1
Introduction

1.1 BACKGROUND

Older population of the world keeps on increasing at an exceptional rate. Today, 8.5% individuals around the world (617 million) are aged 65 and above. As indicated by National Institute of Health (NIH) report, " An Aging world:2015" this rate is predicted to reach to almost 17 percent of the total world's population by 2050 (1.6 Billion)[He *et al.* [2016]]. With respect to the situation in India, the proportion of older people is lower than that of there in western countries, with currently 5.6% of people aged over 65, compared to 17.6% in developed countries. However, the elderly population in India is growing rapidly, with an estimation of 13.4% population would be aged over 65 years by 2050 [DESA [2015]]. As far as the present scenario is concern, India has 73.8 million total number of older people, which almost represents 12% of the world's elderly population.

Sarcopenia is age-related decrease in muscle mass, which results in a loss of muscle strength and functional performance [Morley *et al.* [2011]]. The term sarcopenia was coined by Rosenberg, based on the Greek words sarx (flesh) and penia (loss) [Rosenberg [1997]]. Consequences of sarcopenia include an increased risk of adverse outcomes such as disability and morbidities, as well as increase in all-cause mortality [Cooper *et al.* [2010]]. Sarcopenia is much similar to the physical aspects of frailty, a condition in which there is a decreased physiological reserve leading to an increased vulnerability to stressors and an associated increased risk of adverse outcomes [Rockwood *et al.* [2005]].

Prevalence of sarcopenia depends on the criteria used for its diagnosis [Beaudart *et al.* [2014]]. In a large-scale UK study, the prevalence of sarcopenia was estimated to be 4.6% in men and 7.9% in women aged over 65 years [Patel *et al.* [2013]]. There is not much information available on the prevalence of sarcopenia in India, except for a couple of specific studies. One of them was published in 2013 in which prevalence rates of 39.5% and 15.8% were reported for people with and without type 2 diabetes, respectively [Anbalagan *et al.* [2013]]. Another study in which the prevalence of sarcopenia, in India, was estimated using the method proposed by [Lee *et al.* [2000]]. They estimated the skeletal muscle mass using weight, height, sex, race, BMI, age, and race. This study used data from the World Health Organisation (WHO) Study on global AGEing and adult health (SAGE) surveys, in which India was one of six countries surveyed. They estimated the prevalence of sarcopenia in India to be 17.5%, which was higher than in any of the other five countries [Tyrovolas *et al.* [2016]].

There is some controversy with respect to the diagnosis of sarcopenia, which can be attributed to many different diagnosis criteria that have been developed. There are five main diagnostic classifications, each of which was developed by a specific working group. The first detection algorithm was published by the European Working Group on Sarcopenia for Older People (EWGSOP) in 2010 [Cruz-Jentoft *et al.* [2010]], followed by different diagnosis protocols from the Society of Sarcopenia, Cachexia and Wasting Disorders (SSCWD) (Morley et al., 2011), the International Working Group on Sarcopenia (IWGS) (Fielding et al., 2011), and the Foundation for the National Institutes of Health (FNIH) sarcopenia project [Studenski *et al.* [2014]]. One more criterion is an Asian-specific version of the EWGSOP developed by the Asian Working Group for Sarcopenia(AWGS) [Chen *et al.* [2014]]. All five diagnostic criteria include an assessment of muscle mass, although they differ with respect to the thresholds used, while the FNIH guideline recommends the use of appendicular skeletal lean mass (ALM), rather than the skeletal muscle mass index (SMI) used by all other diagnostic criteria (8). Three

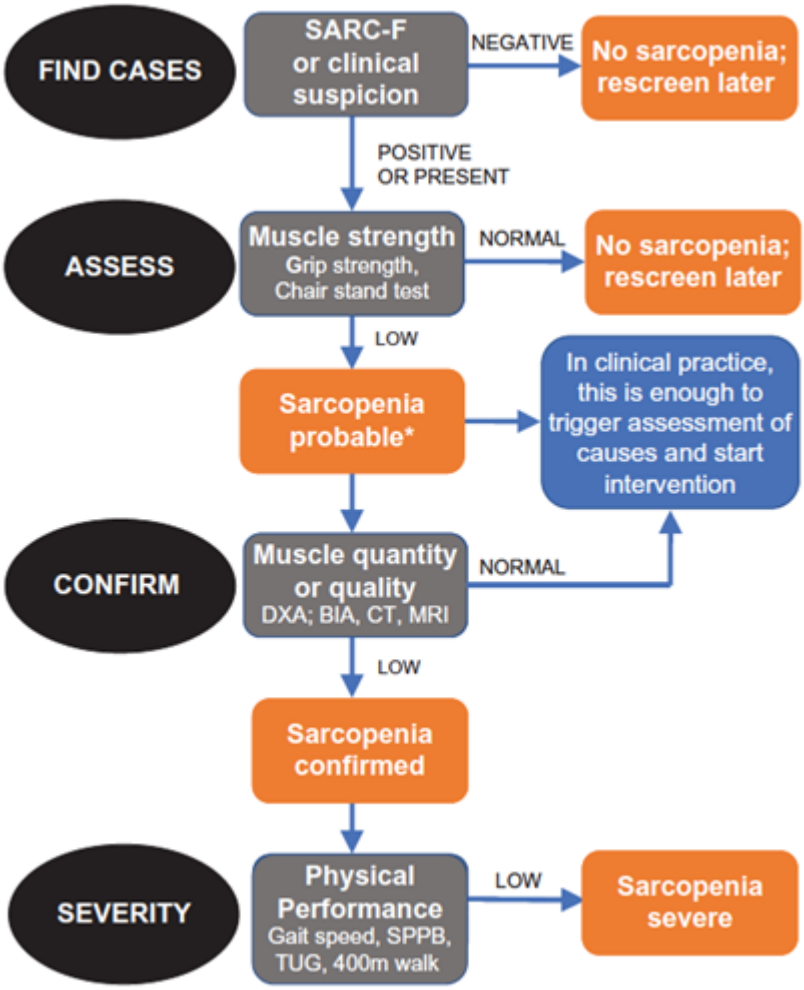

Figure 1.1 : Modified EWGSOP algorithm to detect sarcopenia

[Cruz-Jentoft *et al.* [2018]]

of the guidelines include an assessment of muscle strength using hand-gripped dynamometry, while the IWGS and SSCWD guidelines do not assess muscle strength. Finally, all of the guidelines, except for FNIH, use a test of physical performance, with three groups opting for gait speed, albeit with different thresholds, while the EWGSOP includes the Short Physical Performance Battery (SPPB), which includes tests of balance, sit-to-stand, and gait speed [Cruz-Jentoft *et al.* [2018]].

EWGSOP has modified its own diagnosis algorithm to take account of recent research developments [Cruz-Jentoft *et al.* [2018]]. The revised algorithm uses a Find, Assess, Confirm and Severity (FACS) pathway. This begins with Finding cases by either using SARC-F, a 5-item self-report screening questionnaire for sarcopenia [Malmstrom and Morley [2013]], or a clinical suspicion. If the SARC-F is positive or there is a clinical suspicion, the next step of the algorithm is to Assess muscle strength using a grip strength test, as in the original method, or the five times sit-to-stand (5STS) also known as the chair stand test. If muscle strength is low, an assessment of muscle mass is required to Confirm the diagnosis, followed by a test of physical performance using either gait speed, the SPPB, the Timed up and Go (TUG), or the 400-m walk test, to determine the Severity of the condition. The EWGSOP2 (modified EWGSOP algorithm) has been reversed, when compared to the original EWGSOP algorithm, which started with an evaluation of gait speed before subsequent tests of muscle mass and strength [Cruz-Jentoft *et al.* [2010]]. A copy of the EWGSOP2 algorithm is shown in Figure 1.1.

The EWGSOP2 algorithm includes an assessment of muscle mass, as do all other diagnosis criteria for sarcopenia. Three scanning methods were recommended for use in both research and clinical practice in the original EWGSOP algorithm [Cruz-Jentoft *et al.* [2010]], with the first two of these, Magnetic Resonance Imaging (MRI) and Computerised Tomography (CT) considered to be the gold standards for estimating muscle mass in research. However, there has been concern about radiation levels in both these methods, along with associated high cost, the requirement for trained personnel, and the lack of well-recognised thresholds [Cruz-Jentoft *et al.* [2018]]. Other options include bio-electrical impedance analyser (BIA) or dual X-ray absorptiometry (DXA). With respect to BIA, an estimate of muscle mass is obtained based on the conductivity of the body, with advantages of the method including low-cost and portability [Kyle *et al.* [2003]]. However, results from BIA vary according to the hydration status of the person being tested, while the equations used to estimate muscle mass are based on tests in a European population, so more tests are needed to determine applicability to an Indian population [Reiss *et al.* [2016], Sergi *et al.* [2015]].

A recent article was published following the establishment of a working group at the 2017 World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases in Florence Buckinx *et al.* [2018]]. The recommendations of this working group were to consider DXA to be the reference standard for the measurement of muscle lean body mass. They further recommended the use of DXA-based definitions of muscle mass for sarcopenia using either ALM (Appendicular Lean Mass), normalised by diving by body weight or by BMI (Body Mass Index) [Cooper *et al.* [2012]].

Grip strength testing is a procedure recommended for the measurement of muscle strength in all three of the diagnostic criteria in which this measurement is included [Locquet *et al.* [2018]]. All three guidelines provide different cut-offs for men and women, with the EWGSOP using 30kg and 20kg for men and women, respectively, with these values based on physical frailty screening thresholds [Fried *et al.* [2001]]. The two remaining guidelines, the AWFS and FNIH, recommend lower thresholds of 26kg for men, although the thresholds for women were different as 18kg and 16 kg for the AWGS and FNIH, respectively [Locquet *et al.* [2018]]. Although, all three guidelines proposed grip strength, a measure of knee flexion and extension power could be more useful in the diagnosis of sarcopenia as older people lose power quicker than strength [Cooper *et al.* [2013]]. Such a change has been made in the updated guidelines of the EWGSOP, with the 5STS proposed as screening test for muscle strength using a threshold of 15 seconds for both men and women [Cruz-Jentoft *et al.* [2018]]. The EWGSOP has also reduced the grip strength thresholds to 27kg and 16kg for men and women, respectively.

The most common test of physical performance, used in the sarcopenia diagnosis guidelines, is gait speed with thresholds of 1.0 m/s used by the SSCWD and the IWGS [Locquet *et al.* [2018]]. A lower threshold of 0.8 m/s was used by the AWGS, with this change due to ethnicities, body size, cultural backgrounds, and lifestyles [Chen *et al.* [2014]]. The SPPB, proposed as part of the original EWGSOP diagnosis criterion, is a composite test of balance, gait speed and the 5STS, with each test scored from 0-4, resulting in a maximal performance of 12 points [Guralnik *et al.* [1994]].

There has been a renewed interest in recent years in the STS, which was initially proposed as a test of muscle strength over 30 years ago [Csuka and McCarty [1985]]. Recent studies have examined the relationships between lower limb muscle strength, as assessed by the STS, with mobility, Quality of Life (QoL), activities of daily living, and frailty [Slaughter *et al.* [2015],Kato *et al.* [2015],Batista *et al.* [2014]]. Indeed, a new QoL assessment tool, specifically for sarcopenia, called the Sarcopenia Quality of Life questionnaire (SarQoL) has recently been developed (Beaudart et al., 2016). The original French version has since been translated into many other languages, including English (Beaudart et al., 2016) and Hindi, although a validation study of the Hindi version is yet to get published.

The recent development of the EWGSOP, to include the 5STS as a measure of muscle strength, has also seen the change from the SPPB to gait speed as a recommended test of physical performance

[Cruz-Jentoft *et al.* [2018]]. However, a recent study has shown that chair stand tests can be used as a surrogate test for gait speed [Nishimura *et al.* [2017]]. This suggests that rather than using two different tests for muscle strength and physical performance, it might be possible to use the STS test for both the components of sarcopenia diagnosis algorithm. This means that the only part of the EWGSOP2 algorithm in which the STS does not directly provide information on the diagnosis of sarcopenia is measurement of muscle mass. However, there have already been several studies in which the STS is used to develop model to estimate muscle mass. These studies are based on relationships between power required to perform the STS and the muscle mass. The relationship between time to perform the STS test and muscle power was demonstrated by Smith et al. [Smith *et al.* [2010]] by developing a statistical model (Equation 1) for prediction of lower-limb muscle power that depends on body mass and number of sit-to-stands performed in 20 seconds. The correlation between predicted power and actual power when performing the STS, as calculated from centre of gravity displacement using motion capture and verified using ground reaction forces from a force plate, was excellent (r=0.90). The 20-second cut-off for the number of STS performed was chosen because all of the subjects, under testing, as some of the subjects were unable to complete the full 30-second STS protocol.

$$P_{sit-stand} = 715.218 + 13.915 * bodymass(kg) + 33.425 * STS\ in\ 20\ seconds \tag{1.1}$$

In an another study, Takai et al. [Takai *et al.* [2009]] also developed a predictive equation for power during the STS, but this time for a version in which 10 STS were performed. Power in the Takai equation also included body mass, 10STS time, but also added leg length, adjusted for the chair height of 0.4 m (Equation 2). Similar results were obtained using the predictive equation and knee extension force measured using a custom-built dynamometer, with a strong correlation observed (r=0.73). However, in addition to estimating knee extension force, a relationship with muscle mass was also demonstrated for the cross-sectional area of the quadriceps assessed using MRI (r=0.80).

$$P_{sit-stand} = \frac{((L - 0.4) * bodymass * g * 10)}{T_{sit-stand}} \tag{1.2}$$

After these initial reports, there have been a dearth of subsequent studies, although one recent Japanese study examined the relationship between STS power, estimated using the Takai equation for two different body positions when performing the STS and mid-thigh cross-sectional area of the quadriceps, obtained from an MRI scan [Saito *et al.* [2017]]. They reported that, regardless of whether the upper body was upright or stooped, the estimated power had a near-identical relationship with muscle mass (r = 0.69 and r= 0.70 for stooped and upright STS positions, respectively). The authors also reported the same relationships between both power and torque measured during maximal knee with muscle mass (r = 0.69 and r= 0.70 for power and torque, respectively).

Indeed, the use of the time taken to complete the 5STS has been proposed as a screening tool for sarcopenia in older women, with each one-second increase in STS time increasing the probability of the participant having sarcopenia by 8% [Pinheiro *et al.* [2016]]. Likewise, STS performance has also been proposed as a surrogate for gait speed when screening for sarcopenia [Nishimura *et al.* [2017]]. In both the cases, these studies were published before the changes made to the EWGSOP sarcopenia diagnosis criteria in which the 5STS has been proposed as an option in the initial stages of the screening process. Other studies have included the development of a regression model to predict sarcopenia using measures of physical function such as walking speed, grip strength, and power developed during the STS [Gray *et al.* [2016]]. Good results were achieved, however, rather than using STS time, the power generated during the STS was measured using a linear position transducer [Glenn *et al.* [2017]]. The use of technology to enhance the accuracy with which a STS can detect older people at risk of adverse events such as falls, frailty, and sarcopenia is becoming increasingly common. For instance, an instrumented STS using accelerometer was able to differentiate between fallers and non-fallers [Doheny *et al.* [2011]]. An instrumented STS using an inertial measurement unit (IMU) has also been

shown to improve frailty status identification [Millor *et al.* [2017]]. A similar STS system has been used to distinguish between groups of older people with different functional status [Regterschot *et al.* [2015]]. Use of such technology offers a notable advantage, that is, certain parameters related to STS performance such as velocity during the sit-to-stand phase of the movement can only be extracted using an instrumented approach [Ejupi *et al.* [2016]]. It follows, therefore, that an instrumented system that can accurately determine not only STS time but also the power developed during the sit-to-stand phase would offer advantages over simply timing the STS when it compares to predicting falls, frailty, and sarcopenia.

It seems logical to conclude from the STS power studies and the instrumented STS work that it should be possible to develop a predictive equation for muscle mass based on an estimation of power developed during the STS test, with better performance achieved using instrumented devices. If this were the case, use of the STS test could simultaneously provide an answer to all of the steps of the EWGSOP algorithm, and thus provide an initial diagnosis of sarcopenia. However, in order for such a test to be usable in a clinical setting, in which sarcopenia would need to be diagnosed, the test would need to be measured automatically with the results used to ailment the predictive equations, which would also need to be performed automatically.

1.2 AIMS AND OBJECTIVES

The aim of this thesis is to develop a novel device that is capable of automatically calculating STS time and the power developed when performing the STS. The device chosen for this purpose is based on an instrumented chair, which will be described in detail in the following chapters. The specific objectives of the thesis are :

1. To evaluate the suitability of the STS test as a functional screening test that could be used to screen for other parts of sarcopenia diagnosis based on the EWGSOP2 algorithm.

2.To determine whether instrumented versions of the STS test are preferable to non-instrumented versions of the STS with respect to prediction of physical functions.

3. To develop and validate an instrumented version of the STS test using a chair that is able to identify different phases of the STS test and to predict muscle strength and power.

1.3 THESIS ORGANIZATION

The literature review provided evidences that an automated device is capable of detecting the beginning and end of an STS. Also, body mass of a subject would be able to provide sufficient data for an algorithm to estimate power and muscle mass. The methodology chosen to diagnose sarcopenia using an iSTS (instrumented sit-to-stand) is to develop a predictive algorithm for each of the Assess, Confirm, and Severity stages of the EWGSOP2 methodology, shown previously in Figure 1.1. The iSTS needs to be able to predict the outcome of each of the tests used in EWGSOP2 in order to use it as a standalone diagnostic test for sarcopenia. The methodology involves a series of studies and experiments, each of which is designed to predict the response of a single stage of the EWGSOP2 algorithm. In addition, an in-depth literature review was carried out in order to determine whether any addition of parameters obtained from an iSTS could provide additional insights over those provided by STS time alone. This literature review is presented as a systematic review in Chapter Two of the thesis.

Following chapters of the thesis are structured as follows -

Chapter Two: Systematic Review of the Instrumented Sit-to-Stand Test (submitted to IEEE Reviews in Biomedical Engineering)

Chapter Three: Prediction of physical function in older people based on STS time:

1.Prediction of muscle power using functional movement tests(presented at iCOMMET)

2. The Sit-to-Stand test as a predictor of muscle power obtained from isokinetic dynamometry (Study carried out on the Newton-Bhabha Fellowship in 2016)

Chapter Four: Classification using machine learning techniques.

Development of a model to predict classification in the EWGSOP2 algorithm for physical performance using machine learning approaches.

Chapter Five: Development of the instrumented chair for the iSTS

Chapter Six: Validation of the instrumented chair part one: a comparison of four approaches to evaluate the STS movement (published in IEEE Trans. Neural Sys Rehab.)

Chapter Seven: Validation of the instrumented chair part two:

1. A fusion-based approach to identify the phases of the sit-to-stand test in older people(Published in IEEE National Conference on Communication 2020)

2.Development of an instrumented chair to identify the phases of the sit-to-stand movement (Submitted to EMBEC 2020)

The links between the studies explained above and the EWGSOP2 is shown in Figure 1.2 below: The PhD thesis concludes with a general discussion in Chapter eight. This includes details of proposed modifications to the instrumented chair to improve performance and a study to develop a predictive algorithm for muscle mass. This study has been funded by the Indian Council for Medical Research. The chapter concludes with a recommendation for future work and the contribution of this thesis to knowledge in the field.

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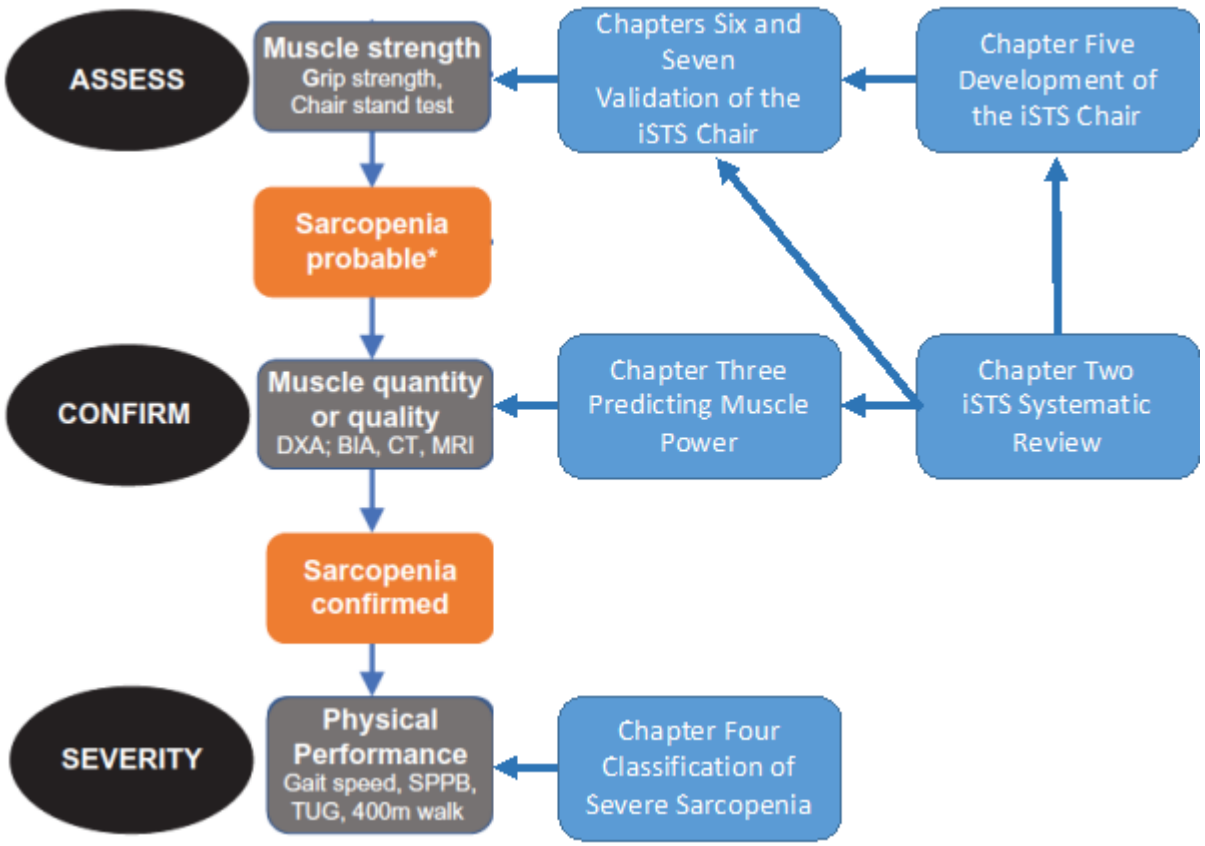

Figure 1.2 : The relationship of the thesis chapters with the EWGSOP2 algorithm for sarcopenia diagnosis