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Influence of nutrition status and body composition on exercise capacity and survival among individuals with interstitial lung disease: a cross-sectional study in an outpatient setting.

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Abstract

Interstitial lung disease (ILD) and its associated treatments have the potential to put patients at nutrition risk. However, minimal is known about the relationship between nutritional status on disease severity and prognosis in ILD. Existing research is limited by its focus on weight and body mass index (BMI). Therefore, the primary objective of this cross-sectional, prospective study was to determine the prevalence of malnutrition using the subjective global assessment (SGA) and to estimate body composition using bioelectrical impedance analysis (BIA) among individuals with ILD (n = 78). A second objective of this research was to investigate the appropriateness of bioimpedance parameters such as standardized phase angle (SPhA) and impedance ratio z-score (z-IR) as surrogate markers of malnutrition. The third objective of this research was to evaluate how nutrition status and body composition are related to functional exercise capacity using 6-minute walk distance (6MWD). The fourth objective explored the relationship between fat-free mass index z-score (z-FFMI) and body fat mass index z-score (z-BFMI), body composition measures which are controlled for age and sex, and nutrition status, with survival. Results indicate that most participants were mildly malnourished (49%). Additionally, 11.5% of patients had normal body composition, 20.5% were classified as sarcopenic, 60% were obese and the remaining 8% were classified as sarcopenic obese. z-FFMI and SGA were significantly associated with exercise capacity independent of lung function. Low BMI, z-FFMI and z-BFMI were associated with severe malnutrition. SPhA did not correlate with nutrition status, however, increased z-IR significantly increased the odds of severe malnutrition. Age, BMI, z-FFMI, z-BFMI, exercise capacity, disease severity, and severe malnutrition were significant predictors of survival. z-FFMI and severe malnutrition were significantly associated with survival independent of disease severity. These results are sufficiently encouraging to warrant further research into the nutritional status of ILD patients. Future research should assess if nutrition interventions can improve fat-free mass and functional exercise capacity in patients with ILD. Assessment of fat-free mass should be considered alongside or in place of BMI as a nutritional variable when analyzing survival risk in ILD patients as it can better identify those as risk of death.

Keywords

Interstitial lung disease, nutrition, subjective global assessment, fat-free mass index, body fat mass index, bioelectrical impedance analysis, exercise capacity, survival, phase angle, impedance ratio.

Summary for Lay Audience

Interstitial lung disease (ILD) and its treatments put patients at risk of poor nutrition. However, little is known about the link between nutrition and ILD, nor about the influence of nutrition on survival in patients with ILD. Most ILD nutrition research has focused on weight and body mass index (BMI). Therefore, the primary objective of this study was to determine how common malnutrition is in ILD patients using the subjective global assessment (SGA), and to estimate body composition (lean body mass and body fat) using bioelectrical impedance analysis (BIA) among 78 individuals diagnosed with ILD. A second objective of this research was to investigate if suspected markers of nutrition status, such as, standardized phase angle (SPhA) and impedance ratio z-score (z-IR) measured using BIA, can be used to accurately identify malnutrition. The third objective of this research was to explore how nutrition status and body composition are related to exercise capacity, using 6-minute walk distance (6MWD). Lastly, the fourth objective explored the relationship between body composition and nutrition status with survival. A large portion of the patients were mildly malnourished (49%). Lean body mass controlled for age, sex and height, and nutrition status were significantly associated with exercise capacity regardless of the severity of ILD. Low BMI, low muscle mass and low body fat were associated with severe malnutrition. z-IR, but not SPhA, was associated with severe malnutrition. Age, BMI, lean body mass, body fat, exercise capacity, disease severity and severe malnutrition predicted survival in ILD patients. Muscle mass controlled for age, sex and height, and severe malnutrition predicted survival regardless of disease severity. These results justify future exploration into the nutritional status of ILD patients which can be used to develop individualized nutrition care plan for patients with ILD. Future research should assess if nutrition interventions can increase muscle mass and/or exercise capacity. When possible, muscle mass should be measured along with or in place of BMI as it can better identify those at risk of death with ILD.

Co-Authorship Statement

The following dissertation includes three integrated articles, one of which has been published, and two of which have been submitted for publication. Reference formatting, sub-heading numbers, table numbers and figure numbers in the published manuscript have been revised for consistency with the present dissertation. Co-authorship details for each of the three manuscripts are as follows:

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Sylvia Rinaldi was primarily responsible for drafting, revising and finalizing the manuscript. Sylvia contributed to acquisition, analysis, and interpretation of the data, drafted the manuscript and critically revised the manuscript.

Jason Gilliland, Colleen O'Connor and Bert Chesworth contributed to the analysis and interpretation of the data and critically revised the manuscript.

Janet Madill contributed to acquisition, analysis, and interpretation of the data and critically revised the manuscript.

All authors read and approved the final manuscript.

Chapter 4 Exercise capacity, nutrition and body composition in patients with ILD

This manuscript has been submitted to *Nutrition in Clinical Practice*, a peer-reviewed medical journal that covers research in the field of nutrition.

Sylvia Rinaldi was primarily responsible for drafting, revising and finalizing the manuscript. Sylvia contributed to acquisition, analysis, and interpretation of the data, drafted the manuscript and critically revised the manuscript.

Jason Gilliland critically revised the manuscript.

Colleen O'Connor critically revised the manuscript.

Jamie Seabrook critically revised the manuscript including the statistical analyses used in the manuscript.

Marco Mura contributed to acquisition, analysis, and interpretation of the data and critically revised the manuscript.

Janet Madill contributed to acquisition, analysis, and interpretation of the data and critically revised the manuscript.

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Chapter 5 Fat-free mass index controlled for age and sex, and malnutrition are predictors of survival in interstitial lung disease.

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Abbreviations

AUC	Area under the curve
β	Standardized beta coefficient
B	Unstandardized beta coefficient
BFMI	Body fat mass index
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CAPD	Continuous ambulatory peritoneal dialysis
CKD	Chronic kidney disease
CLD	Chronic liver disease
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
DL_{co}	Diffusing capacity for carbon monoxide
FEV	Forced expiratory volume
FFMI	Fat-free mass index
FVC	Forced vital capacity
GC	Gastric cancer
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HD	Hemodialysis
HNC	Head and neck cancer
HR	Hazard ratio
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis

IR	Impedance Ratio
LOS	Length of stay
NS	Not significant
OR	Odds ratio
PG-SGA	Patient-generated subjective global assessment
PhA	Phase angle
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
r	Pearson’s correlation coefficient
r_s	Spearman's rank correlation coefficient/Spearman’s rho
RD	Registered dietitian
ROC	Receiver operator characteristics
SE	Standard error
SGA	Subjective global assessment
SPhA	Standardized phase angle
Tx	Transplant
z-BFMI	Body fat mass index z-score
z-FFMI	Fat-free mass index z-score
z-IR	Impedance ratio z-score
$\%DL_{co}$	Percent predicted diffusing capacity for carbon monoxide
$\%FEV_1$	Percent predicted forced expiratory volume
%FVC	Percent predicted forced vital capacity
6MWD	6-minute walk distance
7p-SGA	7-point modified subjective global assessment

Clinical Terms

Anorexia	Loss of appetite
Alveoli	balloon-shaped air sacs in the lungs
Body cell mass	Total mass of all the metabolically active cellular elements of the body
Bronchial tree	A series of passageways for air to move into and out of the lungs
Dyspepsia	Indigestion
Dyspnea	Shortness of breath
Edema	Swelling caused by excess fluid trapped in body tissues
Encephalopathy	Damage or disease to the brain, usually resulting in confusion or altered mental state
Parenchyma	The functional tissue of an organ
Pleura	A membrane that folds back on itself forming a two-layered membrane which attaches the lungs to the chest cavity
Varices	Abnormally dilated vessel

Chapter 1

1 Introduction

1.1 Background

We take roughly 20,000 breaths each day, most of which we take no notice. However, for most people it is not until breathing becomes a struggle, that it becomes obvious how profound an impact the ability to breathe has on daily life. Interstitial lung disease (ILD) comprises a heterogeneous range of chronic lung disorders which involve irritation and swelling of the tissue lining the lungs making it difficult to breath (Bradley et al. 2008; Cottin et al. 2019). ILD is associated with significant morbidity and mortality as survival after diagnosis of some ILDs is only 2.5 to 5 years (Richeldi et al. 2003). The management strategy of ILD includes home oxygen (Crockett, Cranston, and Antic 2001), pulmonary rehabilitation (Holland and Hill 2008; Nakazawa, Cox, and Holland 2017), and weight optimization (Alakhras et al. 2007). However, little is known about the relationship between nutritional status and clinical course of ILD, a potentially important implication on the outcome and quality of life of these patients.

Ample research indicates that ILD, its treatments and medication side-effects put patients at nutrition risk (Quinn, Wisse, and Manns 2019; Trawinska, Rupesinghe, and Hart 2016). However, little is known about the relationship between nutritional status and disease severity or prognosis in ILD patients. Existing research is limited by its focus on weight and body mass index (BMI), and overlooks the components of body mass; fat-free mass and body fat mass. Nutrition intervention can have a significant impact on clinical outcomes such as improved quality of life and better tolerance to medical treatments (Charney 2008). No nutrition recommendations are included in ILD best practice guidelines (Raghu et al. 2015; Travis et al. 2013). Research using gold standard and well-accepted clinical assessment tools is needed to determine the prevalence of malnutrition and body composition concerns, such as inadequate fat-free mass, in ILD patients. Addressing this research gap will help to establish best practice guidelines to be used by clinicians to provide evidence-based and quality nutrition care to their ILD patients.

At present, nutrition professionals such as registered dietitians (RDs) are not part of the standard of care of ILD patients. For many, it is not until their disease has significantly progressed that an RD may become involved in their care. For example, this may occur due to a hospitalization or lung transplant assessment. For those individuals that require lung transplantation assessment, this may be the first involvement of a RD in their care, and the RD's involvement is generally focused on weight management. As many ILD patients are overweight or obese (Alakhras et al. 2007), therefore, weight loss may be required to meet BMI cut-offs in order to receive a lung transplant. However, at this point in their disease, many barriers, such as reduced exercise capacity (energy output) and increase appetite secondary to medication use (energy input), make weight loss very difficult to achieve. Additionally, due to disease exacerbations patients may end up in hospital. Although, inpatient RD involvement can help address nutrition issues, that is if the inpatient RD is referred to ILD patients in the first place, the hospital setting itself can contribute to further malnutrition in these patients. Specifically, even just 1-week of bed rest can lead to substantial loss of muscle mass and strength (Dirks et al. 2016) resulting in patients leaving hospital deconditioned. Without adequate supports to address loss of muscle mass post-hospital admission, this further contributes to the progressive loss of functional capacity and risk of malnutrition in ILD patients.

Diminished exercise capacity in ILD is multifaceted with pathophysiological factors such as impaired gas exchange in the lungs, altered respiratory mechanics, limited pulmonary circulation and peripheral muscle dysfunction (Holland et al. 2008; Raghu et al. 2011). No studies have explored the influence of poor nutrition status on diminished exercise capacity in ILD. Clinical nutrition research is needed to determine if a relationship exists between nutrition status and exercise capacity as this would provide justification for future research into nutrition intervention as a non-exercise component in pulmonary rehabilitation programs (Nakazawa, Cox, and Holland 2017).

The subjective global assessment (SGA) is the gold standard of nutrition assessment which evaluates nutritional status subjectively. Phase angle (PhA), an indicator of cell health, is obtained using bioelectrical impedance analysis (BIA) and is strictly an objective measure. Unlike SGA, which requires a comprehensive assessment by a trained evaluator, PhA

measurement is a simple and non-invasive bedside technique. Research focused on the utility of PhA as a surrogate marker of malnutrition has a low evidence quality (Rinaldi et al. 2019). However, at present research is limited to only four disease states. The use of PhA in nutrition assessment in disease has not been validated, therefore, more extensive research in a variety of disease states, including ILD, is needed(Rinaldi et al. 2019)(Rinaldi et al. 2019)(Rinaldi et al. 2019)(Rinaldi et al. 2019)(Rinaldi et al. 2019).

It has been suggested that increased BMI is correlated with an increased survival in ILD (Alakhras et al. 2007). However, this reverse epidemiological effect of increased BMI fails to recognize the important contribution of fat-free mass to health. ILD research has only recently focused on fat-free mass as a promising predictor of survival (Nishiyama et al. 2017). Having identified fat-free mass as an important component of survival, it is pertinent that research focused on how specific components of body weight, specifically fat-free mass and body fat mass, influence survival in ILD continues. This area of research may directly benefit ILD patients through improving the prognosis of their disease.

1.2 Research Purpose and Objectives of the Research

The **overarching purpose** of this dissertation research is to gain a better understanding of nutritional concerns in ILD patients. Related to this purpose, this dissertation intends to meet the following four research objectives.

1) *The **first objective** of this research was to determine the prevalence of malnutrition using the gold standard of nutrition assessment, subjective global assessment (SGA), and to estimate body composition (fat-free mass index (FFMI) and body fat mass index (BFMI)) using BIA, among individuals with ILD.*

2) *The **second objective** of this research was to evaluate how nutrition status and body composition are related to functional exercise capacity using 6-minute walk distance (6MWD).*

3) *The **third objective** of this research was to investigate the utility of bioimpedance parameters controlled for age, sex and/or BMI, such as 50 kHz PhA and 200/5 kHz impedance ratio (IR) as surrogate markers of nutrition status in patients with ILD.*

4) *The **fourth objective** was to examine whether FFMI and BFMI controlled for age and sex, and nutrition status were independent predictors of survival in ILD patients.*

1.3 Study Area and Population

ILD typically affects middle-aged and older adults, with approximately two-thirds of patients being 60 years and older at time of presentation of ILD (Kim 2006). The primary population for this dissertation research was adults 18 years and older who were diagnosed with ILD. Participants were recruited from one respiratory clinic taking place at London Health Sciences Centre, Victoria Hospital in London, Ontario.

1.4 Outline of Dissertation

This dissertation is formatted in an integrated article approach. In the following chapters, this dissertation addresses these four objectives. Following this introduction, **Chapter 2** provides a literature review on background information relevant to these objectives including disease background, nutrition-related knowledge to date in ILD including a review of BIA and bioimpedance surrogate markers of nutrition status, nutrition-related concerns with ILD medication use, and exercise capacity.

A literature review continues through **Chapter 3** with a published review article on the gold standard method of nutrition assessment, SGA, as well as, PhA, a measure of cell health obtained using BIA. PhA is theorized to be an objective measure of nutrition status. This published review assesses the literature on SGA and PhA, and critically reviews the quality of evidence supporting PhA as a surrogate measure of nutrition status.

Chapter 4 specifically addresses the first three objectives of this dissertation; 1) to determine prevalence of malnutrition and estimate body composition measures in ILD patients, 2) to evaluate how nutrition status and body composition are related to functional exercise capacity and 3) to determine the appropriateness of bioimpedance parameters to identify malnutrition in ILD patients.

Chapter 5 addresses the fourth objective to examine whether nutrition status, and FFMI and BFMI, controlled for age and sex, are independent predictors of survival in ILD patients.

Lastly, **Chapter 6** provides overall conclusions including the contributions to research, clinical implications and recommendations, challenges and limitations of this thesis research, and outlines plans and recommendations for future research directions.

Chapter 2

2 Literature Review – Part I
Nutrition-Related Concerns in Interstitial Lung Disease

This literature review is organized into two parts. This chapter concentrates on nutrition-related concerns in interstitial lung disease (ILD). The second part of the literature review, found in **Chapter 3**, is a published systematic review focused on assessing phase angle (PhA) as a surrogate marker of nutrition using Subjective Global Assessment (SGA) as the reference standard.

This chapter first provides a review of ILD etiology, prognosis and disease management before turning to a review of the various nutrition-related concerns affecting ILD patients, including body weight, body mass index (BMI), body composition concerns, nutrition-related side effects associated with ILD medications, and functional exercise capacity as it relates to nutrition status. Overviews of bioelectrical impedance analysis (BIA) and bioimpedance surrogate markers of nutrition status which were used in this research are also integrated in this section to provide appropriate background and context for the discussed nutrition and ILD focused literature.

2.1 Interstitial Lung Disease

2.1.1 Etiology

Interstitial lung disease comprises a heterogeneous range of chronic lung disorders which cause various degrees of inflammation or fibrosis in the pulmonary parenchyma including the alveoli, trachea, bronchial tree, or blood vessels, and/or pleura (Bradley et al. 2008; Cottin et al. 2019). One of the most common ILDs is idiopathic pulmonary fibrosis (IPF). IPF is characterized by progressive fibrosis and architectural distortion of the lining of the air sacs of the lungs, or alveoli, and is relentlessly progressive (Raghu et al. 2018). Other fibrotic ILD subtypes include connective tissues disease-associated ILD, idiopathic nonspecific interstitial pneumonias and chronic hypersensitivity pneumonitis (Ryerson et al. 2016). While the etiology of some ILDs, including IPF, remains unknown (Travis et al. 2013), others are caused by occupational, inorganic or organic exposures, drug-induced

toxicities, or are secondary to CTD (Bradley et al. 2008). Reports of the incidence of ILD subtypes is limited by the broad range of ILD and the rarity of some ILD subtypes (Olson et al. 2018). In 2011, IPF affected 42 in 100,000 Canadians, of which the prevalence of IPF was greater in males than females and drastically increased with advancing age (Hopkins et al. 2016). As many ILDs are rare, recognizing and diagnosing specific subtypes require considerable expertise.

2.1.2 Prognosis

The clinical course and outcome of ILD are highly variable between different subtypes (Bradley et al. 2008), however, in general, ILD is associated with significant morbidity and mortality (Richeldi et al. 2003). In IPF, survival after diagnosis is only 2.5 to 5 years in the absence of treatment (Collard et al. 2003; Mura et al. 2012). Prognosis varies among and within disease subtypes, and by a variety of clinical and demographic parameters. Epidemiological data such as advancing age, male sex, and clinical features such as symptoms of dyspnea are reliable predictors of survival at diagnosis of IPF (Fernández Fabrellas et al. 2018). Clinical markers such as abnormal pulmonary function tests, 6-minute walk distance (6MWD), dyspnea scores and BMI can help predict survival in ILD (Alakhras et al. 2007; Collard et al. 2003; Manali et al. 2008). Specific clinical parameters such as percent predicted diffusing capacity for carbon monoxide ($\%DL_{co}$) $\leq$ 40% at the time of diagnosis, or a decline in $\%DL_{co}$ or percent predicted forced vital capacity (%FVC) overtime can predict survival in IPF (Fernández Fabrellas et al. 2018). A decline in %FVC over time has been shown to be the best predictor of mortality, however, the minimum clinically relevant change needed to predict mortality has varied (Fernández Fabrellas et al. 2018). A one-time point measurement of $\%DL_{co}$, however, is considered the main predictor of survival (Collard et al. 2003; Fernández Fabrellas et al. 2018; Hamada et al. 2007). For example, in a study of 78 IPF patients, $\%DL_{co}$, was the only significant predictor of 5-year survival ($r=0.557$, $p<0.0001$) when controlled for age, sex, and cardiorespiratory parameters (Hamada et al. 2007). Review of body mass, body composition and exercise capacity as predictors of survival in ILD will be discussed in sections 2.2.1 and 2.2.2.2 of this chapter.

2.1.3 Disease Management

Medical therapeutic options vary among different types of ILD. Early identification, aggressive treatment and lung transplantation remain the only recommendations for the treatment of ILD (Travis et al. 2013). Treatments may include immunosuppressive therapy (Richeldi et al. 2003; Spagnolo et al. 2010), anti-fibrotic or anti-inflammatory agents (Hunninghake 2014; Richeldi et al. 2014), and, when medical therapy fails in eligible patients, lung transplantation. Regardless of the etiology, the management strategy of ILD includes supportive therapy such as home oxygen (Crockett, Cranston, and Antic 2001), pulmonary rehabilitation (Holland and Hill 2008; Nakazawa, Cox, and Holland 2017), and weight optimization (Alakhras et al. 2007). Guidance related to weight optimization in ILD is limited and based on research related to body weight. Weight related research will be discussed in the following sections.

2.2 Nutrition-Related Knowledge to Date

Little is known about the influence of nutritional status on the clinical course of ILD, a potentially important implication on the outcome, functional capacity and quality of life of these patients. Existing research is limited by its focus on weight and BMI as measures of nutrition status. Therefore, current research does not fully address the influence of body composition and overlooks the importance of a comprehensive nutrition assessment.

2.2.1 Body Mass

Body mass impacts the ability to breath, and thereby health status in ILD patients. Patients with greater weight losses, especially lean body mass, have the greatest deterioration in lung function (Tynan and Hasse 2004). Alternatively, obesity complicates breathing and results in an increased workload and decreased functional exercise capacity (Tynan and Hasse 2004). Therefore, in general, improving any patient's nutritional status through appropriate weight management should lead to an improved quality of life and improved disease management.

Interestingly, multiple studies have found that increased BMI is correlated with an increased survival rate in IPF patients (Alakhras et al. 2007; Mura et al. 2012). Alakhras et

al. found that obesity (BMI >30 kg/m^2) had a protective effect on morbidity of IPF patients as compared to overweight (BMI 25-24.9 kg/m^2) and normal weight (BMI <25 kg/m^2) patients. Mura et al. (2012) reported that for every 1-unit increase in BMI there was an 11% lower risk of death at 3-year follow-up (HR 0.89, p=0.0155). The concept of obesity being protective suggests an inverse epidemiological effect, in that, increased weight may offer protection against malnutrition and protect against potential harsh effects of medical treatments (Alakhras et al. 2007). In support of this, progressive weight loss (greater than 5% of total body weight in 1 year) has also been found to be an independent predictor of decreased survival in IPF (Nakatsuka et al. 2018). Although literature is largely focused within IPF cases, one study, which included a diverse group of ILDs, including connective tissues disease-associated ILD, chronic hypersensitivity pneumonitis, and unclassifiable subtypes, found that a loss in BMI greater than 5% in 1 year was associated with significantly shorter survival times, as well had a 2-fold higher risk of death compared to those with a less than or equal to a 5% loss in BMI in 1 year (Pugashetti et al. 2018). However, when assessed across ILD subtypes, the association between BMI decline and survival was found to be significant in IPF and unclassifiable ILD, but not connective tissues disease-associated ILD nor chronic hypersensitivity pneumonitis (Pugashetti et al. 2018). However, these results may have been limited by small sample size in the connective tissues disease-associated ILD and chronic hypersensitivity pneumonitis subtypes.

Collectively, these studies have not fully explored the influence of body mass across many ILD subtypes, nor have they addressed the influence of fat-free mass or body fat mass on survival. In other disease states, the obesity paradox, or the hypothesis that increased body fat mass is protective only if fat-free mass is adequate, has been validated (Gonzalez et al. 2014). This suggests that BMI alone does not provide a complete picture of health.

2.2.2 Body Composition

Current research has failed to consider the impact of body composition as part of the protective effect of increased BMI in ILD patients. A burgeoning area of research involves the investigation of sarcopenia. Sarcopenia is a muscle disease defined by low muscle quantity and strength, and in severe cases low physical performance (Cruz-Jentoft et al.

2010). Presence of sarcopenia has been found to be associated with increased mortality, infection, and hospital length of stay (Kyle et al. 2005). For the purpose of this dissertation, sarcopenia and sarcopenic obesity have been identified using sex-specific cut-offs of quantity of estimated fat-free mass index (FFMI) and body-fat mass index (BFMI) obtained using BIA as outlined by Kyle et al. (2005). These cut-offs have been used by other groups to identify sarcopenia and sarcopenic obesity (Gonzalez et al. 2014; Guida et al. 2019). FFMI and BFMI are calculated according to the following equations; $FFMI = \frac{fat-free\ mass\ (FFM)\ (kg)}{height^2\ (m^2)}$ and $BFMI = \frac{body\ fat\ mass\ (BFM)\ (kg)}{height^2\ (m^2)}$.

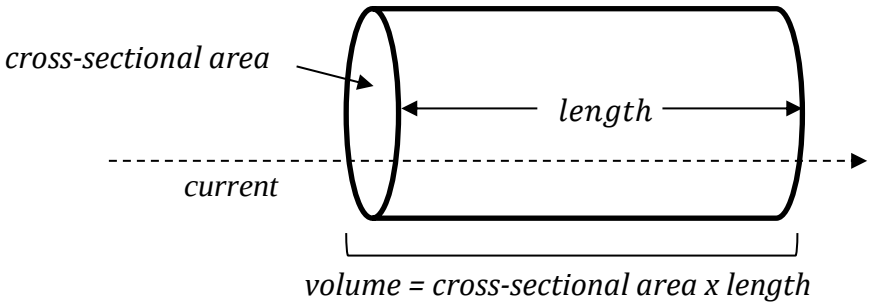
Low FFMI have been shown to be a predictor of mortality in various disease states such as chronic obstructive pulmonary disease (COPD) (Schols et al. 2005) and liver cirrhosis (Chang et al. 2019). Age, sex and height are main biological factors affecting fat-free mass, but it may also be affected by environmental factors such as physical activity (Kyle et al. 2003). Nishiyama et al. (2017), were the first to demonstrate that FFMI, determined using BIA, was a significant and independent predictor of survival in a cohort of Japanese IPF patients. Specifically, a 36% lower risk of death with every 1 unit increase in FFMI (HR 0.64, 95% CI (0.43–0.94), p=0.02) was observed (Nishiyama et al. 2017). Conversely, results from a conference abstract indicated no significant association between FFMI, determined using BIA, and all-cause mortality at 1-year in IPF patients (Patel et al. 2018). Of note, neither of these studies controlled for age or sex differences in their analyses of FFMI. Therefore, one cannot distinguish whether it is disease-related and age-related muscle loss that is associated with decreased survival.

The following subsections review BIA, its theoretical foundation, conditions and contradictions for use, limitations, and comparison to alternative body composition assessment methods.

2.2.2.1 Principles of Bioelectrical Impedance Analysis

BIA leverages the fact that body tissues vary in water and ionic (electrolyte) concentrations and thus act as either conductors or insulators to an electrical current travelling through the body. Muscle mass and body water, due to its large amounts of water and electrolytes, act

as effective conductors. In other words, these body compartments offer less resistance to an electrical current passing through them. Conversely, fat and bone mass are insulators as the electrical current experiences more resistance due to the limited amount or lack of water or ionic substances in these components. Therefore, body composition can be estimated based on the underlying principle that the impedance of a cylindrical conductor with uniform cross-sectional area (CSA) relates to its length, and specific resistivity (ρ) applied at a fixed frequency, illustrated in **Figure 1** (Kushner 1992).



1) $$impedance = \frac{resistivity(length)}{cross\text{-}sectional\ area}$$

2) $$volume = \frac{resistivity(length)^2}{impedance}$$

Figure 1 Cylindrical model of the relationship between the impedance of a current to the specific resistivity (**ρ**), length (L), cross-sectional area (CSA) and volume (V) of a conductor.

We know that anatomically the body is not a single, symmetrical cylinder with uniform cross-sectional area (Mulasi et al. 2015). Rather, BIA approximates the body as five cylinders; one for each arm, one for each leg and one for the trunk. Therefore, these components of the body collectively contribute to the total body impedance. Additionally, the impedance of a conductor is a function of resistance and reactance according to the following equation, $impedance^2 = resistance^2 + reactance^2$ (Kushner 1992). R is the resistive effect exhibited on the current as it travels through water and electrolytes in fluid

and tissues (Lukaski, Kyle, and Kondrup 2017). Reactance is related to the electrical charge of the current through cells, tissues and non-ionic substances (Lukaski, Kyle, and Kondrup 2017). It is these raw bioimpedance measures that may be used in regression equations to estimate various components of body composition such as muscle mass, body-fat or body water. Generally, these equations are both age and sex specific, and are validated against other methods of body composition assessment.

2.2.2.2 BIA Methods and Contraindications

BIA should be performed in ideal conditions to reduce measurement error. For instance, participants should not exercise in the 24 hours prior to the completion of BIA testing. Participants should abstain from eating or drinking within 4 hours of the test and should be asked to empty their bladders just prior to the test to reduce inaccurate contributions of consumed food or fluid in the BIA results (National Health Nutrition and Examination Survery (NHANES) 2000). Electrodes through which the battery powered current flows are placed on the surfaces of the hand and foot. See **Appendix C** for BIA testing protocol including images on the proper placement of electrodes and body positioning. At the time of the test, limb position should be controlled to prevent the limbs and trunk from touching one another. Participants should be supine for 5-10 mins to help equalize body water in order to account for potential fluid retention (Kyle, Genton, and Pichard 2013). In cases of significant edema, results may be confounded. Therefore, clinical judgement may be necessary to assess appropriateness of BIA in specific cases. In our cohort of ILD patients, we did not note any patients with significant edema in our clinical assessments.

There are special cases where BIA is contraindicated. BIA is not recommended to be used in pregnant or lactating women. BIA should not be completed on individuals with metal implants as the presence of metal will interfere with the measurement of Z, R and X_c producing inaccurate results. As well, individuals with pacemakers should not undergo BIA measurement as the electrical current may interfere with their implanted device causing harm to the participant (Kyle et al. 2004).

2.2.2.3 Limitations

Measurement instruments have inherent limitations. Although the underlying principles of BIA allow for body composition estimation, they also contain some inaccuracies. First, the CSA of the body's limbs and trunk are not of uniform area, nor perfectly symmetrical as stated in the underlying principle of BIA. Secondly, it is assumed that current density remains uniform across a conductor, however, the body is not homogeneous. Therefore, current density will vary even when travelling through muscle, for example, due to intramuscular fat. Additionally, body composition data obtained from BIA are predicted values or estimations from regression equations developed for specific populations based on age, sex and/or disease state. Generally, these regression equations are proprietary to the manufacturer of the equipment, which is the case in the BIA device (BodyStat® 1500MD) used in this research. Therefore, one cannot say with absolute confidence that these estimates are accurate in specific age ranges or disease. Regression equations based on raw values of resistance and reactance are published for specific disease states, such as COPD (de Blasio et al. 2017), however, there have been no regression equations published within the ILD or IPF patient population. Although inherent limitations of the BIA principles are not able to be controlled for, efforts should be made to minimize limitations which can be controlled such as ensuring patients adhere to pre-testing guidelines, accurate electrode and body positioning, and when possible patient specific regression equations should be used.

2.2.2.4 Advantages and Comparison to Other Assessment Techniques

Although BIA has notable limitations, it is important to acknowledge that BIA is a portable, quick and non-invasive technique. It is a relatively inexpensive tool which can be used in clinical practice to obtain a variety of detailed information related to body composition and cell health. Other, more precise, measurement techniques such as the use of dual energy X-ray absorptiometry scans, magnetic resonance imaging or computed tomography scans measure body composition at the organ and tissue level (Prado, Birdsell, and Baracos 2009). However, major limitations to the use of dual energy X-ray absorptiometry, magnetic resonance imaging and computed tomography imaging are their cost, availability

and, most notably, radiation exposure to participants. Therefore, the ability to use the techniques in research is generally limited, and when used these scans likely have been previously completed for diagnostic or medical monitoring purposes which are typically leveraged retrospectively for research purposes.

2.2.3 Malnutrition

Malnutrition has been defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass (total cellular components of the body) leading to diminished physical and mental function and impaired clinical outcome from disease" (Cederholm et al. 2015). Early identification of malnutrition in chronic diseases is important in order to implement appropriate nutrition care plans, thereby improving quality of life and tolerance to medical treatments (Charney 2008). Individuals at risk of malnutrition may be identified using nutrition screening tools such as the Mini Nutrition Assessment®. Mini Nutrition Assessment® is a malnutrition screening tool validated for older adults defined by age >65 years (See **Appendix D**) (Bauer et al. 2008). Once identified as being at risk of malnutrition, individuals should undergo in-depth nutrition assessment in order to identify nutritional deficiencies and determine degree of malnutrition. The gold standard of nutrition assessment is the subjective global assessment (SGA) developed by Detsky et al. 1987 (See **Appendix B** for SGA scoring sheet) (Keith 2008). SGA combines dietary, weight, functional, gastrointestinal and disease history with a physical examination to arrive at a categorical ranking. SGA will be reviewed in further detail in **Chapter 3** including its components and various versions developed for specific patient populations.

To date, only a few nutrition screening tools, such as the Mini Nutrition Assessment® have been used to assess risk of malnutrition in ILD/IPF patients, but no studies have used in-depth nutrition assessments in ILD/IPF. An American study evaluated the nutrition status of IPF patients using the Mini Nutrition Assessment®. Results from this study revealed that approximately one quarter of participants were at risk of malnutrition while the remaining were identified as normal nutritional status (Autore et al. 2013). Although, IPF prevalence increases with age, authors concluded that the application of the Mini Nutrition Assessment® in the general IPF population was not appropriate due to wide range of ages.

Additionally, malnutrition prevalence in ILD has been estimated using single anthropometric measures and varies greatly. For instance, a study of 81 IPF patients, of which 88% were male, found that 28% of patients were malnourished using fat-free mass, 4% were malnourished using BMI, and 5% were malnourished using mid-arm circumference (Jouneau et al. 2019). In ILD, the prevalence of malnutrition using standardized and validated nutrition assessment tools is not well established.

2.2.3.1 Measurements of Nutritional Indicators

Trained clinicians, such as registered dietitians (RDs), needed to perform the SGA may not be readily available as part of standard care, therefore surrogate markers of nutrition, such as raw measures of BIA including PhA and impedance ratio (IR), have been suggested in a number of different disease states (Kuchnia et al. 2017; Kyle et al. 2012; Kyle, Genton, and Pichard 2013; Malecka-Massalska et al. 2016; Ott et al. 1995; Plank and Li 2013). PhA will be discussed in further detail in **Chapter 2**.

IR and nutrition status are theorized to relate to each other through their common association with alterations in body composition and body cell mass. IR is the ratio of impedances at 200kHz and 5kHz obtained using BIA. As described in section 2.2.2.1.1., impedance includes two components; the resistance and reactance of a current as it passes through the body. This research used multi-frequency BIA. multi-frequency BIA provides the advantage of differentiating body water components; intracellular water and extracellular water. Total body water is estimated when impedance is measured at high frequencies (200kHz) which can pass through cell walls. However, impedance at low frequencies (5kHz) have limited capacity to penetrate cell walls, therefore only extracellular water is estimated. Therefore, $\text{IR} = \frac{\text{impedance at 200kHz}}{\text{impedance at 5kHz}} = \frac{\text{total body water}}{\text{extracellular water}}$ (Rinninella et al. 2018). In healthy individuals, there is a large variation in impedances at 200kHz and 5kHz resulting in a lower value of IR. However, in malnutrition and disease, cell walls can become damaged or weakened, allowing intracellular water to leak into the extracellular space which may result in edema or third-spacing (Rinninella et al. 2018). Therefore, the impedance at 5hHz, representing extracellular water, will approach that of the total body water, and IR will near a value of 1. An IR closer to 1 is theorized to indicate

poorer cellular health, abnormal hydration status and malnutrition (Kuchnia et al. 2017; Lukaski, Kyle, and Kondrup 2017; Rinninella et al. 2018).

Although there has been growing interest in the use of raw bioimpedance parameters as prognostic indicators and surrogate markers of nutrition status, no studies to date have explored the relationship between PhA nor IR in ILD. As well, limited research exists on the relationship between IR and nutrition status. Using total body protein as a measure of nutrition status, Plank and Li (2013), demonstrated that a high IR, defined as >0.78 in males and >0.82 in females, established from healthy volunteers, had significantly greater odds of malnutrition [OR 4.15, CI 95% (1.77-9.75), p=0.001]. However, no studies have compared IR with nutrition status assessed using nutrition screening tools, nor comprehensive nutrition assessment methods such as SGA. Furthermore, the overall body of research on IR and nutrition is lacking in its validation in clinical settings. Although IR cut-offs have been suggested in other populations such as hospitalized inpatients (Plank and Li 2013), in order to determine appropriate IR cut-off points population reference norms are required. Recently, an American study using the National Health and Nutrition Examination Survey 1999–2004 database published population reference values of PhA and IR, therefore establishing cut-off points in a diverse American sample (Kuchnia et al. 2017). Further studies are needed to continue to validate IR as an accurate and appropriate marker of nutrition status in health and disease.

2.2.4 Drugs and Nutrition

There is no cure for ILD aside from lung transplantation. Medical therapies are not curative, rather they act to slow or stop disease progression (Trawinska, Rupesinghe, and Hart 2016). In general, ILD/IPF medical therapies are used for either their anti-fibrotic, anti-inflammatory or immune suppressing effects. However, these medications come with risks of adverse events. Adverse events are the most common reason for patients to discontinue medications (Trawinska, Rupesinghe, and Hart 2016). In general, medication-related gastrointestinal (GI) adverse events can be managed through dose adjustment, treatment interruption, and/or symptoms management (Quinn, Wisse, and Manns 2019). Therefore, involvement of healthcare professionals to provide symptomatic and supportive care to

patients in order to manage these medication-related adverse events is an important component of ILD/IPF management.

2.2.4.1 Corticosteroids

Corticosteroids have anti-inflammatory properties which in early ILD management were thought to be able to slow or stop the progression of fibrosis, respiratory failure and death (Kim and Meyer 2008). Over the years, corticosteroids have not shown to be the most effective therapy they were once expected to be. Therefore, previous clinical guidelines have suggested, based on very-low quality evidence, that only a minority of patients with acute exacerbations of their disease will experience a treatment benefit with corticosteroids (Kim and Meyer 2008; Raghu et al. 2011). Nevertheless, corticosteroids, such as prednisone, may be used in clinical practice. Common nutrition-related side effects, depending on the dosage, include weight gain related to increased appetite or fluid retention (US FDA approved prescribing information 1955). Several other ILD medications have shown to be effective in the management of ILD which are discussed in the following subsections.

2.2.4.2 Pirfenidone (Esbriet®)

Pirfenidone is an anti-fibrotic medication used in IPF patients and acts to suppress the activity of fibrosis-associated pathways (Oku et al. 2008; Trawinska, Rupesinghe, and Hart 2016). Pirfenidone is also used for its antioxidant and anti-inflammatory effects (Somogyi et al. 2019). A serious side-effect of pirfenidone includes photosensitivity. Patients are instructed to limit their sun exposure and to use sun protective clothing and sun blocks while on this medication (Kreuter 2014). Therefore, patients on pirfenidone have limited vitamin D synthesis through the skin and must rely solely on diet and supplementation to meet their vitamin D needs. Research has shown that ILD patients have a high incidence of vitamin D deficiency (Hagaman et al. 2011), osteopenia and osteoporosis (Alhamad and Nadama 2015). Other observed side effects with pirfenidone use are nausea, diarrhea, vomiting, anorexia and dyspepsia/gastroesophageal reflux disease (Galli et al. 2017). In clinical trials, the most common GI-associated adverse events were nausea and dyspepsia/

gastroesophageal reflux disease which occurred in 36% and 18.5% of cases, respectively (Galli et al. 2017).

2.2.4.3 Nintedanib (OFEV®)

Nintedanib is an anti-fibrotic medication used in IPF to slow the rate of lung function decline (Galli et al. 2017; Trawinska, Rupesinghe, and Hart 2016). The most common GI side effect experienced by patients is diarrhea. In clinical trials, 62% of patients experienced diarrhea, 24.5% experienced nausea, 12% experienced vomiting and 11% experienced anorexia (Galli et al. 2017). Additionally, over half of the adverse events resulting in drug discontinuation were related to GI-associated adverse events (Galli et al. 2017).

2.2.4.4 N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is an oral or inhaled antioxidant used in the treatment of IPF to help prevent damage to the lungs (Trawinska, Rupesinghe, and Hart 2016). Common adverse reactions can include nausea and vomiting, however, a double-blind, placebo-controlled trial showed no significant difference in adverse events in NAC versus placebo (Martinez et al. 2014). Although it has been proven to be safe and well tolerated (Martinez et al. 2014), current clinical practice guidelines, however, have stipulated a conditional recommendation against its use due to non-significant changes in lung function nor survival rates associated with its use (Raghu et al. 2015).

2.2.4.5 Mycophenolate Mofetil (CellCept®, Myfortic®)

Mycophenolate Mofetil (MMF) is a potent immunosuppressive and anti-inflammatory medication typically used to prevent rejection after organ transplant. However, research has suggested that MMF may also have an anti-fibrotic effect. Therefore, its use in certain ILDs including connective tissues disease-associated ILD and chronic hypersensitivity pneumonitis has grown. However, in IPF, only small, low-powered studies have been published and provide mixed results (Nambiar, Anzueto, and Peters 2017). The most common GI-associated adverse events include constipation, nausea, diarrhea, vomiting, and dyspepsia (US FDA approved prescribing information 2015). Studies involving ILD

patients have noted diarrhea to be the most frequent GI-associated symptom (Omair, Alahmadi, and Johnson 2015). Despite its proposed anti-fibrotic effects, current clinical practice guideline do not include recommendations for its use in IPF patients (Raghu et al. 2015).

2.2.4.6 Antacids

Antacids, such as, protein pump inhibitors for management of gastroesophageal reflux disease are commonly prescribed in ILD patients to manage adverse effects resulting from ILD/IPF medications. As well, there is a high incidence of gastroesophageal reflux disease in IPF (Trawinska, Rupesinghe, and Hart 2016). This has led some to believe that gastroesophageal reflux disease plays a role in the development and progression of IPF, or many be an underlying cause of chronic cough in IPF (Raghu et al. 2006; Trawinska, Rupesinghe, and Hart 2016).

It has been reported that prevalence of ILD increases with age (Olson et al. 2018). Nutritional deficiencies associated with aging, confounded by nutrient-drug interactions common in the ILD population puts ILD/IPF patients at higher risks of deficiencies. For example, absorption of vitamin B12 first requires enough acid content in the stomach to be able to release vitamin B12 from the protein it is attached to in food. However, with age stomach acidity tends to decrease, and confounding this, protein pump inhibitors act to reduce gastric acid secretion (McCaddon 2013). Therefore, especially in older patients with IPF/ILD on protein pump inhibitors, absorptive capacity of vitamin B12 can be reduced affecting patients' serum blood levels leading to deficiency.

In summary, from a nutrition perspective, use of ILD medications puts patients at risk of malnutrition whether it be through poor intake, decreased appetite, malabsorption, or any combination of these. Therefore, specific and therapeutic nutritional support to manage medication adverse events can help to prevent and/or correct malnutrition in ILD patients. Therefore, it is important to be familiar with these medications and aware of their side effects when assessing nutrition status of ILD patients.

2.3 Exercise Capacity and Nutrition

Diminished exercise capacity is common among individuals with ILD (Mendes et al. 2015), which negatively contributes to their ability to participate in normal activities of daily living, and thus compromises quality of life (Hansen and Wasserman 1996; Mendes et al. 2015). Exercise capacity is measured using the six-minute walk test which is a routine component in the standard care of ILD monitoring and management. The six-minute walk test is a reliable and validated tool in ILD patients (Du Bois et al. 2011; Eaton et al. 2005; Lederer et al. 2006; Serajeddini, Rogliani, and Mura 2018) which involves participants walking as far and fast as they are able for 6 minutes. A change of 30 meters is generally considered a clinically significant change in 6MWD in IPF patients (Fernández Fabrellas et al. 2018; Nathan et al. 2015). Interestingly, six-minute walk test guidelines (American Thoracic Society (ATS) 2002) suggest poor nutrition as a potential underlying cause of low 6MWD and indicate that it should be further investigated.

Diminished exercise capacity in ILD is multifaceted with pathophysiological factors such as impaired of gas exchange, altered respiratory mechanics, limited pulmonary circulation and peripheral muscle dysfunction (Holland et al. 2008; Raghu et al. 2011). In other chronic lung diseases, such as COPD, low 6MWD was associated with significantly greater odds of poor nutrition status assessed using the Mini Nutrition Assessment® [OR 0.835 95% CI (0.735-0.908), p=0.005] (Matkovic et al. 2017). Similarly, worsened nutrition status assessed using Mini Nutrition Assessment® was associated with worse dyspnea score [OR 22.888, 95% CI (2.103-249.065), p=0.01], and lung function (FEV_1/FVC ratio) [OR 0.898, 95% CI (0.826-0.977), p=0.012] in COPD patients (Mete et al. 2018).

In ILD, nutrition support is noted as a non-exercise component in pulmonary rehabilitation programs (Nakazawa, Cox, and Holland 2017). However, specific nutrition recommendations are not included in best practice guidelines (Raghu et al. 2015; Travis et al. 2013). No studies have explored the influence of poor nutrition status on diminished exercise capacity in ILD, therefore, research in this area is needed to better understand the complex needs of this patient population.

There are notable nutrition-related concerns associated with ILD and its management. These concerns include maintaining a healthy body weight, optimizing body composition and managing medication side-effects. In addition, poor nutrition status may be negatively impact ILD patients' functional level of exercise of everyday physical activities and thus quality of life. Identifying and correcting malnutrition requires specialized skills and assessment tools. Unfortunately, nutrition professions such as RDs needed to complete these assessments may not be part of the health care team in standard ILD care. Therefore, nutrition concerns in ILD patients may not be identified, nor appropriately managed. The following chapter reviews the appropriateness and accuracy of PhA as an objective, surrogate marker of nutrition status using SGA as the reference standard.

Chapter 3

3 Literature Review – Part II
Is Phase Angle an Appropriate Indicator of Malnutrition in Different Disease States? A Systematic Review

Publication citation: Rinaldi S, Gilliland J, O'Connor C, Chesworth B, Madill J. 2018. "Is phase angle an appropriate indicator of malnutrition in different disease states? A systematic review." *Clinical Nutrition European Society for Parenteral and Enteral Nutrition* 29: 1-14. doi:https://doi.org/10.1016/j.clnesp.2018.10.010.

3.1 Abstract

Background & aims: The subjective global assessment (SGA) classifies malnutrition severity via a simple bedside assessment. Phase angle (PhA) is an indicator of cell integrity and has been suggested to be indicator of nutritional status.
Objective: To explore the relationship between PhA and SGA.
Methods: Relevant studies published through October 31, 2017 were identified using 7 electronic databases. Articles were included for review if they included comparison data between SGA and PhA within adult disease populations. Evidence quality was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines and methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.
Results: 33 articles within four disease states (liver, hospitalization, oncology and renal) met inclusion criteria for review. Results were limited by restricting the database search to articles published in English only, and by the inherent difficulty of comparing 2 methods which are both influenced by the operator.
Conclusion: Based on GRADE guidelines, evidence quality received a grade of Low. Based on QUADAS-2, 61% of studies had high risk of bias in the index test (PhA), while all other domains had low risk. It is not possible to conclude that PhA is an accurate independent indicator of malnutrition. PROSPERO no. CRD42016050876.

3.2 Introduction

Malnutrition is a common concern in both chronic and acute disease with significant implications on survival, quality of life, medical complications, and other socioeconomic issues (McWhirter and Pennington 1994; K. Norman, Pichard, et al. 2008; Pirlich et al. 2005). There is a broad range of methods for nutrition assessment available to clinicians (White et al. 2013). Subjective Global Assessment (SGA) is a nutritional assessment method which classifies malnutrition severity via a bedside assessment (Detsky et al. 1987). It is the gold standard method to identify malnutrition (Keith 2008), and has been validated in many disease states and clinical settings (Baccaro et al. 2007; Baker et al. 1982; Cooper et al. 2002; Correia and Waitzberg 2003; Jerin et al. 2003; Kondrup et al. 2003; Pirlich et al. 2005). SGA combines dietary, weight, functional, gastrointestinal and disease history with a physical examination to arrive at a category ranking. SGA-A represents a well-nourished state, SGA-B represents moderate malnutrition or suspected of being malnourished and SGA-C represents severe malnutrition (Detsky et al. 1987).

Since its initial development, SGA has been adapted by various groups. Hasse et al., 1993 developed an adapted-SGA for liver disease, which accounts for additional clinical conditions such as encephalopathy, infection, kidney function, and varices (Hasse et al. 1993). The CANADA-USA Peritoneal Dialysis Study Group developed a 7-point modified SGA (7p-SGA) (Churchill, Taylor, and Keshaviah 1996). Kalantar-Zadeh and colleagues, proposed a quantitative scoring system known as the quantitative-SGA (QSGA), also referred to as Dialysis Malnutrition Score (Kalantar-Zadeh et al. 1999). The Patient-Generated SGA (PG-SGA) combines a patient-generated component with a professional assessment and is used most commonly in oncology and chronic catabolic conditions (Bauer, Capra, and Ferguson 2002; Ottery 1996; Ottery and Jager-Wittenaar 2014).

Whereas SGA evaluates nutritional status subjectively, phase angle (PhA) is strictly an objective measure. Unlike SGA which requires a comprehensive assessment by a trained evaluator, PhA measurement is a simple, quick and non-invasive technique. PhA is a measure of the resistance and reactance of a current as it passes through tissues of the body via bioelectrical impedance analysis (BIA) (Barbosa-Silva and Barros 2005).

Resistance is affected by the amount of fluid in the tissues of the body, whereas reactance is affected by the type of body cells and their related permeability (Norman et al. 2015). Age, sex, and BMI are the main biological factors affecting PhA (Norman et al. 2012). PhA may also be affected by level of physical activity, fluid status, and body composition (Norman et al. 2012; Tynan and Hasse 2004). The calculation of a standardized phase angle (SPhA) aims to account for these confounding factors. A SPhA is calculated as a z-score which may be based on established population reference values stratified by a combination of age, sex, BMI, or ethnicity (Barbosa-Silva et al. 2005; Barbosa-Silva, Barros, and Larsson 2008; Bosy-Westphal et al. 2006; Kyle et al. 2001; Kyle et al. 2004).

PhA has been suggested to be a prognostic, health, functional and nutrition indicator (Ott et al. 1995; Schwenk et al. 2000; Selberg and Selberg 2002). Generally, a low PhA indicates cell membrane breakdown and thus an altered ability to store energy and complete metabolic functions (Norman et al. 2012). Conversely, a high PhA indicates intact cell membranes and high body cell mass (Norman et al. 2012). Thus, as PhA reflects the quantity and types of tissues, such as muscle and fat mass, including hydration status, it is hypothesized that PhA could reflect nutritional status. It is thought that metabolic changes, such as those in cell membranes, are first affected by malnutrition (Barbosa-Silva 2008). Thus, PhA may be able to detect malnutrition at an early stage and may be useful in evaluating the effectiveness of nutrition therapy, before improvements in nutritional status can be detected by other assessment methods such as SGA. To this end, many studies have used PhA cut-off points to identify malnutrition (Antunes et al. 2012; Selberg and Selberg 2002). Many of these PhA cut-off points were derived using survival as its reference standard (Barbosa-Silva and Barros 2005; Fernandes et al. 2012; Mattar 1995; Máttar 1996; Paiva et al. 2010). Thus, the reliability of these cut-offs to identify malnutrition is unknown.

Therefore, the aim of this study is to evaluate the relationship between bioelectrical phase angle and malnutrition severity as measured by the Subjective Global Assessment in acute or chronically ill adults ≥18 years through a systematic review of cross-sectional and/or retrospective studies.

3.3 Methods

The systematic review protocol was registered on PROSPERO (no. CRD42016050876). The current systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies were selected using the following inclusion criteria: 1) original research published in English, 2) assessment of malnutrition using SGA and its adapted versions, with comparison to PhA or SPhA, and 3) individuals >18 years with acute or chronic disease/illness.

3.3.1 Data Sources

Relevant studies were identified by searching 7 electronic bibliographic databases: Scopus, CINAHL, PubMed, ProQuest Nursing and Allied Health, Medline, Cochrane, and ProQuest Dissertation and Thesis. Search terms used were ‘phase angle’ AND (‘subjective global assessment’ OR SGA), including their MeSH terms. The search was limited to human studies published in English through October 31, 2017. Reference lists of all relevant studies, and relevant reviews were examined for other relevant studies, although none were identified. Two investigators independently reviewed titles and abstracts to select potentially eligible articles for document screening. If discordance existed between the 2 reviewers, a decision was made by a third reviewer.

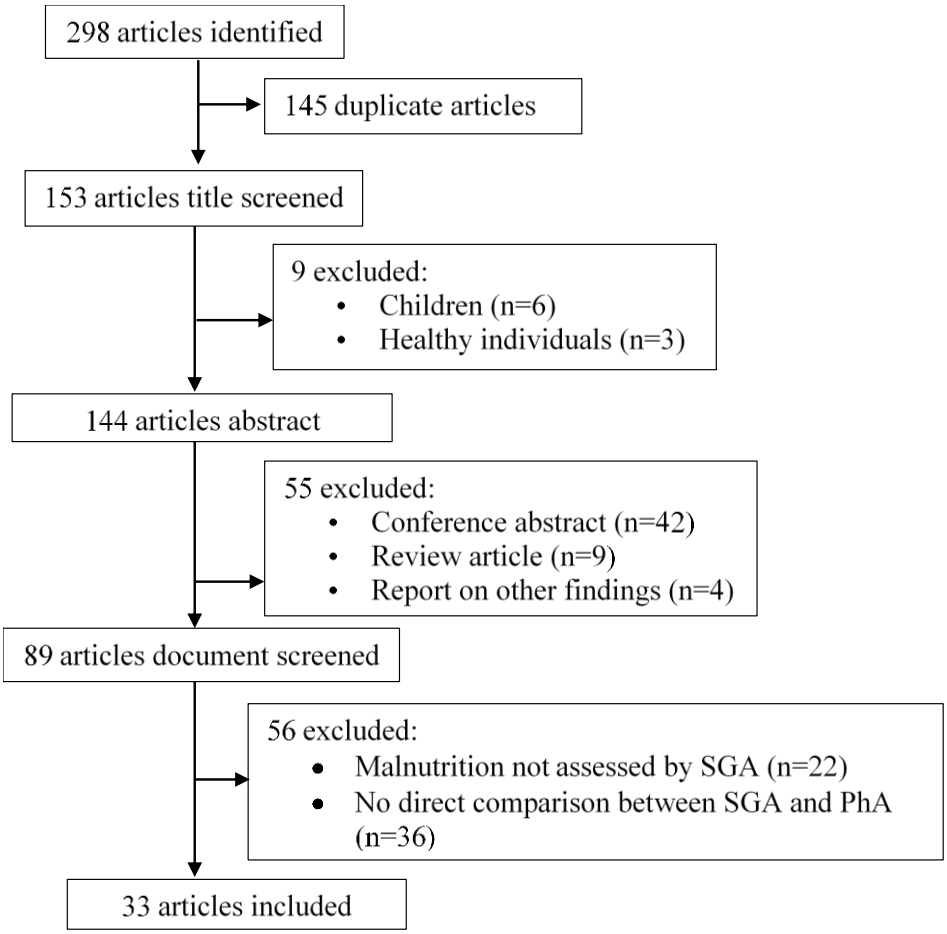


Figure 2 Flowchart of selecting studies for the systemati**c** review

3.3.2 Data Extraction and Synthesis

One reviewer independently extracted study information and then verified by a second reviewer. Data was organized in an excel spreadsheet which included authors, year of publication, country of origin, study objective, study population (clinical setting, sample size, sex and age), subjective method(s) of nutritional assessment, BIA model used, PhA cut-off, analyses between PhA and SGA and limitations of the study. A meta-analysis was not performed as a variety of previously derived cut-off values were used which did not allow for agreement statistics. Data were synthesized by disease group to allow for more direct comparison between study results. Within each disease group, differences in findings were compared and reasons for these differences such as heterogeneity, study design, size and population were identified.

3.3.3 Data Evaluation and Quality Assessment

The articles were evaluated by two reviewers using two quality assessment tools: the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines (Guyatt et al. 2011) and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting et al. 2011). The GRADE approach provides a quality rating of scientific evidence ranging from Very Low to High. This approach is widely used in systematic reviews and meta-analyses in the development of clinical practice guidelines and health care recommendations (Guyatt et al. 2011). Although the GRADE approach is a highly regarded tool, a second quality assessment tool designed specific for diagnostic accuracy was also used to assess methodological quality. The QUADAS-2 tool is recommended for use in systematic reviews involving diagnostic accuracy studies. QUADAS-2 evaluates the risk of bias and applicability within four domains observed in diagnostic accuracy studies: patient selection, index test, reference standard and flow and timing. QUADAS-2 does not generate a quality score, instead it allows the user to summarize the number of studies found at low, high or unclear risk of bias and applicability across domains. To indicate an overall utility of PhA or SPhA as a nutritional indictor in disease, quality assessment using the GRADE approach and the QUADAS-2 tool was completed within each disease group separately and across all studies. Both researchers involved in data extraction (SR and JM) were trained in the use of GRADE guidelines and the QUADA-2 tool.

For the purposes of data extraction, articles with reported κ coefficients (kappa) were interpreted as previously recommended by Altman (1991): $\kappa < 0.20$ (poor agreement); $0.21 \leq \kappa \leq 0.40$ (fair agreement); $0.41 \leq \kappa \leq 0.60$ (moderate agreement); $0.61 \leq \kappa \leq 0.80$ (good agreement); $\kappa > 0.80$ (very good agreement) (Altman 1991).

3.4 Results

Database searches resulted in 298 articles. All articles were exported into a reference management system and merged to remove duplicates, with 153 articles retained for screening. A final 33 articles were identified as relevant and reviewed further. Publication

years ranged from 1993 to 2017. Study characteristics are displayed in **Table 1**. Study results are displayed in **Table 2**.

Table 1 Study characteristics of the literature on the comparison between PhA and SGA in malnutrition assessment

Author, Year	**County**	**Participant characteristics**	**Sample size (% male)**	**Age (years)** mean ± SD, medium (range)	**BIA device**
Liver Disease					
(Wagner et al. 2011)	Austria	Years after Tx: *Group A*: <5 *Group B*: 5-10 *Group C*: >10	*Group A*: n=11 *Group B*: n=19 *Group C*: n= 41 Sex not specified	*Group A*: 58 ± 8 *Group B*: 59 ± 6 *Group C*: 58 ± 10	RJL-101
(Bakshi and Singh 2016)	India	End-stage liver disease patients admitted to hospital for liver Tx	n=54 (n=20 underwent BIA) Sex not specified	48.3 ± 10.2	MC-180MA (Tanita)
(Peres et al. 2012)	Brazil	CLD	n=66 (57.6%M)	59 (41-79)	RJL-101
(Liboredo et al. 2015)	Brazil	Liver Tx	n=18 (83%M)	59 (41-79)	RJL Quantum X
Hospitalized Patients					
(Barbosa-Silva et al. 2003)	Brazil	Preoperative elective GI surgery	n=279 (31%M)	50.4 years	RJL Quantum 101
(Cardinal et al. 2010)	Brazil	Preoperative elective GI surgery	n=125 (46.4%M)	M: 50.8 F: 51.0	Biodynamics model 310
(Meireles et al. 2012)	Brazil	Preoperative elective GI surgery	n=124 (43.5%M)	52.26 ± 14.95	Biodynamics model 310e

(Scheunemann et al. 2011)	Brazil	Preoperative elective GI surgery	n=98 (32.7%M)	46.3 ± 13.6	Biodynamics model 310e
(Kyle et al. 2012)	Switzerland	Medical, surgical, trauma patients	*Patients*: n=649 (59%M) *Controls*: n=649 (59%M)	*Patients*: M: 39.8 ± 12.7 F: 38.6 ± 14.1 *Controls*: M: 39.7 ± 12.6 F: 38.4 ± 13.6	RJL-101
(Kyle, Genton, and Pichard 2013)	Switzerland	Medical, surgical, trauma and cancer patients	*Patients:* n=983 (53%M) C*ontrols:* n=983 (53%M)	*Patients:* M: 49.8 ± 19.7 F: 56.4 ± 23.2 *Controls:* M: 49.6 ± 19.6 F: 56.2 ± 22.9	RJL-101
(Guerra et al. 2015)	Portugal	Long and short LOS hospitalized patients	*Short LOS*: n=311 (45.2%M); *Long LOS*: n=371 (54.8%M)	*Short LOS*: 55 (IQR 24) *Long LOS*: 61 (IQR 19)	Biodynamics 450
(Norman, Smoliner, et al. 2008)	Germany	Hospitalized gastro-enterology, hepatology and endocrinology patients	n=242 (50%M)	*SGA-A*: 60.3 (IQR 42.1-68.3) *SGA-B*: 57.1 (IQR 33.5-66.4) *SGA-C*: 56.2 (IQR 39.3-67.6)	Nutriguard M (Data Input)

(Stobäus et al. 2012)	Germany	Cardiology, general surgery, hepatology, endocrinology and GI patients	n=777 (47%M)	53.6 ± 16.7	Nutriguard M (Data Input)
Oncology					
(Gupta et al. 2004)	USA	Stage IV pancreatic cancer	n=58 (60.3%M) *SGA completed in n=51	At diagnosis: 56.2 ± 1.5	RJL-101Q
(Gupta et al. 2008)	USA	Advanced CRC	n=73 (50.6%M)	At diagnosis: 56 ± 11.4	RJL-101Q
(Abe Vicente et al. 2013)	Brazil	*Group 1*: Active gastric or CRC *Group 2*: treatment follow-up patients, tumor free >3 months	*Group 1*: n=75 (48%M) *Group 2*: n=62 (45.2%M)	*Group 1*: 60.2 ± 12.2 *Group 2*: 61.3 ± 11.6	Biodynamics 450
(Maurício et al. 2013)	Brazil	CRC	n=70 (44.3%M)	M: 60.1 ± 14.0 F: 60.7 ± 14.8	RJL Quantum X
(da Silva et al. 2013)	Brazil	Patients with esophageal and stomach cancer	n=43 (60.5%M);	Not reported	Not reported
(Malecka-Massalska et al. 2016)	Poland	Newly diagnosed HNC	n=75 (89.3%M)	At diagnosis: 56.88 ± 8.21	SFB7 BioImp v1.55

(Wladysiuk et al. 2016)	Poland	Presurgical, treatment-naïve, HNC	n=75 (89.3%M)	56.88 ± 8.21	SFB7 BioImp v1.55
(Mulasi et al. 2016)	USA	HNC patients after 3 months of chemo-radiotherapy	n=19 (94.7%M)	59 ± 7	QuadScan 4000
(Maasberg et al. 2017)	Germany	Neuro-endocrine neoplasia	n=203 (48.3%M)	Mean: 63.4	Nutriguard M (Data Input)
(Norman et al. 2010)	Germany	Solid or hematologic tumor disease	n=399 (52.1%M)	63.0 ± 11.8	Nutriguard M (Data Input)
(Motta, Castanho, and Velarde 2015)	Brazil	Pre-radiotherapy cancer patients	n=93 (72%M)	62 ± 12.74	Biodynamics 450
Renal Disease					
(Guerra et al. 2015)	Brazil	Pre-dialysis patients with Stage II-CKD	n=75; Sex not specified.	64.8 ± 11.6	Biodynamics 450
(Passadakis et al. 1999)	India	CAPD	n=47 (55.3%M)	M: 58.9 ± 14.6 F: 56.2 ± 18.3	Not reported
(Gu et al. 2008)	China	CAPD	n=124 (41.1%M)	59.9 ± 12.8	Hydra analyzer (Xitron Tech)
(Enia et al. 1993)	Italy	HD and CAPD	n=59 (64.4%M); n=36 HD, n=23 CAPD	58 (25-80)	RJL-101

(Santin et al. 2018)	Brazil	HD	n=104 (70.2%M)	70.9 ± 6.9	Biodynamics 450
(Maggiore et al. 1996)	Italy	HD	*Patients*: n=131 (49.6%M); *Controls*: n=272 (50%M)	*Patients*: 61.6 ± 14.5 *Controls*: 62.5 ± 13.6	RJL-101 *Measured post HD
(Rimsevicius et al. 2016)	Lithuania	HD	n=99 (58.7%M)	58.7 ± 14.38	Biospace InBody S10
(Vannini et al. 2009)	Brazil	HD	n=52 (67.3%M)	55 ± 13.6	Biodynamics 450
(de Oliveira et al. 2010)	Brazil	HD	n=58 (47.3%M)	49.22 ± 14.85	Not specified

CAPD: continuous ambulatory peritoneal dialysis; CKD: chronic kidney disease; CLD: chronic liver disease; CRC: colorectal cancer; F: female; GI: gastrointestinal; HD: hemodialysis; HNC: head and neck cancer; LOS: length of stay; M: male; Tx: transplantation.

Table 2 Study results of the literature on the comparison between PhA and SGA in malnutrition assessment

Ref	SGA	PhA/SPhA cut-off	Results	Agreement Analysis	Interpretation
Liver Disease					
(Wagner et al. 2011)	SGA	<5.0°	*Prevalence of malnutrition:* *Group A*: 18.2% (SGA), 81.2% (PhA) *Group B*: 10.5% (SGA), 31.6% (PhA) *Group C*: 4.8% (SGA), 31.7% (PhA)	-	No correlation between SGA and PhA
(Bakshi and Singh 2016)	SGA	<4.4˚normal, 4.4-5.4˚ borderline, >5.4˚ abnormal	*Prevalence of malnutrition*: 75% (PhA), 88.9% (SGA-B+C)	κ=0.44 (90% agreement) Sensitivity: 94.4%; Specificity: 50%	Moderate agreement between PhA and SGA
(Peres et al. 2012)	Adapted SGA	median PhA (5.18°)	*Total*: 5.18° (range: 1.86°-8.40°) *SGA-A*: 5.31° (range: 3.45°-7.42°) *SGA-B+C*: 4.35° (range: 1.86°-6.73°), **p=0.005**	-	No significant difference between sexes (p=0.59). PhA was significantly reduced in malnourished patients.

(Liboredo et al. 2015)	Adapted SGA	<5.44°	*Prevalence of malnutrition*: 50% (PhA), 66.7% (SGA). *Total*: 5.3° (range: 2.2°-6.9°); *SGA-A*: 6.0° (range: 4.2°-6.9°); *SGA-B+C*: 4.8° (range: 2.2°-6.1°), NS	-	Median PhA was not significantly correlated with any clinical parameter. No significant difference in PhA between SGA groups.
Hospitalized Patients					
(Barbosa-Silva et al. 2003)	SGA	<5.0°	*Male*: *SGA-A*: 6.65° [95% CI (6.33°-6.98°)] *SGA-B*: 6.13° [95% CI (5.75°-6.50°)] *SGA-C*: 4.70° [95% CI (4.03°-5.36°)], **p<0.001** Fe*male*: *SGA-A*: 6.36° [95% CI (6.23°-6.50°)] *SGA-B:* 5.14° [95% CI (4.82°-5.46°)] *SGA-C*: 4.22° [95% CI (3.02°-5.43°)], **p<0.001**	κ=0.39 [95% CI (0.26-0.51)] *Male*: κ=0.27 [95% CI (0.07-0.47)] Sensitivity: 31%; Specificity: 97% *Female*: κ=0.46 [95% CI (0.31-0.61)] Sensitivity: 47%; Specificity: 94%	PhA significantly decreased with worsening level of malnutrition for the total sample and within each sex group. Fair agreement between SGA and PhA in all participants and males, and moderate agreement in females. Optimal PhA cut-off could not be obtained. Cut-off with best balance of sensitivity and specificity was 6.3° (AUC: 0.72) for males and 5.9° (AUC: 0.83) for females.

(Meireles et al. 2012)	SGA	<-1.65 SD	*Prevalence of malnutrition:* 31.5% (SGA-B), 4% (SGA-C) 4.8% (PhA)	*Total*: κ=0.038 [95% CI (-0.068-0.144)] *Male*: κ=0.041 [95% CI (-0.135-0.216)] *Female*: κ=0.029 [95% CI (-0.092-0.150)]	SPhA was significantly reduced in malnourished versus well-nourished patients. Moderate agreement between PhA and SGA in males, and fair in all participants and females.
(Cardinal et al. 2010)	SGA	<-0.8 SD	*Total:* *SGA-A*: 0.3 ± 0.1 SD; *SGA-B+C*: -0.8 ± 0.2 SD, **p<0.001** M*ale:* *SGA-A*: 0.3 ± 0.2 SD; *SGA-B+C*: -0.7 ± 0.3 SD, **p=0.001** *Female:* *SGA-A*: 0.3 ± 0.1 SD; *SGA-B+C*: -1.0 ± 0.5 SD, **p=0.018**	κ=0.45 [95% CI (0.25 to 0.65)]	SPhA was significantly reduced in malnourished versus well-nourished patients in the total group and in each sex group. Moderate agreement between SPhA and SGA.

(Scheunemann et al. 2011)	SGA	<-0.8 SD	*Total*: *SGA-A*: 0.0 SD [95% CI (-0.2-0.3)] *SGA-B+C*: -0.7 SD [95% CI (-1.2-0.2)], **p=0.001** *Male*: *SGA-A*: 0.1 SD [95% CI (-0.4-0.6)] *SGA-B+C*: -1.2 [95% CI (-1.8-0.6)], **p=0.002** Fe*male*: *SGA-A*: 0.0 [95% CI (-0.3-0.3)] *SGA-B+C*: -0.5 [95% (CI -1.9-0.1)], NS	*Total*: κ=0.27 [95% CI (0.06-0.48)] Sensitivity: 82.6% Specificity: 40.6% *Male*: κ=0.39 [95% CI (0.04-0.73)] *Female*: κ=0.21 [95% CI (-0.04-0.47)]	Significant difference in SPhA between malnourished and well-nourished groups in all patients and male patients, but not in female patients. Optimal SPhA cut-off obtained was -0.63 SD with 72.4% sensitivity and 68.1% specificity.
(Kyle et al. 2012)	SGA	<4.6° F, <5.0° M	*Patients*: *Male*: 6.6° ± 1.1° *Female*: 5.8° ± 0.96°, **p<0.001** *Controls*: *Male*: 7.55° ± 0.95° *Female*: 6.5 ± 0.08°, **p<0.001**	*Male:* κ=0.489, **p<0.001** AUC 0.83 Sensitivity: 73.3%; Specificity: 76.6% *Female*: κ=0.412, **p<0.001** AUC 0.8 Sensitivity: 64.5%; Specificity: 76.1%	PhA was significantly greater in controls versus patients for both sexes. Moderate agreement between PhA and SGA in males and females. Optimal PhA cut-offs were determined to be <4.6° for females and <5.0° for males.

(Kyle, Genton, and Pichard 2013)	SGA	<4.6° F, <5.0° M (Kyle et al. 2012)	*Patients*: *Male*: 6.0° ± 1.4° *Female*: 5.0° ± 1.3°, **p<0.05** *Controls*: *Male*: 7.1° ± 1.2° *Female*: 6.0 ± 1.2°, **p<0.05** *SGA-A*: RR 1.4 [95% CI (1.0-2.1)], **p=0.046** *SGA-B*: RR 3.8 [95% CI (2.9-4.9)], **p<0.001** *SGA-C*: RR 7.2 [95% CI (5.7-9.0)], **p<0.001**	-	PhA was significantly greater in controls versus patients for both sexes. Patients with moderate malnutrition were 3.8 times more likely to have a low PhA than healthy subjects. Patients classified with severe malnutrition were 7.2 times more likely to have a low PhA than healthy subjects.
(Guerra et al. 2015)	PG-SGA	<4.6° F, <5.0° M (Kyle et al. 2012)	*Prevalence of malnutrition*: Short LOS, Long LOS 6.5%, 16.7% (PhA) 30%, 14% (SGA-B) 30%, 13% (SGA-C)	κ=0.17 (60.5% agreement)	Poor agreement between PhA and SGA in both short and long LOS.
(Norman, Smoliner, et al. 2008)	SGA	N/A	*SGA-A*: 5.39° (IQR 4.72°-6.05°) *SGA-B*: 5.02° (IQR 4.42°-5.65°) *SGA-C*: 4.17° (IQR 3.50°-5.20°) *SGA-A vs SGA-B,*	-	PhA significantly decreased with worsening level of malnutrition.

			p=0.033 *SGA-B vs SGA-C,* ***p<0.0001*** *SGA-C vs SGA-A,* ***p<0.001***		
(Stobäus et al. 2012)	SGA	N/A	*Total*: 4.91° ± 1.17° (range, 1.62° - 8.51°; -7.2 - 2.5 SD) *PhA Linear regression*: *SGA-B*: ß=-0.538 (12.6% estimate of effect) **p<0.0001** *SGA-C*: ß =-0.935 (26.5% estimate of effect) **p<0.0001** *SPhA Linear regression*: *SGA-B*: ß=-0.743 (27.2% estimate of effect) **p<0.0001** *SGA-C*: ß=-1.307 (58.2% estimate of effect) **p<0.0001**	-	PhA was significantly greater in males. PhA and SPhA were significantly lower in malnourished versus well-nourished patients. Moderate and severe malnutrition were significant determinants of PhA and SPhA.

<table>
<tr><td colspan="6">Oncology Patients</td></tr>
<tr><td>(Gupta et al. 2004)</td><td>SGA</td><td>median PhA (5.0°)</td><td>Correlation: r=-0.26, p=0.10</td><td>-</td><td>No significant correlation between PhA and SGA.</td></tr>
<tr><td>(Gupta et al. 2008)</td><td>SGA</td><td>Optimal cut-off determined</td><td>Median PhA:
SGA-A: 6.12°
SGA-B+C: 5.18°, p=0.005
Correlation: ρ=0.33, p=0.004</td><td>AUC=0.7 [95% CI (0.57-0.820)], p=0.005
ROC curves:<table><tr><td>PhA</td><td>Sens</td><td>Spec</td></tr><tr><td><5.2°</td><td>51.7%</td><td>79.5%</td></tr><tr><td><5.3°</td><td>55.7%</td><td>68.2%</td></tr><tr><td><5.5°</td><td>58.6%</td><td>65.9%</td></tr><tr><td><5.7°</td><td>69.0%</td><td>56.8%</td></tr><tr><td><6.0°</td><td>82.8%</td><td>54.5%</td></tr></table></td><td>PhA was significantly reduced in malnourished versus well-nourished patients.
Fair agreement between PhA and SGA.
PhA cut-off 5.9° in males with progressive disease had the best balance of sensitivity (100%) and specificity (73.3%)</td></tr>
<tr><td>(Abe Vicente et al. 2013)</td><td>PG-SGA validated Portuguese version</td><td><25th percentile (5.1°)</td><td>Prevalence of malnutrition:
Group 1:
66.6% (PG-SGA); 36% (PhA)
Group 2:
30.9% (PG-SGA); 14.5% (PhA)</td><td>Group 1:
Sensitivity: 44%;
Specificity: 80%
Group 2:
Sensitivity: 38.4%;
Specificity: 91.2%</td><td>Significant association between PhA and PG-SGA in Group 1 (p=0.041) and Group 2 (p=0.006)</td></tr>
<tr><td>(Maurício et al. 2013)</td><td>SGA</td><td>Not specified</td><td>SGA-A: 5.5° ± 0.6°
SGA-B: 5.4° ± 1.0°
SGA-C: 4.9° ± 1.1°,
*p<0.05 between SGA-A and SGA-C</td><td>κ=0.11, p<0.05</td><td>PhA was significantly reduced in severely malnourished versus well-nourished patients only.
Poor agreement between PhA and SGA.</td></tr>
</table>

(da Silva et al. 2013)	SGA	<5th percentile (-1.65 SD)	*SGA-A*: 6.7° (5.6-7.4)° *SGA-B*: 5.1° (3.8-6.0)° *SGA-C*: 4.5° (2.6-6.4)° *SGA-A: vs SGA-C,* ***p<0.05*** *SGA-A vs SGA-B,* ***p<0.05*** *SGA-B vs SGA-C, NS*	κ<0.20	PhA was significantly reduced in malnourished versus well-nourished patients. Poor agreement between SGA and PhA.
(Malecka-Massalska et al. 2016)	SGA	Optimal cut-off determined	*Total*: 5.04° ± 0.88°, *SGA-A*: 5.25° ± 0.76°, *SGA-B+C*: 4.73° ± 0.96°, **p=0.0009**	*Optimal cut-off point* (4.733°): AUC=0.7 [95% CI (0.57-0.82)], **p=0.005** Sensitivity: 80%; Specificity: 56%	PhA was significantly reduced in malnourished versus well-nourished patients. Optimal PhA cut-off point was <4.733°.
(Wladysiuk et al. 2016)	SGA	median PhA (4.733°)	*SGA-A*: 5.25° ± 0.76°; *SGA-B+C*: 4.73° ± 0.96°, **p=0.0009** *Correlation*: r=-0.35, **p=0.0022**	-	PhA was significantly reduced in malnourished versus well-nourished patients. PhA was negatively correlated with worsening SGA score.
(Mulasi et al. 2016)	PG-SGA	N/A	*PG-SGA-A*: 5.5° ± 0.96° *PG-SGA-B+C*: 5.3° ± 0.84°, p=0.62 *Correlation*: r=-0.35, **p<0.01**	-	No significant difference in PhA between well-nourished and malnourished patients. PhA was negatively correlated with worsening SGA score.

(Maasberg et al. 2017)	SGA	N/A	*Total*: *SGA-A*: 5.3° *SGA-B+C*: 4.2°, **p<0.001** *Male*: *SGA-A*: 5.4° ± 1.0° *SGA-B+C*: 4.5° ±1.1°, **p<0.05** *Female*: *SGA-A*: 5.1° ± 0.8° *SGA-B+C*: 4.0° ±1.1°, **p<0.05**	-	PhA was significantly reduced in malnourished versus well-nourished patients.
(Norman et al. 2010)	SGA	PhA <5th percentile	*Total*: 4.59° ± 1.12° *Male*: 4.70° ± 1.17°, *Female*: 4.47° ± 1.04°, **p<0.043** *Multinomial logistic regression*: SPhA and SGA-B: OR 0.633 [(95% CI (0.504-0.794)], **p<0.0001** SPhA and SGA-C: OR 0.449 [(95% CI (0.337-0.597)], **p<0.0001**	-	Patients with a high SPhA had 1.5 times lower odds of being classified as moderately malnourished and 2.2 times lower odds of being classified as severely malnourished than the odds of being identified as well-nourished.

(Motta, Castanho, and Velarde 2015)	PG-SGA; PG-SGA categorical	<-1.65 SD; Optimal cut-off determined	*Median PhA/SPhA*: 5.95° ± 1.00°; -1.04 ± 0.98 SD *Median PG-SGA score*: 4 ± 4	*PhA and PG-SGA (5.9°):* κ=0.25 AUC=0.72 [95% CI (0.61-0.83)] *PhA and PG-SGA categorical (5.4°):* κ=0.26 AUC=0.84 [95% CI (0.69-0.99)]	Fair agreement between SPhA and PG-SGA, and SPhA and PG-SGA categorical. Optimal PhA cut-off points using PG-SGA and PG-SGA categorical as gold standard were <5.9° and <5.4°, respectively.
Renal Disease					
(Guerra et al. 2015)	SGA	N/A	*SGA-A*: 6.4° ± 0.7° *SGA-B*: 5.6° ± 0.9° *SGA-C*: 5.3° ± 0.6°, **p<0.01** *SGA-A versus SGA-B,* ***p<0.05*** *SGA-A versus SGA-C,* ***p<0.05*** *SGA-B versus SGA-C, NS*	-	PhA was significantly reduced in mildly and severely malnourished patients as compared to well-nourished patients, but, there was no significant difference between mildly and severely malnourished patients.
(Passadakis et al. 1999)	SGA	N/A	*Male*: PhA=5.06° ± 1.3° *Females*: 4.79° ± 1.4°, p=0.56 *SGA-A*: 5.41° ± 1.15°, *SGA-B*: 4.62° ± 1.21°, *SGA-C*: 3.5° ± 1.53° *A versus B,* ***p=0.087***		No significant difference in PhA between males and females. PhA was significantly reduced in mildly and moderately malnourished patients as compared to well-nourished patients, however, there was no significant difference in PhA

			A versus C, ***p=0.021*** *B versus C, p=0.193* *Spearman's rank test*: R=0.48, **p=0.0048**	between mildly and moderately malnourished patients. PhA was negatively correlated with worsening SGA-score.
(Gu et al. 2008)	SGA	N/A	*SGA-A*: 4.79° ± 1.04°; *SGA-B+C*: 3.83° ± 0.86°, **p<0.001**	PhA was significantly reduced in malnourished versus well-nourished patients.
(Enia et al. 1993)	SGA	N/A	*Male:* *SGA-A*: 6.32° ± 1.37°; *SGA-B+C*: 4.56° ± 0.91°, **p<0.001** *Female*: *SGA-A*: 5.76° ± 1.26°; *SGA-B+C*: 4.02° ± 0.72°, **p=0.009** CAPD: *SGA-A*: 4.82° ± 0.78°; *SGA-B+C*: 4.05° ± 0.49°, **p=0.016** HD: *SGA-A*: 6.76° ± 1.06°; *SGA-B+C*: 4.76° ± 1.05°, **p<0.001** *Univariate analysis*: r=-0.58, **p<0.001**	PhA was significantly reduced in malnourished versus well-nourished patients in each sex group and in CAPD and HD groups. In total sample, PhA was negatively correlated with worsening SGA-score.

(Santin et al. 2018)	7p-SGA	N/A	*Linear regression coefficient of the repeated measures model in time:* *Male*: ß=0.05 (0.02 SE), **p=0.03** *Female*: ß=0.39 (0.11 SE), **p=0.002** **adjusted for age and dialysis vintage*		1-unit increase in 7p-SGA was significantly associated with an increase of 0.05° and 0.39° in PhA for males and females, respectively.
(Maggiore et al. 1996)	SGA	lower quartile and <10th percentile to identify SGA-C	*Spearman's rank correlation coefficient*: r_s=-0.43, **p≤0.01**	*Lower quartile cut-off*: Sensitivity: 67% Specificity: 78% *<10th percentile cut-off*: Sensitivity: 91% Specificity: 33%	PhA was negatively correlated with worsening SGA-score.
(Rimseviciu s et al. 2016)	SGA	Optimal cut-off determined	*Multivariate analysis*: OR 3.69 [95% CI (1.59-8.62)], **p=0.002**	*Optimal PhA cut-offs*: *SGA-B*: <25th percentile AUC 0.70 [95% CI (0.60-0.81)], **P=0.01**) *SGA-C*: <15th percentile AUC 0.74 [95% CI (0.62-0.85)], **P=0.005**)	Mild malnutrition was most accurately identified by PhA <25th percentile. Severe malnutrition was most accurately identified by PhA <15th percentile. Patients with a higher PhA had 3.68 times lower odds of being classified as malnourished than the odds of being identified as well-nourished.

(Vannini et al. 2009)	7p-SGA	median PhA (<6.4°)	*SGA-A*: 6.76° ± 1.4° *SGA-B+C*: 6.2° ± 1.7°, p=0.10 *Multivariate analysis*: OR = 0.42, **p=0.011**		No significant difference between malnourished and well-nourished patients. Patients with a higher PhA had 2.4 times lower odds of being classified as malnourished than the odds of being identified as well-nourished.
(de Oliveira et al. 2010)	SGA; Adapted-SGA (Kalantar-Zadeh et al. 1999); PG-SGA	<5.0°	*Total*: 6.19° ± 1.33° *Male*: 6.70° ± 1.23°; *Female*: 5.73° ± 1.27°, **p=0.005** *Linear correlation*: Adapted SGA and PhA: r=-0.533, **p<0.001** PG-SGA and PhA: r=-0.453, **p<0.001**	*SGA and PhA*: κ=0.316	PhA was significantly higher in males versus females. Moderate agreement between PhA and adapted SGA. PhA was negatively correlated with worsening adapted SGA and PG-SGA scores.

AUC: area under the curve; CAPD: continuous ambulatory peritoneal dialysis; HD: hemodialysis; NS: not significant; OR: odds ratio; PhA: phase angle; ROC: receiver operator characteristics; SE: standard error; SGA-A: well-nourished; SGA-B: mild-moderately malnourished; SGA-C: severely malnourished; SPhA: standardized phase angle

3.4.1 Liver Disease

Four studies included participants with liver disease, two in chronic liver disease, one in pre-transplant (Tx) patients and one in post-Tx patients. Two additional studies were identified which assessed both SGA and PhA, however, all patients were assessed as SGA-A which did not allow for any direct comparison between SGA-score and PhA. Thus, these two articles were not included in this systematic review (Nunes et al. 2016; Saxena, Sharma, and Gupta 2016).

Two studies aimed to identify malnutrition using predetermined PhA cut-offs. Wagner et al. (2011) found a PhA cut-off of <5° in individuals post liver Tx did not correlate with SGA, and malnutrition was underestimated by SGA compared with PhA cut-offs. While Bakshi and Singh (2016) reported a moderate agreement between SGA and a PhA cut-off of <4.4° in hospitalized, end-stage liver disease patients. Additionally, Peres et al. (2012) found that PhA was significantly higher ($p=0.005$) in well-nourished patients compared to malnourished patients with chronic lung disease (CLD). Whereas, in a small study of eligible transplant patients with cirrhosis, no significant difference ($p>0.05$) was found between the mean PhA of well-nourished and malnourished patients (Liboredo et al. 2015). In summary, an association between PhA and SGA within liver disease patients is not clear. Although a trend toward decreasing PhA with worsening malnutrition exists, most studies found no correlation between PhA and SGA.

3.4.2 Hospitalized Patients

Nine studies involved hospitalized patients with a variety of clinical conditions. In preoperative GI patients, Barbosa-Silva et al. (2003) found a moderate agreement ($\kappa=0.39$) between SGA and a PhA cut-off of <5.0°, however, optimal cut-offs of 6.3° and 5.9° in males and females, respectively, had the best balances of sensitivity and specificity. Using a SPhA cut-off of <-1.65 SD, Meireless et al. (2012) found a weak agreement in females and a moderate agreement in males between SGA and SPhA. Two studies used a SPhA of <-0.8 SD. Cardinal et al. (2010) found a moderate agreement between SGA and SPhA, while Scheunemann et al. (2011) found weak agreements in the

total sample and each sex-group. As well, Scheunemann et al. (2011) determined an optimal SPhA cut-off of <-0.63 SD.

In medical, surgical and trauma patients, Kyle et al. (2012) determined an optimal PhA cut-off of <5.0° for men and <4.6° for women. Using these cut-offs, Kyle et al. (2013) found that the relative risk of low PhA increased with worsening malnutrition and Guerra et al. (2015) reported a 60.5% agreement with PG-SGA in both long and short stay hospitalized patients. In GI, hepatology, endocrinology, cardiology and general surgery patients, Norman et al. (2008) found that PhA was significantly reduced with worsening nutrition status ($p<0.05$). Stobaus et al. (2012) found reduced SPhA with worsening nutrition status. Overall, the body of research in hospitalized patients shows a significant reduction in PhA and/or SPhA with worsening malnutrition assessed using SGA. Despite this, agreement between the two methods ranged from weak to moderate as a variety of different PhA and SPhA cut-offs were used.

3.4.3 Oncology

Eleven studies were identified in oncology patient populations. Diagnoses included pancreatic cancer, gastric cancer (GC) and colorectal cancer (CRC), neuroendocrine neoplasia, and head and neck cancers (HNC). In patients with pancreatic cancer, Gupta et al. (2004) found a non-significant weak negative correlation between PhA and SGA ($r=-0.26$, $p=0.10$). Gupta et al. (2008) found that median PhA of well-nourished patients was significantly greater ($p=0.005$) than that of malnourished patients in advanced CRC patients. Authors were only able to determine an optimal PhA cut-off of <5.9° in males. Vicente et al. (2013) found a significant association between malnutrition identified using PG-SGA and a PhA cut-off of <5.1° ($p=0.041$) in patients with active GC and CRC, and those tumor free for >3 months. Mauricio et al. (2013) found a weak agreement between SGA and SPhA in CRC patients, and only a significant difference in SPhA between the well-nourished and severely malnourished group ($p<0.05$). da Silva et al. (2013) also found a weak agreement between SGA and a SPhA cut-off <-1.65 SD in esophageal and GC patients.

Three studies were completed in HNC patients. Malecka-Massalska et al. (2016) found that PhA was significantly higher in well-nourished patients than in malnourished patients ($p=0.0009$) and an optimal cut-off of 4.733° was determined. Wladysiuk et al. (2016) also found significant difference between PhA in well-nourished and malnourished patients ($p=0.0009$), and PhA was found to be negatively correlated with SGA ($r= -0.35$, $p=0.0022$). Whereas, Mulasi et al. (2016) found no significant difference between PhA in well-nourished patients and malnourished patients ($p=0.62$) however, had a negative correlation of $r=-0.35$ ($p<0.01$).

Maasberg et al. (2017) assessed malnutrition in patients with neuroendocrine neoplasia using SGA and PhA. Mean PhA was significantly higher ($p<0.001$) in the well-nourished group as compared to the malnourished group and continued to be significant when stratified by sex ($p<0.05$). Norman et al. (2010) studied the relationship between SPhA and SGA in patients with cancerous tumors. SPhA had a strong positive effect on SGA-B ($p<0.0001$), and SGA-C ($p<0.0001$). Using a SPhA cut-off <-1.65 SD, Motta et al. (2015) found fair agreement between SPhA and PG-SGA, and SPhA and PG-SGA categorical. An optimal PhA cut-off of <5.9° was determined using PG-SGA as the reference method, and <5.4° using PG-SGA categorical as the reference method. Articles with a broad range of cancer diagnoses were identified in our search. Although studies reported significant agreements between PhA and/or SPhA with SGA, strengths of agreements ranged from fair to poor.

3.4.4 Renal Disease

Nine studies included participants with renal disease, including predialysis chronic kidney disease (CKD), continuous ambulatory peritoneal dialysis (CAPD) patients and hemodialysis (HD). Guerra et al. (2015) found a significant difference in PhA between well-nourished and malnourished groups ($p<0.05$), but not between mildly and severely malnourished groups ($p>0.05$) in pre-dialysis patients with Stage II-CKD. Two studies evaluated PhA in patients on CAPD. One study by Gu et al. (2008) found that PhA was significantly higher in well-nourished as compared to malnourished patients ($p<0.001$). While Passadakis et al. (1999) found that PhA was only significantly different between well-nourished and severely malnourished groups ($p=0.021$) with a weak correlation

(r=0.48, p=0.0048) between SGA and PhA. Enia et al. (1993) found that PhA was significantly higher in well-nourished patients than in malnourished patients in both HD and CAPD patient groups with a significant negative correlation of r=-0.58 between SGA and PhA, (p<0.001). In HD patients, Santin et al. (2017) found that for every 1-unit increase in 7p-SGA PhA (improved nutritional status) was associated with an increase of 0.05° in males and 0.39° in females, respectively.

Four studies analyzed PhA cut-offs in HD patients. Maggiore et al. (1996) found that a PhA cut-off of <25th percentile used to identify severe malnutrition had a 67% sensitivity and 78% specificity. However, a lowered cut-off of <10th percentile had an improved sensitivity of 91% but a reduced specificity of 33%. Rimsevicius et al. (2016) found that moderately and severely malnourished patients were most accurately identified by adjusted PhA cut-offs of <25th and <15th percentile, respectively. Vannini et al. (2009) used a PhA cut-off of <6.4° and found no significant difference between mean PhA of the well-nourished and malnourished groups (p=0.10) but had an odds ratio of 0.42 (p=0.011). de Oliveira et al. (2010), found that PhA had a significant negative linear relationship with QSGA and PG-SGA, and a moderate agreement with SGA using a PhA cut-off of <5.0°. Although no studies used SPhA in their analyses, the majority of studies in the renal disease population reported significant trends of decreased PhA with worsening malnutrition.

3.4.5 Quality Assessment

Evidence quality was assessed by both GRADE Guidelines and the QUADAS-2 tool. Results of the quality assessment using the GRADE guidelines are shown in **Table 3**. Results of the quality assessment using the QUADAS-2 tool are shown in **Figure 3**.

Table 3 Summary of Findings

<table>
<tr><td colspan="5">Bioelectrical phase angle compared to Subjective Global Assessment as an indicator of malnutrition</td></tr>
<tr><td colspan="5">Patient or Population: acute or chronically ill adult patients
Setting: inpatient and outpatient
Intervention: Measurement of phase angle
Comparison: Subjective Global Assessment</td></tr>
<tr><td>Patient Population</td><td>Outcome</td><td>Number of Participants (Studies)</td><td colspan="2">Quality and Justification</td></tr>
<tr><td>Liver Disease</td><td rowspan="4">Relationship between PhA/SPhA and SGA</td><td>246 (4 cross-sectional studies)</td><td>●○○○ Very Low[1,2]</td><td rowspan="4">●●○○ Low[1,2,4]</td></tr>
<tr><td>Hospitalized Patients</td><td>3717 + 1632 controls (9 cross-sectional studies)</td><td>●●●○ Moderate[3,4]</td></tr>
<tr><td>Oncology</td><td>1238 (2 retrospective chart reviews + 9 cross-sectional studies)</td><td>●●●○ Moderate[3,4]</td></tr>
<tr><td>Renal Disease</td><td>749 + 272 controls (1 longitudinal + 8 cross-sectional studies)</td><td>●●○○ Low[2,4]</td></tr>
<tr><td colspan="5">[1]Inconsistency in results
[2]Risk of bias: no sex comparison, minimal to no use of SPhA
[3]Large magnitude of effect: significant difference in PhA between well-nourished and malnourished patients
[4]Dose response – PhA significantly decreases with worsening malnutrition (SGA-B vs SGA-C)</td></tr>
</table>

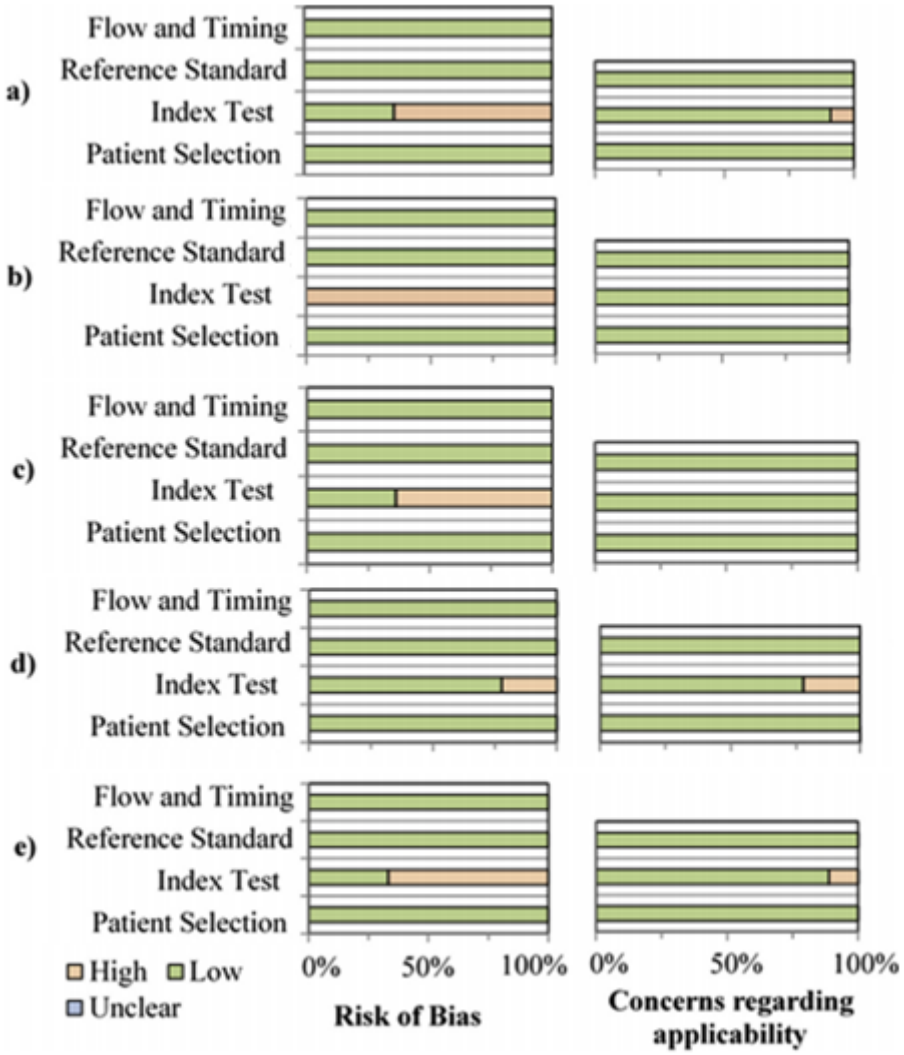


Figure 3 QUADAS-2 Results.

The proportion of studies with low, high and unclear risk of bias and concerns regarding applicability between the index test (PhA) and SGA are shown according to QUADAS-2 domains. **a)** Overall, 61% of studies had high risk of bias of the index test, PhA, and 9% of studies had high concerns for the applicability of the index test, **b)** Liver disease: Due to the lack of any PhA standardization methods, 100% of the articles reviewed had a high risk of bias of the index test, PhA **c)** Oncology patients: 34% of studies had high risk of bias of the index test. **d)** Hospitalized patients - 64% of studies had high risk of bias in the use of PhA. Two studies (22% of studies) had concerns related to the applicability of the index test due to exclusion of participants where PhA measurement and SGA would have been appropriate. These studies excluded participants based on the inability to

obtain anthropometric parameters due to patients being bedridden. **e)** Renal disease - Only a third of articles (**Figure 3e**) attempted to control for confounding factors through testing for sex differences or analyzing results by sex, therefore 67% of studies had high risk of bias of the index test. 11% of studies had concerns related to the applicability of the index test due to exclusion of participants where PhA measurement and SGA would have been appropriate.

3.5 Discussion

This study aimed to evaluate the relationship between bioelectrical phase angle and malnutrition severity as measured by the Subjective Global Assessment in acute or chronically ill adults. Many studies used different PhA cut-offs, for example, sample median, lower quartile or cut-offs determined from previous studies which may not be translatable to all disease states. As the full biological meaning of PhA is not understood it would be difficult to predict how PhA may vary by disease even with controlling for confounding factors such as nutrition status, weight, age or gender. It is difficult to say with certainty that PhA cut-offs determined within one disease state, or based on non-nutritional parameters such as survival, are appropriate in all clinical situations. Therefore, the overall evidence quality determined in this systematic review received a grade of Low.

Many nutritional assessment tools exist; however, their use within specific disease populations can be limited. Within liver disease, complications such as fluid retention and hypoproteinemia associated with hepatic deterioration can confound nutritional assessment techniques such as BIA, biochemical markers, and BMI (Tynan and Hasse 2004). Use of SGA in CLD is recommended by the European Society for Parenteral and Enteral Nutrition to screen for malnutrition in liver disease including alcoholic steatohepatitis, cirrhosis, surgery, and transplantation (Plauth et al. 2006). A recent review also identified SGA as a tool to use in nutritional assessment in liver cirrhosis (Tandon et al. 2017). Despite its acknowledged limitations in individuals with ascites, European Society for Parenteral and Enteral Nutrition recommends PhA to quantify undernutrition in cirrhosis, and in liver transplantation and surgery and PhA is said to be superior to anthropometry and 24 hour creatinine excretion (Plauth et al. 2006).

Interestingly, in these guidelines, the use of SGA in CLD received an evidence grade of C, while the use of PhA received a grade of B. Additionally, clinical practice guideline recommendations, evidence quality of the use of PhA in malnutrition assessment received the lowest grade.

Hospital malnutrition is a well-established issue (Butterworth 1974), and has been associated with pressure ulcers, infection, impaired wound healing, increased length of hospital stay and readmission risk, all of which create a greater burden on health care costs and, ultimately, quality of life for patients (Tappenden et al. 2013). The American Society for Parenteral and Enteral Nutrition and European Society for Parenteral and Enteral Nutrition have recommended routine use of nutrition screening to identify malnutrition in hospitalized patients, including using SGA (Kondrup et al. 2003; Mueller et al. 2011). Currently, no published guidelines have identified the use of PhA in malnutrition screening or assessment.

Many elements of kidney disease such as fluid retention can complicate clinical assessments and jeopardize nutrition (de Oliveira et al. 2010). The utility of PhA and other BIA measures in dialysis patients is limited due to overhydration pre-dialysis and body water compartments not yet in steady state immediately post-dialysis. The National Kidney Foundation's Kidney Dialysis Outcomes Quality Initiative clinical guidelines have identified the need for frequent nutrition assessment and recommend SGA as a valid and clinically useful tool in the overall nutritional assessment of non-dialyzed and dialyzed individuals (Johansen et al. 2001). The National Kidney Foundation's Kidney Dialysis Outcomes Quality Initiative guidelines recommend The CANADA-USA Peritoneal Dialysis Study Group Study's 7p-SGA (Churchill, Taylor, and Keshaviah 1996) as the preferred SGA technique. The National Kidney Foundation's Kidney Dialysis Outcomes Quality Initiative identify valid methods of protein-energy malnutrition through anthropometric analysis, however, use of BIA in nutrition assessment is not mentioned in these guidelines. More recently, the 2010 Chronic Kidney Disease (CKD) Evidence-Based Nutrition Practice Guideline (The American Dietetic Association 2010) from Academy of Nutrition and Dietetics concluded that any valid measurement methodology including anthropometrics and body compartment estimates

such as dual energy x-ray absorptiometry or BIA, are appropriate in CKD. However, as no reference standard for assessing body composition in CKD patients has been established, no one test has been shown to be superior to another with respect to assessing body composition.

Nutrition status in oncology patients can be affected by surgery, radiation and chemotherapy treatment as well as the pathophysiology of cancer itself (Lis et al. 2012). Prevalence of malnutrition is estimated to range between 50-80% depending on cancer diagnosis (Lis et al. 2012). Clinical practice guidelines have recommended the use of SGA and PG-SGA in the oncology population (August, Bozzetti, and Huhmann 2009; Fearon et al. 2011). As well, in their review of available tools within the adult oncology population, the Academy of Nutrition and Dietetics' Oncology Expert Work Group identified both the SGA and PG-SGA as valid and reliable tools in nutrition diagnosis within ambulatory and acute care settings (Nutrition and the Adult Oncology Patient 2013). No published guidelines have identified use of PhA in malnutrition screening or assessment.

Standardizing PhA with reference values for healthy populations may work to resolve this issue of PhA variation through accounting for individual variations from population norms (Norman et al. 2010). Thus, SPhA allows for results that are translatable and comparable between studies and disease states. Of the 33 articles identified in this systematic review, only nine used SPhAs. Despite SPhA providing greater rigor than absolute values of PhA alone, variation can still exist based on the reference data used. For example, population norms determined in a German population (Bosy-Westphal et al. 2006) may be different than those determined in a Brazilian population (Barbosa-Silva, Barros, and Larsson 2008). Population norms can be standardized in a number of different ways. For instance, most published norms are presented in age- and sex-stratified groups, with fewer studies also including or ethnicity. Future research should make use of a SPhA, however, published data on PhA norms reflecting more diverse populations is needed. Thus, careful consideration is necessary when choosing appropriate reference values within existing population data.

Only six studies attempted to determine an ideal PhA or SPhA cut-off to diagnose malnutrition using SGA as the reference standard. Within hospitalized patients, one study identified a SPhA cut-off of <-0.63 SD (Scheunemann et al. 2011), while two studies suggested gender-specific cut-offs of <6.3° in males and <5.9° in females (Barbosa-Silva et al. 2003), and <5.0° in males and <4.6°in females, respectively (Kyle, Genton, and Pichard 2013). Within cancer patients, suggested PhA cut-off values included <4.733° (Malecka-Massalska et al. 2016), <5.9° (Motta, Castanho, and Velarde 2015), <5.4° (Motta, Castanho, and Velarde 2015), and <5.9° (Gupta et al. 2008) in males with progressive disease. Although other PhA and SPhA cut-offs exist, it is important to note that other cut-offs present in the literature may have been determined using non-nutrition related reference standards limiting their ability to accurately identify malnutrition. Limitations of SGA-derived PhA or SPhA cut-offs, such as their diagnostic accuracy, should not be overlooked. Additionally, we acknowledge that including only articles published in English can bias the results found in this systematic review.

A limitation of using a single PhA or SPhA cut-off value is that it restricts an individual's nutrition status into two binary categories: well-nourished or malnourished. Rather, nutrition status exists on a spectrum. One small study (n=20) identified in this review used two PhA cut-offs to classify patients into three categories; normal, borderline and abnormal (Bakshi and Singh 2016). However, no patients were identified as having borderline PhAs, therefore, no comparison was made between comparable SGA-B and borderline PhA groups. Thus, in addition to controlling for confounding factors using a SPhA, and carefully choosing an appropriate cut-off value, future research should attempt to identify varying degrees of malnutrition using multiple SPhA cut-offs.

A major limitation of this review is attempting to find a meaningful relationship between two methodologies that may both be influenced by the operator. However, many studies have already used PhA as a nutritional marker to diagnose malnutrition despite its lack of validation. Therefore, it is important to comprehensively study the appropriateness of its use in both research and clinical practice. The current body of research indicates that PhA cannot independently identify malnutrition in disease, however, PhA or SPhA may show more promise in its use within nutrition monitoring. As an objective measure, SPhA may

be able to detect more sensitive changes in nutrition status as compared to other nutrition assessment tools, which can be useful in assessing effectiveness of nutrition interventions. However, further research is needed to explore the relationship between nutrition status and PhA over time.

3.6 Conclusion

Early identification of malnutrition or the risk of malnutrition is vital in order to provide appropriate nutrition therapy as preventing worsening malnutrition or correcting nutritional deficiencies can help improve overall nutritional status and prognosis. Thus, the idea of a simple, quick and objective measure to identify malnutrition is appealing. Although the results of this systematic review are sufficiently encouraging to warrant further research in utilizing PhA, we are not able to conclude that PhA can independently identify malnutrition in disease.

Future research using PhA in nutritional assessment should focus on utilizing a standardized PhA. Additionally, further research should investigate the change in SPhA over time to determine if improvement or decline in nutritional status will affect SPhA. Within a clinical practice perspective, inclusion of SPhA in nutritional assessment can complement other nutrition assessment methods, as one method alone may not be sensitive enough to capture all factors that influence nutritional status.

Chapter 4

4 Exercise Capacity and its Relationship with Body Composition and Nutrition Status in Patients with Interstitial Lung Disease

4.1 Abstract

Background: Individuals with interstitial lung disease (ILD) are known to have diminished exercise ability. In ILD, neither the impact of body composition nor nutrition status on functional exercise capacity has been fully explored. The primary objective of this study was to explore the relationship between nutrition status and body composition parameters with exercise capacity in a cohort of patients with fibrotic ILD. Our second objective focused on assessing the appropriateness of surrogate markers of nutrition status in ILD patients. *Methods*: Seventy-eight patients diagnosed with fibrotic ILD were recruited from the ILD clinic in London, Ontario, Canada. Lung function was determined by % predicted forced vital capacity (%FVC). Exercise capacity was determined the 6-minute walk distance (6MWD). Nutrition status was assessed using the validated subjective global assessment (SGA), standardized phase angle (SPhA) and impedance ratio z-score (z-IR). Body composition parameters fat-free mass index z-score (z-FFMI) and body fat mass index z-score (z-BFMI) were determined using bioelectrical impedance analysis. *Results*: A total of 57% of participants were moderately to severely malnourished according to SGA. z-FFMI ($r=0.42$, $p=0.02$) and SGA ($r=0.49$, $p<0.01$) were significantly associated with 6MWD independent of %FVC. Age [OR 1.1, CI 95% (1.01-1.25), $p=0.04$], low body mass index [OR 0.73, 95% CI (0.57-0.92), $p=0.01$], z-FFMI [OR 0.34, CI 95% (0.17-0.68), $p<0.01$], z-BFMI [OR 0.39, CI 95% (0.17-0.91), $p=0.03$] were significantly associated with severe malnutrition (SGA-C). SPhA did not show to be a surrogate marker of nutrition status in our sample, however, mean z-IR was significantly greater in the severe malnutrition group compared to the well-nourished ($p<0.01$) and moderate malnutrition ($p=0.04$) groups. A higher z-IR significantly increased the odds of severe malnutrition [OR 2.75, 95% CI (1.27-6.03), $p=0.02$]. *Conclusion*: Decreased z-FFMI and SGA-C independent of lung function were significantly associated with exercise capacity in fibrotic ILD. z-IR was significantly

greater in severe malnutrition versus the well-nourished group indicating worsened cell health in severe malnutrition.

4.1 Introduction

Individuals with interstitial lung disease (ILD) are known to have limited exercise ability (Mendes et al. 2015), which can significantly impact their ability to participate in normal activities of daily living, compromising their quality of life (Hansen and Wasserman 1996; Mendes et al. 2015). Diminished exercise capacity in ILD is multifaceted including pathophysiological factors such as impaired gas exchange, altered respiratory mechanics, limited pulmonary circulation and peripheral muscle dysfunction (Holland et al. 2008; Raghu et al. 2011).

The six minute walk test is a reliable and validated tool in ILD patients routinely used to measure functional exercise capacity, or in other words, the functional level of exercise of everyday physical activities (Du Bois et al. 2011; Eaton et al. 2005; Lederer et al. 2006; Serajeddini, Rogliani, and Mura 2018). A decline in 6-minute walk distance (6MWD) predicts both poor survival and mortality in patients on a lung transplant waitlist (Du Bois et al. 2011; Lederer et al. 2006). The 6MWD has high prognostic value as it is independent from lung function (Serajeddini, Rogliani, and Mura 2018).

In other chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), poor nutrition status has a negative effect on exercise capacity and muscle dysfunction (Sabino, Silva, and Brunetto 2010; Shan et al. 2015). As well, nutrition intervention and education have the potential to improve exercise capacity in COPD patients (Hill, Vogiatzis, and Burtin 2013; Steiner et al. 2003). However, in ILD, no studies have assessed the relationship between nutrition status and exercise capacity, nor has the potential for nutrition intervention in ILD as part of pulmonary rehabilitation been established. Components of overall nutrition status, such as body mass index (BMI), and more recently lean body mass, have been shown to be predictors of survival in patients with idiopathic pulmonary fibrosis (IPF), a common component of ILD. In ILD, neither the impact of low fat-free mass nor nutrition status on functional exercise capacity have been fully explored.

The primary objective of this study was to explore the relationship between nutrition status assessed using the subjective global assessment (SGA), and body composition parameters assessed using bioelectrical impedance analysis (BIA) with exercise capacity in a cohort of patients with fibrotic ILD. Since obtaining SGA requires trained personnel, who may not be readily available as part of standard ILD care, our second objective focused on assessing the appropriateness of surrogate markers of nutrition status, such as standardized phase angle (SPhA) and impedance ratio (IR), in ILD patients.

4.2 Methods

4.2.1 Study Population

In this cross-sectional study, patients diagnosed with fibrotic ILD (n=78) were recruited from the ILD clinic in London, Ontario, Canada. Inclusion criteria included ambulatory patients over 18 years of age attending an ILD clinic. Patients were excluded according to the following criteria: inability to provide consent due to communication issues (cognitive and motor), presence of cardiac implantable electrical devices, non-stable ILD patients defined as those with infections and/or fever, admitted to hospital in the previous month, presence of an unstable co-morbid illness or combined pulmonary fibrosis and emphysema (CPFE). The study protocol was approved by the Western University Research Ethics Board (protocol n. 104028).

4.2.2 Diagnosis and Disease Severity

The presence of fibrotic ILD was defined based on high-resolution chest computed tomography scan and compatible pulmonary function tests. After excluding all known causes of ILD, IPF was diagnosed based on clinical and radiographic criteria, and when necessary, on surgical lung biopsies, followed by multi-disciplinary discussion (Flaherty et al. 2004; Raghu et al. 2018). The diagnosis of fibrotic ILD other than IPF was based on clinical presentation, laboratoristic, bronchoscopic, radiographic investigations and, when indicated (e.g. non-specific interstitial pneumonia cases), surgical lung biopsies. Patient charts were also reviewed for current medications and results of pulmonary function tests

and six-minute walk tests. Pulmonary function tests and six-minute walk tests were performed as part of patients' standard of care and according to the American Thoracic Society guidelines (American Thoracic Society (ATS) 2002; Standardization of Spirometry, 1994 Update. American Thoracic Society. 1995).

4.2.3 Bioelectrical Impedance Analysis: Body Composition

Estimates of fat-free mass index (FFMI) and body-fat mass index (BFMI) were determined using dual frequency BIA (BodyStat 1500MD, UK). BIA is an easy and convenient bedside tool validated in a variety of clinical settings (Fuller, Sawyer, and Elia 1994; Ghosh et al. 1997; Steiner et al. 2002) whereby a 50 kHz electrical current is passed through the body via two electrodes placed on the surfaces of the right hand and foot measured at fixed frequencies (BodyStat 2017). FFMI and BFMI were calculated using estimates of fat-free mass and body fat mass obtained using BIA according to the following equations: FFMI= fat-free mass (kg) / [height (m)]^2, and BFMI= body fat mass (kg) / [height (m)]^2, respectively. FFMI and BFMI are affected by factors such as sex and age, therefore, FFMI and BFMI z-scores (z-FFMI and z-BFMI) were calculated to account for these factors based on population norms (Kyle et al. 2001). A z-score of zero indicates a value equal to the population mean of healthy subjects, a positive z-score indicates a value is greater than the population mean, and a negative z-score indicates a value less than the population mean. z-FFMI and z-BFMI were calculated according to the following equation: z-score = $(x - x_{\text{population mean}})$/ standard deviation$_{\text{population}}$ (SD).

4.2.4 Nutrition Assessment

The gold standard of nutrition assessment is the SGA. The SGA collectively considers diet and weight history, disease history as it relates to catabolism, nutrition-related functional status, gastrointestinal issues, and a physical examination to detect clinical signs of muscle wasting, subcutaneous fat loss and edema taken all together to determine overall nutrition status (Detsky et al. 1987). SGA categories, A, B and C, represent well-nourished, moderate malnutrition or suspected of being malnourished, and severe malnutrition, respectively. SGA has been validated in a variety of disease states (Baccaro et al. 2007;

Detsky et al. 1987). SGA was completed according to the method outlined by Detsky et al. (1987) (Detsky et al. 1987)(Detsky et al. 1987)(Detsky et al. 1987)(Detsky et al. 1987)(Detsky et al. 1987)and was performed by a registered dietitian (SR).

4.2.5 Surrogate Markers of Nutrition Status: Phase Angle and Impedance Ratio

PhA and IR are raw measures of BIA thought to be surrogate markers of nutrition status in various clinical populations (Kuchnia et al. 2017; Rinaldi et al. 2019). PhA is related to the resistance and reactance of a current as it travels through the body at a constant frequency of 50kHz (PhA = arctan(reactance/resistance)). The IR is the ratio of impedances at 200 kHz and 5 kHz. A lower PhA or an IR closer to 1 indicates poorer cellular health. Age, sex and BMI can affect raw values of PhA and IR; therefore, to control for these confounding factors, a standardized phase angle (SPhA) and IR z-score (z-IR) were calculated using population norms (Bosy-Westphal et al. 2006; Kuchnia et al. 2017) according to the z-score equation noted above.

4.2.6 Statistical Analysis

Quantitative variables are expressed as mean ± standard deviation (SD) and qualitative variables are displayed as frequencies. The Shapiro-Wilk test was used to determine normality of variables. To test for significant across groups a one-way ANOVA was used with parametric data and the Kruskal-Wallis test was used with nonparametric data. To test for between group significance, the independent samples t-test was used with parametric data and the Mann-Whitney U test was used with nonparametric data. The Pearson's correlation coefficient (r) was used to determine the strength and direction of two continuous parametric variables, and the Spearman's rho (r_s) was used for comparison of nonparametric continuous variables or comparison of a continuous and categorical variable. Correlation coefficients were interpreted as previously suggested (Cohen 1988); Pearson's correlation coefficient: r = 0.10-0.29 = a small; r = 030-0.49 = medium; r = 0.50-1.00 = large; Spearman's rho,: r_s < .16 = too low to be meaningful; r_s = 0.16-0.29 = weak to low; r_s = 0.3-0.49 = low to moderate; r_s = 0.5-0.69 = moderate; r_s = 0.7- 0.89 = strong; r_s

= 0.9-1 = very strong. Stepwise multiple regression analysis selected the independent contributors of 6MWD. Multinomial logistic regression was used to determine odds ratios and 95% confidence intervals among factors with SGA groups. P-values <0.05 were regarded as significant. Statistical analysis was performed with IBM® SPSS® Statistics Version 26 software package.

4.3 Results

Sociodemographic patient characteristics and fibrotic ILD diagnoses are shown in **Table 4**. Anthropometric and nutrition status data are displayed in **Table 5**. 43% of participants were identified as SGA-A (well-nourished), 49% were SGA-B (moderately malnourished), and the remaining 8% were SGA-C (severely malnourished). Raw values of PhA and IR were significantly greater and significantly lower in males, respectively. Mean SPhA was -0.44 ± 1.08 SD, and mean z-IR was 5.73 ± 1.52. 6MWD was not significantly different between males and females.

Table 4 Patient characteristics (N=78).

Demographics/Clinical Characteristics	Mean ± SD or Frequency (%)
Age (years)	68.4 ± 10.0
Sex	
Male	38 (48.7)
Female	40 (51.3)
Diagnosis	
Idiopathic pulmonary fibrosis	36 (46.2)
Drug-induced toxicity	10 (12.8)
Rheumatoid arthritis related ILD	8 (10.3)
Non-specific interstitial pneumonia	8 (10.3)
Chronic hypersensitivity pneumonitis	5 (6.4)
Unclassifiable ILD	4 (5.1)
Scleroderma-related ILD	3 (3.8)
Sarcoidosis (stages III-IV)	2 (2.6)
Vasculitis-related ILD	2 (2.6)
Medication usage	
Proton pump inhibitors	43 (55.1)
Pirfenidone	16 (20.5)
N-acetylcysteine	12 (15.4)
Mycophenolate mofetil	9 (11.5)
Nintedanib	2 (2.6)
Pulmonary Function and Exercise Capacity	
FEV_1 (% predicted)	75.1 ± 18.9
FVC (% predicted)	71.2 ± 19.5
DL_{CO} (% predicted)	40.6 ± 17.1
6MWD (m)	335.6 ± 109.8
Male	335.4 ± 120.2
Female	335.8 ± 100.5

Continuous variables are expressed as mean ± standard deviation. ILD, interstitial lung disease; FEV, forced expiratory volume; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; 6MWD, six-minute walk distance.

Table 5 Anthropometric and nutrition data (N=78).

Clinical Characteristics	Mean ± SD or Frequency (%)
Anthropometry	
BMI (kg/m^2)	30.8 ± 7.3
z-FFMI (SD)	0.39 ± 1.98
z-BFMI (SD)	2.27 ± 2.15
Nutritional Indices	
SGA-A (well-nourished)	34 (43.6)
SGA-B (moderate malnutrition)	38 (48.7)
SGA-C (severe malnutrition)	6 (7.7)
Phase angle (°) (n=77)	
Male	5.55 ± 1.15§
Female	4.90 ± 0.81
Standardized phase angle (SD)	-0.44 ± 1.08
Impedance ratio (n=65)	
Male	0.881 ± 0.813†
Female	0.899 ± 0.028
Impedance ratio z-score (SD)	5.73 ± 1.52

Continuous variables are expressed as mean ± standard deviation. BMI, body mass index; SD, standard deviation; SGA, subjective global assessment; z-BFMI, body-fat mass index z-score; z-FFMI, fat-free mass index z-score.
§ Significant difference between sexes of $p<0.01$.
† Significant difference between sexes of $p=0.02$.

Results of the bivariate correlation analysis are shown in **Table 6**. The relationship between age, z-FFMI, %FVC and SGA with 6MWD was statistically significant ($p<0.05$). The relationships between 6MWD and sex, BMI, and z-BFMI were not statistically significant. Variables significantly correlated with 6MWD were then tested together in a stepwise regression analysis displayed in **Table 7**. As SGA accounts for loss of fat-free mass in its assessment, z-FFMI and SGA were analyzed in separate models. When controlling for lung function using %FVC, z-FFMI ($\beta=15.68$, $p=0.02$) and SGA ($\beta=-67.82$, $p=0.01$) were still significant independent predictors of exercise capacity (**Table 7**).

Table 6 Relationship between physiological, clinical variables and 6-minute walk distance.

Variable	r	p-value
Age	0.31	**0.01**
%FVC	0.30	**0.01**
BMI	0.03	0.79
z-FFMI	0.28	**0.02**
	r_s	**p-value**
Sex	-0.04	0.74
z-BFMI	0.00	0.99
SGA	-0.38	<**0.01**

BMI, body mass index; %FVC, percent predicted forced vital capacity; r, Pearson's correlation coefficient; r_s, Spearman's rho; SGA, subjective global assessment; z-BFMI, body-fat mass index z-score; z-FFMI, fat-free mass index z-score.

Table 7 Linear regression: predictors of 6-minute walk distance.

	Variables	r	R^2	B	β	95% CI	p-value
Model 1	%FVC	0.42	0.17	1.67	0.29	0.36-2.98	**0.01**
	z-FFMI			15.68	0.29	3.18-28.18	**0.02**
Model 2	%FVC	0.49	0.24	1.71	0.30	0.46-2.97	<**0.01**
	SGA			-67.82	-0.39	-106.09-(-29.54)	<**0.01**

B; unstandardized beta coefficient; β, standardized beta coefficient; %FVC, percent predicted forced vital capacity; r, Pearson's correlation coefficient; SGA, subjective global assessment, z-FFMI, fat-free mass index z-score.

Mean SPhA was not significantly different across SGA groups; however, mean z-IR was significantly greater in the SGA-C group versus the SGA-A ($p<0.01$) and SGA-B ($p=0.04$) groups (**Table 5**). No variables significantly affected the odds of moderate malnutrition (SGA-B) compared to the well-nourished group (SGA-A) (**Table 6**). However, increased age [OR 1.10, 95% CI (1.01-1.25), p=0.04] and z-IR [OR 2.76, 95% CI (1.27-6.03), p=0.02] had increased odds of severe malnutrition (SGA-C) as compared to the well-nourished group (SGA-A). Increased z-FFMI [OR 0.34, 95% CI (0.17-0.68), p=0.03], z-BFMI (OR 0.39, 95% CI (0.17-0.91), p=0.03) and BMI [OR 0.73, 95% CI

(0.57-0.92), p=0.01] had decreased odds of severe malnutrition (SGA-C) as compared to the well-nourished group (SGA-A).

Table 8 Mean SPhA and z-IR across SGA categories

SGA Category	SPha (SD)	z-IR (SD)[δ]
SGA-A (well-nourished)	-0.07 ± 0.92	5.39 ± 1.34[†]
SGA-B (moderate malnutrition)	-0.78 ± 1.14	5.77 ± 1.55[‡]
SGA-C (severe malnutrition)	-0.70 ± 1.21	7.40 ± 1.51

A one-way ANOVA was used to compare means across groups. An independent sample t-test was used to compare between 2 groups. SD, standard deviation; SGA, subjective global assessment; SPhA, standardized phase angle; z-IR, impedance ratio z-score.
[δ]p=0.02 across groups
[†]p<0.01 between SGA-A vs SGA-C
‡p=0.04 between SGA-B and SGA-C

Table 9 Multinomial logistic regression using SGA-A (well-nourished) as the reference category.

Variables	**R^2**	**SGA-A (well-nourished)**	**SGA-B (moderate malnutrition)**		**SGA-C (severe malnutrition)**	
		OR (95% CI)	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age	0.08	1	1.03 (0.98-1.08)	0.27	1.10 (1.01-1.25)	**0.04**
%FVC	0.00	1	1.00 (0.98-1.03)	0.79	1.00 (0.96-1.05)	0.98
BMI	0.18	1	0.97 (0.91-1.04)	0.41	0.73 (0.57-0.92)	**0.01**
z-FFMI	0.21	1	0.80 (0.62-1.05)	0.11	0.34 (0.17-0.68)	**<0.01**
z-BFMI	0.12	1	0.91 (0.73-1.14)	0.41	0.39 (0.17-0.91)	**0.03**
SPhA	0.05	1	0.68 (0.44-1.07)	0.10	0.60 (0.26-1.42)	0.25
z-IR	0.14	1	1.21 (0.84-1.73)	0.32	2.76 (1.27-6.03)	**0.02**

BMI, body mass index; CI, confidence interval; OR, odds ratio; %FVC, percent predicted forced vital capacity; R^2, Nagelkerke's R squared; SPhA, standardized phase angle; z-BFMI, body fat mass index z-score; z-FFMI, fat-free mass index z-score; z-IR, impedance ratio z-score.

Due to limited numbers in the SGA-C group, we were not able to test for association between nutrition status and medication use across all three SGA categories. Between well-nourished (SGA-A) and malnourished groups combined (SGA-B+C), no significant associations with medication use were found (data not shown). Additionally, z-FFMI was not significantly different between type of ILD medication groups (data not shown). Similarly, with limited numbers across diagnoses we were not able to test for significant

associations between nutrition status and diagnosis. However, of note, all 6 participants with severe malnutrition (SGA-C) had IPF.

4.4 Discussion

This study examined the influence of body composition and nutrition status on exercise capacity in a cohort of patients with fibrotic ILDs. z-FFMI had a small relationship (r=0.28) with exercise capacity and was a significant predictor of exercise capacity when controlled for lung function. Worsened nutrition status had a low to moderate relationship (r=-0.38) with exercise capacity and was significantly associated with decreased exercise capacity independent of lung function.

Muscle dysfunction may be worsened by factors such as age, inactivity and medication side effects (Nakazawa, Cox, and Holland 2017). In various ILDs, characteristics suggestive of muscle dysfunction related to inactivity or disuse have been observed. In a study of individuals with advanced ILD listed for lung transplant, muscle atrophy and weakness were seen in greater amounts in lower limb muscles of the quadriceps compared with upper limb muscles of the biceps (Mendes et al. 2015). Similarly, in fibrotic idiopathic interstitial pneumonias, quadricep muscle strength and endurance was significantly lower when compared to healthy controls (Mendoza et al. 2014). Interestingly, quadriceps muscle strength (r=0.44, p=0.03), but not total fat-free mass (r=-0.05, p=0.78), was shown to be a significantly correlated with 6MWD in the healthy controls (Mendoza et al. 2014). We demonstrated that z-FFMI, which controlled fat-free mass for height, age and sex, was significantly associated with exercise capacity independent of lung function. This is in line with previous data which suggests that muscle dysfunction as a result of disuse, or loss of muscle mass is indicative of exercise capacity (Holland et al. 2008; Raghu et al. 2011).

Our results demonstrated a positive relationship between exercise capacity and nutrition. However, the influence of poor nutrition status on exercise capacity has not been well explored in ILD patients. In other chronic lung diseases, such as COPD, there appears to be a nutritional influence on exercise capacity. Specifically, normal versus low 6MWD was associated with lower odds of malnutrition assessed using the Mini Nutrition

Assessment® [OR 0.835 95% CI (0.735-0.908), p=0.005] in a group of COPD patients (Matkovic et al. 2017). Additionally, worsened nutrition status assessed using Mini Nutrition Assessment® was associated with worse dyspnea scores [OR 22.888, 95% CI (2.103-249.065), p=0.01], and lung function (FEV_1/FVC ratio) [OR 0.898, 95% CI (0.826-0.977), p=0.012] (Mete et al. 2018). In ILD, nutrition support is included as a non-exercise component in pulmonary rehabilitation programs (Nakazawa, Cox, and Holland 2017). Specific nutrition recommendations, however, are limited in best practice guidelines (Raghu et al. 2011; Travis et al. 2013), and to the best of our knowledge, no studies have thoroughly explored the influence of poor nutrition status on diminished exercise capacity in ILD patients. Our results demonstrated a positive relationship between exercise capacity and nutrition status independent of lung function. With each SGA nutrition category improvement, we would expect 6MWD to increase by an average of 67.8 metres (β=-67.8). These promising results support the theory that nutritional rehabilitation as part of ILD care has the potential to improve functional exercise capacity.

Few studies have assessed the prevalence of malnutrition in ILD. The majority of nutrition-related research in ILD has related to weight, BMI (Nishiyama et al. 2017) and FFMI (Nishiyama et al. 2017); however, no studies have assessed overall nutrition status comprehensively (Rinaldi, Mura, and Madill 2017). In this study, nutrition status was comprehensively assessed using the gold standard for nutrition assessment, SGA, which considers weight change, disease history, gastrointestinal and medication-related side effects and clinical characteristics such as edema, muscle wasting and fat loss (Detsky et al. 1987). We found that the majority of fibrotic ILD patients, according to SGA, were malnourished. Specifically, 49% of participants were moderately malnourished, and 8% were severely malnourished. Additionally, we found that increased age and various anthropometric measures such as BMI, z-FFMI and z-BFMI were associated with risk of severe malnutrition. As SGA captures factors such as weight loss, and signs of muscle wasting and subcutaneous fat loss using a clinical assessment, it is not surprising that greater values of BMI, and lean body mass and body fat were associated with lower odds of severe malnutrition. Interestingly, lung function assessed using %FVC was not associated with moderate nor severe malnutrition.

Trained clinicians, such as dietitians, needed to perform the SGA may not be readily available as part of standard care, therefore surrogate markers of nutrition, such as PhA and IR, have been suggested in a number of different disease states (Kuchnia et al. 2017; Kyle et al. 2012; Kyle, Genton, and Pichard 2013; Malecka-Massalska et al. 2016; Ott et al. 1995; Plank and Li 2013). No studies to date have explored the relationship between PhA nor IR in ILD. In this study, we did not observe any significant differences in mean SPhA between SGA groups. However, a greater z-IR, which indicates poorer cellular health, had significantly increased odds of severe malnutrition as compared to the well-nourished group. This is in line with previous research that suggests PhA may not be an appropriate standalone measure of nutrition (Rinaldi et al. 2019) and that IR may be a more robust measure of nutrition than PhA (Castillo Martinez et al. 2007; Plank and Li 2013).

Our study has some limitations. For example, the moderate sample size (N=78) limited our ability to assess the influence of specific diagnosis or medication use on nutrition status. Common ILD medications are known to have nutrition-related side effects. For example, anti-fibrotic agents are commonly associated with decreased appetite, nausea and diarrhea which would very likely affect an individual's ability to maintain good nutrition. Therefore, further research is needed to thoroughly explore the risk of malnutrition with specific medication use and between ILD subtypes. Additionally, we acknowledge that ILD patients are a heterogeneous group, however, our study population included only fibrotic-ILDs which aimed to limit diagnosis-specific differences among our participants. As this study was cross-sectional, we were not able to control for recent changes in disease severity. As such, future research should assess 6-month or 1-year changes in %FVC (Fernández Fabrellas et al. 2018) to control for worsening, stable or improved disease states. There is limited knowledge about the relationship of nutritional status on the clinical course of ILD, a potentially important implication on the outcome and quality of life of these patients. This research provides justification for the need of nutrition professionals in the standard of care of ILD patients. Future research should explore nutrition interventions, for example, aimed at improving lean body mass, and assess how improving nutrition can affect functional exercise capacity in patients with ILD.

4.5 Conclusion

Decreased FFMI controlled for age and sex and severe malnutrition independent of lung function were significantly associated with exercise capacity in fibrotic ILD. SPhA was not significantly different between SGA groups, however, z-IR was significantly greater in the SGA-C (severe malnutrition) versus SGA-A (well-nourished) groups indicating worsened cell health in severe malnutrition.

Chapter 5

5 Fat-free mass index controlled for age and sex, and malnutrition are predictors of survival in interstitial lung disease.

5.1 Abstract

Background: Literature focusing on nutritional variables and survival in interstitial lung disease (ILD) is limited by its focus on weight and body mass index (BMI) and has not considered body composition. Objectives: The primary objective of this study was to examine whether body composition measures, specifically fat-free mass index z-score (z-FFMI) and body fat mass index z-score (z-BFMI), were predictors of survival in ILD patients. The second objective was to examine if nutrition status was a predictor of survival. *Method*: 78 outpatients diagnosed with fibrotic ILD were recruited in this cross-sectional study. Body composition data using dual frequency bioelectrical impedance analysis (BodyStat 1500MD, UK), and nutrition status was determined using the subjective global assessment (SGA). To control for age and sex, z-FFMI and z-BFMI were calculated using population means. Participant charts were reviewed for diagnosis age, disease severity and exercise capacity. *Results*: Age [HR 1.08, 95% CI (1.03-1.13), p<0.01], BMI [HR 0.90, 95% CI (0.84-0.97), p<0.01)], z-FFMI [HR 0.70, 95% CI (0.56-0.87), p=0.02], z-BFMI [HR 0.74, 95% CI (0.57-0.96), p<0.01], six-minute walk distance (6MWD) [HR 0.99, 95% CI (0.99-1.00), p<0.01], % predicted diffusing capacity for carbon monoxide (%DLco) [HR 0.93, 95% CI (0.89-0.97), p<0.01] and severe malnutrition (SGA-C) [HR 6.98, 95% CI (2.00-24.27), p<0.01] were significant predictors of survival. When controlled for exercise capacity and disease severity, z-FFMI and severe malnutrition were significant predictors of survival independent of %DLco. *Conclusion*: z-FFMI and severe malnutrition were significant predictors of survival in fibrotic ILD patients independent of disease severity.

5.2 Introduction

Interstitial lung disease (ILD) is a group of disorders that involve disruption of the distal lung parenchyma, with various degrees of inflammation and/or fibrosis. A common form of ILD is idiopathic pulmonary fibrosis (IPF) and is characterized by progressive scaring of the lung parenchyma, with minimal inflammation. IPF is relentlessly progressive, with a dismal prognosis of 2-5 years, in the absence of treatment (Raghu et al. 2011). Clinical markers such as lung function, 6-minute walk distance (6MWD), dyspnea scores and body mass index (BMI) are reliable predictors of survival in ILD (Alakhras et al. 2007; Collard et al. 2003; Manali et al. 2008). To date, research examining the relationship between nutritional factors and survival in ILD is limited by its focus on weight and BMI and has not fully addressed the influence of body composition and overall nutrition status on survival.

Low fat-free mass index (FFMI), fat-free mass standardized for height, has been shown to be a predictor of mortality in various disease states (Chang et al. 2019; Schols et al. 2005). In IPF, Nishiyama et al. (2017) found that FFMI, but not BMI, was a significant predictor of survival. Age, sex and height are core biological factors affecting fat-free mass, but it may also be affected by environmental factors such as physical activity and protein intake. Therefore, the calculation of a FFMI z-score (z-FFMI) aims to account for some of these confounding factors by generating a value indicating how far away an individual's measure is from the mean of healthy population reference values. Similarly, this can be used to calculate body fat mass index z-scores (z-BFMI).

In other chronic lung diseases, a significant portion of patients have been identified as malnourished (Günay et al. 2013; Gupta, Kant, and Mishra 2010). In ILD, the prevalence of malnutrition is not well established. The gold standard of nutrition assessment is the subjective global assessment (SGA) which has been validated in a variety of disease states (Baccaro et al. 2007; Detsky et al. 1987). SGA considers diet, weight history, functional status, gastrointestinal issues, and disease history, combined with a physical examination to identify signs of muscle wasting, subcutaneous fat loss, and edema, taken together to determine nutritional status.

The primary objective of this study was to examine whether measures of body composition, specifically z-FFMI and z-BFMI, are independent predictors of survival in ILD patients. The second objective was to determine the prevalence of malnutrition using SGA and examine if nutrition status is a predictor of survival.

5.3 Methods

5.3.1 Study Population

In this cross-sectional study, 78 patients diagnosed with fibrotic ILD were recruited from an outpatient ILD clinic. Inclusion criteria included ambulatory patients over 18 years of age with diagnosis of a fibrotic ILD. Patients were excluded according to the following criteria: inability to provide consent due to communication issues (cognitive and motor), presence of cardiac implantable electrical devices, non-stable ILD patients defined as those with infections and/or fever, admitted to hospital in the previous month, or presence of an unstable co-morbid illness. The study protocol was approved by the Western University Research Ethics Board (protocol n. 104028 and 103186).

5.3.2 Diagnosis, Disease Severity and 6-Minute Walk Test

The presence of fibrotic ILD was defined based on high-resolution chest computed tomography scan and compatible pulmonary function tests. After excluding all known causes of ILD, IPF was diagnosed based on clinical and radiographic criteria, and when necessary, on surgical lung biopsies, followed by multi-disciplinary discussion (Flaherty et al. 2004; Raghu et al. 2018). The diagnosis of fibrotic ILD other than IPF was based on clinical presentation, laboratoristic, bronchoscopic, radiographic investigations, and when indicated (e.g. non-specific interstitial pneumonia cases), surgical lung biopsies. Patients with combined pulmonary fibrosis and emphysema (CPFE) were also excluded from the study, and coexisting emphysema was always minimal (≤5% of total lung volume). Patient charts were also reviewed for current medications and results of pulmonary function tests and six-minute walk tests. Pulmonary function tests and six-minute walk tests were performed as part of patients' standard of care and according to the American Thoracic Society guidelines (American Thoracic Society (ATS) 2002; Standardization of

Spirometry, 1994 Update. American Thoracic Society. 1995). Time from diagnosis was calculated from date ILD was diagnosed to study recruitment date.

5.3.3 Body Composition Assessment

Body composition data were obtained using dual frequency bioelectrical impedance analysis (BIA) (BodyStat 1500MD, UK). BIA is an easy and convenient bedside tool that is validated in a variety of clinical settings (Fuller, Sawyer, and Elia 1994; Ghosh et al. 1997; Steiner et al. 2002). Participants were asked to rest supine on a bed in the clinic while breathing normally. Resistance and reactance were measured via passing a 50 kHz electrical current through the body via two electrodes placed on the surfaces of the right hand and foot while measuring the impedance at fixed frequencies (BodyStat 2017). FFMI and BFMI were calculated using estimates of fat-free mass and body fat mass obtained using BIA according to the following equations: FFMI= fat-free mass (kg) / [height (m)]^2, and BFMI= body fat mass (kg) / [height (m)]^2, respectively. z-FFMI and z-BFMI were then calculated using population means by age and sex groups (Kyle et al. 2001) according to the following equation: z-score = $(x - x_{\text{population mean}})$/ standard deviation$_{\text{population}}$ (SD). FFMI and BFMI cut-offs suggested by Kyle et al. (2001) were used to classify patients into the following categories: normal (normal FFMI and BFMI), sarcopenia (low FFMI and normal BFMI), obesity (normal FFMI and high BFMI), and sarcopenic obesity (low FFMI and high BFMI) (Kyle et al. 2005).

5.3.4 Nutrition Assessment

SGA was completed according to the method outlined by Detsky et al (1987) and was completed by a registered dietitian (SR). SGA is considered the gold standard method to identify malnutrition combining dietary, weight, functional, gastrointestinal and disease history with a physical examination to arrive at a categorical ranking. Categories A, B and C represent well-nourished, moderate malnutrition or suspected of being malnourished, and severe malnutrition, respectively.

5.3.5 Outcome

The primary outcome measure was 2-year lung transplant-free survival. The survival of patients was assessed starting from the time of their BIA assessment up to 2 years following this date.

5.3.6 Statistical Analysis

Descriptive statistics were evaluated; continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are displayed as frequencies. An independent samples t-test was used to compare differences in means between sexes. Cox proportional hazard regression models were performed to identify significant predictors of survival. Receiver operator characteristic (ROC) analyses were used to determine the best cut point of a variable towards the endpoint, by examining accuracy of predicting endpoints (sum of sensitivity and specificity). Lung transplant-free survival was evaluated using Kaplan-Meier curves and the log rank test. P-values <0.05 were regarded as significant. Statistical analysis was performed with IBM® SPSS® Statistics Version 26 software package.

5.4 Results

Patient characteristics including diagnosis, clinical characteristics, body composition and nutrition status are shown in **Table 10.** Mean age was 68.4±10.0 years. 51.3% of participants were female. Mean BMI was 30.8±7.3 kg/m^2. As expected, FFMI was significantly greater in males versus females ($p<0.001$), and BFMI was significantly lower in males versus females ($p<0.001$). Mean z-FFMI and z-BFMI, standardized for age and sex population norms (Kyle et al. 2001), were 0.39±1.98 SD and 2.27±2.15 SD, respectively. Most patients were diagnosed with moderate malnutrition (49%). 60.3% of participants were classified as obese, while 11.5% had a normal body composition, 20.5% had sarcopenia and 7.7% were sarcopenic obese. Mean observation time was 19.4±7.3 months. At the end of the 2-year observation period, 26% (n=20) of participants had passed or were transplanted.

Table 10 Patient demographics (N=78).

Clinical Characteristics	Mean ± SD or Frequency (%)
Age (years)	68.4 ± 10.0
Sex	
Male	38 (48.7)
Female	40 (51.3)
Diagnosis	
Idiopathic pulmonary fibrosis	36 (46.2)
Drug-induced toxicity	10 (12.8)
Rheumatoid arthritis related ILD	8 (10.3)
Non-specific interstitial pneumonia	8 (10.3)
Chronic hypersensitivity pneumonitis	5 (6.4)
Unclassifiable ILD	4 (5.1)
Scleroderma-related ILD	3 (3.8)
Vasculitis-related ILD	2 (2.6)
Sarcoidosis (stages III-IV)	2 (2.6)
Years from diagnosis [median (range)]	1 (0-13)
ILD Medications	
Proton pump inhibitors	43 (55.1)
Oxygen supplementation	24 (30.8)
Pirfenidone	16 (20.5)
N-acetylcysteine	12 (15.4)
Nintedanib	2 (2.6)
Anthropometry and Nutritional Indices	
BMI (kg/m^2)	30.8 ± 7.3
FFMI (kg/m^2)	18.2 ± 3.6*
male	20.0 ± 3.6
female	16.4 ± 2.7
BFMI (kg/m^2)	12.6 ± 5.5*
male	9.9 ± 3.8
female	15.2 ± 5.7
FFMI z-score (SD)	0.39 ± 1.98
BFMI z-score (SD)	2.27 ± 2.15
Body Composition	
Normal	9 (11.5)
Sarcopenia	16 (20.5)
Obesity	47 (60.3)
Sarcopenic Obesity	6 (7.7)
Nutrition Status [n (%)]	

SGA-A (well-nourished)	34 (43.6)
SGA-B (moderate malnutrition)	38 (48.7)
SGA-C (severe malnutrition)	6 (7.7)
Pulmonary Function and Exercise Capacity	
FEV_1 (% predicted)	75.1 ± 18.9
FVC (% predicted)	71.1 ± 19.5
DL_{CO} (% predicted)	40.6 ± 17.1
6MWD (m)	335.6 ± 109.8
6MWD (% predicted)	74.4 ± 22.9

Continuous variables are expressed as mean ± standard deviation. BFMI, body-fat mass index; BMI, body mass index; FFMI, fat-free mass index; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; SD, standard deviation; SGA, subjective global assessment; 6MWD, six-minute walk distance; $\%DL_{CO}$, percent predicted diffusing capacity for carbon monoxide; %FEV, percent predicted forced expiratory volume; %FVC, percent predicted forced vital capacity.
* independent samples t-test indicated significant difference ($p<0.001$) between sexes

The results of the univariate Cox proportional hazard model are summarized in **Table 11**. Age was not included in the models as z-FFMI, z-BFMI and %DLco values control for differences in age. z-FFMI and SGA were not included in the same model as a component of SGA includes assessment of loss of fat-free mass. The results of the multiple Cox proportional hazard models are shown in **Table 12**. z-FFMI was a significant predictor of survival independent of z-BFMI and %DLco but not 6MWD (**Models 1-3, Table 12**). SGA-C (severe malnutrition) as compared to SGA-A (well-nourished) was a significant predictor of survival independent of %DLco but not 6MWD **(Models 4-5, Table 12**).

Table 11 Univariate Cox proportional analysis.

Variable	HR	95% CI	p-value
Sex	1.76	(0.72-4.32)	0.22
Age	1.08	(1.03-1.13)	**<0.01**
Time from diagnosis	1.00	(0.85-1.17)	0.96
Prednisone	0.75	(0.29-1.95)	0.56
Pirfenidone	1.91	(0.73-4.98)	0.19
N-acetylcysteine	3.17	(1.21-8.28)	**0.02**
Supplemental oxygen	1.76	(0.72-4.31)	0.22
MMF	0.04	(0.00-10.03)	0.25
$\%FEV_1$	0.99	(0.97-1.02)	0.51
%FVC	0.99	(0.97-1.01)	0.36
$\%DL_{CO}$	0.93	(0.89-0.97)	**<0.01**
BMI	0.90	(0.84-0.97)	**<0.01**
z-FFMI	0.70	(0.56-0.87)	**<0.01**
z-BFMI	0.74	(0.57-0.96)	**0.02**
6MWD	0.99	(0.99-1.00)	**<0.01**
SGA-A (well-nourished)	1	---	---
SGA-B (moderate malnutrition)	2.04	(0.70-5.96)	0.20
SGA-C (severe malnutrition)	6.98	(2.00-24.27)	**<0.01**
Normal	1	----	---
Sarcopenia	5.49	(0.69-43.97)	0.11
Obesity	1.66	(0.21-13.28)	0.63
Sarcopenic Obesity	5.61	(0.58-54.06)	0.14
Obesity	1	----	---
Sarcopenic Obesity	3.23	(0.85-12.21)	0.08

BMI, body mass index; CI, confidence interval; HR, hazard ratio; SGA, subjective global assessment; z-BFMI, body-fat mass index z-score; z-FFMI, fat-free mass index z-score; 6MWD, six-minute walk distance; $\%DL_{CO}$, percent predicted diffusing capacity for carbon monoxide; $\%FEV_1$, percent predicted forced expiratory volume; %FVC, percent predicted forced vital capacity.

Table 12 Cox regression analyses to identify independent predictors of lung transplant-free survival.

Variables	HR	95% CI	p-value
Model 1			
z-FFMI (SD)	0.72	(0.53-0.98)	**0.03**
z-BFMI (SD)	0.78	(0.69-1.32)	0.78
Model 2			
z-FFMI (SD)	0.67	(0.51-0.86)	**<0.01**
$\%DL_{CO}$	0.92	(0.88-0.97)	**<0.01**
Model 3			
z-FFMI (SD)	0.82	(0.65-1.03)	0.09
6MWD (m)	0.99	(0.99-1.00)	**<0.01**
Model 4			
SGA-A (well-nourished)	1	------	-----
SGA-B (moderate malnutrition)	2.06	(0.56-7.63)	0.28
SGA-C (severe malnutrition)	7.24	(1.68-31.15)	**<0.01**
%DLco	0.93	(0.89-0.97)	**<0.01**
Model 5			
SGA-A (well-nourished)	1	----	----
SGA-B (moderate malnutrition)	1.42	(0.47-4.26)	0.54
SGA-C (severe malnutrition)	3.13	(0.75-13.01)	0.12
6MWD (m)	0.99	(0.99-1.00)	**<0.01**

CI, confidence interval; HR, hazard ratio; SD, standard deviation; SGA, subjective global assessment; z-FFMI, fat-free mass index z-score; z-BFMI, body-fat mass index z-score; 6MWD, six-minute walk distance; $\%DL_{CO}$, percent predicted diffusing capacity for carbon monoxide.

Results of ROC analysis for z-FFMI is displayed in **Table 13**. The ideal z-FFMI cut-off was <0.37 SD with 62.1% sensitivity and 80.0% specificity. Kaplan-Meier survival curves using the ideal cut-offs determined using ROC analysis for z-FFMI is shown in **Figure 4**.

Table 13 Results of receiver operator characteristic analysis

	AUC (95% CI)	p-value	Cut-off (SD)	Sensitivity (%)	Specificity (%)
z-FFMI	0.74 (0.62-0.87)	<0.01	0.37	62.1	80.0

AUC, area under the curve; CI, confidence interval; SD, standard deviation; z-FFMI, fat-free mass index z-score.

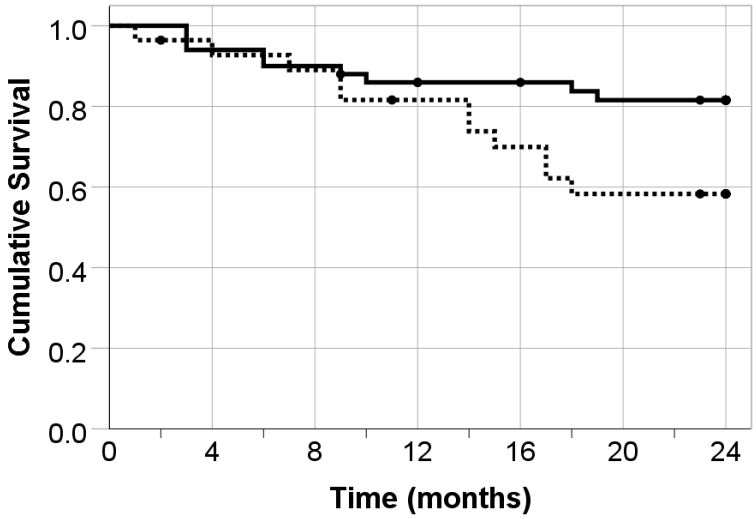


Figure 4 Kaplan–Meier survival curve using ideal cut-off for fat-free mass index z-score (z-FFMI) (p=0.001). The solid line represents z-FFMI ≥ 0.37 SD and the dotted line represents z-FFMI <0.37 SD. Survival curves was compared using log-rank statistics (• represent censored cases).

5.5 Discussion

This study examined the influence of body composition parameters, z-FFMI and z-BFMI, and nutrition status on survival in a group of fibrotic ILD patients. z-FFMI, z-BFMI and severe malnutrition (SGA-C) were shown to be significant predictors of survival in ILD. However, when controlled for disease severity only z-FFMI and severe malnutrition were independent predictors of survival in ILD patients.

In our univariate analysis BMI was found to be a significant predictor of survival in ILD patients. Research focusing on BMI and survival in IPF patients has demonstrated a paradoxical effect of obesity on survival, in that, an increased BMI acts as a protective factor on mortality. In a study by Alakhras et al. (2007), individuals with BMIs in the obese category (>30kg/m^2) were shown to have significantly greater survival times than those with BMIs in the overweight category (25-30kg/m^2) and normal category (<25kg/m^2). Similarly, Mura et al. (2012) reported that for every 1-unit increase in BMI there was a 11% lower risk of death at 3-year follow-up in IPF patients (HR 0.89, 95% CI (0.80–0.98), p=0.0165). Adding to these results, progressive weight loss greater than 5% of total body weight in 1 year has also been found to be an independent predictor of decreased survival in IPF (Nakatsuka et al. 2018). Limited studies exist showing the relationship between increased BMI and decreased mortality in ILDs other than IPF. One recent study, which included a diverse group of ILDs including ILD secondary to connective tissue disease, hypersensitivity pneumonitis, and unclassifiable subtypes found that a loss in BMI greater than 5% in 1 year was associated with significantly shorter survival times, and there was a 2-fold higher risk of death compared to those with a ≤5% loss in BMI in 1 year (Pugashetti et al. 2018). These results suggest that excess weight may act as a nutritional reserve in times of poor intake secondary to harsh side effects of medications, or during acute exacerbations of the disease. Interestingly, we found that only use of N-acetylcholine, an ILD medication used for its antioxidant effect (Sun, Liu, and Zhao 2016), was associated with worsened mortality, but corticosteroids, and other anti-fibrotic and anti-inflammatory medications were not related to survival.

A strong relationship exists between decreased FFMI and poor prognosis in other chronic respiratory diseases such as chronic obstructive pulmonary disease (Gologanu et al. 2014; Schols et al. 2005; Vestbo et al. 2006); however, fewer studies exist in ILD. We demonstrated a 30% reduction in risk of death for every 1 SD increase in z-FFMI in our sample of 78 fibrotic ILD patients. Two recent studies exist examining FFMI and survival in IPF patients. The first study by Nishiyama et al. (2017) found a 36% lower risk of death with every 1-unit increase in FFMI (HR 0.64, 95% CI (0.43–0.94), p=0.02) in a group of Japanese IPF patients. Conversely, in a study of IPF patients by Patel et al. (2018) there was no significant association between FFMI and all-cause mortality at 1-year. Although conflicting results, neither study controlled for age or sex when analyzing FFMI. Notably, despite not controlling for confounding factors, Nishiyama et al. (2017) did demonstrate FFMI to be a significant predictor of survival in their study. This could be due to a non-significant difference in FFMI in males versus females in this sample. Different body composition norms in Japanese versus Caucasian cohorts such as lower BMI and FFMI have been demonstrated in previous studies (Jensen et al. 2019). However, between sex statistics were not reported. Patel et al. (2018) did not adjust for sex differences in their univariate analysis using FFMI as a continuous variable, however, when FFMI was used as a categorical variable, sex specific cut-offs were applied (FFMI $\geq$15 kg/m^2 for females and $\geq$17 kg/m^2 for males). A reference source for these cut-offs was not indicated, however, it is assumed that these cut-offs are based on the European Society for Parenteral and Enteral Nutrition diagnostic criteria for malnutrition (Cederholm et al. 2015). Although an important contributor to survival, cuts-offs derived for identification of malnutrition may not be sensitive or specific to predicting survival outcomes, thus, influencing these non-significant findings. Our study intended to control for patient characteristics such as age and sex which influence FFMI. Using z-FFMI we were able to include both males and females together in our analyses, and we were able to control for factors such as age-related fat-free mass loss which can skew results.

We also addressed the impact of body fat on survival. Interestingly, we found that z-BFMI was a significant predictor of survival. Although it has been demonstrated that excess weight can increase the workload of breathing and decrease physical performance (Tynan and Hasse 2004), our results seem to suggest that greater amounts of body fat may be

protective on survival. It is very likely that the protective effect of excess body fat on survival observed in this study is related to the relationship between fat-free mass and body fat mass, in that, as body fat mass increases, greater amounts of fat-free mass may be required to support this excess weight. Therefore, FFMI may be maintained through a weight bearing effect. This is further supported by results of our analysis, in which z-BFMI was no longer a significant predictor of survival when controlled for z-FFMI. These results appear to suggest a component of sarcopenic obesity affecting the significance of z-BFMI as a predictor of survival in the presence of worsened disease status and poor exercise capacity. Specifically, research has shown that excess body fat mass, especially in the presence of fat-free mass, can have direct detrimental effects on physical performance (Joppa et al. 2016), systemic inflammation (Joppa et al. 2016), quality of life (Joppa et al. 2016; Öztürk et al. 2018) and prognosis (Gonzalez et al. 2014). We attempted to determine the influence of body composition on survival, however, we found no significant difference in odds of death in those with sarcopenia, obesity, nor sarcopenic obesity versus those with a normal body composition. Additionally, we assessed the specific difference between the obese and sarcopenic obese groups, however, there was no significant difference ($p=0.085$) in chance of death in sarcopenic obesity versus obesity. However, with only 6 patients identified as sarcopenic obese, our statistical power was limited.

Prevalence of malnutrition in ILD patients has been understudied, and clinical practice guidelines for the treatment and management of ILD offer limited guidance related to nutrition (Raghu et al. 2011, 2018). Of the existing research, malnutrition prevalence varies greatly, and is often identified by a single measure. Jouneau et al. (2019) found that 28% of patients were malnourished using fat-free mass, 4% were malnourished using BMI, and 5% were malnourished using mid-arm circumference. A conference abstract by Autore et al. (2013) reported that 26% of patients were at risk of malnutrition using the Mini Nutritional Assessment Short Form, a validated screening tool designed for populations >65 years. In our study, the majority of patients were diagnosed with malnutrition, and those with severe malnutrition, had a 7-fold increased risk of death compared to well-nourished patients. To the best of our knowledge, this study is the first to use a comprehensive nutrition assessment tool validated to diagnose malnutrition.

The modest sample size was a limiting factor of this study. First, we were limited to including no more than two predictor variables in the multiple Cox regression models keeping in line with the general recommendation that for every one predictor variable n=10 outcomes, in this case deaths, are required to reduce the risk of overfitting the model (Norman 2013). Therefore, we were not able to control for both disease severity and exercise capacity with body composition parameters and nutrition status in the same model which may have produced different results. Second, with only 6 participants identified as sarcopenic obese we were not able to fully address the question of whether increased body fat is protective in all cases. Similarly, limited numbers in our severe malnutrition group limited statistical power in our analyses. Our cross-sectional study only assessed body composition, disease severity and exercise capacity at one time point, however, monitoring changes over time, such as change in body composition or change in %FVC, can provide additional insights into their influences on survival. Additionally, we did not use a cohort of healthy individuals for comparison with our sample. However, the nature of calculating z-scores of body composition parameters innately compares our sample to healthy population norms of FFMI and BFMI. Lastly, it would be remiss to not acknowledge that BIA provides estimations of body composition using prediction equations. Therefore, our results are limited due to the use of estimates of fat-free mass and body fat mass rather than actual measurements. However, our results are in-line with previous research that has shown that adiposity (Alakhras et al. 2007) and low muscle mass (Mendes et al. 2015) is common in ILD.

5.6 Conclusion

These results are sufficiently encouraging to warrant further research into the nutritional status of ILD patients. Future research should focus on the influence of sarcopenic obesity on survival, and how nutrition interventions targeted at maintaining or increasing muscle mass over time can affect survival in ILD patients. Furthermore, assessment of fat-free mass should be considered alongside or in place of BMI as a nutritional variable when analyzing survival risk of ILD patients as it can better identify those as risk of death. Additionally, chest computed tomography scans which are completed as part of diagnosis and clinical monitoring of ILD should be leveraged to measure body

composition parameters using a gold standard method. In conclusion, in our sample of 78 fibrotic ILD patients, z-FFMI and severe malnutrition independent of disease severity were significant predictors of survival in ILD patients.

Chapter 6

6 Overall Conclusion and Future Directions

The overarching purpose of this dissertation research was to better understand the nutritional concerns in interstitial lung disease (ILD) patients through investigating the contributions of body composition and nutrition status on exercise capacity and survival in patients with ILD. This final chapter will discuss the contributions to research, clinical implications and recommendations, the challenges and limitations of this thesis research, future research plans, and end with an overall conclusion.

6.1 Research Contributions

This dissertation makes several key contributions to knowledge. **Chapter 2** reviewed the literature on ILD background and nutrition-related knowledge to date in ILD. The key finding from this literature review was that there are numerous nutrition-related concerns associated with ILD and its treatment which put patients at nutritional risk. Despite this, nutrition professionals such as registered dietitians (RDs) may not be part of the standard ILD health care team. This overlooks an important opportunity to improve quality of life and survival through supporting patients' nutritional needs.

Chapter 3 examined the appropriateness of phase angle (PhA) as a nutrition indictor in various disease states. This study was the first systematic review comparing the subjective global assessment (SGA) which is the gold standard of nutrition assessment with bioimpedance PhA. The key finding of this systematic review was that overall evidence quality received a grade of Low, and that continued research is needed in this area to validate surrogate markers of nutrition status in a variety of disease states.

The objective of **Chapter 4** was to examine the relationship between nutrition status and body composition with functional exercise capacity, and to determine the appropriateness of bioimpedance parameters (PhA and impedance ratio (IR)) to identify malnutrition in ILD patients. The results of **Chapter 4** showed that SGA-C (severe malnutrition) and low fat-free mass index z-score (z-FFMI) were associated with worsened exercise capacity in patients with fibrotic ILD, and that IR z-score (z-IR), but not standardized PhA (SPhA),

was associated with severe malnutrition. A research gaps exists in the areas of body composition, nutrition status and surrogate markers of nutrition in ILD. The results of this chapter address these research gaps. These finding are important to the body of research on nutrition status and body composition in ILD as it demonstrates that malnutrition or loss of fat-free mass can negatively impact a person's ability to perform their activities of daily living and therefore affect their quality of life.

The purpose of **Chapter 5** was to evaluate body composition measures and nutrition status as predictors of survival in ILD. The results of **Chapter 5** revealed that z-FFMI and SGA-C (severe malnutrition) are independent predictors of survival in patients with ILD. The findings in this chapter are important to the research field as it challenges previous research that has narrowly focused on increased weight as a protective factor in the survival of ILD patients. Rather, this research indicates that increased fat-free mass is an important component of body weight which offers a protective effect on survival in ILD. Also, this research is the first to assess the relationship between nutrition status and survival. The key finding that severe malnutrition, but not moderate malnutrition, was associated with decreased survival in ILD adds to the ILD knowledge base and warrants further research exploration.

6.2 Clinical Implications

This research provides justification for the need of nutrition professionals as part of a holistic approach in the care of ILD patients. Previous research has identified patient education, symptom relief and management of comorbidities as vital components of supportive care in ILD management (Quinn, Wisse, and Manns 2019). RDs can support patients in each of these three supportive care components using their nutrition expertise and skills.

ILD medications are commonly associated with adverse events such as decreased appetite, nausea or diarrhea, which put patients at nutritional risk. For example, diarrhea is a common adverse event of the medication Nintedanib (OFEV®), and many patients may discontinue its use due to this side effect (Galli et al. 2017). Specific nutrition counselling and patient education on bowel management has the potential to reduce

bowel frequency as well as prevent additional complications such as dehydration and malabsorption. Additionally, RDs can support patients to correct or prevent malnutrition. For example, decreased intake and/or increased energy requirements related to the increased work of breathing can result in loss of fat-free mass and malnutrition.

RDs can address and educate patients on the conflicting weight-related research in ILD. For instance, as thoroughly discussed in **Chapter 2**, an increased body mass index (BMI) is associated with decreased mortality in ILD patients (Alakhras et al. 2007; Mura et al. 2012), however, this conflicts with both general health weight recommendations and BMI cut-offs required for lung transplantation. Dietetics is an evidenced-based profession; therefore, RDs can address nutrition misconceptions and misunderstandings and provide credible, evidence-based information to ILD patients. RDs can help patients establish and maintain their own individualized weight and body composition targets. RDs are qualified to identify indictors of muscle or body fat loss and therefore assess for risk of sarcopenia and sarcopenic obesity. Therefore, RDs should be included in standard ILD care in order to establish targetable nutrition care plans for common nutrition problems thereby improving symptom management and quality of life.

6.3 Reflections on Research Challenges

Although the research process can provide a great deal of gratification it also can bring about challenges. A main difficulty I encountered with this dissertation research was related to recruitment and timing. Participant recruitment in a relatively rare and specialized disease can be difficult. In my case, I was fortunate to be working in the ILD clinic serving southwestern Ontario. However, this meant that patients were frequently travelling from out of town for their clinic visit with their respirologist, and for some, this also meant that they were not willing to stay the extra time required for the data collection required for this study. Furthermore, being a specialized clinic, it only occurred on one half day per week. Therefore, there were only a limited number of participants available to recruit each week.

A large challenge was our recruitment capacity at each clinic, specifically related to limited clinic space to see patients, having only one bioelectrical impedance analysis

(BIA) device (BodyStat® 1500MDD) for data collection and having only one RD available to complete the SGA. For example, if all scheduled clinic patients were to consent to this research study, our capacity as a research team (myself, the RD required for specific data collection and a variable number of student volunteers each week) would only be able to collect data on 4-5 participants per clinic at a maximum. As well, patient clinic visits were generally scheduled 4-6 months apart which meant that if a patient was interested in participating in the research study, but was not able to be seen on that day due to time restraints, the research team would possibly have to wait another 4-6 months to see that patient again. Lastly, with respect to our survival research, our study timeline was lengthened to allow for a 2-year survival time. Therefore, in preparation for this dissertation research we were required to limit our cohort to N=78 participants in order to have the necessary survival data for our analyses.

6.4 Limitations

The main limitation of this research was sample size. Our sample size of n=78 in both studies limited our ability to assess the influence of specific diagnoses, medication use and body composition categories, such as sarcopenic obesity, in our analyses. Specifically, we have limited statistical power to assess the influence of sarcopenic obesity (n=6) on survival. As a result, we were not able to fully address the question of whether increased body fat mass was protective in all cases. Similarly, although we reported significance in our analyses of the SGA-C (severe malnutrition) group in its association with exercise capacity and survival, SGA-C (severe malnutrition) was no longer a significant predictor of survival when controlled for exercise capacity. As well, we found no significant difference in SPhA across SGA groups. Therefore, without greater sample size, we could not say with certainty if there is truly no relationship or if these non-significant results were due to limited statistical power.

In our survival analyses in **Chapter 5**, we were limited to including no more than two predictor variables in the multiple Cox regression models keeping in line with the general recommendation that n=10 outcomes, in this case deaths, are required for every one predictor variable to reduce the risk of overfitting the model (Norman 2013). Therefore, we were not able to control for both disease severity and exercise capacity with body

composition parameters and nutrition status within the same model which may have produced different results.

Another limitation of this study is that it is cross-sectional in nature and only assessed body composition, lung function and exercise capacity at only one time-point; however, monitoring changes over time, such as change in body composition or change in percent forced vital capacity (%FVC) would provide more valuable insights into their influences on survival and exercise capacity. Additionally, we acknowledge that ILD patients are a heterogeneous group, however, our study population included only fibrotic-ILDs which aimed to limit diagnosis-specific differences among our participants. Furthermore, we did not use a cohort of healthy individuals for comparison with our sample. However, the nature of calculating z-scores innately compares our sample to healthy population norms of FFMI, body-fat mass index (BFMI), PhA and IR. Lastly, it would be remiss to not acknowledge that BIA provides estimations of body composition using prediction equations as discussed in **Chapter 2 Section 2.2.2.1.3**; therefore, our results are limited due to the use of estimates of fat-free mass and body-fat mass rather than actual measurements. However, in a clinical setting, BIA is the most cost-efficient and practical application. Although, this research was limited by sample size and, therefore, we could not preform subgroup statistical analyses, there is reason to believe that individuals with ILD would benefit from nutrition intervention and support.

6.5 Future Research Recommendations and Plans

Continued research is needed to better understand the complex needs of patients with ILD. There are many research areas that can be further explored within the ILD population; however, we have identified the most notable research gaps warranting further exploration. Continued nutrition-related research is needed to increase study samples size in order to thoroughly explore the risk of malnutrition with specific medication use and between ILD subtypes, as well as to further explore the influence of sarcopenic obesity on survival. This may be achieved by a multi-site research study.

There is a notable gap in the research regarding nutrition interventions in ILD, despite mention in clinical practice guidelines and pulmonary rehabilitation best practice

guidelines. First, monitoring of nutrition status and body composition longitudinally is needed to better understand how they relate to clinical parameters such as lung function, exercise capacity, and survival. Second, research should explore the impact of nutrition interventions, for example, to improve or preserve muscle mass and explore its relation to survival, exercise capacity and/or quality of life of patients with ILD. Lastly, within these future directions, there is great possibility for interprofessional collaboration. For example, collaboration with physiotherapists would be important to examine the potential synergistic effect between nutrition interventions and physiotherapy as part of pulmonary rehabilitation aimed at increasing muscle mass and exercise capacity, and thus improving patient outcomes.

This research was part of a larger overall study which collected dietary intake information, biochemical data such as calcium and vitamin D serum levels and functional data such as hand-grip strength. Data analysis is planned to assess adequacy of intake in our sample population. This will allow for exploration into the relationship between protein intake and body composition, and vitamin D intake and serum blood levels in ILD patients. As well, the relationship between hand-grip strength, a quick and easy measure of functional capacity, and nutrition status and body composition will be explored. The results of this planned research may help lay the foundation for further interventional research.

As this research was limited by its use of bioelectrical impedance analysis to determine estimated, rather than measured, body composition parameters, we are currently completing a research study on the use of chest computed topography (CT) scans to measure body composition parameters using a gold standard method. This research project aims to determine the prevalence of sarcopenia, or low muscle mass, and sarcopenic obesity using computed tomography scans in ILD patients both at diagnosis and through disease progression and which will be used to assess for survival risk. As well, fat-free mass and body fat mass measured using computed tomography imaging, in select cases, will be correlated with predictions of body composition assessed using BIA in order to determine ILD-specific derived BIA regression equations. See **Appendix E** for additional information on this project.

6.6 Conclusion

In conclusion, in our sample of 78 fibrotic ILD patients, decreased z-FFMI which was controlled for age and sex, and SGA-C (severe malnutrition) were significantly associated with exercise capacity in fibrotic ILD patients independent of lung function. SPhA was not significantly different between SGA groups, however, z-IR, which measures cell health, was significantly greater in the SGA-C (severe malnutrition) versus SGA-A (well-nourished) group indicating worsened cell health in severe malnutrition. z-FFMI and severe malnutrition independent of disease severity were significant predictors of survival in ILD patients. Continued research should focus on nutrition assessment, intervention and monitoring as this will result in improved understanding of the complex nutritional concerns of ILD patients. Better understanding these complex needs and involving nutrition professionals such as RDs in the standard care of ILD patients can help ensure that ILD patients are provided with the appropriate supports to best manage their disease.

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Appendices

Appendix A: Letter of Information and Consent Form

NUTRITIONAL STATUS OF PATIENTS WITH INTERSTITIAL LUNG DISEASE: A CROSS SECTIONAL STUDY

LETTER OF INFORMATION

Introduction

My name is Dr. Janet Madill and I am a Professor in the Foods and Nutrition Department at Brescia University College. I am currently conducting research into the nutritional status of patients with interstitial lung disease and would like to invite you to participate in this study. I am working with Dr. Marco Mura, your respirologist. The purpose of this information letter is to provide you with enough information for you to decide if you would like to participate in the study.

Purpose of the study

The purpose of this study is to assess the nutritional status of patients with interstitial lung disease (ILD), as there is currently little to no information available for patients with ILD. ILD is a disease process whereby the lungs become inflamed and scarred. The aim of the study is to measure body composition and nutritional status as this relates to disease and to determine the appropriate nutrition care plan for patients with interstitial lung disease.

If you agree to participate

If you agree to participate in this study, during your clinic visit, we will review with you what you have eaten in the last 24-hours. We will provide you with a 3-day food record sheet, for you to take home and explain to you how to fill in the sheets. We will also ask you if you would prefer, we call you at the end of each of the 3-days to record what you have eating, or you may fill in the 3-day food record on your own. As well, we will record your height and weight. Your body composition, or the amount of muscle, fat and fluid in your body, will be measured using a *BodyStat Analyzer.* This will involve resting comfortably on a bed in the clinic and breathing normally. We will attach 2 electrodes each to the surface of your foot and hand and record for 2-3 minutes. The *BodyStat Analyzer* is a non-invasive device, which measures the impedance value of the body providing quick and effective analysis of body composition. This is a painless process and it works by passing a safe battery generated signal through the body and measuring the impedance at a fixed frequency. We will measure the thickness of your quadriceps femoris muscle in your thigh using a portable ultrasound machine. This will require you to lay flat on a clinic bed during the measurement and will require you to expose the skin of your mid though so we can access to the skin surface. Ultrasound gel and probe will be placed directly on skin surface using light pressure to produce an ultrasound image used to measure the thickness of your muscle. Lastly, we will measure your hand-grip strength. This will require you to sit upright in a chair, and using each hand, squeeze a dynamometer machine as hard as you can. This

will be repeated three times for accuracy. All testing will be completed during your normal clinic visit and no additional visits will be required. You **may** need to stay an additional thirty to sixty minutes to complete this study. In some cases, if you are not able to make it to clinic, you may be approached for a visit to take place in the community where members of the study team will visit you at home to complete the above mentioned data collection. In this case, we will need to collect your address and postal code solely for travel purposes. Your address and postal code will not be used for data analysis.

Confidentiality

The information collected will be used for research purposes only, and neither your name nor information which could identify you will be used in any publication or presentation of the study results. We will look in your patient records from the hospital including your personal health information and we will collect only the information we need for this study. With your consent, we will be contacting your primary physician to obtain any existing blood work test results on file. All information collected for the study will be kept confidential. All consent forms will be kept in a locked cabinet file owned by Dr. Marco Mura at Victoria Hospital in London, ON. Study data will be destroyed after 5 years.

Risks & Benefits

There are no foreseen risks to participating in this study. The only inconvenience experienced will be that will be meeting with a dietitian to discuss your weight history, and to talk about what you have eaten in the last 24 hours and to ask you to record what you eat for 3 days. We will review with you how to complete this and will provide you with the forms to use to record your food intake. The benefit to the participant is that their future nutrition care interventions may be better directed.

Voluntary Participation

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions, complete any portion of the study or withdraw from the study at any time with no effect on your medical care. Should you choose not to participate any information about your study results will not be used.
You will not be compensated for your time should you choose to participate.

Questions

If you have any questions about the conduct of this study or your rights as a research participant you may contact the Office of Research Ethics, Western University at [redacted]. If you have any questions about this study, please contact the principal investigator, Dr. Janet Madill, RD, 1285 Western Road, Brescia University College, London N6G 1H2, [redacted], or the research associate, Sylvia [redacted].

This letter is yours to keep for future reference.

NUTRITIONAL STATUS OF PATIENTS WITH INTERSTITIAL LUNG DISEASE: A CROSS-SECTIONAL STUDY

Dr. Janet Madill, Professor of Foods and Nutrition
Brescia University College

CONSENT FORM

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Name (please print):

Signature: Date:

Name of Person Obtaining Informed Consent:

Signature of Person Obtaining Informed Consent:

Date:

Appendix B: Study Data Collection Forms

Study #:_____ Date:_____

WEIGHT			NUTRITION RELATED		
	UBW			Appetite	Good / Fair / Poor
	BMI				Duration
	Weight Δ	↑ ↓ Intentional/Unintentional		Nausea	
	6 months			Vomiting	
	2 weeks			Diarrhea	
	Goal			Constipation	
				Chewing	
				Swallowing	

Medications:		IPAQ		
		Vigorous Activity	Days	
			Time Spent	
		Moderate Activity	Days	
Vitamin/Mineral Supplements:			Tim e Spent	
		Walking for at least 10 minutes	Days	
			Time Spent	
		Laying down/sitting	Days	
Herbal Supplements:			Time Spent	

MEDICAL HISTORY	Diagnosis: □ Diabetes: Type 1/Type 2 Insulin: Y/N Oral meds: Y/N Neuropathy: _____ □ CVD: HTN / ↑cholesterol / ↑TG / stroke / MI □ Liver Disease □ Renal Disease □ Gastroesophageal reflux disease/Hiatal Hernia □ Skin Breakdown/Wound Healing: Location: _____ □ Cancer: _____ □ Surgical Procedures: Other:
Occupation:	
Smoking Hx *(from pulmonary function test sheet)*	Pack years: Years Quit:

Labs (Date: _____)		3D-FIR given: mail / email / fax / call x 2 weeks
Calcium		
Vitamin D		

Study #:_____ Date:_____

Subjective Global Assessment Scoring Sheet

PART 1: MEDICAL HISTORY

1. WEIGHT CHANGE

A. Overall change in past 6 months: _____ kg / lb

B. Percent change: _____ gain - <5% loss
_____ 5 – 10% loss
_____ >10% loss

C. Change in past 2 weeks: _____ increase
_____ no change; normal weight
_____ no change; below usual weight
_____ decrease

2. DIETARY INTAKE

_____ no change, adequate
_____ no change, inadequate
_____ change (duration_____)

Current intake: _____ suboptimal or _____ full fluid
_____ hypocaloric liquid or _____ starvation
_____ Intake borderline; increasing
_____ Intake borderline; decreasing
_____ Intake poor; no change
_____ Intake poor; increasing
_____ Intake poor; decreasing

3. GASTROINTESTINAL SYMPTOMS (persisting for > 2 weeks)

Frequency: _____ nausea; _____ vomiting;
_____ diarrhea; _____ constipation;
_____ anorexia; _____ chewing/swallowing issues

_____ None
_____ Some (daily > 2weeks)
_____ All (daily > 2weeks)

4. FUNCTIONAL IMPAIRMENT (nutritionally related)

A. Overall impairment: _____ none
_____ moderate (difficulty ambulating/ ADLs)
_____ severe (bed/chair-ridden)

B. Change in past 2 weeks: _____ improved
_____ no change
_____ regressed+

C.

PART 2: PHYSICAL EXAMINATION

Evidence of: Loss of subcutaneous fat
Muscle wasting
Edema
Ascites

SGA Score		
A	B	C

PART 3: SGA RATING (check one)

Well-Nourished:		Mildy-Moderately Malnourished:			Severely Malnourished:	
□A	□A-	□B+	□B	□B-	□C+	□C-

Study # : _____ Date: _____

BodyStat Output (Test # _____)

If possible, the electrodes should be placed on **the right side** of the body.
Electrodes have been placed on: □ RIGHT □ LEFT
Indicate the logistical circumstances for electrodes be placed on the left side:
_____
(*Note*: Electrode placement should be on the SAME SIDE of the body as was used for the first measurement for subsequent measurements)
Presence of pacemaker or metal in body: □ YES □ NO
Is the patient lying flat? □ YES □ NO
If supine position is not possible, indicate the position when measurement is being taken
_____
(Note: If supine position is not possible, head of bed should be elevated to 30 degrees)
Treat results with caution? □ YES □ NO

Measure		Value	
Height (cm)			
Weight (kg)			
Age			
Body Fat	%		
	kg		
Lean body mass (kg)			
Total (kg)			
Dry			
Body Water	%		
	L		
Extracellular water			
Intracellular water			
Basal Metabolic Rate			
kcal/kg			
BMI			
BFMI			
FFMI			
Wellness Marker			
Impedance		5 kHz	50 kHz
Resistance			
Reactance			
Phase Angle			

Study # : _____ Date: _____

Quadricep Muscle Layer Thickness Ultrasound Output (Researcher initials: _____)					
	Length (cm)			**QMLT at Min Pressure (cm)**	
	Right	**Left**		**Right**	**Left**
ASIS to top of patella			*Mid-point*		
Midpoint distance from top of patella			*2/3 point*		
1/3 distance from top of patella			***Mean***		

Handgrip Strength			
Dominant hand: □ RIGHT □ LEFT Other Considerations:_____			
Left Hand		**Right Hand**	
Test 1		*Test 1*	
Test 2		*Test 2*	
Test 3		*Test 3*	
Mean		***Mean***	
Pop. mean +/- SD		*Pop. mean +/- SD*	

6-Min Walk Test (Date:_____)						
FiO_2	**SaO_2 (rest)**	**SaO_2 (exercise)**	**Distance (m)**	**Predicted (m)**	**Borg (rest)**	**Borg (exercise)**

Pulmonary function tests (Date:_____)			
	Predicted	**Actual**	**% Predicted**
FEV_1			
DLCO			
FVC			

Checklist:

□ Vitamin D and calcium requisition
□SGA
□ PFTs
□ 24-hr Recall
□ 3D-FIR given to participant (call x 2 weeks / email / mail / fax)
□ Medication and Supplement list

Appendix C: Bioelectrical Impedance Analysis Protocol

Bioelectrical Impedance Analysis Protocol

Adapted from the Body Composition Procedures Manual
(National Health Nutrition and Examination Survery 2000)

This dissertation research used the BodyStat® 1500MDD device which estimates body composition using multifrequency bioelectrical impedance analysis.

Figure 5 BodyStat ® 1500MD device

Protocol

Body Position

Position participant in a supine position (lying flat) with legs separated and arms away from the trunk of the body (See **Figure 6**). If the participant is unable to keep their arms and legs adequately separated, a towel can be placed between the legs or between the arm and the trunk to ensure separation through the test.

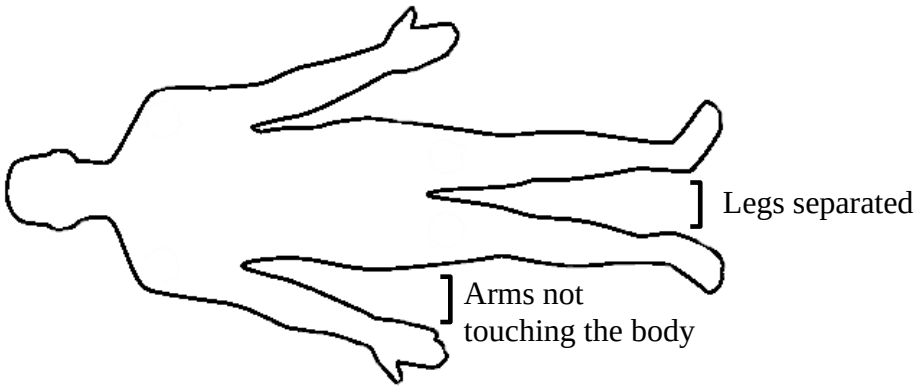

Figure 6 Proper body position

Electrode Placement

Two electrode pads are placed on each of the right hand and foot (**Figure 7**). Clean the surface of the hand and foot with an alcohol swap before placement of the electrode pads.

Right Hand: Place one pad on the surface of the top of the hand just before the knuckles. Place the second electrode sticker on the surface of the wrist along the midline of the ulnar bone (prominent bone on the outer side of the wrist).

Right Foot: Place one pad on the surface of the top of the foot just before the knuckles of the toes. Place the second electrode sticker on the surface of the ankle along the midline of the lateral malleoli (prominent bone on the outer side of the ankle).

Connect electrode leads (cords) to the BodyStat® device. Connect the black electrode lead to the electrode pad on the wrist/ankle using the alligator clip and connect the red electrode lead to the electrode pads closest to the fingers/toes using the alligator clip.

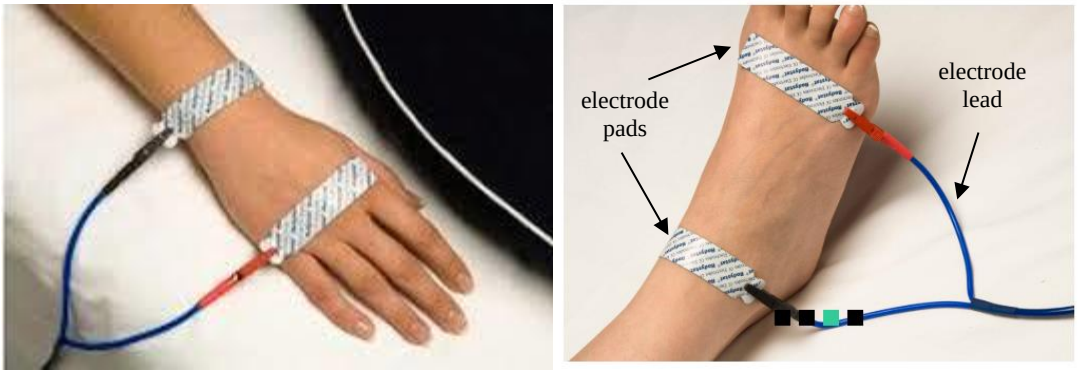

Figure 7 Electrode placement on right hand and foot (BodyStat 2017).

Data Input

Input the participants sex, age, height and weight into the device. Once the participant is in correct position and electrodes are properly set up, the test can be run. This should take approximately 5 seconds. Test results will appear on the screen. The test is complete and the electrodes and leads may be removed from the participant.

Appendix D: Mini Nutrition Assessment®

Mini Nutritional Assessment

MNA®

Nestlé Nutrition Institute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers. Total the numbers for the final screening score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F1 Body Mass Index (BMI) (weight in kg) / (height in m)^2 ☐
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2.
DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.

F2 Calf circumference (CC) in cm
0 = CC less than 31
3 = CC 31 or greater ☐

Screening score ☐☐
(max. 14 points)

12-14 points: ☐ Normal nutritional status
8-11 points: ☐ At risk of malnutrition
0-7 points: ☐ Malnourished

Save Print Reset

Ref. Vellas B, Villars H, Abellan G, et al. *Overview of the MNA® - Its History and Challenges.* J Nutr Health Aging 2006;10:456-465.
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. Geront 2001;56A: M366-377.
Guigoz Y. *The Mini-Nutritional Assessment (MNA®) Review of the Literature - What does it tell us?* J Nutr Health Aging 2006; 10:466-487.
Kaiser MJ, Bauer JM, Ramsch C, et al. *Validation of the Mini Nutritional Assessment Short-Form (MNA®-SF): A practical tool for identification of nutritional status.* J Nutr Health Aging 2009; 13:782-788.

For more information: www.mna-elderly.com

Appendix E: Research Project Proposal Abstract

Computed Tomography Scan Study Proposal

Interstitial lung disease (ILD) is a group of disorders that involve irritation and swelling of the tissue lining the lungs. Patients with ILD make up 26-44% of those that receive a lung transplant in Canada. A component of lung candidacy is patient body mass index, and often patients are required to lose weight in order to be listed for lung transplant. However, there is little information known about nutritional concerns of this patient population through disease progression or leading up to potential lung transplant. Thus, better understanding nutritional issues has the potential to impact patients' long-term outcomes. This study aims to address the question, is the amount of muscle mass at diagnosis and through disease progression an outcome indicator in ILD? The **primary** objective is to determine the prevalence of sarcopenia, or low muscle mass, and sarcopenic obesity in patients with ILD at diagnosis and through disease progression. The **secondary** objective is to examine if sarcopenia and sarcopenic obesity are associated with survival time. The **tertiary** objective is to determine if body fat and lean muscle mass measured by computed tomography imaging, in select cases, is correlated with measures of body composition assessed using BIA. The research team will review patient files from a previous pilot study. Previously completed CT-scans will be used to measure the amount of skeletal mass at various stages of ILD beginning at diagnosis. In select cases, muscle mass determined using CT-scans will be used to validate previously completed body composition measures via bioelectrical impedance analysis from the pilot study. This research addresses a large research potential regarding computed tomography imaging within the ILD/IPF patient population in the literature. As minimal information is known about the nutritional status of ILD patients, new and novel research is needed to understand this vulnerable patient population. It is hoped that the knowledge gained from the study will help health professionals proactively provide *best nutrition care* to their patients beginning at diagnosis.

This research is funded by the Ontario Respiratory Care Society Research grant.

Appendix F: Ethics Approval

Western Research

Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Janet Madill
File Number:104028
Review Level: Delegated
Approved Local Adult Participants:50
Approved Local Minor Participants:0
Protocol Title: Nutritional Status of Patients with Interstitial Lung Disease: A Cross-Sectional Study
Department & Institution: Brescia\Nutrition and Food Sciences,Brescia University College
Sponsor: Brescia Grant

Ethics Approval Date: September 25, 2013 **Expiry Date:**September 30, 2016
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Other	Reference list to 2.2.	2013/07/08
Western University Protocol		
Other	Recommended changes document completed. Version date is Aug	
Instruments	3-day food record document attached, as requested.	
Instruments	SGA form with identifiers removed, as requested.	
Recommendations Form	Recommendations	2013/08/14
Letter of Information & Consent	Final copy of LOI and consent form with letterhead	2013/08/16

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Ethics Officer to Contact for Further Information

Erika Basile	Grace Kelly	Vikki Tran
[redacted]	[redacted]	[redacted]

This is an official document. Please retain the original in your files.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6A 3K7 [redacted] www.uwo.ca/research/services/ethics

*Included above is the initial ethics approval notice, however, since this was obtained, multiple amendments applications have been made and approved to increase sample size, add new assessment techniques (not included in this research), and to extend study length.

Appendix G: Study Timeline and Data Collected

Research Timeline

September 2013	*Commencement of study* • Ethics approval was received from The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) on September 25th, 2013.
October 2013	*Recruitment of subjects and data collection*
May 2016	*Additional study parameters added* • hand-grip strength • quadricep muscle layer thickness via ultrasound technology
January 2019	*Data analysis* • Participants recruited up until January 2017 (to allow for 2-year survival time) used in data analysis • Recruitment on-going related to hand-grip strength and quadricep muscle layer thickness data collection

Data Collected

During clinic visit

- Bioelectrical impedance analysis*
- Subjective global assessment*
- 24-hr recall
- Handgrip strength and quadricep muscle layer thickness (added May 2016)

Outside of clinic visit

- 3-day food intake record (obtained by phone, e-mail, mail or fax)

Review of patient charts

- Height*
- Weight*
- Age*
- Specific diagnosis*
- Time from diagnosis*
- Pulmonary function tests*
- 6-min walk distance*
- Medications*
- Comorbidities

*included in this dissertation's research

Curriculum Vitae

Sylvia Rinaldi, RD, MScFN
PhD (candidate)

EDUCATION

PhD candidate in Health and Rehabilitation Sciences with focus in Health & Aging Sept 2015 – April 2020
Western University, London ON
Thesis: Influence of nutrition status and body composition on exercise capacity and survival among individuals with interstitial lung disease
Supervisors: Janet Madill, RD, PhD & Jason Gilliland, PhD
Co-investigator: Dr. Marco Mura, MD, PhD

MSc in Foods & Nutrition (Internship Stream) Sept 2013 – Apr 2015
Brescia University College at Western University, London ON

BScFN Honours Specialization in Nutrition & Dietetics with distinction Sept 2011 – Apr 2013
Brescia University College at Western University, London ON

BSc Honours Biochemistry Sept 2007 – Apr 2011
University of Windsor, Windsor ON

CERTIFICATIONS & SPECIALIZED TRAINING

- Member of the College of Dietitians of Ontario (Registration # 14090)

RESEARCH AND ACADEMIC INTERESTS

- nutritional assessment
- interstitial lung disease (ILD)
- pulmonary hypertension (PH)
- body composition
- sarcopenia
- phase angle as a nutritional indicator

AWARDS, DISTINCTIONS AND FUNDING

- Dean's Honor Roll of Teaching 2015-2016, 2017-2018
  School of Food and Nutritional Sciences, Brescia University College

Sept 2018	$16,000	Ontario Respiratory Care Society (ORCS) Research Grant *Primary Investigator* "Use of computed tomography to assess muscle mass in patients with interstitial lung disease at diagnosis and through disease progression: a retrospective pilot study".
Sept 2018	$6,955.25	ORCS Fellowship Award

May 2018	$15,000	Ontario Graduate Scholarship (OGS)
Sept 2017	$9,179	ORCS Fellowship Award
June 2017	$10,000	Paroian Family Pulmonary Hypertension Association (PHA) Canada PH Research Award
May 2017	$15,000	OGS
Jan 2016	$10,000	Paroian Family PHA Canada PH Research Award
Sept 2016	$10,000	ORCS Fellowship Award

TEACHING

Sessional Contract Faulty
Division of Foods and Nutritional Sciences, Brescia University College

- Nutrition through the Lifecycle (FN1241B) — Winter 2020
- Nutritional Assessment (FN3344A) — Fall 2019
- Nutrition through the Lifecycle (FN2241B) — Winter 2018 & 2019
- Clinical Nutrition I (FN3351A) — Fall 2015 & 2016

PROFESSIONAL EXPERIENCE

Clinical Inpatient Dietitian November 2018 – present
St. Thomas Elgin General Hospital, St. Thomas ON

- Provide comprehensive nutritional care to adult and pediatric patients including implementing and monitoring nutrition support (EN and PN) and counsel patients to meet their individual nutritional needs

Research Assistant/Registered Dietitian May 2015 – August 2018
Human Environments Analysis Laboratory, Western University *Supervisor: Dr. Jason Gilliland*

- As a registered dietitian, approved message content for credibility, accuracy and readability for the Smart APPetite research project and facilitated focus groups pilot testing adolescent-focused massages
- Applied nutrition expertise through involvement preparing funding applications and dissemination

PUBLICATIONS

PEER REVIEWED *Cited by: 57*

1. **Rinaldi S**, Gilliland J, O'Connor C, Chesworth B, Madill J. Is phase angle an appropriate indicator of malnutrition in different disease states? A systematic review. Clinical Nutrition European Society for Parenteral and Enteral Nutrition. 2019;29:1-14. doi:https://doi.org/10.1016/jclnesp.2018.10.010.
   - Involved in manuscript conception, preparation, submission & revisions (85% contribution)
   - Cited by: 4

2. Tulsieram K, **Rinaldi S** & Shelley J. Recommendations: Will the Tobacco and Vaping Products Act go Far Enough? 2017;108(3). Canadian Journal of Public Health. doi:10.17269/cjph.108.6039.
    - Responsible for reviewing and editing manuscript (5% contribution)
    - Cited by: 3

3. **Rinaldi S**, Horne J, Madill J. An evolving understanding of modifiable risk factors for post-transplant mortality. 2017. Transpl Int. 2017;30(5):533-4. doi:10.1111/tri.12938.
    - Manuscript preparation, submission & revisions (90% contribution)
    - Cited by: 1

4. **Rinaldi S**, Mura M, Madill J. Interstitial Lung Disease, Body Mass Index, Energy Expenditure and Malnutrition – a Review. Curr Pulmonol Rep. 2017;6(1):70-4. doi:10.1007/s13665-017-0168-x.
    - Involved in manuscript conception, preparation, submission & revisions (85% contribution)
    - Cited by: 4

5. Horne J, O'Connor C, Madill J, **Rinaldi S**, Gilliland J. Re: "Polymorphisms of three genes (ACE, AGT and CYP11B2) in the renin-angiotensin-aldosterone system are not associated with blood pressure salt sensitivity: a systematic meta-analysis". Blood Pressure. 2016. doi:10.1080/08037051.2016.1270164.
    - Responsible for reviewing and editing manuscript (5% contribution)
    - Cited by: 3

6. **Rinaldi S**, Campbell E, Fournier J, O'Connor C, Madill J. A Comprehensive Review of the Literature Supporting Recommendations From The Canadian Diabetes Association for the Use of a Plant Based Diet for Type 2 Diabetes Management. Canadian Journal of Diabetes. 2016;40(5):471-7. doi:10.1016/j.jcjd.2016.02.011.
    - Responsible for manuscript conception, development, manuscript preparation, submission & revisions (60% contribution)
    - Cited by: 42