SARCOPENIA AMONG MALAYSIAN PERITONEAL DIALYSIS PATIENTS USING BIO-ELECTRICAL IMPEDANCE ANALYSIS-DERIVED PHASE ANGLE IN A TERTIARY HOSPITAL IN THE KLANG VALLEY, MALAYSIA

By

LEE SHI WAH

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

May 2024

FPSK (m) 2024 11

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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Sarcopenia, characterized by the simultaneous reduction in both muscle mass and function, is prevalent among individuals undergoing peritoneal dialysis (PD). Early detection is vital, but universal screening in this population is often hindered by the intricate diagnostic algorithm and limited clinical resources. Phase angle (PhA), a parameter derived from bioelectrical impedance analysis (BIA), has emerged as a surrogate measure for identifying sarcopenia in various populations, but its validation in PD patients particularly in Southeast Asian population like Malaysia, is lacking. Hence, this study aimed to investigate the ability of PhA, a non-invasive and cost-effective measure, in detecting sarcopenia among Malaysian PD patients. This was a single-center cross-sectional study conducted among 130 multi-ethnic PD patients in a tertiary government hospital in Klang Valley, Malaysia. Malaysian outpatients aged ⩾18 years, who have been undergoing regular PD treatment for at least six months, free of terminal disease, recent history of infection, surgery or trauma, or any condition

that could bias the study findings were consecutively recruited. Sarcopenia was assessed in complete adherence to the Asian Working Group for Sarcopenia (AWGS) 2019 diagnostic algorithm, encompassing the evaluation of muscle mass, muscle strength, and physical performance. PhA was assessed using a multi-frequency BIA at 50kHz. Nutrition status was evaluated by anthropometric measurement, BIA, and a 3-day diet history, whereas sociodemographic characteristics were collected via face-to-face interviews. Statistical analysis was performed by using Statistical Package for Social Sciences software version 26.0. Multivariable logistic regression was used to determine the predictability of PhA on sarcopenia. Receiver operating characteristics (ROC) analysis was employed to assess the diagnostic accuracy of PhA in identifying sarcopenia. Optimal PhA cut-off value for sarcopenia detection was established based on desired sensitivity and specificity. Demographic characteristics of the subjects aligned with national data reflecting a representative sample. The subjects had an average age of 53.1 years, with 50.8% male and 49.2% female. The majority were Malays (68.5%), followed by Chinese (26.2%), and Indians (5.4%). Most subjects were married, unemployed, held secondary-level education, and belonged to the bottom 40% household income category. The median dialysis vintage and Kt/V were 26.5 months and 1.9, respectively. Sarcopenia was evident in 25.4% of PD patients according to the AWGS 2019 criteria. PhA emerged as an independent predictor of sarcopenia (adjOR=0.153; 95% CI = 0.044-0.457; p =0.003), with a lower reading observed in sarcopenic group than non-sarcopenic group (3.28° ± 0.80 versus 4.05° ± 0.94, p <0.001). Based on ROC analysis, PhA exhibited acceptable discriminative power in identifying sarcopenia in the raw model (AUC = 0.736; 95% CI: 0.639-0.832, p<0.001), and demonstrated excellent discriminative power after adjusting for covariates (adjAUC = 0.818; 95% CI: 0.737-0.899, p<0.001). The optimal PhA cut-

off value for sarcopenia detection in PD patients was ≤3.95° (81.8% sensitivity and 52.6% specificity). In conclusion, sarcopenia is pervasive in Malaysian PD patients. PhA holds promise as a pragmatic screening tool for identifying multi-ethnic Malaysian PD patients at risk of sarcopenia.

Keywords: Bioelectrical Impedance Analysis, Peritoneal Dialysis, Phase Angle, Sarcopenia

SDG: Goal 3: Good Health and Well-Being

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

SARKOPENIA DALAM KALANGAN PESAKIT DIALISIS PERITONEAL MALAYSIA BERDASARKAN SUDUT FASA ANALISIS IMPEDANS BIOELEKTRIK DI HOSPITAL TERTIARI LEMBAH KLANG, MALAYSIA

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Sarkopenia, yang dicirikan oleh pengurangan serentak jisim dan fungsi otot, adalah lazim dalam kalangan individu yang menjalani dialisis peritoneal (PD). Pengesanan awal adalah penting, tetapi saringan universal dalam populasi ini sering terhalang oleh algoritma diagnostik yang rumit dan sumber klinikal yang terhad. Sudut fasa (PhA), yang merupakan sebahagian daripada analisis impedans bioelektrik (BIA), muncul sebagai proksi untuk mengenalpasti sarkopenia dalam pelbagai populasi, tetapi pengesahannya dalam pesakit PD terutamanya dalam populasi Asia Tenggara seperti Malaysia, masih tidak mencukupi. Oleh itu, kajian ini bertujuan untuk mengenalpasti kebolehan PhA, suatu ukuran yang tidak invasif dan berkos efektif, dalam mengesan sarkopenia di kalangan pesakit PD Malaysia. Ini adalah kajian keratan rentas tunggal yang dijalankan dalam kalangan 130 pesakit PD pelbagai etnik di sebuah hospital tertier kerajaan di Lembah Klang, Malaysia. Pesakit berusia $\geqslant$ 18 tahun yang menjalani rawatan PD secara tetap selama sekurang-kurangnya enam bulan, bebas dari penyakit terminal, sejarah jangkitan, pembedahan atau trauma kebelakangan ini, atau

sebarang keadaan yang boleh menjejaskan dapatan kajian, telah diambil secara berturutan. Sarkopenia dinilai dengan pematuhan penuh kepada algoritma diagnostik *Asian Working Group for Sarcopenia* (AWGS) 2019, merangkumi penilaian jisim otot, kekuatan otot, dan prestasi fizikal. PhA dinilai dengan menggunakan BIA multi-frekuensi pada 50kHz. Status pemakanan dinilai melalui pengukuran antropometrik, BIA, dan sejarah pemakanan 3 hari, manakala ciri sosiodemografi dikumpulkan melalui temubual bersemuka. Analisis statistik dilakukan dengan mengguna perisian Statistical Package for Social Sciences versi 26.0. Regresi logistik multivariabel digunakan untuk menentukan keupayaan PhA dalam meramal sarkopenia. Analisis ciri operasi penerima (ROC) digunakan untuk menilai ketepatan diagnostik PhA dalam mengenalpasti sarkopenia bagi kalangan pesakit PD. Nilai ambang PhA optimum untuk pengesanan sarkopenia ditetapkan berdasarkan sensitiviti dan spesifisiti yang dikehendaki. Ciri demografi subjek adalah sejajar dengan data kebangsaan dan mencerminkan populasi yang diwakili. Subjek mempunyai purata umur 53.1 tahun, dengan taburan jantina 50.8% lelaki dan 49.2% perempuan. Kebanyakan adalah Melayu (68.5%), diikuti oleh Cina (26.2%), dan India (5.4%). Majoriti subjek telah berkahwin, menganggur, memiliki pendidikan peringkat sekolah menengah, dan tergolong dalam kategori pendapatan isi rumah 40% terbawah. Median tempoh dialisis dan Kt/V bagi subjek masing-masing adalah 26.5 bulan dan 1.9. Seramai 25.4% pesakit PD didapati mengalami sarkopenia berdasarkan kriteria AWGS 2019. PhA muncul sebagai peramal bebas sarkopenia (adjOR=0.153; 95% CI = 0.044-0.457; p =0.003), dengan bacaan lebih rendah diperhatikan dalam kumpulan sarkopenik berbanding kumpulan bukan sarkopenik (3.28° ± 0.80 berbanding 4.05° ± 0.94, p <0.001). Berdasarkan analisis ROC, PhA menunjukkan kuasa pembezaan yang boleh diterima dalam mengenalpasti sarkopenia dalam model asal (AUC = 0.736; 95%

CI: 0.639-0.832, p<0.001), dan menunjukkan kuasa pembezaan yang sangat baik selepas pelarasan kovariat (adjAUC = 0.818; 95% CI: 0.737-0.899, p<0.001). Nilai ambang PhA yang optimum untuk pengesanan sarkopenia dalam kalangan pesakit PD adalah ≤3.95° (81.8% sensitiviti dan 52.6% spesifisiti). Secara keseluruhan, masalah sarkopenia adalah meluas dalam kalangan pesakit PD di Malaysia. PhA dapat digunakan sebagai alat saringan pragmatik untuk mengenalpasti pesakit PD Malaysia daripada pelbagai etnik yang berisiko terhadap sarkopenia.

Keywords: Analisis Impedans Bioelektrik, Dialisis Peritoneal, Sarkopenia, Sudut Fasa

SDG: MATLAMAT 3: Kesihatan yang Baik and Kesejahteraan

ACKNOWLEDGEMENTS

Foremost, I extend my deepest appreciation to Assoc. Prof. Dr. Zulfitri Azuan Mat Daud, my esteemed supervisor, and Prof. Dr. Chan Yoke Mun, my co-supervisor. Their continuous support and guidance have been the cornerstone of my master's study journey. Their expertise, mentorship, and encouragement have not only shaped the trajectory of this research but have also contributed significantly to my academic growth.

The insightful comments and invaluable assistance in the arrangement of the study collection process provided by Dr. Nor Fadhlina Zakaria and Dr. Fairol Huda Ibrahim, both esteemed Nephrologists, deserve special mention. Their expertise has significantly enriched the quality of this study.

I am indebted to the invaluable contributions of my mentors in my master study, Mr. Lim Jun Hao Lim and Ms. Cordelia Lim Kheng May. Their substantial insights into conceptual design and statistical analyses have been pivotal. Beyond the academic realm, their continuous mental support and motivation have been a source of strength throughout this process.

Next, a heartfelt thank you is extended to the patients, dedicated nurses and staff at the Peritoneal Dialysis Unit of Hospital Sultan Idris Shah Serdang, for being cooperative and supportive throughout the data collection process. A special mention goes to Ms. Imliya Ibrahim, Ms. Nuha Ismail, and Ms. Cordelia Lim Kheng May, for their dedicated assistance in the data collection phase. I would also like to extend my sincere

gratitude to all my dietitian colleagues in the Dietetic and Food Service Department at Hospital Sultan Idris Shah Serdang for their support during my study journey.

Last but not least, to my parents, my husband, and my daughters, I owe an immeasurable debt of gratitude. Their unwavering support and understanding during this tight-scheduled journey have been my driving force. Without their unconditional love and sacrifice, this academic pursuit would not have been possible.

In conclusion, this journey has been enriched by the collaborative spirit and support of these individuals. I extend my deepest thanks to each one of you for being an integral part of this academic expedition.

This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

CKD	Chronic kidney disease
5TCST	5-time chair stand test
6mWT	6-meter walk test
ARB	angiotensin 2 receptor blocker
ASM	appendicular skeletal muscle mass
ASMI	appendicular skeletal muscle mass index
AUC	area under curve
AUROC	area under receiver operating characteristic curve
AWGS	Asian Working Group for Sarcopenia
BCAA	branched-chain amino acid
BFM	body fat mass
BFP	body fat percentage
BIA	bioelectrical impedance analysis
BMI	body mass index
BMI	Body Mass Index
CAPD	continuous ambulatory peritoneal dialysis
CC	calf circumference
CT	computed tomography
DPI	dietary protein intake
DXA	Dual-energy X-ray absorptiometry
EAA	essential amino acid
ECW	extracellular water
ECW/TBW	extracellular water/ total body water
ESRD	end-stage renal disease
EWGSOP	European Working Group on Sarcopenia for Older People

FFM	fat-free mass
FNIH	Foundation for the National Institutes of Health
GFR	glomerular filtration rate
HD	hemodialysis
HGS	Handgrip strength
HIV	human immunodeficiency virus
HMB	β-hydroxy-β-methylbutyrate
HR	hazard ratios
IBW	ideal body weight
ICW	intracellular water
IQR	Interquartile Range
ISAK	International Society of Advancement in Kinanthropometry
ISRNM	International Society of Renal Nutrition and Metabolism
IWGS	International Working Group on Sarcopenia
MDTR	Malaysian Dialysis and Transplant Registry
MFBIA	multi-frequency BIA
MRI	Magnetic resonance imaging
MUAC	Mid-upper arm circumference
NMRR	Ethics Committee of the National Medical Research Register
PD	peritoneal dialysis
PEW	protein-energy wasting
PhA	phase angle
PPE	personal protective equipment
QoL	quality of life
R	resistance
ROC	receiver operating characteristic

SFBIA	single-frequency BIA
SMM	skeletal muscle mass
SMMI	skeletal muscle mass index
SOP	standard operating procedures
SOP	standard operating procedures
SPPB	Short Physical Performance Battery
SSCWD	Society of Sarcopenia, Cachexia and Wasting Disorder
TBW	total body water
TEI	total energy intake
TIBC	total iron binding capacity
Xc	reactance

CHAPTER 1

INTRODUCTION

1.1 Background

Chronic kidney disease (CKD) is a disease characterized by progressive and irreversible loss of kidney function, that presents for at least three months (Levin et al., 2013). It constitutes a major global public health issue, with a prevalence of 13.4% among the world population (Hill et al., 2016). CKD represents the 12th leading cause of death in 2017, and it is projected to rise to the fifth position by 2040 (Kovesdy, 2022). In Malaysia, the prevalence of CKD has increased significantly by 70.7%, from 9.1% in 2011 to 15.5% in 2018 (Saminathan et al., 2020), making it the 6th leading cause of mortality in the country (Institute for Health Metrics and Evaluation, 2021).

CKD is primarily categorized into five stages based on the results of estimated glomerular filtration rate (GFR) derived from endogenous renal function markers, such as serum creatinine (Levin et al., 2013). As the disease advances, the GFR gradually decreases, and once it falls below the threshold of 15 ml/min/1.73m^2, the disease reaches its final stage known as end-stage renal disease (ESRD). This detrimental health issue affects more than 5 million people worldwide and is on the rise, attributed to the increased prevalence of diabetes mellitus, hypertension, obesity, and aging (Lv & Zhang, 2019). Based on the annual report of the United States Renal Data System (United States Renal Data System, 2018), Malaysia was ranked as the eighth country for having the highest incidence rate of treated ESRD in 2016, and the fifth country for showing the greatest increase in ESRD incidence between 2003 and 2016. Due to limited opportunities for transplant, renal replacement therapy, including

hemodialysis (HD) and peritoneal dialysis (PD), represents the mainstream treatment for approximately 98.7% of ESRD in Malaysia (Ministry of Health Malaysia, 2018). According to the 29th report of the Malaysian Dialysis and Transplant Registry in 2021 (MDTR 2021), the number of patients receiving dialysis treatment in Malaysia has increased by 1.9 times over the past 10 years, from 26,480 patients in 2011 to 49,770 patients in 2021 (Hooi & Ong, 2023).

PD is a medical treatment that utilizes the peritoneum to filter waste and excess fluids from the blood when the kidneys are no longer able to function normally. Dialysate is introduced into the peritoneal cavity through a catheter placed in the abdomen, which flows through the peritoneum and removes waste and extra fluid from the blood. The cycle is repeated several times a day and can be done manually or with automation, either at home or in a medical facility. Compared to HD, PD has several advantages, including greater autonomy for patients, better preserves residual kidney function, gentler on the cardiovascular system and lower treatment cost (François & Bargman, 2014). Studies have shown that patients receiving PD treatment demonstrated better satisfaction and quality of life than patients receiving HD treatment (Flanagin et al., 2020; Tao et al., 2021). As such, PD-preferred policy has been adopted by numerous countries (Moura-Neto et al., 2021). For example, China is expecting an annual growth rate of 5.56% for PD uptake from 2015 to 2025 (Sun et al., 2016), whereas the United States is aiming to increase PD treatment from 10% to 50% by 2025 (Flanagin et al., 2020). Similar trend was observed in Malaysia, whereby the PD uptake rate of new dialysis patients had increased by 79% between 2011 and 2021 (Hooi & Ong, 2023). The overall PD uptake rate was reported at 11.7% in 2021, with the Malaysian government aiming to increase it to 30% by 2025 (Ministry of Health Malaysia, 2020).

Therefore, it can be anticipated that in the near future, the number of PD patients, and subsequently the workload of PD clinics, will significantly increase.

Kidney failure is a highly catabolic condition accompanied by anorexia and exacerbated by protein loss during treatment. As a result, dialysis patients are at increased risk of nutrition-related disorders, including a condition called sarcopenia, which has received growing attention in recent years (Shu et al., 2022). Sarcopenia, granted with International Classification of Diseases code, is a progressive and generalized skeletal muscle disorder (Cruz-Jentoft et al., 2019), characterized by a decline in skeletal muscle mass, strength and function (L. K. Chen et al., 2020).

This issue is prevalent among patients undergoing PD, secondary to multiple predisposing factors, including chronic inflammation, hormone derangement, dialysate nutrient loss, and nutrition insufficiency resulting from dietary restriction and anorexia (Sabatino et al., 2020). Previous studies have reported a prevalence range of 10.0-32.1% for sarcopenia in this population (Y. Chen et al., 2022; M. Z. C. da Silva et al., 2019; Davenport, 2022a; Do et al., 2021b). Evidence from dialysis papulations shows that sarcopenia is associated with depression, disability, reduced quality of life, increased fall risk, increased morbidity and mortality (Chatzipetrou et al., 2022; Sabatino et al., 2020). Additionally, it is linked to a significant rise in healthcare expenses as a result of loss of independence and frequent hospitalization (Lo et al., 2017).

1.2 Problem Statement

Early identification and intervention represent the cornerstone of sarcopenia treatment (Cruz-Jentoft et al., 2019). However, detecting sarcopenia can be challenging as it may not manifest in the physical appearance and laboratory findings, often leading to oversight by clinicians (Cruz-Jentoft & Sayer, 2019). Therefore, periodic universal screening with comprehensive diagnostic algorithm is essential to detect sarcopenia.

The Asian Working Group for Sarcopenia (AWGS) proposed a protocol for diagnosing sarcopenia in Asians. However, its applicability is limited due to the complexity of its diagnostic algorithm, and the requirement for additional manpower, equipment and set-up. For example, the appendicular skeletal muscle mass index (ASMI), a necessary parameter for sarcopenia diagnosis, may not be available on certain models of bioelectrical impedance analysis (BIA) and multi-frequency BIA (MFBIA) devices. Although being non-invasive, AWGS assessment is not entirely safe as it poses a risk of falling during the physical test. Besides, AWGS protocol is not applicable to certain patient groups, such as those who are unable to conduct physical tests (i.e., amputation, arthritis, etc.) or follow test instructions (i.e., language barrier, mental disorders and cognitive impairment).

Noteworthily, PD is a fundamentally self-care dialysis modality that requires independent functional capabilities. As such, it is imperative for PD patients to prevent sarcopenia and sustain physical independence in order to continue PD treatment (Tao et al., 2021). Moreover, given that PD is a home-based dialysis treatment with fewer clinic visits, the universal screening of sarcopenia may be more challenging for PD patients compared to HD patients.

The role of dietitians is crucial in the assessment and treatment of nutrition status-related issues, including the identification of sarcopenia. However, their effectiveness is often hampered by a shortage of dietitians, a prevalent issue in middle-income countries. This shortage has led to 44-57% of dietitians in these regions reportedly being unable to conduct formal nutritional assessments for their renal patients (A. Y. M. Wang et al. 2022). As a middle-income country, Malaysia is not exempt from this problem. Although specific data for PD patients are lacking, the findings reported by Khor et al. (2018) regarding the inadequate availability of dietitians for HD outpatients can be considered a relevant reference. Due to the above-mentioned challenges, sarcopenia identification and treatment is currently not standard care for Malaysian PD patients. Furthermore, the expected increase in PD uptake (from 11.7% in 2021 to 30% in 2025) will further challenge the availability of dietitians for this population (Ministry of Health Malaysia, 2020). Therefore, finding a convenient alternative for sarcopenia detection is of great significance.

BIA is a convenient and reliable technology for estimating body composition and hydration status. BIA devices are commonly available in clinical settings for routine hydration and nutrition monitoring in dialysis patients. The BIA-derived phase angle (PhA), a raw impedance parameter that is determined by the ratio of reactance (Xc) and resistance ®, is unique in its correlation with cell mass, cell function and cellular integrity. Therefore, PhA has been considered as a useful surrogate for muscle mass and strength (Norman et al., 2012; Sardinha, 2018).

Notably, the European Working Group on Sarcopenia in Older People (EWGSOP) Consensus 2019 has identified PhA as one of the potential markers for sarcopenia,

expecting it to guide sarcopenia intervention strategies in the future (Cruz-Jentoft et al., 2019). While growing evidence supports the use of PhA as a prognostic indicator in various populations, but the evidence in PD patients is limited (Di Vincenzo et al., 2021). PhA is a parameter influenceable by medical background and ethnicity, as evidenced by the wide range of PhA cut-off values (from 3.55° to 5.60°) suggested for sarcopenia detection in different diseased populations and ethnicity groups (Hirose et al., 2020; Kosoku et al., 2020; Ruiz-Margáin et al., 2021; Yamada et al., 2019). Therefore, PhA cut-off values obtained from other populations could not be extrapolated to PD patients.

Despite two recent studies that examined the relationship between PhA and sarcopenia among PD patients, both studies used an older version of the AWGS algorithm to diagnose sarcopenia (Y. Chen et al., 2022; Do et al., 2021a). The importance of using an up-to-date consensus for diagnosing sarcopenia was underscored by a study that evaluated the sarcopenia prevalence across two versions of diagnostic algorithm from the EWGSOP. This study discovered a 150% variation in sarcopenia prevalence in the same group of PD patients (M. Z. C. da Silva et al., 2019).

Furthermore, there is a lack of evidence from Southeast Asian countries with diverse ethnicities. Ethnicity is a proven factor that affects PhA. Based on a national health survey conducted in the United States, Kuchnia et al. (2022) found that PhA is significantly different by ethnicity, with Hispanic and Black populations showing higher values than other ethnicities. Similarly, PhA was found to differ significantly between ethnicities in a local study among HD patients (C. K. M. Lim et al., 2021). Since PhA is heavily influenced by body composition, the relationship between

ethnicity and PhA could be attributed to differences in body composition between ethnic groups (Jaremków et al., 2021; Ravindranath et al., 2016). Yoowannakul et al. (2018) reported that sarcopenia prevalence in PD patients was affected by ethnicity, with muscle mass in Asians being significantly lower than in non-Asians. Additionally, body composition was found to differ significantly even among Asians from different regions, namely Southeast Asia, East Asia, and South Asia (T. D. Wang et al., 2010). Besides the ethnic makeup, lifestyle differences are another regional factor that could lead to variations in PhA and sarcopenia prevalence. For example, Jaremków et al. (2021) showed that PhA was significantly associated with dietary and physical activity patterns in young people. Moreover, the association between physical activity levels and PhA was supported by a meta-analysis (Mundstock et al., 2019).

Overall, it is evident that PhA and sarcopenia are affected by regional factors such as ethnic makeup and lifestyle. Malaysia, in particular, has a distinct ethnic composition and lifestyle patterns that could affect PhA performance, muscle mass, and function (C. K. M. Lim et al., 2021; Mundstock et al., 2019; T. D. Wang et al., 2010). Therefore, previous findings from other populations may not be reliably extrapolated to this population.

1.3 Significance of the Study

Sarcopenia is a severe and often underdiagnosed disease due to the complexity of existing diagnostic algorithms and limited healthcare resources. This study, to the best of our knowledge, is the first from a Southeast Asian country investigating the ability of BIA-derived PhA in predicting sarcopenia among PD patients. Furthermore, the study defines sarcopenia in full compliance with the latest AWGS 2019 diagnostic

algorithm. As such, this study offers valuable information on the optimal PhA cut-off for the early identification of sarcopenia among PD patients in Malaysia.

Given that PhA can be easily assessed, and readily available from the existing BIA records of routine hydration and nutrition status monitoring, it could serve as a pragmatic marker in sarcopenia detection. The study findings could facilitate sarcopenia detection in clinical setting, allowing early identification and treatment, thereby improving treatment outcomes and survival of PD patients and ultimately reducing healthcare costs associated with this disorder. This study is especially pertinent to the dietetic field, considering the shortage of dietitians is a major limitation in the nutrition care process in many countries, including Malaysia (A. Y. M. Wang et al., 2022; Khor et al. 2018). Due to the differences between dietary treatment for sarcopenia and other nutrition status-related issues, a convenient yet accurate detection of sarcopenia would allow dietitians to provide patients with more targeted and accurate dietary advice to combat this far-reaching health issue. This study is particularly relevant given the anticipated increase in the number of PD patients in Malaysia due to the PD-preferred policy, which could create additional strain on the healthcare workforce responsible for providing PD care. Besides, this study aligns with the Strategic Framework of Medical Programme 2021-2025 of Ministry of Health Malaysia, which encourages the use of health technology assessment as a tool for decision and policy-making process toward value-based healthcare, and emphasizes optimizing care of dialysis patients (Ministry of Health Malaysia, 2020).

Furthermore, as the first study investigating sarcopenia prevalence among Malaysian PD patients, the study's outcome could play a crucial role in shaping future healthcare

policy-making process. For instance, it may contribute to the inclusion of routine sarcopenia assessment and treatment in clinical practice guidelines and medical nutrition therapy guideline. Given the scarcity of local studies on the PD population, this research is timely, especially in conjunction with the implementation of PD-preferred policy in Malaysia.

1.4 Research Questions

1. What are the sociodemographic characteristics, clinical features, nutritional status and PhA of PD patients, both overall and stratified by sarcopenia status?
2. What is the prevalence of sarcopenia among PD patients?
3. Can PhA significantly predict sarcopenia among PD patients?
4. What is the optimal population-specific PhA cut-off value to detect sarcopenia among Malaysian PD patients?

1.5 Research Objective

1.5.1 General Objective

To assess sarcopenia among Malaysian PD patients using BIA-derived PhA.

1.5.2 Specific Objective

1. To determine the sociodemographic characteristics, clinical features, nutritional status and PhA of PD patients, both in the overall population and stratified by sarcopenia status.
2. To determine the prevalence of sarcopenia among PD patients.

3. To assess whether PhA can significantly predict sarcopenia among PD patients.

4. To establish a population-specific PhA cut-off value with acceptable discriminative power for sarcopenia detection among Malaysian PD patients.

1.6 Research Hypothesis

Specific objective 3 and 4 involve hypothesis testing, with the tested hypotheses as follows:

1. PhA can significantly predict sarcopenia among Malaysian PD patients.

2. The established PhA cut-off value will have significant acceptable discriminative power to detect sarcopenia among Malaysian PD patients.

1.7 Conceptual Framework

Figure 1.1 depicts the conceptual framework of the study, which encompasses three main parts. The first part describes the patients' characteristics in the overall population (independent variables) and when stratified by sarcopenia status (dependent variable), as stated in objective 1. The second part displays the sarcopenia prevalence in study population (objective 2). The third part involves hypothesis testing to determine whether PhA can significantly predict sarcopenia among PD patients (objective 3) and to establish an optimal PhA cut-off for sarcopenia detection (objective 4).

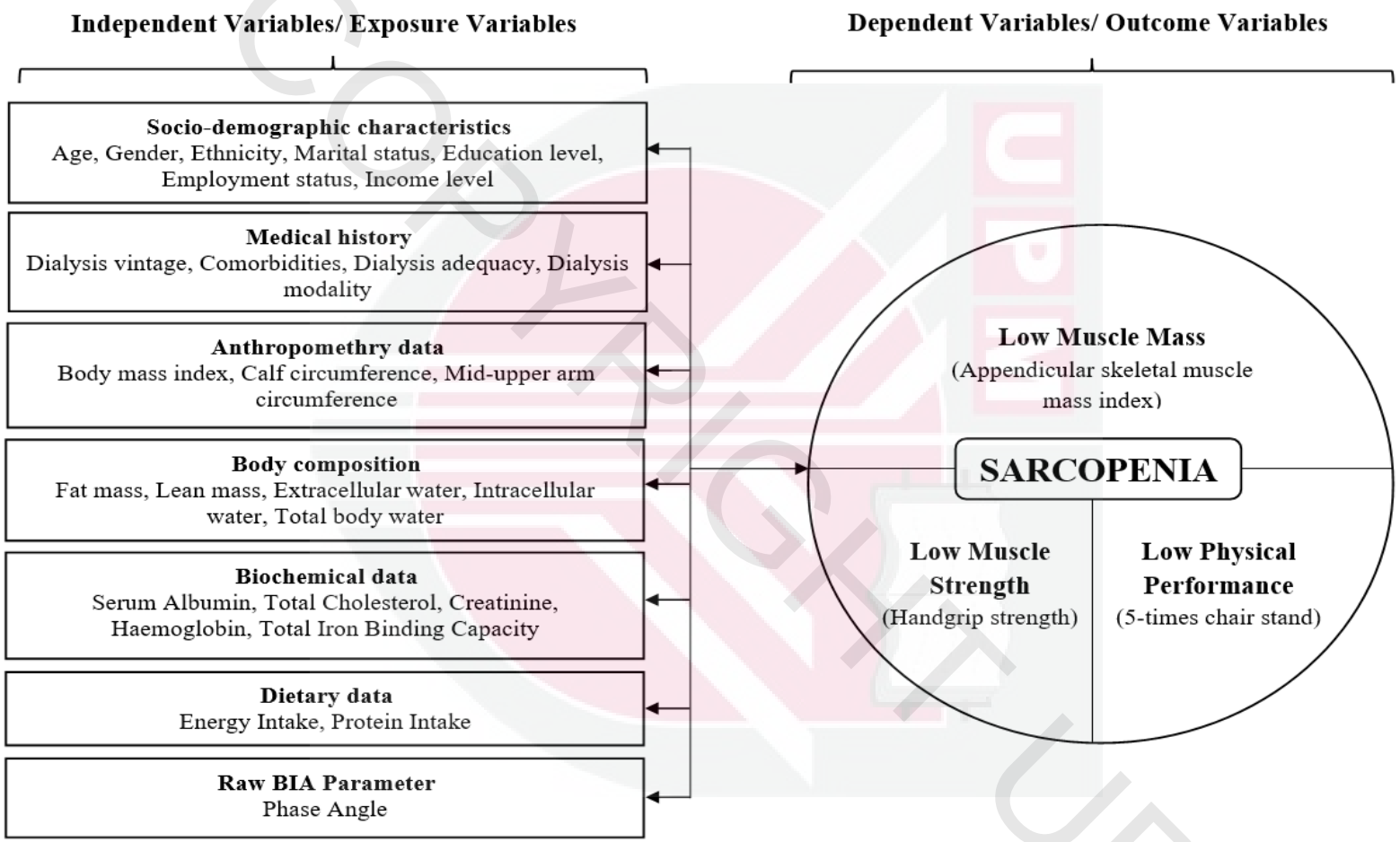


Figure 1.1 : Conceptual Framework of the Study

CHAPTER 2

LITERATURE REVIEW

2.1 Sarcopenia in PD Patients

2.1.1 Background and Definition of Sarcopenia

Sarcopenia is a progressive and generalized skeletal muscle disorder (Cruz-Jentoft et al., 2019), characterized by a decline in skeletal muscle mass along with low muscle strength and/or low physical performance (L. K. Chen et al., 2020). The evolution of sarcopenia definition can be traced through three significant milestones. The first milestone occurred in the 1980s when Irwin Rosenberg introduced the term "sarcopenia" to solely represent the age-associated loss of muscle mass. The term, derived from the Greek words "sarx" for flesh and "penia" for loss (Cruz-Jentoft et al., 2010), laid the foundation for sarcopenia-related studies. However, for many years, the term primarily denoted the loss of muscle mass without reference to physical function (Cruz-Jentoft & Sayer, 2019).

The second milestone, since 2010, involved the incorporation of muscle function component into the sarcopenia definition by all the sarcopenia diagnostic consensus (Cruz-Jentoft et al., 2010). Sarcopenia was then defined as a concomitant decline in muscle mass and muscle function. This amendment aimed to recognize that poor muscle function is a similarly crucial predictor of adverse health outcomes, just as reduced muscle mass. Additionally, it helped distinguish sarcopenia from other muscle mass-related syndromes (such as malnutrition), enabling precise treatment strategy (Cruz-Jentoft & Sayer, 2019).

The third milestone occurred in 2016 when sarcopenia was granted an International Classification of Diseases, Tenth Revision diagnosis code (M62.84) (Anker et al., 2016). This recognition facilitated the translation of sarcopenia into clinical practice. Subsequently, relevant clinical practice guidelines were published to support its implementation, including International Clinical Practice Guidelines for Sarcopenia (Dent et al., 2018), Japan Clinical Management of Sarcopenia (Arai, 2020) and Singapore Clinical Practice Guideline for Sarcopenia (W. S. Lim et al., 2022).

2.1.2 Prevalence of Sarcopenia in PD Patients

Sarcopenia is prevalent among CKD patients, and its prevalence increases with disease progression. In a cross-sectional study involving 260 patients, Ishikawa et al. (2018) reported sarcopenia prevalence of 17% in CKD 3a, 20% in CKD 3b, 29% in CKD 4 and 38% in CKD 5. This finding is further supported by a study indicating that lower appendicular skeletal muscle mass index (ASMI) correlates with a decline in glomerular filtration rate (GFR), where every 0.03kg/m^2 decrease in ASMI is associated with a 1ml/min/1.73m^2 decline in GFR (Y. Zhou et al., 2018).

A meta-analysis, encompassing 10 studies involving 2323 PD patients, reported a wide-range of sarcopenia prevalence (4.0-48.0%) in the PD population (Shu et al., 2022). The variability in prevalence is attributed to heterogeneity in sarcopenia definition, muscle assessment approach, reference cut-off of diagnostic criteria and population characteristics, including age, ethnicity and gender distribution. When considering studies with sarcopenia based on consensual definition by major international groups, the prevalence among PD patients ranged 10.0-32.1% (see Table 2.1). Importantly, data on sarcopenia prevalence in PD patients from Southeast Asian

countries, including Malaysia, is currently lacking. The absence of this data limits our understanding of the extent and impact of sarcopenia within this specific population, hindering the development of appropriate strategies for early detection, prevention, and management of sarcopenia. This gap may lead to suboptimal patient outcomes and quality of care.

Table 2.1 : Prevalence of Sarcopenia among PD Patients

No	Authors (year)	Country	Sample Size	Mean age (years)	Prevalence (%)	Diagnostic Protocol	Diagnostic Criteria
1	Abro et al. (2018)	UK	155	63.0	11.0	EWGSOP 2010	MM, MS
2	As'Habi et al. (2018)	Iran	79	NA	11.4	EWGSOP 2010	MM, MS, PP
3	Kamijo et al. (2018)	Japan	119	66.8	10.9	AWGS 2014	MM, MS, PP
4	M.Z.C. da Silva et al. (2019)	Brazil	50	55.7	10.0	EWGSOP 2019	MM, MS, PP
5	Do et al. (2021b)	South Korea	199	55.6	32.1	AWGS 2014	MM, MS
6	Davenport (2022a)	UK	368	60.9	17.7	EWGSOP 2019 & AWGS 2019	MM, MS
7	Y. Chen et al., (2022)	China	101	51.3	29.7	AWGS 2014	MM, MS

Abbreviation: EWGSOP, European Working Group on Sarcopenia in Older People; AWGS, Asian Working Group for Sarcopenia; MM, muscle mass; MS, muscle strength; PP, physical performance.

2.1.3 Etiology of Sarcopenia in PD Patients

Sarcopenia is a multifaceted condition influenced by various factors. In addition to the natural aging process, diseases with inflammatory nature, along with malnutrition and physical inactivity, are widely recognized as primary determinants of sarcopenia (Cruz-Jentoft et al., 2019). Unfortunately, dialysis patients are particularly vulnerable

to all of these factors, making them highly susceptible to sarcopenia (Sabatino et al., 2020).

2.1.3.1 Aging

Based on the Concise Summary of Essential Statistics from the Malaysian Dialysis and Transplant Registry for the year 2020, 46.7% of Malaysian PD patients are between 45-64 years old, with 16.5% aged 65 years old and above (Ong, 2022). Therefore, it is sensible to infer that majority of Malaysian PD patients are susceptible to age-related sarcopenia.

Muscle mass and strength peak in early adulthood and gradually decrease over the years, with muscle strength declining faster in older adulthood (Ferrucci et al., 2012). Muscle mass declines by about 3–8% per decade after the age of 30 (Volpi et al., 2004). After the age of 50, the estimated muscle loss is about 1-2% per year, and this rate can further accelerate after the age of 70 to around 13-24% per decade (Filippin et al., 2015; von Haehling et al., 2010). On the other hand, accelerated muscle strength loss is reported to begin after the age of 50-60 at a rate of 2-4% per year, which is approximately three times greater than muscle mass loss (Distefano & Goodpaster, 2018).

Contributing factors to aging-associated muscle atrophy include reduced mitochondrial integrity, oxidative stress, impaired satellite cell function, and inflammation. On the other hand, factors contributing to age-associated strength loss include reduced myofiber size and quantity, intra-muscular fat infiltration, impaired

neuromuscular coordination, and impaired fiber contraction function (Cruz-Jentoft & Sayer, 2019; Distefano & Goodpaster, 2018).

2.1.3.2 Chronic Kidney Disease

CKD contributes to the development and progression of sarcopenia through the complex interplay of inflammatory, metabolic, nutritional and physical factors.

Inflammation represents an important contributor to sarcopenia in the CKD population, as evidenced by an inverse association between inflammatory markers and the incidence of sarcopenia found in dialysis patients (Chatzipetrou et al., 2022; Kaizu et al., 2003). Several mechanisms have been proposed for the impact of inflammation on muscle wasting, including the attenuation of insulin-stimulated muscle synthesis, inhibition of myocyte differentiation, increased muscle proteolysis, and promotion of muscle degradation (Fahal, 2014). PD patients often experience both chronic and acute inflammation. Chronic inflammation in this population is attributed to the loss of residual renal function, leading to reduced cytokines clearance and the stimulation of cytokines synthesis. Additionally, inflammation that triggered by PD treatment involves cumulative membrane injury due to bioincompatibility of the dialysate fluid and the placement of a PD catheter. Endotoxemia caused by bowel edema, malnutrition and uremia, further contributes to chronic inflammation, leading to the translocation of macromolecules from the gut to the blood. On the other hand, acute inflammation can be induced by bacterial infections, including intraperitoneal infection and systemic infection (Cho et al., 2014; Leung et al., 2013).

Aside from inflammation, metabolic acidosis is also considered one of the primary factors contributing to sarcopenia in the CKD population (Fahal, 2014). The kidneys play a crucial role in maintaining acid-base balance, and the decline in renal net acid excretion can lead to metabolic acidosis, which is prevalent among CKD patients. Metabolic acidosis promotes protein catabolism through various mechanisms, including upregulation of the ubiquitin-proteasome pathway, activation of caspase-3 proteolysis, stimulation of pro-inflammatory cytokine secretion, and induction of insulin and growth hormone resistance. Additionally, metabolic acidosis is associated with impaired bone health, glucose intolerance, and impaired appetite, which further contribute to the development of sarcopenia. (Kraut & Madias, 2017).

Besides, vitamin D insufficiency represents another primary contributing factor to the development of sarcopenia in the CKD population. Robust evidence supports the positive association between serum vitamin D levels and muscle mass and strength (Fahal, 2014). The theorized mechanisms of Vitamin D in improving muscle function and quantity include mediating the vitamin D receptor, suppressing activity of atrophy-related genes, stimulating protein synthesis, and improving the function of skeletal muscle mitochondria (Uchitomi et al., 2020). Unfortunately, due to impaired vitamin D synthesis and metabolism associated with CKD, vitamin D deficiency is prevalent among CKD patients (Jean et al., 2017). A study in HD patients showed that serum vitamin D levels were approximately 30% lower in the sarcopenia group compared to the non-sarcopenia group (Kim et al., 2019). The association between vitamin D deficiency and sarcopenia in CKD patients is further supported by the similarities in muscle morphology and contraction characteristics observed in CKD patients and individuals with pronounced vitamin D deficiency. For example, both

groups displayed predominant type 2 muscle fiber atrophy, increased fat infiltration and glycogen deposition in muscle fibers, and prolongation of the relaxation phase in muscle contraction (Fahal, 2014; Fahal et al., 1997; Crescioli, 2021).

Nevertheless, other CKD-related factors that contribute to sarcopenia include impaired regeneration of injured muscle cells due to CKD-associated abnormalities in satellite cells, increased catabolism and reduced protein synthesis secondary to hormonal derangements (such as insulin resistance, growth hormone resistance, and testosterone deficiency), as well as comorbid conditions (Fahal, 2014).

2.1.3.3 Malnutrition

In the dialysis population, sarcopenia is often accompanied by protein-energy wasting (PEW) (Sabatino et al., 2020). Studies conducted in the dialysis population have shown that sarcopenic patients have lower body mass index (BMI) and poorer nutritional status compared to non-sarcopenic individuals (Chatzipetrou et al., 2022). Furthermore, research has demonstrated that well-nourished dialysis patients exhibit greater muscle strength and larger type-2 muscle fibers compared to their malnourished counterparts (Fahal et al., 1997). One of the main contributing factors to this condition is inadequate protein and energy intake, which can result in muscle loss by reducing protein synthesis and increasing protein degradation (Fahal et al., 1997; Sabatino et al., 2020).

Anorexia and poor appetite are common among CKD patients, and these symptoms tend to worsen as the disease progresses. The prevalence of anorexia in CKD and HD patients has been reported to be between 35-50% (Carrero, 2009; Sung et al., 2021).

A study comparing hunger response between PD patients and healthy controls found that PD patients exhibit significantly lower pre-meal hunger peaks and flatter hunger profiles, indicating a disturbed appetite pattern (Wright et al., 2003). Several factors have been identified as contributors to anorexia among CKD patients, including uremia-related gastrointestinal symptoms, inflammation, appetite-regulating hormones derangement, gut dysbiosis and depression (Chung et al., 2011; Fahal, 2014; Sung et al., 2021). Additionally, anorexia can be caused by PD treatment. Studies have shown that intraperitoneal infusion of glucose-containing dialysate can result in a decrease in plasma ghrelin levels, leading to reduced appetite. Animal studies have also supported this finding, demonstrating that intraperitoneal dialysate infusion can cause hypophagia (Zheng et al., 2009, 2001). Furthermore, the presence of dialysate in the intraperitoneal cavity can contribute to feelings of fullness and early satiety, which can aggravate the issue of poor oral intake (Fahal, 2014). In addition to poor appetite, dietary restrictions are another well-known factor that impairs the dietary intake of dialysis patients (Sabatino et al., 2020).

In addition to inadequate dietary intake, the loss of amino acids during dialysis is a significant factor that predisposes dialysis patients to malnutrition and sarcopenia. For instance, the daily peritoneal protein loss in adult patients has been estimated to range from 5 to 15 grams per day (Guedes, 2019). Nevertheless, it is important to note that adiposity also plays a crucial role in contributing to sarcopenia (Sabatino et al., 2020). As a result of the continuous glucose absorption from the dialysate, PD patients are susceptible to excessive fat gain. Excessive body fat can act as a pro-inflammatory factor by promoting cytokine synthesis, which can lead to muscle degradation (Leung et al., 2013). Moreover, adiposity can exacerbate intramuscular fat infiltration and

impair muscle regeneration, thereby affecting both muscle mass and strength. This can create a vicious cycle where increased intramuscular fat infiltration and reduced muscle regeneration contribute to obesity, ultimately leading to a complex health condition known as "sarcopenic obesity" (Li et al., 2022).

2.1.3.4 Inactivity

Physical inactivity can lead to muscle mass and strength loss through various pathways, including the suppression of anabolism and energetic metabolism, induction of negative changes in musculotendinous morphology, increased oxidative stress, promotion of catabolism, inflammation, and denervation (Pillard et al., 2011). This issue is prevalent at all stages of CKD and tends to worsen as renal dysfunction progresses. A multicenter study conducted in the United Kingdom reported that only 8% of PD patients achieved an active level of physical activity (Wilkinson et al., 2021). Additionally, Painter et al. (2017) found that 46.3% of PD patients did not engage in any regular exercise. The same study revealed that the physical activity level of the PD population was lower compared to their gender- and age-matched healthy counterparts. Furthermore, the weekly caloric expenditure of PD patients, with a mean age of 49 years, was found to be comparable to that of community-dwelling elderly individuals aged above 70 years. Several factors have been identified as predictors of insufficient physical activity among dialysis patients, including advanced age, low serum hemoglobin levels, cardiovascular disease, malnutrition, fatigue, and depression (Cobo et al., 2015; Kopple et al., 2015; Stack & Murthy, 2008; Wilkinson et al., 2021).

2.1.4 Consequences of Sarcopenia in PD Patients

CKD is often considered a condition associated with "accelerated aging." Therefore, it is reasonable to find that the relationship between sarcopenia status and health outcomes is similar to that observed in the general population, albeit with a different magnitude of association (Moorthi & Avin, 2017). Sarcopenia is associated with an increased mortality rate and cardiovascular events among dialysis patients. Findings from multiple longitudinal studies consistently demonstrated a higher mortality rate among sarcopenic dialysis patients, with hazard ratios (HR) ranging from 1.93 to 6.99 (Giglio et al., 2018; Isoyama et al., 2014; Kim et al., 2019), and a significantly higher incidence of cardiovascular events among sarcopenic patients compared to their non-sarcopenic counterparts (HR: 4.33).

In addition, sarcopenia is significantly associated with disability and impaired physical function in PD patients (Kamijo et al., 2018). In this regard, sarcopenic patients were found associated with a higher risk of fall trauma and fracture (Aly et al., 2019). The underlying mechanisms leading sarcopenia to fractures include an increased risk of falls due to impaired physical function, loss of cushioning provided by muscle during falls, decreased bone mineral density resulting from a lack of muscle-generated mechanical stimulation, and undesirable muscle-bone interaction through the secretomes secretion (Inaba et al., 2021). Of note, the association between reduced bone mineral and sarcopenia has been demonstrated by studies in PD patients (Davenport, 2022b; Kang et al., 2022b). Additionally, sarcopenia has been found to be associated with psychological conditions among dialysis patients, including depression, cognitive impairment, and anxiety (Alston et al., 2018; Chatzipetrou et al., 2022). Furthermore, sarcopenia is associated with higher hospitalization rates, poor

quality of life, protein-energy wasting, and inflammation in this population (Giglio et al., 2018; Isoyama et al., 2014; Sabatino et al., 2020).

On top of the negative health consequences, sarcopenia can negatively impact the healthcare burden of a country. Based on local statistics, the public sector expenditure for ESRD was approximately MYR 1.12 billion in 2016 (Ismail et al., 2019), and it was forecasted to reach MYR 2.36 billion in 2030 (Bujang et al., 2017). Unfortunately, sarcopenia can further exacerbate healthcare expenses due to the increased risk of falls, fractures, depression, post-operative complications, hospitalization, slow recovery, and physical dependence (Norman & Otten, 2019; Sabatino et al., 2020). For instance, Sousa et al. (2016) reported a 45% higher hospitalization cost for a single admission among sarcopenic patients compared to non-sarcopenic patients. Additionally, a longitudinal study in community-dwelling Taiwanese elderly found that the annual medical expenditure in individuals with a low skeletal muscle mass index (SMMI) was 51% higher compared to those with a normal SMMI (Lo et al., 2017).

2.1.5 Treatment Strategies for Sarcopenia in PD Patients

Early intervention is paramount in reversing sarcopenia and postponing the negative health consequences associated with it (Cruz-Jentoft et al., 2019). The treatment for sarcopenia typically involves a multifaceted approach that focuses on both exercise and nutrition, while pharmacological interventions have been actively explored in recent years (Chatzipetrou et al., 2022).

2.1.5.1 Exercise Intervention

Resistance exercise represents the key treatment in sarcopenia, as this type of exercise theoretically helps to build muscle mass and increase muscle strength. Two meta-analyses based on studies conducted in CKD and dialysis populations have demonstrated that resistance exercise increases muscle mass, strength, physical performance, and health-related quality of life in this population (Cheema et al., 2014; Lu et al., 2019). On the other hand, aerobic exercise has been shown to improve functional fitness and physical performance in dialysis patients, despite no change in muscle mass (Lu et al., 2019). Notably, combined aerobic and resistance training is more effective in improving physical performance compared to resistance training alone (Orcy et al., 2012). A systematic review article suggested that performing aerobic or combined exercise three times a week for a duration of 8 weeks to 12 months can confer functional advantages for HD patients (M. Huang et al., 2019).

2.1.5.2 Nutrition Intervention

Since sarcopenia is closely associated with protein-energy wasting (PEW), addressing malnutrition is a cornerstone of sarcopenia treatment (Giglio et al., 2018; Sabatino et al., 2020). A meta-analysis demonstrated that oral nutrition supplements with a mixture of macronutrients can significantly increase lean mass in dialysis patients, despite inconsistent findings were reported for muscle strength (Lu et al., 2021). Protein supplementation alone confers limited benefits in dialysis patients, likely due to the presence of anabolic resistance in this population (Sabatino et al., 2020). However, whey protein supplementation has been reported to improve muscle strength in HD patients, despite no change in muscle mass (Tomayko et al., 2015).

Additionally, supplementation with essential amino acids (EAAs) and branched-chain amino acids (BCAAs) has been found to be beneficial in sarcopenia treatment (Slee & Reid, 2018). Supplementation with 3.6g of EAAs for 3 months has shown a significant increase in hand grip strength in dialysis patients, despite no change in muscle mass being observed (Eustace et al., 2000). Similarly, a study on BCAA supplementation (12g/day) for six months in HD patients demonstrated beneficial effects on lean body mass, protein intake, and energy intake (Hiroshige et al., 2001). Moreover, vitamin D supplementation has been shown to improve muscle strength, balance, and functional ability in PD patients (Taskapan et al., 2011).

Although β-hydroxy-β-methylbutyrate (HMB) supplementation has been proven to reduce muscle loss in the elderly, this effect has failed to be replicated in the HD population (Fitschen et al., 2017). Similarly, while the benefits of omega-3 supplementation on muscle strength and mass have been well-established in the general population, evidence from the CKD population is still lacking (Bird et al., 2021). Notably, treating fluid overload is beneficial in combating sarcopenia, as fluid overload can contribute to physical fatigue and reduced physical activity (Workeneh et al., 2021). Overall, emerging evidence supports the role of nutritional intervention in sarcopenia treatment. However, more evidence from the dialysis population is needed for the formulation of precise recommendations.

2.1.5.3 Pharmacological Intervention

Certain anabolic steroids (e.g., nandrolone decanoate and oxymetholone), as well as growth hormone, have been found to be helpful in improving muscle mass, strength, and physical performance in dialysis patients (Chatzipetrou et al., 2022). Interestingly,

angiotensin 2 receptor blockers (ARBs), which are commonly used as antihypertensive medication, have shown potential in attenuating muscle weakening in dialysis patients (Sabatino et al., 2020). Additionally, correcting acidosis in dialysis patients through the use of oral sodium bicarbonate or alkalized peritoneal dialysate has been found to be effective in promoting muscle gain (Chatzipetrou et al., 2022). Last but not least, several drugs have demonstrated beneficial outcomes in reversing sarcopenia in animal studies, including AST-120 (adsorbent of uremic acid in intestine) and ghrelin (appetite-regulating hormone) and myostatin antagonist (Sabatino et al., 2020).

2.2 Distinguishing between Sarcopenia, Protein Energy Wasting, Cachexia and Physical Frailty

As a result of alterations in multiple pathways that regulate energy balance and protein turnover, muscle derangement is prevalent in the later stages of CKD (Slee & Reid, 2018). There are several medical conditions associated with muscle derangement that are prominent in the dialysis population, including sarcopenia, protein-energy wasting (PEW), cachexia, and physical frailty (see Figure 2.1). Despite having common criteria and clinical outcomes, these disorders are defined differently (Sabatino et al., 2020). In a study of PD patients, Davenport (2022a) demonstrated poor to fair agreement between the diagnoses of sarcopenia, PEW, and frailty. Misconceptions can lead to underdiagnosis and undertreatment. For example, clinicians may associate sarcopenia with leanness and therefore underdiagnose cases of sarcopenic obesity, resulting in adverse outcomes, increased disability, and mortality (Cruz-Jentoft & Sayer, 2019). Precise differentiation between these medical conditions is crucial as the treatment strategies for each may vary significantly (Reid et al., 2016).

Sarcopenia is diagnosed by the concomitant decline in muscle quantity and muscle function (L. K. Chen et al., 2020). Unlike sarcopenia, muscle function assessment is not required for the diagnosis of PEW. PEW is a disease-specific syndrome for the CKD population, proposed by the International Society of Renal Nutrition and Metabolism (ISRNM). It is defined as "a state of protein and energy depletion accompanied by diminished functional capacity related to metabolic derangements that cannot be corrected by dietary interventions alone" (Fouque et al., 2008). It differs from general insufficient energy and protein intake, with CKD-related low-grade inflammation being an additional etiology (Sabatino et al., 2020). Compared to PEW, cachexia is a more severe form of metabolic depletion that is associated with higher-grade chronic inflammation (Reid et al., 2016). It is defined as a complex metabolic depletion associated with chronic inflammatory diseases (such as cancer, acquired immunodeficiency syndrome, and end-stage organ failure), characterized by severe muscle loss and weight loss that may or may not be accompanied by loss of fat (Cruz-Jentoft & Sayer, 2019; Slee & Reid, 2018). Unlike PEW and cachexia, sarcopenia is not necessarily associated with weight loss, poor dietary intake, and abnormal nutrition-related biochemical markers. It is worth noting that sarcopenia can occur in overweight and obese individuals (Slee & Reid, 2018). On the other hand, frailty is defined as "a state of increased vulnerability secondary to age-related functional decline in multiple organ systems". Physical frailty, a subset of frailty, is commonly assessed with Fried's frailty phenotype through five criteria, namely weakness, slowness, low physical activity level, self-reported fatigue, and unintentional weight loss (World Health Organization, 2017). Despite sharing similarities in some diagnostic criteria, sarcopenia and physical frailty are still distinct in terms of (1) sarcopenia being a recognized disease while frailty is a geriatric syndrome and (2)

sarcopenia being a major contributor to physical frailty (Cruz-Jentoft et al., 2019; Jang, 2018; W. S. Lim et al., 2022). Lastly, it is noteworthy that these medical conditions can coexist with each other. For example, a cachexic patient may present with physical frailty, PEW, and sarcopenia simultaneously.

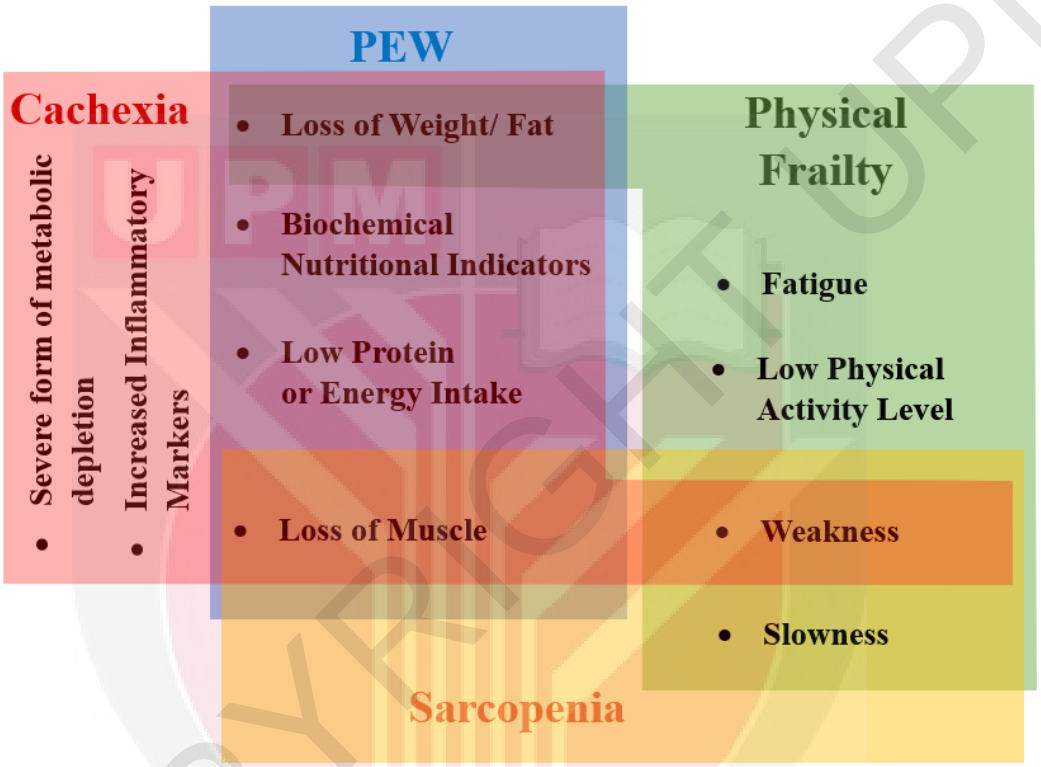


Figure 2.1 : Conceptual Overlapping between Sarcopenia, PEW, Cachexia and Physical Frailty

2.3 Diagnosis of Sarcopenia

2.3.1 Contemporary Consensus on Sarcopenia Diagnosis

Several sarcopenia diagnostic protocols have been developed by different research groups, including the European Working Group on Sarcopenia for Older People (EWGSOP), International Working Group on Sarcopenia (IWGS), Society of Sarcopenia, Cachexia and Wasting Disorder (SSCWD), Asian Working Group for

Sarcopenia (AWGS), and Foundation for the National Institutes of Health (FNIH). While all these protocols define sarcopenia as a decline in muscle mass and muscle function, they differ in their diagnostic criteria, protocols, and cut-off values (see Table 2.2). Among them, the diagnostic algorithms proposed by EWGSOP and AWGS are the most widely adopted in research and clinical practice.

The EWGSOP was the first to issue a consensus on the definition and diagnosis of sarcopenia in 2010 (Cruz-Jentoft et al., 2010). This consensus, which laid the foundation for subsequent consensuses, was revised in 2019 to incorporate the latest scientific and clinical evidence (Cruz-Jentoft et al., 2019). Although not region-specific, this consensus is based on relevant scientific evidence from around the world, with a majority of the references coming from Western nations.

To address differences related to ethnicity, anatomy, lifestyle and culture, the AWGS developed an Asian-specific diagnostic protocol for sarcopenia in 2014 (L. K. Chen et al., 2014). An updated consensus, generally known as AWGS 2019, was published in 2019 to reflect the latest scientific and clinical evidence specific to Asian populations (L. K. Chen et al., 2020). Since 2014, many studies conducted in Asian countries have adopted this protocol, and AWGS-defined sarcopenia has been shown to be significantly associated with physical limitations, slowness, and 10-year mortality. The AWGS diagnostic algorithm for sarcopenia has been adopted into several clinical practice guidelines for sarcopenia in Asian countries, including Japan (Arai, 2020) and Singapore (W. S. Lim et al., 2022).

Currently, there is no disease-specific sarcopenia diagnostic algorithm available for renal patients. Therefore, many studies have adopted existing consensus algorithms, particularly those of EWGSOP and AWGS, to define sarcopenia in the renal population (Shu et al., 2022). Researchers generally agree that it is reasonable to utilize these existing diagnostic algorithms until a CKD- or ESRD-specific algorithm is established, as it will contribute valuable information to develop screening, diagnosis, and intervention strategies for this specific population (Sabatino et al., 2020). Notably, previous research has demonstrated that body composition and muscle strength in Asian dialysis patients differ from those of white and black patients, underscoring the importance of employing ethnicity- or region-specific protocols in diagnosing sarcopenia (Giglio et al., 2018; Yoowannakul et al., 2018).

Historically, sarcopenia was regarded as a geriatric syndrome that particularly associated with the aging process. However, following emerging evidences revealed multiple contributing factors other than ageing (e.g., chronic disease, lifestyle, nutrition and early life development influence), the pioneering international group on sarcopenia has recognized that sarcopenia can be both age-related and non-age-related (Cruz-Jentoft et al., 2010, 2019). Specifically, chronic kidney disease is a disease manifested by an accelerated aging phenotype, with premature aging symptoms appearing ahead of the actual biological age (Kooman et al., 2014; Sabatino et al., 2020). This is supported by a meta-analysis on sarcopenia in dialysis patients, which showed that sarcopenia prevalence was not associated with patients' age, and advocating for sarcopenia screening even in young dialysis patients (Shu et al., 2022). Therefore, most of the previous studies on the association between PhA and sarcopenia in dialysis populations have not excluded non-elderly patients from their

studies (Y. Chen et al., 2022; Ding et al., 2022; Do et al., 2021a). This practice allows the findings to be generalized to the entire adult dialysis population, including non-elderly patients who also represent a high-risk group for sarcopenia that require sarcopenia screening. Similarly, numerous studies in other diseased populations (e.g., liver disease, lung disease, cancer, and post-renal transplantation patients etc.) have not excluded non-elderly patients (Espirito Santo Silva et al., 2019; Kosoku et al., 2020; Ruiz-Margáin et al., 2021; Valisoltani et al., 2024; Zuo et al., 2024).

Table 2.2 : Summary of Contemporary Consensus on Sarcopenia Diagnosis

Consensus (Publication Year)	Diagnostic Criteria			Sarcopenia Definition
	Muscle Quantity	Muscle Strength	Physical Performance	
AWGS 2019 (2020)	**Male** ASM/Ht^2 < 7.0 kg/m^2 (DXA or BIA) **Female** ASM/Ht^2 < 5.4 kg/m^2 (DXA) *Or* ASM/Ht^2 < 5.7 kg/m^2 (BIA)	**Male** HGS < 28kg **Female** HGS < 18kg	Gait Speed ≤ 1.0 m/s *Or* Chair test: ≥ 12s for 5 times *Or* SPPB: ≤ 9 points score	"Sarcopenia" if low muscle quantity + low muscle strength/ low physical performance. "Severe sarcopenia" if low muscle quantity + low muscle strength + low physical performance.
EWGSOP (2019)	**Male** ASM < 20kg *Or* ASM/Ht^2 <7.0kg/m^2 **Female** ASM < 15kg *Or* ASM/Ht^2 <5.5kg/m^2	**Male** HGS < 27kg *Or* Chair test: > 15s for 5 times **Female** HGS < 16kg	Gait Speed ≤ 0.8m/s *Or* SPPB: ≤ 8 points score *Or* TUG: ≥ 20 seconds *Or* 400m walk test: non-completion or ≥6min for completion	"Sarcopenia" if low muscle quantity + low muscle strength. "Severe sarcopenia" if low muscle quantity + low muscle strength + low physical performance.

Table 2.2 : Continued

FNIH (2014)	**Male** ALM-to-BMI ratio <0.789 kg/BMI *Or* ALM < 19.75 kg **Female** ALM-to-BMI ratio <0.512 kg/BMI *Or* ALM <15.02 kg	**Male** HGS < 26kg **Female** HGS < 16kg	NA	"Sarcopenia" if low muscle quantity + low muscle strength.
IWGS (2011)	**Male** ALM/Ht^2 <7.23 kg/m^2 **Female** ALM/Ht^2 <5.67 kg/m^2	NA	Gait Speed <1.0 m/s	"Sarcopenia" if low muscle quantity + low physical performance.
SSCWD (2011)	ALM/Ht^2 ≤ 2 SD below mean value for young healthy persons (age 20–30 years) of the same ethnic group	NA	Gait Speed ≤ 1 m/s or 6-minute walk test: < 400m	"Sarcopenia" if low muscle quantity + low physical performance.

Abbreviations: ASM, appendicular skeletal muscle mass; ALM, appendicular lean mass; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; HGS, handgrip strength; Ht, height; kg; kilogram; m, meter; min, minute; SD, standard deviation; s, second; SPPB, short physical performance battery; TUG, timed-up-and-go test.

2.3.2 Diagnostic Criteria of Asian Working Group for Sarcopenia 2019 Consensus (AWGS 2019)

AWGS 2019 defined sarcopenia as low muscle mass with low muscle function (either low muscle strength or low physical performance, or both of them) (L. K. Chen et al., 2020).

2.3.2.1 Assessment for Muscle Mass

Magnetic resonance imaging (MRI) and computed tomography (CT) are widely regarded as the most accurate non-invasive approaches for quantifying skeletal muscle mass (Rangel Peniche et al., 2015). However, their use in research and clinical settings is limited by factors such as high cost, lack of portability, and operational complexity. Nevertheless, the lack of established cut-off recommendations for MRI- and CT-derived muscle mass further limits their use in sarcopenia diagnosis (Cruz-Jentoft et al., 2019; Tavoian et al., 2019). In comparison, dual-energy X-ray absorptiometry (DXA) provides a precise estimate of body composition at a reduced cost and with a simpler operational procedure (Shepherd et al., 2017; Tavoian et al., 2019). Nevertheless, disadvantages in portability and affordability have limited DXA application in clinical and community settings (Cruz-Jentoft et al., 2019). On the other hand, BIA stands out owing to its portability, affordability, safety and simplicity of operation. The accuracy of BIA in body composition estimation is highly dependent on the technology that a device applies. Multi-frequency BIA (MFBIA) has been proven to correlate closely with appendicular skeletal muscle mass (ASM) (H. Wang et al., 2016), and hence recommended by AWGS 2019 in sarcopenia assessment. Of note, both DXA and BIA-measured ASM are affected by body hydration status (Cruz-Jentoft et al., 2019; W. S. Lim et al., 2022). Several new tools are under evaluation for their ability to assess muscle quantity and quality, including lumbar 3rd vertebra imaging by CT, mid-thigh muscle imaging by MRI or CT, creatine dilution test, and muscle assessment by ultrasonography. However, none of these tools have been adopted in sarcopenia diagnostic guidelines until more scientific evidence becomes available (L. K. Chen et al., 2020; Cruz-Jentoft et al., 2019).

ASM is associated with body size, whereby taller and heavier individuals commonly have higher ASM. Therefore, normalizing this parameter is logical to reflect muscle sufficiency levels (Cruz-Jentoft et al., 2019). Several normalization approaches are currently under investigation, including ASM adjusted to height squared (ASM/Ht^2), body weight (% ASM), and BMI (ASM/BMI ratio). ASM adjusted to height squared tends to underestimate sarcopenia in obese HD patients, while ASM adjusted to body weight tends to underestimate sarcopenia in underweight HD patients (Kittiskulnam et al., 2017). However, Hung et al. (2017) reported a better detection of low muscle mass cases among PD patients using the ASM/Ht^2 cut-off compared to ASM/BMI or unadjusted ASM cut-off, which may be explained by the low prevalence of obesity sarcopenia rate among PD patients. To date, no consensus has been reached regarding the most appropriate normalization approach. ASM/Ht^2, being the most commonly studied parameter, is adopted in the majority of sarcopenia diagnostic protocols, including AWGS 2019, EWGSOP 2019, and SSCWD 2011 (L. K. Chen et al., 2020; Cruz-Jentoft et al., 2019; Morley et al., 2011). Low ASM/Ht^2 has been proven to be associated with a higher risk of mortality and osteoporosis among the elderly (de Santana et al., 2021; Furushima et al., 2017). Similar findings have been reported by studies in PD patients (Davenport, 2022b; Jin et al., 2017).

In summary, AWGS 2019 recommended height-adjusted ASM (also known as appendicular skeletal muscle mass index, ASMI) cut-offs based on DXA and MFBIA, considering higher instrument accessibility and relatively abundant scientific evidence availability. The validity of the AWGS-defined ASMI cut-off recommendation in PD patients is supported by a longitudinal study, which demonstrated low ASMI as an independent risk factor for mortality (Jin et al., 2017).

2.3.2.2 Assessment for Muscle Strength

Initially, poor muscle strength was theorized as a consequence of low muscle mass (Rosenberg, 1997). However, this concept has been challenged by emerging evidence. A longitudinal study involving 1880 elderly individuals found that muscle strength declines at a faster rate than muscle mass loss, and the decline in muscle strength can occur without concurrent muscle loss (Goodpaster et al., 2006). Similar findings have been reported in the dialysis population. Studies conducted on PD patients have reported a higher prevalence of low muscle strength compared to low muscle mass (Abro et al., 2018; As'Habi et al., 2018; M. Z. C. da Silva et al., 2019). Additionally, it has been observed that HD patients exhibit lower strength compared to age- and gender-matched healthy individuals, despite having comparable muscle mass (Johansen et al., 2003). Given the potential dissociation between the development of low muscle mass and low muscle strength, the inclusion of muscle strength assessment is crucial for diagnosing muscle derangement in both the healthy and dialysis populations (Sabatino et al., 2020).

Handgrip strength (HGS) is the most popular tool for assessing muscle strength. It is considered a convenient and reliable surrogate for other complex muscle strength tests, as it moderately correlates with muscle strength in other body parts. Poor HGS has been clinically proven to be a strong predictor of prolonged hospitalization, impaired physical ability, poor health-related quality of life and higher mortality risk (Cruz-Jentoft et al., 2019). A meta-analysis has shown that low muscle strength is more strongly associated with functional decline than low muscle mass in the general population (Schaap et al., 2013). Similar findings have been reported in longitudinal studies in dialysis patients, whereby low HGS demonstrated greater predictability for

poor quality of life, increased hospitalization and mortality compared to low muscle mass (Giglio et al., 2018; Isoyama et al., 2014).

According to AWGS 2019, most studies related to sarcopenia in Asia have adopted HGS as the indicator of muscle strength. As such, AWGS 2019 has proposed HGS as a diagnostic criterion for sarcopenia, with its cut-off derived from eight Asian cohorts involving 21,984 participants (L. K. Chen et al., 2020). This consensus recommends the use of spring-type dynamometer (e.g., Smedley) or hydraulic-type dynamometer (e.g., Jamar) for HGS assessment and emphasizes that the assessment protocol should be specific to the model used. For instance, the American Society of Hand Therapists and the Southampton protocol are recommended for the Jamar dynamometer, while the US National Health and Nutrition Examination Survey protocol is recommended for the Smedley dynamometer.

2.3.2.3 Assessment for Physical Performance

Physical performance is defined as an objective measure of whole-body function related to locomotion, encompassing muscle function as well as central and peripheral nervous system function (Cruz-Jentoft et al., 2019). AWGS 2019 recommends three tests for assessing physical performance, namely gait speed test (i.e., 6-m walk test), chair stand test (i.e., 5-time chair stand test) and Short Physical Performance Battery (SPPB) (L. K. Chen et al., 2020). As a complimentary assessment to HGS, these tests involve assessment of lower extremity strength and whole-body balancing ability.

Gait speed test is a simple and reliable test for the assessment of physical performance (Cruz-Jentoft et al., 2019). It provides instructive information about overall health

status, as walking involves the coordination of the circulatory system, nervous system, and musculoskeletal system (Kutner et al., 2015). The gait speed test is included in most sarcopenia diagnostic algorithms (see Table 2.2) with varying protocols and cut-off recommendations. AWGS 2019 recommends the 6-meter walk test with a usual gait cut-off of 1.0 meters/second for sarcopenia assessment, as this approach has been extensively examined in frailty and functional disability studies (L. K. Chen et al., 2020). Dialysis patients are particularly prone to low gait speed and have been reported to exhibit slower gait speeds compared to the general population (Painter et al., 2017). A longitudinal study on patients new to HD observed a low overall gait speed at baseline, and a continual decline in gait speed in 54.2% of subjects over a two-year period (Moorthi et al., 2020). Low gait speed is strongly associated with adverse outcomes related to sarcopenia, including disability, impaired mobility, cognitive impairment, hospitalization and mortality in the general population (L. K. Chen et al., 2020; Cruz-Jentoft et al., 2019). Furthermore, evidence from the dialysis population indicates that low gait speed is associated with hospitalization, difficulties in daily living activities and mortality (Kittiskulnam et al., 2017; Kuki et al., 2019; Kutner et al., 2015; M. Z. C. Silva et al., 2023)

Nevertheless, measuring gait speed necessitates a specific amount and condition of space (i.e., at least 8 meters length of a safe space with flat floor), which might not be practical in clinical setting. Therefore, AWGS 2019 recommended the use of the 5-time chair stand test (5TCST) as a surrogate for gait speed in the diagnosis of sarcopenia. The recommended cut-off for the 5TCST (i.e., ≥12 seconds), corresponds to a usual walking gait of 1.0m/s, as recommended by AWGS in 2019 (Nishimura et al., 2017).

2.4 Bioelectrical Impedance Analysis

2.4.1 Principles of Bioelectrical Impedance Analysis

Bioelectrical Impedance Analysis (BIA) is defined as the measurement of the ability of biological tissue to resist the flow of alternating electrical current. BIA measurement involves the use of two pairs of electrodes: the first pair sends an imperceptible alternating electric current through the body, while the second pair from another end receives the current that has been impeded by the body's tissues, enabling the measurement of resistance (R) and reactance (Xc). Subsequently, impedance (Z) is calculated based on R and Xc (Brantlov et al., 2017). Impedance is influenced by the electrical properties of biological tissues. Higher fluid and electrolyte content results in higher conductivity and lower impedance. This enables the differentiation between tissues with high water content (e.g., muscle) and tissues with low water content (e.g., fat and bones). Estimating body composition using BIA involves a series of mathematical equations. Firstly, total body water (TBW) is calculated using the impedance data. Then, fat-free mass (FFM) is calculated by assuming a constant ratio between FFM and TBW. Subsequently, body fat mass (BFM) is calculated by subtracting FFM from body weight. Other body composition parameters are then derived based on this basis (Mialich et al., 2014).

2.4.2 Multi-Frequency Bioelectrical Impedance Analysis

Notably, the recommended BIA technology for assessing sarcopenia by AWGS 2019 is multi-frequency BIA (MFBIA), not single-frequency BIA (SFBIA). SFBIA, the first generation of BIA technology used for body composition analysis, was commercially introduced in 1985. It applies a single-frequency electrical current of

50kHz in measurement and relies on empirically-derived algorithms to estimate body composition. However, at the frequency of 50kHz, the current can only partially penetrate the cell membrane, and a higher frequency current is required for full penetration through the cell membrane (Ward, 2019). Thus, the accuracy of SFBIA is hindered, especially in individuals with altered hydration, and it is considered an inferior BIA technology in body composition analysis (Brantlov et al., 2017; Mialich et al., 2014).

MFBIA technology was developed to counteract this issue. MFBIA exerts an electrical current at several different frequencies (typically 4-8 frequencies ranging from 1-1000kHz), and impedances are calculated at the respective current frequencies (Brantlov et al., 2017). At lower frequencies, the current fails to penetrate the cell membrane but flows in the extracellular water (ECW) space, enabling the measurement of ECW volume. On the contrary, at higher frequencies (>50 kHz), the current allows penetration of the cell membrane, thus enabling the quantification of intracellular water (ICW) and ECW. By combining impedance data from different frequencies, a relatively precise estimation of body composition is made possible (Ward, 2019). This feature is especially important for populations susceptible to fluid dislocation (e.g., renal disease and cardiovascular disease), in which a precise estimation of ECW and ICW is crucial (Mialich et al., 2014). As such, MFBIA has been proven to be an effective method in assessing volume status in PD patients (Vujicic et al., 2019). Given that muscle mass is proportionately estimated from total body water, inaccurate volume estimation will directly impair the accuracy of muscle mass estimation. Therefore, AWGS 2019 has recommended using MFBIA over SFBIA in sarcopenia assessment.

2.5 BIA-Derived Phase Angle

2.5.1 Concept of BIA-Derived Phase Angle

As explained in subchapter 2.4.1, the estimation of body composition (e.g., body fat, FFM, TBW, etc.) by BIA is based on empirically-derived algorithms that are mostly developed in healthy populations. Therefore, applying these algorithms in diseased populations may result in algorithmic discrepancies. Consequently, BIA-derived PhA has gained popularity over time as a raw impedance parameter that is capable of reflecting body cell mass and cell integrity, without requiring assumptions (e.g., normal hydration distribution) or relying on empirically-derived algorithms (Norman et al., 2012). In human body, the cell membrane is composed of a non-conductive lipid layer situated between two layers of conductive protein molecules. This configuration of the cell membrane renders it a capacitive element, behaving as capacitor when subjected to alternating current (Kumar et al., 2012). When an alternating current passes through a body cell, the cell membrane acts as a capacitor, storing energy and causing a delay in voltage after the current is released. The better the cell membrane integrity, the more energy it stores, hence leading to a larger time delay between current and voltage. The phase shift caused by the separation of current and voltage is quantified as PhA (see Figure 2.2).

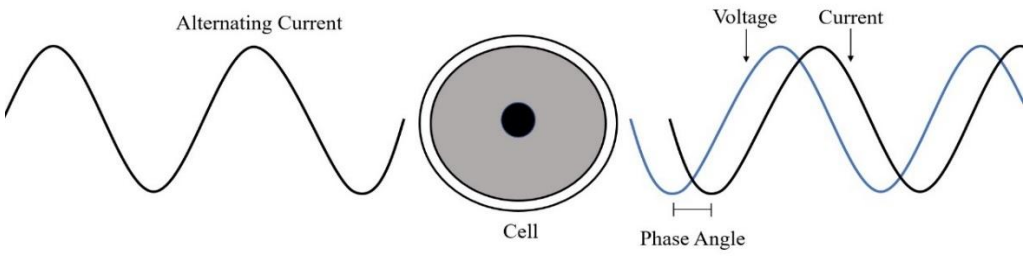


Figure 2.2 : Illustration of PhA Concept

Technically, PhA is a BIA-derive parameter that determined by the ratio of reactance (Xc) and resistance (R), which is calculated as arc tangent = (Xc / R) x 180° / π, and expressed in degree (°) unit (Sardinha, 2018) (see Figure 2.3). PhA is measured using a single frequency of 50kHz, as both reactance and PhA are considered highest at this wavelength in humans (López-Gómez, 2011). Xc reflects the cell membrane's capacity to store energy, while R represents the opposition generated by the resistive substance to the flow of current (Brantlov et al., 2017). Based on the formula of PhA calculation, it is understandable that PhA is the integrated result of body cell mass, membrane integrity, body composition and hydration status (Kumar et al., 2012). With these properties, PhA is widely regarded as a proxy for cellular health. It is hypothesized that impaired or less healthy cells have lower membrane integrity, leading to a reduced ability to store energy and leakage of intracellular water into the interstitial space, resulting in lower PhA (Sardinha, 2018). This concept is supported by evidence from focal BIA studies, which have shown a proportional decrease in localized PhA corresponding to the severity of regional muscle injury (Nescolarde et al., 2015, 2017).

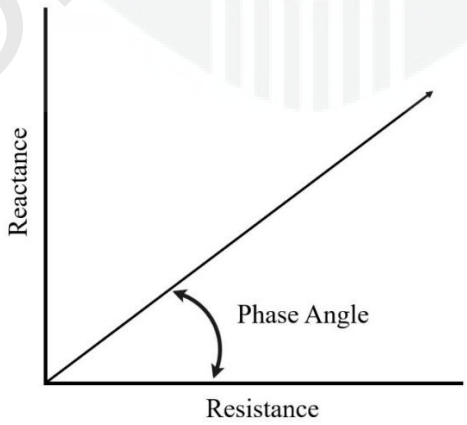


Figure 2.3 : Geometric Relationship between Reactance, Resistance and Phase Angle

2.5.2 Determinants of Phase Angle

A recent local study in HD patients identified several factors affecting PhA, including age, gender, ethnicity, body composition, hydration status, comorbidities, nutrition status and muscle strength (C. K. M. Lim et al., 2021). These findings are consistent with previous studies in PD population (Abad et al., 2011; Han et al., 2018) and general population (Norman et al., 2012).

2.5.2.1 Body Composition

Body composition is the main determinant of PhA, and it was reported that the association between PhA with age, ethnicity and gender is mediated by body composition (C. K. M. Lim, 2022). Being the largest conductive tissue in the body, the muscle quantity plays a crucial role in determining the phase angle value. Muscle cells consist primarily of water, comprising approximately 70 to 85% of their composition and 1-3% of ions. The presence of water and ions in muscle cells facilitates the conduction of electrical current, resulting in low resistance to electrical flow. On the other hand, reactance is the measure of cell membrane's ability to function as an electrostatic field that stores voltage, which is highly associated with the quantity and integrity of muscle cells (Martins et al., 2023).

Regarding the association between PhA and body fat, mixed findings have been reported in different populations (Martins et al., 2023), including the dialysis population (Abad et al., 2011; Do et al., 2021a; Han et al., 2018). However, a consistent negative association between PhA and body fat has been observed in studies involving only obese individuals (Di Vincenzo et al., 2021). This could be attributed to lower body fat in non-obese individuals might be associated with malnutrition,

resulting in lower cell mass and integrity, and consequently, lower PhA. In contrast, in obese individuals, higher adiposity is generally associated with lower muscle quality due to altered metabolic, structural, and functional characteristics of the muscles (Barbat-Artigas et al., 2014). Furthermore, excessive adipose tissue could lead to an increased release of inflammatory cytokines, resulting in a lower PhA (Trayhurn & Wood, 2005).

2.5.2.2 Body Mass Index

A higher body mass index (BMI) is associated with a higher PhA in the dialysis population (Do et al., 2021a; C. K. M. Lim et al., 2021), which can be attributed to the increased quantity and quality of muscle cells in individuals with higher BMI. However, this relationship was found to be lost in individuals with a BMI of 30-40 kg/m^2 and inverted in individuals with a BMI $\geq$40 kg/m^2 (Bosy-Westphal et al., 2006). This could be due to the common occurrence of fluid overload in severely obese individuals (Mager, 2009). Additionally, excessive adiposity, as discussed in subchapter 2.5.2.1, may also contribute to this inversion.

2.5.2.3 Fluid Distribution

Water constitutes 50-60% of the human body in normal hydration status, which is distributed across intracellular water (ICW) and extracellular water (ECW). ICW refers to the fluid contained within the cells, constituting approximately 40% of body weight; whereas ECW represents the fluid located outside the cells, accounting for approximately 20% of body weight (Brinkman et al., 2018). In BIA, hydration status is typically evaluated by comparing the ratio between ECW and ICW or total body water (TBW). PhA is highly correlated to the ratio between ECW and ICW (Jacobs et

al., 2010). Overhydration is negatively associated with PhA in both dialysis and non-dialysis populations (Han et al., 2018; Martins et al., 2023). Excessive ECW can exert pressure on cell membranes, leading to compromised membrane integrity, and resulting in lower reactance and PhA (InBody Co. Ltd, 2018b; Nescolarde et al., 2023). Notably, low ICW resulting from malnutrition is also associated with low PhA (Jacobs et al., 2010).

2.5.2.4 Sociodemographic Factors

PhA decreases with age, primarily attributed to a decline in reactance that corresponds to aging-related muscle loss (Distefano & Goodpaster, 2018). Additionally, there is an increase in resistance as the proportion of body water decreases and fat mass increases with advancing age (Norman et al., 2012). On the other hand, women generally exhibit lower PhA compared to men, primarily due to their relatively lower body muscle mass (lower reactance) and higher body fat mass (higher resistance) compared to men with similar BMI (Karastergiou et al., 2012). Furthermore, PhA has been found to be significantly associated with ethnicity (Jensen et al., 2019; Kuchnia et al., 2017; C. K. M. Lim et al., 2021). This can be attributed to differences in muscle mass and fat mass among ethnicities (Wulan et al., 2010; Yoowannakul et al., 2018).

2.5.2.5 Health Status

PhA is frequently lower in diseased populations (Norman et al., 2012), and it could happen independent of changes in anthropometry differences (Johansen et al., 2003; Shah et al., 2001). It was suggested that some elements of the disease itself could lower PhA, such as infection, inflammation and oxidative stress (B. R. da Silva et al., 2023). Chronic diseases can induce inflammation and oxidative stress, resulting in cellular

injury that impairs cell membrane integrity and function. Additionally, imbalanced fluid distribution observed in various chronic diseases can contribute to a decrease in PhA (B. R. da Silva et al., 2023). Studies showed there was a significant weak-to-moderate correlation between phase angle and inflammation markers such as C-reactive protein and albumin in PD and HD patients (Abad et al., 2011; Demirci et al., 2011). Therefore, a lower PhA has been found to be associated with a higher Charlson comorbidities index (Shin et al., 2017) and a greater number of comorbidities (C. K. M. Lim et al., 2021) in HD patients. Additionally, it has been observed that dialysis vintage is negatively correlated with PhA, even in the absence of significant changes in body composition (Johansen et al., 2003). Furthermore, lower PhA has been identified as an independent risk factor for mortality in dialysis patients (Abad et al., 2011; Shin et al., 2017).

2.5.3 Clinical Significance and Utility of BIA-Derived Phase Angle

Robust evidence has supported the role of PhA as a health indicator. For example, PhA has been found to be associated with disease severity, disease prognosis, inflammation, infection, overhydration, hospitalization, and mortality in different populations. In addition, PhA has been reported as a good predictor of nutrition status and physical performance (Norman et al., 2012), which is explainable by the fact that PhA is highly correlated with muscle mass, fat mass, and hydration status (InBody Co. Ltd, 2018b). Evidence from the dialysis population has shown that PhA is a useful indicator for predicting nutrition status and inflammation status (Demirci et al., 2011; Leal-Escobar et al., 2019). Moreover, lower PhA has been associated with both all-cause and cardiovascular death in patients undergoing PD (R. Huang et al., 2020). Last

but not least, PhA has shown good potential in predicting sarcopenia in both dialysis and non-dialysis populations (Di Vincenzo et al., 2021; Ding et al., 2022).

Theoretically, a higher PhA reflects better health condition and physical fitness. However, the ideal PhA range is still under investigation. Studies have shown that PhA in healthy populations ranges between 5-7° (Bosy-Westphal et al., 2006), while athletes can achieve >9.5° (Torres et al., 2008). Conversely, a lower PhA is associated with impaired clinical outcomes. The close association between PhA and disease severity, as well as clinical outcomes, has highlighted its potential as a diagnostic and prognostic indicator. The prognostic ability of PhA in terms of survival has been tested in various disease settings, such as human immunodeficiency virus (HIV) infection, cancer, dialysis, heart failure, and neurological diseases, with reported disease-specific prognostic cut-off values ranging from 2.5-6.0 ° (Norman et al., 2012). In a longitudinal study conducted on PD patients, patients with PhA ≥ 6 ° showed significantly higher cumulative survival rates at 1 year, 2.5 years, and 5 years (Avram et al., 2006). Furthermore, studies in HD population have suggested PhA cut-off values for detecting PEW, such as 4.6° for the Chinese population (Tan et al., 2019), and 4.26° and 3.30° for Malaysian males and females, respectively (C. K. M. Lim et al., 2021).

2.5.4 Phase Angle and Sarcopenia

Given its association with muscle mass and strength, PhA emerges as a potential proxy for detecting sarcopenia (Norman et al., 2012). Supported by growing evidence, EWGSOP 2019 has identified PhA as a potential marker for sarcopenia detection, which is expected to guide future intervention strategies for sarcopenia (Cruz-Jentoft

et al., 2019). A systematic review that included 13 relevant studies from different populations (e.g., community-dwelling elderly, hospitalized elderly, cancer patients, cirrhotic patients, kidney transplant recipients, and patients with chronic obstructive pulmonary disease) concluded that individuals with sarcopenia have lower PhA, and prevalence of sarcopenia is higher in individuals with low PhA. Besides, weak-to-moderate correlations have been reported between PhA and muscle mass, HGS, and gait speed (Di Vincenzo et al., 2021). Various PhA cut-off values (ranging from 3.55° to 5.05°) for sarcopenia detection in different populations have been recommended, including for elderly individuals (Kilic et al., 2017; Yamada et al., 2019), cirrhotic patients (Espirito Santo Silva et al., 2019), cardiovascular disease patients (Hirose et al., 2020), and kidney transplantation recipients (Kosoku et al., 2020). The disparity in these recommended PhA cut-off values indicates the inappropriateness of extrapolating these findings to another population, underscoring the need to establish the population-specific or disease-specific PhA cut-off for sarcopenia detection (see Table 2.3).

In recent years, emerging evidence regarding the association between PhA and sarcopenia has been reported in the dialysis population (see Table 2.3). A study from South Korea reported that PD patients with PhA in the low tertile were 9.8 times and 52.8 times more likely to be sarcopenic compared to patients with PhA in the middle and high tertiles (Do et al., 2021a). This association between PhA and sarcopenia was supported by a study from China, which proposed a PhA cut-off of $\leq 5.3^\circ$ for sarcopenia detection in PD patients, with a reported sensitivity of 80% and specificity of approximately 73%. Additionally, this study suggested gender-specific PhA cut-offs of $\leq 5.3^\circ$ for men and $\leq 5.0^\circ$ for women (Y. Chen et al., 2022). Similar findings

were reported in patients undergoing HD. A study from China demonstrated strong predictability of PhA for sarcopenia and proposed an overall PhA cut-off of 4.67°, a male-specific cut-off of 4.67°, and a female-specific cut-off of 4.60° for sarcopenia detection, with sensitivity ranging between 85-88% and specificity ranging between 67-69% (Ding et al., 2022). Furthermore, PhA was found to be significantly associated with muscle strength and physical performance in HD patients (Beberashvili et al., 2014; Delgado et al., 2013). However, a study from China that defined sarcopenia as low appendicular muscle mass (<20kg in males and <15kg in females) reported no association between PhA and sarcopenia in a multi-variable logistic regression analysis (Bae et al., 2022).

To date, there is a lack of studies from Southeast Asian countries that examine the predictive capability of PhA in sarcopenia among the dialysis population. Southeast Asians exhibit distinct body composition characteristics that differ not only from Caucasians, but also from East Asians and South Asians, due to the diverse ethnic makeup within the region (T. D. Wang et al., 2010; Wulan et al., 2010). Notably, ethnicity has been shown to affect both muscle strength and PhA (Giglio et al., 2018; Kuchnia et al., 2017). Additionally, lifestyle patterns (e.g., dietary and physical activity patterns) have been identified as factors associated with PhA (Jaremków et al., 2021). These findings suggest the need to establish country-specific PhA cut-offs for sarcopenia identification, particularly for Malaysia, which possesses a unique ethnic composition and lifestyle patterns that may influence the performance of PhA in assessing sarcopenia. Furthermore, the differences in PhA and body composition between HD and PD patients (Abad et al., 2011; Harvinder et al., 2013) highlight the

importance of establishing dialysis modality-specific PhA cut-offs for sarcopenia diagnosis.

Table 2.3 : Summary of Studies Proposing PhA Cut-off for Sarcopenia Detection

First Author (year)	Country	Study Population	Sample size	Male (%)	Mean Age (years)	Sarcopenia definition	BIA model	BIA type	PhA cut-off	AUC	Sen (%)	Spe (%)
Non-dialysis Populations												
Hirose (2020)	Japan	CVD patients	412	67.2	70.0	AWGS 2014	InBody S10	MFBIA	(M) ≤ 4.55◦ (F) ≤ 4.25◦	0.821 0.777	76.0 74.0	61.4 86.8
Kosuku (2020)	Japan	Kidney transplant recipients	210	58.1	55.0	AWGS 2014	InBody S10	MFBIA	≤ 4.46◦	0.730	74.0	70.0
Espirito Santa Silva (2019)	Brazil	Cirrhotic patients	119	100.0	54.4	EWGSOP 2019	Bodystat 4000	MFBIA[b]	≤ 5.05◦	0.730	73.3	61.5
Yamada (2019)	Japan	Community - dwelling elderly	1009	28.2	80.6	AWGS 2014	TANITA MC-780A	MFBIA	(M) ≤ 4.05◦ (F) ≤ 3.55◦	0.718 0.721	82.0 71.4	52.2 65.8
Kilic (2017)	Turkey	Community - dwelling and hospitalized elderly	263	41.8	73.3	EWGSOP 2010	Quadscan and Inbody[a]	MFBIA	≤ 4.55◦	0.703	70.0	65.9
Dialysis Populations												
Y. Chen (2022)	China	PD Patients	101	52.5	51.3	AWGS 2014	AINST 2018	MFBIA	≤ 5.3◦ (M) ≤ 5.3◦ (F) ≤ 5.0◦	0.790 0.850 0.700	80.0 NA NA	73.2 NA NA
Ding (2022)	China	HD Patients	346	61.6	58.2	AWGS 2019	SECA 515	MFBIA	≤ 4.67◦ (M) ≤ 4.67◦ (F) ≤ 4.60◦	0.820 0.820 0.830	86.7 87.9 85.5	67.4 69.0 66.7

Table 2.3 : Continued

Do (2021a)	Korea	PD Patients	200	55.5	57.0	AWGS 2014	InBody 770	MFBIA[b]	≤ 4.4◦	0.730	81.3	59.6

Abbreviations: AUC, area under curve; AWGS, Asian Working Group for Sarcopenia; CVD, cardiovascular disease; EWGSOP, European Working Group on Sarcopenia in Older People; PhA, phase angle; MFBIA, multi-frequency bioelectrical impedance analysis; NA, not available; Sen, sensitivity; Spe, specificity. [a] Model not declared; [b] muscle mass was estimated by dual-energy x-ray absorptiometry (DXA).

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study Design

This study employed a single-center cross-sectional design, whereby subjects were assessed at a single time point in the Nephrology Clinic of Hospital Serdang.

3.2 Study Location

This study was conducted at the Nephrology Clinic of Hospital Serdang in Selangor. The Nephrology department at Hospital Serdang serves as a tertiary referral center in the field of Nephrology and caters to a total of 317 active PD patients as of January 2022.

3.3 Subject Criteria

3.3.1 Inclusion Criteria

Malaysian individuals aged 18 years and above, who had been receiving regular PD treatment for a minimum of 6 months.

3.3.2 Exclusion Criteria

Patients were excluded if they had:

- Communication barriers or difficulties in following instructions, such as blindness, muteness, deafness, language barriers, or diagnosed with intellectual disabilities.
- Contraindications for BIA (e.g., amputation, implanted metallic devices, and the presence of a pacemaker).

- Acquired immunodeficiency syndrome (AIDS) or malignancy.
- History of peritonitis, infections, trauma, or surgical procedures in the past 3 months.
- Physical impairments unrelated to sarcopenia, such as Parkinson's Disease, stroke, arthritis, or limb amputation.

3.4 Sampling Method

Consecutive sampling was adopted for patient recruitment, which means all patients who fulfilled study criteria were recruited until the required sample size was achieved.

3.5 Study Population

3.5.1 General Population Size

General population refers to the entire population that carries a similar characteristic of interest (Turner, 2013), which includes individuals who violate the subject criteria of a study (Asiamah et al., 2017). As of January 2022, there were 317 active PD patients under the care of the Nephrology Clinic in Hospital Serdang, representing the general population of the present study.

3.5.2 Target Population Size

Target population refers to a refined general population wherein individuals violating the research assumption and objective are excluded (Asiamah et al., 2017). Out of these 317 PD patients under the care of Nephrology Clinic in Hospital Serdang, 222 patients (70.0%) were found eligible for this study.

3.6 Sample Size Calculation

Different objective requires varying sample size to ensure adequate power for hypothesis testing (Hazra & Gogtay, 2016). Therefore, sample size calculation was conducted for each specific objective (except objective that is merely descriptive) and the highest number was adopted in this study.

3.6.1 Sample Size Calculation for Specific Objective 1

Specific Objective 1: To determine the sociodemographic characteristics, clinical features, nutritional status and PhA of PD patients, both in the overall population and stratified by sarcopenia status.

Sample size calculation is not required as these data are merely descriptive.

3.6.2 Sample Size Calculation for Specific Objective 2

Specific Objective 2: To determine the prevalence of sarcopenia among PD patients.

Sample size was calculated according to one proportion formula (Daniel, 1999) with finite population correction as shown below:

$$n' = \frac{NZ^2 P(1-P)}{d^2 (N-1) + Z^2 P(1-P)}$$

where

n' = sample size with finite population correction,

N = Population size,

Z = Z statistic for level of confidence,

P = Expected proportion (in proportion of one), and

d = Precision (in proportion of one)

Below figures were substituted into the formula:

P: 17.8% (based on weighted rate of six previous studies about sarcopenia prevalence among PD patients, listed in Appendix 1)

N: 222 (target population size)

Z: 1.96 (95% confidence interval)

d: 0.05 (5% precision)

Therefore,

$$n' = \frac{222\ (1.96)^2\ (0.178)\ (1-0.178)}{0.05^2\ (222-1) + 1.96^2\ (0.178)\ (1-0.178)}$$

n' = 112

Considering a non-response rate of 20%;

Total sample size needed = 112 / (1.0-0.2)

= **140 subjects**

3.6.3 Sample Size Calculation for Specific Objective 3

Specific Objective 3: To assess whether PhA can significantly predict sarcopenia among PD patients.

Sample size was calculated using logistic regression formula in G*Power version 3.1.9.4 (Franz Faul, Universitat Kiel, Germany) statistical software (Figure 3.1):

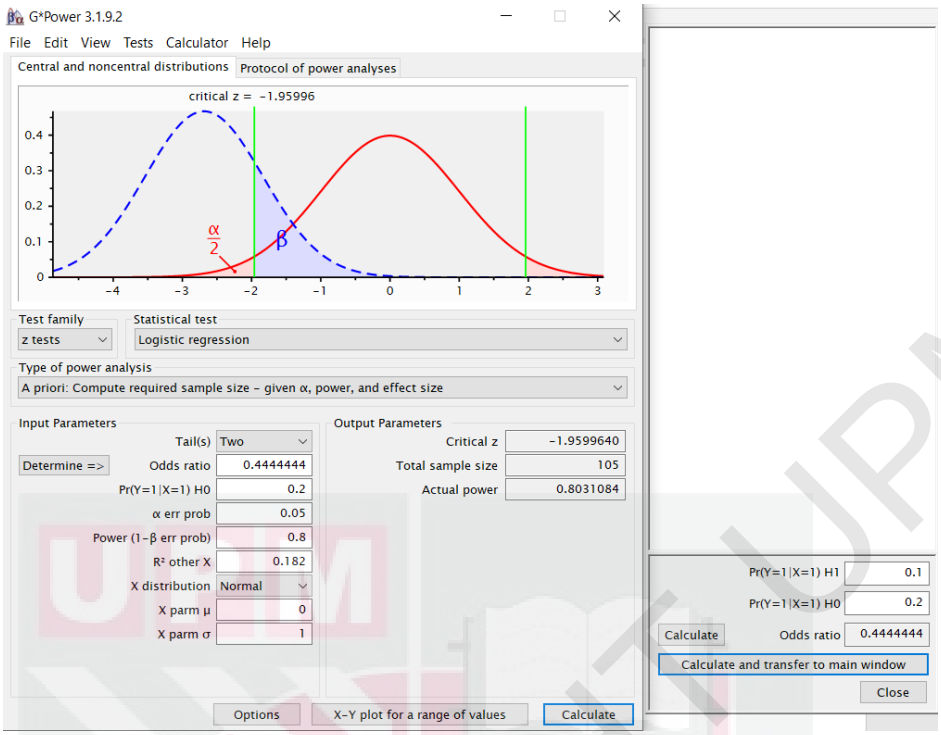


Figure 3.1 : Sample Size Calculation (Logistic Regression)

The inputted figures for Pr (Y=1|X=1) H0 (which is 0.2) and Pr (Y=1|X=1) H1 (which is 0.1) were obtained from a pilot study that involved 30 PD patients. Odd ratio was then automatically-calculated by the software. Alpha (α) level was set as 0.05 (95% confidence interval), whereas power (1-β) was set as 0.8.

The calculated sample size was 105

Considering a non-response rate of 20%;

Total sample size needed = 105/ (1.0-0.2)

= 131 subjects

3.6.4 Sample Size Calculation for Specific Objective 4

Specific Objective 4: To establish a population-specific PhA cut-off value with acceptable discriminative power for sarcopenia detection among Malaysian PD patients.

Sample size was calculated using MedCalc version 19.2.0 software (Figure 3.2):

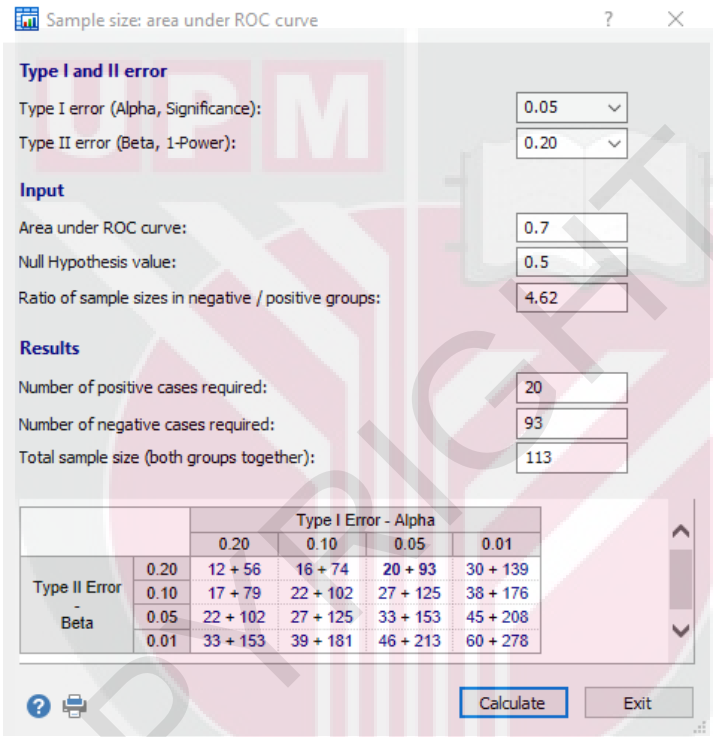


Figure 3.2 : Sample Size Calculation (Area under ROC Curve)

The inputted figure for ratio of sample size in negative/positive group (which is 4.62) was obtained from the weighted rate of 6 previous studies about sarcopenia incidences among PD patients (Abro et al., 2018; As'Habi et al., 2018; M. Z. C. da Silva et al., 2019; Davenport, 2022a; Do et al., 2021b; Kamijo et al., 2018). Alpha (α) level was set as 0.05 (95% confidence interval), beta (β) level was set as 0.2 (study power is 0.8), area under ROC curve was set as 0.7 (acceptable discriminative power) (Hosmer et al., 2013).

The calculated sample size was 113

Considering a non-response rate of 20%;

Total sample size needed = 113/ (1.0-0.2)

= **142 subjects**

3.6.5 Summary of Sample Size Calculation

Table 3.1 shows the summary of sample size based on specific objectives. Sample size with the highest number was chosen in this study, which is 142 subjects.

Table 3.1 : Summary of Sample Size Based on Specific Objectives

Specific Objective	Method	Required Sample Size
1	No required as data is merely descriptive	Not Available
2	Finite Population Correction (Daniel, 1999)	140
3	G-Power Software (Logistic regression)	131
4	MedCalc (ROC curve)	142

3.7 Research Instruments

The instruments employed in this study are defined operationally as follows:

3.7.1 Sociodemographic Characteristics

Socio-demographic characteristics such as age, gender ethnicity, marital status, education background, employment status and monthly household income were gathered through face-to-face interviews. Based on the Household Income and Basic Amenities Survey Report 2019, household income was categorized into B40, M40, and T20. The B40 group refers to the bottom 40% of households with a monthly income of RM4,849 or less, the M40 group refers to the 40% of households with a

monthly income ranging from RM4,850 to RM10,959, while the T20 group refers to the top 20% of households with a monthly income of RM10,960 or more (Department of Statistics Malaysia, 2020).

3.7.2 Clinical Characteristics

Patients' information regarding history of dialysis modality, dialysis vintage, presence of comorbidity and dialysis adequacy were retrieved from electronic-based medical records. If there was any missing data from medical records, additional information was then obtained directly from patients during the interview session.

3.7.3 Anthropometry Measurement

All anthropometry measurements were conducted in accordance with International Society of Advancement in Kinanthropometry (ISAK) protocol by trained researchers.

3.7.3.1 Body Height and Weight

Patients were measured for their height using a portable stadiometer (Model 213, Seca, Hambury, Germany) and for their weight using a digital weighing scale (Model HD-319, Tanita, Tokyo, Japan) (Appendix 4). Patient's weight was measured in minimal clothing, without shoes and any objects in pocket. Measurement was recorded to the nearest 0.1kg. For patients with dialysate-instilled during measurement, the weight of instilled dialysate was deducted from the measured weight, in order to reflect patients' actual body weight. The body mass index (BMI) was calculated using the formula of weight (kg)/height (m^2). Patient's dry weight (which was retrieved from medical record) was used in BMI calculation.

3.7.3.2 Mid-upper Arm Circumference

Mid-upper arm circumference (MUAC) was measured using a non-stretchable Lufkin® metal measuring tape (Apex Tool Group, LLC, NC, USA) (Appendix 4). The landmarks of acromiale, radiale, and mid-acromiale-radiale were identified and marked on patients' relaxed right arm. MUAC was subsequently measured on the mid-acromiale-radiale point. To calculate the mean value, two measurements were taken and recorded to the closest 0.1 cm. When the discrepancy between the first and second measurements is greater than 1%, a third measurement was then taken, as per ISAK protocol (Stewart et al., 2011).

3.7.3.3 Calf Circumference

Calf circumference was measured using a non-stretchable Lufkin® metal measuring tape (Apex Tool Group, LLC, NC, USA) (Appendix 4). Measurements were done on patient's right calf in a supine position, with the knee bent at 90° and the foot placed on the bed in a relaxed condition. Measuring tape was wrapped perpendicularly around the lower calf, and measurement was taken at its maximum girth. To calculate the mean value, two measurements were taken and recorded to the closest 0.1 cm. When the discrepancy between the first and second measurement is greater than 1%, a third measurement was then taken, as per ISAK protocol (Stewart et al., 2011).

3.7.4 Bioelectrical Impedance Analysis

BIA measurement was performed using a portable direct segmental multifrequency (1-1000kHz) bio-impedance analysis (MFBIA) device (Inbody S10, InBody Co., Ltd, Seoul, Korea) (Appendix 4). This is in compliance with the recommendation of

AWGS 2019 to use MFBIA in sarcopenia assessment (AWGS 2019). Moreover, direct segmental BIA technology can provide improved precision in muscle estimation compared to total body BIA technology (Tanaka et al., 2007). The output accuracy of this device has been validated among dialysis patients by a previous study (Jayanama et al., 2018).

BIA measurements were performed in lying position using tetrapolar 8-points touch-type electrodes attached to corresponding body parts as per the manufacturer's measurement protocol (InBody Co. Ltd, 2019). For patients with dialysate-instilled during measurement, the weight of the instilled dialysate was subtracted from the measured weight to account for the patients' actual body weight, and the BIA measurements were conducted without draining the dialysate. The primary rationale for not requiring patients to drain the dialysate before measurement was to minimize the risk of peritoneal infection due to performing dialysate exchange in an unfamiliar environment and manner, as advised by nephrologists in our setting. Additionally, recognizing that draining the dialysate before BIA measurement can be both risky and time-consuming, making it impractical in many clinical settings, we aimed to establish a PhA cut-off value that reflects real-world practice and can be applied accordingly. To validate the BIA measurement approach, a pilot study involving 30 PD patients was conducted using the MFBIA device from the present study (InBody S10) to evaluate the impact of dialysate on BIA measurements. It was found that when dialysate-excluded body weight (i.e., the instilled dialysate was subtracted from the measured weight) was used, it effectively minimized dialysate-induced bias in MFBIA measurements to a level considered clinically insignificant. Specifically, this approach did not introduce statistically or clinically significant measurement bias in the BIA

parameters examined in the current study, namely PhA and appendicular skeletal muscle mass index (ASMI) (see list of publications).

PhA was collected as a raw data from the BIA device at the frequency of 50 kHz. ASMI, expressed in kg/m^2, was calculated as appendicular mass divided by squared height (InBody Co. Ltd, 2018a). Other BIA-derived measurements reported in this study included body fat percentage (BFP), skeletal muscle mass (SMM) and extracellular water/ total body water ratio (ECW/TBW ratio).

The procedures for performing BIA measurements are as follows:

1) Patients were measured for weight and height. For patients with dialysate-instilled, the weight of the instilled dialysate was deducted from their current body weight to obtain their actual weight.

2) Patients were required to remove any metals and other electricity conductors from their body (e.g., necklace, ring, bracelet, belt, etc.).

3) Patients were asked to lie in a supine position on a medical bed in the Nephrology Clinic, with their legs apart and arms not touching their torso (Figure 3.3). They had to remain in this lying posture for 15 minutes before the test to allow for even body water distribution.

4) Patients' information was entered into the device.

5) Prior to connecting the electrode to patients' both hands (i.e., thumb and middle finger) and feet (i.e., between the anklebone and heel), the electrode-connecting areas were wiped and moisturized with a non-alcohol wet tissue.

6) The BIA assessment was then carried out after proper electrode placement.

7) Patients were instructed to stay still throughout the assessment.

8) Patients' data was stored in a thumb drive and later transferred to a personal computer connected with the Inbody Lookin' Body Dongle.

9) The software's output was then extracted for data analysis purposes.

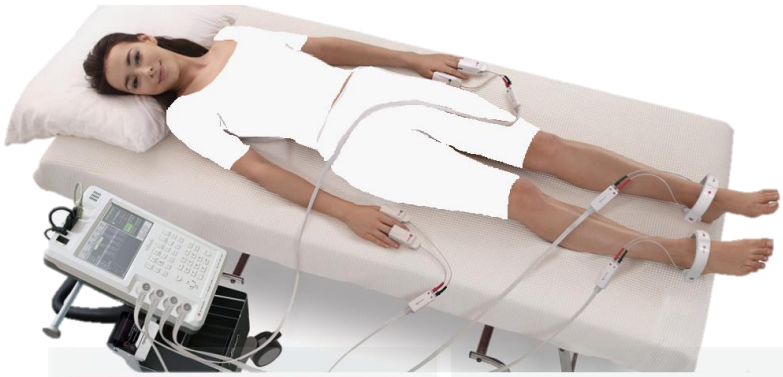


Figure 3.3 : BIA Measurements Using Inbody S10

3.7.5 Physical Function and Performance

3.7.5.1 Handgrip Strength

Handgrip Strength (HGS) was measured using a Jamar Plus Digital hand dynamometer (Paterson Medical, Green Bay, WI, USA) (Appendix 4), following the HGS measurement protocol recommended by AWGS 2019 (L. K. Chen et al., 2020). HGS was measured on the dominant arm of patient, in sitting position, with 90° elbow flexion (Figure 3.4). HGS measurements were repeated for three times and the highest value was recorded.

Figure 3.4 : Handgrip Strength Measurement

3.7.5.2 Five-Time Chair Stand Test (5TCST)

The 5TCST test was conducted in accordance with AWGS 2019 guidelines. A stopwatch and a chair with straight back and seat height of 43cm were required for this test. Patients were instructed to fold their arms across their chest and perform sit-to-stand movements five times at their fastest speed (Figure 3.5). A demonstration was conducted by the researcher before the test. The test was performed two times with a five-minute interval, and the average reading was recorded. Due to safety concerns, patients who failed to complete 5TCST due to physical weakness were not forced to complete it but were considered to have failed the test.

Figure 3.5 : 5-time Chair Stand Test

3.7.6 Biochemical Measurement

Patients' biochemical measurements were obtained based on the routine blood test performed by the in-house hospital laboratories. The latest result (i.e., within a month) of biochemical parameters of interest were collected, including renal profile (e.g., serum urea and serum creatinine), liver profile (e.g., serum albumin), lipid profile (e.g., serum cholesterol), hemoglobin and total iron binding capacity (TIBC). Additionally, the dialysis treatment adequacy (Kt/V) was retrieved from the electronic medical records system of the hospital.

3.7.7 Three-day Diet History

Dietary intake was collected for 3 days (2 weekdays and 1 weekend day) using the diet recall method by a trained dietitian. Diet recall method is a widely-utilized instrument in both research and clinical settings, as it has been proven to have high precision and validity, save time and enhance response rate (Castell et al., 2015). The first-day diet recall was performed in face-to-face interview, whereas subsequent diet recalls were conducted via phone interview. The portion size of food and drink intake was estimated using a set of household measurement tools, which consisted of small bowl, medium bowl, large bowl, cup, glass, dessertspoon and teaspoon (Appendix 4).

Nutrient intake, specifically energy and protein intake, was analyzed via the Nutritionist Pro Software (Version 4.0.0, Axxya Systems, LLA, USA, 2019). The amount of glucose absorbed from the peritoneal dialysate was factored into the calculation of total energy intake (TEI). The adequacy of TEI and dietary protein intake (DPI) were interpreted as TEI and DPI adjusted to patient's ideal body weight (IBW). IBW was defined according to the recommendation of the Renal Association Clinical Practice Guideline on Nutrition in CKD by the United Kingdom Renal Association, which was calculated at BMI 20 if patient's BMI was < 20 kg/m^2; calculated at BMI 25 if patient's BMI was >25 kg/m^2; or using actual body weight if patient's BMI was between 20 and 25kg/m^2 (Wright & Jones, 2011). The ratio of TEI to basal metabolic rate (BMR) was assessed to identify inaccuracies in dietary reporting (Goldberg et al., 1991). The BMR was calculated using the Harris-Benedict equation based on the patient's ideal body weight.

3.7.8 Diagnosis of Sarcopenia

The Asian Working Group for Sarcopenia (AWGS) diagnostic protocol was used to diagnose sarcopenia in this study. Three main criteria are included in AWGS diagnostic protocol, namely (i) low appendicular skeletal muscle mass index (ASMI), (ii) low muscle strength, and (iii) low physical performance.

AWGS 2019 defined sarcopenia as low muscle mass with low muscle function (either low muscle strength or low physical performance, or both of them), as depicted in Figure 3.6. When all three criteria of low ASMI, low muscle strength and low physical performance are met, it is defined as severe sarcopenia (L. K. Chen et al., 2020).

Three test options were suggested for physical performance assessment, namely the 6-meter walk test (6mWT), short physical performance battery test (SPPB), and five times chair stand test (5TCST). In the current study, 5TCST was adopted over the other options because both 6mWT and SPPB imposed a higher fall risk and required a specific amount and condition of space that was not applicable in the study location.

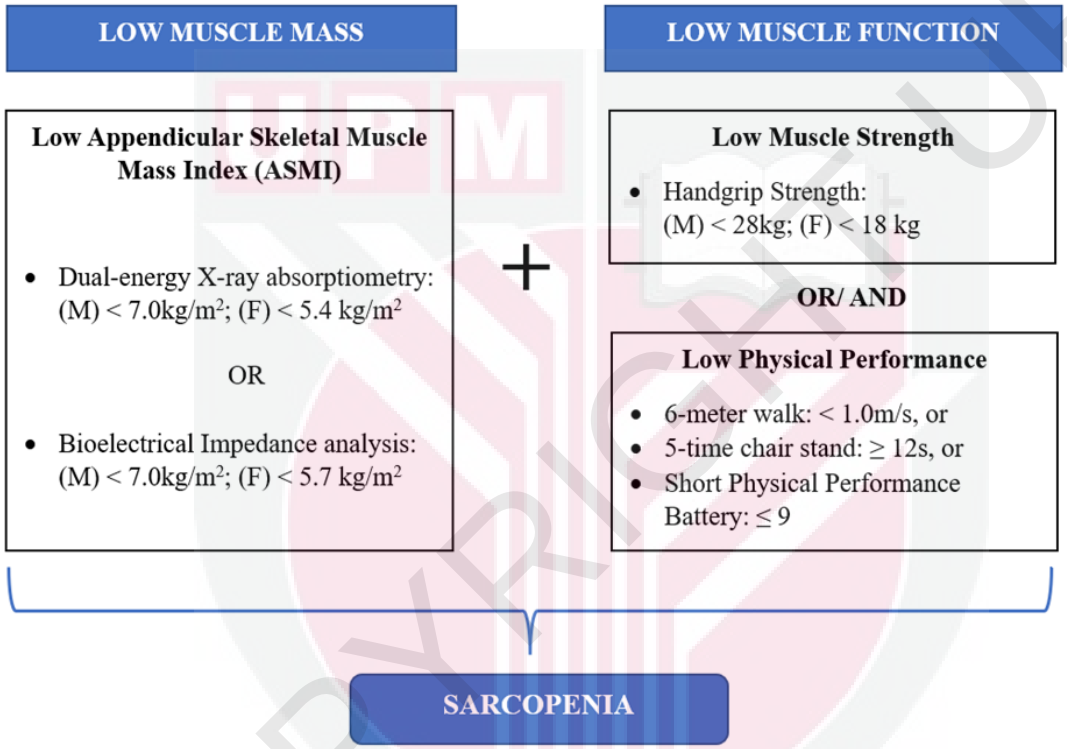


Figure 3.6 : Sarcopenia Diagnostic Algorithms of AWGS 2019

3.8 Study Procedure

3.8.1 Ethics Application

This study has been reviewed and approved by the Ethics Committee of the National Medical Research Register (NMRR) with the reference number NMRR-21-790-59396 (Appendix 2). Additionally, permission for data collection activities at the study site (Nephrology Clinic in Hospital Serdang) was obtained from the Hospital Director

prior to the commencement of the study. All research activities were conducted in accordance with the regulations of Good Clinical Practice.

3.8.2 Screening Activity and Patients' Recruitment

The patient list was obtained from the clinic approximately one week before their appointment date and screened for patients selection criteria via the electronic medical record (Electronic Hospital Information System [eHIS]) of Hospital Serdang. To address the possibility of incomplete information in eHIS (*e.g.*, medical conditions that were treated in other medical facilities, communication ability *etc.*), a face-to-face interview was conducted prior to data collection to ensure that only patients who fulfilled the study criteria were selected. The entire process of research activities was explained to every selected patient, and written consent was obtained before conducting data collection. Participants were allowed to withdraw from this study at any time and for any reason.

3.8.3 Data Collection

Data collection was carried out from January to April 2022, during the COVID-19 pandemic in Malaysia. Therefore, all the research activities were conducted in compliance with COVID-19-specific standard operating procedures (SOP). Researchers underwent a web-based health screening assessment designed by Hospital Serdang and had their body temperature checked before entering the premises. They were equipped with personal protective equipment (PPE) when encountering patients, including medical grade N95 respirator, field shield, medical apron and gloves. Face-to-face interview was conducted with a minimum 1-meter physical distance between researcher and patient.

A set of interviewer-administered questionnaires was used to collect all the patient's information, including (i) sociodemographic data; (ii) medical history; (iii) anthropometry data; (iv) BIA data; (v) physical function and performance data; (vi) biochemical data; (vii) clinical data; and (viii) dietary data. The questionnaire included a combination of closed-ended and open-ended questions based on appropriateness. A sample of this questionnaire is attached as Appendix 3.

The data collection process involved two sessions: one face-to-face assessment during patients' routine appointments in the Nephrology Clinic, and one phone interview conducted on the subsequent weekend. Three researchers with dietetic background were trained for data collection. They underwent detailed protocol training and hands-on training (mock data collection session) two weeks prior the data collection, to maintain standardization and reduce biases in data collection. In the first interview session, trained researchers assessed sociodemographic information and conducted a one-day diet recall in a face-to-face manner. Following that, physical measurements, BIA measurements, handgrip strength (HGS) test, and 5-time chair stand test (5TCST) were performed. Sarcopenia diagnosis was made based on the criteria proposed by AWGS 2019.

After that, the details of patients' medical information was retrieved from the electronic-based medical record (eHIS) of Hospital Serdang, which included medical history (e.g., history of dialysis modality, dialysis vintage, presence of major comorbidity), biochemical data (i.e., latest blood test results), anthropometry data (e.g., dry weight, weight history), and dialysis adequacy (i.e., KT/V). Lastly, during

the subsequent weekend, the second interview session was conducted via phone call to collect the remaining two days of diet recall information.

Figure 3.7 depicts the flow chart of the whole data collection process.

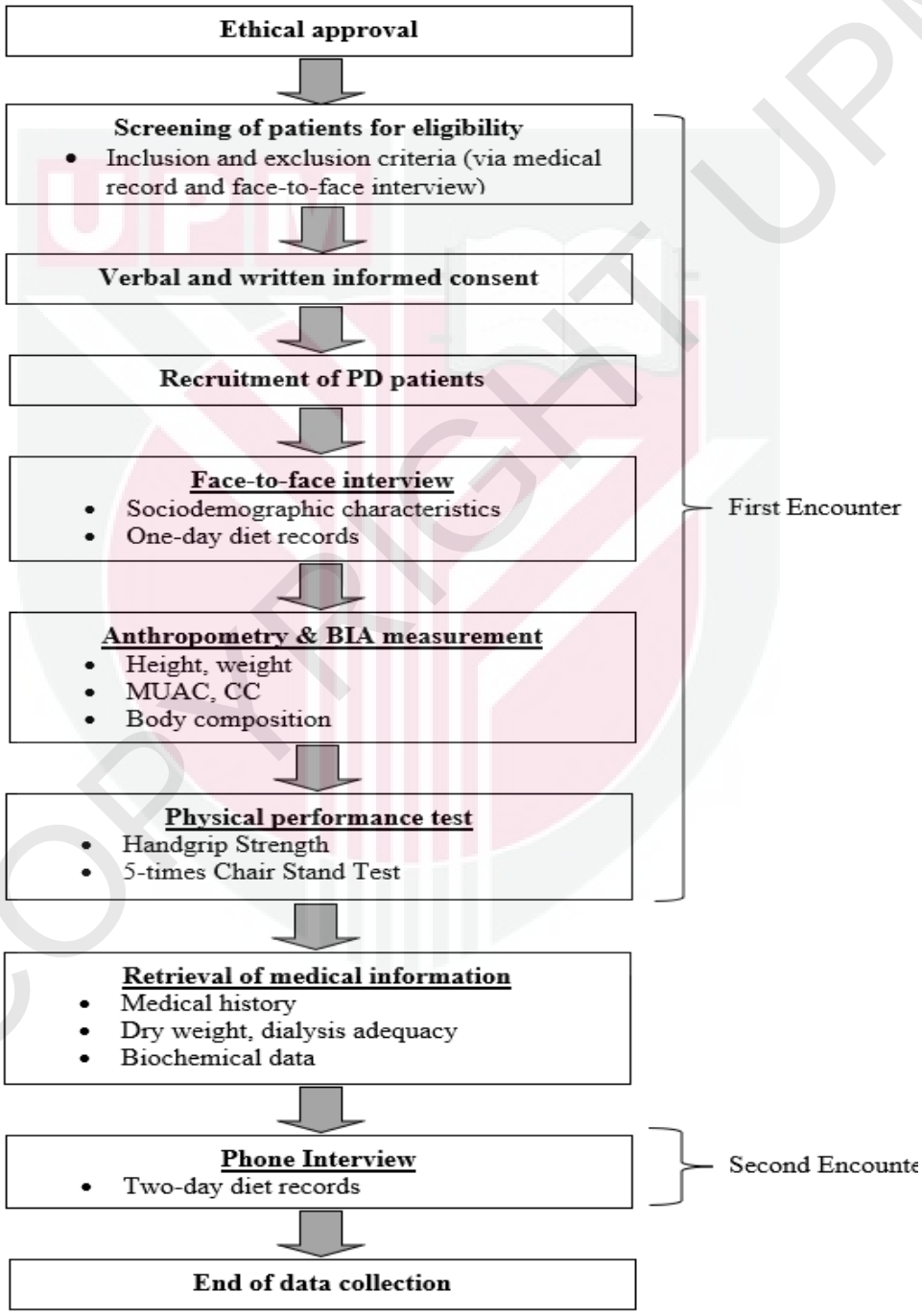


Figure 3.7 : Flow Chart of Data Collection Process

3.9 Statistical Analysis

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) software version 26.0 (IBM, Chicago, IL, USA). Sarcopenia status was dichotomized into sarcopenia (including both sarcopenia and severe sarcopenia) and non-sarcopenia for statistical analysis purpose. Prior to statistical analysis, data were checked with normality using Shapiro-Wilk test, skewness and kurtosis analysis and graphical method (histogram plot). All continuous data were found to be normally distributed, except for dialysis vintage and dialysis adequacy parameter (kt/V). The threshold of statistical significance was set at p-value <0.05 for all analyses in this study.

3.9.1 Patients' Characteristics

Patients' distribution by socio-demographic characteristics, medical background and nutrition status were presented in general and based on sarcopenia status. Continuous data were presented in mean ± standard deviation for normally-distributed data, or median (q1-q3) for non-normally distributed data. Categorical data were presented in frequency, percentage and range. Associations between variables were tested using independent t-test, Chi-square test, and Fisher's Exact test.

3.9.2 Prevalence of Sarcopenia among PD Patients

Prevalence of sarcopenia and its distribution across all individual diagnostic criteria were presented as frequency, percentage, pie chart and bar chart. The differences in the individual diagnostic criteria between sarcopenia and non-sarcopenia patients were tested using independent t-test and chi-square test.

3.9.3 Predictive Power of Phase Angle in Sarcopenia Identification among PD Patients

The predictive power of PhA in sarcopenia identification was determined via logistic regression analysis after adjusting for patients' characteristics. Requirements of binomial logistic regression were checked and assured before running the analysis, including (1) absence of significant outliers, (2) presence of linearity between independent variables and logit-transformed dependent variable, and (3) absence of multicollinearity (Appendix 5).

Firstly, outliers were checked at the univariate level for every continuous variable. To ensure there were no univariate outliers included in the analysis, a total of 4 sets of data with outliers were removed, and the dialysis vintage data was logit-transformed. Secondly, logistic regression analysis was performed to examine the linearity between independent variables and the logit-transformed dependent variable. All independent variables were found to be linearly associated with the logit of the dependent variable. Finally, the absence of multicollinearity was confirmed by the Variance Inflation Factor (VIF) value (≤10 for all variables) in the linear regression model (Hair et al., 1995).

The result of the overall sarcopenia diagnosis and individual diagnostic criteria were dichotomized according to the cut-off recommended by AWGS 2019. Multi-variable logistic regression was conducted to determine the odd ratio for PhA in predicting sarcopenia and sarcopenia criteria, after adjusting for patients' characteristics.

3.9.4 Recommended Phase Angle Cut-off for Sarcopenia Detection among Malaysian PD Patients

Discriminative performance of PhA in identifying sarcopenia incidence among PD patients was examined using receiver operating characteristic (ROC) curve analysis. Covariates were adjusted to prevent their contribution to discrimination performance (Janes & Pepe, 2008). The discriminative power of the test was indicated by the area under curve (AUC). According to Hosmer et al. (2013), discrimination is considered as acceptable if the AUC is between 0.7 and <0.8, excellent if it is between 0.8 and <0.9, and outstanding if it is ≥0.9.

The PhA cut-off value was then determined based on its sensitivity and specificity in sarcopenia identification. Since this study aims to discover a pragmatic screening instrument for sarcopenia detection, sufficient sensitivity is necessary to minimize false negative cases (Habibzadeh et al., 2016). Hence, sensitivity was prioritized over specificity in the recommendation of PhA cut-off for sarcopenia detection.

CHAPTER 4

RESULTS

4.1 Screening and Recruitment

Figure 4.1 illustrates the flow for subjects screening and recruitment. As of January 2022, there were 317 active PD patients under the care of Hospital Serdang Nephrology Clinic. Out of these, 222 patients were found eligible for the current study, whereas 95 patients were excluded due to reasons listed in Figure 4.1 and 142 out of 222 eligible patients were approached based on consecutive sampling method. Twelve patients refused to participate resulting in the successful recruitment of 130 patients for the study. The response rate for the current study was 91.5%.

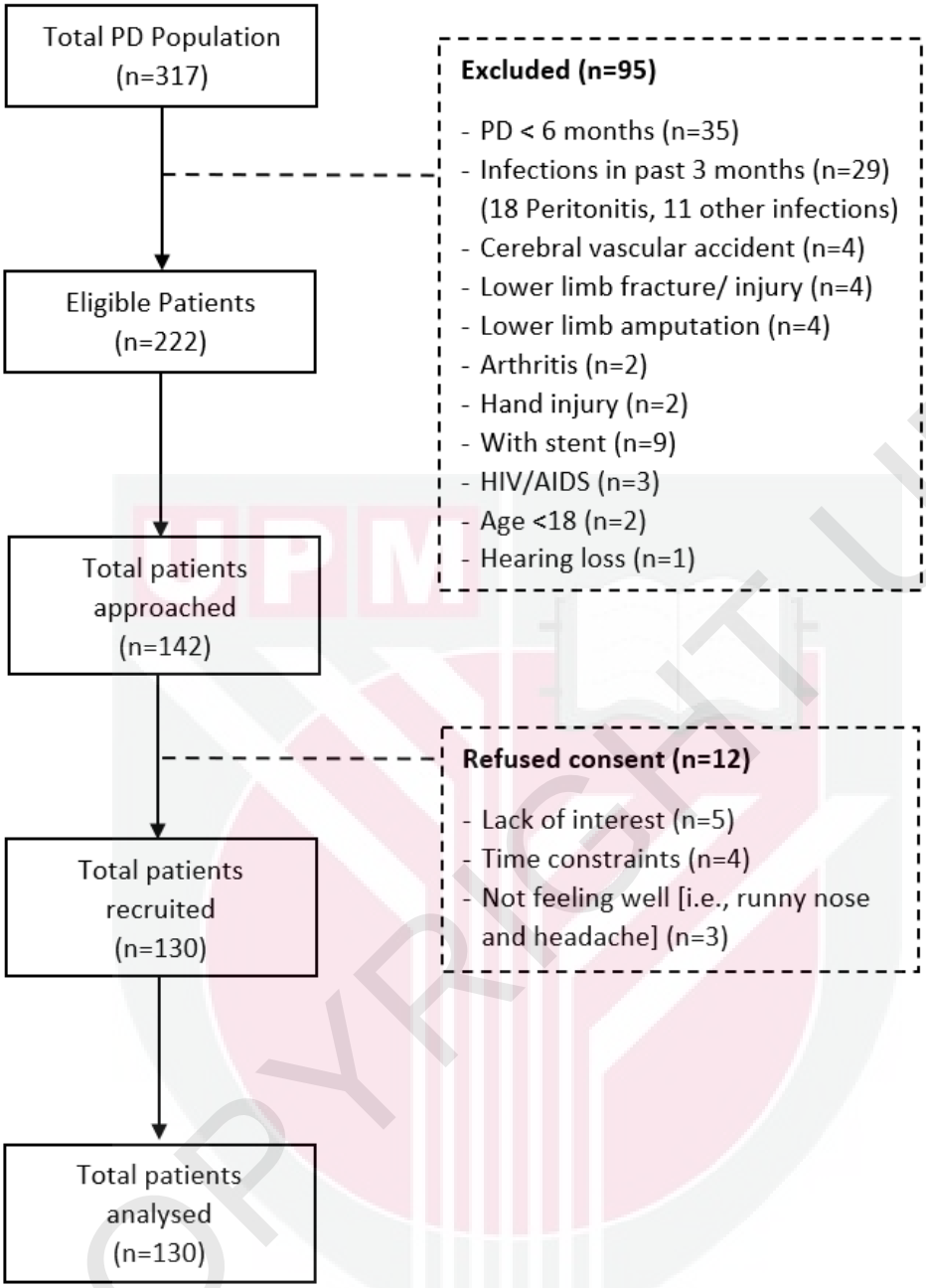


Figure 4.1 : Flowchart of Subjects Screening and Recruitment

4.2 Patients' Characteristics

4.2.1 Overall Patients' Characteristics

4.2.1.1 Sociodemographic Characteristics

Table 4.1 demonstrates patients' sociodemographic characteristics. The mean age of patients was 53.1 ± 13.3 years, with 21.5.% of them aged 65 years and above. The gender distribution was fairly balanced, with male patients (50.8%) slightly exceeding female patients (49.2%). Majority of the patients are married (82.3%). The education level distribution showed most of the patients received secondary education (45.4%), followed by tertiary education (36.2%) and primary education or lower (18.5%). A significant portion of the patients were unemployed (75.4%) and fell under the B40 category for household income (67.7%).

Table 4.1 : Patients' Sociodemographic Characteristics (n = 130)

Variables	n (%)	Mean ± SD	Range
Age (years)		53.1 ± 13.3	24 - 75
18-34	17 (13.1)		
35-44	20 (15.4)		
45-54	24 (18.5)		
55-64	41 (31.5)		
65-74	26 (20.0)		
≥75	2 (1.5)		
Gender			
Male	66 (50.8)		
Female	64 (49.2)		
Ethnicity			
Malay	89 (68.5)		
Chinese	34 (26.2)		
Indian	7 (5.4)		
Marital Status			
Single/ Divorced	23 (17.7)		
Married	107 (82.3)		
Education Level			
≤ Primary	24 (18.5)		
Secondary	59 (45.4)		
Tertiary	47 (36.2)		
Employment Status			
Employed	32 (24.6)		
Unemployed	98 (75.4)		
Household Income			
B40 (≤ RM4,849)	88 (67.7)		
M40 (RM4,850-10,959)	42 (32.3)		
T20 (≥ RM 10,960)	0 (0.0)		

4.2.1.2 Clinical Characteristics

Table 4.2 presents the clinical characteristics of PD patients in current study. Majority of patients had hypertension (95.4%), diabetes mellitus (64.6%) and hyperlipidemia (54.6%). Besides, cardiac vascular disease (22.3%) and hyperuricemia (13.1%) were prevalent among patients. Majority of the patients (57.7%) had at least three coexisting medical conditions. More than half (56.2%) of the patients had dialysis vintage between 12-48 months, with the median of 26.5 (Interquartile range [IQR]=16.0, 50.3) months. More than half of the patients (64.6%) achieved Kt/V of ≥ 1.7, with the

median of 1.9 (IQR=1.6, 2.1). A total of 64.6% of the patients were undergoing manual peritoneal dialysis (i.e., continuous ambulatory peritoneal dialysis and daytime ambulatory peritoneal dialysis), 33.8% were undergoing automated PD (i.e., nocturnal intermittent peritoneal dialysis), whereas 1.5% of them were on peritoneal dialysis that combined both manual and automated modality (i.e., PD-Plus method which performs automated PD at night-time and manual PD in daytime).

Table 4.2 : Patients' Clinical Characteristics (n = 130)

Variables	n (%)	Median (q1-q3)	Range
Comorbidities			
Hypertension	124 (95.4)		
Diabetes mellitus	84 (64.6)		
Hyperlipidemia	71 (54.6)		
Cardiac Vascular Disease	29 (22.3)		
Hyperuricemia	17 (13.1)		
Others[a]	28 (21.5)		
No. of Comorbidities			
One	17 (13.1)		
Two	38 (29.2)		
Three	44 (33.8)		
Four	27 (20.8)		
Five	4 (3.1)		
Dialysis Vintage (months)		26.5 (16.0-50.3)	6.0 - 265.0
< 12	23 (17.7)		
12-48	73 (56.2)		
> 48	34 (26.2)		
Dialysis Adequacy (Kt/V)		1.9 (1.6-2.1)	0.9 - 3.9
≥ 1.7	84 (64.6)		
< 1.7	46 (35.4)		
Modality of PD			
Manual	84 (64.6)		
Automated	44 (33.8)		
Combined[b]	2 (1.5)		

[a]Other comorbidities included bronchial asthma (4 cases), hepatitis B (4 cases), hypothyroidism (3 cases), systemic lupus erythematosus (3 cases), polycystic ovary syndrome (2 cases), benign prostatic hyperplasia (2 cases), chronic gastritis (2 cases), gastroesophageal reflux disease (1 case), hepatitis C (1 case), thalassemia (1 case), Kyrle's disease (1 case), autoimmune lymphoproliferative syndrome (1 case), bronchiectasis (1 case), epilepsy (1 case), iron-deficiency anemia (1 case). [b] Combined manual and automated modality; Abbreviation: PD, peritoneal dialysis.

4.2.1.3 Nutrition Status-Related Characteristics

Table 4.3 provides an overview of parameters that related to patients' nutrition status. The average dry weight and actual weight were 60.5 ± 11.6 kg and 62.9 ± 12.4 kg, respectively. Only 9.2% of patients were found underweight, whereas 53.1% with normal BMI, 30.0% were overweight and 7.7% were obese. Likewise, most of the patients had either normal (16.2%) or excessive (79.2%) body fat percentage (BFP), with only 4.6% patients had inadequate body fat. Average body fat percentage of patients was 31.1 ± 9.6%, which ranges from 9.3-51.8%. Average skeletal muscle mass (SMM) and PhA are respectively 22.4 ± 4.6 kg and 3.85 ± 0.97°. Most of the patients (83.8%) had mid-upper arm circumference (MUAC) >24cm, whereas half of the patients (50.0%) had calf circumference (CC) within the recommended range. Most of the patients (76.2%) have ECW/TBW ratio ≥ 0.400, with the mean value of 0.408 ± 0.013, which indicates overhydration. The average serum albumin level for patients was 29.8 ± 5.1 g/L, with 96.9% of patients having serum albumin <38.0 g/L. Majority of patients (99.2%) had serum cholesterol ≥ 2.59 mmol/l, with the mean value of 5.0 ± 1.3 mmol/l. The mean value for serum creatinine, total iron binding capacity (TIBC) and hemoglobin were 1002.3 ± 317.3 umol/L, 196.6 ± 36.4 umol/L and 10.8 ± 1.9 g/dL, respectively. Majority of patients had total energy intake (TEI) and dietary protein intake (DPI) lower than the ISRNM cut-off for PEW diagnosis (Fouque et al., 2008), with 63.8% of them having TEI <25kcal/kg/day and 58.5% having DPI <0.8g/kg/day. The average TEI and DPI were reported at 23.8 ± 6.3 kcal/kg/day and 0.77 ± 0.29 g/kg/day, respectively.

Table 4.3 : Patients' Nutritional Status-Related Characteristics (n = 130)

Variables	n (%)	Mean ± SD	Range
Dry Weight (kg)		60.5 ± 11.6	34.0 – 90.0
Actual Weight[a] (kg)		62.9 ±12.4	33.9 – 95.8
Body Mass Index (kg/m^2)		23.8 ± 3.7	15.1 - 32.4
Underweight (< 18.5)	12 (9.2)		
Normal (18.5 - 24.9)	69 (53.1)		
Overweight (25.0 – 29.9)	39 (30.0)		
Obese (≥ 30.0)	10 (7.7)		
Body Fat Percentage (%)		31.1 ± 9.6	9.3 -51.8
Under (M:<10; F: <18)	6 (4.6)		
Normal (M:10-20; F: 18-28)	21 (16.2)		
Over (M >20; F> 28)	103 (79.2)		
Skeletal Muscle Mass (kg)		22.4 ± 4.6	12.9 – 33.3
MUAC (cm)		27.9 ± 3.9	18.3 – 37.1
≤ 24	21 (16.2)		
> 24	109 (83.8)		
Calf Circumference (cm)		33.6 ± 3.7	25.1 - 44.0
< 34 (M); <33 (F)	65 (50.0)		
≥ 34 (M); ≥33 (F)	65 (50.0)		
ECW/TBW Ratio		0.408 ± 0.013	0.376 - 0.441
< 0.400	31 (23.8)		
≥ 0.400	99 (76.2)		
PhA (°)		3.85 ± 0.97	1.90-6.60
Serum Albumin (g/L)		29.8 ± 5.1	12.0 – 40.0
< 38	126 (96.9)		
≥ 38	4 (3.1)		
Serum Cholesterol (mmol/L)		5.0 ± 1.3	2.3 – 9.0
< 2.59	1 (0.8)		
≥ 2.59	129 (99.2)		
Serum Creatinine (umol/L)		1002.3 ± 317.3	214.0 - 2017.0
Serum TIBC (ug/dL)		196.6 ± 36.4	108.9–300.0
Serum Hemoglobin (g/dL)		10.8 ± 1.9	6.3 – 17.3
TEI (kcal/kg BW/day)		23.8 ± 6.3	9.1 – 40.9
< 25	83 (63.8)		
≥ 25	47 (36.2)		
DPI (g/kg BW/day)		0.77 ± 0.29	0.15 – 1.77
< 0.8	76 (58.5)		
≥ 0.8	54 (41.5)		

[a]Actual weight denote weight without dialysate; Abbreviation: BW, body weight; DPI, dietary protein intake; ECW, extracellular water; F, female; M, male; MUAC, mid-upper arm circumference; PhA, phase angle; TEI, total energy intake; TIBC, total iron binding capacity; TBW, total body water.

4.2.2 Patients' Characteristics Based on Sarcopenia Status

4.2.2.1 Sociodemographic Characteristics

Table 4.4 depicts the association of sociodemographic characteristics between sarcopenia and non-sarcopenia group. Sarcopenic patients were significantly older (59.1 ± 10.6 years old *vs* 51.0 ± 13.5 years old, p =0.001) and received lower level of education than non-sarcopenic patients. No significant difference was observed between sarcopenia group and non-sarcopenia group for other sociodemographic variables.

Table 4.4 : Comparison of Sociodemographic Characteristics between Sarcopenia and Non-Sarcopenia Patients (n= 130)

Variables	Sarcopenia (n=33)	Non-Sarcopenia (n=97)	χ^2 or t-value	*p*
Gender				
Male	14 (42.4)	52 (53.6)	1.232	0.267
Female	19 (57.6)	45 (46.4)		
Age	59.1 ± 10.6	51.0 ± 13.5	-3.529	**0.001**
< 60 years old	16 (48.5)	64 (66.0)	3.184	0.074
≥ 60 years old	17 (51.5)	33 (34.0)		
Ethnicity				
Malay	20 (60.6)	69 (71.1)	1.264[a]	0.261[a]
Chinese	11 (33.3)	23 (23.7)		
Indian	2 (6.1)	5 (5.2)		
Marital Status				
Single/ Divorced	4 (12.1)	19 (19.6)	0.943	0.332
Married	29 (87.9)	78 (80.4)		
Education Level				
≤ Secondary	28 (84.8)	55 (56.7)	8.704	**0.013**
Tertiary	5 (15.2)	42 (43.3)		
Employment Status				
Employed	5 (15.2)	27 (27.8)	2.135	0.144
Unemployed	28 (84.8)	70 (72.2)		
Household Income				
B40 (≤ RM4849)	25 (75.8)	63 (64.9)	1.315	0.251
Non-B40 (≥ RM4850)	8 (24.2)	34 (35.1)		

Data are presented as n (% column) or mean ± SD; Data were analyzed by Pearson χ^2 test and independent t-test; [a]Data was analyzed between Malay group and Non-Malay group, as analysis without recategorization is not possible due to existence of cell with expected value < 5.

4.2.2.2 Clinical Characteristics

Table 4.5 depicts the association of clinical characteristics between sarcopenia and non-sarcopenia group. No significant association was observed between sarcopenia and non-sarcopenia group for number of comorbidities, dialysis vintage and dialysis adequacy.

Table 4.5 : Comparison of Clinical Characteristics between Sarcopenia and Non-Sarcopenia Patients (n= 130)

Variables	Sarcopenia (n=33)	Non-Sarcopenia (n=97)	χ^2 or *t*- / *U*-value	*p*
No. of Comorbidities	2.8 ± 1.1	2.7 ± 1.0	-0.464	0.643
1 to 2	13 (39.4)	42 (43.3)	0.154	0.695
3 to 5	20 (60.6)	55 (56.7)		
Dialysis Vintage (months)	27.0 (18.5-66.0)	26.0 (15.5-49.5)	1458.500[a]	0.447[a]
< 12	5 (15.2)	18 (18.6)	0.198	0.906
12-48	19 (57.6)	54 (55.7)		
> 48	9 (27.3)	25 (25.8)		
Dialysis Adequacy (Kt/V)	1.9 (1.6-2.2)	1.9 (1.6-2.1)	1511.500[a]	0.634[a]
< 1.7	12 (36.4)	34 (45.1)	0.019	0.892
≥ 1.7	21 (63.6)	63 (64.9)		

Categorical data was presented as n (% column); normally-distributed continuous data was presented as mean ± SD, whereas skewed data was presented as median (q1-q3); categorical data was analyzed by Pearson χ^2 test; normally-distributed continuous data was analyzed with independent t-test, whereas skewed data was analyzed with Mann-Whitney test. [a] Data was analyzed with Mann-Whitney test.

4.2.2.3 Nutrition Status-Related Characteristics

Table 4.6 depicts the association of nutrition status-related characteristics between sarcopenia and non-sarcopenia group. In comparison to non-sarcopenic patients, sarcopenic patients were significantly lower in dry weight (53.8 ± 9.0kg vs 62.8 ± 11.5kg, p <0.001), BMI (22.0 ± 3.2kg/m^2 vs 24.4 ± 3.6kg/m^2, p =0.001), SMM (18.4 ± 3.0kg vs 23.8 ± 4.3, p <0.001), MUAC (26.0 ± 3.6cm vs 28.5 ± 3.9cm, p =0.001), CC (30.7 ± 3.0cm vs 34.6 ± 3.4cm, p <0.001), serum albumin (28.0 ± 5.7 g/L vs 30.4

± 4.7g/L, p <0.05), serum creatinine (872.6 ± 282.6 umol/L vs 1046.5 ± 317.7 umol/L, p <0.05) and PhA (3.28 ± 0.80 vs 4.05 ± 0.94, p <0.001), but higher ECW/ TBW ratio (0.413 ± 0.010 vs 0.407 ± 0.014, p <0.05). No significant difference was observed between sarcopenic and non-sarcopenic patients for mean BFP, serum cholesterol, TIBC, hemoglobin, TEI and DPI (p>0.05). The Chi-square test showed a significantly higher proportion of sarcopenic patients with BMI < 23kg/m^2 (χ2= 12.004, p =0.001), CC < 34cm (for male) and < 33cm (for female) (χ2= 14.661, p <0.001), and ECW/TBW ratio ≥ 0.400 (χ2= 5.302, p =0.021). On the contrary, no significant difference in sarcopenia proportion was detected between different categories of BFP, MUAC, serum albumin, serum cholesterol, TEI and DPI (p >0.05).

Table 4.6 : Comparison of Nutrition Status-Related Characteristics between Sarcopenia and Non-sarcopenia Patients (n= 130)

Variables	Sarcopenia (n=33)	Non-Sarcopenia (n=97)	χ^2 or t-value	*p*
Dry Weight (kg)	53.8 ± 9.0	62.8 ± 11.5	4.090	**<0.001**
BMI (kg/m^2)	22.0 ± 3.2	24.4 ± 3.6	3.455	**0.001**
< 23	23 (69.7)	34 (35.1)	12.004	**0.001**
≥ 23	10 (30.3)	63 (64.9)		
BFP (%)	33.1 ± 9.6	30.4 ± 9.5	-1.368	0.174
< 10	0 (0.0)	3 (3.1)	NA	0.571[a]
≥ 10	33 (100.0)	94 (96.9)		
SMM (kg)	18.4 ± 3.0	23.8 ± 4.3	7.819	**<0.001**
MUAC (cm)	26.0 ± 3.6	28.5 ± 3.9	3.261	**0.001**
≤ 24	8 (24.2)	13 (13.4)	2.136	0.144
> 24	25 (75.8)	84 (88.6)		
CC (cm)	30.7 ± 3.0	34.6 ± 3.4	5.830	**<0.001**
< 34 (M); <33 (F)	26 (78.8)	39 (40.2)	14.661	**<0.001**
≥ 34 (M); ≥33 (F)	7 (21.2)	58 (59.8)		
ECW/TBW Ratio	0.413 ± 0.010	0.407 ± 0.014	-3.014	**0.003**
< 0.400	3 (9.1)	28 (28.9)	5.302	0.021
≥ 0.400	30 (90.9)	69 (71.1)		
PhA (°)	3.28 ± 0.80	4.05 ± 0.94	4.237	**<0.001**
SE Albumin (g/L)	28.0 ± 5.7	30.4 ± 4.7	2.439	**0.016**
< 38	31 (93.9)	95 (97.9)	NA	0.267[a]
≥ 38	2 (6.1)	2 (2.1)		
SE Creatinine (umol/L)	872.6 ± 282.6	1046.5 ± 317.7	2.789	**0.006**
SE Cholesterol (mmol/L)	4.8 ± 1.4	5.1 ± 1.3	1.013	0.313
< 2.59	1 (3.0)	0 (0.0)	NA	0.254[a]
≥ 2.59	32 (97.0)	97 (100.0)		
SE TIBC (ug/dL)	185.4 ± 45.4	200.4 ± 32.1	1.763	0.085
SE Hemoglobin (g/dL)	10.8 ± 1.8	10.7 ± 2.0	-0.055	0.956
TEI (kcal/kg BW/day)	24.5 ± 7.0	23.5 ± 6.0	-0.719	0.473
< 25	19 (57.6)	64 (66.0)	0.753	0.385
≥ 25	14 (42.4)	33 (34.0)		
DPI (g/kg BW/day)	0.84 ± 0.35	0.74 ± 0.26	-1.479	0.146
< 0.8	15 (45.5)	61 (62.9)	3.081	0.079
≥ 0.8	18 (54.5)	36 (37.1)		

Data are presented as n (% column) or mean ± SD; Data were analyzed by Pearson χ^2 test and independent t-test; Superscript[a] indicated data were analyzed by Fisher's exact test; NA: data was not available as there was cell with expected value < 5; Abbreviation: BMI, body mass index; BFP, body fat percentage; BW, body weight; CC, calf circumference; DPI, dietary protein intake; ECW, extracellular water; MUAC, mid-upper arm circumference; PhA, phase angle; SE, serum; SMM, skeletal muscle mass; TEI, total energy intake; TIBC, total iron binding capacity; TBW, total body water.

4.3 Sarcopenia Diagnosis according to AWGS 2019 Criteria

4.3.1 Prevalence of Sarcopenia

Figure 4.2 illustrates the prevalence of sarcopenia among patients based on AWGS 2019 diagnostic algorithm and classification. There was a total of 25.4% of patients diagnosed with sarcopenia, with 17.7% of them under severe sarcopenia category.

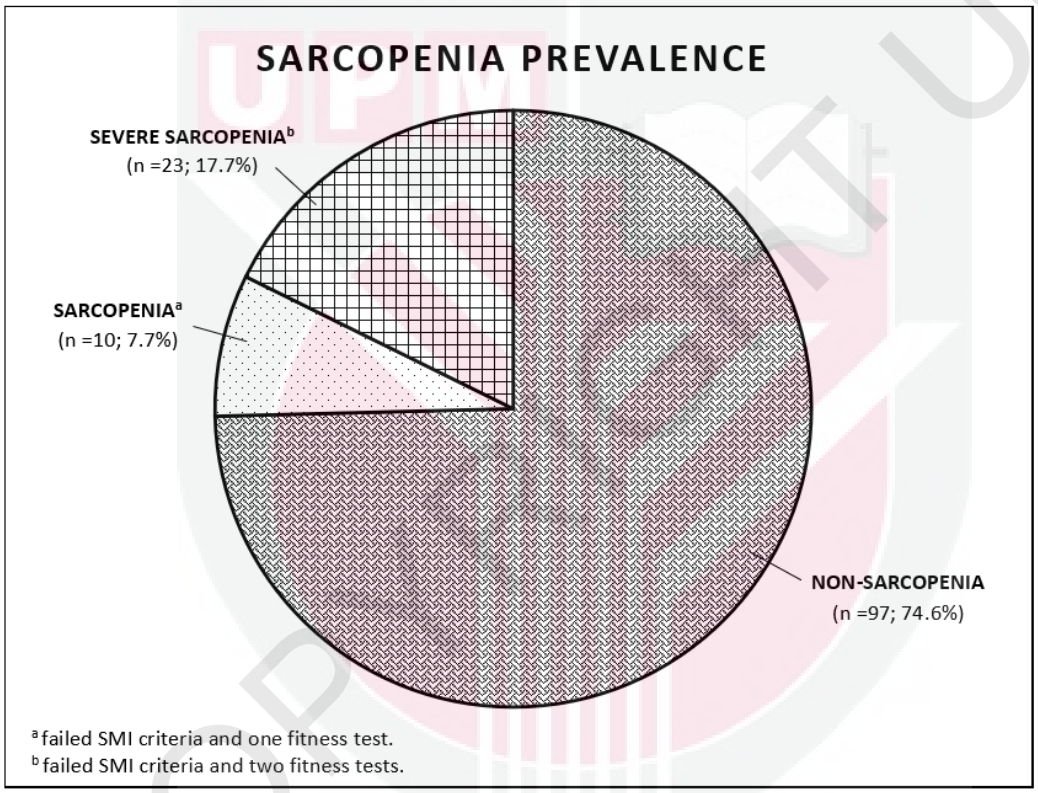


Figure 4.2 : Prevalence of Sarcopenia among PD Patients (n= 130)

4.3.2 Patients' Distribution Based on Individual Sarcopenia Diagnostic Criteria

Figure 4.3 depicts the distribution of patients based on individual diagnostic criteria of sarcopenia. Half of the patients (50.0%) fulfilled the criterion of 5TCST ≥ 12s, and 46.6% of the patients fulfilled the criterion of low HGS for sarcopenia diagnosis. On

the other hand, 34.6% of patients had fulfilled the criterion of low ASMI for sarcopenia diagnosis.

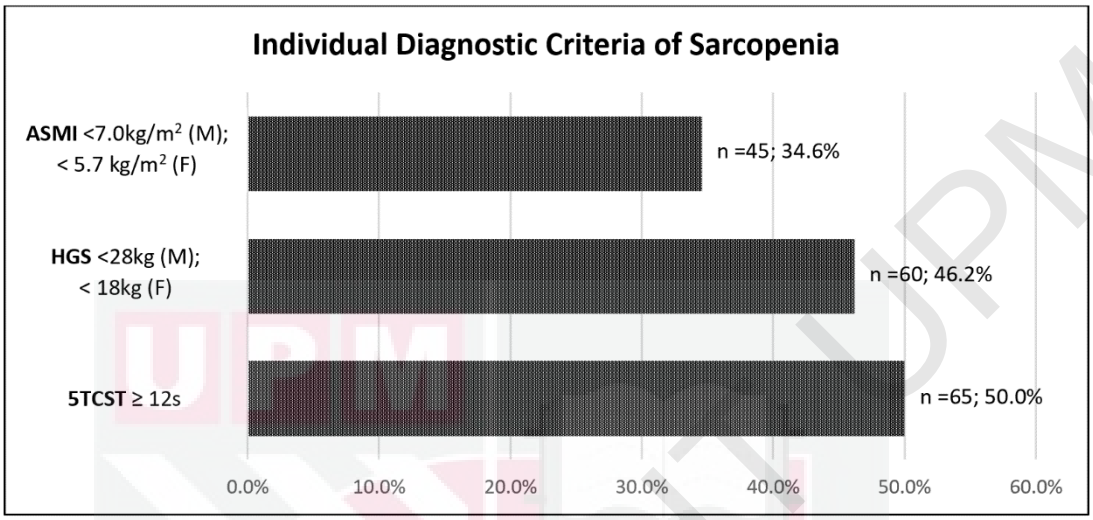


Figure 4.3 : Distribution of PD Patients by Individual Sarcopenia Diagnostic Criteria (n =130)

4.3.3 Patients' Characteristics Based on Individual Sarcopenia Diagnostic Criteria between Sarcopenia and Non-Sarcopenia Group

Table 4.4 shows the association of sarcopenia diagnostic criteria between sarcopenia and non-sarcopenia group. In comparison to non-sarcopenic patients, sarcopenic patients had significantly lower mean ASMI (5.6 ± 0.8 kg/m^2 *vs* 7.2 ± 1.1 kg/m^2) and HGS (17.1 ± 6.2kg *vs* 26.6 ± 7.8kg). On the other hand, there was a significantly higher proportion of sarcopenic patients had failed ASMI criterion (χ^2= 83.540, p< 0.001), HGS criterion (χ^2= 26.646, p< 0.001), and 5TCST criterion (χ^2= 21.484, p< 0.001).

Table 4.7 : Patients' Characteristics Based on Individual Diagnostic Criteria between Sarcopenia and Non-Sarcopenia Patients (n= 130)

Diagnostic Criteria of Sarcopenia	Sarcopenia (n=33)	Non-Sarcopenia (n=97)	t-value or χ^2	*p*
ASMI (kg/m^2)	5.6 ± 0.8	7.2 ± 1.1	7.967	<0.001
Failed (M< 7.0; F: <5.7)	33 (100.0)	12 (12.4)	83.540	<0.001
Passed (M≥ 7.0; F: ≥5.7)	0 (0.0)	85 (87.6)		
HGS (kg)	17.1 ± 6.2	26.6 ± 7.8	6.307	<0.001
Failed (M< 28.0; F: <18.0)	28 (84.8)	32 (33.0)	26.646	<0.001
Passed (M≥28.0; F: <18.0)	5 (15.2)	65 (67.0)		
5TCST (s)	NA	NA	NA	NA
Failed (≥ 12)	28 (84.8)	37 (38.1)	21.484	<0.001
Passed (<12)	5 (15.2)	60 (61.9)		

Variables were categorized according to AWGS 2019 classification. Data are presented as n (% column) or mean ± SD; Data were analyzed by Pearson χ^2 test and independent t-test; NA: unbiased analysis of mean was impossible as some patients failed to complete the test due to physical weakness.

4.4 Predictive Power of Phase Angle in Sarcopenia Identification among Malaysian PD Patients

Table 4.8 shows the predictive ability of PhA on the overall diagnosis of sarcopenia according to AWGS 2019. PhA remains a significant predictor of sarcopenia both before and after adjustment for patient's characteristics in different models.

Table 4.8 : Predictive Power of PhA for Sarcopenia Identification in PD Patients in Univariate and Multi-Variable Models

	Model 1	Model 2	Model 3	Model 4
OR	0.366	0.396	0.165	0.147
p-value	<0.001	0.002	0.003	0.003
95% CI	0.216-0.621	0.222-0.704	0.050-0.539	0.042-0.516

Model 1: Univariate model (n=129); Model 2: adjusted for age, gender, ethnicity (n=129); Model 3: adjusted for age, gender, ethnicity, no. of comorbidities, Kt/V, log-transformed dialysis vintage and ECW/TBW ratio (n=126); Model 4: adjusted for age, gender, ethnicity, education level, marital status, employment status, monthly household income, no. of comorbidities, Kt/V, log-transformed dialysis vintage and ECW/TBW ratio (n=126). Datasets with outliers in respective models were excluded from analysis.

Table 4.9 presents the results of multiple logistic regression of model 4, which covers majority of the sociodemographic and clinical variables. This logistic regression model was statistically significant for Omnibus test, χ^2 (df = 14, N =126) = 29.964, *p* = 0.008, but not significant for the Hosmer-Lameshow test, χ^2 (df = 8, N =126) = 8.305, *p* = 0.404, which indicates a good logistic regression model fit. This model explained 31.0% (Nagelkerke R^2)–of the variance in sarcopenia, and correctly predicted 77.0% of sarcopenia cases. Sensitivity was 33.3%, specificity was 92.5%, positive predictive value was 61.1% and negative predictive value was 79.6%. Results demonstrated that, after accounting for patients' characteristics, PhA is the only significant predictor of sarcopenia (adjOR: 0.147, 95% CI = 0.042-0.516, p=0.003). With an decrease in one unit of PhA, the odds of having sarcopenia increased by 6.8 times.

Power analysis was performed using G. Power version 3.1.9.2 statistical software. With an odd ratio = 0.147, Pr(Y=1|X=1)H0=0.192, alpha error level = 0.005, sample size = 126 and R^2 other X = 0.310, the statistical power was 99.999% (Appendix 6). Meanwhile, the results remain robust in the sensitivity analysis (Appendix 7). Therefore, we could conclude that PhA is a significant predictor for sarcopenia in PD patients.

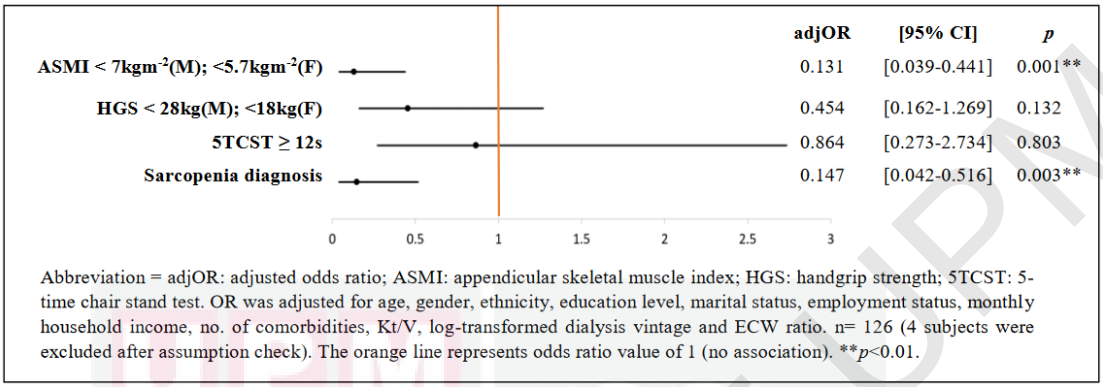
Table 4.9 : Predictive Power of PhA for Sarcopenia Identification in PD Patients (n = 126)

Variables	B	SE	adjOR	95% CI	*p*
Age (years)	0.047	0.029	1.048	0.991-1.109	0.099
Gender					
Female	-0.147	0.591	0.863	0.271-2.747	0.804
Ethnicity					
Chinese	0.610	0.596	1.840	0.573-5.914	0.306
Indian	0.298	1.178	1.347	0.134-13.557	0.800
Education level					
Secondary	-0.295	0.673	0.744	0.199-2.782	0.661
Tertiary	-0.643	0.919	0.526	0.087-3.183	0.484
Marital status					
Married	0.023	0.825	1.024	0.203-5.155	0.977
Employment status					
Unemployed	-0.900	0.806	0.407	0.084-1.974	0.264
Monthly household income					
Non-B40	-0.391	0.603	0.676	0.208-2.204	0.517
No. of comorbidities	-0.128	0.276	0.880	0.512-1.513	0.644
Kt/V	0.172	0.810	1.188	0.243-5.810	0.832
Log dialysis vintage	0.158	0.289	1.171	0.665-2.065	0.584
ECW/TBW Ratio[a]	-0.083	0.044	0.921	0.844-1.004	0.061
PhA (°)	-1.916	0.640	0.147	0.042-0.516	**0.003**

Note: Gender is for female in comparison to male; Ethnicity is for Chinese and Indian in comparison to Malay; Education level is for secondary and tertiary in comparison to ≤ primary; Marital status is for married in comparison to single; Employment status is for unemployed in comparison to employed; Monthly household income is for non-B40 (> RM4850) in comparison to B40 (≤ RM4850); OR was adjusted for age, gender, ethnicity, education level, marital status, employment status, monthly household income, no. of comorbidities, Kt/V, log-transformed dialysis vintage and ECW/TBW ratio; [a]ECW/TBW ratio per increase of 0.001; n= 126 (4 sets data with outliers was excluded).

Figure 4.4 depicts the predictive ability of PhA on the overall sarcopenia diagnosis and individual diagnostic criteria of sarcopenia. Sarcopenia diagnostic criteria were dichotomized according to the cut-off suggested by AWGS 2019. After adjusting for patients' characteristics, PhA was found to be a significant predictor of the sarcopenia diagnosis (adjOR=0.147; 95% CI = 0.042-0.516; p =0.003). For every one unit decrease in PhA, the odds of being diagnosed with sarcopenia was increased by 6.5 times. Nevertheless, PhA could only significantly predict one out of three of the diagnostic criteria, namely low ASMI (adjOR=0.131; 95% CI = 0.039-0.441; p

=0.001). For every one unit decrease in PhA, the odds of being diagnosed with low ASMI was increased by 7.4 times.



Abbreviation = adjOR: adjusted odds ratio; ASMI: appendicular skeletal muscle index; HGS: handgrip strength; 5TCST: 5-time chair stand test. OR was adjusted for age, gender, ethnicity, education level, marital status, employment status, monthly household income, no. of comorbidities, Kt/V, log-transformed dialysis vintage and ECW ratio. n= 126 (4 subjects were excluded after assumption check). The orange line represents odds ratio value of 1 (no association). $^{**}p<0.01$.

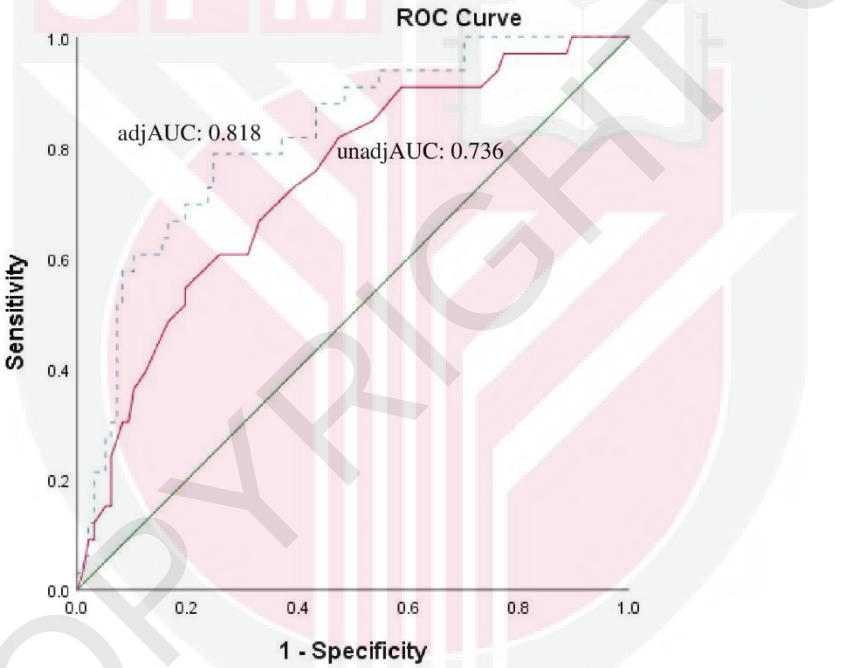
Figure 4.4 : Forest Plot for Adjusted Odds Ratio of PhA as per Diagnostic Criteria Recommended by AWGS 2019

4.5 Recommended Phase Angle Cut-Off for Sarcopenia Detection among Malaysian PD Patients

Figure 4.5 depicts the discriminative performance of PhA in sarcopenia identification. The unadjusted ROC (red line) demonstrated an area under the curve (AUC) of 0.736 (95% CI: 0.639-0.832, p <0.001), significantly outperforming the random classifier (AUC = 0.5). This indicates the acceptable discriminative ability of the raw model in distinguishing between sarcopenia and non-sarcopenia cases. Notably, after adjusting to sociodemographic and clinical characteristics, the AUC of PhA improved significantly to 0.818 (95% CI: 0.737-0.899, p <0.001), with a good overall model quality of 0.74 (Appendix 8), indicating an excellent discriminative performance in identifying sarcopenia among PD patients. The recommended PhA cut-off for sarcopenia identification was ≤3.95°, with 81.8% sensitivity and 52.6% specificity (appendix 9). The ROC curve and associated metrics highlight the effectiveness of

PhA as a diagnostic tool for sarcopenia in the context of PD, with improved performance after accounting for patient characteristics.

Power analysis was performed using "pOCR" package in R software. With an significance level = 0.005, number of cases = 33 and number of subjects = 97, the statistical power was 98.822% and 99.998 for unadjusted and adjusted ROC analysis, respectively (Appendix 10).



	AUC	95% CI	p-value	Indicator	Sensitivity (%)	Specificity (%)
Unadjusted ROC	0.736	0.639-0.832	<0.001	PhA ≤ 3.95°	81.8	52.6
Adjusted ROC	0.818	0.737-0.899	<0.001			

Abbreviations= ROC: receiver operating characteristics; adjAUC: area under curve adjusted for age, gender, ethnicity, education level, marital status, employment status, monthly household income, no. of comorbidities, Kt/V, log-transformed dialysis vintage and ECW/TBW ratio; unadjAUC: area under curve of unadjusted ROC.

Figure 4.5 : ROC Curve Analysis Illustrating True Positive Rate (sensitivity) and False Positive Rate (1-specificity) for PhA to Identify Sarcopenia Incidence among PD Patients

CHAPTER 5

DISCUSSION

5.1 Patients' Characteristics

5.1.1 Overall Patients' Characteristics

5.1.1.1 Sociodemographic Characteristics

The sociodemographic characteristics (i.e., age and gender distribution) of the PD patients in this study align with the national data in year 2020 reported by the National Renal Registry of the Malaysian Society of Nephrology (Ong, 2022). Additionally, the distribution of the ethnic groups in our study aligns with the ethnic distribution reported by the Department of Statistics Malaysia in 2022 (Department of Statistics Malaysia, 2022) and previous local studies of PD patients (Harvinder et al., 2013; Lau et al., 2022; Surendra et al., 2019). Therefore, these findings substantiate the representativeness of our study cohort, suggesting potential relevance to the broader PD population in Malaysia.

The majority of participants in the present study were married (82.3%), which is consistent with the marriage rates reported in previous local studies on HD patients (89.5% and 85.4%) (Ho & Chan, 2018; C. K. M. Lim et al., 2021). On the other hand, the majority of PD patients (45.4%) in this study had received education up to secondary level, which is in line with previous local studies in dialysis population (Harvinder et al., 2013; C. K. M. Lim et al., 2021; Mohd Shahrin et al., 2019). Majority of the patients fell into the B40 group (67.7%), which may be attributed to the high unemployment rate (75.4%) reported in the study population. Similar high

unemployment rates (75.0% and 81.1%) were reported in previous studies in local dialysis patients (Harvinder et al., 2013; Surendra et al., 2019). Some factors were identified as contributors to the high unemployment rate in this population, including functional decline, frequent dialysis schedule, co-morbidities (e.g., anemia and heart failure), depression, and old age (Kutner & Zhang, 2017; Law et al., 2016; Muehrer et al., 2011). Evidence from Malaysia showed that the unemployment rate among CKD patients was associated with several sociodemographic factors, namely age, gender, and education level. (Bay et al., 2024). According to this study, female patients were more likely to be unemployed due to cultural reasons, specifically their greater involvement in domestic tasks and child-rearing responsibilities. On the other hand, patients with lower education levels were more likely to be unemployed, which might be due to their greater involvement in blue-collar jobs that are more labour-intensive. As a significant proportion of PD patients were female, elderly and had lower educational attainment, this could explain the high unemployment rate reported in the current study. Consistent with an overseas study (Alma et al., 2023), Bay et al. (2024) found that ethnicity was not associated with the unemployment rate among CKD patients.

5.1.1.2 Clinical Characteristics

Present study found that hypertension and diabetes mellitus were the two main comorbidities in the study subjects, which is consistent with previous local studies conducted in PD patients (Harvinder et al., 2016; Surendra et al., 2019). The majority of study subjects had at least two types of comorbidities, which is in line with findings from previous local studies (Harvinder et al., 2016; C. K. M. Lim et al., 2021). Consistent with the 29th report of the Malaysian Dialysis and Transplant Registry

(MDTR) in 2021, majority of patients in present study were on CAPD over automated PD (Hooi & Ong, 2023). Additionally, the majority of PD patients (56.2%) in our study had dialysis vintage between 12-48 months, which is identical to the findings from MDTR 2021 (54.4% patients with dialysis vintage between 12-48 months). Besides, 64.6% of study patients achieved target solute clearance of ≥1.7 per week, which is also identical to MDTR 2021 (65% patients with kt/V ≥1.7).

5.1.1.3 Nutrition Status-Related Characteristics

The overall nutritional status of patients of present study is consistent with what has been reported in the MDTR 2018 report for PD patients (National Renal Registry, 2018). For example, our patients had a mean BMI of 23.8 kg/m^2, with 9.2% underweight patients (BMI<18.5 kg/m^2), while the mean BMI reported in MDTR 2018 was 24.7 kg/m^2, with 9.5% underweight patients. Additionally, our patients had a mean serum albumin of 29.8 mmol/l, mean total cholesterol of 5.0mmol/l and mean hemoglobin of 10.8g/dL, which are comparable to findings reported by MDTR 2018 (mean serum albumin of 32.3 mmol/l, mean total cholesterol of 4.8mmol/l and mean hemoglobin of 10.3g/dL). However, the serum creatinine of the patients in present study is higher than reported in MDTR 2018 (1002.3 ummol/L versus 849.0 ummol/L). The reason behind this could be the recent paradigm shift in clinical practice where there is less emphasis on targeting high solute clearance for providing high-quality PD care (Hooi & Ong, 2023). Historically, high solute clearance was targeted in dialysis prescriptions. However, recent evidence has revealed that various other factors influence the treatment outcomes and quality of life of dialysis patients, including residual kidney function, volume status, nutritional status, comorbidities, treatment burden, and patient preferences. As a result, recent guidelines have evolved

to adopt a holistic, patient-centered approach that focuses on both clinical outcomes and patient experience, placing less emphasis on solute clearance targets (Auguste & Bargman, 2023; Slon-Roblero et al., 2024).

The mean body fat percentage (BFP) observed in the present study (31.1%) falls within the range reported in previous local studies on PD patients (28.0% and 33.2%) (Cader et al., 2013; Koh et al., 2011). Among these studies, Koh et al. (2011) reported the lowest BFP (28.0%), which may be attributed to the use of a single-frequency BIA device, which is known to underestimate fat mass in hypervolemic populations (Lukaski, 2013). Nevertheless, although a more recent study reported a BFP of 26.3% in PD patients, this result is not considered comparable, as the clinical trial exclusively recruited malnourished PD patients (Sahathevan et al., 2018). On the other hand, Koh et al. (2011) reported a higher mean PhA than the current study (4.7° versus 3.85°). This difference may be attributed to multiple factors, including variation in sociodemographic factors (such as age, gender proportion, and ethnicity distribution), clinical factors, nutrition status, and the difference in BIA devices used in the two studies, which represent known factors that could affect PhA measurement (SECA, 2016). For example, the study population in that study was younger (48 ± 1.2 years old), had a higher proportion of female (53.9%) and non-Malay subjects (50.0%), with higher BMI (24.3 ± 0.4kgm^{-2}), and used a single-frequency BIA device (Metron BioScan 916 v3 analyzer). Most of our study subjects were overhydrated, which is consistent with previous local study (Cader et al., 2014). In regards to mid-upper arm circumference (MUAC), the mean MUAC of current study (27.9cm) is identical to a previous local study in PD population (27.5cm) (Harvinder et al., 2013). Besides, the mean TIBC (208.3ug/dL) reported by Harvinder et al. (2013) is comparable to the

finding of current study (196.6ug/dL). The local data on calf circumference (CC) among PD patients is still lacking; however, the mean CC of the current study (33.6 cm) is identical to that of a local study in HD population (33.2 cm) (Md Yusop et al., 2013).

The mean total energy intake (TEI) and dietary protein intake (DPI) of the study subjects were 23.8 kcal/kg BW/day and 0.77 g/kg BW/day, respectively, which align with the findings reported in a previous local study on the PD population by Harvinder et al., (2013). In that study, the authors reported a mean TEI of 23 kcal/kg BW/day in patients aged ≥60 years and 25 kcal/kg BW/day in patients aged <60 years, while the overall DPI was reported as 0.82 g/kg BW/day. Notably, approximately 19.4% of the TEI (equivalent to 4.6 kcal/kg BW/day) was attributed to glucose absorption from the dialysate. These findings are consistent with previous studies that reported dialysate contributed 20.3% of the TEI (Grodstein et al., 1981) and approximately 3.8 kcal/kg BW/day of TEI among PD patients (A. Y. M. Wang et al., 2003). The majority of the study subjects had a TEI of less than 25 kcal/kg/day (63.8%) and a DPI of less than 0.8 g/kg/day (58.5%), which represents the diagnostic criteria for PEW outlined by The International Society of Renal Nutrition and Metabolism (ISRNM) guideline (Fouque et al., 2008). This finding is alarming, as PEW is a well-known cause of sarcopenia, as well as poor quality of life and increased mortality risk (Hara et al. 2018). Several contributing factors to inadequate TEI and DPI in dialysis patients have been identified, including loss of appetite, poor social network, depression, lack of daily diet variation, dialysis vintage, and residual renal function (Therrien et al., 2015). A recent local study reported a similar prevalence of TEI < 25 kcal/kg/day (63.8%) among HD patients, but a lower rate of DPI < 0.8 g/kg/day (42.1%) compared to the

present study (C. K. M. Lim, 2022). This finding is consistent with a previous local study that reported significantly lower DPI in PD patients compared to HD patients, despite comparable TEI (Harvinder et al., 2013).

5.1.2 Patients' Characteristics Based on Sarcopenia Status

5.1.2.1 Sociodemographic Characteristics

In tandem with previous studies in PD patients (Jin et al., 2017; Kamijo et al., 2018), bivariate analysis depicted that sarcopenic patients were significantly older than non-sarcopenic patients. The underlying etiology behind this association includes aging-induced oxidative stress, inflammation, reduced mitochondrial integrity, impaired satellite cell function, reduced myofiber size and quantity, intramuscular fat infiltration, impaired neuromuscular coordination and impaired fiber contraction function (Cruz-Jentoft & Sayer, 2019; Distefano & Goodpaster, 2018). Additionally, a lower education level was observed in sarcopenia patients. This could be attributed to the fact that patients with a lower education level were significantly older than their counterparts with a higher educational level in our study population (appendix 11).

5.1.2.2 Clinical Characteristics

No association was found between the sarcopenia status and comorbidity, dialysis vintage and dialysis adequacy. These results are in tandem with previous studies in PD population, which found these variables were not associated with both muscle mass and muscle strength (As'Habi et al., 2018; Y. Chen et al., 2022; Davenport, 2022b; Hung et al., 2017; Kamijo et al., 2018).

5.1.2.3 Nutrition-Status Related Characteristics

Consistent with previous studies, significant bivariate associations were found between sarcopenia and several nutritional markers. Sarcopenic patients had significantly lower SMM, MUAC, CC and serum creatinine. These outcomes are expected, as these parameters are well-recognized muscle mass markers, which represent an important criterion in sarcopenia diagnosis. Similar results have been reported in previous studies (Y. Chen et al., 2022; Davenport, 2022b; Giglio et al., 2018). Being a generally recognized inflammatory and nutritional parameter, serum albumin was found to be associated with sarcopenia. This finding is in agreement with previous studies that showed sarcopenia is accelerated by inflammation and poor nutritional status (Y. Chen et al., 2022; Fahal, 2014; Kamijo et al., 2018). Additionally, sarcopenia was found to be significantly associated with higher edema index (i.e., ECW/TBW ratio). Similar findings were reported by previous studies in renal patients (Kang, et al., 2022c; C. Zhou et al., 2023). For example, C. Zhou et al. (2023) reported that a higher edema index is independently associated with a higher sarcopenia rate in HD patients.

On the other hand, dry weight and BMI were found to be significantly associated with sarcopenia, which could be attributed to higher muscle mass and better nutritional status in patients with higher dry weight and BMI. Similar results have been reported in previous studies (Abro et al., 2018; Kamijo et al., 2018). Notably, there was no significant association observed between TEI and DPI with sarcopenia status. These findings are consistent with previous studies in PD patients conducted by As'Habi et al. (2018) and Hung et al. (2017). A potential reason for this lack of association is the under-reporting of dietary intake in this study. The TEI: BMR ratio indicated that

73.1% of patients had a ratio below 1.2. A TEI:BMR ratio under 1.2 is generally inconsistent with normal intake patterns and often indicates that energy intake is being under-reported (Black, 2000). Similar under-reporting issues have been reported by local studies in HD population. For example, Sahathevan et al. (2015) and Md Yusop et al. (2013) reported TEI:BMR ratio < 1.2 in 68.3% and 62.0% of HD patients in their studies, respectively. Additionally, the absence of an association between TEI and DPI with sarcopenia status could be attributed to the fact that some of the sarcopenic patients in our study may have been receiving medical nutrition treatment for PEW, a condition often found in conjunction with sarcopenia.

5.2 Prevalence of Sarcopenia in Malaysian PD Patients

The present study, being the first to investigate sarcopenia prevalence in Malaysian PD patients, reports a sarcopenia prevalence of 25.4% in this population. This finding indicates that approximately one in every four Malaysian adult PD patients is sarcopenic. This result lies within the range of sarcopenia prevalence reported by previous studies involving PD patients, which varied from 10.0% to 32.1% (see table Table 2.1). The observed range in sarcopenia prevalence listed in that table and current study is likely influenced by differences in patients' characteristics (such as ethnicity, age, and gender proportion) and variations in the diagnostic algorithm and devices employed across different studies.

Among studies conducted in Asian countries, Kamijo et al. (2018) reported the lowest sarcopenia rate in Japanese PD patients (10.9%), whereas (Do et al., 2021b) reported the highest sarcopenia rate in South Korean PD patients (32.1%). Two main reasons could explain the relatively lower prevalence reported by Kamijo et al. (2018). Firstly,

the cut-off values adopted for sarcopenia diagnosis are based on the AWGS 2014 consensus. It was found that the cut-off values in this consensus for muscle strength and physical performance are lower than the latest AWGS 2019 version, which would result in a lower prevalence of sarcopenia. Secondly, it could be ascribed to the active lifestyle practiced by the Japanese. Of note, physical inactivity is a proven contributor to the loss of muscle mass and strength at any age (Pillard et al., 2011).

In contrast, the higher prevalence of sarcopenia reported by Do et al. (2021b) could be related to the subjects' selection criteria and the muscle measurement approach in that study. This study adopted broader selection criteria, whereby patients with recent hospitalization, recent surgery, acute disease or inflammatory disease were not excluded. In other words, this study probably included cases of acute and transient sarcopenia, resulting in a higher sarcopenia prevalence than other studies in the PD population. Nonetheless, compared to MFBIA, the use of DXA in estimating lean mass performs better in attenuating edema-associated muscle overestimation (Fürstenberg & Davenport, 2011), which allows better detection of sarcopenia incidence in that study.

Severe sarcopenia is defined by the coexistence of all sarcopenia diagnostic sub-criteria, namely low muscle mass, low muscle strength, and low physical performance. Out of all the sarcopenia cases, 69.7% were classified as severe sarcopenia. This high prevalence may indicate that sarcopenia is being underdiagnosed and undertreated in the PD population, since routine screening for sarcopenia is not currently part of standard care. This is concerning because the severity of sarcopenia can complicate treatment efficacy. While exercise represents one of the integral treatment strategies

for sarcopenia, the implementation of exercise treatment in patients with severe sarcopenia could be complicated by safety concerns and the need for additional healthcare resources (Hurst & Sayer, 2022; Peterson & Serra, 2021).

Additional analysis (appendix 12) revealed that 20.0% of our patients aged below 60 years were sarcopenic (versus 34.0% of patients aged 60 years and above), with no statistically significant difference in sarcopenia prevalence between these two groups ($\chi^2 = 3.184$, $p = 0.074$). This finding suggests that in the PD population, sarcopenia is not merely a consequence of the aging process but involves factors associated with the disease itself. Additionally, it indicates the need for a pragmatic screening tool not only for elderly patients but also for non-elderly PD patients.

On the other hand, it was found that 68.5% of non-sarcopenic patients had met at least one sarcopenia diagnostic criteria (appendix 13), suggesting a higher risk of transitioning into sarcopenia in the future. Taken together, these findings underscore the importance of periodic screening, early diagnosis and intervention in treating sarcopenia in this population.

5.2.1 Patients' Distribution by Individual Diagnostic Criteria

Based on AWGS 2019 definition, the prevalence of low muscle mass was lower than low muscle strength and low physical performance in our study population. This result is in line with previous studies conducted in PD patients (Abro et al., 2018; As'Habi et al., 2018; M. Z. C. da Silva et al., 2019). The observed imbalance may be attributed to the varying rates of deterioration in muscle mass and strength. Previous studies have shown that in the aging process of the general population, the decline in muscle

strength is three times higher than that in muscle mass (Distefano & Goodpaster, 2018; Goodpaster et al., 2006; Koster et al., 2011).

In addition, our study revealed that low physical performance was more common than low muscle strength. This could be attributed to the fact that physical performance assessment covers a wider range of elements beyond strength, including balancing, coordination between multiple muscle groups, and endurance. Besides, it could also be due to the difference in strength loss between the upper limbs and lower limbs, since the muscle strength test (i.e., HGS) primarily assesses the strength of upper limbs, whereas the physical performance test (i.e., 5TCST) primarily assesses the strength of lower limbs. Noteworthily, studies in the general population had reported a faster rate of strength loss in lower limbs than in upper limbs, which is consistent with our findings (Amaral et al., 2014; Landers et al., 2001). Furthermore, Hara et al. (2018) demonstrated that muscle loss in the lower limbs of dialysis patients was more pronounced than that in the upper limbs, providing further explanation for our findings. It is noteworthy that the high prevalence of low physical performance in PD patients is alarming, as it may indicate a higher risk of falls in this population.

Last but not least, the prevalence analysis based on individual diagnostic criteria highlights the importance of using a complete diagnostic algorithm in diagnosing sarcopenia. Many previous studies investigating sarcopenia in PD patients have used incomplete diagnostic criteria in sarcopenia diagnosis, in which sarcopenia was defined by concurrent low muscle mass and muscle strength only, without involving physical performance assessment (see Table 2.1). This practice could lead to underdiagnosis of sarcopenia. Using our study population as an example, if sarcopenia

were defined by concurrent low muscle mass and low muscle strength only, 15.2% of sarcopenic patients would have been underdiagnosed (appendix 13).

5.3 Predictive Power of Phase Angle in Sarcopenia Identification among Malaysian PD Patients

The current study has identified PhA as an independent predictor of sarcopenia in Malaysian PD patients through multi-variable logistic regression analysis. This discovery aligns with numerous studies conducted in diverse populations, including dialysis patients, kidney transplant recipients, individuals with cardiovascular disease, cirrhotic patients, cancer patients, and elderly adults (Y. Chen et al., 2022; Di Vincenzo et al., 2021; Ding et al., 2022; Do et al., 2021a). PhA has been recognized as a viable surrogate for the evaluation of sarcopenia, owing to its distinctive characteristic of correlating directly with cell mass, cell function, and cell integrity. Theoretically, an increase in muscle cell mass results in higher reactance and lower resistance, subsequently leading to a higher PhA. Furthermore, greater muscle strength is linked to increased muscle mass and healthier muscle cells, both of which are reflected in a higher PhA (Norman et al., 2012).

Although PhA has been identified as an independent predictor of sarcopenia in numerous studies, some investigations have yielded contrary results. One possible rationale for this discrepancy can be attributed to the variability in muscle mass estimation methods. For instance, a systematic review that examined the relationship between PhA and sarcopenia across diverse populations found that two out of twelve studies did not detect a statistically significant association between PhA and sarcopenia (Di Vincenzo et al., 2021). The unfavorable outcomes in these two studies

might be ascribed to the utilization of a single-frequency BIA (SFBIA) device for assessing muscle mass (Dos Reis et al., 2019; Pessoa et al., 2020). Notably, the AWGS 2019 guidelines emphasize the necessity of using multi-frequency BIA (MFBIA) instead of SFBIA for diagnosing sarcopenia to achieve optimal diagnostic accuracy (L. K. Chen et al., 2020).

Additionally, the differences in diagnostic criteria employed in various studies might potentially contribute to variations in results. For example, Bae et al., (2022) reported an insignificant association between PhA and sarcopenia in HD patients. This finding might be linked to their use of non-Asian-specific diagnostic criteria (i.e., EWGSOP 2019) for sarcopenia, even though the majority of their study population consisted of Asian subjects. The importance of adopting the appropriate sarcopenia diagnostic protocol is underscored by a study conducted in an Asian elderly population, which revealed a substantial difference in sarcopenia prevalence when defined with AWGS 2019 (22.8%) compared to EWGSOP 2019 (11.8%) criteria (Liu et al., 2021).

The predictive capability of PhA for individual diagnostic sub-criteria of the AWGS 2019 algorithm was also analyzed using multi-variable logistic regression. PhA was identified as an independent predictor of ASMI status, where higher PhA values were associated with better ASMI status. PhA is a measure of the relationship between resistance (R) and reactance (Xc) in electrical signals as they pass through biological tissues. It is calculated using the arctan formula (Xc/R) (Sardinha, 2018). Muscle cells excel in conducting electricity owing to their substantial water and electrolyte content, and their cell membranes endow them with excellent capacitive characteristics. Consequently, muscle cells exhibit relatively lower resistance and higher reactance

compared to other body compartments. Within the body, skeletal muscle mass represents the largest conductive tissue. As such, an increase in muscle cell mass would lead to increased reactance and decreased resistance, resulting in a higher PhA (López-Gómez, 2011). Therefore, it is not surprising that our study discovered PhA to be an independent predictor of ASMI status, with higher PhA levels associated with better ASMI status.

Similar findings have been reported in previous studies. For example, Han et al., (2018) observed a significant independent association between the lean mass index and PhA in a study involving chronic kidney disease and PD patients. A separate investigation conducted on HD patients has also documented a significant predictive ability of PhA on muscle mass index (Kang et al., 2022a). On the other hand, (Akamatsu et al., 2022) discovered that PhA exhibited the strongest correlation with ASMI compared to other body composition and muscle strength parameters in both young adult and elderly populations.

Interestingly, despite the predictive ability of PhA for overall sarcopenia diagnosis and ASMI criterion, we did not find a significant association between PhA with another two AWGS 2019 diagnostic criteria, namely HGS (i.e., muscle strength) and 5TCST (i.e., physical performance). This finding is consistent with a previous study involving physically active elderly women (Pessoa et al., 2020) and another study conducted among post-kidney transplantation patients even when a different measure of physical performance (i.e., gait speed) was used (Dos Reis et al., 2019). This intriguing finding challenges the theoretical expectation that higher muscle mass, and subsequently higher PhA, should be accompanied by greater muscle strength and physical

performance. The lack of significant association between PhA and muscle strength and physical performance could be influenced by factors beyond skeletal muscle mass, such as anemia, joint pain, heart problems, neurological problems, depression and mental state (Yoowannakul et al., 2018). It's worth noting that the aforementioned medical issues are prevalent in PD patients, potentially influencing the strength and physical performance of this population. For example, additional analysis showed that the patients who failed the HGS and 5TCST criteria in our study had significantly lower serum potassium than their counterparts. Furthermore, this is supported by the observed difference in decline rates between muscle mass and strength, where the annual decline in strength was found to be 3-5 times higher than the rate of muscle loss (Distefano & Goodpaster, 2018; Sabatino et al., 2020), indicating the multifactorial nature of muscle strength. Notably, the association of PhA with physical performance is relatively poor. This phenomenon may be attributed to the involvement of more complex elements in physical performance, including but not limited to coordination and balance.

Noteworthily, given that ageing could be a potential confounding factor for the association between PhA, muscle strength and physical performance, the existing statistical analysis has adjusted for age, ensuring that the results are independent of age influence. Besides, additional analysis has been done separately on the elderly group (aged 60 years and above) and the non-elderly group (aged below 60 years), which showed a similarly insignificant association between PhA and muscle strength and physical performance in both groups of patients (Appendix 14).

5.4 PhA Cut-Off to Detect Sarcopenia in Malaysian PD Patients

A receiver operating characteristic (ROC) curve is a graphical plot that illustrates the performance of a binary classification model over the range of discrimination thresholds, while area under ROC (AUROC) is an objective evaluation of the diagnostic ability of the classifier. Generally, higher AUROC represents a better diagnostic ability of the classifier (Yang & Berdine, 2017). Based on literature review (see Table 2.3), AUROC for PhA to discriminate sarcopenia status in non-dialysis populations (0.703-0.821) and dialysis populations (0.700-0.850) are comparable, indicating PhA has a similar efficacy in classifying sarcopenia status for elderly and different diseased populations.

Current study reported a AUROC of 0.736, which is within the range of the non-gender-specific AUROC reported from studies among PD patients (0.730-0.790), indicating acceptable discriminative power in identifying sarcopenia in this population (Y. Chen et al., 2022; Do et al., 2021a). The discrepancy in AUC could be attributed to the differences in patients' characteristics, diagnostic protocols and applied BIA devices. Notably, an excellent discriminative ability (AUROC: 0.820) had been reported in a study in HD patients (Ding et al., 2022). The difference could be attributed to the difference in nutritional status and body composition between PD and HD patients (Harvinder et al., 2013; National Renal Registry, 2018). Besides the difference in patients' characteristics, the enhanced AUROC could be attributed to the study design. Unlike other studies in dialysis population, Ding et al., (2022) excluded hypervolemic patients from their studies. In addition, BIA was done after dialysis, which is when fluid overload issue is slightest. Fluid overload has been proven to be associated strongly with PhA, in which the higher the severity of fluid overload, the

lower the PhA (Denneman et al., 2020). On the other hand, due to the assumptions in BIA concept that hydration status in fat-free mass is constant, lean body mass can be overestimated in hypervolemic state (Sergi et al., 2017). Therefore, the issues of hypervolemia-related PhA suppression and impaired accuracy of lean mass estimation were minimized in this study, which might have resulted in better discrimination ability in predicting sarcopenia. This inference is supported by a sub-analysis result (appendix 15), that showed AUROC of current study improved from 0.736 to 0.774 after adjusting to ECW/TBW ratio.

It is important to recognize that the validity of the current cross-sectional study may be affected by confounding variables. In order to improve the accuracy of PhA's discriminative capability and strengthen the reliability of our results, an adjusted model that takes into account common demographic and clinical variables was employed. The adjusted ROC model resulted in an improved predictive performance of PhA in identifying sarcopenia in PD patients (adjAUC = 0.818), enhancing the internal validity and robustness of our study findings. Furthermore, it infers that the discriminative performance of PhA on sarcopenia diagnosis may be improved by establishing subgroup-specific cut-off values. For example, age-decade-specific-, hydration status-specific and gender-specific cut-off. The optimal PhA cut-off value was established based on the unadjusted ROC curve. The rationale for this approach was to establish a cut-off value that is both robust and generalizable, thereby facilitating its practical application in real-world scenarios.

Wide range of PhA cut-off has been recommended for detecting sarcopenia in different populations, which ranged from 3.55-5.30° (see Table 2.3). This could be

attributed to multiple reasons, including the differences in sarcopenia definition, patients' characteristics (i.e., age, gender, ethnicity), medical background, nutritional status, inflammatory status, hydration status, and BIA device selection (Norman et al., 2012). Current study has identified the optimal PhA cut-off value of ≤3.95° for sarcopenia detection in Malaysian PD patients, which is lower than two previous studies in PD population.

Y. Chen et al., (2022) have suggested the highest PhA cut-off value (≤5.30°) for sarcopenia detection in PD patients, which could be explainable by several reasons. For instance, this study has implemented broader exclusion criteria, leading to a higher degree of exclusion of patients who may have a pre-existing predisposition to low PhA secondary to other medical conditions. Additionally, their subjects are generally less oedematous and younger compared to current study. The effects from aforementioned reasons are reflected in the average PhA value of subjects, which stands at 5.24°, surpassing the value observed in current study, which is 3.85°. On the other hand, Do et al. (2021a) suggested a sarcopenia detection PhA cut-off value (≤4.40°) that is slightly higher than current study (3.95°) for PD patients in South Korea. Besides patients' characteristics (higher male proportion and less hypervolemic), it could be as well attributed to the use of DXA in muscle estimation in that study. Given that edema-related overestimation of muscle mass is slighter in DXA than MFBIA, estimating muscle mass with DXA allows earlier detection of sarcopenia in hypervolemic patients, which subsequently resulted in higher PhA cut-off value for sarcopenia detection (Fürstenberg & Davenport, 2011).

Nonetheless, the differences in recommended PhA cut-off for sarcopenia detection in PD patients between studies could be due to the differences in sarcopenia definition, BIA device, ethnicity and lifestyle pattern of the study population. Notably, ethnicity and lifestyle patterns have been shown to be associated with both PhA and sarcopenia diagnostic criteria (i.e., muscle mass and muscle strength) (Giglio et al., 2018; Jaremków et al., 2021; Kuchnia et al., 2017; T. D. Wang et al., 2010). These findings further underscore the need for the establishment of population-specific PhA cut-off values that account for the ethnic makeup and lifestyle pattern when identifying sarcopenia.

Ideally, a good discriminative cut-off value should have high sensitivity and specificity. However, sensitivity and specificity are mutually exclusive in nature. There is no standard rule in determining a discriminative cut-off value, researchers should consider the cost of false negativity and false positivity when deciding a discriminative cut-off. For example, for the identification of diseases with severe complications or highly infectious, sensitivity is usually prioritized over specificity. On the contrary, when the subsequent diagnostic testing is unsafe or expensive, the specificity will be prioritized (Habibzadeh et al., 2016). When deciding PhA cut-off value for sarcopenia detection, consistent with majority of previous studies (see Table 2.3), current study has prioritized sensitivity (81.8%) over specificity (52.6%), after considering the misclassification cost. Despite the higher false negative rate of sarcopenia with this cut-off value, however, it provides additional prognostic value as it allows the identification of patients who have early signs of sarcopenia and subsequently facilitates prevention strategy. For example, additional analysis based on current study demonstrates that 80.8% of patients with PhA $\leq 3.95°$ did meet at least

one of the sarcopenia diagnostic criteria, indicating a need for intervention (appendix 16). In contrast, the consequences of false negativity in sarcopenia detection are dreadful and far-reaching, from causing multiple physical and mental health issues, impaired quality of life, to reduced survival. Worse still, late intervention could impair the efficacy of sarcopenia treatment, which further corroborates the importance of early diagnosis and pre-emptive intervention (Sabatino et al., 2020). Therefore, sensitivity is preferred over specificity in current study. Furthermore, additional analysis demonstrates that the odds of sarcopenia in PD patients with PhA $\leq 3.95°$ is 5 times higher than PD patients with PhA higher than that, indicating thorough sarcopenia screening in this group of patients is efficacious (appendix 17).

CHAPTER 6

CONCLUSION, STRENGTHS, LIMITATIONS AND RECOMMENDATIONS OF THE STUDY

6.1 Summary of Result

This was a single-center cross-sectional study conducted among 130 multi-ethnic PD patients in a PD clinic of a tertiary government hospital in the Klang Valley, Malaysia. Adult Malaysian outpatients who have been undergoing regular PD treatment for at least 6 months, free of terminal disease, history of infection, surgery or trauma in past 3 months, communication barriers, cognitive impairment, contraindication to MFBIA assessment, or any condition that could bias the study findings were consecutively recruited. This study aims to assess sarcopenia using BIA-derived PhA in the PD population.

The patients had an average age of 53.1 years and the gender distribution was approximately balanced, closely mirroring the national data reported by the National Renal Registry in the year 2020. The ethnic distribution of patients was consistent with Malaysian's ethnic distribution and previous local studies on PD patients. The majority of patients were married, unemployed, held secondary-level education, and belonged to the bottom 40% household income category. The median dialysis vintage and Kt/V for patients were 26.5 months and 1.9, respectively.

Sarcopenia was evident in 25.4% of the PD patients according to AWGS 2019 criteria. Patients with sarcopenia were significantly older and had a lower educational attainment. In addition, they displayed significantly higher ECW/TBW ratio, and

lower values of dry weight, BMI, SMM, MAC, CC, serum albumin, serum creatinine and PhA.

PhA was found as an independent predictor of sarcopenia in PD patients, with every one-unit increase in PhA corresponding to a 6.8 times decrease in the odds of being diagnosed with sarcopenia. PhA demonstrated acceptable discriminative performance in detecting sarcopenia in unadjusted ROC analysis and excellent discriminative performance after adjusting for basic sociodemographic and clinical characteristics. The optimal PhA cut-off value for sarcopenia detection in PD patients was ≤3.95°, with a sensitivity of 81.8% and a specificity of 52.6%.

6.2 Conclusion

In conclusion, this study provides compelling evidence that BIA-derived PhA emerges as an independent predictor of sarcopenia in PD patients. Given the inherent challenges associated with universal screening for sarcopenia in clinical settings, the readily available PhA data, derived from routine hydration or body composition BIA tests, can serve as a pragmatic biomarker screening tool for identifying multi-ethnic Malaysian PD patients at risk of sarcopenia. Therefore, in situations where universal screening is impractical, healthcare professionals, particularly dietitians, who play a crucial role in body composition monitoring and sarcopenia treatment, should consider incorporating PhA measurement into nutrition assessment. This proactive approach contributes to the multidisciplinary team's identification of sarcopenic patients, streamlining the diagnostic process and facilitating early intervention for enhanced patient outcomes.

6.3 Strengths of the Study

The study has several notable strengths. Firstly, it is the pioneering investigation into the predictive efficacy of PhA for diagnosing sarcopenia in PD patients within Southeast Asia. Given the unique ethnic composition and lifestyle patterns of Southeast Asians, and the established association between these factors and muscle mass, strength and PhA (Giglio et al., 2018; Jaremków et al., 2021; Jensen et al., 2019), a region-specific study is instrumental in providing valuable insights. Specifically, this study represents the inaugural exploration of the predictive efficacy of PhA for identifying sarcopenia in the multi-ethnic Malaysian PD patient population, offering novel insights within this specific context. Moreover, the establishment of the recommended PhA cut-off value was tailored specifically for this population, thereby enhancing the precision of sarcopenia detection.

Additionally, the present study adhered to the most recent Asian Working Group for Sarcopenis (AWGS) 2019 consensus, representing the latest Asian-specific sarcopenia diagnostic protocol. This distinguishes it from previous studies that utilized older versions of diagnostic guidelines and incomplete diagnostic criteria for sarcopenia while establishing PhA cut-off recommendations. Our data revealed that 15.2% of sarcopenic patients would be misclassified if either muscle strength or physical performance examination was not conducted (appendix 13). Furthermore, potential confounding factors were adjusted for in the data analysis. Therefore, the present study offers a comprehensive insight into the relevance of using PhA as a tool to detect sarcopenia in Malaysian patients undergoing PD.

6.4 Limitations of the Study

However, the present study has several limitations. Firstly, due to its cross-sectional study design, it lacks a temporal scope to establish the causal relationship between PhA and sarcopenia. Secondly, since the study is conducted in a single center using non-probability sampling method, the findings may not be generalized to the entire Malaysian population. Thirdly, the estimation of muscle mass was carried out using the MFBIA device, which may be less precise in hypervolemic populations as compared to DXA. Although the results may not be entirely precise, the MFBIA model (InBody S10) used in the current study demonstrated excellent agreement with DXA in a validation analysis conducted in dialysis population (Jayanama et al., 2018). Lastly, the BIA measurements were conducted without draining the dialysate, contrary to general recommendations. However, It was previously confirmed in our pilot study that the dialysate-induced measurement bias remains within clinically acceptable limits.

6.5 Recommendations of the Study

6.5.1 Recommendations for Practice

Sarcopenia in PD patients is a significant concern due to its high prevalence and its association with poor treatment outcomes and increased mortality. Given the challenging identification of sarcopenia, which may not always be evident through physical appearance or laboratory tests, universal screening is necessary. In healthcare organizations facing staff shortages for universal screening of PD patients, the recommended PhA cut-off can serve as a convenient screening tool to identify individuals at risk of sarcopenia. High-risk patients can subsequently undergo further

diagnostic testing using a full diagnostic algorithm. This approach effectively reduces the workload for sarcopenia screening, especially when PhA data is readily available from routine nutrition status and hydration monitoring records using BIA. By employing this convenient sarcopenia detection tool, periodic screening can be implemented in numerous organizations.

For organizations lacking the necessary equipment (e.g., hand dynamometer or BIA device capable of measuring segmental lean mass) and trained personnel to conduct a full diagnostic protocol for sarcopenia diagnosis confirmation, the recommended PhA cut-off can serve as a reference for healthcare providers to evaluate the risk of sarcopenia in PD patients. Specifically in the Malaysian context, many PD centers are using the Fresenius Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany), which provides PhA output but lacks the ASMI parameter. Therefore, the recommended PhA cut-off may serve as a reference for evaluating patients' risk of sarcopenia in centers using the BCM. Treatment may be initiated for patients at risk without further diagnostic testing, as early interventions (such as exercise and nutrition) are cost-effective and beneficial, even for patients in the pre-sarcopenia stage. A similar approach could be applied to patients who are unable to undergo a full sarcopenia diagnostic protocol, such as those with joint pain, amputation, language barriers, mental disorders, or cognitive impairment.

Additionally, data on the prevalence of sarcopenia in Malaysian PD patients can be used to raise awareness among healthcare professionals and patients about the importance of preventing and treating sarcopenia in this vulnerable population. This

information can also provide valuable insights into the need for regular screening and the establishment of specific treatment protocols for sarcopenia in this population.

6.5.2 Recommendations for Future Study

In future research, it is advisable to conduct a longitudinal observational study to examine the predictive ability of the recommended PhA cut-off in relation to various clinical outcomes, such as disability, hospitalization, mental health, quality of life, and mortality. Furthermore, it is recommended to conduct an inter-devices validation study to assess the generalizability of the recommended PhA cut-off on other BIA devices. In addition, future research aimed at enhancing generalizability may consider adopting a multicentre approach using probability sampling techniques to obtain a more representative sample, thereby improving the external validity of the results. Moreover, researchers can explore the use of DXA to assess body composition, which may provide more precise estimates of muscle mass and improve the accuracy of sarcopenia diagnosis. To further enhance the accuracy of PhA in detecting sarcopenia, consideration should be given to establishing age-decade-specific, hydration status-specific, gender-specific, and even ethnicity-specific cut-offs.

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APPENDICES

Appendix 1

Weighted Prevalence of Sarcopenia

Author & Year	Country	Diagnostic Guideline	Prevalence (%)	Sample Size	Weight	Weighted Rate (%)
Abro et al., 2018	UK	EWGSOP	11.0	155	0.160	1.8
As'Habi et al., 2018	Iran	EWGSOP	11.4	79	0.081	0.9
Kamijo et al., 2018	Japan	AWGS	10.9	119	0.123	1.3
Do et al., 2021b	Korea	AWGS	32.1	199	0.205	6.6
Davenport, 2022a	UK	EWGSOP & AWGS	17.7	368	0.379	6.7
M.Z.C. da Silva et al., 2019	Brazil	EWGSOP	10.0	50	0.052	0.5
			Total:	**970**	**1**	**17.8**

Appendix 2

Ethical Approval

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*MEDICAL RESEARCH & ETHICS COMMITTEE*)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Kompleks Institut Kesihatan Negara (NIH)
No.1, Jalan Setia Murni U13/52,
Seksyen U13 Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel.: +(6)03-33628888/ 33628205

Ref. : KKM/NIHSEC/P21-923(12)
Date : **1-June-2021**

DR. ZULFITRI 'AZUAN BIN MAT DAUD
UNIVERSITY PUTRA MALAYSIA (UPM)

Dear Dato'/ Dr/ Sir/ Madam,

LETTER OF ETHICAL APPROVAL:

NMRR-21-790-59396 (IIR)
ASSESSING SARCOPENIA AMONG MALAYSIAN PERITONEAL DIALYSIS PATIENTS USING BIO-ELECTRICAL IMPEDANCE ANALYSIS-DERIVED PHASE ANGLE

This letter is made in reference to the matter above.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator/ Hospital Director and all relevant heads of departments /units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations including the Access to the Biological and Benefit Sharing Act 2017.

3. The investigators and sites involved in this study are:

Hospital Serdang
Dr. Zulfitri 'Azuan Bin Mat Daud (Principal / Coordinating Investigator)
Dr. Nor Fadhlina Binti Zakaria
Imliya Binti Ibrahim
Cordelia Lim Kheng May
Lee Shi Wah

4. The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:

1. Cover letter to MREC (Version 2, dated 28-05-2021)
2. Declaration of Conflict of Interest (COI) (Version 1, dated 22-04-2021)
3. Protocol (Version 2, dated 21-05-2021)
4. English: Patient Information Sheet/ Informed Consent Form (Version 2, dated 19-05-2021)
5. Malay: Patient Information Sheet/ Informed Consent Form (Version 2, dated 19-05-2021)
6. Data Collection Form (Version 1, dated 10-04-2021)
7. Follow-up Review Report (Version 1, dated 23-05-2021)

…/2-

Appendix 3

Case Report Form

CASE REPORT FORMS

ASSESSING SARCOPENIA
AMONG MALAYSIAN PERITONEAL DIALYSIS PATIENTS
USING BIO-ELECTRICAL IMPEDANCE ANALYSIS-DERIVED
PHASE ANGLE

Subject Initials:

Subject Code:

Date (DD/MM/YY):

Study Location: Hospital Serdang

NMRR-	Subject code:

Questionnaire

A. Sociodemographic characteristics ☐

B. Medical history ☐

C. Anthropometry assessment ☐

D. Bio-electrical impedance analysis (BIA) ☐

E. Physical function and performance test ☐

F. Biochemical data ☐

G. 3-day diet records (3DDR) ☐

NMRR-	Subject code:

Subject criteria

Inclusion criteria

Please tick (/) for subject's eligibility

1. Malaysian ≥18 years old ☐
2. Undergoing regular PD treatment for at least 6 months. ☐

Exclusion criteria

Please cross (x) for subject's eligibility

1. Blind, mute and deaf ☐
2. With contraindications for bia (i.e. Limb amputations, implanted metallic devices and presence of **pacemaker**) ☐
3. With acquired immunodeficiency syndrome (aids) or malignancy ☐
4. With history of peritonitis, infections, trauma or surgical procedure in past 3 months ☐
5. With physical impairment secondary to non-sarcopenia reasons (i.e. Lower limb amputation, stroke, parkinson's disease, arthritis) ☐

NMRR-	Subject code:

Questionnaire (Please tick or fill in the blanks as appropriate)

A. Sociodemographic characteristics

1. Gender: ☐ Male ☐ Female 2. Date of birth: |__|__| |__|__| |__|__| 3. Age: |__|__| years old
DD MM YY

5. Ethnicity: ☐ Malay ☐ Chinese ☐ Indian ☐ Other, please specify _____

6. Marital status: ☐ Single ☐ Married ☐ Other, please specify _____

7. Education background: ☐ No formal education ☐ Primary ☐ Secondary ☐ College/University

8. Employment status: ☐ Employed ☐ Unemployed

9. Household income: ☐ <RM500 ☐ RM 2001- RM 3000 ☐ >RM 5000
☐ RM 501 - RM 1000 ☐ RM 3001 - RM 4000
☐ RM 1001- RM 2000 ☐ RM 4001 – RM 5000

B. Medical history

1. Date diagnosed with end-stage renal failure_____ (month/year).

2. Dialysis history:
- Hemodialysis, HD (if any) : _____(month/year) until _____(month/year)
- Duration on HD (if any) : _____(months)
- Peritoneal dialysis, PD : _____(month/year) until present
- Duration on PD : _____(months)

3. Major Comorbidities:

☐	Diabetes Mellitus	☐	Liver failure
☐	Hypertension	☐	HIV
☐	Hyperlipidemia	☐	Cancer
☐	Cardiovascular disease (CVD)	☐	SLE
☐	Hepatitis B	☐	Gouty Arthritis
☐	Hepatitis C	☐	Others:

4. Residual Urine Output (ml/d)
☐ < 250ml ☐ 250-500ml ☐ >500ml ☐ >1000ml

5. Vitamin D Receptor Analogue (VDRA): ☐ YES ☐ NO
6. Smoking: ☐ YES ☐ NO
7. Regular alcohol intake: ☐ YES ☐ NO

NMRR-	Subject code:

8. PD Modality: ☐ Manual (CAPD) ☐ Automated ☐ Combined

9. 3-days record of PD Regimen

Date:			
	Concentration	**Volume**	**Modality**
Dialysate Bag 1			Manual/Automated
Dialysate Bag 2			Manual/Automated
Dialysate Bag 3			Manual/Automated
Dialysate Bag 4			Manual/Automated

Date:			
	Concentration	**Volume**	**Modality**
Dialysate Bag 1			Manual/Automated
Dialysate Bag 2			Manual/Automated
Dialysate Bag 3			Manual/Automated
Dialysate Bag 4			Manual/Automated

Date:			
	Concentration	**Volume**	**Modality**
Dialysate Bag 1			Manual/Automated
Dialysate Bag 2			Manual/Automated
Dialysate Bag 3			Manual/Automated
Dialysate Bag 4			Manual/Automated

5

NMRR-	Subject code:

C. Anthropometry assessment

Height: _____(m)

Dry-weight: _____(kg)

Body Mass Index: _____(kg/m^2)

Current Weight :_____(before deduct dialysate wt, kg); _____(after deduct dialysate wt, kg)

Dry-weight (3 months ago): _____(kg) Dry-weight (6 months ago): _____(kg)

***Right Limbs**standing position**	**Reading 1**	**Reading 2**	**Reading 3**	**Mean**
Length from acromiale to radiale (cm)				
Midpoint between acromiale and radiale (cm)				
Mid-upper arm circumference (cm)			(If diff exceed 1%)	
Calf circumference (cm)			(If diff exceed 1%)	

NMRR-	Subject code:

D. Bio-electrical impedance analysis measurement

Gender: ☐ Male ☐ Female

Age:_____(years) Height:_____(cm)

Applied weight:

☐ Actual body weight, when no dialysate instilled (_____kg) *labelled as "66XX01"*

☐ DIBW – dialysate wt (_____kg) *labelled as "66XX02"*

☐ DIBW (_____kg) *labelled as "66XX03"*

(If measure with dialysate): volume: _____L ; concentration : _____%

(For Female): During menstrual period? ☐ YES ☐ NO

PARAMETERS	Overall	Right Arm	Left Arm	Trunk	Right Arm	Left Arm
PhA (°)						
Segmental Lean Body Mass (kg)						
SMI (kg/m^2)						
SMM (kg)						
ECW/TBW Ratio						
Body Fat Mass (kg)						
Body Fat Percentage (%)						
Body Cell Mass (kg)						

NMRR-	Subject code:

E. Physical function and performance

	Reading 1	Reading 2	Reading 3	Final Result
Handgrip strength (kg)				(Highest Reading)
5-times stand test			NA	(Average Reading)

F. Biochemical data

Parameters	Blood test results Current (Date)_____	Normal range
Urea (mmol/L)		
Creatinine (mmol/L)		
Serum albumin (g/L)		
Serum cholesterol (mmol/L)		
Serum TIBC (µmol/L)		
Serum Phosphate (mmol/l)		
Serum Haemoglobin (g/dL)		
When TIBC reading not available (please fill the data below)		
Iron (µmol/L)		
UIBC (µmol/L)		
TIBC (ug/dL)		
Miscellaneous		
Kt/V		

NMRR-	Subject code:

G. 3-day diet records

Diet recall Day 1 (date): _____

PD patient: ☐ Weekday ☐ Weekday ☐ Weekend

Place eaten/Time	Description of food and drink	Portion size	Preparation method

NMRR-	Subject code:

Diet recall Day 2 (date): _____

PD patient: ☐ Weekday ☐ Weekday ☐ Weekend

Place eaten/Time	Description of food and drink	Portion size	Preparation method

NMRR-	Subject code:

Diet recall Day 3 (date): _____

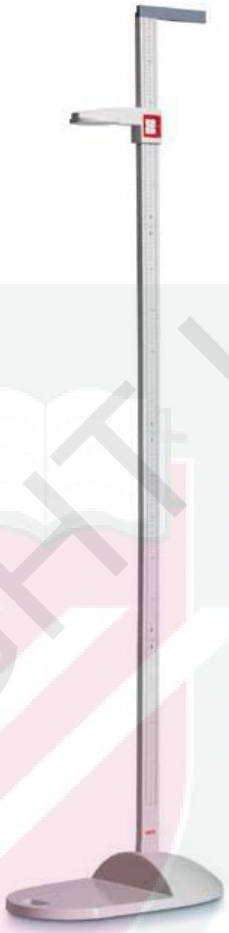
PD patient: ☐ Weekday ☐ Weekday ☐ Weekend

Place eaten/Time	Description of food and drink	Portion size	Preparation method

Appendix 4

Study Instruments

MFBIA Body Composition Analyzer (Inbody S10)



Stadiometer (SECA 213)

Weighing Scale (Tanita HD-319)

Lufkin flexible steel tape

Jamar handgrip dynamometer

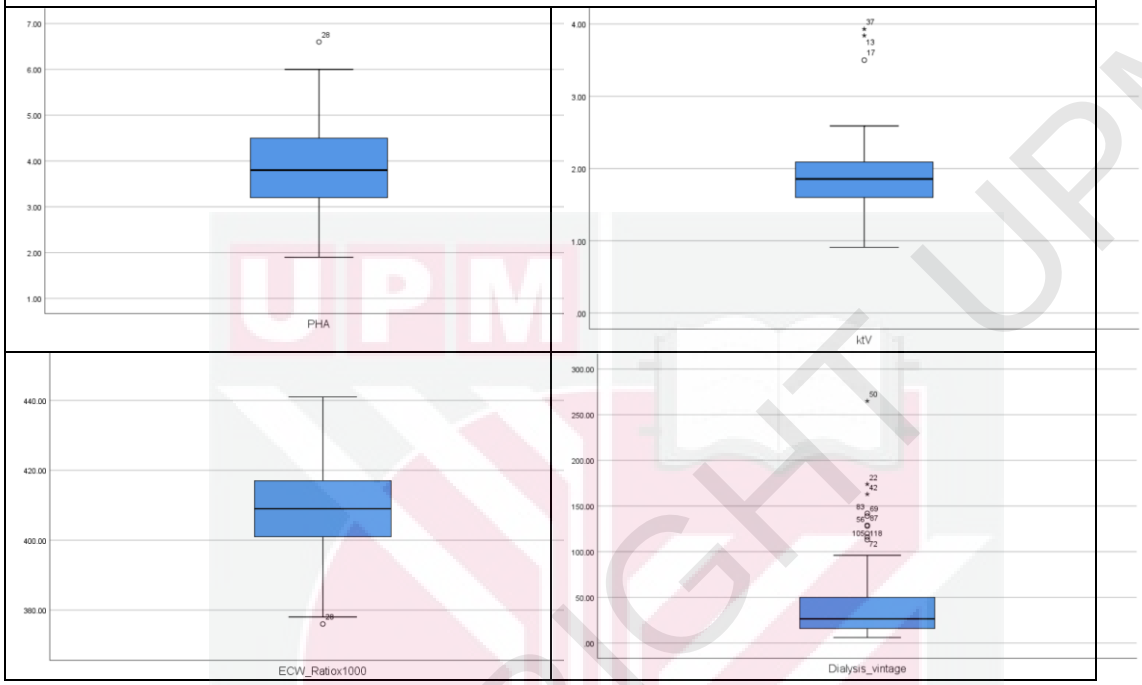
Standard Household Measurement Tools

Appendix 5

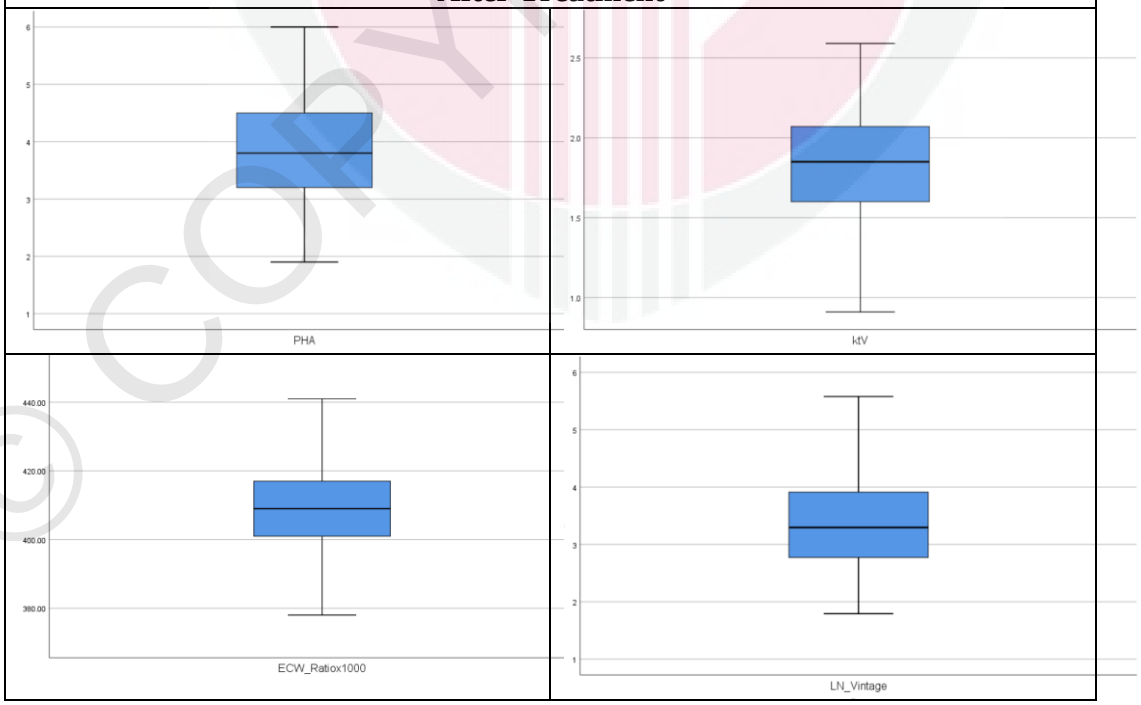
Assumption Checking for Logistic Regression

1) Absence of Outliers

Before Treatment



After Treatment



2) Linearity between Independent Variables and Logit-Transformed Dependent Variable

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Age	1.706	1.064	2.574	1	.109	5.509
	Gender(1)	.090	.647	.019	1	.889	1.095
	Ethnicity			1.235	2	.539	
	Ethnicity(1)	.728	.657	1.229	1	.268	2.071
	Ethnicity(2)	.464	1.208	.148	1	.701	1.591
	EDU_3CAT			.135	2	.935	
	EDU_3CAT(1)	-.249	.731	.116	1	.733	.780
	EDU_3CAT(2)	-.117	.986	.014	1	.905	.889
	Marital_2CAT(1)	-.191	.922	.043	1	.836	.826
	Employment_status(1)	-1.314	.900	2.128	1	.145	.269
	Income5k_2Cat(1)	-.406	.661	.377	1	.539	.666
	ECW_Ratio_1k	26.116	18.328	2.030	1	.154	2.197E+11
	ktV	.793	5.736	.019	1	.890	2.209
	Numbers_of_comorbids	-5.892	2.359	6.241	1	.012	.003
	LN_Vintage	-1.196	4.241	.080	1	.778	.302
	PHA	-7.694	8.279	.864	1	.353	.000
	ECW_Ratio_1k by LN_ECW_Ratio_1k	-3.734	2.610	2.047	1	.153	.024
	LN_PHA by PHA	2.357	3.717	.402	1	.526	10.559
	LN_ktV by ktV	-.428	3.288	.017	1	.896	.652
	Age by LN_AGE	-.332	.213	2.436	1	.119	.717
	LN_No_Comorbid by Numbers_of_comorbids	2.904	1.178	6.073	1	.014	18.240
	LN_LN_Vintage by LN_Vintage	.561	1.935	.084	1	.772	1.752
	Constant	-1490.929	1068.190	1.948	1	.163	.000

a. Variable(s) entered on step 1: Age, Gender, Ethnicity, EDU_3CAT, Marital_2CAT, Employment_status, Income5k_2Cat, ECW_Ratio_1k, ktV, Numbers_of_comorbids, LN_Vintage, PHA, ECW_Ratio_1k * LN_ECW_Ratio_1k , LN_PHA * PHA , LN_ktV * ktV , Age * LN_AGE , LN_No_Comorbid * Numbers_of_comorbids , LN_LN_Vintage * LN_Vintage .

3) Absence of Multicollinearity

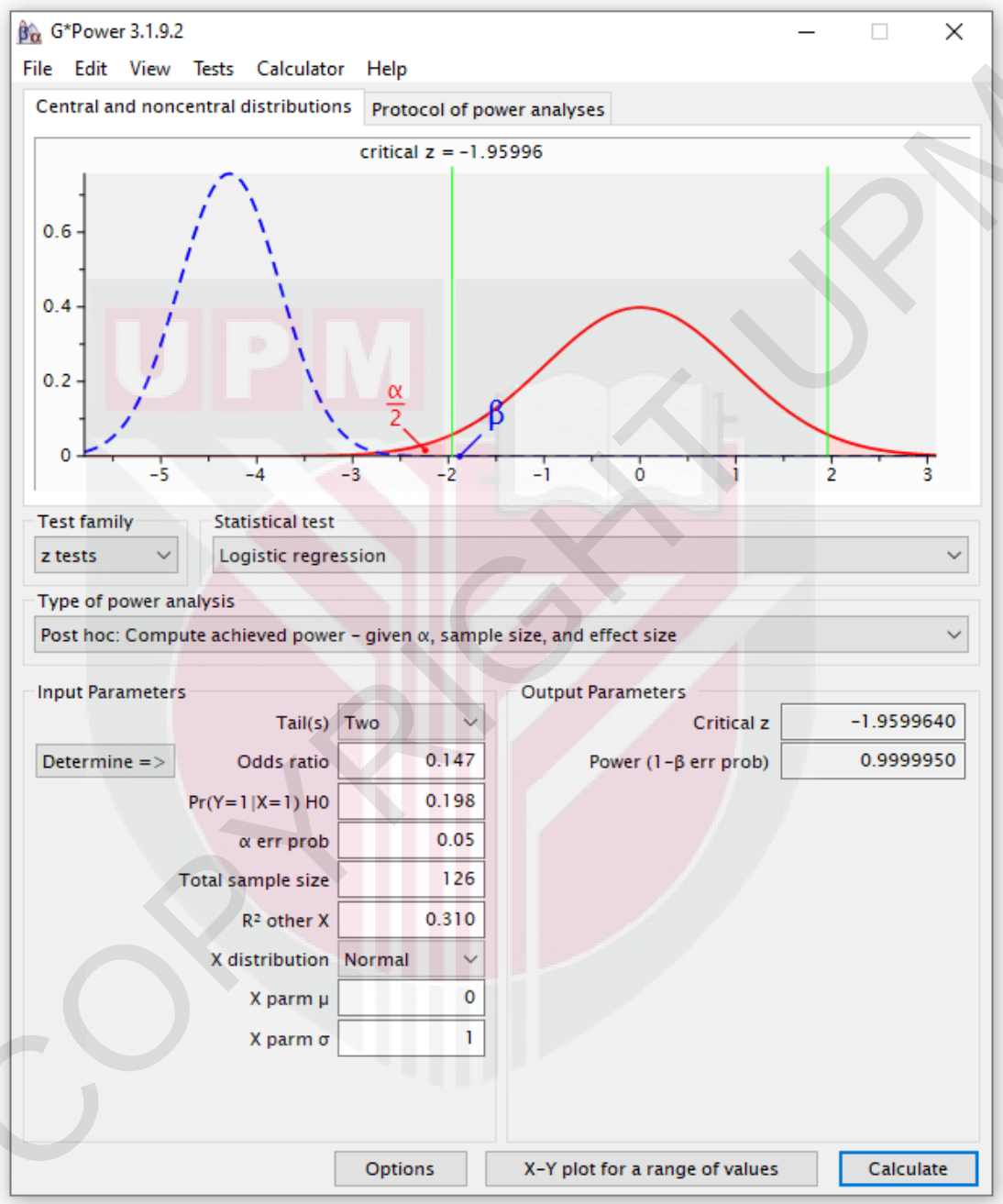
Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	7.501	2.961		2.533	.013		
	Age	.008	.004	.226	1.826	.071	.455	2.198
	Gender	-.037	.093	-.043	-.402	.688	.621	1.610
	Ethnicity	.040	.069	.054	.584	.560	.816	1.225
	EDU_3CAT	-.057	.071	-.093	-.806	.422	.520	1.921
	Marital_2CAT	-.018	.119	-.015	-.151	.880	.658	1.520
	Employment_status	-.119	.114	-.116	-1.039	.301	.554	1.805
	Income5k_2Cat	-.026	.094	-.027	-.275	.784	.705	1.419
	ktV	.063	.125	.047	.500	.618	.800	1.250
	Numbers_of_comorbids	-.024	.042	-.055	-.562	.575	.725	1.379
	LN_Vintage	.025	.046	.051	.543	.588	.802	1.247
	ECW_Ratio_1k	-.015	.006	-.438	-2.370	.019	.203	4.925
	PHA	-.317	.089	-.677	-3.578	.001	.194	5.153

a. Dependent Variable: SARC_DX_CALC

Appendix 6

Power Analysis Logistic Regression Model



Appendix 7

Sensitivity Analysis (Multi-Variable Logistic Regression with 130 Subjects)

Variables in the Equation

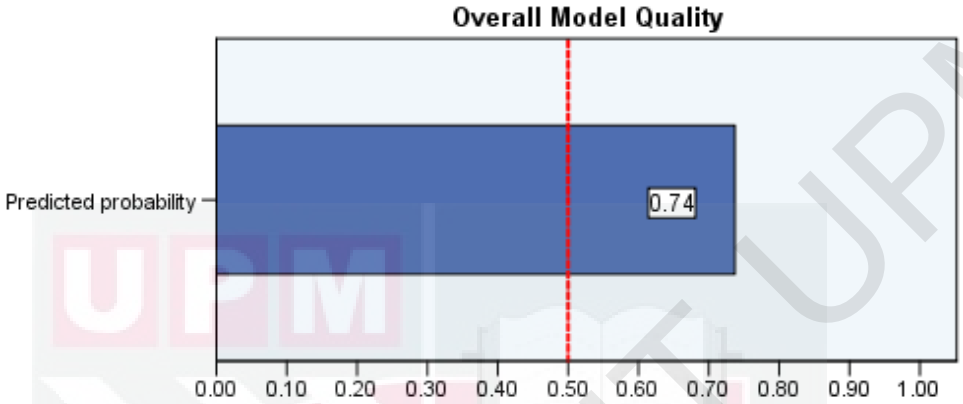
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Age	.047	.029	2.655	1	.103	1.048	.991	1.109
	Gender(1)	-.068	.580	.014	1	.906	.934	.300	2.911
	Ethnicity			1.146	2	.564			
	Ethnicity(1)	.637	.595	1.145	1	.285	1.890	.589	6.068
	Ethnicity(2)	.234	1.190	.039	1	.844	1.264	.123	13.016
	EDU_3CAT			.613	2	.736			
	EDU_3CAT(1)	-.272	.670	.165	1	.685	.762	.205	2.831
	EDU_3CAT(2)	-.702	.913	.591	1	.442	.496	.083	2.969
	Marital_2CAT(1)	.053	.828	.004	1	.949	1.054	.208	5.345
	Employment_status(1)	-.950	.812	1.368	1	.242	.387	.079	1.900
	Income5k_2Cat(1)	-.452	.601	.566	1	.452	.636	.196	2.066
	Numbers_of_comorbids	-.136	.275	.243	1	.622	.873	.509	1.497
	ktV	-.151	.669	.051	1	.821	.860	.232	3.186
	LN_Vintage	.133	.288	.213	1	.644	1.142	.649	2.010
	ECW_Ratio_1k	-.086	.044	3.706	1	.054	.918	.841	1.002
	PHA	-1.971	.647	9.268	1	.002	.139	.039	.496
	Constant	39.867	20.673	3.719	1	.054	2.061E+17		

a. Variable(s) entered on step 1: Age, Gender, Ethnicity, EDU_3CAT, Marital_2CAT, Employment_status, Income5k_2Cat, Numbers_of_comorbids, ktV, LN_Vintage, ECW_Ratio_1k, PHA.

Appendix 8

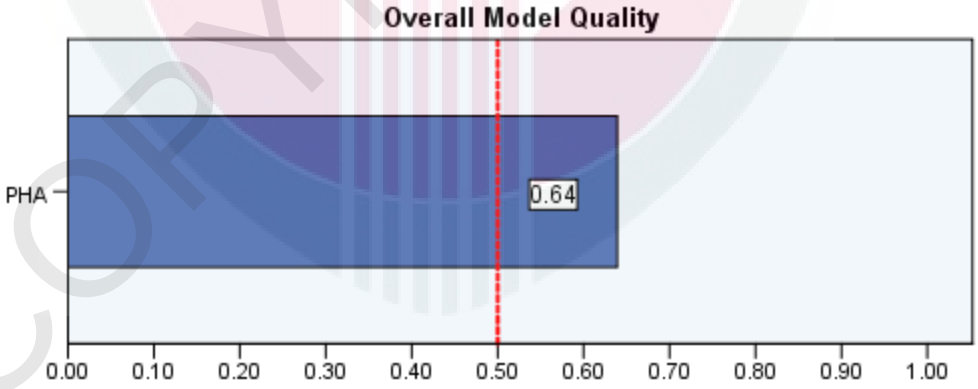
Overall Model Quality

Overall Model Quality of Adjusted ROC



A good model has a value above 0.5
A value less than 0.5 indicates the model is no better than random prediction

Overall Model Quality of Unadjusted ROC



A good model has a value above 0.5
A value less than 0.5 indicates the model is no better than random prediction

Appendix 9

Sensitivity and Specificity Calculation

The result of Sarcopenia Diagnosis by recommended PhA cut-off and AWGS Criteria

PhA ≤ 3.95°	**AWGS Criteria**		
	Sarcopenia Positive	**Sarcopenia Negative**	**Total (n,%)**
Test Positive	27	46	73 (56.2%)
Test Negative	6	51	57 (43.8%)
Total (n, %)	33 (25.4%)	97 (74.6%)	130

Abbreviation = AWGS: Asian Working Group of Sarcopenia

Sensitivity = 27/ (27+6)
= **81.8%**

Specificity = 51/ (46+51)
= **52.6%**

Appendix 10

Power Analysis of ROC Analysis

```
> power.roc.test(result_roc_unadj)

     One ROC curve power calculation

           ncases = 33
        ncontrols = 97
              auc = 0.7355514
        sig.level = 0.05
            power = 0.9882193

> power.roc.test(result_roc_adj)

     One ROC curve power calculation

           ncases = 33
        ncontrols = 97
              auc = 0.8181818
        sig.level = 0.05
            power = 0.999978

>
```

Appendix 11

Association between Education Level and Age

One-way ANOVA Analysis Between Education Level and Age

Variables	Total (n=130)	≤ Primary	Secondary	Tertiary	p-value
Age (years)	53.0 ± 13.3	61.8 ± 9.7[ab]	55.4 ± 11.6 [ac]	45.7 ± 13.3[bc]	< 0.001

Data are presented as mean ± SD; Data were analyzed using One-way ANOVA. Data shared the same superscript indicates that they are significant different with each other.

Appendix 12

Prevalence of Sarcopenia in Non-Elderly Patients

SARC_DX_CALC * Age_2C_lessthan60 Crosstabulation

			Age_2C_lessthan60		
			<60yo	>=60yo	Total
SARC_DX_CALC	NO	Count	64	33	97
		% within SARC_DX_CALC	66.0%	34.0%	100.0%
		% within Age_2C_lessthan60	80.0%	66.0%	74.6%
		% of Total	49.2%	25.4%	74.6%
	YES	Count	16	17	33
		% within SARC_DX_CALC	48.5%	51.5%	100.0%
		% within Age_2C_lessthan60	20.0%	34.0%	25.4%
		% of Total	12.3%	13.1%	25.4%
Total		Count	80	50	130
		% within SARC_DX_CALC	61.5%	38.5%	100.0%
		% within Age_2C_lessthan60	100.0%	100.0%	100.0%
		% of Total	61.5%	38.5%	100.0%

Appendix 13

Detailed Breakdown of Sarcopenia Prevalence

	n (%)
Non-Sarcopenia	***97 (74.6)***
Passed all criteria	41 (31.5)
Low muscle mass	12 (9.2)
Low muscle strength	7 (5.4)
Low physical performance	12 (9.2)
Low muscle strength + Low physical performance	25 (19.2)
Sarcopenia	***10 (7.7)***
Low muscle mass + Low muscle strength	5 (3.8)
Low muscle mass + Low physical performance	5 (3.8)
Severe Sarcopenia	***23 (17.7)***
Low muscle mass + Low muscle strength + Low physical performance	23 (17.7)

False negative rate when sarcopenia was defined as "low muscle mass + low muscle strength":
5/33 = 15.2%

False negative rate when sarcopenia was defined as "low muscle mass + low physical performance":
5/33 = 15.2%

Appendix 14

Multi-Variable Logistic Regression of the Status of HGS and 5TCST by Age Category

Analysis for Non-Elderly Patients (< 60 years old):

HGS

Classification Table[a]

Observed			Predicted HGS_Status: Pass	Fail	Percentage Correct
Step 1	HGS_Status	Pass	48	6	88.9
		Fail	12	14	53.8
	Overall Percentage				77.5

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	PHA	-.933	.659	2.001	1	.157	.394
	Age	.069	.042	2.656	1	.103	1.071
	Gender(1)	-.775	.786	.973	1	.324	.461
	Ethnicity			.472	2	.790	
	Ethnicity(1)	.494	.772	.410	1	.522	1.639
	Ethnicity(2)	.477	1.084	.194	1	.660	1.612
	Marital_2CAT(1)	-.133	.900	.022	1	.882	.875
	EDU_3CAT			.670	2	.715	
	EDU_3CAT(1)	.496	1.111	.199	1	.655	1.642
	EDU_3CAT(2)	-.067	1.245	.003	1	.957	.936
	Income5k_2Cat(1)	.562	.842	.445	1	.505	1.754
	Employment_status(1)	.045	.821	.003	1	.956	1.046
	Numbers_of_comorbids	-.443	.385	1.322	1	.250	.642
	ktV	-.349	1.117	.097	1	.755	.706
	LN_Vintage	-.242	.386	.392	1	.531	.785
	ECW_Ratio_1k	.014	.044	.100	1	.751	1.014
	Constant	-3.616	20.300	.032	1	.859	.027

a. Variable(s) entered on step 1: PHA, Age, Gender, Ethnicity, Marital_2CAT, EDU_3CAT, Income5k_2Cat, Employment_status, Numbers_of_comorbids, ktV, LN_Vintage, ECW_Ratio_1k.

5TCST

Classification Table[a]

Observed			Predicted STS_Status: Pass	Fail	Percentage Correct
Step 1	STS_Status	Pass	49	5	90.7
		Fail	9	17	65.4
	Overall Percentage				82.5

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	PHA	.177	.827	.046	1	.831	1.193
	Age	.163	.052	9.730	1	.002	1.177
	Gender(1)	.740	.918	.650	1	.420	2.096
	Ethnicity			1.522	2	.467	
	Ethnicity(1)	-1.182	.985	1.439	1	.230	.307
	Ethnicity(2)	-.072	1.124	.004	1	.949	.930
	Marital_2CAT(1)	-2.046	1.087	3.540	1	.060	.129
	EDU_3CAT			1.356	2	.508	
	EDU_3CAT(1)	1.395	1.279	1.190	1	.275	4.035
	EDU_3CAT(2)	.851	1.392	.374	1	.541	2.343
	Income5k_2Cat(1)	1.129	1.033	1.194	1	.275	3.092
	Employment_status(1)	.751	.997	.567	1	.451	2.119
	Numbers_of_comorbids	-.426	.488	.761	1	.383	.653
	ktV	-2.546	1.408	3.269	1	.071	.078
	LN_Vintage	-.832	.466	3.184	1	.074	.435
	ECW_Ratio_1k	.120	.060	4.015	1	.045	1.128
	Constant	-50.144	27.536	3.316	1	.069	.000

a. Variable(s) entered on step 1: PHA, Age, Gender, Ethnicity, Marital_2CAT, EDU_3CAT, Income5k_2Cat, Employment_status, Numbers_of_comorbids, ktV, LN_Vintage, ECW_Ratio_1k.

Analysis for Elderly Patients (≥ 60 years old):

HGS

Classification Table[a]

Observed			Predicted HGS_Status: Pass	Fail	Percentage Correct
Step 1	HGS_Status	Pass	11	5	68.8
		Fail	2	32	94.1
	Overall Percentage				86.0

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	PHA	-.860	1.648	.272	1	.602	.423
	Age	-.172	.179	.923	1	.337	.842
	Gender(1)	.027	1.256	.000	1	.983	1.027
	Ethnicity			.464	2	.793	
	Ethnicity(1)	-.861	1.263	.464	1	.496	.423
	Ethnicity(2)	-.425	9.535	.002	1	.964	.654
	Marital_2CAT(1)	-14.821	40192.962	.000	1	1.000	.000
	EDU_3CAT			.871	2	.647	
	EDU_3CAT(1)	.900	1.547	.338	1	.561	2.459
	EDU_3CAT(2)	-.423	1.897	.050	1	.824	.655
	Income5k_2Cat(1)	-2.391	1.430	2.797	1	.094	.092
	Employment_status(1)	38.144	56841.432	.000	1	.999	3.680E+16
	Numbers_of_comorbids	.674	.711	.899	1	.343	1.963
	ktV	.880	1.375	.410	1	.522	2.411
	LN_Vintage	.577	.843	.468	1	.494	1.780
	ECW_Ratio_1k	.222	.135	2.724	1	.099	1.249
	Constant	-103.630	40193.015	.000	1	.998	.000

a. Variable(s) entered on step 1: PHA, Age, Gender, Ethnicity, Marital_2CAT, EDU_3CAT, Income5k_2Cat, Employment_status, Numbers_of_comorbids, ktV, LN_Vintage, ECW_Ratio_1k.

5TCST

Classification Table[a]

Observed			Predicted STS_Status: Pass	Fail	Percentage Correct
Step 1	STS_Status	Pass	11	0	100.0
		Fail	0	39	100.0
	Overall Percentage				100.0

a. The cut value is .500

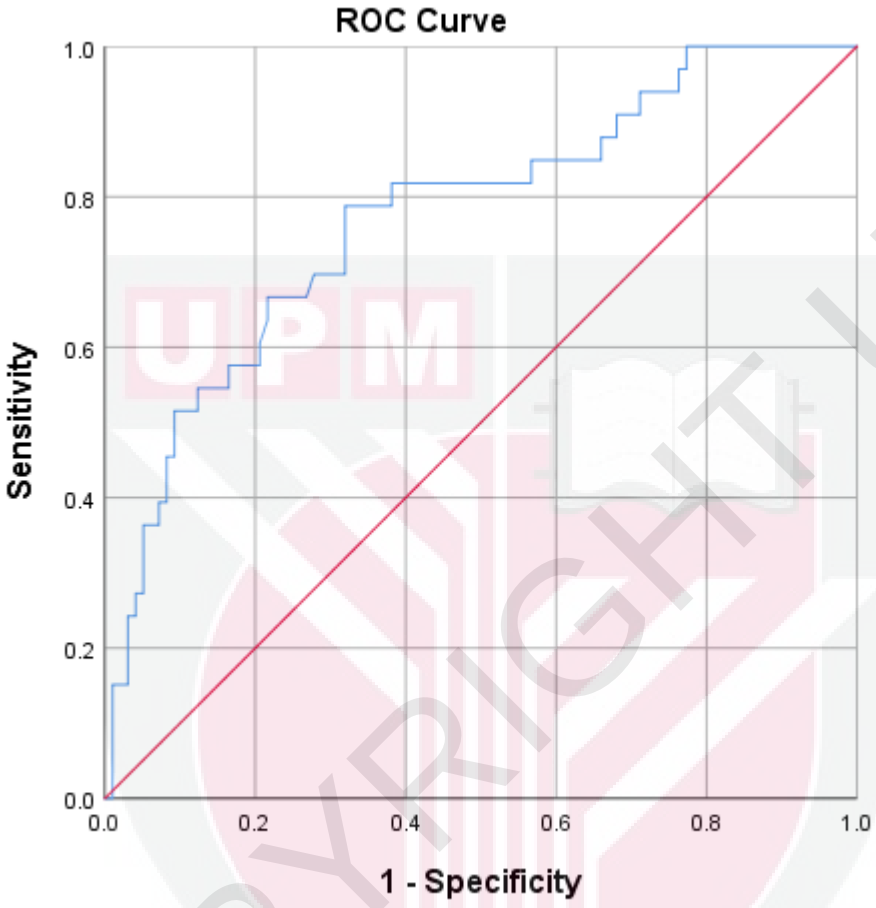
Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	PHA	-575.966	28464.256	.000	1	.984	.000
	Age	-43.985	3047.175	.000	1	.988	.000
	Gender(1)	-51.951	4413.572	.000	1	.991	.000
	Ethnicity			.001	2	1.000	
	Ethnicity(1)	-264.954	9456.059	.001	1	.978	.000
	Ethnicity(2)	-512.347	9.059E+10	.000	1	1.000	.000
	Marital_2CAT(1)	489.576	56296.598	.000	1	.993	4.171E+212
	EDU_3CAT			.001	2	.999	
	EDU_3CAT(1)	386.023	12305.773	.001	1	.975	4.441E+167
	EDU_3CAT(2)	-146.118	6450.890	.001	1	.982	.000
	Income5k_2Cat(1)	320.593	13136.837	.001	1	.981	1.706E+139
	Employment_status(1)	217.309	57426.567	.000	1	.997	2.377E+94
	Numbers_of_comorbids	141.558	5040.122	.001	1	.978	3.004E+61
	ktV	-488.320	19274.977	.001	1	.980	.000
	LN_Vintage	109.164	9037.386	.000	1	.990	2.567E+47
	ECW_Ratio_1k	-17.900	662.392	.001	1	.978	.000
	Constant	11977.548	502043.191	.001	1	.981	.

a. Variable(s) entered on step 1: PHA, Age, Gender, Ethnicity, Marital_2CAT, EDU_3CAT, Income5k_2Cat, Employment_status, Numbers_of_comorbids, ktV, LN_Vintage, ECW_Ratio_1k.

Appendix 15

Discriminative Ability of PhA in Sarcopenia Detection After Adjusted to ECW/TBW Ratio



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s): Predicted probability

Area
.774

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

Appendix 16

Discriminative Performance of Recommended PhA Cut-Off in Detecting Individuals That Fail at Least One Sarcopenia Diagnostic Criteria

PhA ≤ 3.95°	AWGS Criteria		
	Failed ≥ 1 criteria	**Passed all criteria**	**Total (n,%)**
Test Positive	59	14	73 (56.2%)
Test Negative	30	27	57 (43.8%)
Total (n, %)	89 (68.5%)	41 (31.5%)	130

Among 73 subjects with PhA ≤ 3.95°, 59 of them (80.8%) failed at least 1 diagnostic criteria of AWGS 2019.

Appendix 17

Chi-Square Analysis of Sarcopenia Odds by Recommended PhA Cut-Off

A chi-square test of independence showed there was significant association between PhA classification (cut-off value 3.95°) and sarcopenia diagnosis, χ^2 (1, N=130) = 11.831, p = 0.001. The odds of having sarcopenia was 4.989 times higher in patients with PhA lower or equal to 3.95° (OR = 4.989; 95% CI= 1.891-13.164), as per depicted in table below:

Variable	Sarcopenia Diagnosis		P- value	Odds ratio	95% CI	
	Positive n (%)	Negative n (%)			Lower	Upper
PhA						
≤ 3.95°	27 (37.0%)	46 (63.0%)	0.001	4.989	1.891	13.164
> 3.95°	6 (10.5%)	51 (89.5%)				

LIST OF PUBLICATIONS

Journals

Lee, S. W., Daud, Z. A. M., Lim, J. H., Lim, C. K. M., Ibrahim, I., Chan, Y. M., & Zakaria, N. F. (2024). A Pragmatic Approach to Derogate Dialysate-Induced Body Composition Bias in Peritoneal Dialysis Patients: Insight from a Single-Center Study. Turkish Journal of Nephrology, 33(1), 68–75. https://doi.org/10.5152/turkjnephrol.2023.23626

Lee, S. W., Daud, Z. A. M., Lim, J. H., Ibrahim, I., Chan, Y. M., & Zakaria, N. F. (2024). Bioelectrical impedance analysis-derived phase angle as a pragmatic screening tool for assessing sarcopenia in multi-ethnic peritoneal dialysis patients. Clinical Nutrition Open Science, 57, 26-38. https://doi.org/10.1016/j.nutos.2024.07.007

Conferences and Proceedings

Lee, S. W., Daud, Z. A. M., Lim, J. H., Lim, C. K. M., Ibrahim, I., Chan, Y. M., & Zakaria, N. F. A Practical Approach to Minimise Dialysate-Induced Body Composition Bias in Peritoneal Dialysis Patients: Insight From A Single Center Study. 9-10 November 2021. 1st International Scientific Conference on Body Composition (ISCBC 2021). [1st Place of Best Oral Presentation Award].

Lee, S. W., Daud, Z. A. M., Lim, J. H., Lim, C. K. M., Ibrahim, I., Chan, Y. M., & Zakaria, N. F. A Practical Approach to Minimise Dialysate-Induced Body Composition Bias in Peritoneal Dialysis Patients: Insight From A Single Center Study. 26-27 July 2022.3rd MOH Dietitians' Quality and Research Convention 2022. Auditorium, Kompleks E, Putrajaya, Malaysia. [1st Place of Best Clinical Research].