PREVALENCE AND FACTORS ASSOCIATED WITH SARCOPENIA IN OUTPATIENT PRE-DIALYSIS PATIENTS IN A TERTIARY CARE CENTRE IN JOHOR

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by

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LIST OF ABBREVIATIONS

ADL	Activity of Daily Living
ALMI	Appendicular lean muscle index
ASM	Appendicular skeletal muscle mass
ASMI	Appendicular skeletal muscle mass index
AWGS	Asian Working Group for Sarcopenia
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CI	Confidence interval
CT	Computerized tomography
DCF	Data collection form
DEXA	Dual-energy x-ray absorptiometry
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
EUGMS	European Union Geriatric Medicine Society
EWGSOP	European Working Group on Sarcopenia in Older People
FNIH	Foundation for the National Institute of Health Sarcopenia Project
GFR	Glomerular filtration rate
GS	Gait speed
HGS/HS	Handgrip strength
HPSF	Hospital Pakar Sultanah Fatimah Muar
IWGS	International Working Group on Sarcopenia
MAMC	Mid-arm circumference

MBI	Modified Barthel Index
MDRD	Modification of Diet in Renal Disease
MREC	Medical research and Ethics Committee
MRI	Magnetic resonance imaging
NEAT	Non-exercise activity thermogenesis
NHMS	National Health and Morbidity Survey
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
REE	Resting energy expenditure
SARC-F	Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls
SARC-F-J	Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls-Japanese
SCI	Spinal cord injury
SGA	Subjective global assessment
SD	Standard deviation
SMM	Skeletal muscle mass
SMMI	Skeletal muscle mass index
SPPB	Short Physical Performance Battery
SPSS	Statistical Package for Social Science
T2DM	Type 2 diabetes mellitus
TUG	Timed-up-and-go
QoL	Quality of life
Kg/m^2	Kilogramme / metre (squared)
m/s	Metre / seconds
ASM/Ht^2	Appendicular skeletal muscle mass / height (squared)

LIST OF APPENDICES

PREVALEN DAN FAKTOR YANG BERKAITAN DENGAN SARKOPENIA DALAM KALANGAN PESAKIT PRA-DIALISIS YANG MENERIMA RAWATAN DI KLINIK PESAKIT LUAR (RENAL) DI SEBUAH PUSAT PERUBATAN TERTIARI DI JOHOR

ABSTRAK

Sarkopenia adalah satu kondisi bercirikan kehilangan jisim dan fungsi otot rangka. Walaupun sarkopenia lazimnya berlaku dalam kalangan warga tua, ianya juga turut dikaitkan dengan faktor risiko berkaitan penyakit kronik yang lain tanpa mengira umur. Oleh yang demikian, adalah penting untuk mengenalpasti kadar prevalen sarkopenia dalam kalangan pesakit kronik buah pinggang dan faktor risiko yang berkaitan dengan sarkopenia. Kajian keratan rentas selama lapan bulan dijalankan dengan melibatkan 250 pesakit kronik buah pinggang yang berumur 18 tahun dan ke atas serta menghadiri rawatan susulan di klinik pakar pesakit luar (nefrologi) Hospital Pakar Sultanah Fatimah Muar, Johor. Hasil kajian mendapati sebanyak 5.2% daripada populasi kajian didapati mempunyai sarcopenia berdasarkan kriteria yang ditetapkan oleh Asian Working Group for Sarcopenia (AWGS). Bilangan pesakit yang mempunyai sarkopenia meningkat seiring dengan kemerosotan fungsi buah pinggang. Selain itu, dapatan inferensi berdasarkan analisis regresi mendapati aspek peningkatan umur ($p = 0.005$), indeks jisim badan ($p = 0.009$), skor Modified Barthel Index ($p = 0.001$), mempunyai sekurang-kurangnya satu penyakit kronik ($p = 0.035$), serum albumin ($p = 0.012$), mempunyai penyakit diabetes mellitus ($p = 0.018$) serta gout ($p = 0.022$) juga menggambarkan hubungan yang signifikan dengan sarkopenia. Konklusinya, hasil kajian membuktikan bahawa risiko mendapat sarkopenia dalam

kalangan populasi ini meningkat sebanyak 39% (OR: 0.390, CI: 0.166 – 0.912) jika indeks jisim badan adalah rendah dan 64.4% (OR: 0.644, CI: 0.470 – 0.884) jika pesakit mencatatkan skor Modified Barthel Index yang tinggi.

PREVALENCE AND FACTORS ASSOCIATED WITH SARCOPENIA IN OUTPATIENT PRE-DIALYSIS PATIENTS IN A TERTIARY CARE CENTRE IN JOHOR

ABSTRACT

Sarcopenia is a condition characterized by loss of skeletal muscle mass and function. Although it is primarily a disease of the elderly, its development may be associated with conditions that are not exclusively seen in elderly population. Hence, it is important to identify the prevalence of sarcopenia in chronic kidney disease population and its associated risk factors in pre-dialysis patients with chronic kidney disease. This eight months cross-sectional study was conducted on 250 pre-dialysis patients with chronic kidney disease aged 18 years or older who attended the out-patient Renal Clinic at Hospital Pakar Sultanah Fatimah Muar Johor. By using the diagnostic methods proposed by AWGS, sarcopenia was detected in 5.2% of pre-dialysis patients with CKD, with CKD stage 3-5 accounting for 0.4%, 0.8%, and 4% respectively. Multiple logistic regression models revealed that sarcopenia was associated with age (AOR: 0.966, 95% CI: 0.801-1.164), body mass index (BMI) (AOR: 0.390, 95% CI: 0.166-0.912), presence of chronic illness (AOR: 0.529, 95% CI: 0.023-12.237), MBI score (AOR: 0.644, 95% CI: 0.470-0.884, and serum albumin (AOR: 0.813, 95% CI: 0.526-1.257). In conclusion, sarcopenia is more prevalent as kidney function deteriorates was found to be associated with a low BMI and a lack of functional independence. Controlling modifiable risk factors may reduce the likelihood of developing sarcopenia.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

The body derives its source of power to execute body functions from the muscle tissues. The muscle mass and strength reduce with increment of age and presence of morbidity. This condition was first documented by Macdonald Critchley a neurologist from London as senile atrophy in 1931 (Critchley, 1931). Baltimore longitudinal study on ageing by Nathan Shock in 1970, emphasized the importance of understanding age-related physiological changes (Shock, 1970). Rosenberg was the first to conceive the term sarcopenia and defined it as being both progressive and generalized skeletal muscle disorder affiliated with the aging process at the New Mexico meeting in1988 (Rosenberg, 1997).

Multitudinous cellular and biochemical events have been postulated to malfunction, possibly contributing to various chronic illnesses and diseases, which include several neurodegenerative conditions, rheumatoid arthritis, atherosclerosis, and other cardiovascular diseases (Prasad, Sung, & Aggarwal, 2013). In addition, skeletal muscle mass also begins to decline progressively at the rate of 3% to 5% per decade after the age of thirty and is accelerated at the rate of 15% per decade in elderly individuals (Kim & Choi, 2013; Ida, Kaneko, Imataka, & Murata, 2019). This continuous deterioration of skeletal muscle mass often leads to detrimental health consequences in older populations such as functional decline, frailty, increased fall risk, poorer quality of life, increased healthcare costs and higher mortality (Fung, 2019).

Due to its negative health consequences, interest in sarcopenia became evident in recent times with much enthusiasm accumulated around this term in the research world with many high-quality numbers of research steering towards the exploration of progressive decline in muscle mass with a deterioration of muscle strength and physical performance. This eventually paved a way to its recognition as an independent disease when it was given a code under the International Classification of Diseases in the year 2016 (Anker, Morley, & von Haehling, 2016).

There are two types of fibres in skeletal muscle. In comparison to type I slow fibres, type II fast fibres have a larger glycolytic potential, lower oxidative capacity, and a faster response. Because of their properties, such as a higher density of mitochondria, capillaries, and myoglobin concentration, type I fibres are characterised as fatigue-resistant fibres. During slow, low intensity activity, most strength generated comes from type I fibers, while in high intensity exercise strength comes from type I and II fibers. Both types of fibres make up the majority of muscle fibres. With age, atrophy almost only affects type II fibers (Kim & Choi, 2013)

In sarcopenia, a number of mechanisms have been postulated to contribute to the rapid decline in skeletal muscle fibres which leads to loss of muscle mass and function. Hence, sarcopenia typically related with numerous aspects such as physiological aging, environmental causes, inflammatory mediators' activation, physical inactivity, mitochondrial defects, lack of neuromuscular junctions, declining of satellite cells counts, hormonal imbalances, and underlying illnesses such as diabetes mellitus and chronic renal impairment (De Souza, 2017; Yoon, Lee, Choi, & Han, 2018; Ida, Kaneko, Imataka, & Murata, 2019). Sarcopenia has been found to be a common occurrence in people with chronic kidney disease in numerous investigations due to persistent imbalances between protein degradation and synthesis

resulting in a loss of muscular protein mass which is more intensive and the first signs can even be detected early in younger patients than it is expected (Ciechanowski, 2012). Sarcopenia has been associated to inferior clinical outcomes, including decreased quality of life, increased hospitalization, and higher mortality rates. Sarcopenia, or the loss of skeletal muscle, has serious repercussions in CKD, even before dialysis started (Sabatino, A., Cuppari, L. & Stenvinkel, P, 2021). Hence, identifying sarcopenia at an early stage of CKD is very important with respect to its relationship with patient-centered outcomes of mobility limitations, functional limitations in activities of daily living, hospitalizations, fractures and mortality.

In fact, research findings have exhibited that the existence of sarcopenia in these patients predicts negative health outcomes (Liccini & Malmstrom, 2016). In the case of chronic kidney disease, the risk of developing sarcopenia is preeminent as the function of renal diminishes, hence it is more prevalent in end-stage renal disease patients regardless of age (Domański & Ciechanowski, 2012; Souza, Oliveira, Mansur, Fernandes, & Bastos, 2015). This is due to the fact that the protein production declines, and protein catabolism accelerates in chronic kidney disease patient. (Kim, 2014; Ren, Gong, Jia, Xu, & Liu, 2016). Eventually, deterioration of muscle protein greatly impacts on muscle's ability to function and perform, thus, contributing to poor clinical outcome, poor patient-centred outcomes, extended hospitalization period and increased mortality among end-stage chronic kidney disease patients (Moorthi & Avin, 2017; Hara, 2018).

Many research have also documented the prevalence of sarcopenia albeit using many different approach and criteria. As a result, it has generated a wide range of prevalence from 0.1% to 85.4% globally. From this, it is evident that the prevalence and associated adverse effects differs by using various diagnostic criteria. (Beaudart,

Rizzoli, Bruyère, Reginster, & Biver, 2014; Moon, Kim, Yoon, Chung, & Hwang, 2015).

Hence, to aid in sarcopenia screening, several muscle mass assessments were proposed as the main diagnosing method with many types of measurement tools recommended. Thereafter, as the research revolving sarcopenia begin to intensify, in contemplation of improving the early detection, identification, and treatment of sarcopenia, several schools of thought were formed to collectively decide the consensus on definition and its diagnosis. Accordingly, muscle quality and physical execution estimation were suggested as the extra strategies for sarcopenia diagnosing. Appendicular skeletal muscle mass (ASM) is the first proposed diagnostic approach for sarcopenia (Baumgartner, 1998). Baumgartner et al. suggested to represent the outcome of the diagnosis of sarcopenia as muscle index by dividing appendicular skeletal muscle mass (ASM) by height square ($height^2$). Since then, there were numerous evidence-based diagnostic approaches proposed by the research community (Chen, 2014; Cruz-Jentoft, 2010; Fielding, 2011; Morley, 2011). At present, there are at least six diagnostic requirements that have been developed by international groups, such as the European Working Group on Sarcopenia in Older People (Cruz-Jentoft, 2018), the Asian Working Group for Sarcopenia (Chen, 2014), the International Working Group on Sarcopenia (Cruz-Jentoft, 2014), and the Foundation for the National Institutes of Health Sarcopenia Project to identify sarcopenia (Woo, Leung, & Morley, 2015). A wide range of techniques can be used to assess muscle mass. Cost, availability and ease of use can determine whether the techniques are better suited to clinical practice or are more useful for research. Table 1.1 lists the suggestions of EWGSOP for use of these techniques in research and in routine clinical practice.

Table 1.1: Measurement of muscle mass, strength, and function in research and clinical practice

Variable	Research	Clinical practice
Muscle mass	Computed tomography (CT) Magnetic resonance imaging (MRI) Dual energy X-ray absorptiometry (DXA) Bioelectrical impedance analysis (BIA) Total or partial body potassium per fat-free soft tissue	BIA DXA Anthropometry
Muscle strength	Handgrip strength Knee flexion / extension Peak expiratory flow	Handgrip strength
Physical performance	Short physical performance battery (SPPB) Usual gait speed Timed get-up-and-go test Stair climb power test	SPPB Usual gait speed Timed get-up-and-go test

Note. Adapted from "Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People." By Cruz-Jentoft, Alfonso J et al. *Age and ageing* vol. 39,4 (2010): 412-23. doi:10.1093/ageing/afq034

Since sarcopenia is commonly found in elderly with advancing age and comorbid, prevalence of sarcopenia is a vital societal and public health concern. As a consequence of the high risk and serious adverse health outcomes, sarcopenia is considered to be a significant contributing factor to healthcare expenditures and even a modest decrease in its occurrence may be projected to result in substantial savings in healthcare funds. Even though, sarcopenia is very common but like most geriatric syndromes, seldom recognized by clinicians. Clinicians should also consider sarcopenia not only in aged patients with clinically compromised physical functioning, tenacity, or health condition but also in patients who has underlying medical conditions related with deprivation of muscle mass such as type 2 diabetes mellitus, malignancies,

rheumatoid arthritis, long term coronary artery diseases, inflammatory lung diseases, and renal impairment. Likewise, this study is of paramount importance considering Malaysia's mixed racial population, in which the outcome might vary from other identical studies. Rate of prevalence and its associated risk factors might give an insight on how to prevent the disease so that the health care system would profit in terms of refining their planning and management of sarcopenic patients among pre-dialysis chronic kidney disease population in Malaysia.

In view of this, the primary purpose of our study is to measure the prevalence of sarcopenia according to the Asian Working Group for Sarcopenia's (AWGS) recommendation among pre-dialysis chronic kidney disease population and identify the associated risk factors. The universal viewpoint is that the diagnostic criteria recommended by AWGS is more relevant in Asian population since the cut-off values were formed from reported data collected around Japan, China, Malaysia and other Asian countries (Du, 2019). Moreover, the AWGS provides recommendations for individuals with Asian ancestry and proposes the implementation of handgrip strength and gait speed as the starting assessment, trailed by European Working Group on Sarcopenia in Older People's (EWGSOP) methodology of muscle mass measurement albeit with different lower cut-off points (Batsis, Villareal, & Health, 2019).

1.2 Problem Statement

The fundamental mechanisms of sarcopenia within long-term renal disease revolve around the deficit of muscle mass. However, it is still uncertain whether reduced physical activity causes muscle loss or loss of muscle leads to reduced activity. Inevitably, this, implicates a negative balance of protein homeostasis due to intensified

protein degradation along with decreased synthesis of muscle among chronic kidney disease population (Moorthi & Avin, 2017).

Several papers have shown that sarcopenia is commonly discovered and confederated with poor outcomes in long-term underlying kidney disease patients. The reported worldwide incidence of chronic kidney disease is between 11% to 13% and the prevalence distribution by stage were as follows: stage 1 with 4.1%, stage 2 with 2%, stage 3 with 2.26%, stage 4 with 0.24%; and stage 5 with 0.36% (Hill, 2016). In the year 2011, a population-based assessment conducted in Malaysia had approximated about 9.1% of Malaysians had chronic kidney disease (Hooi, 2013). It also shows the prevalence of sarcopenia in pre-dialysis chronic kidney disease patients varies due to differences in the definition of sarcopenia, the measurement of muscle mass, and ethnicity. In a study conducted by Foley et al. showed that according to stage of chronic kidney disease, the prevalence of sarcopenia was 3.8%, 5.3%, and 9.4% in chronic kidney disease stage 1, 2, and 3–5, respectively (Foley et al., 2007).

Unfortunately, screening for sarcopenia in a vulnerable population such as chronic kidney disease patients is warranted and often, the studies are limited to elderly haemodialysis patients (De Souza et al., 2017). Considering the limited number of studies evaluating sarcopenia in pre-dialysis chronic kidney disease patients and the potentially unfavourable outcomes associated with this syndrome, it is important to measure the prevalence of sarcopenia in this population in order to implement strategies or therapeutic options at an early stage to slow the progression of sarcopenia.

Furthermore, the heterogeneity in the classification and assessment techniques reflect the great variance of its prevalence in different populations. These variances of data reinforce the need for population-specific studies so that it becomes possible to

standardize the diagnosis of sarcopenia and, especially, define cut-off points for muscle mass measures (Chen et al., 2016)

Currently, there are limited research on factors contributing to sarcopenia among chronic kidney disease patients in South East Asia and possibly none in Malaysia. Recognizing the contributing factors to sarcopenia is imperative as it could lead to a change in policy to increase the functionality and independence of patients with renal impairment (Janssen, Shepard, Katzmarzyk, Roubenoff, & Mhs, 2004).

Many studies have been conducted comparing different diagnostic criteria for sarcopenia and the relationship between its prevalence and adverse outcomes. The results have shown low agreement when the various methods are compared. Rate of prevalence also varies according to the instrument and cut-off points used for evaluation of muscle mass. Additionally, method of measurement used for each criterion to define sarcopenia among different population surveyed has also resulted in varying degree of prevalence rate.

A questionnaire which acts as a brief and inexpensive screening test for sarcopenia by evaluating an individual's capabilities in terms of strength, assistance with walking, rising from a chair, climbing stairs, and previous history of falls (SARC-F) would also be helpful for clinicians especially nephrologists to identify patients with muscle weakness that may be amendable to treatment. This would allow referrals of patients with positive SARC-F scores for further evaluation and to involve them in therapeutic interventions such as resistance exercise program to improve adverse outcomes such physical disability, poor quality of life and even death.

1.3 Objectives of the Study

1.3.1 General Objective:

General objective of this study is to assess the prevalence and factors associated with sarcopenia in outpatient's pre-dialysis patients of Hospital Pakar Sultanah Fatimah Muar Johor using a locally validated tool.

1.3.2 Specific Objectives

I. To assess the prevalence of sarcopenia among outpatient pre-dialysis chronic kidney disease patients in Hospital Pakar Sultanah Fatimah Muar Johor.

II. To compare the prevalence of sarcopenia in each stages of chronic kidney disease among outpatient pre-dialysis chronic kidney disease patients.

III. To estimate the functional measures of sarcopenia between the genders.

IV. To identify the factors associated with sarcopenia among pre-dialysis patients with chronic kidney disease.

1.4 Significance of Study

Sarcopenia was found to be a strong predictor of mortality in hemodialysis patients as well as in chronic kidney disease patients at the pre-dialysis stage (Hirai, Ookawara, & Morishita, 2016). Even though only 0.36% of the total Malaysian population was affected by chronic kidney disease stage 5, the total annual expenditure of end-stage renal disease (ESRD) by the public sector in Malaysia has grown by 94% over a period of 7 years, from MYR 572 million in 2010 to MYR 1.12 billion. The

average ESRD expenditure between the year 2010 and 2016 was a staggering MYR 823 million per year with an average annual growth of expenditure of 11.89%. The increasing trend in total ESRD expenditure was not contributed by the increase in the cost of the treatment alone, but rather, it is contributed by the overall increase in the prevalence of ESRD (Ismail, 2016).

In view of the high health expenditure used in combating chronic kidney disease and its related adverse health outcomes such as sarcopenia, optimization of health resources by public sector investments is warranted in pursuance of maximizing the health benefits of the public. Policy making and strategy reviews, as well as holistic approach to the management of chronic kidney disease and its related adverse health outcomes is vital to prevent or slow the progression of chronic kidney disease and its adverse health effects. This is pivotal to reduce the cost of managing chronic kidney disease because evidence have shown that consequences of sarcopenia are indeed a prognostic indicator of public health burden, due to the development of physical disability, nursing home admission, depression, increased risk of hospitalization, and even mortality.

This could be achieved by investigating the prevalence of sarcopenia among chronic kidney disease patients in a local hospital setting. In general, few studies have been conducted on sarcopenia among Malaysian elderly, however to the best of our knowledge no studies have discussed the prevalence of sarcopenia among outpatient pre-dialysis chronic kidney disease patients in Malaysia despite a sharp increase in chronic kidney disease prevalence from 9.07% of the adult population in 2011 to 15.5% in 2018 had been reported by Malaysian Society of Nephrology.

For this reason, evaluation of sarcopenia among chronic kidney disease patients will provide novel baseline data on prevalence status and possible significant factors associated with sarcopenia in a tertiary hospital at local setting. This baseline data will be helpful in aiding more research in the future to identify suitable prevention strategies. The result will fill the gap of knowledge and can be used as a reference guide for future research as well. While healthcare professionals are now better at detecting sarcopenia, many study findings have not yet been translated into clinical settings. By identifying the prevalence, it will allow our healthcare professionals to provide future screening and risk stratification process which is essential in preventing, delaying, treating, and even reversing sarcopenia by planning early and effective interventions such as optimal protein intake, supplementation of vitamin D, and physical exercise to improve the quality of life in chronic kidney disease patients.

To identify sarcopenia at an early stage, an effective, convenient, and rapid screening tool is needed since the diagnosis of sarcopenia is complicated and often difficult to perform in routine care. To tackle this issue, SARC-F questionnaire is a convenient and feasible tool, which can be used to diagnose a person at a risk of sarcopenia with precedence. The English version of SARC-F was found not suitable for local environment due to language barriers and cultural differences. To overcome this, the English version of SARC-F must be translated into the Malay language before it can be used locally. The Malay version of SARC-F can be used by a clinical pharmacist to assist nephrologist in screening for persons at risk of sarcopenia with precedence. Hence, to our knowledge, this would be the first study that translates the English version of SARC-F to Malay language which would be significant to policy, practice, and patient care.

1.5 Chapter Outline

This is a brief outline of the chapters that are presented in this thesis:

Chapter 1 – This chapter provides an insight into the background of the development of the term sarcopenia. A comprehensive overview of its problem statement, general and specific objectives, and the significance of conducting this study are further defined and discussed broadly.

Chapter 2 – This chapter is a review of the literature tied to the objectives of this study and provides a detailed reading on the current prevalence status of sarcopenia. The chapter starts by providing details of the prevalence and burden of the disease, with reference to the worldwide setting. This is then expanded to include topics relevant to this study comprising the measurement of sarcopenia among different stages of chronic kidney disease and its factors associated with the occurrence of sarcopenia. This chapter also explains in detail the cross-cultural adaptation and reliability of the SARC-F to assess sarcopenia in our local setting which is also tied to the objectives of this study and explains why it is an essential component of the study.

Chapter 3 – In this chapter, the explanation and justification behind this study are presented in detail. The components of this chapter are study design, study setting, study period, study population, sample size, sampling techniques, ethical approval and instruments utilised. The final section in this chapter is the description of the study procedure and data analysis.

Chapter 4 – The results of the study are presented in detail in this chapter. A complete overview of the statistical analysis showing the prevalence of sarcopenia as well as their associations and chronic kidney disease among the pre-dialysis chronic kidney disease patients are described and presented in tables and figures.

Chapter 5 – This chapter includes a detailed description of the findings in this study as well as the learning points that can be derived from the results. A comparison of the similarities and differences with other studies are also listed here.

Chapter 6 – This chapter is a conclusion and final summary with the strengths andlimitations of the study. The implications for the Malaysian setting and recommendations for further research are included in this chapter.

CHAPTER 2

LITERATURE REVIEW

2.1 Sarcopenia

Skeletal muscle protein synthesis and degradation is a controlled, stable process in healthy young adults, with no net change observed in skeletal muscle mass. Regression of muscle tissue occurs gradually with aging and this leads to reduced muscle mass and strength, a condition known as sarcopenia (Marcell, 2017). This gradual loss of muscle mass with aging has been estimated at about 8% per decade until the age of 70 years, after which the loss increases to 15% per decade (Kim & Choi, 2013). However, there is a minimal amount of muscle mass and strength required by a person in order not to cross the threshold disability due to sarcopenia (Marcell, 2017).

Presence of sarcopenia regardless of age is determined by two factors, which are; the initial amount of muscle mass and, the rate at which it declines. These factors show a clear relationship existing between loss of muscle strength and loss of independence, which eventually contributes to falls, fractures, and nursing home admissions (Cruz-Jentoft, 2010).

2.1.1 Definitions of sarcopenia

2.1.1(a) Definitions of sarcopenia based on skeletal muscle mass

Muscle quantity can be reported as total body skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), or muscle cross-sectional area of specific muscle groups or body locations (Cruz-Jentoft, 2018).

The most commonly used device to estimate skeletal muscle mass are dual-energy X-ray absorptiometry (DEXA), anthropometry and bioelectrical impedance analysis (BIA) due to low cost and widely accessible in healthcare settings. On the other hand, magnetic resonance imaging (MRI), computerized tomography (CT) and creatinine excretion are the most specific standards for assessing muscle mass or cross-sectional muscle area (Kim & Choi, 2013). In particular, MRI and CT are considered to be the gold standard and most accurate imaging methods to assess muscle mass, muscle cross-sectional area, and muscle quality as determined by muscle density and intramuscular fat infiltration but not commonly used in clinical settings due to high cost and operational complexity (Kim & Choi, 2013).

Fundamentally, muscle mass is correlated with body size, which means, individuals with a larger body size normally have larger muscle mass. Thus, when quantifying muscle mass, the absolute level of skeletal muscle mass or appendicular skeletal muscle mass need to be adjusted for body size, and this can be done in variety of ways, using height squared (ASM/height^2) (Marcell, 2017), weight (ASM/weight) (Janssen, 2002) or body mass index (ASM/bmi) (Cawthon, 2014).

2.1.1(b) Definitions of sarcopenia based on skeletal muscle mass index with muscle strength and function

Recent studies have shown that muscle strength does not depend solely on muscle mass alone. In fact, the relationship between muscle mass and muscle strength has been found not to be linear (Kim & Choi, 2013). Hereafter, the initial definition of sarcopenia revolving around 'age-related loss in skeletal muscle', subsequently evolved to the current operative definitions simultaneously capturing the importance of both poor muscle quantity and quality in determining the diagnosis of sarcopenia. Accordingly, muscle quality is assessed based on the muscle strength and performance. Currently, the most widely used measurement of muscle strength in sarcopenia related research is the handgrip strength because it correlates moderately with strength in other body compartments as well, hence, it serves as a reliable surrogate for more complicated measures of arm and leg strength (Cruz-Jentoft, 2018). Knee flexion or extension and peak expiratory flow are also recommended, although, they are less commonly used. As for assessment for muscle performances, a wide range of tests such as Short Physical Performance Battery (SPPB), usual gait speed, stair climb power test, and the timed-up-and-go test (TUG) are recommended (Chen, 2014).

2.1.2 Operational definitions of sarcopenia according to various algorithm

In 2009, the European Union Geriatric Medicine Society (EUGMS) decided to create a Sarcopenia Working Group in order to develop a practical clinical definition and consensus diagnostic criteria for age-related sarcopenia. Later, the European Working Group on Sarcopenia in Older People (EWGSOP) was created and proposed the definition of sarcopenia based on an algorithm revolving the preliminary screening of low gait speed and low handgrip strength. Thus, the EWGSOP recommends routine

screening for sarcopenia among community-dwelling people aged 65 years and older using the presence of both low muscle mass and low muscle function including strength and gait performance for the diagnosis of sarcopenia because defining sarcopenia only in terms of muscle mass is too narrow and may be of limited clinical value (Cruz-Jentoft, 2010). However, low gait performance with a cut-off point of more than 0.8 m/s was introduced as the first step to identify risk of sarcopenia in the EWGSOP algorithm, which, unfortunately, was identified as a disadvantage as it poses a risk of not detecting sarcopenia in older adults with high gait performance but, has evidence of muscle atrophy (Yoshida, 2014). In fact, Yoshida et al. concluded that it is debatable whether inclusion of gait speed is necessary when screening for sarcopenia in community-dwelling older adults and future research should examine the necessity of including gait speed in algorithms and the validity of cut-off values. Nonetheless, the cut-off thresholds for skeletal muscle mass indexes via BIA were designated at < 9.2 kg/m^2 for males and < 7.4 kg/m^2 for females, respectively (Bahat, Tufan, Tufan, Kilic, & Selçuk, 2016). Evaluation of muscle strength was done via handgrip strength with cut-off point of < 30 kg for men and < 20 kg for women (De Souza, 2017).

Additionally, in the year 2018, revised EWGSOP report further categorized sarcopenia into three staging that reflects the severity of the condition. These categories are pre-sarcopenia stage which is characterized by low muscle mass without impact on muscle strength or physical performance, sarcopenia stage; characterized by low muscle mass and low muscle strength or low physical performance, and severe sarcopenia is characterized by low muscle mass, low muscle strength and low physical performance (Cruz-Jentoft, 2018).

Table 2.1: Sarcopenia Staging Criteria

Stage	Low Muscle mass	Low muscle strength	Low muscle performance
Pre-sarcopenia	√		
Sarcopenia	√	√ or	√
Severe sarcopenia	√	√	√

Adapted from Sarcopenia and the New ICD-10-CM Code: Screening, Staging, and Diagnosis Considerations. *Federal Practitioner : For the Health Care Professionals of the VA, DoD, and PHS*, *34*(7), 24–32.

Meanwhile, the Asian Working Group of Sarcopenia (AWGS) decided to take similar approaches for sarcopenia diagnosis as EWGSOP, despite, wider screening. Community-dwelling older people as well as older people with certain clinical conditions in healthcare settings such as; presence of recent functional decline or functional impairment, unintentional body weight loss for over 5% in a month, depressive mood or cognitive impairment, repeated falls, undernutrition, chronic conditions with examples of chronic heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, connective tissue disease, tuberculosis infection, and other chronic wasting conditions was included. In this set of population, AWGS recommended measuring both muscle strength (hand-grip strength) and physical performance (usual gait speed) as the screening test (Limpawattana, Kotruchin, & Pongchaiyakul, 2015).

The recommended cut-off values were adjusted to cater specifically for Asian populations since ethnicities, body size, lifestyles, and cultural backgrounds, may differ from those in Caucasians (Chen, 2014). The current accepted cut-off points for muscle mass measurements is < 7.0 kg/m^2 for men and < 5.4 kg/m^2 for women by

using dual-energy X-ray absorptiometry, and < 7.0 kg/m^2 for men and < 5.7 kg/m^2 for women by using bioimpedance analysis, handgrip strength with < 26 kg for men and < 18 kg for women, and usual gait speed is less than 0.8 m/s (Chen, 2014).

The International Working Group on Sarcopenia (IWGS) also proposed an operational definition of sarcopenia, which was more suitable in clinical settings and targeted to individuals with functional decline, mobility-related difficulties, history of recurrent falls, recent unintentional body weight loss, post-hospitalization, and chronic conditions such as type 2 diabetes, chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease, rheumatoid arthritis, and cancer. IWGS recommends assessing patients with reduced physical functioning or patients with habitual gait speed < 1.0 m/s (by 4m course) to assess body composition by dual-energy x-ray absorptiometry (DEXA). Non-ambulatory patients or those who cannot rise from a chair unassisted is sarcopenic even without DEXA measurements. Unlike EWGSOP, IWGS does not specify the age for sarcopenia diagnosis. The cut-off value for muscle mass was set at < 7.23kg/m^2 in men and < 5.67kg/m^2 in women (Morley, Anker, & von Haehling, 2014).

Notably, although skeletal muscle mass measurement is critically important in all the criteria listed, however, currently, no single skeletal muscle mass index was universally recommended and has been generally agreed by different working groups for sarcopenia in the world. But, it has been agreed that sarcopenia should be defined through a combine approach of muscle mass and muscle quality. However, selecting appropriate diagnostic cut-off values for all the measurements particularly in Asian populations is challenging since Asia is a rapidly aging region with a huge population, so the impact of sarcopenia in this region is estimated to be huge as well.

Alternatively, another approach to sarcopenia assessment is seen in the SARC-F. SARC-F is an acronym of five domains included in the questionnaire: 1) Strength, 2) Assistance in walking, 3) Arising from a chair, 4) Climbing stairs, and 5) Falls. It is a short questionnaire designed for clinical screening which considers falls, stair climb and lifting/carrying as functional deficits related to muscle dysfunction but does not consider markers of muscle mass (Malmstrom & Morley, 2013). SARC-F has been validated against three consensus definitions of sarcopenia from Europe, United States and Asia (European Working Group for Sarcopenia in Older People (EWGSOP), International Working Group for Sarcopenia (IWGS), Asian Working group for Sarcopenia (Cruz-Jentoft, 2018).

2.2 Prevalence of Sarcopenia

2.2.1 Prevalence of sarcopenia

A high prevalence of sarcopenia has been reported in developed and developing countries around the world, and this disorder affects both healthy individuals and individuals with chronic diseases, such as hypertension, diabetes, and chronic kidney disease (De Souza, 2017). This prevalence of sarcopenia tends to depend on the definition applied and the attributes of the target population. As such, European Working Group on Sarcopenia in Older People (EWGSOP), International Working group on Sarcopenia (IWGS) and Asian Working Group for Sarcopenia (AWGS) has released papers for the purpose of establishing international consensus to minimize the differences between the various definitions of sarcopenia, and with this, the overall estimation of prevalence of sarcopenia provided with the EWGSOP's definition ranged between 1% to 29%. The lowest prevalence of sarcopenia till date was taken from a study by Patil et al., who screened a total of 409 independently living

Finnish women between the age of 70 to 80 years old using two diagnostic methods recommended by EWGSOP and IWGS. Patil found only 0.9% was sarcopenic by EWGSOP diagnostic criteria and the same population yielded 2.7% by using IWGS diagnostic criteria (Patil, Pasanen, & Kannus, 2013).

Conversely, in another study with almost the same sample size, showed that, in 354 community-dwelling older subjects in Italy with the mean age of 85.8 years, 29.1% had evidence of sarcopenia. In this study, no difference between men and women was observed (27.1 vs 30.1%, $p = 0.32$) respectively (Landi, Liperoti, & Russo, 2013). The higher prevalence rate among Italian elderly population could be due to the loss of muscle mass that forms a link between anorexia, malnutrition, and negative outcomes in frail elderly subjects. According to a report from an earlier study, it has been shown that anorexia is common among community older subjects in Italy and it negatively affects physical function especially among those who are also suffering from weight loss (Landi, Russo, Liperoti, & Tosato, 2010). However, the discrepancy of the prevalence of sarcopenia reported shows that, it might as well be due to the diagnostic criteria and techniques utilised, tools used to measure muscle strength, methods of determining cut-off values and different populations, further proving that specifying the prevalence of sarcopenia is difficult.

The factors leading to wide discrepancy is further supported by other systematic reviews of studies done from as early as 1988, which included twelve studies adopting different diagnostic criteria among adults $\geq$ 50 years old using bioelectrical impedance analysis to measure body composition. Eight were carried out in community-dwelling elderly people, two in nursing home residents, one in a convalescence and rehabilitation unit and one in hospitalized population. Prevalence of sarcopenia, when defined as a decrease in skeletal muscle mass alone, shows, a

prevalence between 6.0% and 85.4% and when defined together with a decrease in gait speed and/or grip strength, as in the EWGSOP definition, the prevalence falls between 7.5% and 77.6% (Lardiés-Sánchez, Sanz-Paris, Boj-Carceller, & Cruz-Jentoft, 2016).

On the other hand, the attributes of target population can also influence the prevalence rate, such as senior citizens residing in care facilities can have prevalence ranging between 14% and 33% (Cruz-Jentoft, 2014), and when this population includes a large proportion of individuals with disabilities or those hospitalized to recover or underwent rehabilitative care, the prevalence rate is estimated to be 78% (Morandi, 2015). These results clearly shows that the broad range of figures provided to describe the prevalence of sarcopenia depends on the individual's characteristics, definition and diagnostic criteria applied (Lardiés-Sánchez, Sanz-Paris, Boj-Carceller, & Cruz-Jentoft, 2016; Mayhew, 2019).

Similar to Europe continent, Asia is a huge and densely populated continent with a wide range of ethnicities, cultural, social, religious backgrounds, and lifestyles. Therefore, the clinical impact of sarcopenia specifically on older generation will intensify conjointly with the increasing growth of elderly population in Asia. It is expected that the prevalence in Asia will vary greatly due to this different population, instruments of measurements, method of determining cut-off values, and definition of sarcopenia used. Due to the rapid population aging and population size, the impact of sarcopenia in Asia is also expected to be stronger and higher than in other continents (Yoshida, 2014). However, a contradicting review article was published in 2016 which summarizes the prevalence and characteristics of sarcopenia in Asia, focusing on sex differences of sarcopenia in this continent, stated in general, the prevalence of sarcopenia in Asia was lower than Western countries after reviewing nine researches (Wu, Hwang, Liu, Peng, & Chen, 2016). The ranges vary from 0.1% in the study done

in Korea which involved non-institutionalized 2332 participants with 1370 women, to 22.1% in a study done in Japan involving 1971 functionally independent, community dwelling older adults with 944 women. As for men, in Taiwan, Wu et al. concluded 5.4% of sarcopenia prevalence was measured in the study which pooled the analysis from five other cohort studies with a collective sample size of 2155 community-dwelling people with half of the sample comprises of males, compared to 21.8% in another study conducted among 1882 healthy community-dwelling older adults in Japan by Yamada et al. The targeted population in eight of the research reviewed was on community-dwelling aged 65 years old and above and one research was on non-institutionalized older adults with total sample size of 18,165. All seven-research reviewed in this article followed the EWGSOP's diagnostic criteria except for two researches which diagnosed sarcopenia by determining muscle mass only. The article stated that Asians tend to have lower muscle mass, weaker grip strength, slower gait speed, and higher body fat mass with central distribution. However, this article only reviewed studies from Japan, Korea, Taiwan, Hong Kong and Beijing without including other Asian countries. It is postulated that; the status of population aging, and economic development varies extensively in different Asian countries which could influences the prevalence of sarcopenia.

The trend of low sarcopenia prevalence rate among Asian population was also seen in another cross-sectional study conducted among 213 males 418 females from Shanghai, China's community-dwelling older adults between 65 to 89 years old in a period of 12 months. The study was performed to explore sex differences in the prevalence of sarcopenia. The prevalence measured according to AWGS criteria was recorded to be 12.2% in males and 6.2% in females. Unlike previous studies, this study interestingly found that males had higher risk of sarcopenia despite the number of male

participants were lower compared to females. This study argued that higher prevalence was seen in males because, with further aging, testosterone and insulin-like growth factor-1 levels keeps decreasing significantly, resulting in rapid loss of muscle mass and strength over time in males. Moreover, weight-adjusted muscle mass is more suitable for overweight and obese people since height-adjusted would underestimate the prevalence in females, who lose height much more during aging and have higher adiposity than males (Du, 2019). In this study, almost 40% of females were in the obese category.

Meanwhile, a multi-continent study in an attempt to get the prevalence of sarcopenia in the world, involving nationally representative data from Finland, Poland, Spain, China, Ghana, India, Mexico, Russia and South Africa was conducted to evaluate the factors associated with low skeletal muscle mass, sarcopenia, and sarcopenic obesity using samples of people aged ≥ 65 years. The required data were pooled from 18,363 participants who participated in the Collaborative Research on Ageing in Europe (COURAGE) survey and the World Health Organization Study on global Ageing and adult health (SAGE) survey between 2007 and 2012. To obtain nationally representative samples, a multi-stage clustered sampling design method was used and a standard design and procedures across all survey populations was applied. This study did not mention which sarcopenia criteria was followed; however, sarcopenia was defined as having low skeletal muscle mass as reflected by lower skeletal muscle mass index (SMMI) and either a slow gait speed or weak handgrip. Sarcopenia was diagnosed in 15.2% of the total sample, with the lowest prevalence measured in Poland (12.6% out of 1313 participants) and conversely, the highest was 17.5% out of 2441 participants from India (Tyrovolas, 2016). In addition, China recorded 15% in sarcopenia prevalence which falls within the range of other East