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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The impact of cardiac rehabilitation on obese vs. non-obese heart failure patients: a retrospective study

Femke Tielemans
Minneke Verbeeck
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij inwendige aandoeningen

PROMOTOR :
Prof. dr. Dominique HANSEN

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Research context

This thesis is situated within the following research domain: rehabilitation of internal complications.

Cardiac rehabilitation is an essential part of maintaining a healthy lifestyle in patients with cardiovascular abnormalities (Ponikowski et al., 2016). In Belgium, cardiac rehabilitation is offered to all patients who have been admitted to the hospital after a cardiac related admission (Ziekenhuis Oost-Limburg., 2021). A large number of patients choose not to participate or cannot physically join these programs. This ultimately leads to a decreased prognosis for these patients (Pardaens et al., 2015). This thesis will analyse which impact cardiac rehabilitation has on different subgroups of heart failure (HF) patients. The different subgroups within this study consist of obese vs. non obese patients.

Obesity is a worldwide metabolic syndrome, and poses a threat for developing multiple cardiovascular diseases, including HF (World Health Organization, 2017). The current HF prevalence is high, and the long-term prognosis is scarcely positive (Ponikowski et al., 2016). Aside from the ongoing debate of the obesity paradox (OP), in which overweight HF patients are proposed to have a more favourable prognosis, not much research on the impact of rehabilitation on the OP has been studied (Lavie et al., 2014).

In continuation of the authors' systematic review in the academic year of 2019-2020, a prospective study was planned. However, predominantly due to the global pandemic of COVID19, a retrospective study design was chosen in agreement with Prof. Dr. Dominique Hansen and Dr. Kenneth Verboven.

Together with the colleagues from the ZOL, decisions were made regarding thesis options, based on what data was available for extraction within the hospital's database. Following this, with guidance of the promotor Prof. Dr. Dominique Hansen, Msc. Lore Jennes and Msc. Mirte Stifter, the study was approved by the ethical committee and Clinical Trial Unit of the Hospital of East-Limburg (ZOL), and by the ethical committee of UHasselt.

Five weeks of intensive data collection was performed by both of the authors in the ZOL hospital. This was done in partnership with two other Master students, who used the same acquired dataset for their thesis.

After mutual thesis proposals from the promotor, co-promotor and both authors of the current study, a topic suggested by the authors was agreed upon. Both authors were involved in extensive literature research before commencing the retrospective study.

The written and statistical processes occurred independently. When the authors finished a written or statistical section, this was sent to their (co)promotor, in which the suggested proposals would either be approved or declined. Feedback received from supervisors was carefully considered and applied to all sections.

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The impact of cardiac rehabilitation on obese vs. non-obese heart failure patients: a retrospective study.

Abstract

Background: Obesity is an important risk factor for the development of heart failure (HF). However, the so-called "obesity paradox" (OP) states that obesity has a protective effect on prognosis once HF is established.

Objectives: This retrospective study analyses the impact of cardiac rehabilitation on mortality and rehospitalisation in both obese and lean HF patients.

Participants: Data from HF patients with a cardiac related hospital admission between 2015 and 2019 in the ZOL hospital were selected. They were stratified into four groups: 1) obese patients following cardiac rehabilitation, 2) non-obese patients following cardiac rehabilitation, 3) obese patients not following cardiac rehabilitation and 4) non-obese patients not following cardiac rehabilitation.

Measurements: All patient information was collected from the hospital's filing software, HIX and Oxygen.

Results: 253 patients were included in the final statistical analysis. Comparison of the mortality between obese vs. non obese groups showed that the non-obese group had a significantly longer survival time ($p=0.0170$). In addition, there were no significant differences regarding the effect of rehabilitation. Subsequent comparisons between all four groups did not indicate any significant differences in mortality and hospitalisation rates. At last, an increase of NT-proBNP and a preserved left ventricular ejection fraction (LVEF) showed a trend towards a better prognosis, but these findings were not substantial.

Conclusion: Cardiac rehabilitation has no significant impact on mortality and hospitalisation rates. In contrast to numerous studies, no signs of the OP were found. Additional research comprising a multicentre, prospective study is required to provide a definite answer to the proposed research question. Anthropometric measurements instead of BMI should be used during future research to further analyse these findings.

Keywords: Heart failure; Prognosis; Cardiac rehabilitation; Obesity; Obesity paradox

1. Introduction

Heart failure (HF) is an anatomical and/or functional cardiac condition, which often co-exists with a reduced cardiac output and/or elevated intracardiac pressure (Ponikowski et al., 2016; Savarese & Lund, 2017). The worldwide prevalence ranges from 1-2% in the adult population and reaches 10% among 70-year-olds and 15% among 80-year-olds (Ceia et al., 2002; Mosterd & Hoes, 2007). HF is predominantly found in men (Bleumink et al., 2004; Strömberg & Mårtensson, 2003). Symptoms often include breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, exercise intolerance, fatigue, increased time to recover after exercise and ankle swelling (Ponikowski et al., 2016). Patients are often classified in one of three groups based on left ventricular ejection fraction (LVEF): HF with a reduced ejection fraction (HFrEF; LVEF <40%), HF with a mid-range ejection fraction (HFmrEF; LVEF 40-49%) and HF with a preserved ejection fraction (HFpEF; LVEF ≥50%). Another way to describe their symptoms and exercise intolerance is the use of the New York Heart Association (NYHA) functional classification, ranging from I to IV (I being the least severe and IV the most) (Mosterd & Hoes, 2007; Ponikowski et al., 2016; Yancy et al., 2013).

Numerous risk factors have been proven to increase the incidence of HF. The most prevalent risk factors being a higher age, obesity (expressed as the body mass index (BMI)), higher systolic blood pressure, heart rate, serum creatinine, smoking, diabetes mellitus, history of coronary artery disease, and the use of antihypertensive drugs (Jacobs et al., 2017; Kenchaiah et al., 2002; Pasquali et al., 2020; World Health Organization, 2020).

Symptoms, signs and structural and/or functional abnormalities of the heart are required for an official diagnosis of HF. A number of symptoms and signs have been mentioned above, whereas the less common symptoms and signs such as nocturnal coughing, wheezing, weight gain (>2kg/week) or weight loss can be found within the guidelines (Ponikowski et al., 2016). Abnormalities of the heart can be tested through a multidimensional examination, one being the plasma concentration of natriuretic peptides (NPs), more specifically N-terminal pro-brain natriuretic peptides (NT-proBNP). Increased NT-proBNP levels may help to identify patients who require further echocardiographic imaging, which is known to be the most comprehensive method for establishing a diagnosis in this particular patient group (based on the LVEF) (Dargie & Mcmurray, 1994; Ponikowski et al., 2016).

Determining a prognosis for specific dysfunctions and mortality may help clinicians finetune a therapy tailored to the needs of each individual patient (Ponikowski et al., 2016). The five most common groups of prognostic measurements in HF are 1) patient characteristics, 2) laboratory testing (e.g., NT-proBNP), 3) functional parameters such as NYHA-class or the 6-minute walk test, 4) ventricular function (LVEF) and 5) any current/previous medical interventions (Levy et al., 2006; Mosterd & Hoes, 2007).

LVEF has been shown to be a strong prognostic factor for patients with HF. A one-year mortality-rate was found to be higher in patients with a reduced LVEF (Chioncel et al., 2017). Additionally, an inverse relationship between LVEF with both mortality and hospitalisation rate was confirmed (Angaran et al., 2020).

Obesity is known to be an independent risk factor for developing HF (Kenchaiah et al.,2002). The association between mortality and obesity in HF patients has often been suggested to have a U-shaped relationship, favouring a BMI around 30kg/m², also known as 'the obesity paradox' (OP) (Carbone et al., 2019; Nagarajan et al., 2016).

Treatment options vary individually among patients but typically involve pharmacotherapy, implantation of devices (e.g., implantable cardioverter-defibrillator, cardiac resynchronisation therapy, pacemaker), heart transplants and cardiac rehabilitation (Achttien et al., 2014; Choi, Park, & Youn, 2019).

HF patients are ideally monitored and treated in a multidisciplinary fashion, which often includes cardiac rehabilitation (Ponikowski et al., 2016). Cardiac rehabilitation has been deemed safe and shows a trend towards lower mortality rates with exercise after a follow up of one year. Exercise also reduces the rate of HF hospitalisations (Fu et al., 2013; O'Connor et al., 2009; Taylor et al., 2014). The impact of cardiac rehabilitation on the OP still poses many questions regarding whether weight loss is beneficial, or if it may just pose a threat to the prognosis of HF patients (Lavie et al., 2014).

Therefore, the objective of this retrospective study is to investigate the relationship between cardiac rehabilitation and the impact it has on mortality and hospitalisation rates in obese and non-obese HF patients. Additionally, an analysis will be executed of the relationship between obesity, proBNP and LVEF with mortality in HF patients.

2. Methods

This study was approved by the ethical committee and Clinical Trial Unit of the Hospital of East-Limburg (ZOL) on March 29th, 2021 (study code ctu2020131), and by the ethical committee of UHasselt in February 2021.

2.1. Participants

All participants in this retrospective study were HF patients. No distinction was made between patients with a preserved or reduced ejection fraction. Information was extracted from the individual medical files through the hospital's programmes, HIX and Oxygen. Patients were retrospectively selected if a clinical cardiac admission was documented between 2015 and 2019, and were excluded when no BMI was recorded, or when there was insufficient follow-up available in their patient file. A follow-up period between 9 and 15 months was obligatory for inclusion.

Four groups were made to study the proposed research question, based on a BMI cut-off of 30 kg/m² and the presence/absence of a cardiac rehabilitation program (hospital based; minimal duration of 20 sessions): 1) obese patients following cardiac rehabilitation, 2) non-obese patients following cardiac rehabilitation, 3) obese patients not following cardiac rehabilitation and 4) non-obese patients not following cardiac rehabilitation. The rehabilitation groups contain patients that were considered compliant during their rehabilitation program, meaning that they completed 20 of the 45 cardiac rehabilitation sessions.

2.2. Procedure

Data extraction commenced March 29th, 2021, in the ZOL, using HIX and Oxygen. Patients remained anonymous by using only their file number for data-collection. An excel document was made, listing the following desired baseline patient characteristics: age, sex, height, weight, BMI, blood pressure, laboratory values, New York Heart Association (NYHA) Classification, left ventricular ejection fraction (LVEF), left diastolic dysfunction grade, domestic circumstances, cardiac rehabilitation setting if present, smoking history, comorbidities, cardiac history and implanted devices. Moreover, mortality, the number of cardiac rehospitalisations, length of stay during hospital admission and months until death was included.

Primary outcomes include mortality and time until death, whereas secondary outcomes consist of cardiac rehospitalisation event rates, and average time spent in hospital during cardiac admissions.

The influence of cardiac rehabilitation on the previously mentioned outcome variables is analysed in this study. The following rehabilitation protocol used within the ZOL shall be described in further detail. HF patients were recruited for cardiac rehabilitation after they had been admitted to the cardiac ward. Once they had been informed about the importance of exercise therapy, they were allowed to start the program within the following week upon hospital discharge. This program consists of 45 sessions with two to three sessions each week. Before their first session, a cardiopulmonary exercise test (CPET) was performed under surveillance of a physiotherapist and a cardiologist to analyse their cardiovascular profile. Prior to their strength training, a one repetition maximum (1RM) was taken on the leg press, lateral pull down, dips and chest press machine (Enraf-Nonius Compass 530). A typical session consisted of the following training modalities: cardiovascular training at 60% of their VO2max and strength training containing 3 sets of 12 repetitions at 60% of 1RM, with the same appliances used for the 1RM measurements. When possible, varying levels of interval training were given to the patients on the cardiovascular machines. Cardiovascular training was executed using a treadmill, hometrainer, rowing machine, step machine, arm-bike and the cross trainer (Enraf-Nonius Kardiomed 700). If the patients had undergone a surgical procedure involving a sternotomy, thoracotomy or an implantation of any type of device within the previous 6-8 weeks of starting the program, they were expected not to perform any exercises utilizing the upper extremities until their wounds were healed.

2.3. Data-analysis

To perform the statistical analysis, JMP PRO 15.2 and SPSS 26.0 software was used. Categorical variables are presented as frequency counts and percentages. Continuous variables are described by means and standard deviations (SDs) when normally distributed, and as medians and interquartile ranges when not normally distributed. Furthermore, the 1-year follow-up data are stratified into mortality, the number of months after the first admission until death, the number of hospitalisations and the average number of days spent hospitalized.

When data was normally distributed, an analysis of variance test was used to compare continuous variables. Kruskal-Wallis test was used to compare nonparametric continuous variables. Then, either Tukey HSD or non-parametric multiple comparison tests were performed to identify any potential statistical relationships. Pearson’s Chi and Fisher's exact tests were used to compare the categorical variables. Means, medians and distributions were seen as statistically significant when there was a p value of <0.05.

Kaplan-Meier curves survival curves regarding mortality were plotted and were then compared using the Log- rank and generalized Wilcoxon test.

Finally, Chi-square test and logistic regression models were performed to see if there was any relationship between LVEF, proBNP and mortality.

3. Results

A total of 367 HF patients were analysed during the data extraction. From this population, 114 were excluded since they had no information regarding their BMI. After the patient selection process, a total of 253 patients were included in this retrospective study (Figure 1). The patients were then categorised into groups based on their BMI (cut-off 30kg/m²), and whether or not they followed cardiac rehabilitation: obese patients following cardiac rehabilitation (n=13), non-obese patients following cardiac rehabilitation (n=26), obese patients not following cardiac rehabilitation (n=71) and non-obese patients not following cardiac rehabilitation (n=143).

3.1. Patient characteristics

A summary of the baseline characteristics of the 253 heart HF is shown in Table 1. The majority of the patients were men (69.57%), with a mean age of 75 (67-81). 62.02% of the patients had an impaired left ventricular ejection fraction, with an end diastolic dysfunction grade of 1 (54.84%). Regarding NYHA classifications, solely 8.83% of the patients were in class IV with the majority belonging to the remaining 3 groups (50% in group III). At baseline, the majority of patients were living at home with a partner or with family (69.52%) and had a history of smoking (60.17%). Almost half of the patients had an implanted device. When analysing comorbidities, diabetes mellitus type 2 was most prevalent within the whole population (35.97%). This metabolic disorder was predominantly found in the two groups containing obese patients: 46.15% in the rehabilitation group and 49.30% of patients who did not attend cardiac rehabilitation.

3.2. Impact of BMI (obese vs. non obese) on primary and secondary outcome measures

The primary and secondary outcome variables were analysed regarding the BMI of the HF patients. These results are shown in Table 2. No statistically significant results were found, aside from the months until death in the non-obese group, which was significantly longer when compared to the obese group (p= 0.0170). Additionally, when analysing the survival curves (Figure 2), no significant difference was seen when looking at BMI classification.

3.3. Impact of rehabilitation on primary and secondary outcome measures

The identical outcome variables were studied regarding rehabilitation status. No statistically significant results were found during the analysis (Table 3 and Figure 3).

3.4. Impact of rehabilitation & BMI on primary and secondary outcome measures

No difference was seen regarding mortality, months until death, the distribution of rehospitalisation rate and average hospital admission time between the four groups, which answers the pre-imposed research question (Table 4). Also, the Kaplan-Meier survival curves and Log Rank analysis showed no significant difference between the four groups (Figure 4).

3.5. Relationship between LVEF, proBNP and mortality

Lastly, the correlation between LVEF and proBNP with mortality were analysed separately. For every decrease of 1 ng/L proBNP, mortality increased by 1%. However, this relationship is not significant. A decrease in LVEF showed a trend towards an increased mortality (Table 5).

4. Discussion

Within this discussion section, the following topics shall be addressed. Firstly, the impact of rehabilitation within this cardiac population shall be assessed and compared to current literature. Secondly, the OP and cachexia will be described into greater detail. Lastly, the combination of both weight classes and rehabilitation will be discussed, and how they impact the primary and secondary outcome measures.

4.1. Rehabilitation in the HF population

Rehabilitation is a core component of treatment in a vast number of pathologies, including HF (Ponikowski et al., 2016). It has a large number of benefits, such as an increase in VO2max, skeletal muscular function (peripheral and skeletal) and improved central haemodynamics (Lavie et al., 2013a). In Belgium, once a patient has been admitted to the hospital due to a cardiac abnormality, they get the opportunity to enter a cardiac rehabilitation program (Kotseva et al., 2012; Ziekenhuis Oost-Limburg., 2021). Even though the importance of cardiac rehabilitation is growing enormously due to its positive impact on life expectancy, rehospitalisation rate and further complications, the referral rates are yet to be improved (Kotseva et al., 2012; Taylor et al., 2019). From all patients who would benefit from cardiac rehabilitation, only 9% join a program and are compliant with their therapy (Pardaens et al., 2015). This retrospective study demonstrates that 15% of the patient group were compliant to cardiac rehabilitation, which is higher compared to the published literature on cardiac rehabilitation. Despite the fact that the ZOL hospital rehabilitation programme follows the recommended training modalities, and the compliance rate was higher (Piepoli et al., 2014; Ponikowski et al., 2016), this study shows that there is no essential impact of rehabilitation on mortality or rehospitalisation rate/length in patients with HF. The methodological shortfalls inherent to retrospective research design, such as inaccurate record keeping, selection bias, misclassification or information bias, may explain the discrepancy in the outcomes.

4.2. The obesity paradox in the HF population

An important aspect of HF is the OP, which states that people with a BMI around and above 30kg/m² have a better prognosis. Literature has described this U-shaped relationship frequently, as it remains a large point of discussion within the scientific research platform (Carbone et al., 2019; Nagarajan et al., 2016). A large number of possible explanations have been formulated to describe the positive relationship between an increased adipose tissue mass and a more favourable prognosis. These shall be discussed in further detail.

Obese patients have a higher risk of developing HF since their excessive weight causes multiple complications such as hypertension and coronary heart diseases, which eventually may result in a left ventricular dysfunction (Kenchaiah et al., 2002). Another common complication of obesity is diabetes (Pantalone et al., 2017), as subscribed by our retrospective study, in which predominantly obese people suffer from this metabolic disorder ($p = 0.03$). Since hypertension, coronary heart disease and diabetes mellitus type 2 are not as prevalent within the lower weight class, it is believed that the etiology of HF in lean patients is caused by more alarming conditions, with a less favourable prognosis. (Andreas et al., 2007; Oga & Eseyin, 2016; Pandey et al.,2015).

It has also been shown that obese patients with HF are often of a younger age, and that this early detection of their cardiac condition might lead to better outcomes (Vogel et al., 2016).

However, in this retrospective study, there was no significant difference in age within the population.

Another major reason which may explain the OP is that HF is a catabolic phenomenon (Oga & Eseyin, 2016). Adipose tissue is known to have an abundance of natriuretic peptide (NP) binding sites, tumour necrosis factor-alpha (TNF-α) receptors and leptin (Taylor et al., 2006; Wannamethee et al., 2014). These receptors may neutralise the effects of harmful substances such as N-terminal pro-b-type Natriuretic Peptide (NT-proBNP) and tumour necrosis factor (TNF-α) respectively (Wannamethee et al., 2014). It is a plausible explanation as to why obese patients, who have an increased body reserve, may be protected against these damaging processes (Futter et al., 2011). Within this study, an increase of proBNP had an inverse relationship with mortality, which contradicts the OP. Due to the dearth of data points acquired for proBNP within the patient files, the issue remains inconclusive. A possible reason for the small amount of data points acquired, is that the Belgian medical aid system doesn't reimburse for proBNP measurements (Ziekenhuis Oost-Limburg., 2021). Also, TNF-α, has been shown to have a catabolic effect on lean mass, in particular muscle mass (Berry & Clark, 2000; Reid & Li., 2001). TNF-α may also contribute to the development of cachexia, which shall be discussed later on (Anker, & Sharma., 2002). As no data on TNF-α was available, it was not possible to determine its impact within the patient population.

Since many studies regarding HF classify patients according to their LVEF, the following relationships were found. Obese patients were frequently seen to have a higher LVEF (Gustafsson et al., 2004; Lupón & Bayes-Genis, 2018; Zafrir et al., 2015). Therefore, obese patients may have a better prognosis due to better cardiac functioning (Pocock et al., 2012). A possible explanation for obese patients having a larger LVEF is that they often suffer from dyspnoea and may be misdiagnosed with HF (Bernhardt et al., 2016). This ultimately means that their LVEF may be completely normal, as there is no evidence of actual HF. These results were not confirmed by the current study. A possible reason for this may be that the ZOL hospital rarely diagnoses a patient with HF without cardiac echography to determine their LVEF (Ziekenhuis Oost-Limburg., 2021). This study did however show a trend, in which a lower LVEF correlates with an increased mortality rate. This last statement is shown in current literature (Angaran et al.m 2020; Chioncel et al., 2017).

It is known smokers are often leaner as their appetite is suppressed, and fat oxidation increases with increasing nicotine uptake (Jensen et al., 1995). Smoking however, leads to multiple comorbidities, such as multiple types of cancers including that of the lungs, lung complications such as obstructive pulmonary disease (COPD) and cardiovascular diseases including atherosclerosis which may ultimately lead to aneurysms (Andreas et al., 2007; Siasos et al., 2014). The damage can largely be reversed by cessation of smoking, although a large variability exists from patient to patient as many factors are involved, including the time exposed to each comorbidity and the impact of (epi)genetic components (Gambardella et al., 2017). The combination of being lean and possibly prone to major comorbidities accompanied with smoking may explain why leaner patients with HF, with less adipose tissue and possibly lower muscle mass to protect them from catabolic effects, have a worse prognosis. No difference in smoking habit was recorded within this retrospective study and may therefore explain the absent evidence of the OP.

Another possible explanation describing the OP is BMI. A large number of observational studies and meta- analyses with regard to the OP solely look at BMI as a prognostic factor within patients with HF (Sharma et al., 2015). However, this prognostic method (BMI) has raised many questions regarding its sensitivity, since it identifies 50% of people as non-obese when they, in fact, have an excess percentage of body fat (Okorodudu et al., 2010). It is also known that BMI does not distinguish between fat, fat-free mass and lean mass (Carbone, Lavie, & Arena, 2017). Carbone, Lavie, & Arena (2017) has shown that preserving or increasing lean mass, in this case, skeletal muscle mass, rather than fat mass, may improve prognosis in patients with HF, including the ones with obesity. No analysis of lean mass was possible within this retrospective study, as this information was not available within the patient files.

A final argument supporting the notion of the OP is cachexia. Cachexia is a multifactorial metabolic disorder associated with underlying illness and is frequently found in chronic health conditions, including HF, where it affects 5-15% of patients (Evans et al., 2008; Loncar et al., 2016; von Haehling & Anker, 2014). It is currently defined as a loss of body mass (corrected for fluid imbalance) of more than 5% within 12 months (or BMI <20 kg/m²), with at least three of the following complications: decreased muscle strength, fatigue, anorexia, low fat-free mass index and abnormalities in blood biomarkers (Anker & Morley, 2015; Evans et al., 2008; Loncar et al., 2016; von Haehling, 2017).

As stated before, TNF-α, aside from its possible contribution to the development of cachexia, has catabolic effect on muscles, including heart musculature. This may lead to a left and right

ventricular dysfunction. Subsequently, patients with cachexia may have a worse prognosis due to the increased risk of reduced LVEF (Anker & Sharma, 2002).
The presence of cachexia is strongly associated with a higher prevalence of adverse events and 18-month mortality in patients with HF (Anker et al., 1997; Melenovsky et al., 2013). In the current study, only four patients (1.58%) were included with a BMI of < 20kg/m². This misrepresentation of the HF population may be another reason why the OP was not apparent within the results of this study.

In this current study, the previously mentioned arguments defending the OP were not detected. However, it is noticeable that the months after admission until mortality are significantly longer in the non-obese group. A possible reason for this may be that the non-obese group had more frequent hospital admissions, which may have led to a more intensive treatment, prolonging their lives.
Although the literature supports the notion that obese patients may have a more favourable prognosis since fat reserves are larger, it generates the question what impact these catabolic mechanisms may have on their quality of life.

4.3. Rehabilitation in the different weight classes in the HF population

As previously mentioned, patients with HF are often prescribed exercise therapy (Ponikowski et al., 2016). Literature supports the recommendation that cardiac rehabilitation has been proven safe and has a positive influence on rehospitalisation and mortality rates (Fu et al., 2013; O'Connor et al., 2009; Taylor et al., 2014). Few studies have analysed what impact cardiac rehabilitation has on the OP. In a study by Lavie et al. (2009), the effect of cardiac rehabilitation on coronary patients was retrospectively studied. The main findings of this study showed a confirmation of the OP. The study also notes that weight loss due to rehabilitation was not harmful, and even improved coronary risk factors. Rehabilitation did not however, improve mortality rates. The same was confirmed for HF patients with a BMI of >35kg/m² regarding the improvement of risk factors, although not much Is known what impact rehabilitation has on their clinical prognosis (Lavie et al., 2014). Aside from the coronary risk factors on which we had very little acquired data points at follow-up, the absent impact on mortality conformed with this retrospective study.

Two studies stated that patients with a good cardiorespiratory fitness (oxygen consumption of >14 ml O2 kg-1min-1) showed no signs of an OP, however, patients with an oxygen consumption below this value showed clear signs of the phenomenon (Clark et al., 2015, Lavie et al., 2013b). This might explain why no significant difference was found between the two groups following rehabilitation within this retrospective study as they possibly had an improved cardiorespiratory fitness. However, this could not be analysed within this study as very little information regarding cardiorespiratory fitness was documented. Not many studies have recognised the relationship between rehabilitation and the OP, therefore more methodological sound research is required.

4.4. Limitations and strengths of the current study

This study has several limitations which have to be considered. Firstly, this is a retrospective study. This means that the incidence of selection bias, and information bias is higher within this study design. Information bias was present as data collection was limited to the information that was available within the patient database of the hospital. Several aspects of the patient's medical records were missing, for example: follow-up of patients regarding their cause of death or reasons for hospitalisations were not reported. Also, a lot of information regarding patient symptoms and prognostic markers were missing, such as ProBNP and NYHA-classification. For each variable, the amount of data points acquired have been given (Table 1). None of the continuous variables were normally distributed within this study. This may have been due to selection bias.

Another limitation was that patient information originated from a single hospital, making this a single-centred study. Data may have been more representative for the HF population if multiple centres were used for data collection.

A final limitation was that the only accessible data representing the body composition of patients was restricted to BMI. This, however, is not a reliable measurement as it does not make a distinction between lean and fat mass in the human body (Carbone, Lavie, & Arena, 2017). Oreopoulos et al (2010) used a DEXA scan and other anthropometric measures to estimate body composition and showed that BMI misclassified body status in 40% of the studied population.

In contrast to the limitations, this study also has several strengths. Firstly, there is a large sample size (n= 253) of which as much information as possible was collected. As mentioned previously, a lot of the data regarding the patients' files were missing. This may be of importance to create awareness for hospitals to improve their patient documentation as this could maximize the quality of their treatment, follow-up and future research. It has become apparent that there is still a lack of rehabilitation in HF. This study shows a compliance to rehabilitation of 15%. This low rate of compliance, disregarding the fact that it is higher than the norm compliance as retrieved from the relevant literature, may raise awareness of the importance for patients to join a rehabilitation program.

4.5. Recommendations for future research

A multicentre, prospective study is required to further analyse the pre-imposed research question, using anthropometric measurements other than BMI. This way, patients can be followed up intensively, and their compliance can be monitored closely. This study also aims to create awareness that complete data capturing in a hospital setting is paramount to safeguard patient care, as it may facilitate the quality of future research. Finally, as previously mentioned, alternative values than BMI, such as DEXA scan, bioelectrical impedance measurements and waist circumference measurements can be implemented for measurements of adiposity, as the former is not a reliable measurement.

5. Conclusion

This retrospective study showed no impact of cardiac rehabilitation on mortality or hospitalisation rates within the four groups of the HF population. No signs of the OP were found, in contrast, a longer survival time was seen within the non-obese population. Regardless of its possible positive impact on prognosis according to literature, the focus should lie on preventing this metabolic disorder in order to minimise its possible lethal complications.

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APPENDIX

Table 1

Baseline Patient Characteristics

	Total (n= 253)	Rehab obese (n= 13)	Rehab non-obese (n= 26)	No rehab – obese (n= 71)	No rehab non-obese (n= 143)	p value	Data points acquired
Age (years)	75 (67-81)	76 (68-81)	72 (64.75-82.25)	74 (68-78)	75 (66-81)	0.9067	253
Women, n (%)	77 (30.43%)	5 (38.46%)	11 (42.31%)	23 (32.39%)	38 (26.57%)	0.3380	253
Height (cm)	168(162.75-175)	162 (159-170.5)	168 (164.5-175)	168 (160-174)	169 (163.5-175)	0.1904	250
Weight (kg)	80 (70-90)	86 (78.5-95.5)	73.5 (64.5-80)	93 (85-108)	74 (67-81)	**<0.0001**	253
BMI (kg/m²)	27.62 (24.77-31.22)	32.77 (30.9-36.01)	25.92 (23.99-27.93)	33.14 (31.25-35.99)	25.83 (24-27.58)	**<0.0001**	253
Blood pressure							
Systolic	125 (111-143)	146.5 (128.25-160.5)	119.5 (111-135.75)	129 (114.5-148)	124 (109-139)	**0.0054**	238
Diastolic	70 (61.5-80)	80.5 (66-86)	71 (64.75-77.5)	72 (64.5-86)	69 (59-78.25)	**0.0050**	237
LVEF						0.130	208
< 40 %	85 (40.87%)	4/12 (33.33%)	10/23 (43.48%)	19/61 (31.15%)	52/112 (46.43%)		
40-49 %	44 (21.15%)	1/12 (8.33%)	8/23 (34.78%)	14/61 (22.95%)	21/112 (18.75%)		
≥ 50 %	79 (37.98%)	7/12 (58.33%)	5/23 (21.74%)	28/61 (45.9%)	39/112 (34.82%)		
DD						**0.0033**	124
I	68 (54.84%)	4/5 (80%)	10/17 (58.82%)	11/36 (30.56%)	43/66 (65.15%)	**0.0037**	
II	43 (34.68%)	1/5 (20%)	7/17 (41.18%)	21/36 (58.33%)	14/66 (21.21%)	**0.0014**	
III	13 (10.48%)	/	/	4/36 (11.11%)	9/66 (13.64%)	0.4215	
ProBNP	2349 (1143-4932)	5299 (2459-13681.5)	3785 (1372-4163)	1387.5 (958.75-4815)	2378 (1424-4959.25)	0.1852	63
NYHA						0.7836	34
I	3 (8.82%)	/	/	1/11 (9.02%)	2/18 (11.11%)		
II	11 (32.35%)	/	1/2 (50%)	5/11 (45.45%)	5/18 (27.78%)		
III	17 (50%)	2/3 (66.67%)	1/2 (50%)	4/11 (36.36%)	10/18 (55.56%)		
IV	3 (8.82%)	1/3 (33.33%)	/	1/11 (9.02%)	1/18 (5.56%)		
Domestic circumstances						0.6506	105
Assisted living	3 (2.86%)	1/9 (11.11%)	/	1/25 (4%)	1/61 (1.64%)		
Alone	27 (25.71%)	2/9 (22.22%)	5/10 (50%)	6/25 (24%)	14/61 (22.95%)		
With family	13 (12.38%)	2/9 (22.22%)	1/10 (10%)	2/25 (8%)	8/61 (13.11%)		
With partner	60 (57.14%)	4/9 (44.44%)	4/10 (40%)	16/25 (64%)	36/61 (59.02%)		

Residential care center	2 (1.90%)	/	/	/	2/61 (3.28%)		
Smoking history						0.8244	241
Stopped	109 (45.23%)	6/13 (46.15%)	10/26 (38.46%)	29/70 (41.43%)	64/132 (48.48%)		
Current smoker	36 (14.94%)	1/13 (7.69%)	6/26 (23.08%)	11/70 (15.71%)	18/132 (13.64%)		
Never smoked	96 (39.83%)	6/13 (46.15%)	10/26 (38.46%)	30/70 (42.86%)	50/132 (37.88%)		
Pack years	32 (16-47)	/	20.5 (13.75-28.75)	37 (20.5-49)	33 (15-46.5)	0.3061	55
Comorbidities							253
T2DM	91 (35.97%)	6/13 (46.15%)	7/26 (26.92%)	35/71 (49.30%)	43/143 (30.07%)	**0.0283**	
COPD	60 (23.72%)	2/13 (15.38%)	2/26 (7.69%)	21/71 (29.58%)	35/143 (24.48%)	0.1281	
Kidney insufficiency	65 (25.69%)	5/13 (38.46%)	7/26 (26.92%)	19/71 (26.76%)	34/143 (23.78%)	0.6537	
Cancer	15 (5.93%)	/	3/26 (11.54%)	1/71 (1.41%)	11/143 (7.69%)	0.0999	
Other	50 (19.76%)	3/13 (23.08%)	6/26 (23.08%)	9/71 (12.68%)	32/143 (22.38%)	0.6921	
Device						0.7150	253
Pacemaker	40 (15.81%)	4/13 (30.77%)	4/26 (15.38%)	10/71 (14.08%)	22/143 (15.38%)		
ICD	40 (15.81%)	2/13 (15.38%)	4/26 (15.38%)	11/71 (15.49%)	23/143 (16.08%)		
CRT	43 (17%)	1/13 (7.69%)	6/26 (23.08%)	8/71 (11.27%)	28/143 (19.58%)		
No device	130 (51.38%)	6/13 (46.15%)	12/26 (46.15%)	42/71 (59.15%)	70/143 (48.95%)		

P values display the ANOVA for normally distributed continuous variables, and nonparametric tests (Kruskal-Wallis) for not when the continuous variables are not normally distributed. Pearson chi-square test and fisher's exact were used for categorical values.

BMI – body mass index; LVEF – left ventricular ejection fraction; DD-- Diastolic dysfunction; proBNP -- brain natriuretic peptide; NYHA – New York Heart Association; T2DM -- Type 2 diabetes mellitus; COPD -- chronic obstructive pulmonary disease; ICD -- implantable cardioverter defibrillator; CRT -- cardiac resynchronization therapy

Table 2

Obese vs Non-obese

	Obese (n= 83)	Non-obese (n= 170)	p value
Rehospitalisation			0.1794
0	35 (42.17%)	58 (34.12%)	
1	25 (30.12%)	44 (25.88%)	
2	14 (16.87%)	32 (18.82%)	
>2	9 (10.84%)	36 (21.18%)	
Mean duration (days)	2 (0-6)	2 (0-5)	0.7509
Deceased	14 (16.87%)	26 (15.29%)	0.7474
Months after first admission	5 (2-11)	11 (6.75-12)	**0.0170**

P values display the ANOVA for normally distributed continuous variables, and nonparametric tests (Kruskal-Wallis) for not when the continuous variables are not normally distributed. Pearson chi-square test and fisher's exact were used for categorical values.

Table 3

Rehabilitation vs. No Rehabilitation

	Rehabilitation (n= 39)	No Rehabilitation (n= 214)	p value
Rehospitalisation			0.1815
0	9 (23.08%)	84 (39.25%)	
1	15 (38.46%)	54 (25.23%)	
2	7 (17.95%)	39 (18.22%)	
>2	8 (20.51%)	37 (17.29%)	
Mean duration (days)	2 (1-5)	2 (0-5)	0.2900
Deceased	3 (7.69%)	37 (17.29%)	0.1308
Months after first admission	7 (6-12)	9 (4-12)	0.9374

P values display the ANOVA for normally distributed continuous variables, and nonparametric tests (Kruskal-Wallis) for not when the continuous variables are not normally distributed. Pearson chi-square test and fisher's exact were used for categorical values.

Table 4

1 Year follow-up

Follow-up						
	Total (n=253)	Rehab obese (n=13)	Rehab non-obese (n=26)	No rehab obese (n=71)	No rehab non-obese (n=143)	p values
Rehospitalisation						0.082
0	93 (36.76%)	4 (30.77%)	5 (19.23%)	31 (43.66%)	53 (37.06%)	
1	69 (27.27%)	8 (61.54%)	7 (26.92%)	17 (23.94%)	37 (25.87%)	
2	46 (18.18%)	/	7 (26.92%)	14 (19.72%)	25 (17.48%)	
>2	45 (17.79%)	1 (7.69%)	7 (26.92%)	9 (12.68%)	28 (19.58%)	
Mean duration (days)	2 (0-5)	2 (0-5)	3 (1-5)	2 (0-6)	2 (0-5)	0.6866
Deceased	40 (15.81%)	0	3 (11.54%)	14 (19.72%)	23 (16.08%)	0.3519
Months after first admission	9 (4.25-12)	/	7 (6-12)	5 (2-11)	11 (7-12)	0.0530

P values display the ANOVA for normally distributed continuous variables, and nonparametric tests (Kruskal-Wallis) for not when the continuous variables are not normally distributed. Pearson chi-square test and fisher's exact were used for categorical values.

Table 5

Univariate regression analysis

	Estimate	Odds ratio (CI 95%)	p value
proBNP (n=63)	-0.0000251	0.99(0.99-1.00)	0.6936
LVEF (n=208)			
<40%	0.15042487		0.5411
40-49%	0.03264183		0.9119
>50%	-0.1830667		0.4853

P values display the Pearson chi-square for categorical variables, and logistic regression for the combination of continuous and categorical variables.
LVEF – left ventricular ejection fraction; proBNP -- brain natriuretic peptide

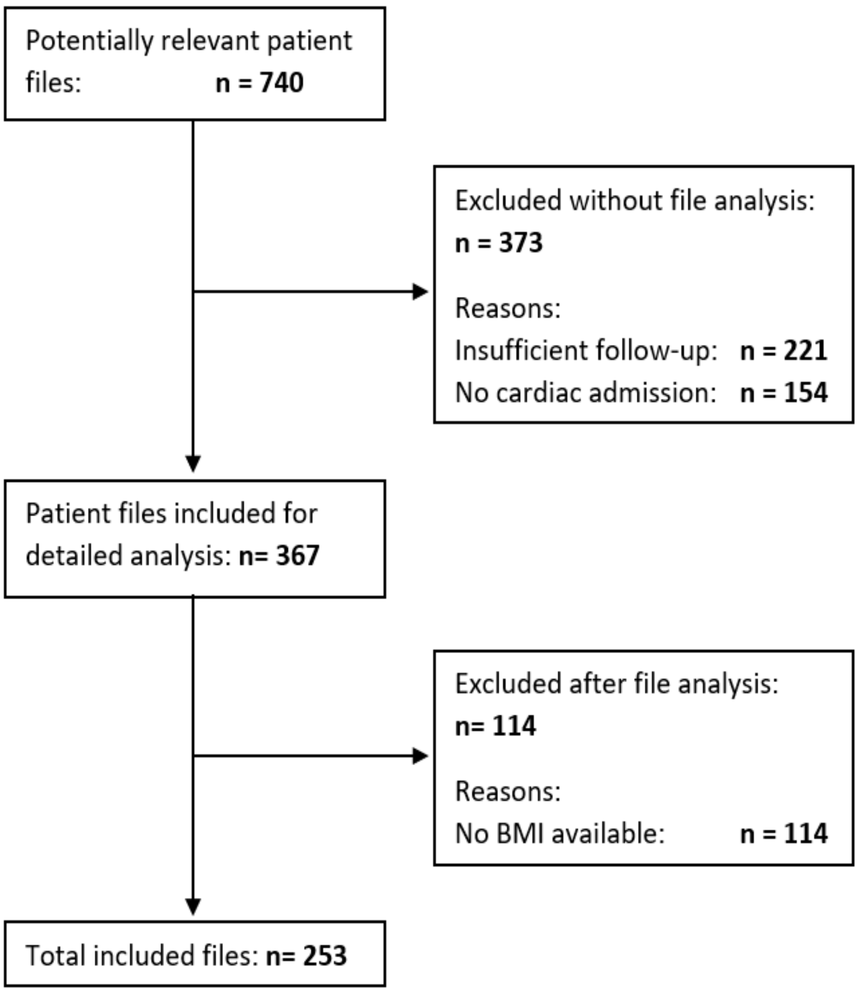

Figure 1. Flowchart participant selection

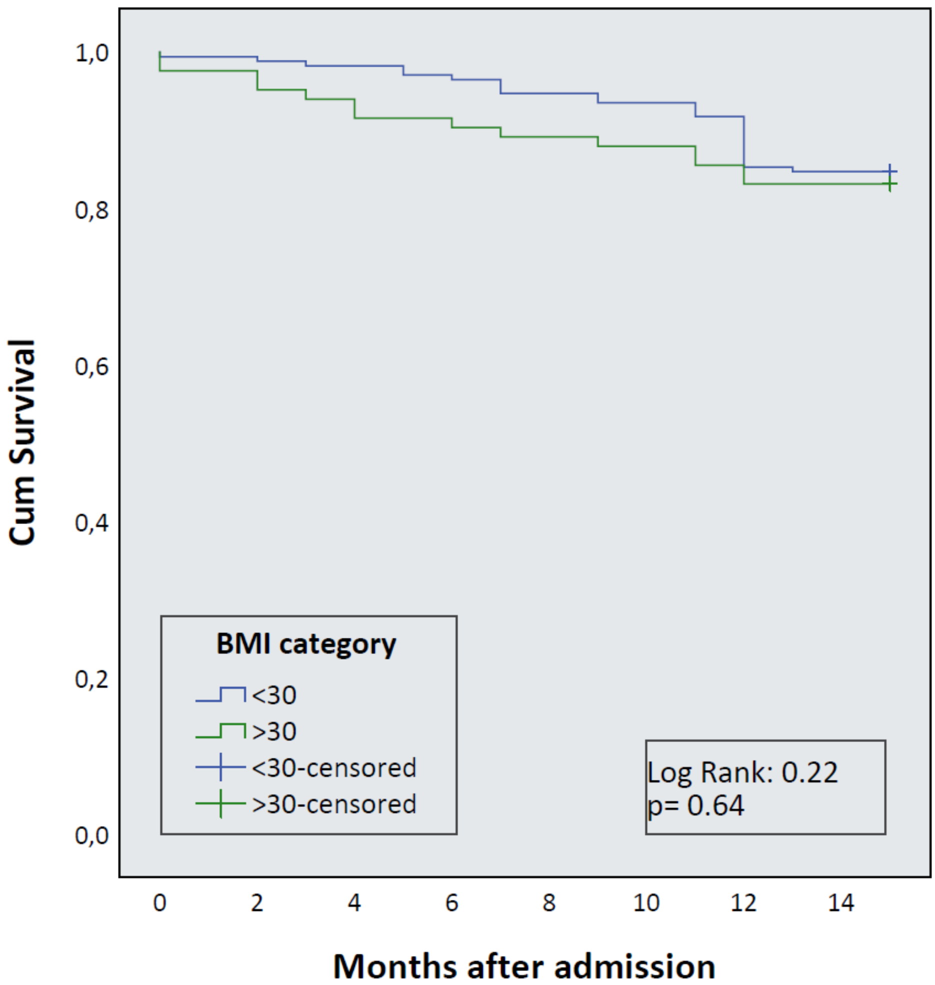

Figure 2. Kaplan-Meier survival curve at 15 months for mortality rate from all causes, obese vs non-obese patients

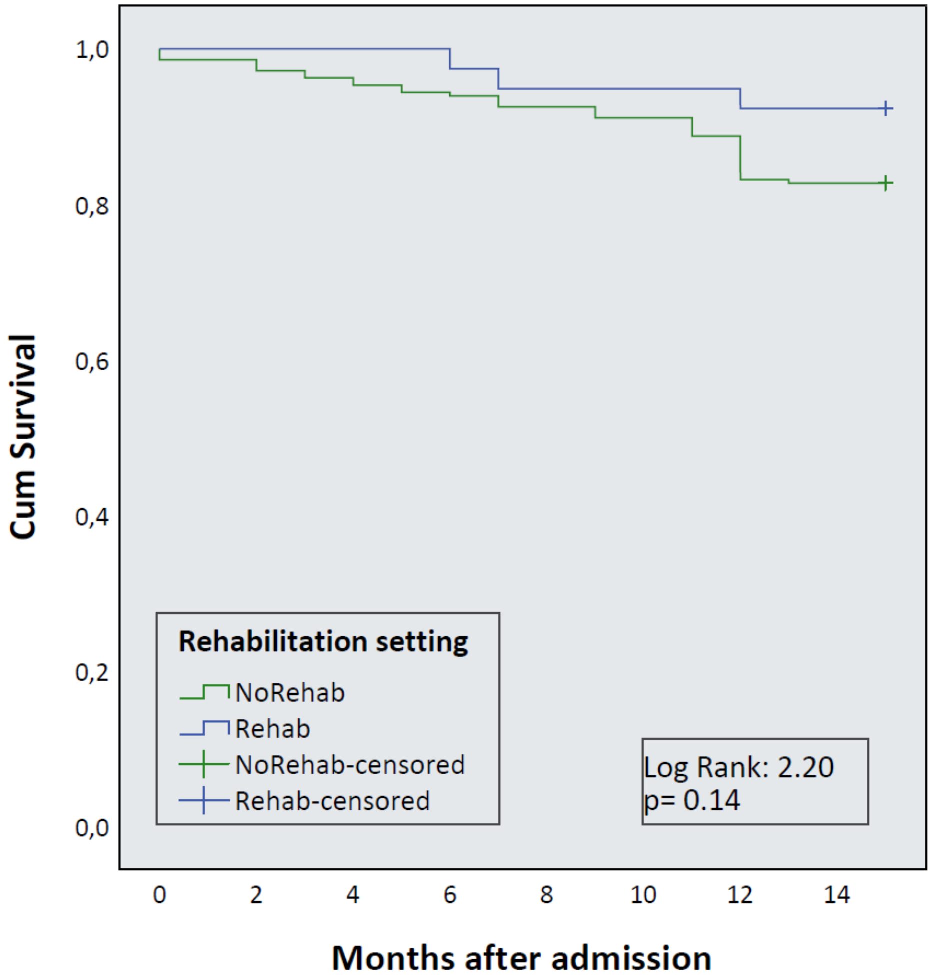

Figure 3. Kaplan-Meier survival curve at 15 months for mortality rate from all causes, rehabilitation vs. no rehabilitation

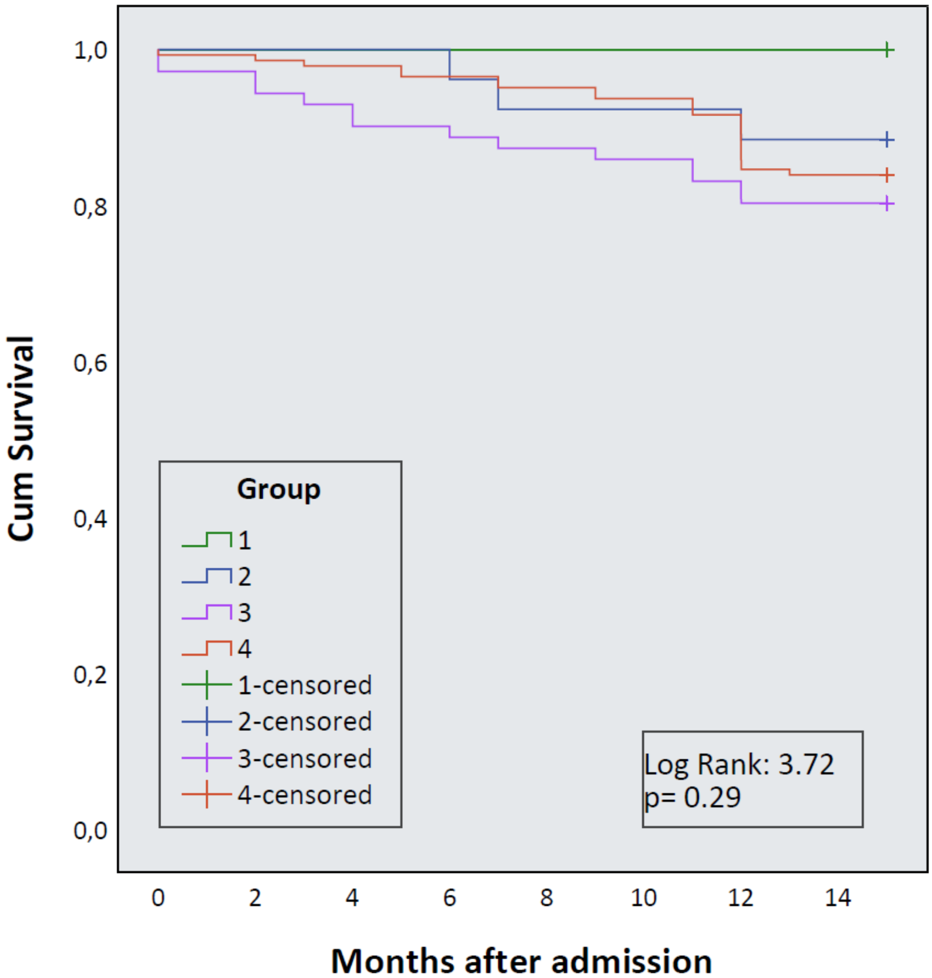

Figure 4. Kaplan-Meier survival curve at 15 months for mortality rate from all causes, 4 groups.

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KNOWLEDGE IN ACTION

Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - *INFORMATION STUDENT*

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1540847 Tielemans Femke**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine kinderen**

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LUIK A - VERPLICHT - IN TE VULLEN DOOR DE STUDENT
PART A - MANDATORY - TO BE FILLED OUT BY THE STUDENT

Titel van Masterproef/*Title of Master's thesis:* THE IMPACT OF CARDIAC REHABILITATION ON OBESE VS. NON-OBESE HEART FAILURE PATIENTS: ~~AR~~ A RETROSPECTIVE STUDY.

☑ behouden - *keep*

O wijzigen - *change to:*

/:

O behouden - *keep*

O wijzigen - *change to*:

In geval van samenwerking tussen studenten, naam van de medestudent(en)/*In case of group work, name of fellow student(s)*: MINNEKE VERBEECK

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LUIK B - VERPLICHT - IN TE VULLEN DOOR DE PROMOTOR(EN)
PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

Wijziging gegevens masterproef in luik A/*Change information Master's thesis in part A:*

⊗ goedgekeurd - *approved*

O goedgekeurd mits wijziging van - *approved if modification of:*

Scriptie/*Thesis:*

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De promotor(en) geeft (geven) de student(en) het niet-bindend advies om de bovenvermelde masterproef in de bovenvermelde periode/*The supervisor(s) give(s) the student(s) the non-binding advice:*

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⊗ de verdediging is openbaar/*in public*

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In tegenstelling tot het niet-bindend advies van de promotor(en) wenst de student de bovenvermelde masterproef in de bovenvermelde periode/*In contrast to the non-binding advice put forward by the supervisor(s), the student wishes:*

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O te verdedigen/*to defend the aforementioned Master's thesis within the aforementioned period of time*

LUIK D - VERPLICHT - IN TE VULLEN DOOR DE STUDENT EN DE PROMOTOR(EN)
PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)

29/05/2021

Datum en handtekening promotor(en)
Date and signature supervisor(s)

31/05/2021

Kenneth Verboven

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Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - *INFORMATION STUDENT*

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1540442 Verbeeck Minneke**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine inwendige**

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/:

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PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)

29/05 /2021

Datum en handtekening promotor(en)
Date and signature supervisor(s)

31/05/2021

Kenneth Verboven

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INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
22/10/2020	Bespreking mogelijkheden onderzoek i.v.m. covid-19	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):
20/11/2020	Bespreking met ZOL-collega's rond mogelijkheden onderzoek	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):
16/04/2021	Bespreking naderend einde van data-collectie: mogelijkheden en struikelblokken rond data-analyse	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):
23/04/2021	Bespreking verdere verloop studie na data-collectie: onderzoeksvraag en data-analyse	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):
4/5/2021	Voorstel data-analyse	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):
19/05/2021	Bespreking data-analyse	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):
26/05/2021	Feedback introductie t.e.m. resultatensectie	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):
31/05/2021	Goedkeuring en laatste feedback omtrent MP	Promotor: Copromotor/Begeleider: Kenneth Verboven Student(e): Student(e):

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): .... **Datum:**......................................

Titel Masterproef:..

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	**NVT**	**1**	**2**	**3**	**4**	**5**
Opstelling onderzoeksvraag	O	O	O	O	O	O
Methodologische uitwerking	O	O	O	O	O	O
Data acquisitie	O	O	O	O	O	O
Data management	O	O	O	O	O	O
Dataverwerking/Statistiek	O	O	O	O	O	O
Rapportage	O	O	O	O	O	O

2) <u>Niet-bindend advies:</u> Student(e) krijgt toelating/geen toelating (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening Student(e)	Datum en handtekening promotor(en)	Datum en handtekening Co-promotor(en)
2/06/2021		03-06-2021