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Nutritional Status of Patients with Heart Failure with Preserved Ejection Fraction

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2022

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Estado Nutricional de Doentes com Insuficiência Cardíaca com Fração de Ejeção Preservada

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Dissertação de candidatura ao grau de Mestre em Nutrição Clínica apresentada à Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto

2022

Agradecimentos

Concluída esta etapa, não podia deixar de expressar o mais profundo agradecimento a todos aqueles que contribuíram para a sua concretização.

Em primeiro lugar, a cada um dos doentes que aceitaram participar neste estudo, o meu mais sincero obrigado.

À Doutora Francisca Almeida Saraiva, estas palavras não chegam para agradecer a sua orientação, a constante motivação e disponibilidade para me receber e ouvir (mesmo fora de horas) com uma paciência infindável, a prontidão para solucionar problemas que foram surgindo e a partilha de tanto conhecimento. Senti-me sempre verdadeiramente orientada.

À minha coorientadora Professora Doutora Cármen Brás Silva pela oportunidade em poder tratar este tema integrada numa equipa espetacular, pela atenção e pelo carinho constantes, pelos conselhos e sugestões. Tenho-lhe uma grande admiração.

A todos os profissionais com quem tive a sorte de me cruzar na UnIC@RISE e que em tanto colaboraram para a concretização deste trabalho e sempre me fizeram sentir “em casa”.

Foram meses de muita aprendizagem e desafios, mas sempre com muita animação.

Cada um(a) tornou alguma parte deste trabalho possível: este é um trabalho nosso, e não um trabalho apenas meu.

Finalmente, a toda a minha família pelo incentivo e apoio incondicional.

Resumo

Introdução: O estado nutricional é um dos fatores mais importantes e determinantes da saúde e a insuficiência cardíaca pode induzir ou intensificar processos que resultam numa deterioração do estado nutricional. A obesidade, a caquexia, a fragilidade, a sarcopenia e a desnutrição são distúrbios comuns do estado nutricional desses doentes e têm impacto significativo no decurso e prognóstico da doença. Embora seja recomendada uma avaliação sistemática do estado nutricional na insuficiência cardíaca, reconhece-se uma lacuna nesta área na maioria dos centros hospitalares, colocando os indivíduos em maior risco de morbimortalidade.

Objetivos: Caracterizar o estado nutricional de doentes com insuficiência cardíaca com fração de ejeção preservada (ICFEP); correlacionar variáveis de diferentes dimensões que caracterizam o estado nutricional; correlacionar o estado nutricional com características cardiovasculares e gravidade da ICFEP.

Métodos: Estudo transversal com doentes em ambulatório com ICFEP de 65 ou mais anos. Os fatores de risco cardiovasculares e comorbilidades, classe funcional da New York Heart Association (NYHA) e dados hematológicos foram recolhidos retrospetivamente. Foram efetuadas medidas antropométricas (peso, altura, perímetros corporais), de composição corporal (por bioimpedância elétrica) e estado funcional (por força de preensão da mão (FPM)) e aplicado o questionário Mini Nutritional Assessment (MNA). A Análise de Componentes Principais foi aplicada para obter uma perceção global do conjunto de dados e selecionar as variáveis mais relevantes associadas ao MNA, FPM, ângulo de fase (AF) e peptídeo natriurético cerebral (BNP). Foram realizadas regressões lineares múltiplas considerando a pontuação final do indicador de desnutrição (MNA), FPM, AF e gravidade da insuficiência cardíaca (através do logBNP) como variáveis dependentes e os componentes principais como variáveis independentes.

Resultados: Foram incluídos 46 doentes, cujo fator de risco cardiovascular mais frequente foi a hipertensão arterial (96%), maioritariamente em classe funcional NYHA II (63%). O MNA classificou 52% dos doentes com estado nutricional normal. A mediana da FPM foi de 15,2 kgf (IQR: 10,9 – 19,7), do BNP foi de 109 pg/mL (IQR: 61-206) e do AF foi de 4,70 º (IQR: 4,00 – 5,40). O AF revelou uma correlação positiva com a FPM e o MNA (rho=0,59, p<0,01 e rho=0,48, p=0,003,

respetivamente); a FPM mostrou-se diretamente associada à albumina (rho= 0,38, p=0,019). A mediana do BNP aumentou à medida que a classe funcional da NYHA piorou (NYHA I: 49 pg/mL (30-92), NYHA II: 154 pg/mL (72-242), NYHA III: 522 pg/mL (152-989), p = 0,002).

Conclusões: O estado nutricional e suas dimensões estão intimamente relacionados com as características cardiovasculares e da insuficiência cardíaca dos indivíduos com ICFEP.

Palavras-Chave: insuficiência cardíaca, insuficiência cardíaca com fração de ejeção preservada, estado nutricional

Abstract

Introduction: The nutritional status is one of the most important factors and determinants of health, and heart failure (HF) can induce or intensify processes that result in a deteriorated nutritional status. Obesity, cachexia, frailty, sarcopenia and malnutrition are common disorders of the nutritional status of these patients and have a significant impact on the course and prognosis of the disease. Although the systematic assessment of nutritional status in HF is recommended, a gap is recognized in this area in most hospital centers, placing individuals at greater risk of morbidity and mortality.

Objectives: To characterize the nutritional status of heart failure with preserved ejection fraction (HFpEF) patient, to correlate variables of different dimensions that characterize nutritional status, and to correlate nutritional status with cardiovascular (CV) features and HFpEF severity.

Methods: Cross-sectional study with HFpEF outpatients aged 65 years or more. CV risk factors and comorbidities, NYHA functional class and haematological data were retrospectively collected. Anthropometric measures (weight, height, body circumferences), body composition (by bioelectrical impedance) and functional status (by hand grip strength) were assessed, and the Mini Nutritional Assessment questionnaire was applied. Principal Component Analysis (PCA) was applied to gain insights of the dataset and select the most relevant variables associated with MNA score, hand grip strength (HGS), phase angle (PA) and brain natriuretic peptide (BNP). Multivariable linear regressions were performed considering malnutrition indicator score (MNA), HGS, PA and HF severity (using logBNP as surrogate) as dependent variables and the PCs as covariates.

Results: Forty-six patients were included, whose most frequent CV risk factor was arterial hypertension (96%) and NYHA class function was II (63%). MNA classified 52% of patients in a normal nutritional status. The overall HGS median was 15,2 kgf (IQR: 10.9 - 19.7). The overall median BNP was 109 pg/mL (IQR: 61-206). The median PA was 4.70 º (IQR: 4.00-5.40). We found that PA was positively correlated with HGS and MNA score (rho=0.59, p <0.01 and rho=0.48, p=0.003, respectively); and HGS directly associated with albumin (rho= 0.38, p=0.019). Median BNP was higher as NYHA functional class worsens (NYHA I: 49 pg/mL (30-92), NYHA II: 154 pg/mL (72-242), NYHA III: 522 pg/mL (152-989), p=0.002)

Conclusions: Nutritional status and its dimensions are closely related to HFpEF patient's CV and HF features.

Keywords: heart failure, heart failure with preserved ejection fraction, nutritional status

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Abbreviations, initials and acronyms

ASPEN- The American Society for Parenteral and Enteral Nutrition

BMI- Body mass index

BNP- Brain natriuretic peptide

CAD- Coronary artery disease

CVD- Cerebrovascular disease

CC- Calf circumference

CHUSJ- Centro Hospitalar Universitário São João

CKD- Chronic kidney disease

CV- Cardiovascular

DM- diabetes mellitus

ESC- European Society of Cardiology

ESPEN- European Society of Parenteral and Enteral Nutrition

EWGSOP2- European Working Group on Sarcopenia in Older People

GFR- Glomerular filtration rate

Hb- Haemoglobin

HF- Heart failure

HFmrEF- HF with midly reduced ejection fraction

HFpEF- Heart failure with preserved ejection fraction

HFrEF- Heart failure with reduced ejection fraction

HGS- Hand grip strength

LVEF- Left ventricular ejection fraction

MNA- Mini Nutritional Assessment

NETDIAMOND- NEw Targets in DIAstolic heart failure: from coMOrbidities to persoNalizeD medicine

NYHA- New York Heart Association

PA- Bioelectrical impedance phase angle

PAD- Peripheral artery disease

PCA- Principal component analysis

SMM- Skeletal muscle mass

WHO- World Health Organization

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Figure 13 – PC3 of BNP

Introduction

1. Heart Failure

Cardiovascular (CV) diseases are the main cause of death worldwide[1] and heart failure (HF) is the world's leading cause of hospitalization[2], being a major and growing public health problem that leads to considerable morbidity and mortality, carrying a heavy burden and costs to the health systems[3].

The true HF prevalence is likely to be higher, as studies usually only include diagnosed cases, but it appears to be 1-2% of adults. The prevalence increases with age: >10% in those aged 70 years or over. Due to populational ageing, the overall incidence is increasing[4].

The European Society of Cardiology (ESC) defines HF as a "clinical syndrome consisting of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise"[4]. Based on the measurement of left ventricular ejection fraction (LVEF), HF is classically classified as:

- HF with reduced ejection fraction (HFrEF): LVEF ≤ 40%
- HF with midly reduced ejection fraction (HFmrEF): LVEF between 41% and 49%
- HF with preserved ejection fraction (HFpEF): LVEF ≥ 50%

2. Heart failure with Preserved Ejection Fraction

HFpEF has become the most common form of HF, with a steadily increasing prevalence with higher rates of morbidity and mortality compared to HFrEF[5-8]. In the community, approximately 50% of patients with HF have a preserved ejection fraction[9] and almost 3/4 of HF patients older than 65 years have HFpEF[10].

The diagnosis of HFpEF remains challenging. According to the ESC Guidelines the diagnosis should include the following:

a) Symptoms and signs of HF;
b) LVEF ≥50%*;
c) Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides.

*Of note, patients with a history of overtly reduced LVEF (≤40%) who later present LVEF≥50%, should be considered to have recovered HFrEF, rather than HFpEF[4].

The pathophysiology of HFpEF is based on a pro-inflammatory state[11]. Ageing and the aforementioned comorbidities induce systemic inflammation, which affects myocardial remodelling and dysfunction through a signalling cascade, starting with coronary microvascular endothelial dysfunction and ending with cardiomyocyte rigidity and hypertrophy. Systemic inflammation not only affects the myocardium, but also other organs such as lungs and kidneys and affects also skeletal muscles leading to different phenotypes[12-14].

Multimorbidity is slightly more severe in HFpEF than in HFrEF, in which approximately 50% of patients have five or more major comorbidities[9]. The clinical profile of a patient with HFpEF is an elderly person, most often female and presenting with cardiovascular risk factors and comorbidities, in particular arterial hypertension, atrial fibrillation, ischemic heart disease, obesity, type 2 diabetes mellitus (DM2), and non-cardiovascular comorbidities such as chronic kidney disease (CKD), anaemia, chronic obstructive pulmonary disease or obstructive sleep apnoea[5, 8, 11-14].

The aetiology of HF varies according to geography: in developed countries, coronary artery disease (CAD) and hypertension are predominant factors, being hypertension the most important cause of HFpEF[4].

According to the most recent guidelines (from 2021), no treatment had been shown to convincingly reduce morbidity and mortality of HFpEF since the drugs used in large clinical trials until then failed to prove beneficial effects. Therefore, the available guidelines recommend therapies for treating comorbidities and controlling the symptoms. Diuretics are by now the only intervention proven to attenuate some symptoms[4, 8, 15]. However, recent trials have been shown potential treatments for HFpEF: the EMPEROR-Preserved trial showed that

empagliflozin reduced the risk of cardiovascular death or hospitalization[16], and the DELIVER Phase III trial had promising results, revealing a statistically significant and clinically meaningful reduction in CV death or worsening of HF with dapagliflozin[17].

HF symptomatology and severity is simply ranked using the New York Heart Association (NYHA) functional classification. However, this staging depends only on the symptoms and there are other indicators of prognosis in HF[4]. Natriuretic peptides such as BNP concentrations are biomarkers of the presence and severity of haemodynamic cardiac stress and HF and cardiac function[18, 19]. BNP levels are strong predictors of risk of death and cardiovascular events in HF patients. Some studies showed that a BNP increase of 100 pg/mL caused a 35% increase in risk of death, and it was the only statistically significant independent predictor of mortality, suggesting that BNP possibly is more useful than traditional predictors of mortality, like the NYHA classification[19, 20]. Bioelectrical impedance phase angle (PA) has been found to be a prognostic marker in several clinical conditions[21-26] and is emerging as a tool in stratifying prognosis in patients with HF[27], being considered a biomarker for cellular mass, membrane integrity and hydration status[27]. In HF, a smaller PA has been associated with a worse functional class and with clinical conditions suggestive of a poor prognosis.[21-23] The aim of a study by Colín-Ramírez et al was to assess the prognostic value of the PA in 389 HF patients, independently of other parameters of a poor prognosis, which endpoint was all-cause mortality. They found that patients below the lowest quartile of PA (<4.2°) had decreased mean body mass index (BMI), HGS, and haemoglobin (Hb) values and a larger proportion of patients in NYHA functional class III and renal failure. Adjusting for age, Hb levels, and diabetes mellitus, a PA <4.2° was found to be an independent predictor of all-cause mortality in HF. Also, patients above the highest quartile of PA (≥5.7°) had better survival, and survival decreased as the PA decreased[21].

Indeed, nutritional disorders are recognized as both risk and prognosis factor for HF[28].

3. Nutritional Status / Nutritional disorders in Heart Failure

As a chronic and progressive disease, HF predisposes patients to various adverse health outcomes and nutritional status seems to be one of the important factors contributing to the development of HF and an important prognostic factor[28-30]. There are two different and broad types of nutritional disorders that frequently affect patients with HF: 1) excessive nutrition, i.e., overweight and obesity, and 2) malnutrition [28].

3.1. Obesity

Obesity is strongly associated with cardiovascular risk factors and diseases, such as arterial hypertension, dyslipidaemia, diabetes mellitus and CAD, which are also related to the development of HFpEF. The systemic inflammation is also a common pathway shared by HF and obesity. Furthermore, adiposity can induce, by itself, changes in cardiac structure and function, overloading the cardiovascular system[6, 31-33]. Obesity may be a major cause of HFpEF and obese HFpEF patients display several pathophysiologic mechanisms that differ from non-obese patients with HFpEF[4].

Several studies show that obesity and overweight in HF have a protective effect in terms of survival, compared to patients of normal weight and low weight - a phenomenon called the "obesity paradox"[4, 5, 29, 32-35]. In this sense, some explanations have been proposed, for example, most studies are based on BMI, which does not take into account neither body composition nor distinguish between metabolically healthy and metabolically unhealthy individuals- patients with greater muscle mass and low adiposity can be wrongly classified as "obese"; as HF is a catabolic state leading to cachexia, obese and overweight patients may have better outcomes because of their higher metabolic reserves; earlier medical attention and diagnosis in the setting of symptoms exacerbated by obesity and/or higher prevalence of comorbidities, such as arterial hypertension and diabetes, may contribute to a potential lead-time bias, giving a false impression of improved survival among HFpEF patients with obesity; adiponectin, an adipocyte-specific cytokine, inversely associated with BMI in subjects with HF (lower adiponectin levels are associated with increased mortality, which means that patients with increased BMI have higher adiponectin and lower mortality)[29, 31-35]. However, the

I-PRESERVE trial suggested a U-shaped relationship of BMI with mortality, showing that severe obesity was not protective[34]. Also, obesity paradox was not observed in patients with diabetes in Zamora et al study where for obese patients with HF and DM2 there is a lower probability of survival compared to obese patients with HF and without DM2[36].

Considering the potential low validity of using BMI in some scenarios, recent studies are shifting the focus from BMI to waist circumference or waist-to-hip ratio as measures of visceral obesity that may have a stronger association to outcomes than BMI, especially in female patients[34, 37, 38]. In a large meta-analysis, looking at the association between BMI and waist circumference with HF incidence and mortality, was found that each 5-unit increment in BMI was associated with an increased risk of HF incidence and mortality, with increased risk for HF incidence starting in the overweight range. Also, each 10-cm increase in waist circumference and each 0.1-unit increase in waist-to-hip ratio increased the risk of incident HF[39]. Some studies have also reported a stronger association between visceral obesity and HFpEF in women than in men[34, 37]. Studies have shown that adiposity measured using waist circumference and hip circumference have effects on metabolic health and CV mortality and are independent of total body fatness assessed with BMI[40].

Recently, malnutrition as well as frailty, sarcopenia and cachexia association with HF have been discussed.

3.2. Cachexia

Cachexia is a complex metabolic syndrome associated with an underlying illness and characterized by loss of muscle with or without loss of fat mass. Is defined by >5% weight loss (or BMI <20 kg/m^2) in ≤ 1 year in the presence of chronic disease, and three of the following five criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry (anaemia, low serum albumin, increased inflammatory markers). Cachexia is a generalized wasting process that may coexist with frailty and affects all compartments of the body: lean tissue, fat tissue and bone tissue. It is associated with reduced functional capacity and decreased survival. HF and cachectic patients have more

severe symptoms and reduced functional capacity, more frequently need for hospitalization and higher mortality[4, 5, 41, 42].

3.3. Frailty

Frailty is a multidimensional dynamic state, independent of age, that makes the individual more vulnerable. It is associated with unfavourable outcomes; reduced access to, and tolerance of, treatments; higher risk of death, hospitalizations, functional decline and longer duration of hospital stay. It may occur in about 45% of the patients, according to a recent meta-analysis[43]. Patients with HF are up to six times more likely to be frail. The prevalence is higher at older ages, correlates significantly with the severity of HF, and contributes to the risk of falls, hospitalization, and death.[4, 41, 42]

3.4. Sarcopenia

The European Consensus on the definition and diagnosis of Sarcopenia defines the disease with three criteria: low muscle strength, low muscle quantity or quality and low physical performance. It occurs physiologically with ageing and is accelerated by chronic diseases, such as HF. Sarcopenia is a major determinant of outcomes outweighing the effect of body weight and BMI, and has a significant impact on functional capacity and is associated with an increased likelihood of events such as falls, fractures, worse neurocognitive profile and death[4, 41, 44].

These three conditions (cachexia, frailty and sarcopenia) overlap and share similar pathophysiological features, where systemic inflammation and hypermetabolism play a key role[41, 42].

3.5. Malnutrition

Malnutrition is also a common condition resulting from energy, proteins, and other macro and micronutrient deficiencies because of low nutritional intake due to intestinal oedema and anorexia, catabolism, among other mechanisms, leading to clinical effects being a consequence of changes in the body's tissues and functions[28]. According to a study by Patrick et al., malnourished HF patients

enter a vicious cycle of "malnutrition, inflammation and cachexia", which causes a great deterioration of the nutritional status[28, 45]. Patients with HFpEF are at an elevated risk for malnutrition, which is associated with an increased risk for CV events. Chronic diseases, such as HF, are associated with increased production of catabolic cytokines, muscle catabolism, and appetite suppression and, thereby, lower albumin levels. Ageing also decreases metabolic reserve of albumin, and therefore, the nutritional status of elderly and chronically ill can be affected[46].
Several studies have outlined the importance of nutritional assessment in clinical practice, especially in target risk groups as HF. Importantly, malnutrition is not only common in underweight/lean individuals but is also common in those who are overweight or obese. The results of a recent study show that while obese patients experience a risk reduction, irrespective of nutritional status, malnutrition at least doubles the risk for death compared with normal weight and normal nutritional status[33]. Since HFpEF is the predominant form of HF in the elderly population and obesity is highly prevalent in HFpEF, there is a high incidence of sarcopenic obesity - the coexistence of obesity and sarcopenia, that is associated with more hospitalizations, worse cardiovascular health, quality of life and mortality[47].

3.6. Nutritional assessment

Nutritional screening and assessment to discriminate malnourished and non-malnourished patients are the first steps in a successful nutritional management in all patients. The American Society for Parenteral and Enteral Nutrition (ASPEN) has defined nutritional assessment as ‘‘a comprehensive approach to diagnosing nutrition problems that uses a combination of the following: medical, nutrition and medication histories; physical examination; anthropometric measurements; and laboratory data’’[45].
Despite the crucial role of undernutrition in the prognosis of HF, no “gold standard” or scientific consensus regarding the nutritional evaluation of patients with HF has been developed. However, several studies suggest that the Mini Nutritional Assessment (MNA) is a candidate tool for the best available method of nutritional assessment in HF[28, 30, 45, 48]. Anthropometric parameters such as BMI and mid-arm circumference, and biochemical parameters such as albumin,

prealbumin and cholesterol, are traditional nutritional evaluation indexes and have long been used in to evaluate nutritional status. Nevertheless, the use of these indexes alone cannot provide comprehensive and accurate indications of nutritional status. The Academy of Nutrition and Dietetics and ASPEN also recommend the use of two or more of the following: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation that may occasionally mask weight loss and diminished functional status as measured by HGS[45, 49].

HGS is the most used method for assessing global muscle strength and is essential when diagnosing sarcopenia and frailty. HGS is becoming a popular marker of nutritional status as muscle function reacts early to nutritional deficiency[50]. Low grip strength is a strong predictor of worse outcomes such as longer hospital stays, increased functional limitations, poor quality of life[44] and a significant indicator of all-cause and cardiovascular mortality[51]. In fact, Leong et al found that HGS was a more strong predictor of cardiovascular mortality than systolic blood pressure[52]. A recent study concluded that higher HGS values were associated with less cardiac hypertrophy and remodelling, which are known to be related with a lower risk of cardiovascular events[53]. The latest guidelines of the European Working Group on Sarcopenia in Older People (EWGSOP2) recommended cut-off points for low HGS as <16 kgf for women and <27 kgf for men[54].

Objectives

The primary objective of the present study is to characterize the nutritional status of HFpEF patients. As secondary objectives, this study aims to

i) correlate variables of different dimensions that characterize the nutritional status- anthropometry, body composition (by bioelectrical impedance), nutritional assessment tool (by MNA), haematological and biochemical analysis and functional status (by HGS);

ii) correlate nutritional status parameters with CV features and HF severity (BNP used as surrogate).

Methods

a) Design

This is a cross-sectional and analytical study of patients included in the NETDIAMOND prospective cohort (NEw Targets in DIAstolic heart failure: from coMOrbidities to persoNalizeD medicine).

b) Setting and Participants

A convenience sample was obtained considering consent patients with HFpEF (clinically defined) and ≥65 years old undergoing first or follow-up appointments at Centro Hospitalar Universitário São João (CHUSJ) between October 2021 and April 2022.

c) Variables

Based on the patients' electronic health records, clinical data was collected including gender, age, NYHA functional class, cardiovascular risk factors (obesity, arterial hypertension, diabetes mellitus, dyslipidaemia, smoking habits), comorbidities (CKD – defined as estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m^2), peripheral arterial disease (PAD), cerebrovascular disease (CVD)), and complementary exams data, such as haematological and biochemical laboratory results.

Data measurement

An anthropometric assessment was performed by measuring weight (kg), height (m) and waist, hip, mid-arm and calf circumferences (cm) by the same operator. BMI (kg/m^2) was calculated and then stratified according to the World Health Organization (WHO) classification[55]. The analysis of body composition was measured by bioelectrical impedance, using the InBody S10 device, being recorded intracellular water (L), extracellular water (L), total body water (L), protein mass (kg), mineral mass (kg), body fat mass (kg), soft lean mass (kg), fat free mass (kg), skeletal muscle mass (kg), percent body fat (%), body water ratio, body cell mass (kg), bone mineral content (kg), visceral fat area (cm^2) and phase angle (°) at 50khz.

HGS (kgf) was measured to assess functional status with a Jammar dynamometer and the mean of three trials was registered, as recommended by the American Society of Hand Therapists[56].

Finally, it was applied a questionnaire to assess nutritional status: MNA. Nutritional status was defined as normal nutritional status, at risk of malnutrition and malnourished according to MNA final score of 24-30 points, 17-23.5 points and <17 points, respectively (Appendix 1).

d) Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics® version 27 and R version 4.1.2. A p-value <0.05 was considered statistically significant. For sample characterization, continuous variables were presented as median and inter-quartile range (IQR), as appropriate, and categorical variables as absolute and relative frequencies. For data exploration and visualization, one unsupervised approach was performed using pairwise complete observations: heatmap and clusters analysis considering both nutritional evaluation and clinical/cardiovascular features.

According to the computed dendrogram, relevant variables were selected to perform Spearman correlations, Mann-Whitney or Kruskall-Wallis tests.

Principal Component Analysis (PCA) was used to gain insights of the dataset and select the most relevant variables for each dependent variable (outcome). PCA produces maps (scores and loadings) showing the relations between the observations and between the variables, simplifying the data interpretation and maximizing information output.

Multivariable linear regressions were done considering malnutrition indicator score (MNA), HGS, PA and heart failure severity (using logBNP as surrogate) as dependent variables and the PCs as covariates. From each significant PC scores ($p<0.05$), the variables that contributed the most were identified. Residuals (error terms, i.e., the differences between the observed value of the dependent variable and the predicted value) distribution were checked for each model.

e) Ethical approval

This study was approved by the CHUSJ Ethics Committee (35-17), and all participants provided written informed consent.

Results

Sample Characterization

A total of 46 HFpEF patients was included in this study. The characteristics of these participants are presented by sex in Table 1. Women represented 56.5% of the sample. The median age was 78 years and it ranged from 65 to 93 years.

The most frequent CV risk factor was arterial hypertension, affecting 96% of these individuals, followed by dyslipidaemia, with 87% cases. Most of the patients (63%) had a NYHA class II, and 8.7% were classified as NYHA III.

Regarding the final score of the MNA questionnaire, 24 patients (52%) had a normal nutritional status, 18 patients (39%) were in risk of malnutrition and 4 patients (8.7%) were malnourished. Table S1 (Appendix 2) represents MNA questionnaire results by question.

The overall HGS median was 15.2 kgf (IQR: 10.9 – 19.7). Men presented higher values than women (19.2 kgf, IQR: 15.0 – 24.6 vs. 14.0 kgf, IQR: 10.1-16.6, p-value: 0.015).

The overall BNP median was 109 pg/ml (IQR: 61 - 206).

Table 1- Sample characterization by sex

Characteristic	Total, n = 46	Women, n = 26	Men, n = 20
Demographics and Anthropometric assessment			
Age, median (IQR), (years)	78 (73, 84)	78 (73, 84)	80 (72, 84)
BMI, median (IQR), (kg/m^2)	29.4 (26.5, 34.4)	30.4 (26.7, 35.1)	28.4 (26.3, 30.3)
Weight, median (IQR), (kg)	77 (68, 87)	72 (64, 84)	79 (74, 87)
Waist circumference, median (IQR), (cm)	91 (81, 97)	85 (80, 98)	93 (86, 96)

Hip circumference, median (IQR), (cm)	94 (90, 106)	100 (90, 112)	92 (90, 99)
Waist-to-hip ratio, median (IQR)	0.91 (0.87, 0.96)	0.88 (0.82, 0.91)	0.96 (0.92, 1.01)
Hand Grip Strength, median (IQR,) (kgf) *(Missing n=5)*	15.2 (10.9, 19.7)	14.0 (10.1, 16.6)	19.2 (15.0, 24.6)
Haematological and Biochemical Results			
Haemoglobin, median (IQR), (g/dL)	12.75 (12.00, 14.35)	12.80 (12.22, 14.12)	12.65 (11.63, 14.75)
Erythrocytes, median (IQR), ($x10^{12}L$)	4.42 (4.08, 4.75)	4.47 (4.10, 4.78)	4.33 (3.81, 4.74)
Albumin, median (IQR), (g/L) *(Missing n=2)*	39.90 (38.18, 41.70)	40.60 (38.65, 41.70)	39.55 (37.72, 41.25)
Total protein, median (IQR), (g/L) *(Missing n=10)*	70.0 (65.2, 72.3)	70.5 (67.9, 72.9)	69.2 (65.1, 71.2)
Total cholesterol, median (IQR), (mg/dL) *(Missing n=2)*	152 (130, 176)	166 (140, 183)	143 (126, 158)
HDL cholesterol, median (IQR), (mg/dL) *(Missing n=2)*	46 (37, 54)	48 (41, 57)	40 (36, 50)
LDL cholesterol, median (IQR), (mg/dL) *(Missing n=2)*	74 (66, 98)	88 (70, 102)	70 (60, 79)
Triglycerides, median (IQR) (mg/dL) *(Missing n=2)*	113 (85, 151)	118 (85, 153)	104 (86, 135)
Apolipoprotein A1, median (IQR), (mg/dL) *(Missing n=15)*	133 (115, 150)	134 (122, 154)	123 (110, 140)
Apolipoprotein B, median (IQR), (mg/dL) *(Missing n=15)*	79 (66, 96)	86 (71, 97)	69 (66, 85)
Lipoprotein (a) , median (IQR), (mg/dL) *(Missing n=15)*	16 (4, 30)	20 (6, 50)	11 (4, 27)
Glucose, median (IQR), (mg/dL) *(Missing n=1)*	120 (100, 143)	110 (98, 139)	128 (110, 173)
HbA1c, median (IQR), (%) *(Missing n=3)*	6.20 (5.60, 6.85)	6.20 (5.70, 6.75)	6.30 (5.52, 7.15)
Iron, median (IQR), (mg/dL) *(Missing n=3)*	74 (60, 96)	80 (68, 95)	66 (56, 94)
Transferrin, median (IQR), (mg/dL) *(Missing n=3)*	256 (237, 305)	254 (238, 307)	256 (230, 296)
Transferrin saturation, median (IQR), (%) *(Missing n=3)*	20 (16, 25)	22 (17, 25)	20 (15, 23)
Ferritin, median (IQR), (ng/mL) *(Missing n=3)*	107 (53, 151)	101 (54, 134)	119 (51, 195)

Vitamin B12, median (IQR), (pg/mL) *(Missing n=6)*	359 (254, 494)	458 (317, 578)	272 (213, 351)
25-OH-Vitamina D, median (IQR), (ng/ml) *(Missing n=4)*	16 (10, 22)	15 (10, 18)	20 (11, 28)
Prealbumin, median (IQR), (mg/dL) *(Missing n=5)*	30 (22, 40)	27 (17, 39)	32 (25, 39)
BNP, median (IQR), (pg/mL)	109 (61, 206)	114 (51, 191)	102 (64, 247)
NYHA			
I, n (%)	13 (28)	6 (23)	7 (35)
II, n (%)	29 (63)	18 (69)	11 (55)
III, n (%)	4 (8.7)	2 (7.7)	2 (10)
Cardiovascular risk factors			
Hypertension, n (%) *(Missing n=1)*	43 (96)	24 (96)	19 (95)
Diabetes, n (%) *(Missing n=1)*	24 (53)	11 (44)	13 (65)
Dyslipidaemia, n (%) *(Missing n=1)*	39 (87)	21 (84)	18 (90)
Smoking habits, n (%)	12 (26)	1 (3.8)	11 (55)
BMI classification (kg/m^2)			
Normal weight (18.5 – 24.9), n (%)	8 (17)	5 (19)	3 (15)
Excess of weight (25 – 29.9), n (%)	20 (43)	8 (31)	12 (60)
Obesity I (30 – 34.9), n (%)	8 (17)	6 (23)	2 (10)
Obesity II (35 – 39.9), n (%)	9 (20)	6 (23)	3 (15)
Obesity III (≥40), n (%)	1 (2.2)	1 (3.8)	0 (0)
Comorbidities			
Atrial fibrillation, n (%)	19 (41)	15 (58)	4 (20)
Peripheral artery disease, n (%)	7 (15)	3 (12)	4 (20)
Anaemia, n (%)	14 (30)	3 (12)	11 (55)
Cerebrovascular disease, n (%)	13 (28)	4 (15)	9 (45)
Coronary artery disease, n (%)	6 (13)	3 (12)	3 (15)

GFR <60 ml/min/1.73m^2, n (%)	28 (64)	12 (48)	16 (84)

The results of the bioelectrical impedance analysis are presented in Table 2, being the median PA 4.70 ° (IQR: 4.00-5.40).

Table 2- Bioelectrical impedance parameters

Parameters	Total, n = 37	Women, n = 19	Men, n = 18
Intracellular water, median (IQR), (L)	22.1 (18.7, 23.9)	18.7 (16.8, 20.9)	23.9 (22.5, 26.1)
Body water ratio, median (IQR)	0.401 (0.391, 0.410)	0.398 (0.386, 0.409)	0.408 (0.395, 0.412)
Extracellular water, median (IQR), (L)	14.90 (11.80, 16.60)	11.80 (11.05, 14.15)	16.60 (15.22, 17.50)
Total body water, median (IQR), (L)	37.0 (30.8, 40.4)	30.8 (28.0, 35.3)	40.8 (37.4, 44.5)
Protein mass, median (IQR), (kg)	9.50 (8.00, 10.30)	8.00 (7.20, 9.00)	10.30 (9.70, 11.28)
Mineral mass, median (IQR), (kg)	3.30 (2.76, 3.55)	2.90 (2.66, 3.22)	3.58 (3.33, 4.10)
Body fat mass, median (IQR), (kg)	30 (24, 36)	31 (28, 39)	27 (23, 32)
Soft lean mass, median (IQR), (kg)	47 (39, 51)	39 (36, 45)	52 (48, 57)
Fat-free mass, median (IQR), (kg)	50 (42, 54)	42 (38, 48)	55 (50, 59)
Skeletal muscle mass, median (IQR), (kg)	26.8 (22.4, 29.2)	22.4 (19.9, 25.3)	29.2 (27.3, 32.1)
Percent body fat, median (IQR), (%)	39 (32, 44)	44 (40, 49)	35 (29, 37)
Body cell mass, median (IQR), (kg)	31.7 (26.8, 34.3)	26.8 (24.0, 30.0)	34.3 (32.2, 37.4)
Bone mineral content, median (IQR), (kg)	2.70 (2.34, 2.91)	2.36 (2.20, 2.69)	2.90 (2.73, 3.32)
Visceral fat area, median (IQR), (cm^2)	140 (99, 154)	150 (128, 177)	121 (97, 146)
Phase angle, median (IQR), (°)	4.70 (4.00, 5.40)	4.70 (3.90, 5.40)	4.70 (4.45, 5.30)

Data Correlation

The heatmap correlating 46 patients and 56 nutritional and cardiovascular features is presented in Figure 1, where stronger correlations can be observed with darker tones and the red colour represents positivity and the blue colour negativity. Figure 2 represents the dendrogram that had grouped 1) body fat variables with body mass index variables (percent body fat, visceral fat area, obesity classes and hip circumference); 2) cardiovascular risk factors, comorbidities, age and HF severity (types of cholesterol, glucose, diabetes, hypertension, dyslipidaemia, chronic kidney disease, BNP, NYHA functional class); 3) nutritional assessment variables, functional status and sex (MNA final score, PA, albumin, HGS, Hb); 4) bioelectrical impedance analysis (extracellular and intracellular water, total body water, skeletal muscle mass, fat-free mass, soft lean mass, bone mineral content, mineral mass), waist and calf circumferences and weight, showing that the lower the height, the more correlated the variables are.

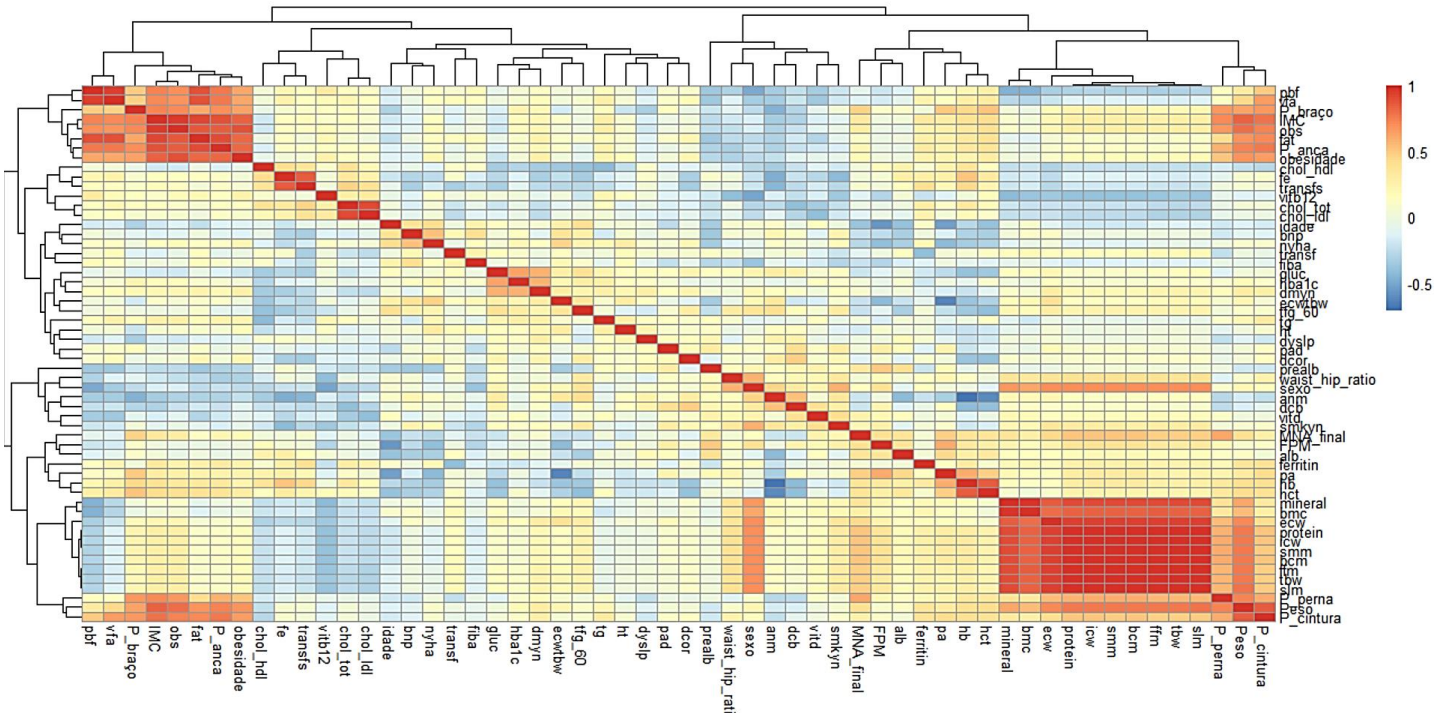

Figure 1- Heatmap of correlations. Pbf- percent body fat; vfa- visceral fat area; P_braço- mid-arm circumference; IMC- BMI; obs- BMI > 30 kg/m^2; fat- fat mass; P_anca- waist circumference; obesidade- obesity; chol_hdl- HDL cholesterol; fe- iron; transfs- transferrin saturation; vitb12- vitamin B12; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; idade- age; bnp- BNP; nyha- NYHA functional class; transf- transferrin; fiba- atrial fibrillation; gluc- glucose; hba1c- hbA1c; dmyn- diabetes mellitus; ecwtbw- body water ratio; tfg_60- chronic kidney disease; tg- triglycerides; ht- arterial hypertension; dyslp- dyslipidaemia; pad- peripheral artery disease; dcor- coronary artery disease; prelab- pre-albumin; waist_hip_ratio- waist-to-hip ratio; sexo- sex; anm- anaemia; dcb- cerebrovascular disease; vitd- vitamin D; smkyn- smoking habits; MNA_final- final score of MNA; FPM- HGS; alb- albumin; pa- phase angle; hb- haemoglobin; hct- erythrocytes; mineral- mineral mass; bmc- bone mineral content; ecw- extracellular water; protein- protein mass; icw- intracellular water; smm- skeletal muscle mass; bcm- body cell mass; ffm- fat-free mass; tbw- total body water; slm- soft lean mass; P_perna- calf circumference; Peso- weight; P_cintura- waist circumference.

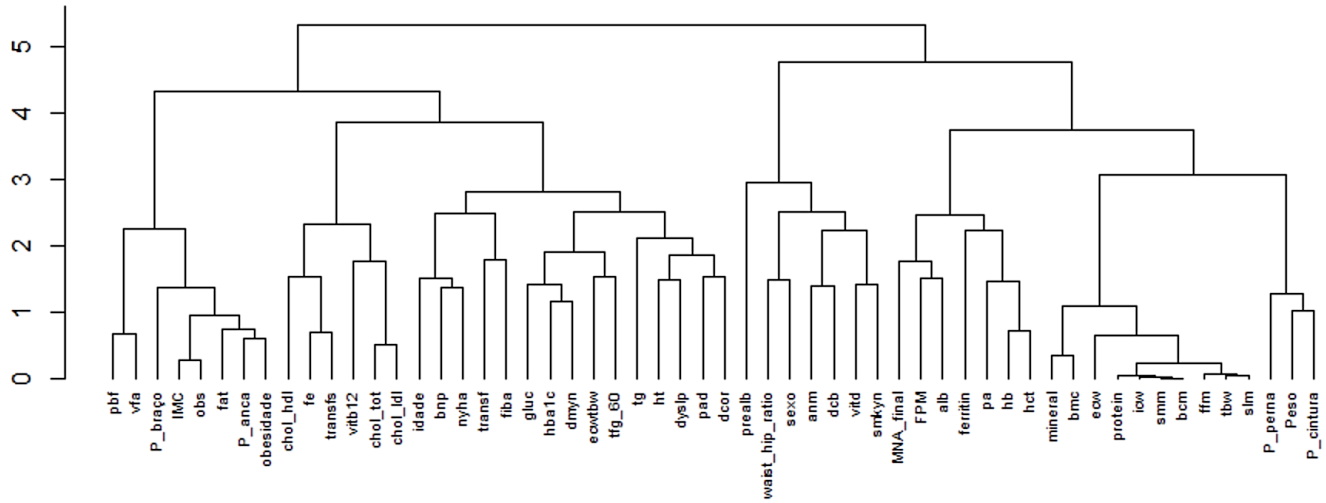

Figure 2- Cluster dendrogram. Pbf- percent body fat; vfa- visceral fat area; P_braço- mid-arm circumference; IMC- BMI; obs- BMI > 30 kg/m^2; fat- fat mass; P_anca- waist circumference; obesidade- obesity; chol_hdl- HDL cholesterol; fe- iron; transfs- transferrin saturation; vitb12- vitamin B12; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; idade- age; bnp- BNP; nyha- NYHA functional class; transf- transferrin; fiba- atrial fibrillation; gluc- glucose; hba1c- hbA1c; dmyn- diabetes mellitus; ecwtbw- body water ratio; tfg_60- chronic kidney disease; tg- triglycerides; ht- arterial hypertension; dyslp- dyslipidaemia; pad- peripheral artery disease; dcor- coronary artery disease; prelab- pre-albumin; waist_hip_ratio- waist-to-hip ratio; sexo- sex; anm- anaemia; dcb- cerebrovascular disease; vitd- vitamin D; smkyn- smoking habits; MNA_final- final score of MNA; FPM- HGS; alb- albumin; pa- phase angle; hb- haemoglobin; hct- erythrocytes; mineral- mineral mass; bmc- bone mineral content; ecw- extracellular water; protein- protein mass; icw- intracellular water; smm- skeletal muscle mass; bcm- body cell mass; ffm- fat-free mass; tbw- total body water; slm- soft lean mass; P_perna- calf circumference; Peso- weight; P_cintura- waist circumference.

MNA and HGS were both positively and significantly correlated with PA (Spearman's rho: 0.48, p= 0.003 and Spearman's rho: 0.59, p <0.001, respectively).

The HGS showed a moderate positive correlation with albumin (Spearman's rho: 0.38, p=0.019).

The median BNP showed increased values according to NYHA functional classes (NYHA I: 49 pg/ml, IQR: 30-92; NYHA II: 154 pg/ml, IQR: 72-242 and NYHA III: 522 pg/ml, IQR: 152-989, p-value=0.002, Kruskall-Wallis test).

Principal Component Analysis

Mini Nutritional Assessment

The first 10 PCs accounted for approximately 75% of the total variance.

The most relevant features linked to MNA final score were extracted from PC1 (Figure 3), PC3 (Figure 4) and PC4 (Figure 5) (Adjusted R-squared of the model: 0.36, $p<0.01$). From PC1, the selected variables were all positive relationships from bioelectrical impedance analysis (total body water, skeletal muscle mass, soft lean mass, protein mass, intracellular water, fat free mass, extracellular water and body cell mass), weight and waist and calf circumferences. The PC3 evidenced cardiovascular risk factors (diabetes mellitus), other comorbidities (chronic kidney disease) and NYHA functional class as inversely related with MNA, and transferrin saturation, haemoglobin, iron, HDL cholesterol and albumin directly related with MNA final score. The PC4 evidenced pre-albumin, albumin, vitamin D and functional status (HGS) as positively related with MNA score, while age, total and LDL cholesterol and severity of HF (BNP) were inversely related with MNA scoring. Of note, cerebrovascular and peripheral artery disease were also positively related with MNA score. Table 3 summarizes these informations.

Table 3- MNA selected variables from PCA

<table>
<tr><th colspan="2">MNA</th></tr>
<tr><th>Positively related</th><th>Negatively related</th></tr>
<tr><td>Body composition
Total body water / Intracellular water / Extracellular water / Soft lean mass / Skeletal muscle mass / Protein mass / Mineral mass / Body cell mass / Fat-free mass
Functional status (HGS)</td><td rowspan="2">CV risk factors
Diabetes / Total cholesterol / LDL cholesterol</td></tr>
<tr><td>Comorbidities
Cerebrovascular / Peripheral artery disease</td></tr>
<tr><td>Anthropometry
Weight / Waist circumference / Calf circumference</td><td>Comorbidities
CKD</td></tr>
<tr><td>Haematological
Transferrin saturation / Haemoglobin / Iron / Albumin / Pre-albumin / HDL cholesterol / Vitamin D</td><td>Heart Failure
NYHA functional class / BNP</td></tr>
<tr><td></td><td>Age</td></tr>
</table>

Hand Grip Strength

The first 10 PCs accounted for approximately 75% of the total variance.

The most relevant variables linked to HGS were extracted from 5 components: PC1 ($p<0.05$), PC3 ($p=0.03$), PC4 ($p<0.01$), PC6 ($p=0.03$) and PC7 ($p=0.03$) (Adjusted R-squared of the model: 0.43, $p<0.01$). From the PC1 (Figure 6), the selected variables were all positive relationships from bioelectrical impedance analysis (total body water, skeletal muscle mass, soft lean mass, protein mass, intracellular water, fat-free mass, extracellular water, body cell mass), weight and waist circumference. PC3 (Figure 7) showed transferrin saturation, haemoglobin, iron, HDL cholesterol and albumin as directly related with HGS, and cardiovascular risk factors (diabetes), other comorbidities (CKD) and NYHA functional class as inversely related with HGS. In the PC4 (Figure 8) it is possible to see that vitamin D, pre-albumin, albumin, cerebrovascular disease and peripheral arterial disease are directly related with HGS, and age, total and LDL cholesterol, BNP and NYHA are inversely related with HGS. The PC6 (Figure 9) shows triglycerides, HbA1c, glucose and diabetes as inversely related with HGS, while ferritin, coronary artery disease and cerebrovascular disease as directly related with HGS. The last component, PC7 (Figure 10) revealed transferrin, arterial hypertension, HbA1c, glucose, atrial fibrillation, diabetes and dyslipidaemia with an inverse relation with HGS, while smoking habits were directly associated with HGS. These informations are summarized in Table 4.

Table 4- HGS selected variables from PCA

HGS	
Positively related	**Negatively related**
Body composition Total body water / Intracellular water / Extracellular water / Soft lean mass / Skeletal muscle mass / Protein mass / Mineral mass / Body cell mass / Fat-free mass	**CV risk factors** Diabetes / HbA1c / glucose Dyslipidaemia / total cholesterol / LDL cholesterol Hypertension

Anthropometry Weight / Waist circumference	
Comorbidities Coronary artery disease / Cerebrovascular disease / Peripheral arterial disease / Smoking habits	**Comorbidities** CKD / Atrial fibrillation
Haematological Ferritin / Transferrin saturation / Haemoglobin / Iron / HDL cholesterol / Albumin / Pre albumin / Vitamin D	Age
	Heart Failure BNP / NYHA functional class

Phase Angle

The first 10 PCs accounted for approximately 75% of the total variance.

The most relevant variables/ features linked to PA were extracted from 2 components: PC1 and PC3 (both $p<0.01$) (Adjusted R-squared of the model: 0.38, $p<0.01$). From PC1 (Figure 11) we found only positive relations with PA from variables of bioelectrical impedance (total body water, skeletal muscle mass, soft lean mass, protein mass, mineral mass, intracellular water, free-fat mass, extracellular water, body cell mass) and weight. The PC3 (Figure 12) demonstrated saturation of transferrin, haemoglobin, iron, HDL cholesterol and albumin as directly associated with PA too, while chronic kidney disease, diabetes and NYHA functional class as inversely related with PA. Table 5 summarizes these informations.

Table 5- PA selected variables from PCA

PA	
Positively related	**Negatively related**

Body composition Total body water / Intracellular water / Extracellular water / Soft lean mass / Skeletal muscle mass / Protein mass / Mineral mass / Body cell mass / Fat-free mass	**CV risk factors** Diabetes
Anthropometry Weight / Waist circumference / Calf circumference	**Comorbidities** CKD
Haematological Transferrin saturation / Haemoglobin / Iron / HDL cholesterol / Albumin	**Heart Failure** NYHA class function

Brain Natriuretic Peptide

The first 10 PCs accounted for approximately 75% of the total variance.

The most relevant variables/ features linked to BNP were extracted from PC3 (Figure 13) ($p<0.01$; adjusted R-squared of the model: 0.20, $p=0.05$); saturation of transferrin, iron, haemoglobin, HDL cholesterol and albumin were inversely associated with BNP while NYHA class function, CV risk factors (diabetes) and other comorbidities (CKD) presented an opposite relation with BNP. These informations are summarized in Table 6.

Table 6- BNP selected variables from PCA

BNP	
Positively related	**Negatively related**
CV risk factors Diabetes	**Haematological** Transferrin saturation / Iron / Haemoglobin / Albumin / HDL cholesterol
Comorbidities CKD	
Heart Failure NYHA class function	

Discussion

In this study, we stated that most patients with clinically defined HFpEF evidenced alterations in nutritional status as assessed by MNA, functional status/muscle strength by HGS and PA. Twenty two out of 46 HFpEF patients were at risk of malnutrition or malnourished. Also, 78% of the patients had low HGS and the median phase angle was 4.70 °.

Furthermore, close relationships were defined between cardiovascular and clinical variables and nutritional features using unsupervised approaches (clusters and PCAs).

Mini Nutritional Assessment

MNA is the most established nutritional screening tool validated for older adults (≥ 65 years). The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends the use of MNA for the non-hospitalized elderly[57], like our population.

Through the PCA of the MNA final score, it is noted that some blood data influenced malnutrition assessed by MNA, which coincident with many other previous studies[58, 59]. In fact, blood biomarkers are often used in clinical practice as aids for malnutrition assessment. A systematic review and meta-analysis evaluated biomarkers association with malnutrition screening tools such as MNA and showed that the most commonly studied blood biomarker (and also studied in the present investigation) was albumin, followed by haemoglobin, total cholesterol, prealbumin, iron and estimated glomerular filtration rate. Among 17 blood biomarkers, the estimated concentrations of albumin ($p < 0.001$), haemoglobin ($p < 0.001$), total cholesterol ($p < 0.001$) and prealbumin ($p < 0.001$) for patients identified by MNA as malnourished were statistically lower than those without a malnutrition risk. The results from this meta-analysis reported that several blood biomarkers, including albumin, prealbumin, haemoglobin and total cholesterol are useful biochemical indicators of malnutrition, but did not find sufficient evidence to support the use of iron as a marker of malnutrition[59]. Similarly, our PCA results also emphasized albumin, prealbumin, haemoglobin and

cholesterol as determinants of MNA. On the contrary, in our sample we found a relationship between iron levels and MNA results, and an association of lower values of total cholesterol with a better nutritional status assessed by MNA.

A study in hospitalized patients admitted to an acute geriatric ward had different findings compared to our ambulatory patients' sample: there was no significant correlation between MNA and serum albumin and prealbumin. Noteworthy, albumin and prealbumin are known to be affected by presence of inflammation, regardless of underlying nutrition status[60]. The same study found a borderline significant association of GFR with MNA (p=0.06)[61], corroborating our results.

MNA incorporates calf circumference as an aid in assessment for malnutrition so, it was expected that these two variables would be positively related. Both calf circumference (CC) and skeletal muscle mass (SMM) and were positively associated with MNA in our study. SMM and function are classic markers of nutritional status closely associated with clinical outcomes, including morbidity and mortality. CC is an anthropometric method receiving interest as marker of SMM. It is generally used in geriatric studies as a muscle marker and recently and was recommended as a muscle marker for sarcopenia by the Asian Working Group for Sarcopenia Consensus[62]**.** Drescher et al findings were similar to the present study as the CC correlated with MNA and other nutrition screening tool, suggesting that the CC represents a valid parameter of malnutrition[61].

Vitamin D is a widely studied vitamin in the nutrition sphere. Here, it appears with a positive association with the result of the MNA questionnaire, like many other studies have found[63-66]. Another Portuguese study in older adults over 65 years old reported that participants classified either at risk of malnutrition or as malnourished based on MNA, had also an increased risk of vitamin D deficiency (<30 nmol/L (<12ng/mL)) when compared to participants in good nutritional condition[65].

Hand Grip Strength

HGS has been used as a marker of the nutritional status and the low muscle strength assessed by HGS constitutes one of the 3 criteria for the definition of sarcopenia. The overall median HGS was 15.2 kgf (IQR: 10.9 – 19.7), being 19.2

kgf (IQR: 15.0 – 24.6) in men and 14.0 kgf (IQR: 10.1-16.6) in women, stating that our HFpEF sample is below the normal limits: 71% of women and 88% of men had HGS values below the recommended cut-off points of <16 kgf for women and <27 kgf for men[44]. In a systematic review and meta-analysis which purpose was to estimate the current prevalence of sarcopenia in patients with HF, the global prevalence of sarcopenia was 26% (95% CI: 16–37%) for ambulatory patients[67], which is significantly lower than our 78% prevalence of HGS below normal. Of note, our study can only assess a probable sarcopenia and further exploration is needed to diagnose sarcopenia considering the EWGSOP2: after a positive questionnaire or a present clinical suspicion, low HGS assesses probable sarcopenia, and then, low muscle quantity/quality confirms sarcopenia[44].

The HGS has also been used to assess frailty. According to Fried et al[68], one of the five criteria for the assessment of frailty phenotype is weakness, evaluated as low HGS adjusted for gender and BMI, and, by just fulfilling 1 or 2 criteria, a subject is classified as pre-frail. Using their classification 94% men and 92% women had low HGS. Again, we can only consider pre-frailty, as these patients showed at least one (low HGS) criterion. A recent study was conducted to estimate the frequency of frailty (according to Fried et al) in a Portuguese sample of 1457 subjects (≥65 years) and reported the frequency of pre-frailty and frailty as 54.3% and 21.5%, respectively[69]. Similarly, in sample of 136 HF outpatients (24-81 years), Valdiviesso et al identified 57.4% as pre-frail and 15.4% as frail, assessed according to Fried criteria[70].

Our study supports several associations between HGS and cardiovascular/clinical features, as also between HGS and other nutritional dimensions. Albumin is a biomarker reported in the literature to be relevant for HGS in later life. Serum albumin, a negative acute phase protein, decreases in older adults because of its increased catabolism and decreased synthesis during inflammation and malnutrition[71]. Several studies have reported that serum albumin level in the elderly is significantly associated with muscle mass, muscle strength and functional capacity[72]. Our study found a positive correlation between the two markers, which consents with the available literature, not only in the cardiovascular field, but also in other populations such as osteoporosis and healthy individuals[71-73]. Schalk et al examined the association between serum albumin

and muscle strength and future decline in muscle strength in older (aged 65 to 88.) men and women. These authors stated that that lower serum albumin was associated with weaker muscle strength ($p < 0.001$), lower serum albumin was associated with muscle strength decline over 3 years ($p < 0.01$), and lower serum albumin was associated with substantial decline in muscle strength[74]. On the contrary, Heimburger et al, who studied patients with CKD closed to start dialysis did not found serum albumin as related with HGS[75]. Anthropometric measures (weight, waist circumference) were positively related with HGS at our study. Much of the results of the available literature showed positive associations with weight too, but negative associations with waist circumference[76-79]. A study in Taiwan that enrolled 2,470 individuals (≥65 years old) was conducted to assess correlations of HGS with various factors concluded, through different statistical tests, that HGS was positively associated with weight and negatively associated with waist circumference[77]. As our analysis was not sex-adjusted or sex-stratified, this result can be explained by the differences between men and women regarding the median waist circumference (men: 93 cm vs. women 85 cm). Features like age, BNP levels, some CV risk factors, biomarkers (glucose, total cholesterol, triglycerides, iron, transferrin saturation) and vitamin D seem to have a negative association with HGS, which some studies corroborate[63, 75, 76, 80-83]: being older, having a more severe HF and worse lipidic and glucose profile is associated with a lower HGS. Iron deficiency (ID) contributes to impaired functional performance and reduced quality of life in patients with chronic illnesses[84]. A study with 140 patients admitted to a stroke unit, showed that HGS was reduced in patients with ID compared to patients without ID ($p<0.001$) at baseline, and after one year patients with ID remained with lower HGS compared to patients with normal iron status, whereas an improvement of HGS was observed in patients with normal iron status[84].

Furthermore, NYHA functional class was negatively related with HGS, like a study that showed that HGS in patients with HF had a significant correlation with NYHA functional class, mortality and hospitalization rates. Therefore, its measurement could be a valuable tool to detect patients with advanced HF[85]. Although some correlations between comorbidities and HGS seemed unexpected or not biologically plausible, such as positive relationships between HGS and smoking

status, cerebrovascular, peripheral, or coronary diseases, these findings can be justified by higher prevalence of these cardiovascular risk factors or diseases in the men subsample for whom higher HGS is expected. For coronary artery disease, our sample presented 50% proportion for women and men, while for smoking, peripheral artery disease and cerebrovascular disease, 93%, 57% and 69% were men, respectively. Indeed, men presented higher HGS than women (median 19 kgf vs 14 kgf, p=0.015).

Phase Angle

The PA has been reported as a measure of cell membrane integrity and vitality, expressing the quantity and quality of soft tissues. Moreover, PA is considered a superior prognostic marker that should be applied as a nutritional screening tool in various patient groups[86-88]. PA was found to be significantly and positively associated with both MNA and HGS, which is in line with more studies[21, 86, 87, 89, 90]. Disease, inflammation and malnutrition decrease PA values compared with healthy individuals. MNA contains a score for acute illness so the information about phase angle and prognosis is particularly relevant[87]. Anthropometric measurements that reflect muscle mass, such as mid-arm and calf circumference, also show relations with the complications of the disease[86], and are two components of the MNA. Disease-related malnutrition is characterized by an increased extracellular water/intracellular water and a concomitant decrease in body cell mass, both lowering PA[87, 88]. Low PA predicts impaired muscular strength, risk of poor nutritional status and decreased survival[87]. The strong correlation between PA, muscle mass and strength, stimulated research to determine the prognosis of phase angle in geriatrics[87]. Reis et al studied 177 hospitalised adults and found that individuals with lower PA values had higher odds of presenting low HGS. Thus, PA explained 29% of the variance in HGS and was positively correlated with HGS[89]. In our sample, the bioelectrical phase angle was directly associated with bioelectrical parameters, such as fat-free mass, and biomarkers such as haemoglobin, iron, albumin, corroborating other studies' results[21, 91]. A study performed in hospitalised patients reported lower PA values being associated with lower weight, fat-free mass, muscle mass and body fat

percentage[89]. Recently, Gonzalez et al, found the highest positive correlation was between the PA and fat-free mass when investigating which were the main predictors of PA[92]. On the other hand, PA was negatively associated with diabetes, CKD and NYHA in our study, which agrees with previous studies[21, 93-96].

Brain Natriuretic Peptide

BNP is secreted by the cardiac ventricles in response to increased wall stress due to volume overload or higher end-diastolic pressure inside the ventricle itself[97, 98], being a biomarker of HF severity. So, it would be expected that BNP values would increase with the severity of the clinical symptoms as NYHA assesses. Indeed, this study showed that BNP values increased with the progression of the NYHA functional class, agreeing with previous studies[97-100]. Moreover, a study revealed that plasma BNP stayed unchanged in patients whose NYHA class remained unchanged, though BNP decreased in those in which NYHA class improved[100].

Having diabetes and CKD was positively associated with BNP values. An interesting prospective study with 79 diabetic patients measured plasma glucose, glycosylated haemoglobin and BNP before and after glycaemic regulation and a significant decrease in BNP levels ($p< 0.001$) were observed, after improving glycaemic control. The decrease in BNP levels was positively correlated with the decrease in HbA1c ($p = 0.003$) and fasting plasma glucose ($p = 0.002$)[101]. In fact, hyperglycaemia may induce dysfunction of the cardiac myocytes, and/or plasma glucose per se, may induce the secretion of cardiac natriuretic peptides[101]. Regarding CKD, BNP plays an important role as a major player in the heart-kidney connection. The elevated levels of BNP may be the result of an increased cardiac release in CKD patients. In CKD patients, the increase in circulatory blood volume, the elevation in BP due to volume overload and arterial stiffness, and the cardiac hypertrophy and HF among others, can contribute to the elevation in BNP. The elevation of BNP in CKD patients is partly due to the impaired clearance of BNP from the kidneys[102]. In a study with 229 subjects, eGFR inversely and significantly correlated with BNP, with BNP levels increasing with the deterioration in kidney

function[103]. Haemoglobin, albumin, iron, transferrin saturation and HDL had a negative relation with BNP at our study, which is in line with other studies[104-108].

Finally, it is possible to note (Table 7) some groups of features that constantly appear together, suggesting that they may be the most important contributors of the four variables:

a) Diabetes, CKD and NYHA functional class appeared in all four, being inversely related with MNA, HGS and PA, and directly related with BNP.
b) Haemoglobin, albumin, iron, transferrin saturation and HDL cholesterol appeared in all four too, as positively associated with MNA (*except HDL), HGS and PA, and negatively associated with BNP.
c) Bioelectrical impedance parameters (total body water, intracellular water, extracellular water, skeletal muscle mass, soft lean mass, fat-free mass, protein mass, body cell mass) always demonstrated positive relations with MNA, HGS and PA, but not with BNP.

Table 7- Main contributors of the four variables

	MNA	HGS	PA	BNP
Diabetes, CKD, NYHA	**-**	**-**	**-**	**+**
Haemoglobin, Albumin, Iron, Transferrin saturation, HDL cholesterol	**+***	**+**	**+**	**-**
Bioelectrical impedance parameters	**+**	**+**	**+**	**NR**

NR- non related

Limitations

This study has limitations that should be considered when interpreting the results. Firstly, the sample size is small, which can limit statistical power. However, it is a reasonable number of patients considering the short time for data collection. Secondly, the cross-sectional design of this study unable to determine the direction of the associations/define causality. Thirdly, the study population was limited to Portuguese patients. Fourthly, variables related with usual medication or supplements were not available for this study. Lastly, irregular fluid distribution

may induce errors in bioelectrical impedance devices and patients did not always meet the optimal conditions necessary for a more precise assessment (for example, they were not always in a fasting condition).

Strengths

To our knowledge, there is no other study that assesses the nutritional status of HFpEF patients in such depth, using not only a nutritional status assessment tool (as most studies do), but also bioelectrical impedance, haematological and biochemical analysis and handgrip strength, and its relationship with CV risk factors and biomarkers. Moreover, all measurements were performed by the same operator and according to the guidelines of the Organizations/Societies.

Future research

It would be interesting to continue this work and add data on food intake and medication/food supplementation, perform food/nutritional interventions and measure CV events/clinical outcomes during follow-up. It would also be important to apply this work on nutritional status assessment in hospitalized with HFpEF as there is no study in Portugal, and it's a much more vulnerable population. It is expected that the incidence of HFpEF will continue to increase due to aging and the increase in the prevalence of associated metabolic comorbidities[6]. Pharmacological therapy has not been shown to be effective in these patients, making it necessary and urgent to study and implement non-pharmacological interventions, in which nutrition can play a key role[109]. In this sense, further studies are needed to demonstrate the impact of food, to assess the effectiveness of intervention on nutritional status in HF (and specifically for HFpEF). Thus, personalized monitoring and intervention by Nutritionists will be valued, to which all patients must have access, as recommended by the most recent guidelines.

Conclusions

Besides being chronically ill, HFpEF patients have several associated comorbidities, putting them in a very vulnerable state. There is, in fact, a close link between the nutritional status and its dimensions and several CV factors linked to HF, contributing to a better or worse progression of this disease. There is an important need of not neglecting the assessment of nutritional status in HF patients.

References

1. Organization WH. Global Health Estimates: Life expectancy and leading causes of death and disability. 2019. Disponível em: https://www.who.int/healthinfo/mortality_data/en/.
2. Ferreira JP, Kraus S, Mitchell S, Perel P, Pineiro D, Chioncel O, et al. World Heart Federation Roadmap for Heart Failure. Glob Heart. 2019; 14(3):197-214.
3. Snipelisky D, Chaudhry SP, Stewart GC. The Many Faces of Heart Failure. Card Electrophysiol Clin. 2019; 11(1):11-20.
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36):3599-726.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27):2129-200.
6. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2020; 17(9):559-73.
7. Senni M, D'Elia E, Emdin M, Vergaro G. Biomarkers of Heart Failure with Preserved and Reduced Ejection Fraction. Handb Exp Pharmacol. 2017; 243:79-108.
8. Iliesiu AM, Hodorogea AS. Treatment of Heart Failure with Preserved Ejection Fraction. Adv Exp Med Biol. 2018; 1067:67-87.
9. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017; 14(10):591-602.
10. Pagel PS, Tawil JN, Boettcher BT, Izquierdo DA, Lazicki TJ, Crystal GJ, et al. Heart Failure With Preserved Ejection Fraction: A Comprehensive Review and Update of Diagnosis, Pathophysiology, Treatment, and Perioperative Implications. J Cardiothorac Vasc Anesth. 2021; 35(6):1839-59.
11. Tromp J, Khan MA, Klip IT, Meyer S, de Boer RA, Jaarsma T, et al. Biomarker Profiles in Heart Failure Patients With Preserved and Reduced Ejection Fraction. J Am Heart Assoc. 2017; 6(4)
12. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation. 2016; 134(1):73-90.
13. van Heerebeek L, Paulus WJ. Understanding heart failure with preserved ejection fraction: where are we today? Neth Heart J. 2016; 24(4):227-36.
14. Upadhya B, Kitzman DW. Heart failure with preserved ejection fraction: New approaches to diagnosis and management. Clin Cardiol. 2020; 43(2):145-55.
15. Tomasoni D, Adamo M, Lombardi CM, Metra M. Highlights in heart failure. ESC Heart Fail. 2019; 6(6):1105-27.
16. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021; 385(16):1451-61.
17. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022

18. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019; 21(6):715-31.
19. Doust J, Lehman R, Glasziou P. The Role of BNP Testing in Heart Failure. American Family Physician. 2006; 74:1893-98.
20. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in HF. British Medical Journal. 2005; 330
21. Colin-Ramirez E, Castillo-Martinez L, Orea-Tejeda A, Vazquez-Duran M, Rodriguez AE, Keirns-Davis C. Bioelectrical impedance phase angle as a prognostic marker in chronic heart failure. Nutrition. 2012; 28(9):901-5.
22. Colin-Ramirez E, Castillo-Martinez L, Orea-Tejeda A, Asensio Lafuente E, Torres Villanueva F, Rebollar Gonzalez V, et al. Body composition and echocardiographic abnormalities associated to anemia and volume overload in heart failure patients. Clin Nutr. 2006; 25(5):746-57.
23. Castillo Martinez L, Colin Ramirez E, Orea Tejeda A, Asensio Lafuente E, Bernal Rosales LP, Rebollar Gonzalez V, et al. Bioelectrical impedance and strength measurements in patients with heart failure: comparison with functional class. Nutrition. 2007; 23(5):412-8.
24. Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL, Grutsch JF, et al. Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. BMC Cancer. 2008; 8:249.
25. Faisy C, Rabbat A, Kouchakji B, Laaban JP. Bioelectrical impedance analysis in estimating nutritional status and outcome of patients with chronic obstructive pulmonary disease and acute respiratory failure. Intensive Care Med. 2000; 26(5):518-25.
26. Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG, Grutsch JF, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. Am J Clin Nutr. 2004; 80(6):1634-8.
27. Scicchitano P, Ciccone MM, Passantino A, Valle R, De Palo M, Sasanelli P, et al. Congestion and nutrition as determinants of bioelectrical phase angle in heart failure. Heart Lung. 2020; 49(6):724-28.
28. Wawrzenczyk A, Anaszewicz M, Wawrzenczyk A, Budzynski J. Clinical significance of nutritional status in patients with chronic heart failure-a systematic review. Heart Fail Rev. 2019; 24(5):671-700.
29. Wleklik M, Uchmanowicz I, Jankowska-Polanska B, Andreae C, Regulska-Ilow B. The Role of Nutritional Status in Elderly Patients with Heart Failure. J Nutr Health Aging. 2018; 22(5):581-88.
30. Joaquin C, Alonso N, Lupon J, de Antonio M, Domingo M, Moliner P, et al. Mini Nutritional Assessment Short Form is a morbi-mortality predictor in outpatients with heart failure and mid-range left ventricular ejection fraction. Clin Nutr. 2020; 39(11):3395-401.
31. Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C, Lennie T, et al. Nutrition, Obesity, and Cachexia in Patients With Heart Failure: A Consensus Statement from the Heart Failure Society of America Scientific Statements Committee. J Card Fail. 2019; 25(5):380-400.
32. Elagizi A, Carbone S, Lavie CJ, Mehra MR, Ventura HO. Implications of obesity across the heart failure continuum. Prog Cardiovasc Dis. 2020; 63(5):561-69.

33. Prausmuller S, Heitzinger G, Pavo N, Spinka G, Goliasch G, Arfsten H, et al. Malnutrition outweighs the effect of the obesity paradox. J Cachexia Sarcopenia Muscle. 2022
34. Koutroumpakis E, Kaur R, Taegtmeyer H, Deswal A. Obesity and Heart Failure with Preserved Ejection Fraction. Heart Fail Clin. 2021; 17(3):345-56.
35. Tadic M, Cuspidi C. Obesity and heart failure with preserved ejection fraction: a paradox or something else? Heart Fail Rev. 2019; 24(3):379-85.
36. Zamora E, Lupon J, Enjuanes C, Pascual-Figal D, de Antonio M, Domingo M, et al. No benefit from the obesity paradox for diabetic patients with heart failure. Eur J Heart Fail. 2016; 18(7):851-8.
37. Streng KW, Voors AA, Hillege HL, Anker SD, Cleland JG, Dickstein K, et al. Waist-to-hip ratio and mortality in heart failure. Eur J Heart Fail. 2018; 20(9):1269-77.
38. Carbone S, Elagizi A, Lavie CJ. Obesity and mortality risk in heart failure: when adipose tissue distribution matters. Eur J Heart Fail. 2018; 20(9):1278-80.
39. Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, et al. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Circulation. 2016; 133(7):639-49.
40. Piche ME, Poirier P, Lemieux I, Despres JP. Overview of Epidemiology and Contribution of Obesity and Body Fat Distribution to Cardiovascular Disease: An Update. Prog Cardiovasc Dis. 2018; 61(2):103-13.
41. Beltrami M, Fumagalli C, Milli M. Frailty, sarcopenia and cachexia in heart failure patients: Different clinical entities of the same painting. World J Cardiol. 2021; 13(1):1-10.
42. Bielecka-Dabrowa A, Ebner N, Dos Santos MR, Ishida J, Hasenfuss G, von Haehling S. Cachexia, muscle wasting, and frailty in cardiovascular disease. Eur J Heart Fail. 2020; 22(12):2314-26.
43. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: A systematic review and meta-analysis. Int J Cardiol. 2017; 236:283-89.
44. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019; 48(1):16-31.
45. Lin H, Zhang H, Lin Z, Li X, Kong X, Sun G. Review of nutritional screening and assessment tools and clinical outcomes in heart failure. Heart Fail Rev. 2016; 21(5):549-65.
46. Minamisawa M, Seidelmann SB, Claggett B, Hegde SM, Shah AM, Desai AS, et al. Impact of Malnutrition Using Geriatric Nutritional Risk Index in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2019; 7(8):664-75.
47. Kirkman DL, Bohmke N, Billingsley HE, Carbone S. Sarcopenic Obesity in Heart Failure With Preserved Ejection Fraction. Front Endocrinol (Lausanne). 2020; 11:558271.
48. Trullas JC. The importance of nutritional status in heart failure. Rev Clin Esp. 2018; 218(2):68-69.
49. Monahan C. Investigation of nutritional status, body composition and functional status of heart failure patients in the outpatient setting. Clinical Nutrition ESPEN. 2018; 28:269.

50. Norman K, Stobaus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr. 2011; 30(2):135-42.
51. Prasitsiriphon O, Pothisiri W. Associations of Grip Strength and Change in Grip Strength With All-Cause and Cardiovascular Mortality in a European Older Population. Clin Med Insights Cardiol. 2018; 12:1179546818771894.
52. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A, Orlandini A, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. The Lancet. 2015; 386(9990):266-73.
53. Beyer SE, Sanghvi MM, Aung N, Hosking A, Cooper JA, Paiva JM, et al. Prospective association between handgrip strength and cardiac structure and function in UK adults. PLoS One. 2018; 13(3):e0193124.
54. Stuck AK, Mader NC, Bertschi D, Limacher A, Kressig RW. Performance of the EWGSOP2 Cut-Points of Low Grip Strength for Identifying Sarcopenia and Frailty Phenotype: A Cross-Sectional Study in Older Inpatients. Int J Environ Res Public Health. 2021; 18(7):3498.
55. Organization WH. A healthy lifestyle- WHO recommendations. 2010. Disponível em: https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations.
56. MacDermid J, Solomon G, Valdes K. Clinical assessment recommendations 3rd edition: Impairment-based conditions. American Society of Hand Therapists; 2015.
57. Kondrup J. ESPEN Guidelines for Nutrition Screening 2002. Clinical Nutrition. 2003; 22(4):415-21.
58. Hsu CI, Wei J, Tung HH, Peng LN, Chen LK, Liu CY. Malnutrition, Family Support, and Possible Sarcopenia in Patients Undergoing Transcatheter Aortic Valve Implantation. J Cardiovasc Nurs. 2021; 36(6):565-72.
59. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of Blood Biomarkers Associated with Risk of Malnutrition in Older Adults: A Systematic Review and Meta-Analysis. Nutrients. 2017; 9(8):829.
60. Evans DC, Corkins MR, Malone A, Miller S, Mogensen KM, Guenter P, et al. The Use of Visceral Proteins as Nutrition Markers: An ASPEN Position Paper. Nutr Clin Pract. 2021; 36(1):22-28.
61. Drescher T, Singler K, Ulrich A, Koller M, Keller U, Christ-Crain M, et al. Comparison of two malnutrition risk screening methods (MNA and NRS 2002) and their association with markers of protein malnutrition in geriatric hospitalized patients. Eur J Clin Nutr. 2010; 64(8):887-93.
62. Gonzalez MC, Mehrnezhad A, Razaviarab N, Barbosa-Silva TG, Heymsfield SB. Calf circumference: cutoff values from the NHANES 1999-2006. Am J Clin Nutr. 2021; 113(6):1679-87.
63. Mendoza-Garces L, Velazquez-Alva MC, Cabrer-Rosales MF, Arrieta-Cruz I, Gutierrez-Juarez R, Irigoyen-Camacho ME. Vitamin D Deficiency is Associated with Handgrip Strength, Nutritional Status and T2DM in Community-Dwelling Older Mexican Women: A Cross-Sectional Study. Nutrients. 2021; 13(3):736.
64. Formiga F, Ferrer A, Almeda J, San Jose A, Gil A, Pujol R. Utility of geriatric assessment tools to identify 85-years old subjects with vitamin D deficiency. J Nutr Health Aging. 2011; 15(2):110-4.
65. Santos A, Amaral TF, Guerra RS, Sousa AS, Alvares L, Moreira P, et al. Vitamin D status and associated factors among Portuguese older adults: results from the Nutrition UP 65 cross-sectional study. BMJ Open. 2017; 7(6):e016123.

66. Tsagari A, Toulis KA, Makras P, Skagias K, Galanos A, Lyritis G. Performance of the mini nutritional assessment score in the detection of vitamin D status in an elderly Greek population. Horm Metab Res. 2012; 44(12):896-9.
67. Zhang Y, Zhang J, Ni W, Yuan X, Zhang H, Li P, et al. Sarcopenia in heart failure: a systematic review and meta-analysis. ESC Heart Fail. 2021; 8(2):1007-17.
68. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56(3):M146-56.
69. Sousa-Santos AR, Afonso C, Moreira P, Padrao P, Santos A, Borges N, et al. Weakness: The most frequent criterion among pre-frail and frail older Portuguese. Arch Gerontol Geriatr. 2018; 74:162-68.
70. Valdiviesso R, Azevedo LF, Moreira E, Ataide R, Martins S, Fernandes L, et al. Frailty phenotype and associated nutritional factors in a sample of Portuguese outpatients with heart failure. Nutr Metab Cardiovasc Dis. 2021; 31(8):2391-97.
71. Granic A, Davies K, Martin-Ruiz C, Jagger C, Kirkwood TBL, von Zglinicki T, et al. Grip strength and inflammatory biomarker profiles in very old adults. Age Ageing. 2017; 46(6):976-82.
72. Kukkurainen ML, Kauppi M, van Eijk-Hustings Y. Relation between serum albumin and physical performance and mobility in a community-based elderly people with osteoporosis. In.; 2018. p. 1831.3-32.
73. Chung CJ, Wu C, Jones M, Kato TS, Dam TT, Givens RC, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. J Card Fail. 2014; 20(5):310-5.
74. Schalk BW, Deeg DJ, Penninx BW, Bouter LM, Visser M. Serum albumin and muscle strength: a longitudinal study in older men and women. J Am Geriatr Soc. 2005; 53(8):1331-8.
75. Heimburger O, Qureshi AR, Blaner WS, Berglund L, Stenvinkel P. Hand-grip muscle strength, lean body mass, and plasma proteins as markers of nutritional status in patients with chronic renal failure close to start of dialysis therapy. Am J Kidney Dis. 2000; 36(6):1213-25.
76. Sayer AA, Syddall HE, Dennison EM, Martin HJ, Phillips DI, Cooper C, et al. Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. QJM. 2007; 100(11):707-13.
77. Pan PJ, Lin CH, Yang NP, Chen HC, Tsao HM, Chou P, et al. Normative data and associated factors of hand grip strength among elderly individuals: The Yilan Study, Taiwan. Sci Rep. 2020; 10(1):6611.
78. Ong HL, Abdin E, Chua BY, Zhang Y, Seow E, Vaingankar JA, et al. Hand-grip strength among older adults in Singapore: a comparison with international norms and associative factors. BMC Geriatr. 2017; 17(1):176.
79. Ramlagan S, Peltzer K, Phaswana-Mafuya N. Hand grip strength and associated factors in non-institutionalised men and women 50 years and older in South Africa. BMC Res Notes. 2014; 7:8.
80. Markus MRP, Ittermann T, Kim S, Schipf S, Siewert-Markus U, Santana CC, et al. Lower muscular strength is associated with smaller left and right chambers and lower cardiac mass in the general population - The Sedentary's Heart. Prog Cardiovasc Dis. 2021; 68:36-51.

81. Lee JE, Kim KW, Paik NJ, Jang HC, Chang CB, Baek GH, et al. Evaluation of factors influencing grip strength in elderly koreans. J Bone Metab. 2012; 19(2):103-10.
82. Lawman HG, Troiano RP, Perna FM, Wang CY, Fryar CD, Ogden CL. Associations of Relative Handgrip Strength and Cardiovascular Disease Biomarkers in U.S. Adults, 2011-2012. Am J Prev Med. 2016; 50(6):677-83.
83. Kim Y, Gonzales JU, Reddy PH. An Investigation of Short-Term Longitudinal Associations Between Handgrip Strength and Cardiovascular Disease Biomarkers Among Middle-Aged to Older Adults: A Project FRONTIER Study. J Aging Phys Act. 2020; 28(1):9-17.
84. Scherbakov N, Sandek A, Valentova M, Mayer A, von Haehling S, Jankowska E, et al. Iron Deficiency and Reduced Muscle Strength in Patients with Acute and Chronic Ischemic Stroke. J Clin Med. 2022; 11(3):595.
85. Amarís-Vergara AA, Palomino Ariza GA, Rodríguez-Hernández BV, Velandia-Carrillo CA, Cadena-Sanabria MO, Enrique Ochoa M. Handgrip strength and functional class as prognostic factors in elderly patients with heart failure in Colombia. FORCE II study. Trends in Medicine. 2018; 18(3)
86. Fernandez-Jimenez R, Dalla-Rovere L, Garcia-Olivares M, Abuin-Fernandez J, Sanchez-Torralvo FJ, Doulatram-Gamgaram VK, et al. Phase Angle and Handgrip Strength as a Predictor of Disease-Related Malnutrition in Admitted Patients: 12-Month Mortality. Nutrients. 2022; 14(9):1851.
87. Lukaski HC, Kyle UG, Kondrup J. Assessment of adult malnutrition and prognosis with bioelectrical impedance analysis: phase angle and impedance ratio. Curr Opin Clin Nutr Metab Care. 2017; 20(5):330-39.
88. Norman K, Stobaus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. Clin Nutr. 2012; 31(6):854-61.
89. Reis BCA, de Branco FMS, Pessoa DF, Barbosa CD, dos Reis AS, de Medeiros LA, et al. Phase Angle Is Positively Associated With Handgrip Strength in Hospitalized Individuals. Topics in Clinical Nutrition. 2018; 33(2):127-33.
90. Slee A, Birc D, Stokoe D. Bioelectrical impedance vector analysis, phase-angle assessment and relationship with malnutrition risk in a cohort of frail older hospital patients in the United Kingdom. Nutrition. 2015; 31(1):132-7.
91. Kim DH, Oh DJ. Phase angle values, a good indicator of nutritional status, are associated with median value of hemoglobin rather than hemoglobin variability in hemodialysis patients. Ren Fail. 2021; 43(1):327-34.
92. Gonzalez MC, Barbosa-Silva TG, Bielemann RM, Gallagher D, Heymsfield SB. Phase angle and its determinants in healthy subjects: influence of body composition. Am J Clin Nutr. 2016; 103(3):712-6.
93. Bansal N, Zelnick LR, Himmelfarb J, Chertow GM. Bioelectrical Impedance Analysis Measures and Clinical Outcomes in CKD. Am J Kidney Dis. 2018; 72(5):662-72.
94. Dittmar M, Reber H, Kahaly GJ. Bioimpedance phase angle indicates catabolism in Type 2 diabetes. Diabet Med. 2015; 32(9):1177-85.
95. Sobieszek G, Mlak R, Skwarek-Dziekanowska A, Jurzak-Mysliwy A, Homa-Mlak I, Malecka-Massalska T. Electrical Changes in Polish Patients with Chronic Heart Failure: Preliminary Observations. Medicina (Kaunas). 2019; 55(8)
96. Han BG, Lee JY, Kim JS, Yang JW. Decreased Bioimpedance Phase Angle in Patients with Diabetic Chronic Kidney Disease Stage 5. Nutrients. 2019; 11(12):2874.

97. Masson S, Vago T, Baldi G, Salio M, De Angelis N, Nicolis E, et al. Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. Clin Chem Lab Med. 2002; 40(8):761-3.
98. Leto L, Testa M, Feola M. Correlation between B-Type Natriuretic Peptide and Functional/Cognitive Parameters in Discharged Congestive Heart Failure Patients. Int J Endocrinol. 2015; 2015:239136.
99. Song BG, Jeon ES, Kim YH, Kang MK, Doh JH, Kim PH, et al. Correlation Between Levels of N-terminal Pro-B-Type Natriuretic Peptide and Degrees of Heart Failure. The Korean Journal of Internal Medicine. 2005; 20(1):26-32.
100. Lee S-C, Stevens TL, Sandberg SM, Heublein DM, Nelson SM, Jougasaki M, et al. The Potential of Brain Natriuretic Peptide as a Biomarker for New York Heart Association Class During the Outpatient Treatment of Heart Failure. Journal of Cardiac Failure. 2002; 8(3):149-54.
101. Dal K, Ata N, Yavuz B, Sen O, Deveci OS, Aksoz Z, et al. The relationship between glycemic control and BNP levels in diabetic patients. Cardiol J. 2014; 21(3):252-6.
102. Okamoto R, Ali Y, Hashizume R, Suzuki N, Ito M. BNP as a Major Player in the Heart-Kidney Connection. Int J Mol Sci. 2019; 20(14):3581.
103. Takase H, Dohi Y. Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal proBNP and their relationship. Eur J Clin Invest. 2014; 44(3):303-8.
104. Tsuji H, Nishino N, Kimura Y, Yamada K, Nukui M, Yamamoto S, et al. Haemoglobin level influences plasma brain natriuretic peptide concentration. Acta Cardiol. 2004; 59(5):527-31.
105. Karakoyun I, Colak A, Arslan FD, Hasturk AG, Duman C. Anemia considerations when assessing natriuretic peptide levels in ED patients. Am J Emerg Med. 2017; 35(11):1677-81.
106. Yi S, Chen M. Decreased albumin is associated with elevated N-terminal pro-brain natriuretic peptide and poor long-term prognosis in patients with chronic heart failure. Medicine (Baltimore). 2020; 99(51):e23872.
107. Chopra VK, Anker SD. Anaemia, iron deficiency and heart failure in 2020: facts and numbers. ESC Heart Fail. 2020; 7(5):2007-11.
108. Yamamoto E, Sato Y, Sawa T, Fujiwara T, Fujiwara H, Takatsu Y. Correlation between serum concentrations of B-type natriuretic peptide and albumin in patients with chronic congestive heart failure. Int Heart J. 2012; 53(4):234-7.
109. Billingsley HE, Hummel SL, Carbone S. The role of diet and nutrition in heart failure: A state-of-the-art narrative review. Prog Cardiovasc Dis. 2020; 63(5):538-51.

Appendices

Appendix 1- MNA Questionnaire

Mini Nutritional Assessment
MNA®

Nestlé NutritionInstitute

Apelido: Nome:

Sexo: Idade: Peso, kg: Altura, cm: Data:

Responda à secção "triagem", preenchendo as caixas com os números adequados. Some os números da secção "triagem".
Se a pontuação obtida for igual ou menor que 11, continue o preenchimento do questionário para obter a pontuação indicadora de desnutrição.

Triagem

A Nos últimos três meses houve diminuição da ingesta alimentar devido a perda de apetite, problemas digestivos ou dificuldade para mastigar ou deglutir?
0 = diminuição grave da ingesta
1 = diminuição moderada da ingesta
2 = sem diminuição da ingesta ☐

B Perda de peso nos últimos 3 meses
0 = superior a três quilos
1 = não sabe informar
2 = entre um e três quilos
3 = sem perda de peso ☐

C Mobilidade
0 = restrito ao leito ou à cadeira de rodas
1 = deambula mas não é capaz de sair de casa
2 = normal ☐

D Passou por algum stress psicológico ou doença aguda nos últimos três meses?
0 = sim 2 = não ☐

E Problemas neuropsicológicos
0 = demência ou depressão graves
1 = demência ligeira
2 = sem problemas psicológicos ☐

F Índice de Massa Corporal = peso em kg / (estatura em m)²
0 = IMC < 19
1 = 19 ≤ IMC < 21
2 = 21 ≤ IMC < 23
3 = IMC ≥ 23 ☐

Pontuação da Triagem (subtotal, máximo de 14 pontos) ☐☐
12-14 pontos: estado nutricional normal
8-11 pontos: sob risco de desnutrição
0-7 pontos: desnutrido
Para uma avaliação mas detalhada,continue com as perguntas G-R

Avaliação global

G O doente vive na sua própria casa (não em instituição geriátrica ou hospital)
1 = sim 0 = não ☐

H Utiliza mais de três medicamentos diferentes por dia?
0 = sim 1 = não ☐

I Lesões de pele ou escaras?
0 = sim 1 = não ☐

J Quantas refeições faz por dia?
0 = uma refeição
1 = duas refeições
2 = três refeições ☐

K O doente consome:
- pelo menos uma porção diária de leite ou derivados (leite, queijo, iogurte)? sim ☐ não ☐
- duas ou mais porções semanais de leguminosas ou ovos? sim ☐ não ☐
- carne, peixe ou aves todos os dias? sim ☐ não ☐

0.0 = nenhuma ou uma resposta «sim»
0.5 = duas respostas «sim»
1.0 = três respostas «sim» ☐☐

L O doente consome duas ou mais porções diárias de fruta ou produtos hortícolas?
0 = não 1 = sim ☐

M Quantos copos de líquidos (água, sumo, café, chá, leite) o doente consome por dia?
0.0 = menos de três copos
0.5 = três a cinco copos
1.0 = mais de cinco copos ☐☐

N Modo de se alimentar
0 = não é capaz de se alimentar sozinho
1 = alimenta-se sozinho, porém com dificuldade
2 = alimenta-se sozinho sem dificuldade ☐

O O doente acredita ter algum problema nutricional?
0 = acredita estar desnutrido
1 = não sabe dizer
2 = acredita não ter um problema nutricional ☐

P Em comparação com outras pessoas da mesma idade, como considera o doente a sua própria saúde?
0.0 = pior
0.5 = não sabe
1.0 = igual
2.0 = melhor ☐☐

Q Perímetro braquial (PB) em cm
0.0 = PB < 21
0.5 = 21 ≤ PB ≤ 22
1.0 = PB > 22 ☐☐

R Perímetro da perna (PP) em cm
0 = PP < 31
1 = PP ≥ 31 ☐

Avaliação global (máximo 16 pontos) ☐☐,☐
Pontuação da triagem ☐☐,☐
Pontuação total (máximo 30 pontos) ☐☐,☐

Avaliação do Estado Nutricional

de 24 a 30 pontos	☐	estado nutricional normal
de 17 a 23,5 pontos	☐	sob risco de desnutrição
menos de 17 pontos	☐	desnutrido

References
1. Vellas B, Villars H, Abellan G, *et al.* Overview of the MNA® - Its History and Challenges. *J Nutr Health Aging.* 2006; **10**:456-465.
2. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini Nutritional Assessment (MNA-SF). *J. Gerontol.* 2001; **56A**: M366-377
3. Guigoz Y. The Mini-Nutritional Assessment (MNA®) Review of the Literature - What does it tell us? *J Nutr Health Aging.* 2006; **10**:466-487.

Para maiores informações: www.mna-elderly.com

Appendix 2- Table S1: MNA by question

Question	Total, n= 46	Women, n= 26	Men, n= 20
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?			
Severe decrease in food intake	1 (2.2%)	1 (3.8%)	0 (0%)
Moderate decrease in food intake	10 (22%)	7 (27%)	3 (15%)
No decrease in food intake	35 (76%)	18 (69%)	17 (85%)
Weight loss during the last 3 months			
Weight loss greater than 3kg	4 (8.7%)	3 (12%)	1 (5.0%)
Does not know	3 (6.5%)	2 (7.7%)	1 (5.0%)
Weight loss between 1 and 3 kg	4 (8.7%)	2 (7.7%)	2 (10%)
No weight loss	35 (76%)	19 (73%)	16 (80%)
Mobility			
Bed or chair bound	1 (2.2%)	1 (3.8%)	0 (0%)
Able to get out of bed/chair but does not go out	14 (30%)	8 (31%)	6 (30%)
Goes out	31 (67%)	17 (65%)	14 (70%)
Has suffered psychological stress or acute disease in the past 3 months?			
Yes	5 (11%)	3 (12%)	2 (10%)
No	41 (89%)	23 (88%)	18 (90%)
Neuropsychological problems			
Mild dementia	10 (22%)	6 (23%)	4 (20%)
No psychological problems	36 (78%)	20 (77%)	16 (80%)
BMI			
BMI 19 to less than 21	1 (2.2%)	0 (0%)	1 (5.0%)
BMI 21 to less than 23	2 (4.3%)	2 (7.7%)	0 (0%)
BMI 23 or greater	43 (93%)	24 (92%)	19 (95%)
Lives independently (not in nursing home or hospital)	45 (98%)	26 (100%)	19 (95%)
Takes more than 3 prescription drugs per day (no)	1 (2.2%)	0 (0%)	1 (5.0%)
Pressure sores or skin ulcers (no)	38 (83%)	21 (81%)	17 (85%)
How many full meals does the patient eat daily?			
1	3 (6.5%)	2 (7.7%)	1 (5.0%)
2	24 (52%)	16 (62%)	8 (40%)
3	19 (41%)	8 (31%)	11 (55%)
At least one serving of dairy products (milk, cheese, yoghurt) per day	30 (65%)	16 (62%)	14 (70%)
Two or more servings of legumes or eggs per week	27 (59%)	17 (65%)	10 (50%)
Meat, fish or poultry every day	39 (85%)	22 (85%)	17 (85%)
Consumes two or more servings of fruit or vegetables per day?	31 (67%)	17 (65%)	14 (70%)
How much fluid (water, juice, coffee, tea, milk...) is consumed per day?			
Less than 3 cups	4 (8.7%)	4 (15%)	0 (0%)
3 to 5 cups	18 (39%)	9 (35%)	9 (45%)
More than 5 cups	24 (52%)	13 (50%)	11 (55%)
Mode of feeding			
Self-fed with some difficulty	5 (11%)	4 (15%)	1 (5.0%)
Self-fed without any problem	41 (89%)	22 (85%)	19 (95%)
Self-view of nutritional status			
Views self as being malnourished	4 (8.7%)	3 (12%)	1 (5.0%)

Is uncertain of nutritional state	13 (28%)	6 (23%)	7 (35%)
Views self as having no nutritional problem	29 (63%)	17 (65%)	12 (60%)
In comparison with other people of the same age, how does the patient consider his / her health status?			
Not as good	6 (13%)	5 (19%)	1 (5.0%)
Does not know	16 (35%)	11 (42%)	5 (25%)
As good	7 (15%)	3 (12%)	4 (20%)
Better	17 (37%)	7 (27%)	10 (50%)
Mid-arm circumference (MAC) in cm			
MAC less than 21	13 (28%)	6 (23%)	7 (35%)
MAC 21 to 22	7 (15%)	2 (7.7%)	5 (25%)
MAC greater than 22	26 (57%)	18 (69%)	8 (40%)
Calf circumference (CC): 31 cm or greater	19 (41%)	11 (42%)	8 (40%)
Final score	24.0 (20.6, 26.5)	23.5 (19.2, 25.0)	25.0 (20.9, 26.6)
Malnutrition Indicator Score			
Normal nutritional status	24 (52%)	12 (46%)	12 (60%)
At risk of malnutrition	18 (39%)	11 (42%)	7 (35%)
Malnourished	4 (8.7%)	3 (12%)	1 (5.0%)

Appendix 3- Principal Components Loading Plots obtained from the MNA model

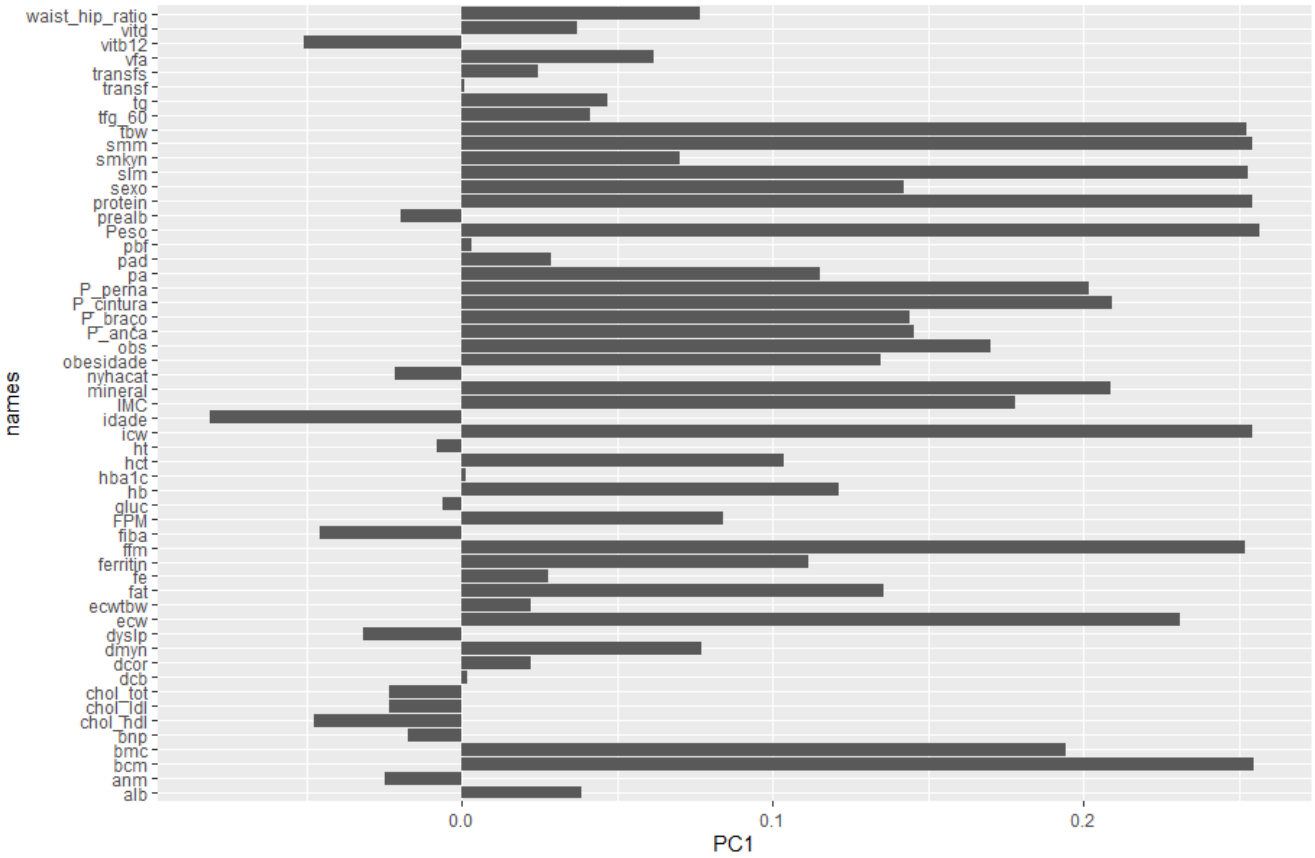

Figure 3- PC1 of MNA. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

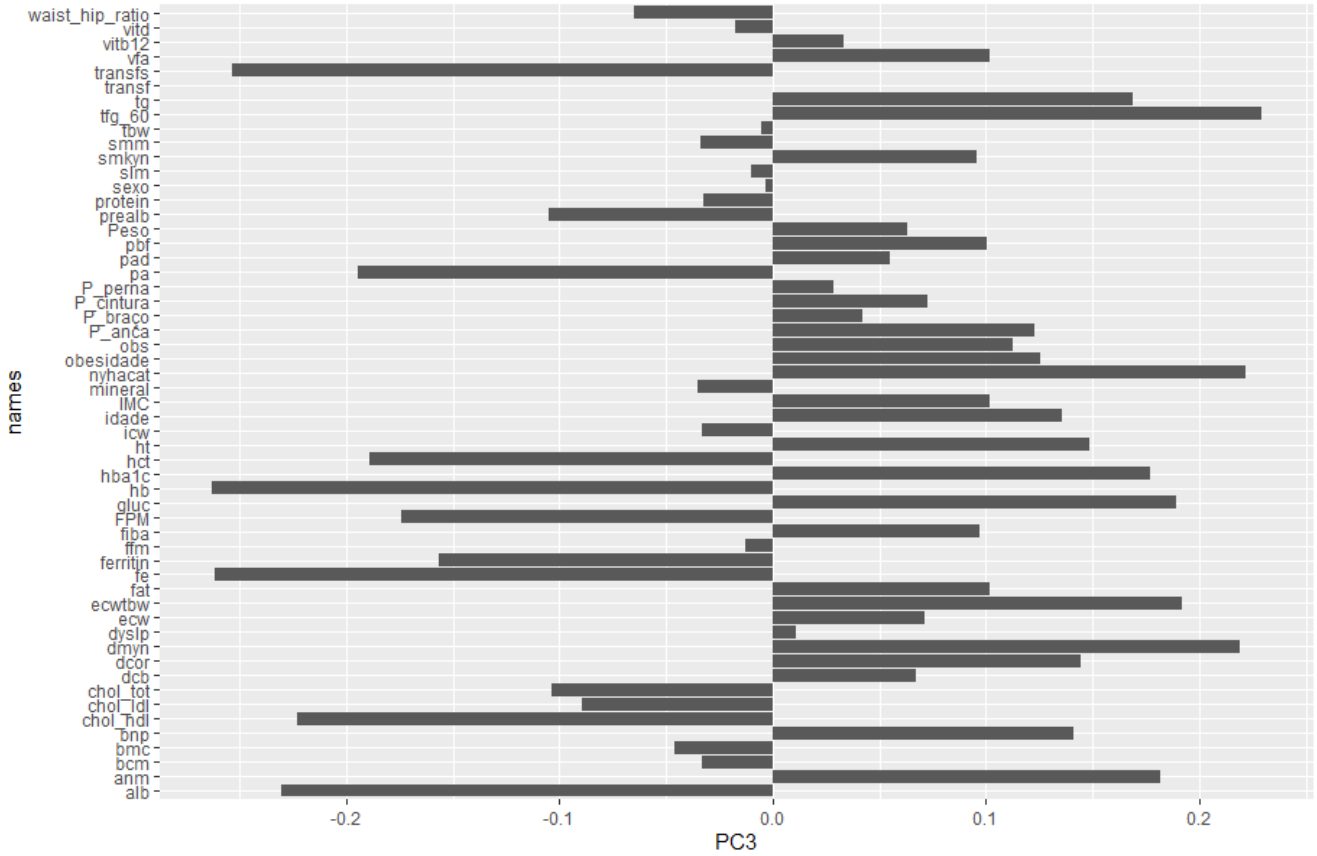

Figure 4- PC3 of MNA. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

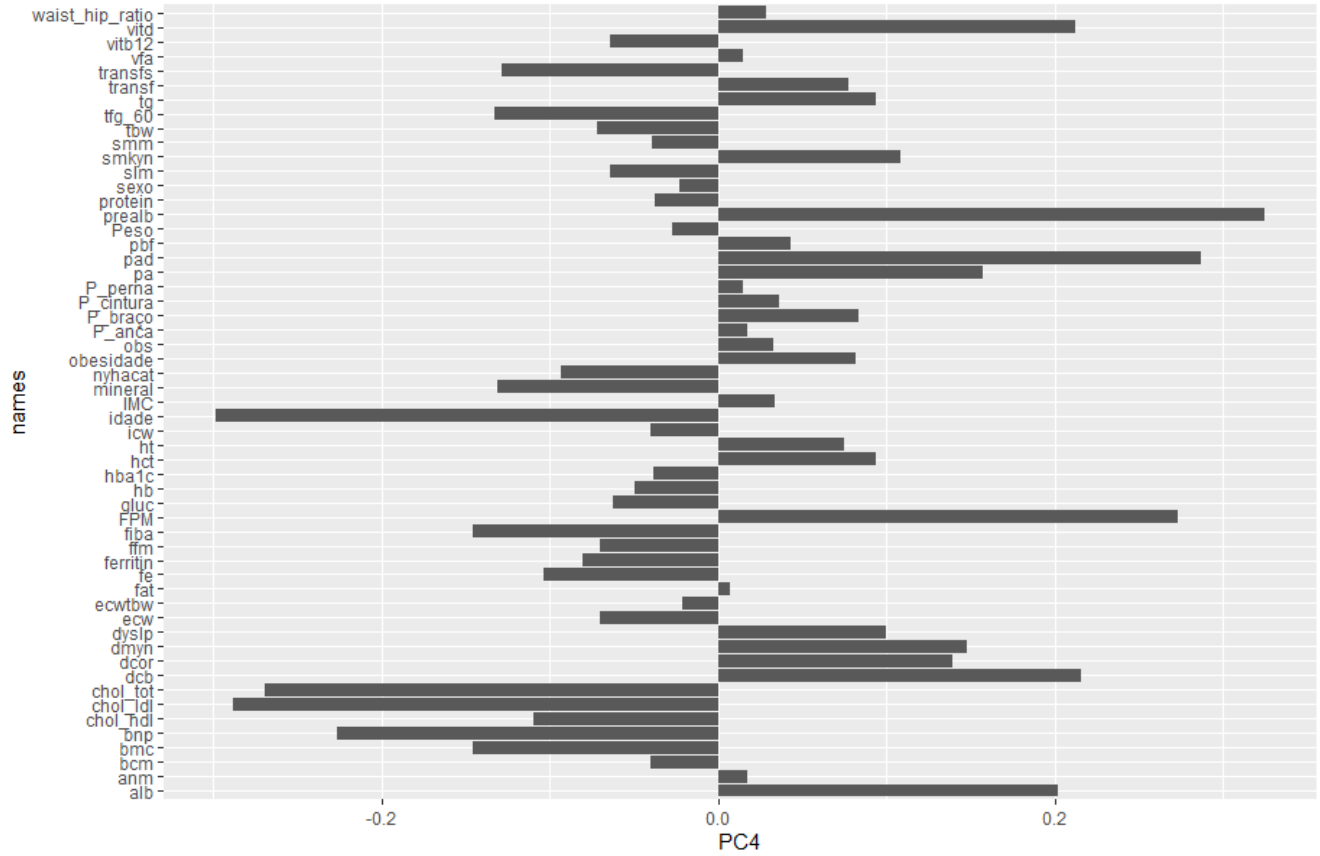

Figure 5- PC4 of MNA. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

Appendix 4- Principal Components Loading Plots obtained from the HGS model

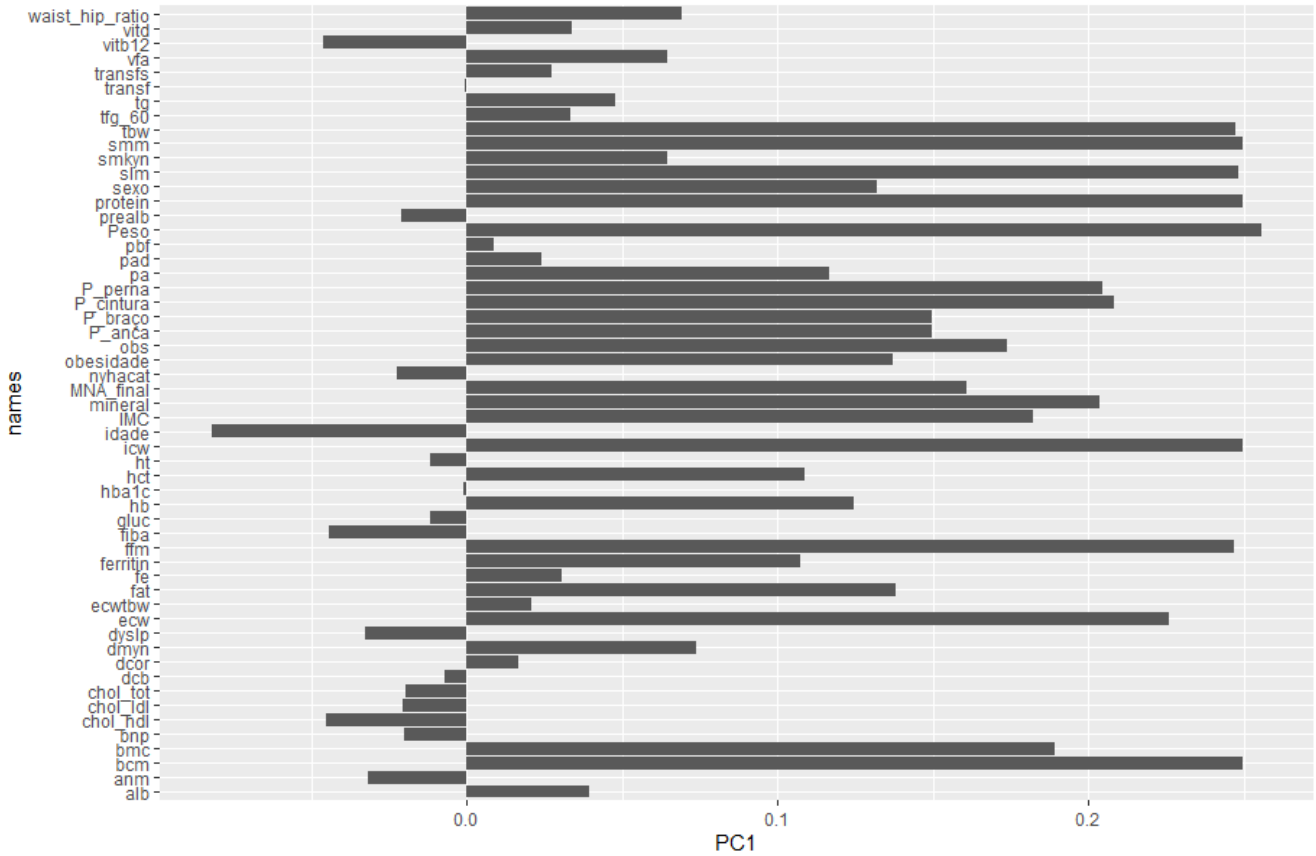

Figure 6- PC1 of HGS. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

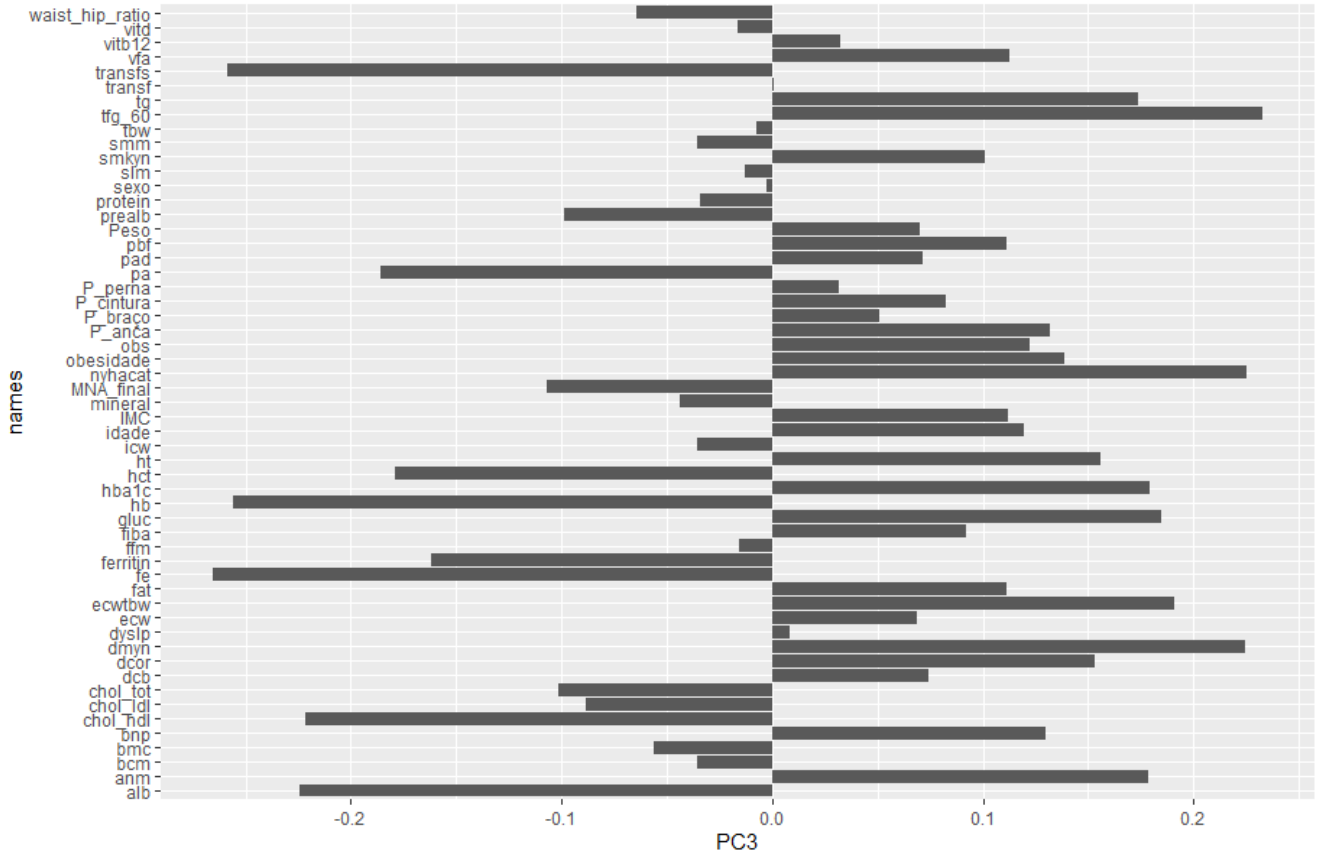

Figure 7- PC3 of HGS. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

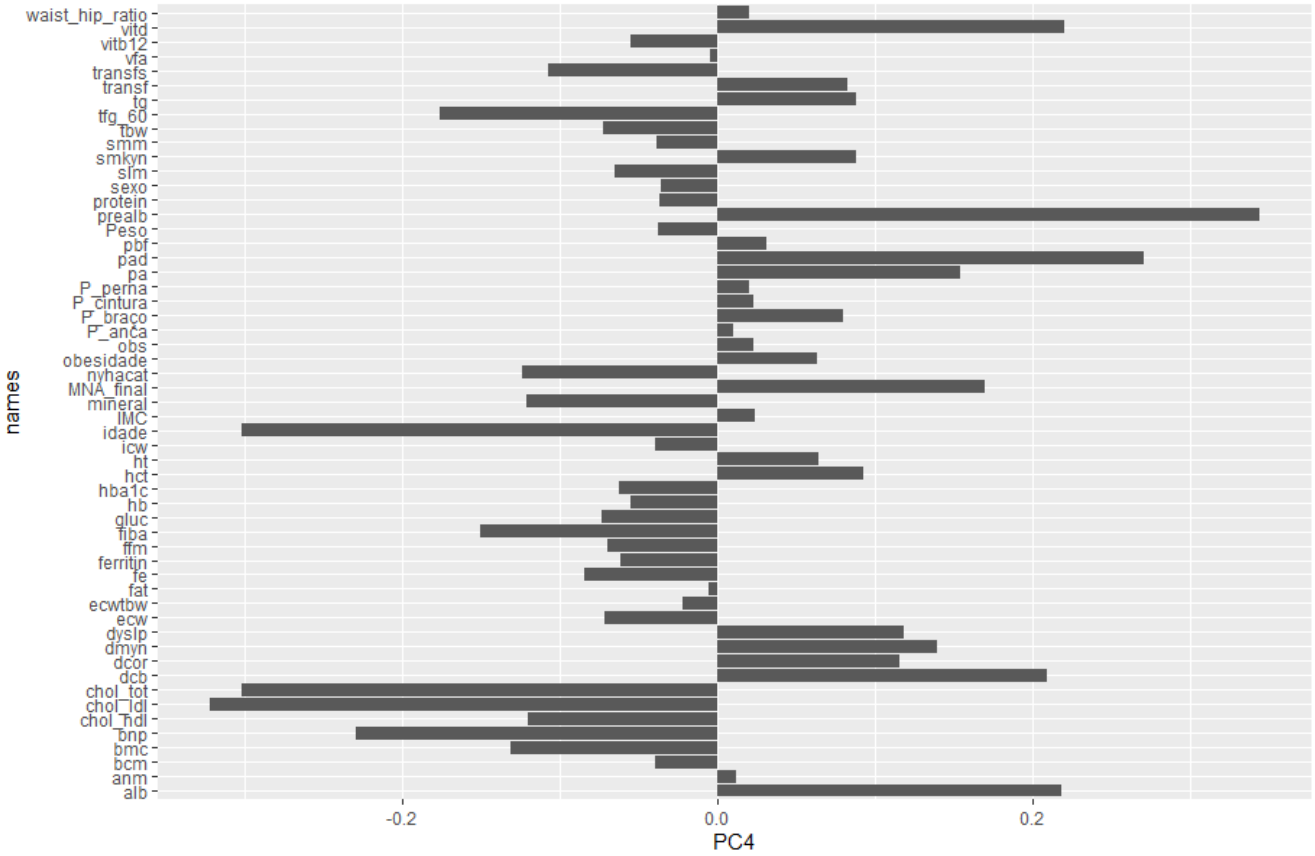

Figure 8- PC4 of HGS. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

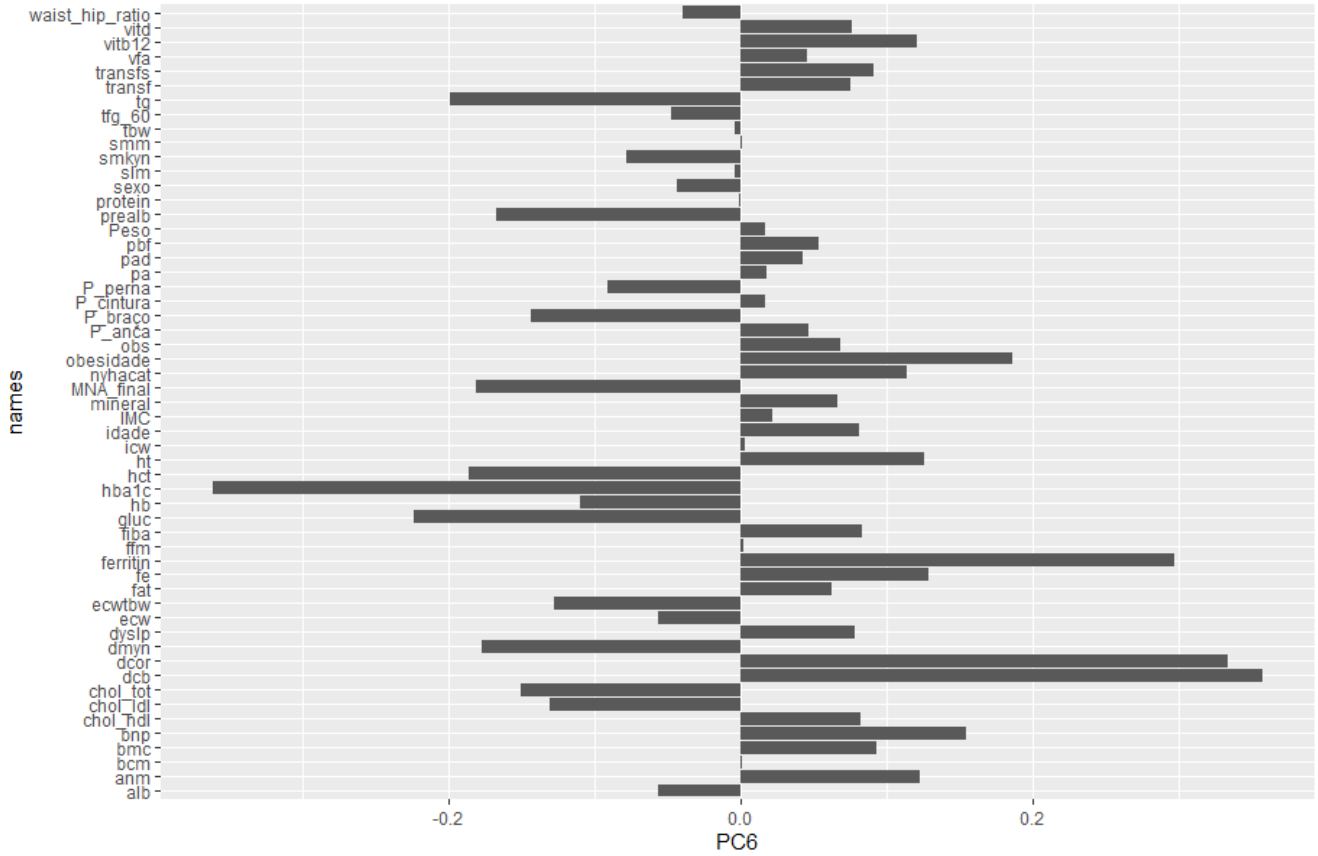

Figure 9- PC6 of HGS. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

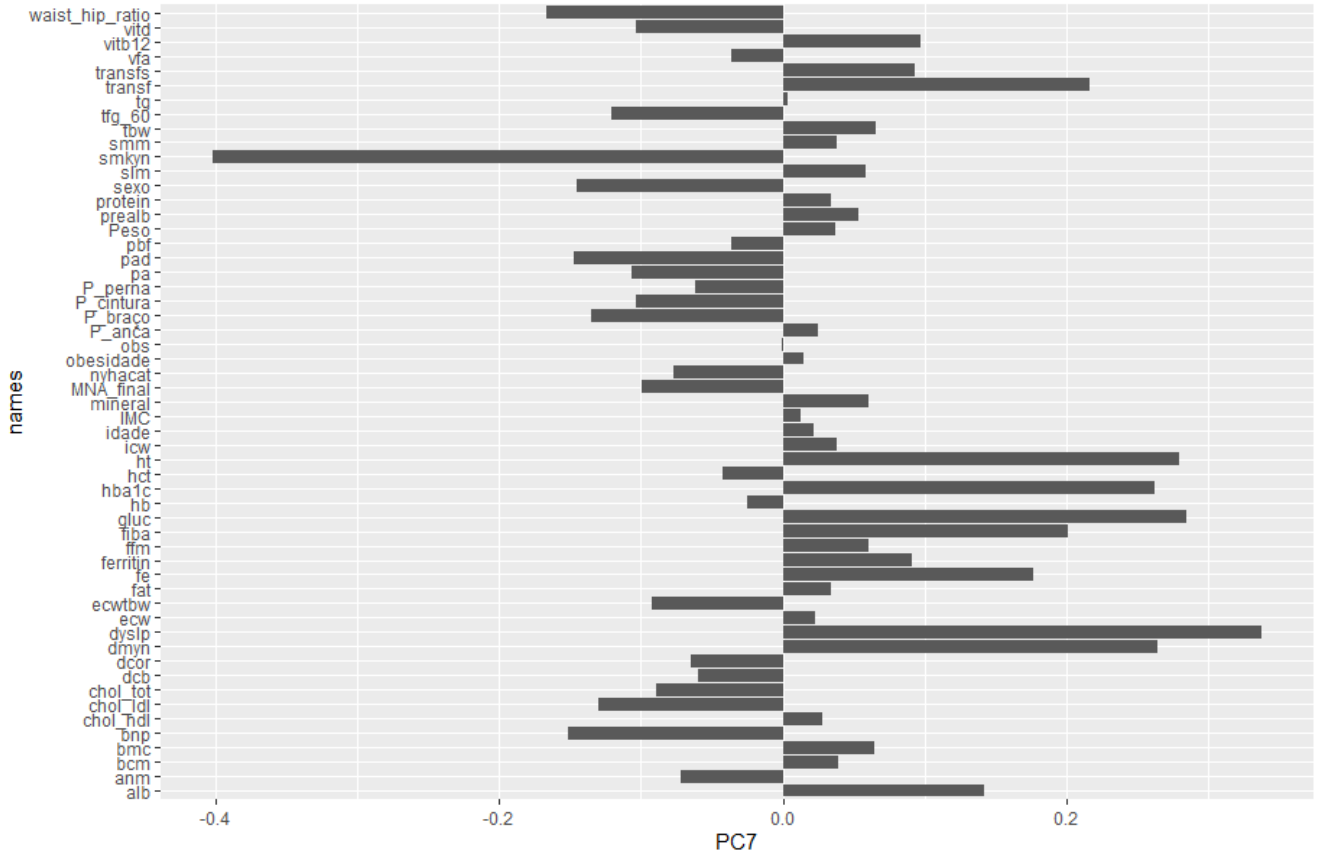

Figure 10- PC7 of HGS. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

Appendix 5- Principal Components Loading Plots obtained from the PA model

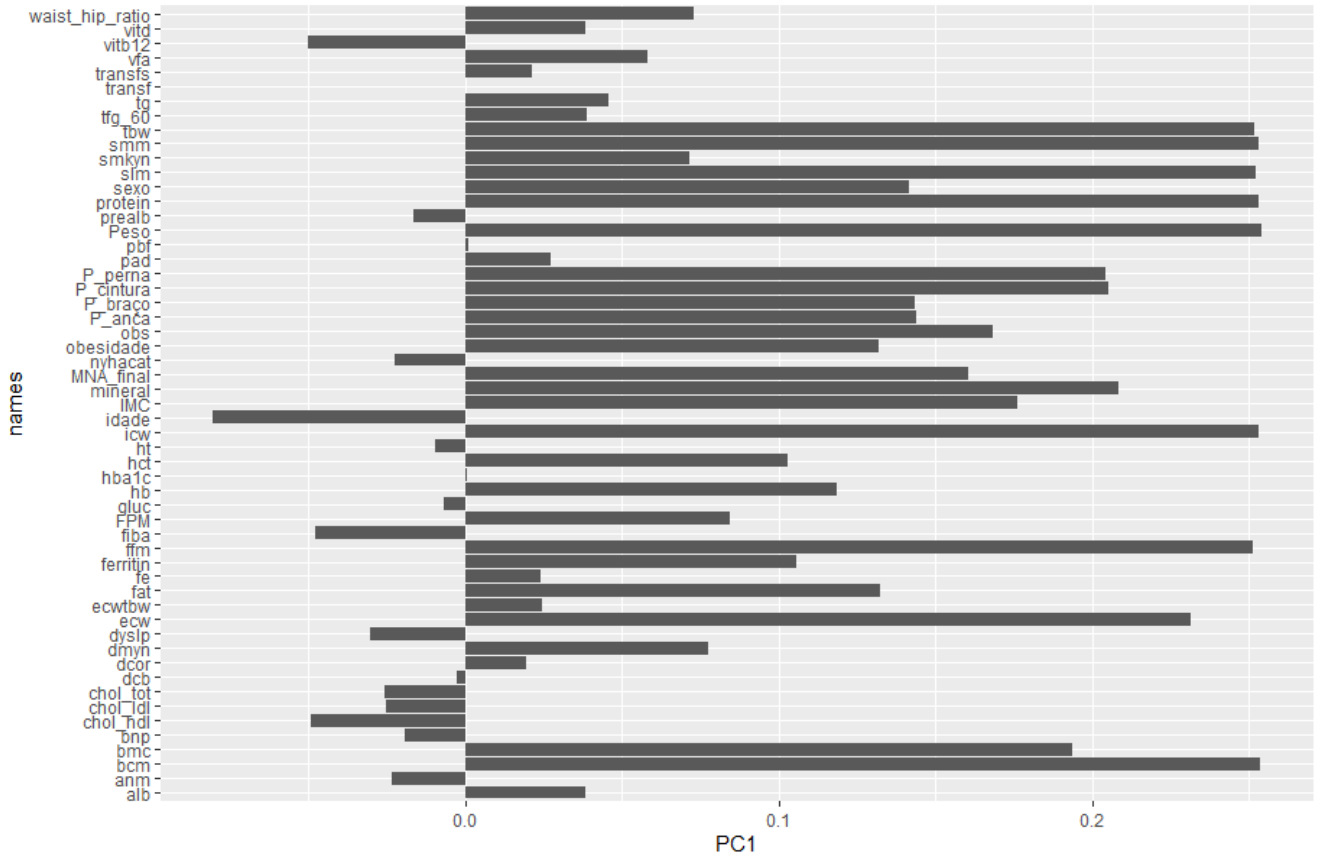

Figure 11- PC1 of PA. wais_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm- soft lean mass; sexo-sex; protein- protein mass; prealb- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- glycated hemoglobin; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol_tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

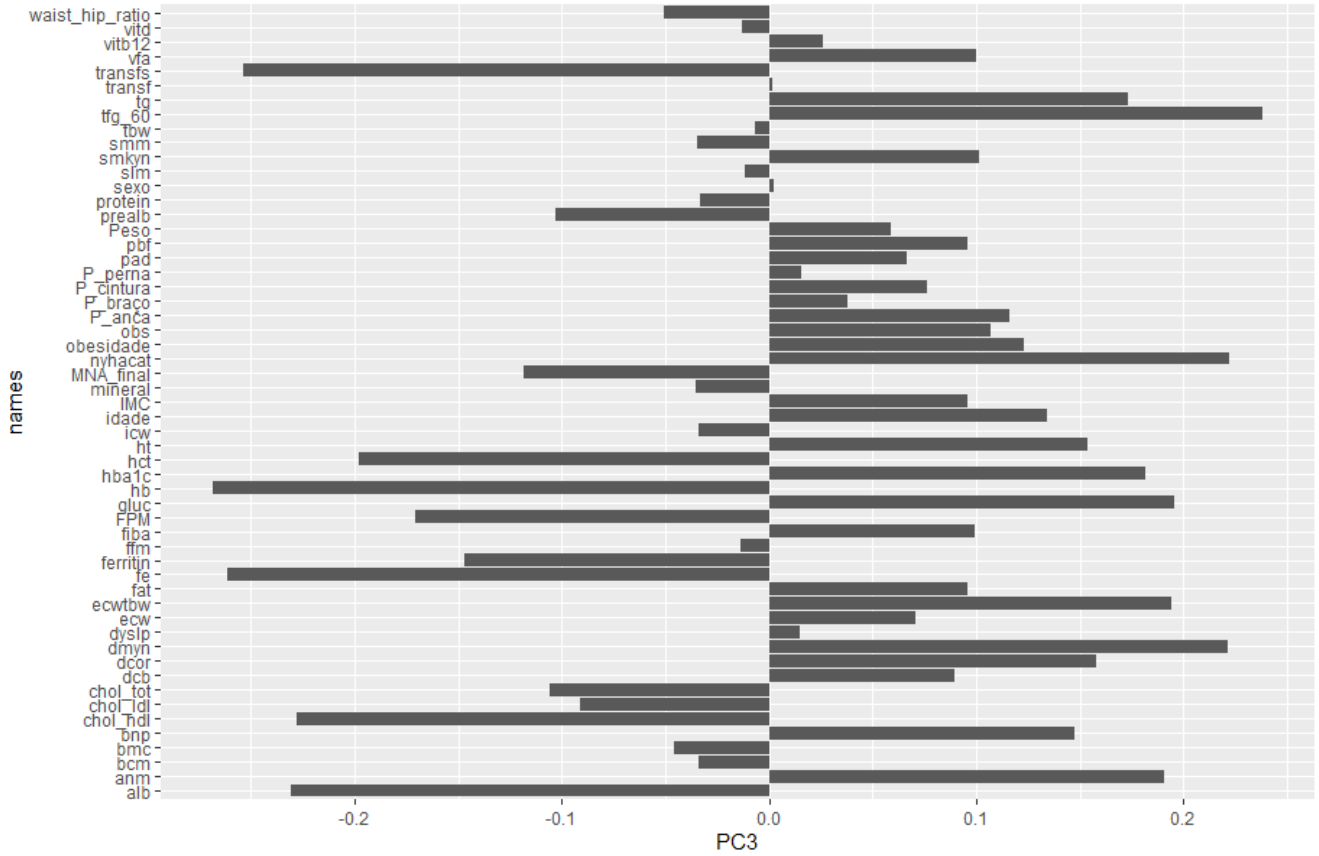

Figure 12- PC3 of PA. waist_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm. soft lean mass; sexo-sex; protein- protein mass; prelab- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- hbA1c; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol:tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.

Appendix 6- Principal Components Loading Plots obtained from the BNP model

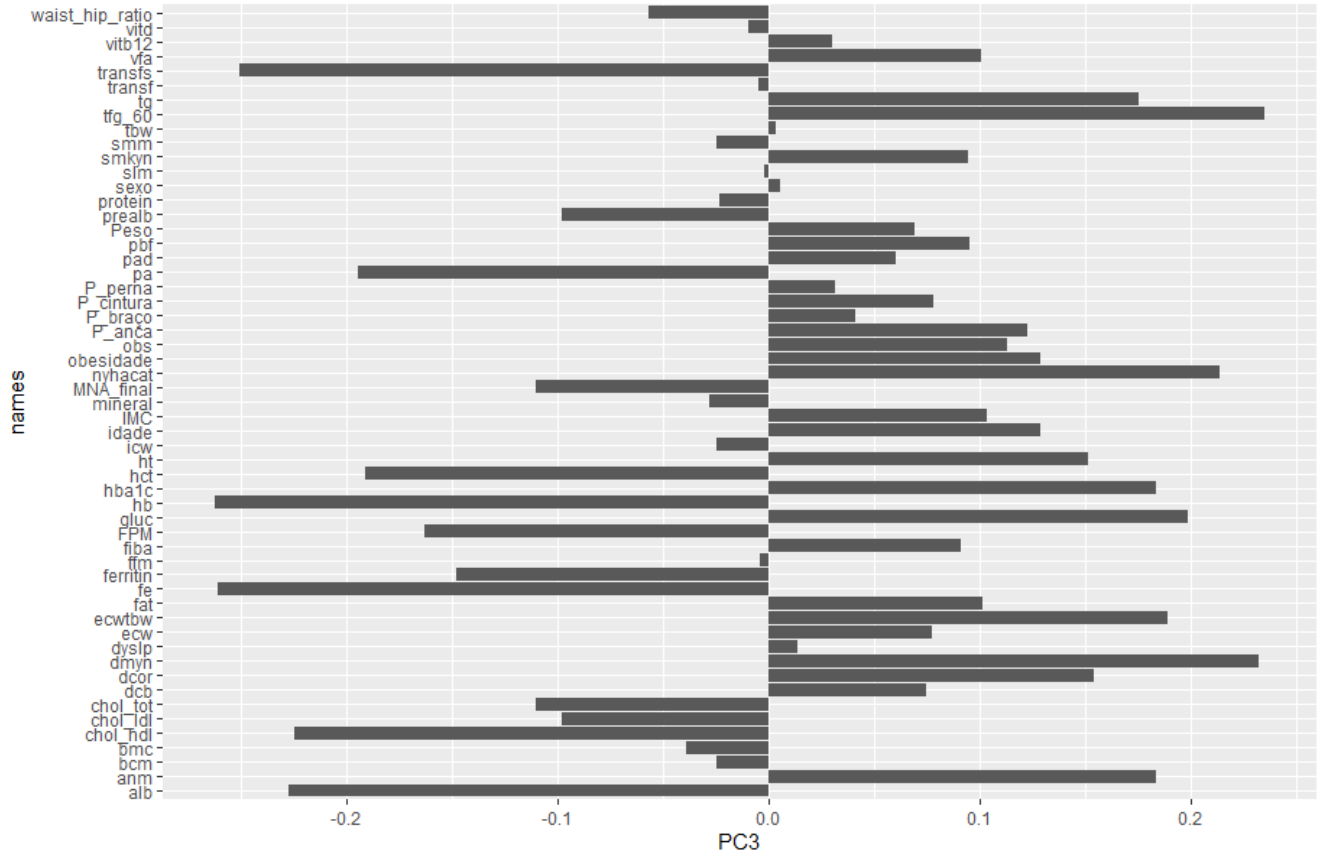

Figure 13- PC3 of BNP. waist_hip_ratio- waist-to-hip ratio; vitd- vitamin D; vitb12- vitamin B12; vfa- visceral fat area; transfs- transferrin saturation; transf- transferrin; tg- triglycerides; tfg_60- chronic kidney disease; tbw- total body water; smm- skeletal muscle mass; smkyn- smoking habits; slm. soft lean mass; sexo-sex; protein- protein mass; prelab- pre albumin; Peso- weight; pbf- percent body fat; pad- peripheral artery disease; pa- phase angle; P_perna- calf circumference; P_cintura- waist circumference; P_braço- mid-arm circumference; P_anca- hip circumference; obs- BMI > 30 kg/m^2; obesidade- obesity; nyhacat- NYHA categories; mineral- mineral mass; IMC- BMI; idade- age; icw- intracellular water; hct- erythrocytes; hba1c- hbA1c; hb- haemoglobin; gluc-glucose; FPM- HGS; fiba- atrial fibrillation; ffm- free-fat mass; fe- iron; fat- fat mass; ecwtbw- body water ratio; ecw- extracellular water; dyslp- dyslipidaemia; dmyn- diabetes mellitus; dcor- coronary artery disease; dcb- cerebrovascular disease; chol:tot- total cholesterol; chol_ldl- LDL cholesterol; chol_hdl- HDL cholesterol; bnp- BNP; bmc- bone mineral content; bcm- body cell mass; anm-anaemia; alb- albumin.