Sum Score

ML machine learning

mmHg millimeter of mercury

NT-proBNP N-terminal pro-B-type natriuretic peptide

NYHA New York Heart Association

PA pulmonary artery

RFE recursive feature elimination

SBMLR stepwise backward multiple linear regression

TIM-HF2 Telemedical Interventional Management in Heart Failure II

TMC telemedicine center

VAS visual analog scale

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