THE IMPACT OF ROBOTIC REHABILITATION ON MID-THIGH AND CALF CIRCUMFERENCES AND FUNCTIONAL OUTCOMES OF STROKE PATIENTS

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By

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

SYMBOL	MEANING
%	Percent
α	A threshold value to determine the significance of the statistical test analysis.
β	The probability of Type II error in a statistical hypothesis test
ϵ	A measurement of the distance of the observation and regression line in statistics.
λ	Used for likelihood ratio in statistics
ρ	Spearman's rank correlation coefficient
df	The degree of freedom: represents the number of independent values that can be changed without breaking any constraints in an analysis.
n	Represent the entire number of observations or population size in a statistic
F stat	One of the values in the ANOVA test or regression analysis to find out if the means between two populations are significantly different
km/h	Kilometre per hour. The unit of speed that express the distance in kilometre travelled within one hour
P-value	The level of marginal significance represents the probability of a certain event occurring within the statistical hypothesis.

ABBREVIATION

LIST OF ABBREVIATIONS

ABBREVIATION	MEANING
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
AAFO	Active ankle-foot orthosis
ANOVA	Analysis of Variance
ASA	American Stroke Association
ASIS	Anterior superior iliac spine
BES	Bio-electrical signal
BIA	Bioelectrical impedance analysis
BLEEX	Berkley lower extremity exoskeleton
BMI	Body mass index
cm	Centimetre
CIC	Cybernics impedance control
CR	Conventional rehabilitation
CT	Computed tomography
CVC	Cybernics voluntary control
DOSM	Department of Statistics Malaysia
DEXA	Dual-energy x-ray absorptiometry
et al.	And others (Latin: *et alii*)
FAC	Functional Ambulation Categories
HAL®	Hybrid Assistive Limb®
I-ADL	Instrumental Activities of Daily Living

KAFO	Knee-ankle-foot orthosis
m	Meters
MOH	Ministry of Health
MRI	Magnetic resonance imaging
OT	Occupational therapy
PT	Physiotherapy
ROM	Range of Motion
RR	Robotic rehabilitation
SOCSO	Social Security Organization
USM	Universiti Sains Malaysia
WHOQOL-BREF	World Health Organization Quality of Life assessment; brief version

LIST OF APPENDICES

THE IMPACT OF ROBOTIC REHABILITATION ON MID-THIGH AND CALF CIRCUMFERENCES AND FUNCTIONAL OUTCOMES OF STROKE PATIENTS

ABSTRAK

Strok telah muncul sebagai penyebab utama kecacatan di banyak negara, termasuk Malaysia. Secara tidak sengaja, peningkatan jumlah mangsa strok telah menyebabkan peningkatan beban yang turut mempengaruhi kesejahteraan ekonomi dan sosial di negara-negara yang terkesan. Terapi robotik telah mencipta satu titik perubahan baru dalam proses pemulihan mangsa strok untuk meningkatkan status fungsional dan kualiti hidup mereka. Oleh itu, kajian ini bertujuan untuk menilai kesan rehabilitasi robotik pada lilitan paha, dan lilitan betis, dan akibat terhadap fungsional seseorang penderita strok.

Dalam kajian kohort prospektif ini, pesakit dibahagikan kepada kumpulan rehabilitasi konvensional (CR) (n=10) dan rehabilitasi robotic (RR) (n=10) dengan menggunakan kaedah persampelan bertujuan (*purposive sampling method*). Kelayakan ke CR dan RR telah dirancang terlebih dahulu oleh pasukan yang merawat sebagai salah satu daripada amalan standard mereka. CR menerima program rehabilitasi berasaskan apa yang dapat mereka lakukan di rumah selama lima hari seminggu, dengan tempoh dua jam sehari, dibahagikan kepada dua sesi dan tiga sesi rehabilitasi di fasiliti selama empat minggu. Program ini menrangkumi program menguatkan otot, keseimbangan, senaman meningkatkan mobility dan terapi fungsional serta terapi cara kerja. RR menerima program fisioterapi konvensional dan terapi cara kejra selama satu jam dan satu jam program terapi robotic dengan menggunakan alat berupa HAL® CYBERDYNE khusus untuk anggota badan bawah, selama lima hari seminggu. Hasil akhir yang diukur merupakan lilitan tengah paha, lilitan betis, *Functional Ambulation Categories* (FAC), *6-Minute Walk Distance* (6MWD) dan soal selidik versi ringkas daripada Organisasi

Kesihatan Dunia (WHOQOL-BREF). Analisis data dilakukan menggunakan kaedah *repeated measures Analysis of Variance* (rmANOVA).

Seramai 20 peserta telah menamatkan kajian ini. Median umur adalah 46.50 (17) tahun, terutama lelaki (65%), dengan disebabkan oleh strok iskemia (90%), dan 60% peserta dalam kategori berat badan berlebihan dalam Indeks jisim badan (BMI). Tempoh permulaan strok median ialah 4.00(3.50). Kesan masa yang ketara diperhatikan dalam kumpulan RR. Terdapat peningkatan ketara lilitan pertengahan paha paretik antara tempoh masa permulaan ke minggu 2 dan permulaan ke minggu 4 ($p<0.05$). Lilitan pada sisi yang normal menunjukkan kesan masa yang ketara dalam tempoh masa antara permulaan hingga minggu 4 ($p<0.05$). Purata lilitan pertengahan paha selepas empat minggu terapi menunjukkan perbezaan yang ketara antara kumpulan CR dan RR ($F_{1,18}$ 12.49, p 0.02). Untuk lilitan betis, kesan masa yang ketara ($p<0.05$) diperhatikan antara permulaan ke minggu 4 dan minggu2 ke minggu 4 pada bahagian normal. Manakala betis bahagian paretik menunjukkan kesan masa yang ketara dalam semua tempoh kajian ($p<0.05$). Kedua-dua kumpulan menunjukkan peningkatan dalam FAC dan 6MWD (ms<0.05). Penambahbaikan dilihat lebih banyak dalam RR pada minggu 4 kerana walaupun RR bermula dari purata permulaan yang lebih rendah namun, pada minggu keempat, purata RR dapat mengatasi CR dalam FAC dan 6MWD.

Dapat disimpulkan bahawa RR telah memberikan kesan yang signifikan pada lilitan pertengahan paha dan betis dan hasil fungsi pesakit strok. Walau bagaimanapun, saiz sampel yang lebih besar dan kajian yang lebih spesifik yang menyasarkan jisim otot harus dipertimbangkan untuk menguatkan bukti.

THE IMPACT OF ROBOTIC REHABILITATION ON MID-THIGH AND CALF CIRCUMFERENCES AND FUNCTIONAL OUTCOMES OF STROKE PATIENTS

ABSTRACT

Stroke has emerged as the global leading cause of disability in many countries, including Malaysia. Inadvertently, due to the escalating numbers of stroke survivors, poses a burden affecting economic and social well-being in these countries. Adjunct robotic treatment has created a major turning point in stroke rehabilitation in improving stroke survivors' functional status and quality of life. Therefore, this study aimed to assess the impact of robotic rehabilitation on the mid-thigh and calf circumferences and functional outcomes of stroke patients.

In this prospective cohort study, stroke patients were divided into conventional rehabilitation (CR) (n=10) and robotic rehabilitation (RR) (n=10) groups by using the purposive sampling method. The managing team pre-planned eligibility into the CR and RR as standard practice. The CR received a five-day-a-week home-based rehabilitation program, with the duration of two hours per day divided into two sessions, and three sessions of rehabilitation at the tertiary centre for four weeks. The program includes muscle strengthening, balance, mobility exercise, functional physiotherapy and occupational therapy. RR received a one-hour traditional conventional physiotherapy and occupational therapy program and one hour of robotic therapy program by using the HAL® Cyberdyne lower-limb, for five days a week. Outcome measures were the mid-thigh circumferences, calf circumferences, Functional Ambulation Categories (FAC), 6-Minute Walk Test (6MWT) and World Health Organization Quality of Life Brief Version (WHOQOL-BREF) questionnaire. For data analysis, repeated measures analysis of variance was used.

A total of 20 participants completed the study. The median age was 46.50 (17) years old, predominant male (65%), with ischaemic stroke in origin (90%), and 60% of participants in the overweight in the Body mass index (BMI) category. The median stroke onset duration was 4.00(3.50). A significant time effect was observed in the RR groups. There is a significant increment of the paretic mid-thigh circumferences between the baseline and week 2 and baseline and week 4 timeframe ($p<0.05$). On the normal side of the mid-thigh circumferences, significant time effects were between baseline to week 4 ($p<0.05$). The average means of mid-thigh circumferences after four weeks of therapy were significantly different between CR and RR groups ($F_{1,18} = 12.49$, $p=0.02$). For the calf circumferences, a significant time effect ($p<0.05$) was observed between baseline and week 4 and week2 to week 4 on the normal side. While the paretic side showed a significant time effect within all study periods ($p<0.05$). Both groups showed improvement in the FAC and 6MWD ($p<0.05$). Improvements were seen more in RR by week 4 as even though RR starts from a lower baseline, by week4, RR was able to overtake the CR in the FAC and 6MWD.

It is concluded that ART has shown significant effects on the mid-thigh and calf circumferences and functional outcomes of stroke patients. However, larger sample size and more specific study targeting the muscle mass should be considered to strengthen the evidence.

CHAPTER 1

INTRODUCTION

1.1. Introduction

Being defined as the insult to the brain function which results in the localised (or global) clinical manifestation that emerges rapidly and lasts longer than 24 hours or leads to death with no other obvious explanation other than vascular origin by the World Health Organization (WHO) (Coupland *et al*., 2017; Mehrholz *et al*., 2020., Nik Ramli *et al.*, 2021), stroke is indeed an eye-popper. While in 2013, silent infarction and silent haemorrhages affecting the cerebral, spinal and retinal blood arteries were included in the definition by the American Stroke Association (ASA) (Coupland *et al*., 2017). Stroke survivors suffer neurological deficits that can affect their physical activities, activities of daily living, and quality of life (QOL) (Mehrholz *et al*., 2020).

As per epidemiological research, over 5.5 million people died every year from stroke globally. The prevalence of stroke is expected to increase to 21.9% by 2030 (Martini *et al*., 2022). The increasing numbers of stroke survivors lead to an increment in stroke burden. It has been reported by Nik Ramli *et al*. (2021) that the expenditure of stroke care management accounted for 33,812 admissions, totalling over RM180 million. According to Feigin (2019), the increment of stroke burden was influenced by three factors. The first factor is the disproportionate increase of death and disability from stroke compared to other diseases over a period. The second factor is that stroke has become the second cause of disability around the world (Feigin, 2019). Stroke has become the third global cause of disability-adjusted life year (DALY), in 2019. DALY represents the loss of the equivalent of one year of full health. DALY is also known as the summary measure that combines the time loss from premature death and time lived to be disabled (WHO, 2020). The third factor is more young people are affected by stroke (Feigin, 2019).

Stroke is a disease that requires care from day one of admission, and continues even after being discharged home. Abdul Aziz *et al*. (2020) revealed that stroke patients spent an average of five to seven days in the hospital before discharged home with outpatient rehabilitation therapy. However, rehabilitation facilities that accommodate post-stroke patients are usually overflowed with the exponential increment of stroke patients globally. It is also due to the nature of rehabilitation post-stroke being time and cost-consuming. To restore functional status, it is crucial to salvaging the affected muscle. Stroke rehabilitation's objective is to prevent the worsening of motor function and promote the improvement of motor function to achieve physical, psychological, social, and financial independence as far as ones can achieve. The development of technologies brings forward the emergence of robotic therapy despite conventional physiotherapy alone. Robotic rehabilitation (RR) improves stroke survivors' functional status and quality of life given the RR's benefit (Nik Ramli *et al*., 2021).

1.2. Problem Statement

1.2.1. Problem statement

Data from the Department of Statistics Malaysia [DOSM] (2021), stated that cerebrovascular diseases accounted for the third leading cause of death in Malaysia, or 8.3% of 109,155 medically certified deaths in 2020, in Malaysia. Globally, the mortality incidence of stroke decreases with the increment in the quality of the healthcare system. Due to the increasing number of stroke survivors, the number of patients with chronic stroke also increases. As a result, the morbidity related to strokes, such as pneumonia, sepsis, and urinary tract infections also increases (Ang *et al*., 2021). Cited from the same article, hospital readmission within 28 days after being diagnosed with haemorrhagic stroke is common within the duration of 2008 until 2015 of study. Recurrent stroke was the most common cause of hospital readmission, accounting for a total of 32.1%, while other causes were complications post-stroke. Stroke rehabilitation usually requires management from multidisciplinary teams. Within ten weeks post-assault to the brain, rapid motor recovery occurs. Stroke rehabilitation that starts in an early period, and more intensive mobilization after an assault may help in walking, functional recovery, and reducing the length of hospital stay. Motor recovery after three to six months after onset usually remains plateau (Marzolini *et al*., 2021; Faulkner & Wright., 2018).

Rehabilitation post stroke improves motor function or activities of daily living (ADL). Stroke survivors usually needed long-term care due to the residual disability post-stroke. Providing high-intensity, repetitive, task-specific therapy is the main aim of using robotic devices in stroke rehabilitation (Taki *et al*., 2020; Faulkner & Wright., 2018). These stimulations to the targeted muscles may stimulate neuroplasticity of the brain, which will result in improvement in functional and motor performance (Faulkner & Wright., 2018). In a study by Taki *et al.* (2020), robotic devices help improve gait quality, functional outcomes, and motor performance in stroke patients. In a different study by Azzolini *et al.* (2021), there was still a scarcity of data on the evaluation of the morphological status of the muscle in the same approach in the clinical setting. Theoretically, physiotherapy per se helps to improve muscle bulk in a stroke patient. The improvement rate between these two groups of subjects, of the one that undergoes conventional rehabilitation and robotic rehabilitation is still questionable. Thus, this study is carried out to evaluate the effects of physiotherapy physically, functionally, and emotionally.

1.2.2. Research questions

a) Does the mid-thigh circumference of patients receiving robotic rehabilitation increase compared to the patients that receive conventional rehabilitation?

b) Does the mid-calf circumference of patients receiving robotic rehabilitation increase compared to the patients that receive conventional rehabilitation?

c) Do patients who undergo robotic rehabilitation require less support when ambulating compared to conventional rehabilitation?

d) Does robotic rehabilitation improve the functional capacity of patients with limited ability compared to conventional rehabilitation?

e) Do patients who receive robotic rehabilitation have a better quality of life compared to patients that receive conventional rehabilitation?

1.3. Justification of the Study and Study Rationale

1.3.1. Justification of the study

This study is mainly to answer the impact that implies to the individual after undergoing conventional rehabilitation (CR) and RR. Comparison between CR and RR is usually done in small samples (n<40), with improvement in standing balance, speed of walking, ability to walk or endurance, and mobility disability can be observed within 12 to 20 sessions of CR or RR (cited from Dierick *et al*., 2017). Globally, there is still a scarcity of data on muscle mass gain following CR and RR. Despite of the fact that muscle mass gain aids in improving the functional status of stroke patients (Nagano *et al*., 2020). This current study tried to investigate the changes that can be seen of the muscle circumferences after CR and RR. In the study by Dierick *et al*. (2017), patients who suffer an ischaemic stroke and haemorrhagic stroke demonstrated a quasi-similar improvement in terms of functional status within four weeks of exercise therapy between CR and RR. Thus, the current study tried to include stroke patients of either type without being biased and eliminating the popular belief that haemorrhagic stroke demonstrated better functional outcomes as compared to patients who suffer an ischaemic stroke. Three continuous weeks of RR is proven to improve gait in subacute stroke patients when measured using the two-minute walk test and Functional Ambulation Criteria (Mizukami *et al*., 2017).

1.3.2. Study rationale

Financially, stroke patients spent from around RM3300 to RM9000 for admissions costs in a stroke ward and RM103 for outpatient clinic follow-up and RM43 per rehabilitation session (Kooi *et al*., 2016). About half of the amount was spent in the first 30 days after being diagnosed with stroke (Ang *et al*., 2021). Considering the high cost needed for stroke management, finding the most cost-effective treatment for stroke patients is needed to improve the financial burdens. Short-term but effective stroke rehabilitation will result in a better quality of life for the patients and more cost-effective outcomes for patients and the health care system. At the same time, this would reduce the overflow of chronic stroke patients in the rehabilitation facilities.

This study would contribute to the development of more conclusive data on the effects of rehabilitation on the physical and functional recovery and the quality of life of stroke survivors. The findings would provide information on the best therapy that is most effective and yet can reduce cost and reduce therapy time.

1.4. Objectives of Study

1.4.1. General objectives

To evaluate the impact of conventional rehabilitation and robotic rehabilitation on mid-thigh and mid-calf circumferences and the functional status of stroke patients.

1.4.2. Specific objectives

a) To compare the mid-thigh circumference of the hemiparetic side between patients that receive conventional rehabilitation and robotic rehabilitation.

b) To compare the mid-calf circumference of the hemiplegic side between patients that receive conventional rehabilitation and robotic rehabilitation.

c) To compare the functional status of the patients that receive conventional rehabilitation and robotic rehabilitation.

   i. By determining the supports required when ambulating

   ii. By determining the functional capacity in persons with limited ability.

d) To compare the quality of life between patients that receive conventional rehabilitation and robotic rehabilitation.

1.5. Hypotheses of the study

1.5.1. The mid-thigh circumference of patients who receives robotic rehabilitation increased compared to the patients that receive conventional rehabilitation.

1.5.2. The mid-calf circumference of patients who receives robotic rehabilitation increased compared to the patients that receive conventional rehabilitation.

1.5.3. Patients who receive robotic rehabilitation have better functional status than conventional rehabilitation.

1.5.4. Patients that receive robotic rehabilitation have a better quality of life compared to patients that receive conventional rehabilitation.

CHAPTER 2

LITERATURE REVIEW

2.1. What Is Stroke?

Sudden onset of symptoms is similar to ‘stroke of God’s hand’, resulting in the first use of the word ‘stroke’ in 1599. While ‘apoplexia’ is being said as the Greek word for stroke, implies being struck with a deadly blow (Coupland *et al*., 2017). Stroke survivors are called chronic stroke patients after six months post insult (Marzolini *et al*., 2021).

There are two types of stroke based on their aetiology, namely ischemic stroke and haemorrhagic stroke (Callegari *et al*., 2021; Nik Ramli *et al.*, 2021). It is named due to the nature of the bleed, in which the ischemic stroke is due to the emboli, while haemorrhagic is due to the injury to the blood vessels in the brain (Callegari *et al*., 2021). It is common to find ischaemic stroke compared to haemorrhagic stroke because the prevalence is seven times more. But ischaemic stroke is less severe than haemorrhagic stroke. Haemorrhagic stroke is commonly linked to higher death risk and significant neurological disorders. Thus, affecting the recovery of the patient after being diagnosed with stroke (Callegari *et al*., 2021).

The risk factors for stroke can be divided into modifiable risk factors and behavioural risk factors. The modifiable risk factor accounted for about 87% of all the risk factors involved. These risk factors include persistently hypertension or high blood pressure, obesity, hyperglycaemia, hyperlipidaemia, and kidney dysfunction. Other risk factors are categorised as behavioural risk factors including smoking, a sedentary lifestyle, and an unhealthy diet. Air pollution also contributed to 30% of stroke risk factors worldwide (American Heart Association [AHA], 2021). Some of the common presentations of stroke are the disturbance in sensation, paralysis or weakness of the facial area as well as one side of the body, changes in mental state, blurred vision, unsteadiness, walking difficulty, and headache (Nik Ramli *et al*., 2021).

Treating stroke survivors is usually time-consuming, thus exposing them to a variety of complications due to the disabilities they suffer, self-perception, and adjusting to a new life, with stroke. It is important to manage acute stroke as early as possible to reduce the risk of getting severe complications post-stroke (Ministry of Health [MOH] Malaysia, 2021). During the acute phases, or the first presentation of the disease, treatment differs based on its aetiology. Recombinant tissue plasminogen activator (tPA), for example, alteplase (activase) injected intravenously is the drug of choice for ischaemic stroke patients within the period of three to four and half hours post insult. The usage of tPA in stroke patients results in the least possible disability or nearly normal self at three months post-assault. The result was seen in 30% of stroke patients treated within three hours post-onset, in contrast to patients treated with a placebo (Cuccurullo *et al.*, 2020). In confirmed cases of haemorrhagic stroke, their main aims are to secure the blood supply to the brain, through neurosurgical team management by clamping or emboli the injured blood vessels (Nik Ramli *et al*., 2021). Managing stroke patients during the acute phase is important in reducing the complications that they may get after insult. In the brain of a stroke survivor, there are two regions called the ischaemic core and ischaemic penumbra. The ischaemic core is where the ischaemia itself occurs, and the brain tissue in that area is destined to die. While ischaemic penumbra is the area surrounding the ischaemic core, where it is still salvageable. Owing to the fact existence of ischaemic penumbra, acute stroke management is extendable up to 24 hours despite the golden period of six hours post insult. Managing stroke survivors within this period had resulting in more stroke survivors but with a wide variety of disabilities according to the area of insult (Nik Ramli *et* al., 2021).

Generally, 48 hours post-stroke is the ideal time to start rehabilitation treatments as the general condition of the patient is already stabilized, to strengthen and improve mobility by doing the range of motion exercise (National Institute of Neurological Disorders and Stroke, 2020). A customized neurorehabilitation program for stroke survivors helps to relearn skills that are lost during the brain damage and compensate for remaining disabilities. Rehabilitation principles, which take advantage of the brain's ability to rewire (neuroplasticity) including specially directed programs, well focused and repetitive actions, help in protecting stroke survivors from developing complications such as pneumonia, urinary tract infections, falls, or formation of clots in a large vein (MOH Malaysia, 2021).

2.2. Disability after stroke

In stroke patients, the sign and symptoms were determined by the type, location and severity of the brain tissue involved. Hence, a narrative on the progression of the disease process, complete physical examination and diagnostic tests were crucial in determining the best treatment. A complete physical examination including the neurological examination, conscious level, and higher mental function status needed to be recorded (MOH Malaysia., 2021). 90.5% of confirmed stroke diagnosis presented with weakness over one side of the body, subsequent 21.4% presented with weakness and convulsion while the remaining complained of headache, vomiting, and visual and speech impairments (Kooi *et al.,* 2016).

Permanent disabilities of varying degrees were seen in one-third of the survivors after being diagnosed with the first episode of stroke. Within the first ten weeks after the assault, 16-42% functional improvement was seen. A total of 60% of stroke patients survived within 5 years after diagnosis. From this 60%, up to 58% were able to achieve ADL independence within two months. Nearly 50% of survivors persist in having disabilities with one-seventh still having periodic follow-ups after a period of ten years (MOH Malaysia., 2021). The morbidity of stroke survivors is contributed by functional disability. Other than functional, disabilities such as difficulty swallowing, deficits in recognising emotion, dementia and sleep-disordered breathing were also reported. Emotional recognition problems correspond with an inability to express frustration, attachment to other people, social distress and behavioural control deficiency. Dementia in stroke was postulated due to stroke and vascular risk factors. Factors such as overall health condition, depression, ADL, and social and family support had an influence on stroke patients with cognitive impairment (Kooi *et al.,* 2019).

Stroke generates changes in the descending neural output, causing functional and structural skeletal muscle changes. As stated in a study by Azzollini *et al.,* (2021), muscle changes in a stroke patients include the morphological modification, muscle metabolism alteration, and electromechanical features of the muscle. Morphological changes of the muscles post stroke including stroke-induced sarcopenia and stiffness. Intrinsic fibres morphological changes give rise to stroke-induced sarcopenia. At this level, there was muscle mass depletion, trimming of muscle thickness, and physiological cross-sectional area reduction (Azzollini *et al.,* 2021). Stroke-induced sarcopenia will be further explained in the next subtopic. Stroke also affected muscle at the tissue level causing rearrangement. Sarcomere shortening and changes in the extracellular matrix can be seen at this level (Azzollini *et al.,* 2021).

Weakness or paresis in stroke patients creates muscle stiffness in long term. Patients who suffered from stiffness were often seen with minimal active voluntary movement and restricted joint range of motion (ROM). Muscle stiffness can be identified by the presence of spasticity, spastic dystonia, contracture of the muscles or soft-tissue fibrosis. Secondary complications after muscle stiffness including soft tissue contractures, pain, pressure wounds, reduction of ADL and isolation from the social will eventually lead to deterioration in the quality of life. Over time, intrinsic muscle properties changed, marked by the increment of intramuscular fat and connective tissues instead of muscle. Abundant amount of hyaluronan in the extracellular matrix (ECM) and intramuscular fat causes muscle immobility in shorten positions. Hyaluronan deposition causes increased collagen content and changes in collagen orientation, leading to transverse tensile stiffness towards radial expansion and fascicle shortening. In this situation, passive motion and stretching benefitted stroke patients if it was performed for more than three months. Continuous stimulation towards the muscle spindle, activating the Ia muscle fibres. Hence, leads to spasticity. In a patient diagnosed with spasticity, muscle stretching alone becomes less beneficial. Injection of Botulinum Toxin Type A (Bont-A) is recommended as it helps release the acetylcholine at the neuromuscular junction, which is essential in promoting chemical denervation. The usage of Bont-A is expected to help calm the overreactive muscle activity (Azzollini *et al.*, 2021).

Stroke rehabilitation helps the survivors to adapt to their disabilities and prevents the worsening of functional status (Martini *et al*., 2022). One of the best ways to assess the efficacy of a stroke rehabilitation program is by measuring the quality of life of the stroke survivor (Martini *et al*., 2022). A study by Callegari *et al* (2021) on assessing the gait in 40 stroke survivors of haemorrhagic and ischemic stroke reveals that there is no optimal time frame on when the rehabilitation program should start for the patient post-stroke. However, the same study stated that the rehabilitation program could be started as early as day three and up to 30 days after a stroke. It is generally agreed that the rehabilitation program would be more effective if started very early. While others also claim that there is the presence of "late plasticity", on which even chronic patients, have the same chances of recovery (Callegari *et al.*, 2021).

One in eight stroke survivors is at a very high risk of developing recurrent stroke, and complications of stroke such as pneumonia, sepsis, and urinary tract infections within 28 days according to a study by Ang *et al.* (2021). These causes of readmissions can be prevented by adding some improvements to the existing program, for example, the stroke-specific care bundle, stroke unit, an integrated stroke care pathway, and engaging in giving education and participation in the community, particularly in higher-risk populations (Ang *et al*., 2021).

2.3. Gross Anatomy of Muscles of Thighs and Legs

In general, the lower limb is classified into four parts, which are the gluteal region, thigh, leg and foot (Vivekanand, 2017). The gluteal region is the most proximal region or the upper part of the lower limb. It is a region where we can find the hip bone, and it covers the area of the side and back of the pelvis (Vivekanand, 2017). Hip bone is made up of three irregularly shaped bones, the ilium, pubis and ischium that are fused at the acetabulum (Vivekanand, 2017; Ellis & Mahadevan, 2019; Drake, Vogl & Mitchell, 2020). In a thin person, the tip of the anterior superior iliac spine (ASIS) can be easily palpated and apparent with naked eyes (Ellis & Mahadevan, 2019). The posteroinferior part of the hip bone was made up of the ischium. The body of ischium, is composed of the upper end and lower end, where the lower end forms the ischial tuberosity. Muscles of the thigh attach to the ischial tuberosity. The semimembranosus muscle originated from the superolateral area, while the semitendinosus and long head of the biceps femoris originated from the inferomedial area. The adductor magnus muscles are from the outer lower area. As for the inner lower area, there were fibrofatty tissue coverings. It helps support body weight during the sitting position. The medial margin is where the sacrotuberous ligament attaches. Lastly, the ishiofemoral ligament attaches to the lateral border of the ischial tuberosity (Drake *et al.,* 2022, Vivekanand., 2017)

The thigh is the area that covers from the hip to the knee and is where the femur bone is located (Vivekanand, 2017). Between thigh and leg, there is the knee joint. Patella is a mobile bone located at the knee providing the bony landmark of the area. The mobility of the patella can be palpated during standing or the quadriceps femoris muscle is relaxed (Ellis & Mahadevan, 2019). The area from the knee to ankle is called the leg or crus, where the tibia and fibula bone is located. And the most distal part is from heel to toes, called the foot. It is made up of 26 bones. It is subdivided into tarsus, metatarsus, and meta phalanges (Vivekanand, 2017). The anatomy of the bones can be found in Appendix A.

In this study, the focus is on the thigh and calf muscles. All these muscles in the thigh and calf are divided into three compartments by fascia, bones and ligaments. The anterior compartment of the thigh is composed of the hip flexors and leg extensors. Psoas major and iliacus were the hip flexors. Quadriceps femoris composed of four muscles including the rectus femoris, vastus medialis, vastus lateralis, and the vastus intermedius muscle. These muscles help extend the leg at the knee joint (Vivekanand, 2017). Nonetheless, rectus femoris also flexes the thigh at the hip joint. In addition, the sartorius muscle, was another muscle of the anterior compartment, were both hip flexor and leg flexors (Drake, Vogl & Mitchell, 2020; Vivekanand, 2017). It is the most prominent muscle of the anterior thigh (Drake, Vogl, Mitchell, 2020). All muscles of the anterior compartment of the thigh are innervated by the femoral nerve (Vivekanand, 2017). The medial compartment, which are the adductor longus, adductor brevis, adductor magnus, gracilis, and pectineus muscles are the adductor muscles of the hip joint. All these muscles were innervated by the obturator nerve and received nutrients from the femoral artery (Vivekanand, 2017). Posterior compartment composed of the knee flexors components. However, special exception for the hamstring muscle. In view of the attachment of the hamstring is at the pelvis and bone of the legs, the hamstrings muscle can also act by extending the hip and flexing the knee (Drake, Vogl & Mitchell, 2020). The muscles of the thigh can be found in Appendix B.

Unlike the thigh which has the anterior, posterior and medial compartment, the leg is subdivided into anterior, posterior and lateral compartments (Drake, Vogl & Mitchell, 2020). Muscles of the leg mainly work on the foot. The lateral compartment is also called the fibular compartment as it is enclosing the fibula bone. These muscles help evert the foot. Muscles of the anterior compartment dorsiflex the foot and extend the digits. The posterior compartment opposes the function of the anterior compartment. It plantarflexes the foot and flexes the digits (Drake, Vogl & Mitchell, 2020). The back of the leg muscles is classified into two groups, which is the superficial and deep muscle. The gastrocnemius, the soleus, and the plantaris muscles are the muscles of the superficial part, while the popliteus, the flexor digitorum longus, flexor hallucis longus and the tibialis posterior muscles are the deep muscles of the back of the leg. The gastrocnemius and soleus muscles are the most prominent muscle of the calf, especially during standing on the toes. Hence, these two muscles play an important role during walking. Together with the plantaris muscle, the gastrocnemius and soleus muscle converge into a thick tendon called the calcaneal tendon. The calcaneal tendon attaches inferior to the posterior surface of the calcaneum. From the posterior, the calcaneal tendon can be palpated as it runs inferiorly from the towards the heel. In view the soleus helps the blood regulation, it is also called the peripheral heart (Vivekanand, 2017). The muscles of the leg can be found in Appendix C.

2.4. Sarcopenia In Stroke Patients

Generally, the focus of rehabilitation is on taking advantage of the neuroplasticity of the brain to restore motor function and frequently disregards the importance of the muscle tissues (Azzolini, Dalise & Chisari, 2021). Loss of muscle tissues is common in the ageing community, which is marked by reducing in muscle mass and muscle strength called sarcopenia (Hunnicutt

& Gregory, 2017; Azzolini, Dalise & Chisari, 2021). It can be diagnosed from as early as 40 years old and is also known as primary sarcopenia (Hunnicutt & Gregory, 2017; Nagano *et al.*, 2020). Sarcopenia that occurs following inflammatory mechanism, disease-related immobility, or dietary malnutrition is called 'specific sarcopenia' or secondary sarcopenia. In the case of stroke, it can also be due to the disuse atrophy and spasticity, inflammation, denervation, reinnervation, and malnutrition and is usually referred to as 'stroke-induced sarcopenia' or 'stroke-related sarcopenia' and is closely suggesting poor clinical outcome and worsening of functional (Nagano *et al.,* 2020; Azzollini, Dalise & Chisari, 2021). Thus, deconditioning, weariness, and worsening of physical functions are direct effects of immobility (Azzollini, Dalise & Chisari, 2021). Sarcopenia in stroke survivors in the community can be up to 16.8% to 60.3% for the patients who received treatments at the rehabilitation wards (cited from Nishioka *et al*., 2021).

Multiple processes contribute to stroke-induced sarcopenia, including immobility and dysfunction atrophy, poor nutrition, inflammation, sympathetic overactivation, and denervation and can be found until up to 34% in patients six months post-stroke (Azzollini, Dalise & Chisari, 2021). It is also believed that sarcopenia also results from the activation of catabolic pathways including ubiquitin protease system (UPS), autophagy, and apoptosis which resulted in reduced skeletal muscle growth rate in the paretic limbs as compared to the non-paretic limb. Even the accumulation of fat over the intramuscular causing hyperinsulinemia and lead to reduced growth of skeletal muscle (Azzollini, Dalise & Chisari, 2021).

Resistance exercise training with dietary supplements may be the most effective combination therapy for sarcopenia in older persons. The resistance training exercise in high intensity has beneficial effects on muscle mass and physical function (cited in Kemmler *et al*., 2021). A study on resistive training three times a week for 12 weeks reduces the fat over the muscular area, and aid in muscle hypertrophy (Azzollini, Dalise & Chisari, 2021). Malnutrition in stroke survivors causes muscle and adipose tissue wasting (Azzollini, Dalise & Chisari, 2021).

Measuring the muscle mass required a specialized machine in a specialized setting and is costly, for example, dual-energy x-ray absorptiometry (DEXA) scan, magnetic resonance imaging (MRI), computed tomography (CT) scan, and bioelectrical impedance analysis (BIA) (Nishioka *et al*., 2021). Other than that, a non-invasive, cheaper, and easier method, anthropometric measurement is still widely used in measuring skeletal muscle mass, as well as nutritional status (Nishioka *et al*., 2021). Usually, the site of measurements is the mid-thigh and lower leg musculature (Hunnicutt & Gregory, 2017). A systematic review by Hunnicutt & Gregory (2017) has shown that the implementation of robotic rehabilitation had reversed the muscle loss and strength in both paretic limbs and normal limbs with the duration of study ranging from 4 weeks until 1 year.

2.5. Conventional Rehabilitation in Stroke Patients

Physiotherapy or also known as physical therapy is a therapy that is targeting on motor and sensory disabilities. It is done by a certified physiotherapist to assist in the restoration of physical function by identifying and treating the issues regarding mobility, balance, and coordination (National Institute of Neurological Disorders and Stroke, 2020). Positioning (the exercises involving the ROM, mobilisation (techniques to compensate for the loss), and endurance training are all part of a standard therapeutic exercise programme (Cuccurullo, Lee & Bagay, 2020). Kirsteins *et al*. (1999) (cited in Cuccurullo., 2020), conventional physiotherapy is a method of improving motor control and coordination by taking the advantage of repetition of specific movements, passive movement and development of the basic movement and basic human postural body control. Functional impairment leading to being disabled is commonly found in stroke survivors. Within the first two weeks post insult, the level of physical functions will fall below normal and usually persists up to more than six months, turning the patients into a chronic state, and leading to cardiorespiratory deconditioning, affecting the activities of daily living, increased risk of mortality, morbidity, and risk of hospitalization (Marzolini *et al.*, 2021).

According to the MOH Malaysia, there were four goals of physiotherapy treatment for stroke recovery. Firstly, physiotherapy can help accelerate neuromuscular system recoveries, such as voluntary limb movement, balance, coordination, and ability to walk. The second goal was to achieve functional status improvement. Next was to have an optimal mobility and independence level. Lastly, the goal was to prevent complications of immobility, such as pressure sore, foot drop, contracture, and respiratory complications (Kooi *et al.*, 2016; Nik Ramli *et al.*, 2021). In a study in 2018 (cited in Marzolini *et al.*, 2021), aerobic and circuit training that was incorporated into physiotherapy helped improve cardiorespiratory fitness and 6-Minute Walk Distance (6MWD). Improvement in this area can be seen by observing the functional mobility, speed of walking and balancing. As a result, fall prevention among stroke survivors is strengthened and injuries related to falls, such as hip fracture and other injuries were prevented from happening Marzolini *et al*., 2021).

It is important to have a stroke unit, as proposed by the MOH Malaysia (2021). The aim was to provide specialized multidisciplinary team management and provide the best plans of management after discharge. This stroke unit comprises of multidisciplinary team unit including medical personnel, medical rehabilitation physicians, pharmacist, nurses, physiotherapists, occupational therapists, and speech therapists. In Malaysia, there are limitations in providing optimized rehabilitation services. The first issue was a shortage of facilities the and time for rehabilitation services. Hence, it is difficult to cater the service based on functional needs and recovery as proposed by the National Stroke Foundation. The second limitation was limited resources, leaving the patients being discharged without a proper discharge plan. There was also shortage of specialized rehabilitation ward in the tertiary centres. Other than that, insufficient of rehabilitation professionals during the acute and recovery phases. Last but not least, physicians still have limited knowledge on the role of neurorehabilitation post-stroke. This will result in stroke survivors are not being referred to rehabilitation team, based on a study cited in Nik Ramli et al (2021).

2.6. Robotic Rehabilitation

Robotic devices are one of the technologies in medical devices, aiding in rehabilitation (Nik Ramli *et al*., 2021). The main action of robotic devices is evaluating the function of the sensorimotor and reorientation of the human brain to improve the quality of life (Iandolo *et al.*, 2019). These robotic devices are classified into assistive robots, prosthetics, orthotics, and therapeutic robots based on their functions. Assistive robots are used in patients with physical or cognitive disabilities or compensate for the loss of function because they can help improve the quality of life of patients with severe or degenerative disabilities. Patients with limb loss benefit more from prosthesis because it helps in the mobility and manipulation abilities of the amputated limbs. Orthotic is a type of exoskeleton with joints with functions of aiding in the movement of the weakened limb or helps in lifting the external weight The last type is the therapeutic robots that are generally used in rehabilitation centres which functions to enhance and broaden the capability of the patient (Nik Ramli *et al.*, 2021). Therapeutic robots are divided into the upper limb and lower limbs based on their location (Nik Ramli *et al.*, 2021). The lower limb robots are categorized into exoskeleton robots and end-effector robot. Lokomat, and LOPES, Active Ankle-Foot Orthosis (AAFO), Knee-Ankle-Foot Orthosis

(KAFO), and Berkley Lower Extremity Exoskeleton (BLEEX) was the example of the exoskeleton, while the Rutgers Ankle, Haptic Walker, Gait Trainer GTI, and the G-EO systems was the example of the end-effector robot (Zhang, Yue & Wang, 2017).

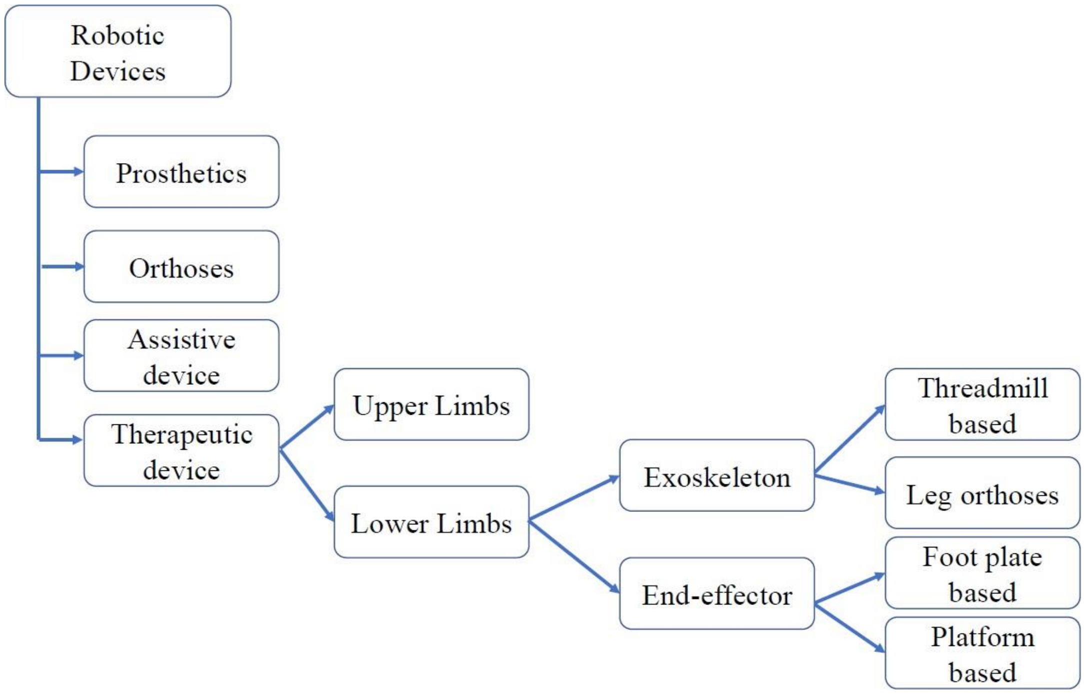

Figure 2.1: Classification of lower-limb robotic devices (adapted from Zhang, Yue & Wang, 2017; Nik Ramli et al., 2021).

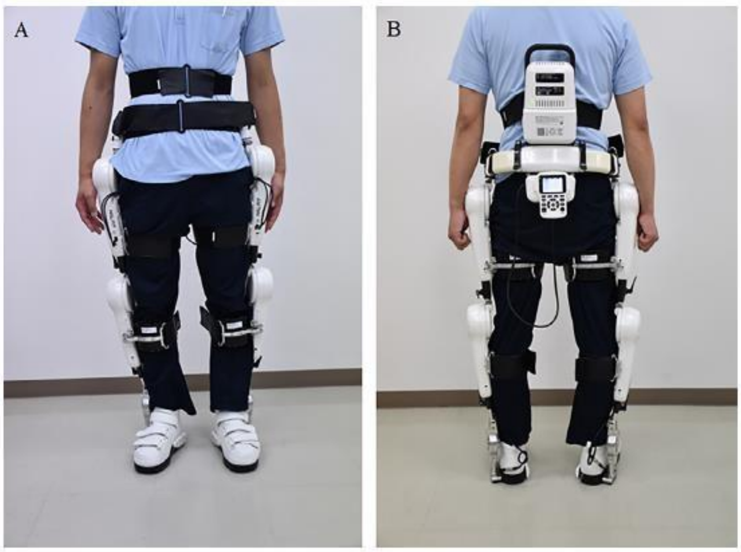

Figure 2.2: Patient wearing the HAL® CYBERDYNE (adapted from Taki *et al.*, 2020)

Hybrid Assistive Limb® (HAL®) is another example of the treadmill-based exoskeleton. The HAL® helps patients that have difficulty in walking, standing, sitting, and walking upstairs or downstairs. This device helps patients to complete the activities of daily lives by providing weight support (Zhang, Yue & Wang, 2017). This type of robotic device assists patients to complete walking using the force feedback from the lower limbs. However, this type of device does not mimic the natural way of walking as they can make the steps appears larger than supposed to. These therapeutic robots enhance gait quality by improving the stride length and step length. It also helps improve the functional status by improving the speed of walking and walking capacity. Lastly, therapeutic robots help improve motor performance due to their nature of providing high-intensity, repetitive, and task-specific therapy (Wright *et al.*, 2021).

Quantitative data collection from these robotic devices can be used to predict the prognosis of a patient. Therapeutic robots can reduce manpower and reduce cost as they can reduce the fee amount of one-to-one therapy (Iandolo *et al.*, 2019; Nik Ramli *et al.*, 2021). Robotic treatment is one of the alternatives to promote recovery and reduce muscle atrophy in patients due to its repetitive exercise mode. In this kind of training mode, the robotic exoskeleton will drive the patient's leg, thus providing passive motion to the lower limbs area (Zhang, Yue & Wang, 2017). Several studies from case series and randomized controlled trials as cited in Wright *et al* (2021) proven the result after as low as less than six weeks, in terms of personal speed, endurance, and balance. Improvement in walking can be seen in training for more than eight weeks. The usage of RR in the rehabilitation centres are limited, due to lack of trained physiotherapist, availability of the device at the centre, costly device, the rehabilitation staffs are still sceptical about using the device as compared to RR, and guidelines on RR to be filled based on the characteristics and history, and motor functions still poor (Dierick *et al.*, 2017).

HAL® by the Cyberdyne Company was used in current study. It is a technology-based on Cybernics, first introduced in 2004. It is certificated by the Japan Quality Assurance (JQA) in February 2013 as the assistive device (Iizuka and Ikeda, 2019). The usage of HAL® is beneficial for in-hospital rehabilitation settings for stroke and spinal cord injury by helping on improving gait function and walking independently,without taking age, sex, and severity of lower limb paresis into account (Wall, Borg and Palmcrantz, 2015). HAL® consist of the exoskeleton framing, working joints and also electromyography electrodes. The movement of the joints was supported by the electric motors. HAL® was controlled and self-initiated by the patient themselves using the surface electromyography electrodes by detecting BES from the hip and knee flexors. Then it will activate the somatosensory feedback loop, which improves brain plasticity and locomotor learning (Sczesny-Kaiser *et al.*, 2019). The motion principle of the HAL® lower-limb can be seen in Figure 2.3.

There were two modes in the setting used in current study, which are the cybernics voluntary control (CVC) and the cybernics impedance control (CIC) mode. The CVC mode allows voluntary control of the limb, with support from the robotic control. While CIC accommodates the weight of the device and the friction without providing any therapeutic benefit. Hence, the CVC was usually used on the paretic limb, while CIC was used on the non-paretic or normal limbs. There were cable connections between the exoskeleton and the patient, which enable the device to be set into CVC and CIC separately. As a result, personalized and adjustable muscle group movement training for bilateral hip and knee flexors and extensors, together with autonomous individual hip and knee joint motion support synchronous with the patients' voluntary movement (Sczesny-Kaiser *et al.*, 2019). The usage of treadmill system help to provide consistent velocity of 0 km/h until 4.5 km/h. The velocity for each individual differs, tailored to the maximum speed that can be tolerated by the patient, but still within comfortable speed tolerated.

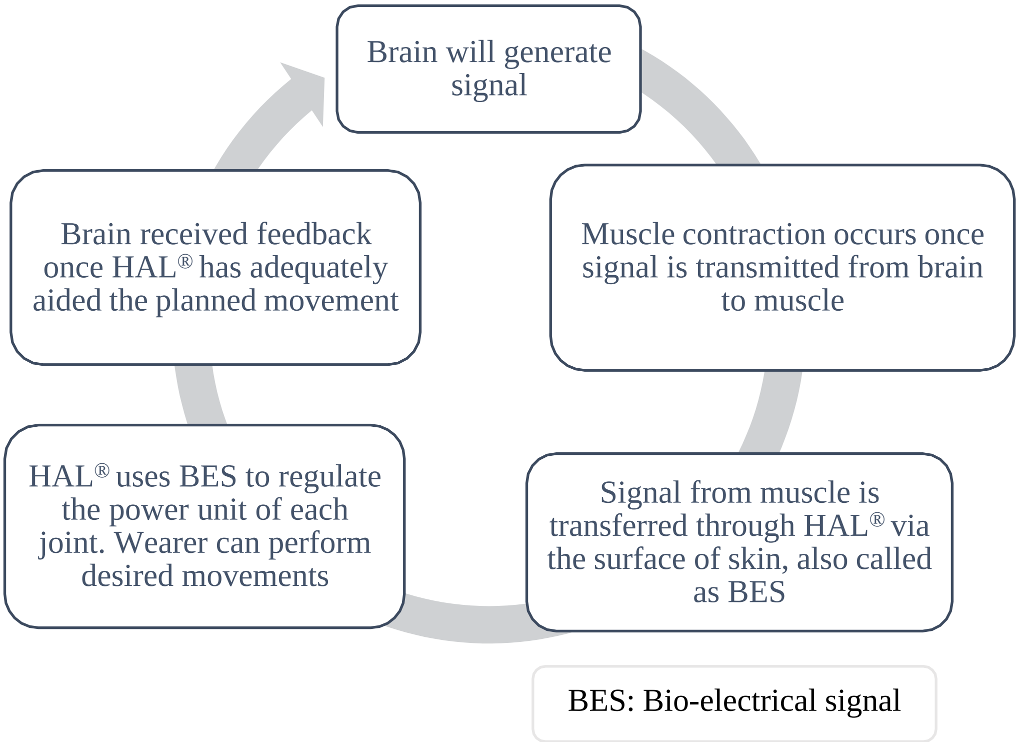

Figure 2.3: The motion principle of HAL® lower limb (adapted from Pusat Rehabilitasi PERKESO Tun Abdul Razak).

2.7. Functional Status of Stroke Patients

Assessing the functional status in rehabilitation is important in getting the crucial information on the functional status of before and after insults (O'Dell *et al.*, 2016; Pelicioni *et al.*, 2016). It is important to better understand the patients' problems, including mobility, ADL, instrumental ADL (I-ADL), communication, cognition, employment, and pleasure, among others. To make sure that the rehabilitation team can design the appropriate treatment plans for the short-term and long-term goals, these data should be accurate and complete as possible (O'Dell *et al.*, 2016). Being able to move plays an important role in the quality of life of a patient because it helps in freedom and safety, or whether the mobility assistive devices such as crutches, canes, walkers, orthoses or wheelchair is needed in daily usage. The assessment for ambulation is done by measuring the walking distance, the need for assistive devices, or the need for resting in between walking.

Gait abnormalities post-stroke are said to be caused by two different factors, which are the disruption of descending neural pathway, and neuronal adaptation. Changes in descending neural pathways can result in gait deviations, such as temporospatial, kinematic, and muscle activity asymmetries. Asymmetrical gait pattern is due to the compensatory mechanism that tries to counteract the changes in descending neural pathways (Swank *et al.*, 2020). Temporal spatial asymmetries and slow speed of walking is the problem that persists in more than 60% of stroke survivors after being diagnosed with stroke. Thus, these patients would require interventions to help them achieve near-normal walk speed (Swank *et al.*, 2020). RR gait training improved the temporospatial symmetry and the speed of walking is improved in a study cited in Swank *et al.* (2020).

ADL is the personal grooming tasks that is including eating, wearing clothes, hygiene, bathing, and toileting. A more complex task is called the I-ADL, which includes caring for others in the household, the usage of telephone, preparing meals, cleaning the house and doing laundry, and as complicated as using public transportation. Patient is said to have a good functional status if they are able to master the ADL. I-ADL helps the stroke patients to enter the community without having problems (O'Dell *et al*, 2016). Before starting the rehabilitation process, the cognition or mental process of knowing and communication skills needed to be assessed as they can interfere with the treatment unless it is properly conveyed (O'Dell *et al*, 2016). Spontaneous motor recovery is usually observed within three months post-stroke. It has been found that by the end of the first-week post-stroke, only 12% of patients are independent in basic ADL (Pelicioni *et al.*, 2016). Patient benefits from more active rehabilitation during the acute phase, which accounted for less than six months post-stroke as it is where cerebral oedema improved and the development of early neuronal connections (Pelicioni *et al.*, 2016). There is also improvement recorded in Functional Ambulation Categories in five out of ten systematic reviews in chronic stroke patients demonstrated in patients who undergo RR compared to CR (cited in Faulkner & Wright, 2018).

2.8. Quality of Life Post Stroke

The quality of life in stroke patients can be largely affected by immobility (Donkor, 2018). Cited in Martini *et al*., (2022), the quality of life of stroke survivors declines if they were to compare before and after being diagnosed with a stroke, and is also lower than the general population. WHOQOL questionnaire is one of the questionnaires that is widely used to measure the quality of life in the general population focusing on the individual perception of their well-being (Martini *et al.*, 2022). Despite great effects on motor function, by causing major disability, stroke can also affect them by affecting largely the quality of life (Schneider *et al*., 2021). Lack of social contact after being diagnosed, reduction of self-esteem, and feeling depressed post-stroke contributed to poor quality of life post stroke (Martini *et al.*, 2022).

A study by Martini *et al*. (2022) in assessing the quality of life of stroke survivors, two years after stroke, shows that the level of satisfaction in the physical health domain is the most affected suggesting that the patients are having difficulty in activities of daily lives, highly depending on medications and treatments, lack of energy and feeling exhausted, also having to experience the pain and discomfort in some time of their life after being diagnosed with stroke (Martini *et al.*, 2022).