EVALUATION OF NUTRITIONAL STATUS IN PATIENTS AFTER ACUTE STROKE

A thesis submitted to the University of Manchester for the degree of Master of Philosophy in the Faculty of Biology, Medicine and Health

2018

Yassin Mohamed M Kama

Faculty of Biology, Medicine and Health

TABLE OF CONTENTS

Word count: 38,174

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BIA	Bioelectrical Impedance Analysis
BAPEN	British Association for Parenteral and Enteral Nutrition
BMI	Body mass index
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DEXA	Dual-energy X-ray absorptiometry
ECW	Extracellular water
EPR	Electronic Patient records
ESPEN	European Society of Parenteral and Enteral Nutrition
FFM	Free-fat mass
FIM	Functional Independence Measure
FM	Fat mass
GCP	Good Clinical Practice
IBW	Ideal body weight
ICW	Intracellular water
LOS	Length of hospital stay
mBI	modified Barthel index
MeSH	Medical subject headings
mNIHSS	modified National Institutes of Health Stroke Severity
MUAC/MAC	mid-upper arm circumference
MNA-SF/LF	Mini-Nutritional Assessment-Short Form/ Long Form
mRS	modified Rankin Scale

MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NGT	Nasogastric tube
PEG	Percutaneous endoscopic gastrostomy tube
NRS 2002	Nutrition Risk Screening
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
QUOROM	Quality of Reporting of Meta-Analyses
RCP	Royal College of Physicians
RCTs	Randomised Control Trials
SD	Standard deviation
SINAP	Stroke Improvement National Audit Program
SLP	Speech-language therapists
SSNAP	Sentinel Stoke National Audit Programme
SU	Stroke unit
TFT/TSF	Triceps skin –fold thickness
TGF-β	Tissue growth factor beta
UTI	Urinary tract infection
VF	Videofluoroscopy
WHO	World Health Organisation

Abstract

MPhil Medicine 2016

Yassin Mohamed M Kama

The University of Manchester

Evaluation of nutritional status in patients after acute stroke

Background: Malnutrition is a major complication that occurs in people after stroke both during admission to the hospital and in the weeks after ictus. Many studies have been conducted to evaluate nutritional status in these patients using several techniques including the Malnutrition Universal Screening Tool (MUST). However, current evidence is limited and the effects of malnutrition after stroke on clinical outcomes remain unclear.

The aim and objectives: The aims of these studies were to ascertain whether being malnourished on admission with stroke is associated with poorer clinical outcome.

Methods: Initially a systematic review was conducted where the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA) were applied. All studies were identified through searching electronic databases and checking reference lists of relevant articles. Medical subject headings (MeSH) were used to search titles and/or abstracts, with terms of: "nutrition in stroke"; "malnutrition in stroke"; "skeletal muscle wasting" and "stroke clinical outcome".

Then a retrospective cohort analysis has been performed of the Malnutrition Universal Screening Tool (MUST) in acute stroke in Salford Royal Hospital using patient information available from January 2013 to March 2016. Data were collected after matching between the Trust specific Sentinel Stoke National Audit Programme (SSNAP) and Electronic Patient records (EPR). Overall, 1,101 patients (539 males and 562 females) were retrieved for analysis using linear regression and Chi-squared tests.

Findings: The systematic review showed, in most studies, that nutritional screening tools can be used as independent predictors of clinical outcome, and highlighted the importance of nutritional status assessment as a routine procedure on hospital admission.

The retrospective cohort study revealed that 66% of patients had MUST at admission. Most patients (78.5%) had no risk of malnutrition, 17.3% had high risk, and 4.1% had medium risk. Additionally, the association between risk of malnutrition and clinical outcomes was statistically significant and proportional (i.e. the greater the risk of malnutrition, the higher the possibility of poorer outcomes). For those who had greater risk of malnutrition their hospital stay was longer ($P< 0.04$), mortality was higher both within the hospital admission ($P< 0.001$), and at 6 months follow-up ($P<0.001$), and infections more prevalent ($P< 0.001$).

Summary/conclusion: The application of the MUST as an independent predictor of clinical outcomes can be used in health care settings with reference to acute stroke. Therefore, early identification of risk of malnutrition in stroke and future provision of early nutritional interventions is likely to become an important priority for the health services in the UK with potential improved clinical outcomes and resources saving.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

COPYRIGHT STATEMENT

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and s/he has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made only in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property University IP Policy (see http://documents.manchester.ac.uk/display.aspx?DocID=24420), in any relevant Thesis restriction declarations deposited in the University Library , The University Library's regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in The University's policy on Presentation of Theses.

ACKNOWLEDGEMENTS

Many thanks to my supervisors, Professor Shaheen Hamdy, Dr Sorrel Burden, and Professor Simon Lal and my PGR advisor, Dr Peter Paine for all their help, time, support and encouragement during my research training.

Many thanks to the Libyan People for the award of a scholarship to allow me to study for this degree.

With much gratitude to all students and staff of the GI Sciences department for their advice and support and for making me feel at home in the department.

I would like to express my deep thanks to my parents and my wife, Hanan for their support and encouragement over the years.

Finally, special thanks to all my children for their patience when their father is busy.

CHAPTER 1

General introduction

Stroke or cerebrovascular accident as a medical condition is a major cause of health disorders and death internationally (1). Indeed, stroke is an increasingly common problem globally, as around five million people internationally who are disabled each year as a result of a stroke. This figure arises because of increases in risk factors for stroke and an increase in the average age of people in the world, which will result in the rate of strokes doubling by 2020 (2). Reportedly, in patients after stroke, between 25% and 50% of deaths occur in hospital due to early post-stroke complications, among which are malnutrition, post-stroke infections, recurrence of stroke, and increased intracranial pressure (3).

Malnutrition is a common complication encountered by patients after a stroke with or without dysphagia in healthcare settings (3-6). Interestingly, malnutrition is associated with poorer clinical outcome in patients after a stroke in healthcare settings. These outcomes include mortality, post-stroke infections, and length of hospital stay (7, 8). Many published studies have been conducted to assess nutritional status in these patients using different nutritional screening tools and if needed further nutritional assessment techniques (7, 8). Hence, it has been recommended that reliable and validated nutritional screening tools should be applied as a routine procedure within 48 hours of hospital admission to recognise both undernourished patients, and patients at risk of malnutrition (9). Accordingly, both the identification of malnutrition, and frequent evaluation of these patients' nutrition thereafter are important priorities for healthcare services internationally. Therefore, early screening for risk of malnutrition will allow for prompt and appropriate nutritional intervention that will in itself, support governments' attempts to improve clinical outcomes, and save health resources.

Several published studies have reported that the prevalence of malnutrition in patients after a stroke varies widely from 8 to 49% (10-14), whilst other studies have reported the rate ranges from 6.1-62% (15). Many reasons will contribute to this wide variation, the type of stroke (whether infarct or haemorrhage), time of evaluation, presence of stroke complications, and co-incidence of chronic disorders, all play an important role on this wide variability. However, it seems likely that the most significant cause of this variation is the discrepancy between nutritional screening and/or assessment tools that used (14, 16). In fact, malnutrition is usually underestimated and untreated in societies and hospitals, and there is currently no nutrition tool or set of guidelines which fully meet the rigorous criteria designed by the British Dietetic Association, Royal College of General Practitioners, and Scottish Intercollegiate Guidelines Network (17).

In the UK, screening of nutritional status is already practiced in most health services, but there is a need to know more precisely the incidence at risk of malnutrition and whether malnutrition has any effect on patients' clinical outcome.

British Association for Parenteral and Enteral Nutrition (BAPEN) has launched guidance as to the most beneficial way to determine which type of nutrition screening tool most successfully evaluates nutritional status and gather precise prevalence of malnutrition or malnutrition risk (17). According to that recommendation, the screening method should be: simple and understandable, rapid to implement, acceptable to both patients and the healthcare team, valid, reliable, and evidence-based.

Several published studies have been performed to manage this issue (7, 8). However, they have often failed to agree on what is the most accurate, validated, simple and rapid tool for use in clinical practice on admission to hospital to assess the exact incidence of risk of malnutrition and the impact of malnutrition on clinical outcome.

Therefore, future research is warranted to determine the most appropriate and most beneficial tool to screen for the presence of risk of malnutrition, and to predict independently its effect on clinical outcome.

The research in this thesis has been aimed to assess the influence of nutritional status on the clinical outcome of post-stroke people, and evaluate the ability of the Malnutrition Universal Screening Tool (MUST) as a rapid, simple and validated tool to determine the risk of malnutrition, and predict clinical outcome in healthcare setting. In turn, early nutritional intervention has the potential to improve patients' outcomes and reduce health services costs. While further work is needed to support this contention, my thesis' results will hopefully provide valuable and novel insights into the current literature and add further evidence that malnutrition plays a critical role in influencing health care in the UK.

CHAPTER 2

Literature Review

2. Literature Review

2.1 Aim of the literature review

The aim of the literature review is to provide a comprehensive search of all appropriate material concerned with the evaluation of nutritional status in patients after a stroke. Accordingly, this review will highlight gaps in the literature, and shortcomings in studies assessing nutritional status and body composition in patients after a stroke.

2.2 Stroke background as a medical condition

Stroke or cerebrovascular accidents have been defined by the World Health Organisation (WHO) as a clinical syndrome composed of progressive development of specific signs due to focal disturbance of cerebral function that last for more than 24 hours or might lead to death with no apparent cause other than vascular origin (18). Stroke symptoms include body paralysis or heaviness, numbness, slurred speech, blurred vision, an impairment at the conscious level, and severe headache (19). A cerebrovascular accident (stroke) mainly consists of three main types, these being: ischemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage. Every pathology has its own sub-types, with specific underlying causes (20).

The cerebrovascular accident is the most common cause of physical dysfunction and the third commonest cause of impairment affecting daily quality of life, following depression and ischemic heart disease among elderly people (21). The presence of other co-morbidities could detrimentally affect the quality of life in stroke patients. These include swallowing disorders, gait and movement dysfunction, depression, and cognitive disorders.

Stroke as a medical condition is a major cause of health illnesses and death internationally (1). After ischemic stroke, between 25% and 50% of deaths occur in hospital due to early post-stroke complications, among which are malnutrition, post-stroke infections, recurrence of stroke, and increased intracranial pressure. Of these complications, malnutrition is the most common observed event (3). Several published studies have revealed that the prevalence of malnutrition in these patients on hospital admission varies widely from 16-49% irrespective of presence or absence of dysphagia (4, 5, 6). Reportedly, undernutrition is linked with poor outcome in patients after a stroke in health settings. These outcomes include mortality, post-stroke infections, and length of hospital stay (7, 8).

It is advised that reliable and validated nutritional status evaluation tools should be applied as a routine procedure within 48 hours of hospital admission to recognise both undernourished patients, and patients at risk of malnutrition (9). Accordingly, both the identification of malnutrition, and frequent evaluation of these patients' nutritional status thereafter are important priorities for health services internationally. Therefore, early screening for risk of malnutrition will allow for prompt and appropriate nutritional support that will in itself, support governments' attempts to improve clinical outcomes, and save health resources.

2.3 Prevalence and Incidence of stroke

Stroke is the third commonest cause of death (after cardiac and cancer causes) and disability in industrialised communities (22). Disability has been found to affect more than 60% of patients after stroke, while around 50% complain of hemiparesis, and almost 30% can only walk with assistance (22). Stroke incidence in Western communities ranges from 100 to 700 cases per 100,000 residents, in Eastern European communities it is at its highest in Poland and Lithuania, and in Southern Europe including Italy and Spain, it is at its lowest (23). In the USA, the prevalence of stroke is 795,000 cases annually, with 75% being new cases (24), while in the United Kingdom, stroke prevalence is 130,000 per year (2). Even after prompt medical therapy after a stroke, approximately two thirds of patients remain in a state of partial recovery (17), and three months after a stroke the onset of disability has been estimated at 15-30%, with approximately 20% of patients requiring institutional care (26). Strokes contribute to about 3% of all adult incapacity around the world (27).

There are five million people internationally who are disabled each year as a result of a stroke. This figure arises because of increases in risk factors for stroke, which include diabetes mellitus, hypertension, hypercholesterolemia, cigarette smoking, excessive alcohol intake, obesity, physical inactivity, and poor nutritional supply (28, 29). This is combined with an increase in the average age of people in the world, which will result in the rate of strokes doubling by 2020 (2). Although the exact mechanisms responsible for the increased stroke frequency as a result of unbalanced diet remain vague and ambiguous, nutritional interventions have been utilised in the management and treatment of risk factors of stroke, which include high blood pressure, obesity, diabetes mellitus, and dyslipidaemias (30). As indicated by the National Cholesterol Educational Program (NCEP) - USA, dietary supply of cholesterol should be limited to not more than 300 mg/dl for low risk people and to less than 200 mg/dl for individuals at high risk (31). Therefore, the nutritional behaviour of those in

the high risk group should be addressed carefully by both physicians and dieticians in health settings.

2.4. General aspects of nutrition in clinical dysphagia and feeding issues

Malnutrition is a very common disorder in stroke patients. The rate of malnutrition ranges from 8-49% among acute stroke patients admitted to hospital (10-14). The clinical outcome of stroke patients is significantly affected by malnutrition (13). Furthermore, patients who are malnourished usually require a longer hospital stay, incur more medical complications including infections, bed sores, and an increased rate of dysphagia (13). They require an increased use of nasogastric tube and/or percutaneous endoscopic gastrostomy compared to those who are well-nourished (13). It is commonly assumed that patients with acute stroke who have low serum albumin (considered as a multifactorial aetiology rather than a nutritional marker) are more prone to require prolonged rehabilitation care after hospital discharge, and are also shown to have a higher mortality rate during their first three months of admission into the hospital (14). Nowadays, the number of older people is progressively increasing, and around 16% of the population is over 65 years, with 2% of the population around the world being over 85 years (32). This is expected to rise significantly over the next 30 years (33). Consequently, there is a need to accurately establish the prevalence of malnutrition in patients after a stroke, and this demands a search for validated, fast, simple and practical methods to assess nutritional status, so that such assessment can be used as a reliable predictor for clinical outcomes.

It has been demonstrated in one study in 2002 that around 63% of people between 65 and 74 years old, and 72% of the population over 75 years old were complaining of chronic disorders (34). Additionally, the negative effects of chronic disorders impact substantially upon the economies of societies (34). Chronic illness substantially influences nutritional status in the elderly (33). There are also important changes occurring in the body composition of elderly people that have a negative influence on their nutrition status (33), for example, there is a loss of muscle and fat tissue that occurs in malnourished older people with chronic disease (33). Therefore, it is crucial to understand what happens during these changes as a result of the ageing process and chronic diseases, so that such understanding can be used by health services to inform their future planning in respect of their efforts to overcome the impact of these changes in elderly people's health, and ultimately save health resources.

There is a consensus in the literature that muscle, skin, bone, and organ tissue, which are commonly referred to fat free mass (FFM), are significantly decreased with age, and this begins at an early age (31-41 years) (35-38). This unplanned weight loss is prevalent in elderly population, with incidence rate of 13% (39). There is no clear formal consensus in the definition of unplanned or unintentional weight loss; however, the United States Omnibus Budget Reconciliation Act of 1987 has defined significant weight loss as the loss of 5% of body weight within one month or 10% within the previous 6 months or longer (40, 41). It has been shown that the central accumulation of fat is associated with an increased probability of cerebrovascular accident, diabetes mellitus, dyslipidaemia, atherosclerosis, and hypertension (42). Fat free mass loss is referred to as skeletal muscles mass loss, and decrease of bone mineralisation, especially in females (37). As mentioned above, skeletal muscle mass is a major portion of fat free mass, and consequently any alteration of muscle mass will lead to attenuation of physical performance, body strength, and an increase in mortality rate (38). Therefore, in old people with an obvious loss of fat free mass, the adverse effects are likely to be more serious, and that warrants the need for early nutritional supplements.

There are three syndromes closely linked to unintentional weight loss, these being wasting, cachexia, and sarcopaenia.

1) Wasting:

Wasting is defined as weight loss as a result of insufficient food intake. It has been referred to disease process and psychological and social factors, which might co-exist with the other disorders of sarcopaenia and cachexia.

2) Cachexia:

Cachexia has been defined as weight reduction of more than 5% of body weight in 12 months or less in the presence of chronic disorders or as a body mass index (BMI) lower than 20 kg/m2. Moreover, cachexia is considered as a clinical syndrome of weight loss that is characterised by muscle mass loss with or without fat mass loss in the presence of the metabolic effects of underlying disorders, and is associated with increased morbidity (43). Cachexia is associated with increased protein degradation, peripheral insulin resistance, anorexia, and the inflammatory process. Moreover, cachexia is quite different from age-related sarcopaenia, wasting as a result of insufficient food intake, malabsorption syndromes, and thyroid dysfunction (43).

3) Sarcopaenia:

Sarcopaenia is defined as a loss of skeletal muscle mass and strength that may accompany the ageing process or be associated with age-related disorders. According to this definition, sarcopaenia can be observed at any age as the result of many factors such as malnutrition, skeletal muscle disuse, pro-inflammatory or endocrine disorders. An increase of fat mass may be accompanied by muscle mass loss fat which is known as sarcopaenic obesity. Changes leading to loss of lean mass occur on cellular, metabolic and biochemical levels. The distinct pathophysiology of this disorder remains ambiguous, although there is a general assumption that sarcopaenia cannot be attributed to the normal ageing process alone even though it is still considered a normal phenomenon as it is obviously seen in normal healthy people. Absence of physical activity and muscle disuse are both associated with the occurrence of sarcopaenia, and the encouragement of muscle exercise will reduce the chance of it arising (44). Nevertheless, increased physical activity does not prevent muscle loss (sarcopaenia). This can be explained by the existence of other factors like hormonal, neural, and cytokine interaction (45) (Fig.2.1).

In general, there are five common mechanisms which might operate variably to an extent that causes tissue loss which is known practically as malnutrition, cachexia, sarcopaenia, and frailty (46):

1. Energy intake insufficient to meet energy requirements: in this situation, if energy intake is insufficient to meet body needs, body tissues will degrade to provide the energy required. The nutrients deficit may be caused by both reduced intake and increased demands. As a result fat mass is the main source of energy and fat loss dominates the wasting in this situation.
2. Increased pro-inflammatory cytokine activity: this includes increased levels of tumour necrosis factor, interferon-[gamma], and interleukin-6. These cytokines are linked with increased thermogenesis, increased muscle breakdown, and decreased muscle mass synthesis.
3. Reduced muscle loading: reduced physical exercise and bed rest are associated with decreased muscle mass synthesis. Additionally, lack of exercise will lead to failure of amino acids to stimulate protein synthesis.
4. Hormonal action: Insulin is a critical hormone required in the synthesis of both muscle and fat. So any Insulin deficiency, for example in diabetes mellitus type 1, is

associated with significant loss of both muscle and fat tissues. Similarly, increased levels of corticosteroids will lead to increased catabolism of fat-free mass which results in thinning of the skin, and loss of muscle and bone. Testosterone levels aid muscle building. Moreover, increases in metabolic rate lead to tissue loss as a result of a heightened level of catecholamines, and sympathetic over-activity.

5. Neuromuscular atrophy: Any Muscle disorders or peripheral neuropathy may cause muscle atrophy.

The above-mentioned mechanisms usually interact in variable degrees to yield specific clinical conditions or syndromes. However, there is a great overlap in the presentation of these conditions clinically, thus making it difficult to identify each syndrome in medical practice (46).

In malnutrition, muscle mass is initially preserved as energy requirements are met by liver glycogen, body fat, and protein stores from the viscera. In this stage some muscle mass loss occurs but can be prevented by physical exercise. However, as the energy requirements are prolonged, live glycogen and body fat disappear and the body then depends entirely upon the consumption of muscle protein. At this point the clinical presentation is more identical to cachexia (46). Clinically, cachexia is the main feature of septic disorders, malignancy, cardiac failure, arthritis, and chronic lung disease. The general consensus on cachexia is that malnutrition has been erroneously used in practice to describe cachexia. This is a mistake as malnutrition might be corrected by the implementation of specific nutritional interventions whilst cachexia cannot (43). The main difference between malnutrition and cachexia is that the muscle reduction is the late feature in malnutrition, while in cachexia muscle mass loss is severe and manifested early (43).

As already mentioned, around 25-50% of deaths inside hospital in patients with ischemic stroke are attributed to post-stroke complications, malnutrition being the commonest one (25). Several mechanisms are involved in the metabolic disarrangement in post-stroke patients that finally lead to decrease the anabolism and increase the catabolism. The net effect is the acceleration of tissue degradation, presented as decreased muscle mass (sarcopaenia) or overall weight loss (cachexia) (47).

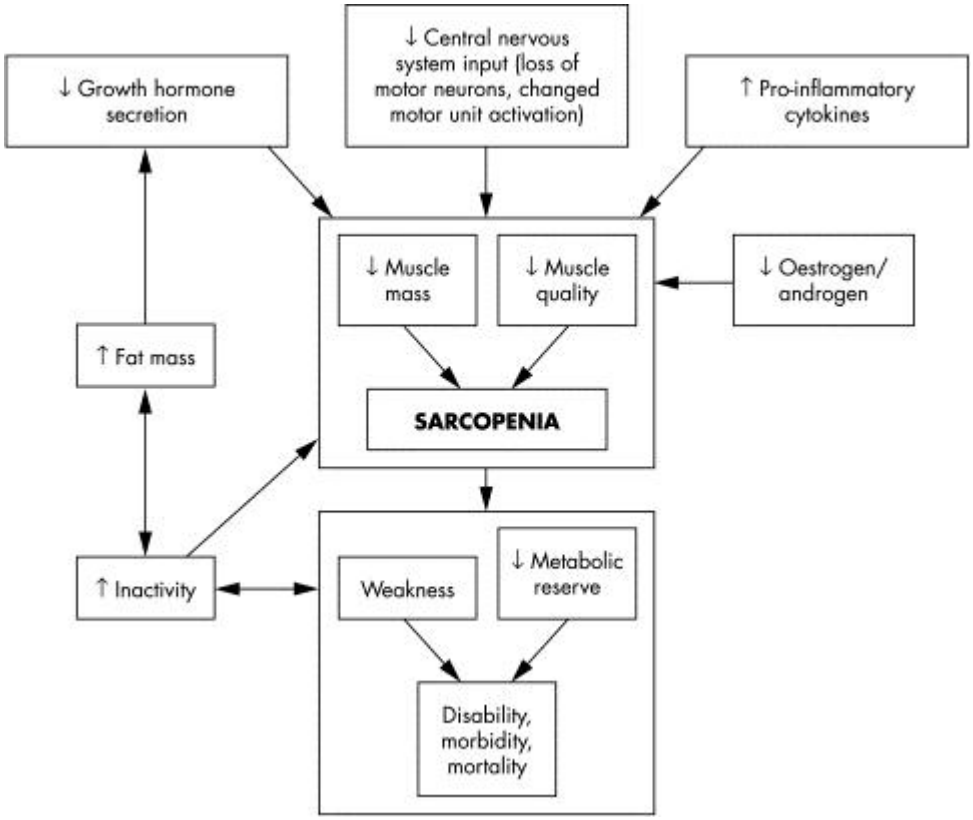


Figure 2.1 Potentially important factors in the aetiology of sarcopaenia (Adapted from Roubenoff) (45)

2.5 Stroke complications including malnutrition and dysphagia

There are many medical complications that can develop as a result of dysphagia, which include respiratory complications (aspiration pneumonia), dehydration, and malnutrition. Malnutrition is a term that is used to describe a huge number of nutritional abnormalities. In acute stroke it is a preventable complication, since it is characterised by a sustained negative imbalance between protein and energy requirements and intake, and that can be changed. In other words, energy and protein intake are often less than body requirements, and this shortfall finally leads to impairment of body composition and abnormal biological status (21). Malnutrition is recognised as the main complication in stroke patients, with an incidence rate of 8-49% (48). In an international multi-centre randomised study in 2005, it was found that following acute stroke, patients demonstrated significant nutritional deficiencies when compared with the control group (5). Likewise, in a previous study of 49 stroke patients, strong evidence emerged of poor nutritional status outcome in patients with dysphagia who had tube feeding during their rehabilitation period. Thus, disruption of nutritional status may

occur as a result of inadequate food intake in relation to actual requirements over the period of hospital stay (7).

2.6 Prognostic aspects of poor nutrition in patients after a stroke with or without dysphagia

Stroke patients are afflicted with a high prevalence (30-65%) of swallowing dysfunction (50, 51). In most stroke patients, swallowing returns to normal spontaneously within the first four weeks after stroke even though a considerable percentage maintains their dysphagia for more than six months (50, 52). Dysphagia in stroke patients is associated with variable medical complications, for example malnutrition, infections, dehydration, poor functional outcome, prolonged hospitalisation, long rehabilitation phase, the necessity of prolonged health care support, and increased mortality (51, 53, 54).These complications affect both the functional and social lives of patients after a stroke, and have repercussions on their overall quality of life and that of their families, whilst also increasingly consuming health resources (55). Moreover, it is very difficult in practice to evaluate stroke patients' nutritional status. Nutritional history intake might be inapplicable due to poor communication ability on the part of the patient, in which case no other source of information would be available.

Recently, the World Health Organisation (WHO) has recommended that the body mass index (BMI) can be used as a useful parameter to measure overweight and obesity in the general population, irrespective of sex and age (56). In this respect, BMIs of >25 kg/m2 and >30 kg/m2 are considered to be overweight and obese in all people regardless of sex and age. This utilisation of a single standard for measuring obesity for all adults was advised because it is thought to be independent of age and gender and can be applied to make global comparisons in research (57). The body mass index is a well-recognised screening tool that can be applied internationally to evaluate person's body fat. It is calculated by dividing weight (in kg) by height (in m^2), and is categorised as follows: underweight (less than 18.5 kg/m^2); normal weight (18.5 to 24.9 kg/m^2); overweight (25 to 29.9 kg/m^2); and obesity (greater than 30 kg/m^2) (58). The BMI has been used as an indirect measure, and several studies have suggested that it is correlated well with direct techniques such as densitometry and dual-energy x-ray absorptiometry (DEXA) (59). However, the BMI has some disadvantages. For instance, it is unable to distinguish between fat free mass and fat mass: athletic people might have a high BMI due to an extra skeletal muscle mass and therefore, might be miscategorised as obese; and on other hand, people with high body fat but low muscle mass, like old people, may be miscategorised as normal BMI. Therefore, BMI is unable to identify fat distribution,

an important factor in measuring metabolic health risk (58). Furthermore, in elderly people fat mass percentage is known to increase, whilst their lean mass declines, but their weight and height do not necessarily reflect such changes in body fat and lean mass (59).

In immobile stroke patients, body mass index as a simple measure to evaluate nutritional status is sometimes impracticable, and in such situations surrogate measures might be used to calculate weight and height. Accordingly, in patients who are unable to stand, the following measurements can be used in practice to calculate the height alternatively; ulna length and knee height. Usual weight before the illness has been collected from the patients, their relatives or recent medical notes (60).

In spite of the high prevalence of malnutrition in elderly hospitalised people, and its negative effect on health resources, malnutrition remains under-estimated and under-treated (61). Therefore, many nutritional screening tools have been recommended in health settings to allow early identification of malnutrition and early nutritional interventions (62-64). Many of these screening techniques have been advised for application with elderly hospitalised people, such as for example, the Malnutrition Screening Tool (MST) (65), the Nutrition Risk Screening (NRS 2002) tool (66), the Mini-Nutritional Assessment Short Form (MNA-SF) (67), the Simplified Nutritional Appetite Questionnaire (SNAQ) (68), and the Rapid Screen (69). At the same time, many validated nutritional assessments have been recommended internationally to evaluate nutritional status and initiate early nutritional intervention, such as for instance, the Subjective Global Assessment (SGA) (70), and the Mini-Nutritional Assessment (MNA) (71). Interestingly, there is a difference between nutritional screening and nutritional assessment (72). The nutritional screening methods have been designed to use as rapid and simple tools for identifying the risk of malnutrition, and to select patients for complete nutritional assessment and treatment interventions. The SGA and MNA are comprehensive nutritional assessments for use by trained personnel (e.g., dietitians, physicians, or research workers) to identify malnutrition and initiate nutritional interventions (73). However, these validated screening tools have no single objective measurement or one gold standard for the evaluation of the degree of malnutrition (74). Therefore, more research is required to improve approaches to the assessment of stroke patients' nutritional status both at admission, and periodically thereafter.

As already noted malnutrition is very common among stroke patients and is generally underestimated in patients who are admitted to hospital. Likewise, many studies have

reported the frequency of malnourished patients after stroke (75). This documented prevalence of malnutrition in patients after a stroke ranges from 8 to 49% (7, 48), with those results reflecting variations in patients' selection, definition of malnutrition, methodology and evaluation times (10). The studies referred to were all dependent on information that had been collected after admission, and thus they exclude patients who were either discharged or died. Moreover, there were certain prognostic factors among malnourished patients who were admitted to hospital such as increased age, history of peptic ulcer, atrial fibrillation, hemorrhagic stroke, dysphagia, diabetes mellitus, and history of previous stroke, all of which might have an effect on their nutritional status (76).

Energy intake in patients with acute stroke might also be influenced as is the case with many other acute medical conditions. Consequently, insufficient food intake and increased nutritional requirement in those patients will have a strong impact upon their nutritional status. Furthermore, post-stroke patients are unable to achieve increased energy demands (77). The prognostic view after stroke is extremely critical, with approximately 25-50% of hospital deaths in patients with ischemic infarction stroke being caused by complications such as infections, increased intracranial pressure, altered nutritional status, in addition to the recurrence of stroke. Decreased of weight seems to be observed mostly in association with these complications (3). Finally, tissue depletion occurs and is manifested as muscle loss (sarcopaenia) or more generally, weight reduction (cachexia) (43). In a multi-centre randomised study estimating various eating policies with a population of 2,955 stroke patients over a six month period, in which nutritional status was evaluated by BMI (3), it was found that underweight patients (BMI<20 Kg/m 2) had poor prognosis and more complications than average weight patients (BMI 20-30 kg/m 2) or overweight victims (BMI > 30kg/m2).

The pattern of weight change is recognised as a significant predictor of poor outcome, strong evidence of this being found in a recent study conducted by the Lund Stroke Registry with a population of 305 stroke patients. In about 25% of patients, weight reduction of more than three kg of both short (four months) and long term (1 year) duration was seen after stroke. The mortality rate of stroke patients who had experienced substantial weight loss was 14% compared with those who had no significant weight loss (4%) (78).

Weight reduction in stroke patients might be seen as a clinical outcome of metabolic imbalance. This effect may be attributed to many reasons like an altered eating process,

physical inactivity, and muscle paralysis. However, negative energy balance could result from other factors such as sympathetic over-activity, fever, infection, altered appetite, pro-inflammatory cytokines, and/or oxygen-free radical accumulation. Therefore, catabolic and anabolic imbalance may emerge as a net result of depressed anabolic signals and stimulation of catabolic drive simultaneously. Eventually this imbalance will lead to fat depletion as a source of energy store, and muscle mass loss manifested clinically as "weight loss" (Fig.2.2) (79). Hence, there is a need for further clinical trials and studies to clarify, explore, and explain the impact of anabolic and catabolic imbalance on stroke patients' health and outcome.

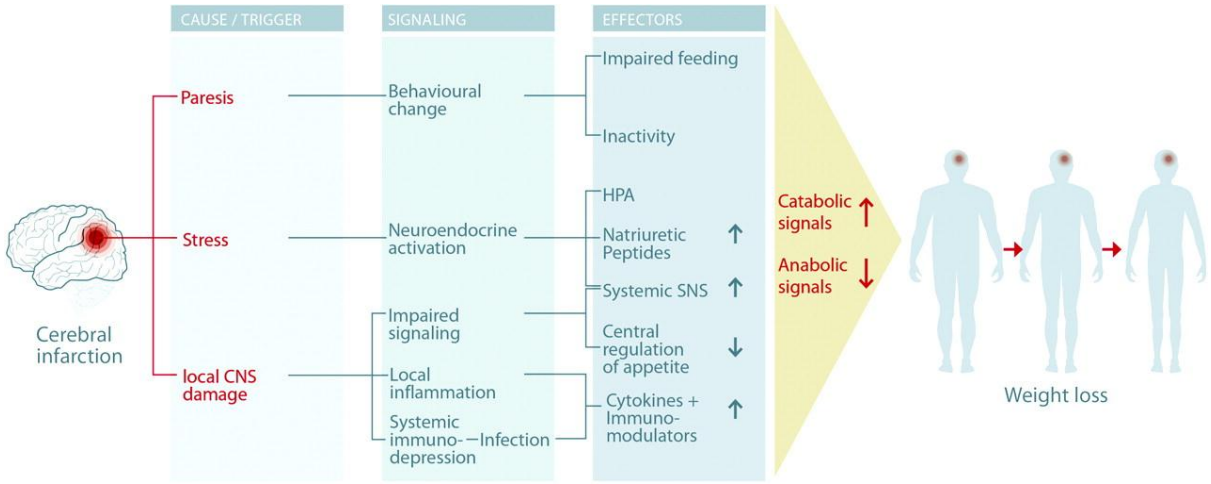


Figure 2.2 Schematic overview of the complex pathophysiology of systemic metabolic changes and weight loss in patients with stroke (Adapted from Scherbakov et al.) (79).

2.7 Nutritional guidelines in stroke

Stroke affects around 15 million individuals annually and has been recognised as the main cause of mortality and physical disability in societies (80). In the UK there are around 150,000 strokes cases annually, and as Townsend et al. (81) reported, stroke causes 50,000 deaths annually, being considered the fourth commonest cause of death after malignancy, cardiovascular diseases, and respiratory disorders. Furthermore, stroke is the second cause of physical disability internationally after dementia (82), leading to approximately 5 million patients being permanently physically disabled every year (83), and more than 50% of all stroke patients (in the UK) becoming dependent on others for help with their daily activities (84). Patients presenting as malnourished on hospital admission have an increased risk of

death and poor clinical outcomes (13). As indicated earlier, on hospital admission, 8-49% of patients with stroke have been shown to be malnourished (78). Moreover, up to 25% of victims become more malnourished within the first week after a stroke and this is associated with increased death rate and post-stroke complications (48), and with poorer clinical outcomes (14). Weight reduction, feeding problems, and dysphagia can persist for a long time after a stroke, thereby having a potential influence on nutritional status and clinical outcome if not properly treated (85).

Many causes of decreased food intake and the subsequent deterioration of nutritional status have been documented including: swallowing dysfunction, physical disabilities, impairment of conscious level, perception and cognitive impairment, and depression (86). Given the association of malnourishment and poorer clinical outcomes in various patients groups (87), it is essential that all stroke patients be screened for evidence of malnutrition. In this respect, several validated screening methods are available in clinical practice, for example: the Malnutrition Universal Screening tool (MUST), Mini-Nutritional Assessment–Short Form (MNA-SF), Mini-Nutritional Assessment–Long Form (MNA-LF), and Subjective Global Assessment (SGA), but the Nutrition Risk Screening (NRS 2002) is the best suitable one (63, 88).

Therefore, early identification of malnutrition or risk of malnutrition in patients after stroke and, and swift efforts to ensure that early nutritional interventions are implemented are likely to become the first priorities in health services internationally, with potential improvement in both clinical outcomes and budget-saving. Much research has been conducted on the issue of dietary support in acute stroke patients, all such support being targeted to develop, implement, and assess evidence-based multi-professional nutritional guidelines (89).

The complications of stroke may be serious and can include; impaired physical daily activities, communication problems, dysphagia, and depression (90). Dysphagia is prevalent in patients after acute stroke with incidence ranges from 40% and up to 78% in some studies (54). There is a significant association between dysphagia in stroke and poor clinical outcomes including a higher mortality, physical disabilities, pneumonia and longer hospital stay. Acute stroke patients with dysphagia are more prone to experience poorer clinical outcomes, and consequently, the need for early identification of dysphagia in all patients with acute stroke is mandatory (54).

The Royal College of Physicians has published the last up- dated and most comprehensive National Clinical Guideline for Stroke (91). This guideline contains valuable nutritional recommendations for these people, which include the following:

1. Patients' hydration status should be tested within 4 hours after hospital admission, and should be reassessed regularly and treated accordingly so that normal patient hydration is kept normal.
2. Patients with acute stroke should be nutritionally screened for malnutrition or the risk of malnutrition on admission, and at least every 7 days thereafter. Screening should be conducted by qualified personnel using structured screening tools for malnutrition, for example the Malnutrition Universal Screening Tool (MUST).
3. Patients with acute stroke who are well-nourished at hospital admission and are able to feed themselves orally should not have any oral nutritional supports.
4. Patients with acute stroke who have risk of malnutrition or who need tube feeding or food modification should be referred to a dietitian for particular nutritional assessment, recommendation, and close monitoring.
5. Special nutritional support should be offered to patients with risk of malnutrition. This support should include oral nutritional supplements, specialist food advice, and/or tube feeding in accordance with patients' expressed wishes or best interests, if they are mentally incapable.
6. If adequate nutrition and fluids cannot be taken orally by patients then the following steps should be taken:

   –the patient should be referred to a dietitian for nutritional assessment, recommendation and follow up;

   – Nasogastric tube feeding within the first day after hospital admission should be considered.

   Approximately 10 to 30% of patients after acute stroke are eligible for tube feeding initially after stroke. However, it is still unclear who gains benefit from this kind of feeding. Clearly, any post-acute stroke patients with severe swallowing dysfunction, impaired consciousness or severe limb paralysis will not want to eat and their dietary intake will be negatively affected with the result that they will become more susceptible to a high risk of malnourishment. Hence, it is this group who are more

likely to benefit from tube feeding, together with those who have pre-existing malnutrition (92).

– if the nasogastric tube requires frequent replacement, a nasal bridle using locally-agreed protocols can be considered;

– if the nasogastric tube and nasal bridle are poorly tolerated, the possibility of percutaneous endoscopic gastrostomy (PEG) can be considered.

7. Patients with acute stroke who need diet or fluid of a modified texture should be:
   – referred to a dietitian for nutritional status assessment, advice and regular follow up;
   – be given their modified food according to nationally-agreed descriptors.
8. PEG should be considered for patients after a stroke if they:
   – are eligible for nasogastric tube (NGT) feeding but cannot tolerate it;
   – cannot swallow sufficient food and liquids orally within 4 weeks after the onset of stroke;
   – are at high risk of being in the malnourished group.
9. Patients after stroke who face challenges when self-feeding should be evaluated and provided with appropriate equipment and assistance such as physical and verbal support to encourage their independence and safe feeding process.
10. Patients who are discharged from specialist health settings with persisting nutritional problems, should have their food intake and nutritional status monitored frequently.
11. Patients after stroke who have end-of-life care (palliative) should not have any restrictions on oral diet and/or liquid intake if those restrictions would exacerbate patients' suffering.

Furthermore, Takahata et al. (93) reported that the best way to supply sufficient food and fluid intake to post-stroke patients with dysphagia is by insertion of a nasogastric tube or percutaneous endoscopic gastrostomy. Nevertheless, severe dysphagia in patients after stroke is considered as an independent predictor for poor outcome. Moreover, increased incidences of both aspiration pneumonia and mortality rate were strongly related to these tools of enteral feeding (94-96). In general, the most available techniques for enteral feeding modalities are nasogastric tube (NGT), percutaneous endoscopic gastrostomy tube (PEG), and radiological-guided gastrostomy or jejunostomy (76).

2.8 Measurements of nutrition (Bioelectrical Impedance Analysis BIA, CT scan, Body Mass Index BMI and absorptiometry DEXA) in general and in stroke patients

Nowadays, evaluation of body composition is considered an important issue in the assessment of nutritional status in clinical practice, and as an invaluable tool in research (97).

The establishment of nutritional status by measuring FM and FFM is the fundamental reason for assessing body composition in medical practice. Certainly, regular assessment of nutritional status is strongly advised for both in-patients and out-patients at risk of malnourishment (63), since malnutrition is usually under-estimated in both hospitalised patients and outpatients, and is a condition that is expected to inflate during the coming years (98). It is defined as a state of insufficient nutrients like energy, protein, vitamins and minerals that may lead to considerable negative effects upon both body composition and clinical outcome. Indeed, malnutrition can be both a cause of ill health and/or the result of it (99). Currently, there are many multi-approach systems to evaluate and assess nutritional status in practice.

Frequent observation of any changes in body composition can promote a better understanding of nutritional status and may thus guide healthcare policy in searching for the best way to spend on nutritional interventions. However, such frequent observation is not routinely evident since body composition focusing on skeletal muscle mass and fat tissue is not assessed as a matter of routine in practice (100). If such measurements were readily available in clinical practice, then this information might be utilised by health services to secure better delivery of nutritional interventions for those patients identified as malnourished.

Many techniques have been created to assess body composition, such as: anthropometry measures like the 4-skinfold method, hydrodenitometry, in vivo neuron activation analysis, anthropogammametry from total body potassium-40, nuclearmagnetic resonance, dual-energy X-ray absorptiometry (DEXA), BIA, and computed tomography (CT). In recent times, the most accurate tools in medical practice are DEXA, BIA and CT (Figure 2.3), as the other tools have some limitations and are more appropriate for the scientific field (98). The need to reduce both sensitivity and reproducibility of the 4-skinfold method, for example, leads to a marked limitation in its use as a body composition evaluation method in practice (101, 102), while BMI and the percentage of weight loss in some chronic disorders cannot yield any knowledge about the particular contribution of FM and FFM in the body mass changes (103).

DEXA is a non-invasive technique used to evaluate the three main body composition compartments. It is adopted in practice to diagnose and follow-up patients with osteoporosis. Undernutrition is associated with numerous medical conditions manifested clinically as osteoporosis, especially in older females, patients with organ failure, COPD, inflammatory bowel disease, and coeliac disease (104). Therefore, DEXA can be used for monitoring both osteoporosis and malnutrition. However, given the reduced availability of DEXA in practice, it is difficult to apply the technique to identify patients with malnutrition or patients at risk of malnutrition as in patients after stroke.

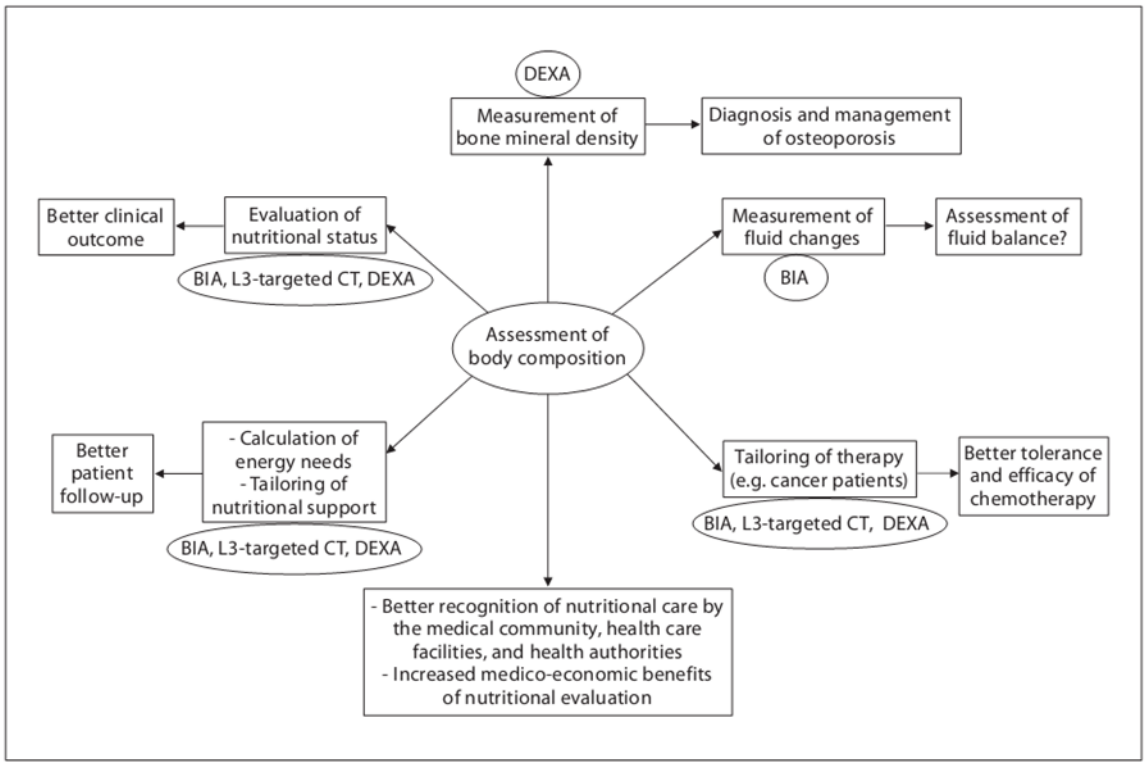


Figure 2.3 Applications of body composition assessment in practice (adapted from Thibault et al.) (98).

BIA is a validated, non-invasive and relatively simple tool used to test elderly patients' body composition comfortably (107). It's ideal usage in practice has been reported in two ESPEN studies (105, 106). The assessment of total body water impedance enables evaluation of the total body water (TBW) which is assumed to be stable, and a validated equation is then used

to measure both FFM and FM. BIA enables the estimation of both TBW and FFM in individuals having no important fluid or electrolyte abnormalities when applied via the established strategies (105). In bioelectrical impedance analysis to estimate body fluid volumes, it is assumed that an electrical current at low frequencies cannot penetrate cell membranes and thus flows through the extracellular water (ECW) compartment only, whilst electrical current at high frequencies can flow through both the ECW and intracellular water (ICW) compartments (108). Any derangement in fluid distribution can give errors in body fluid analyses and, therefore, in the determination of fat and fat-free mass (106). In BIA a multi-frequency bioelectrical impedance spectroscopy (BIS) is used to estimate ECW and ICW, as well as to assess FM, FFM, lean body mass and body cell mass (108). BIA is clinically valid for usage in COPD, HIV patients, organ transplantation, anorexia nervosa, and older populations including patients after a stroke. It correlates well with DEXA (109). TBW as measured by BIA must be validated through other tools like densitometry. Several methods have been used to estimate both body composition and TBW such as, isotope dilution, DEXA, underwater weighing, portable methods, and air-displacement plethysmography (110). Although computed tomography and magnetic resonance imaging are used to assess abdominal and visceral fat, they need extraordinary services and are not available for daily monitoring of body composition in health settings (110). Kafri et al. (109) stated that the above mentioned techniques may also used to assess body composition in patients with stroke. However, many of these methods are limited clinically due to difficulty in availability, cost effectiveness and imprecise measurements and other technical issues that might be encountered in sick and weak individuals. Bearing this in mind, Multi-frequency bioelectrical impedance analysis (MF-BIA) may offer a relatively easy, rapid technique to measure body composition in patients after a stroke, since it is portable, relatively inexpensive, and does not require well-trained personnel to use it (109). Furthermore, due to its accessibility, simplicity, high sensitivity and reproducibility in medical practice, BIA is the best choice for assessment and evaluation of FFM and FM in both out-patients with chronic diseases, and hospitalised patients.

On the other hand BIA has certain drawbacks such as: lack of BIA to specific equation renders this method invalid in patients with extreme BMI values, i.e. less than 17 or higher than 33.8, and in cases of fluid overload or dehydration (105, 106). Also in some critical disorders when there is fluid in third spaces such as ascites, anasarca, severe peripheral oedema, pleural effusion, and massive over hydration, BIA might be not a good method to

measure TBW. Additionally, in people with severe disorders, the ratio of TBW/FFM is often variable and the ratio of body impedance/TBW is usually different. Therefore, in respect of critical disorders, the BIA tool can only be utilised in the research domain (110).

Recently, many studies have reported the beneficial application of CT which can precisely detect whole-body fat and FFM through imaging the third lumbar vertebra area when compared with DEXA. This technique is now used to evaluate body composition in malignancies, being used in routine diagnosis, staging, and follow up. The CT machine is targeted on the L3 area to assess FFM via imaging of the muscle cross-sectional area from L3 to the iliac crest. Muscles involved in measuring the muscle cross-sectional area are the psoas, paraspinal muscles group (erector spinae, quadratus lumborum), and abdominal wall muscles (transversus abdominis, external and internal obliques, rectus abdominis) (111). Furthermore, CT imaging can give more information on specific muscles, fat tissues and organs than can other methods such as BIA and DEXA. Future research might be warranted to assess the possibility of using the CT technique to estimate nutritional status in stroke, particularly if imaging of the lumber area can be taken at the same time as head imaging. This will open up a new horizon for the use of this precise technique and bring the advantage of producing extremely accurate results about the patient's body composition.

Overall, DEXA, BIA, and CT are all capable of evaluating body composition precisely, but the selection of which method will be determined entirely by the clinical situation, the hardware available, and the amount of knowledge possessed about these tools. For example, DEXA assessment of body composition should be used with patients undergoing routine examination of bone mineral density; CT imaging of the third lumbar vertebra area is the best technique to assess body composition in malignancies (111); and BIA could be widely implemented as the best tool to assess body composition and follow-up in a great number of in and outpatients. Further research should aim to determine whether a routine assessment of body composition would be able to detect an early increase in FFM catabolism related to serious disorders (98).

2.9 Sarcopaenia in general and in stroke

Sarcopaenia is defined as an age-associated skeletal muscle mass loss and decreased strength, commencing as early as the fourth decade of life. Previous evidence suggests that voluntary muscle mass and strength both decrease in a linear pattern. Almost 50% of skeletal mass is lost by the age of eighty. Skeletal muscle mass accounts for about 60% of total body mass,

any abnormal changes to this significant metabolically-active compartment can have serious results on the health of older and adult people. The outcome of sarcopaenia is usually more dangerous in the older population, as the decrease of both skeletal muscle mass, and the presence of functions that accompany sarcopaenia can lead to numerous drawbacks, including drop of functional performance, incapability, and frailty. Additionally, sarcopaenia is related to acute and chronic medical conditions, increased insulin demand due to increased peripheral resistance, fatigue, falls, and mortality (112).

Sarcopaenic obesity is the combination of reduced fat-free mass (FFM) and increased fat mass (FM) with advancing age. This phenomenon is often contributing with sarcopaenia and plays an important role in the overall sarcopaenia process in the elderly population. Recently, in 2012, Framingham et al. demonstrated the importance of sarcopaenia obesity in reducing functional capacity and physical performance in old people. Additionally, they determined that fat mass gain was correlated with declining muscle quality and increased free-fat mass loss (113).

It is necessary here to discuss exactly what the main causes of sarcopaenia or sarcopaenia obesity are. Generally, it is believed that the cause of sarcopaenia is multifactorial in nature, encompassing environmental factors, medical illnesses, inflammatory mechanism stimulation, mitochondrial disorders, neuro-muscular junction abnormalities, satellite cell reduction, and hormonal disturbances, all of which are thought to be main causes of sarcopaenia. Furthermore, sources of evidence demonstrate that molecular mechanisms might be related to skeletal muscle maintenance, and they further clarify the role of Tissue growth factor (TGF)-β singling, apoptosis trigger and deterioration in mitochondrial performance as important mechanisms in sarcopaenia pathogenesis (112).

In stroke, data are still not available on the structural, metabolic, and functional features of skeletal muscle, and on how profoundly sarcopaenia impacts on the outcomes of these patients. Additionally, there is growing interest about the effects of skeletal muscle pathology in stroke on disease recovery and functional outcome (114).

2.10 Summary

In this literature review, certain gaps in knowledge have been identified which could be expressed briefly as follows:

- Although several studies have been conducted on nutritional status in patients after a stroke, there is still a need to know how much effect on clinical outcomes is caused by the deterioration of nutrition.
- There is a great variation in the prevalence of malnutrition among patients after a stroke, and many reasons account for this. However, the most significant relates to the discrepancies among the nutritional screening tools that used. This requires the need to develop a simple, quick, accurate and validated method for use in clinical practice.
- Despite the use of some accurate nutritional assessment techniques (DEXA, BIA and CT scan) in certain clinical settings, this use is limited and impracticable elsewhere.
- In the absence of a single golden standard tool to determine the presence or risk of malnutrition, further research is recommended to determine the most appropriate method to screen for malnourishment and to predict its influence on clinical outcomes.
- Early identification of malnourished individuals will enable health services to give top priority to early nutritional interventions to avoid poor clinical outcome and to save health resources.

CHAPTER 3

The Systematic Review

The influence of nutritional status on clinical outcome of people after a stroke

3.1. The influence of nutritional status on clinical outcome of people after a stroke

Aims and objectives of this systematic review:

- To explore the literature on the nutritional status of patients after stroke, and their clinical outcomes including, length of hospital stay, infections, and mortality rate.
- To determine the influence of deterioration of nutritional status on patients' clinical outcomes.

3.1.1. Introduction

As mentioned in Chapter two (section 2.2), stroke is documented as the third commonest cause of death after coronary heart disease and cancer, and the main cause of physical disability in developed societies (22). Although stroke mortality has been declining over the past few decades in Western countries, the consequences of the residual disabilities are become increasingly relevant (114). One of these disabling factors is undernutrition, which is very common among patients after a stroke. Malnutrition has already been defined (chapter 2, section 2.5) as a deficiency of important nutrients that include energy, protein, vitamins and minerals that might lead to significant negative effects on an individual's body composition and clinical outcome (99).

Malnutrition is not just a potential outcome of stroke; it is has also been considered as a risk factor for stoke. The British Association for Parenteral and Enteral Nutrition (BAPEN) has defined malnutrition as "a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function and clinical outcome" (17, http://www.bapen.org.uk/ introduction to malnutrition/page1 what is malnutrition). This particular definition includes obesity as malnutrition. As previously demonstrated in Chapter two (section 2.3), obesity, dyslipidemia and unbalanced diet are considered as modifiable risk

factors for stroke (30, 31). Therefore, it is important to precisely evaluate and understand the role of malnutrition as a potential consequence and simultaneously, as a cause of a stroke, in order to formulate a clear policy for healthcare providers as a means of reducing the global burden of stroke (30). In addition, the over-consumption of nutrient-dense meals has turned out to be convincing, as also has the difficulty experienced by individuals in following low-calorific foods to minimise body weight in the long term. Beverages that contain sweeteners are strong contributors to the risk of stroke as they add extra sugar, and hence weight gain. A diet rich in whole grains, fruits, and vegetable-rich food might help to reduce obesity and supply adequate amounts of flavonoids, carotenoids, minerals, and trace elements, which in turn can help to reduce risk of stroke and other chronic disorders (30).

The prevalence of malnutrition in stroke patients when admitted to hospital varies widely ranging from 8% and 49% (21, 78), a factor which might be attributed to many causes, one being that nutritional markers and the definitions of malnutrition have been different in the studies reported. For instance, several studies have addressed nutritional assessment or screening tools using different types of nutritional parameters that include a range of anthropometric and haematological markers (8,14, 16), whereas others have relied on clinicians' decisions (3) or patient-generated global assessment (13, 115). The timing of assessment has also varied in these studies with some evaluations occurring within 24 hours (8, 115), others 48 hours (13, 14) or 7 days after the onset of stroke (3). Additionally, in some studies, people after both ischemic and haemorrhagic stroke were assessed together (13, 14, 47, 16), even though malnutrition occurs more frequently in haemorrhagic compared to ischemic patients (8). Malnutrition is considered as an avoidable consequence in patients with acute stroke, and has been used to describe a wide range of nutritional deficiencies. Malnutrition is associated with poor clinical outcome in these patients (47). There are multiple clinical outcome measures that can be undertaken in people after a stroke which include the Barthel index (8), the modified Rankin Scale (mRS), hospital stay (13, 14), post-stroke complications (3), and mortality (6, 14). Patients who are under-nourished often have an increased length of hospital stay and are more prone to complications, including infections, falls, increased possibility of dysphagia, and tube feeding (13). The nutritional screening for risk of malnutrition is paramount in clinical practice to evaluate the influence of nutrition on patients' clinical outcome. However, the nutritional screening is not a simple task because of the following issues; firstly, dietary evaluation is difficult to obtain as a result of

inconsistent reporting and communication problems. Secondly, in patients who are paralysed it is difficult to measure both body weight and the height.

Many methods have been applied in clinical practice to screen for risk of malnutrition and further assessment of nutritional status. As previously mentioned, there is quite a difference between nutritional assessment and nutritional screening in the medical field (72). The application of the nutritional screening tools is the first step in clinical practice, as they are considered to be quick, easy and accurate tools to identify risk of malnutrition. Consequently, selected patients should be subjected to complete nutrition assessments and treatment interventions. In such assessments, well-trained professionals conduct further investigations to determine whether a genuine nutrition problem exists, and if so its nature, and how health services can provide particular nutritional strategies for the patients concerned (72). Several screening tools are available for use in practice such as: MST, MUST, NRS 2002, MNA-SF, SNAQ and Rapid Screen, and SGA and MNA are validated and accepted nutrition assessment measures (73). It is also the case that other indicators like body weight, body mass index, triceps skin folds, and mid-arm muscle circumference are still widely used (116). Some laboratory indices like haemoglobin, total protein, albumen, pre-albumen, and serum transferrin are simple and easily available in practice, but low levels of these indicators occur in several illnesses and do not really reflect a patient's nutrition. Additionally, in all acute disorders, the albumen level tends to fall as a result of increased catabolism and synthesis of acute phase reactant (76).

Clearly, the strengths and weaknesses of each above mentioned method need to be acknowledged in the evaluation of degree of malnutrition, and a combination of more than one marker might be advisable in the absence of one gold standard (15). As referencing in previous chapter , the most precise and accurate tools for measuring body composition in medical practice are dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), and computed tomography (CT). However, there are other tools that are simple, quick, and more practicable to undertake at ward level and in research (98).

This review focuses on how patients' nutrition is tested and the effect of malnutrition on their clinical outcome using.

Several studies have been conducted on the nutritional status of patients after stroke and the effect of under-nutrition on clinical outcome. However, from these it is not clear which is the

most accurate and user-friendly tool for use in medical practice to screen for nutritional risk and/or assess nutritional status.

3.1.2. Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis PRIMSA guideline has been followed in this review (117). All studies have been identified by searching electronic databases and checking reference lists of relevant articles. The search has been applied to: Embase database, Ovid Medline database, The European Society of Parenteral and Enteral Nutrition (ESPEN) abstracts, The British Association for Parenteral and Enteral Nutrition (BAPEN) abstracts, and Cochrane databases (Cochrane Library, Cochrane Methodology Register Database Guide, and Cochrane Database of Systematic Reviews). Medical subject headings (MeSH) were used to search titles and/or abstracts, and the headings included were: "nutrition in stroke"; "malnutrition in stroke"; and "stroke clinical outcome".

Study eligibility and exclusion criteria

Participant type: All adult patients (over 18 years) who had suffered a stroke and been admitted to the hospital, and had undergone some form of nutritional screening and/or assessment as part of their routine assessment, were included. Data on participants after a stroke is presented independently.

Intervention type: Studies selected for review included those evaluating any assessment and/or screening of nutritional status with or without nutritional intervention which included enteral, parenteral nutrition or oral feeding.

There are no recognised exclusion criteria in this review.

Types of outcome measure

Primary outcomes: Incidence of malnutrition, clinical outcomes, clinical complications (pneumonia, chest, and urinary tract infection), pressure sore and recurrent stroke. The definition of infections used in the studies will be recorded.

Secondary outcomes: dietary intake, disability, and biochemistry.

Types of nutritional assessment used in the selected studies:

The nutritional assessment may range from a quick nutritional screening to a comprehensive nutritional assessment. Components may include the following:

1. Nutritional history
2. Clinical assessment (MUST, BIA and MNA)
3. Anthropometric parameters, such as weight, BMI, MUAC, TSF, and AMC.
4. Biochemical parameters like albumin, pre-albumin, transferrin, serum protein, and haemoglobin.

Both nutritional assessments and nutritional screening tools were subjected to validity and reliability tests. The validity of nutritional screening and assessment techniques is established by determining the ability of those techniques to precisely identify the nutritional problem (118); however, sometimes it is very difficult to apply tests of validity in clinical practice. Test reliability means the test is able to give the same results every time it is utilised under different given circumstances (72).

Types of study design

Studies that were case-controlled, cohort studies, randomised controlled trials, and relevant systematic reviews containing appropriate data were collected. All the participants in these studies were patients after a stroke. Studies were restricted to those published in the English language, and to those published in or after 2000 since prior to that date the current methods of measuring body composition were not available.

Data extraction:

Appraisal of study and synthesis

The eligibility of the studies selected was determined systematically. Selected papers were transferred to Endnote X5 (Thomson Reuters, Philadelphia, PA, USA), duplicates were removed; the titles and abstracts were screened to ensure they met the inclusion criteria, and those not meeting these were excluded. The full texts of studies deemed to meet the criteria were then reviewed to ensure compliance.

The information collected from each of the selected papers included the study aims, study design, and subjects' characteristics, which in themselves were: age, gender, BMI, weight, and stroke sub-type. The type of intervention was recorded to provide details of: the method used for assessing nutritional status (whether screening for risk of malnutrition or full nutritional assessment), definition of malnutrition, and clinical outcome.

Critical Appraisal Skills Programme (CASP) checklists (119) were used to assess the quality of the methodology and validity of the results in respect of all the included studies. Different CASP tools available for the type of study (randomised controlled trial, case controlled studies, systematic reviews and cohort studies) and accordingly the corresponding checklist were used to assess each study (Appendices A, B and C) .

3.1.3. Results

Results of systematic literature searches

Sixty five studies were identified, of which seven met the inclusion criteria for the systamatic review. The PRIMSA guidance flowchart shows the search results (Fig. 3.1). Having initially met the inclusion criteria as determined by their titles, abstracts, and reference lists, these seven studies were then read in full to further confirm their eligibility for inclusion.

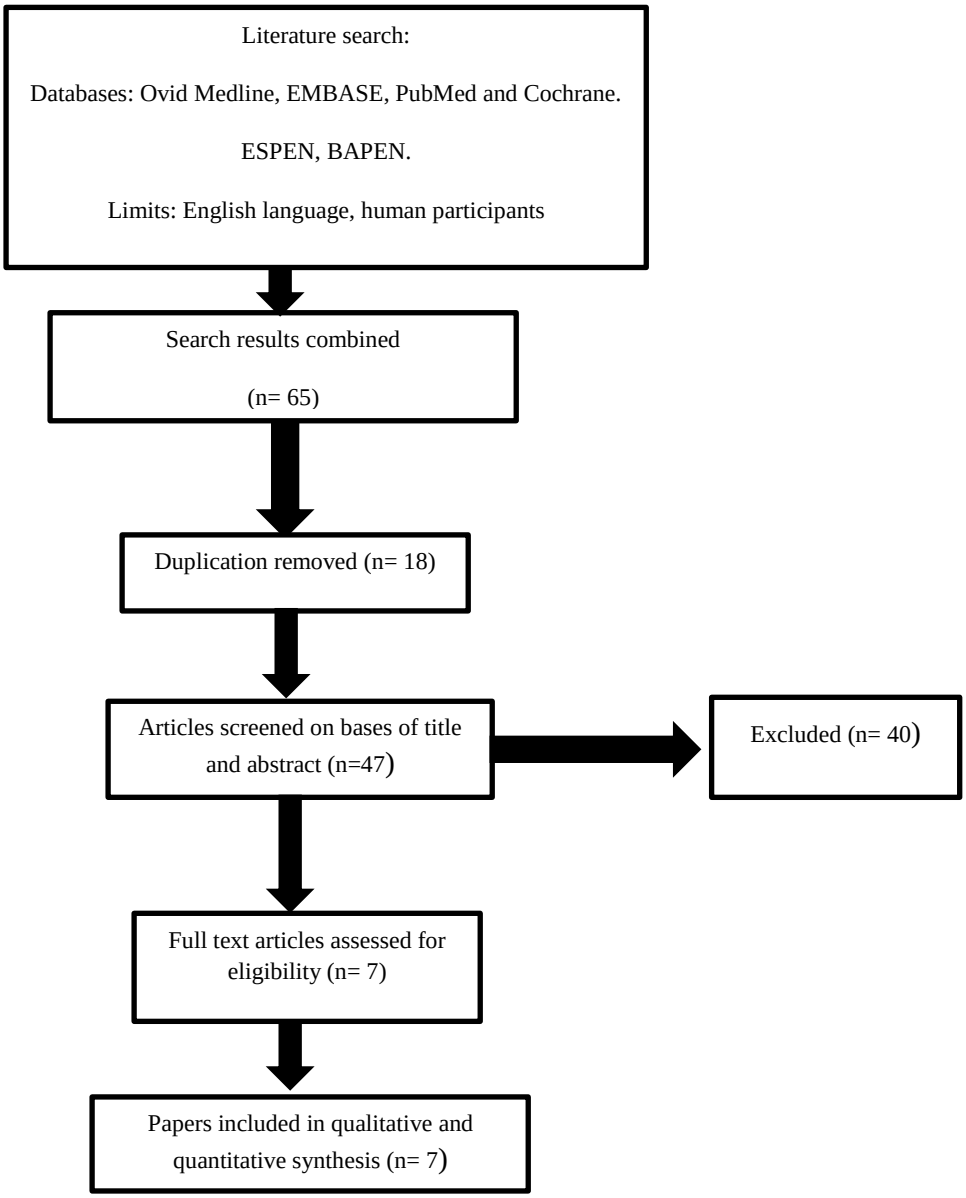


Figure 3.1 PRISMA flowchart showing selection procedure of articles

Characteristics of the studies included

Of the seven studies which met the criteria, four were randomised control trials (25,122-124), two were cohort studies (120, 121), and one was a systematic review (125). In total, 10,798

participants, whose characteristics appear in Table 3.1, were involved in these seven studies. Of the four randomised control trials, two (same centre) were conducted in Norway (122, 124), one in the United States of America (123), and one was conducted across 16 countries, the names of which were not given (110). The two cohort studies were both conducted in the United Kingdom (120, 121); the systematic review reported on 33 trials held in Italy, China, the UK, Australia, USA, Norway, Malaysia, Egypt, and Korea; and 15, 15 and 11 countries were included in FOOD 1, FOOD 2 and FOOD 3, respectively (countries' names not mentioned (125)). All trials were based at a single centre, except for one that included patients from two hyperacute stroke units (121), and two others that were conducted at multi-centres involving over 57 sittings (3, 125).

One study recruited 100 subjects (120) at baseline assessment, but only 38 patients completed in-hospital assessment, the others 62 patients not being included due to following reasons: 51 discharged within two weeks of admission; five withdrew; four had cognitive decline (because the study included verbal assessments and data not reported), and two died. In another study all involved subjects (543) completed baseline and follow-up variables, except for six patients for whom it was impossible to measure weight loss because their usual weight could not be obtained from any source at admission (121). In the trial reported by Lisa et al. (122), although a total of 165 patients were recruited at baseline assessment, only 124 were reassessed and completed the study after three months follow-up due to specific reasons (22 died and 19 refused to attend the follow-up). One hundred and sixteen (123) subjects were recruited in another trial but only 102 patients completed it, since 14 were either transferred to an acute facility or had no completed data about them (123). In the next trial (124), 170 patients were randomised at baseline, but only 124 of these completed and were able to be part of the final analysis due to many reasons (death, withdrawal, weight not obtained, did not have stroke, refused to eat and drink, and refused to participate in the follow-up). In another trial enrolling 3,012, a total of 2,955 (98%) were reported as having been followed after six months; no reasons were given to indicate why the remaining 57 did not participate in the follow-up (3). In the systematic review (125), the authors identified 33 studies involving 6,779 patients but no information was provided about final numbers (dropout rate) at the end of these studies.

Table 3.1 Study characteristics

Authors	Location	Sample size	Age, years, mean (SD)	Gender M/F	Type of stroke	Study design	Follow up
Nip et al. (120)	South London National Health Service Acute Trust hospital, UK	100	69 (15)	47/53	Not available (N/A)	Prospective cohort study	Until discharge
Gomes et al. (121)	Hyperacute stroke units, south London, UK	543	74.7 (13.5)	277/266	Ischemic, Haemorrhagic, and Subarachnoid haemorrhage	Prospective cohort study	6 months
Lisa et al. (122)	Østfold Hospital Trust in Østfold County, Norway	124	79.1 (7.1)	60/64	Ischemic and cerebral haemorrhage	Randomised control trial	3 months
Rabadi et al. (123)	Burke Rehabilitation Hospital, USA	116	74.29 (11.8)	68/10	Ischemic and haemorrhagic stroke	Randomised control trial	Until discharge
Lisa et al. (124)	Østfold Hospital Trust in Østfold County, Norway	124	79.1 (7.1)	60/64	Ischemic and cerebral haemorrhage	Randomised control trial	3 months
Food Trial Collaboration (3)	One hundred and twelve hospitals in 16 countries included in this trial	3012	73.3 (12.0)	1520/1492	Ischemic and cerebral haemorrhage	Randomised control trial	6 months
Geeganage et al. (125)	Italy, china, UK, Australia, USA, Norway, Malaysia, Egypt, Korea, in FOOD 1 (15 countries included), FOOD 2(15 countries included) and FOOD 3 (11 countries included)	6779	71 (--)	N/A	Ischemic or haemorrhagic	Systematic review	6 months

Continue-table 3.1

Authors	Method of nutritional assessment	Criteria used for definition of nutritional status	Intervention needed (for RCT)	Relevant comments
Nip et al. (120)	Nutritional screening and Nutritional assessment tools	MNA and BMI	-	-
Gomes et al. (121)	Nutritional screening tool	MUST	-	-
Lisa et al. (122)	Nutritional screening and Nutritional assessment tools	Body weight, BMI, MUAC, TSF,AMC, MUST score and BIA	Nutritional intervention	Any patients presented with at least one marker of risk of malnutrition were included
Rabadi et al. (123)	Nutritional screening tools	Body weight, % IBW, albumin, pre-albumin, transferrin	Intensive nutritional supplement	-
Lisa et al. (124)	Nutritional screening tools	MUST, BMI, TSF, MUAC	Nutritional intervention	Body mass index's lower cut-off point was set to $\leq 20 kg/m^2$
Food Trial Collaboration (3)	Nutritional screening tools	Bedside assessment , body weight, height, dietary history and blood tests	No nutritional intervention	Bedside assessment has been done by professionals without accurate criteria or good training
Geeganage et al. (125)	Nutritional screening tools	BMI, Demiqute index, malnutrition risk, weight, MAC, albumin level	Swallowing therapy for dysphagia; Feeding and fluids intervention	BMI has been replaced by Demiqute index where height is difficult to take and in old people.

Abbreviations: SD, standard deviation; N/A, not available; MNA, mini-nutritional assessment; BMI, body mass index; MUST, malnutrition universal screening tool; RCT, randomised controlled trial; IBW, ideal body weight; TSF, triceps skinfold thickness; MUAC/MAC, mid upper arm circumference/mid arm circumference;

Regarding the gender of participants there was an approximate homogenous distribution. In study (125), however, no information about gender was provided.

Regarding the age of participants, the mean age in the different studies ranged from 69.1 to 79.1 years.

The types of stroke reported were ischemic stroke and haemorrhagic stroke in five trials (123-125), and ischemic stroke, subarachnoid haemorrhage, and haemorrhagic stroke in one study (121). Another study (120) did not report on the type of stroke included.

Five studies used nutritional screening tools as a method of nutritional assessment (25,121,123-125), whilst two studies used both nutritional screening tools and nutritional assessment tools as methods of nutritional assessment (120,122).

Four RCTs addressed the nutritional interventions as an intervention (122-124,125), but one study has no nutritional intervention (3).

In both reports by Lisa et al. (122,124), the risk of malnourishment was screened for within 7 days after admission using the MUST; the cut-off value for BMI in older people was set at ≤ 20 kg/m^2.

In the Geeganage et al. (125) review, it is shown that where the height is hard to measure and in older people, the Demiqute index can be used instead of BMI as a subjective assessment of nutrition.

Assessment quality of included studies

Using the PRISMA guidance, seven studies were subjected to quality assessment and thus, exposed to the CASP checklist according to their type.

The studies of Nip et al. and Gomes et al. (120, 121) are classified as cohort prospective studies, so the CASP cohort study checklist was used to assess their quality. In these studies clearly focused questions were addressed in terms of studied population, risk factors, and clinical outcomes (Appendix A). Patients were recruited in an appropriate way and all who met the inclusion criteria were included. The measurements used in these studies were objective, and had been validated to maximise the overall quality of the research efforts involved. Furthermore similar measurement methods were adopted to evaluate the outcome in the different groups to maximise the quality. In respect of study 120, both patients and assessor were blind at the time of the outcome measurement, whereas it was unknown whether subjects and assessors were blind or otherwise in study 121. The authors in one study addressed certain confounding factors (potentially predicting rehabilitation outcomes) in their

discussion section. Specifically, they identified: age, stroke severity scored using the modified National Institute of Health Stroke Severity score (mNIHSS), mBI, nutritional status (MNA), and energy and protein intake at first assessment. However, one such factor was omitted, namely the type of stroke (whether ischemic, haemorrhage or subarachnoid haemorrhage stroke) (120). In the study by Gomes et al. (121), the authors identified all the important confounding factors. They took account of such variables in the results section, providing comments on: age, gender, ethnicity, severity of stroke, type of stroke, hypertension, diabetes, dyslipidemia, smoking, ischemic heart disease, heart failure, atrial fibrillation, previous transit ischemic attack and heavy alcohol consumption. These different variables may have an effect on clinical outcome (6-month mortality, LOS, and hospitalisation costs). As observed in this study, age, severity of stroke, hypertension, ischemic heart disease, and heart failure were associated with high mortality rate. Furthermore, age, severity of stroke, diabetes mellitus, and heart failure were significantly associated with LOS, and hospitalisation costs.

In the former study (120) which began with 100 patients, only 38 (38%) subjects completed the second assessment in the week before discharge. Fifty one (51) patients were discharged within two weeks of admission, five withdrew, four had cognitive decline, and two died (62 in total). Therefore, these 69 patients who were lost to follow-up may have had different outcomes from those observed at their last assessment. Indeed, the two week duration of this study seems to be insufficient to reveal the effect of nutritional and dietary factors on rehabilitation outcomes. In another study (121) lasting for six months, 543 patients were recruited and completed the follow-up assessment.

The results of first study (120) revealed that younger age, lower Barthel index, and a higher energy intake in the early stages of admission predict the extent and rate of restoration of functional ability by discharge. On the other hand in the Gomes et al. (121) study, the results showed a highly significant increase in mortality with increasing risk of malnutrition ($P < 0.001$). This association remained significant after adjusting for age, severity of stroke, and a range of stroke risk factors ($P < 0.001$). For those patients who survived, the LOS and hospitalisation costs increased with increasing risk of malnutrition ($P < 0.001$ and $P = 0.049$, respectively). This association remained significant in the adjusted model ($P <0 .001$ and $P = 0.001$, respectively).

There were no confidence intervals available in the results obtained by Nip et al. (120), whereas in the Gomes et al. (121) study, the 95% CIs of different variables that included risk of malnutrition (medium or high), age, severity of stroke, hypertension and heart failure on six months mortality were as follows: 1.59-7.73, 3.23-9.69, 1.02-1.08, 1.05-1.13, 1.3-3.8 and 1.54-6.64, respectively. For further explanation, the authors were 95% confident that the means of the different variables relating to the patients studied were located between the above- mentioned values. The narrower the values of the confidence intervals, the more precise are the results.

As a large number of patients were excluded from the beginning (n=243) due to multiple reasons, and a further 69 subjects were lost before discharge also due to other causes, meaning that only 31 patients completed the final assessment, it is hard to have confidence in the results from study 120. In contrast, the results obtained by Gomes et al. (121) are convincing since the association was strong enough even after adjusting for a range of confounding factors, and the study's design and methodology were sufficiently robust to lend reliability to the results.

Although study 120 was conducted in the UK at the South London National Health Service Acute Trust Hospital, it is difficult to generalise the result to the local population, since it is not known whether medical management was the same in that place and in the local health settings. However, the results agree with some previously published evidence. In study 121, the same observations can be made since in this one also it is unclear whether the medical intervention was same or not. The results of this study were also consistent with other available evidence.

Although the results from study 120 are supported by the general nutrition literature, as this was only a small study, a much larger one involving multi-centres is required to examine the effects of nutritional and dietary factors on patients' rehabilitation outcomes. In the study conducted by Gomes et al. (121), however, the chance of clinical practice being able to benefit is very good, due to the fact that a relatively large sample size was involved, and the results are consistent with the nutritional screening that carried out. Moreover, the study's outcomes are in line with those from other published studies, thereby confirming their validity as a basis for recommending changes to health policy-makers

For the other four studies (3,122-124), the CASP randomised controlled trial checklist was used. In all four of these RCTs (3,122-124), as shown in Appendix B, the trials had a clear

focus and identified the populations studied, the interventions and comparators, and the outcomes which were properly considered. Additionally, the patients were assigned to their treatments in a randomised way via a computer-generated randomisation list obtained by an individual not involved in patient assessments (122, 123). People recruited in trial 123 were randomised prospectively using sealed, opaque envelope block randomisation of ten patients (five subjects in each group) at a time. Envelopes were similar to both study groups. Subjects were allocated to either the intervention or control group by a designated dietician not associated with the study. The FOOD trial (3) comprised three randomised control trials, all following the same randomisation system. When all baseline data were entered and checked, allocation to treatment was made by computer. Randomisation was stratified on the basis of the randomising study personnel's judgment of the patient's nutritional status as under-nourished, normal or over weight, and the allocation sequence was concealed from both patients and researchers.

All the subjects who entered these trials were properly accounted for at their conclusion, all the trials completed their designated durations, and all subjects were analysed in the same groups to which they were randomised.

In two trials (122, 124), both patients and health workers were blind to treatment but health workers were not blind to which treatment the patient was assigned at baseline time. In order to minimise the possibility of bias arising from not being blind to patients' nutritional interventions at their study entry, all information about such allocations were made inaccessible to the assessors during the three month trial periods. In the other two trials (3, 123) patients, health workers, and assessors were blind to treatment allocation, baseline data, and assessments.

In the three trials 122-124, all groups were similar at the start of the trial and there was no significant difference in terms of age, gender, and social class between them. In the other trial (3), the undernourished group was older and lived alone before stroke more frequently than the other two groups. Although adjustments were made for patient age and living circumstances, thus weakening these relationships, they did nonetheless, remain statistically significant ($P \leq 0.05$).

In all trials the groups were treated similarly inside the hospital apart from the nutritional intervention.

The outcomes measured in the trial reported by Lisa et al. (122) included: body mass, fat and fat-free mass. The primary outcome was clearly determined. Body composition was assessed using anthropometry and bioelectrical impedance analysis (BIA) to evaluate body mass, fat and fat-free mass at baseline, after one week and after three months of admission in both groups. As the results reveal, the intervention group had less body weight loss after one week compared with the control group. Body weight loss and fat mass loss were significant in both control and intervention groups in both males and females. Nevertheless, body mass loss and fat mass loss in females were significantly smaller in the intervention group compared with the control group. Moreover, the evaluation of fat and fat-free mass correlated well between BIA and anthropometry, and a high correlation was also found between mid-upper arm circumference (MUAC) and body mass index (BMI). In the paper by Rabadi et al. (123), the primary outcome was a change in the total score on the Functional Independence Measure (FIM), which was clearly specified, whereas the secondary outcome measurements included the FIM motor and cognitive sub-scores, length of stay, 2-minute and 6-minute timed walk tests, and discharge disposition. There were improvements in measures of total FIM, FIM motor sub-score, 2-minute and 6-minute timed walk tests in subjects on intensive nutritional support compared with those on standard nutritional support. Moreover, patients receiving intensive nutritional supplements were able to go back home rather than to institutional centres. In the trial reported by Lisa et al. (124), the percentage of patients with weight loss ≥5% had this addressed as a primary outcome, whereas quality of life (QoL), handgrip strength, and length of hospital stay were considered as secondary outcomes. Moreover, the primary outcome was clearly defined in this study. There was a significantly lower weight loss, higher increase in QoL score and handgrip strength in the intervention group compared with the control group, whilst there was no difference in the length of hospital stay between the groups. In the last trial (3) the clinical outcomes measured included: post-stroke complications (pneumonia, other infections, pulmonary embolism, deep vein thrombosis, pressure sores, gastrointestinal haemorrhage and other complications), length of hospital stay, functional ability (modified Rankin Scale (mRS)) and mortality rate. The primary outcome was unspecified. The outcomes were as follows: the undernourished patients had more pneumonia, other infections and gastrointestinal bleeds than others; patients of normal nutritional status were less likely to develop pressure sores than others; the undernourished patients were significantly more likely to be dead or dependent than patients of normal weight; there was no significant difference in length of hospital stay between study groups.

In the Lisa et al. study (122) the accuracy of the estimate of the treatment effect can be assessed by referring to the Confidence Interval (CI) or correlation (r value) of the association between mid-upper arm circumference (MUAC) measurements and body mass index (BMI). The authors found that there was a strong correlation (r = 0.87) between MUAC and BMI. That is mean MUAC can be used as a marker of nutritional risk instead of BMI in immobilised stroke patients.

The accuracy of the estimate of the treatment effect in the Rabadi et al. paper (123) was as follows: there was 95% confident that the difference in total FIM score at admission and at discharge in control group was from -0.17 to 46.05, the difference in motor FIM sub-score of same group was from -2.18 to 35.6, of cognitive FIM sub-score the difference was from -2.55 to11.29, of 2-minute walk test the difference in feet ranged was from-78.44 to 166.4, and 6-minute walk test the difference was from -218.6 to559.87 feet, whilst in the intensive group, there was 95% confident that the difference in total FIM score at admission and discharge was from 3.54 to 59.44, in motor FIM sub-score the difference was from 1.06 to 47.44, in cognitive FIM sub-score the difference ranged from -1.8 to 11.02, in 2-minute walk test the difference was from -54.04 to 257.24 (feet), in 6-minute walk test the difference from -95.74 to 694.3 (feet).

In study 124 (Lisa et al.) there was a higher increase in handgrip strength among the intervention group compared with the control group (P =0.002), and there was 95% confidence that the difference between study groups (intervention and control) was from 1.0 to 4.2 (kg). Furthermore, total daily energy intake was higher in the intervention group than in the control group (P =0.032), and there was 95% confidence that the difference between both groups was from 58 to 1216 (kJ/day), whereas in the daily protein intake the difference was not statistically significant between the two study groups (P =0.34) and there was 95% confident that the difference in this case was from 3.3 to 9.8 (g/day).

The accuracy of the estimation of the treatment effect in Food Trial Collaboration (3) was determined by searching for CIs as follows: From logistic regression the undernourished people were significantly more likely to die during follow up (six months) than people of normal weight (there was 95% confidence that the difference in mortality rate between two groups ranged from 1.78 to 3.02). In contrast, the overweight group was not significantly different from the normal weight group (there was 95% confidence that the difference in mortality rate was from 0.65 to 1.08). Additionally, the undernourished people were more

likely to be dead or functionally dependent (a modified Rankin score of 3 to 5) than people of normal weight at six months' follow-up (there was 95% confidence that the difference in mRS between the two groups was from 1.5 to 2.88), while no significant difference in survival and independency was evident between overweight people and normal weight people during the same period (with 95% confidence that the difference in survival and independency between study groups ranged from 0.77 to 1.18).

The trial results can be applied to the UK as the studies were conducted in European societies which are highly consistent with UK society in terms of patient characteristics (ethnicity, age, and social class).

All the important clinical outcomes were considered in these trials, and no other information pertinent to the final decisions was required.

Finally, the important findings in these trials make the pros outweigh the cons, i.e., in general the benefits outweigh the harms and costs as shown in the conclusions reached. Hence, the accumulative recommendations of these studies can be applied in practice, thereby avoiding the unnecessary waste of health resources, and preserving health budgets.

Geeganage et al. (125) conducted a systematic review using the CASP checklist (Appendix C). The process they followed was as follows:

They clearly focused their paper in respect of the population studied, the risk factors, and outcomes.

They searched for studies that addressed the review question and all collected studies (n=33) were Randomised Control Trials (RCTs). All relevant and important trials were included, and searches were made of several bibliographic databases (the Cochrane Stroke Group Trial Register, Medline, Embase, CINAHL, and the Conference Proceeding Citation Index-Science). Additionally, the reference lists of relevant trials, and Current Controlled Trials were examined and the researchers involved were contacted. Trials in all languages were included; with translations being made of trials published in languages other than English was arranged. Moreover, all efforts were made to locate details of unpublished trials, and those ongoing.

In assessing the quality of the studies included, Geeganage et al. obtained the full text of all relevant studies based on the review inclusion criteria, and any disagreements about

fulfillment of the criteria for inclusion were resolved through discussion and consultation with another reviewer on the team.

The results of the included trials were displayed. Of 33 studies, the results from 18 were similar; these trials assessed the effect of swallowing therapy on functional outcome (death or dependency/disability). Results from five other studies were similar; they compared the effect of Percutaneous Endoscopic Gastrostomy (PEG), with that of Nasogastric Tube (NGT) feeding on the same functional outcome. The results from another seven trials were similar, reporting the effect of nutritional support on functional outcome. One study focused on evaluating the effect of feeding time on functional outcome.

The overall results of the review and the CIs were: Swallowing therapy had no significant effect on case fatality or combined death or dependency (functional outcome). However, dysphagia at end-of trial was reduced by acupuncture and behavioural interventions. Route of feeding did not differ for case fatality or the composite outcome of death or dependency, but PEG was associated with fewer treatment failures and gastrointestinal bleeding, and higher feed delivery and albumin concentration. Although looped NGT versus conventional NGT feeding did not differ in respect of end-of-trial case fatality or death or dependency, feed delivery was higher with looped NGT. Timing of feeding: there was no difference for case fatality, or death or dependency, with early feeding as compared to late feeding. Fluid supplementation: there was no difference for case fatality, or death or dependency, with fluid supplementation. Nutritional supplementation: there was no difference for case fatality, or death or dependency, with nutritional supplementation. However, nutritional supplementation was associated with reduced pressure sores, and, by definition, increased energy intake and protein intake.

The results obtained from this systematic review undertaken by Geeganage et al. can be applied to the local UK population, since many of the trials included were conducted in the UK, and in other European countries, where the local settings are unlikely to show disparities.

All the important outcomes primary and secondary were considered.

Regarding the benefits of this review, it can be argued that the information provided by it is useful for practitioners since the pros of various interventions can be seen to outweigh the cons. For example, acupuncture and behavioural therapy may reduce dysphagia in people

after a stroke, and other evidence suggests that patients may do better if the feeding process is started as early as possible after stroke onset. Furthermore, for those patients who need long-term feeding supplements, PEG might result in less treatment failure, less gastrointestinal bleeding, and better feed delivery than NG. Finally, nutritional support may reduce the possibility of bed sores in those people who are admitted with malnutrition or who are at risk of malnutrition.

Methodology of included studies

All the studies included in this review, addressed a clearly focused question, and all except one (122) concentrated on either clinical or quality of life outcomes in relation to nutritional status or nutritional supports. All the studies recruited their samples in an appropriate manner, with the use of stroke centre and electronic patient databases for identification of eligible patients and data collection. Three studies recruited large sample sizes (3,121,125) which allowed for increased generalisability, whilst four recruited relatively small sample sizes (120, 122, 123 and 124). The largest sample size was 6,779 which came from a review of 33 studies, and which involved all stroke-referred patients (125). In all studies, the recruited subjects had a confirmed diagnosis of stroke, and validated and objective measurements were used to assess clinical outcomes. All studies' exposure and/or intervention as well as outcomes were blinded (3,120, 122-124). In the review of 33 trials (125), seven studies were double blind, one study was single blind, and in eight studies the outcomes were assessed blindly, except for one cohort (121) and 17 studies where the blinding information was not available or unclear. All studies used analysts who were well-qualified in malnutrition assessment/treatment intervention and clinical outcomes (3,120-125).

Nutritional interventions in the included studies

The aim of the study by Nip et al. study (120) was also to investigate the influence of nutritional and food intervention on rehabilitation outcomes. In this study, the patients' dietary intake via both hospital meals and non-hospital snacks during a 24-hour period, was calculated. Patients had eaten mean (SD) 5,792 (2,883) KJ energy and 53.6 (20.4) g protein daily within two weeks of hospital admission. The pattern of dietary intake within two weeks of admission included normal oral feeding and NGT, and of the patients involve, 26% were allocated to texture-modified food (soft and puree), while 83% had normal texture diets, 17%

had soft, and 3% received pureed diets before discharge. The hospital's food data were analysed using nutritional composition information by the dietetic department and Diet plan 5 for Windows (Forestfield Software Ltd., Horsham, UK), and for food supplied from outside the hospital, the nutritional amount was analysed using food composition tablets and an immigrant food supplement. These sources of food data were compared with national recommendations, and the following results obtained: before discharge, energy intakes were 6% higher than at first measurement, and protein intakes before discharge were 3% higher than earlier measurements. Additionally, the results showed that protein and energy consumption were significantly associated with food provided by the hospital early after admission and before discharge (both $P<0.001$). As a result of natural stroke recovery and rehabilitation, the patients' functional activities were expected to improve with time. However, this study also revealed that early energy consumption (but no protein intakes) within two weeks of admission can significantly predict the extent and rate of improvement of functional activities (measured by mBI). It should be noted that the influence of energy intakes early after admission on functional abilities had not been discussed in the literature before this study, and that the report highlights the importance of energy intake as a modifiable rehabilitation factor for patients after a stroke. Although this was a small study, it nonetheless signals the important need for healthcare services to develop nutritional intervention at an early stage to improve clinical outcomes for stroke patients.

There was no nutritional intervention in study 121.

In study by Lisa et al. (122) nutritional intervention occurred through giving energy and protein-enriched food within the first week of admission. The patterns of dietary intake included oral feeding and/or enteral tube feeding (offered to patients with severe dysphagia). The assigned individual nutritional consumption plans were calculated using Schofield equations and prepared for each participant, showing food type, amount, and method of eating. Intervention patients were discharged with nutritional advice from the dieticians to prevent the onset of malnutrition (three months follow up). In contrast, in the control patients there was no further nutritional intake assessment, and they were not given an individualised food plan. Both groups were nutritionally evaluated after one week of admission and after three months follow up. The study demonstrated that patients who had individualised nutritional support experienced lower weight loss than those in the control group who had routine nutritional supply after one week of admission. The amount of energy intake in the intervention participants was significant and 14% more than that of the control participants,

which might explain the lower weight loss among the intervention patients than in the control patients. On the other hand, at three months follow up, both groups had significant weight and fat loss but the weight and fat loss among women in the intervention group was lower than in women in the control group. One explanation for this outcome is the nutritional advice given before discharge, and the fact that the women in the intervention group were given a mean of 83 KJ and 0.9 gm protein per kg which were higher amounts (and more significant) than those received by the control group during their stay in the hospital. These results suggest that acute stroke patients who receive individualised nutritional intake after admission to hospital might experience less body weight loss whilst in hospital than those in the control group. Moreover, this nutritional support for females in the intervention group might reduce the catabolism after three months follow up.

In the study by Rabadi et al. (123), the focus was on assessing the effect of adding an intensive nutritional supplement to patients' diet, to eventual outcome as compared with normal diet supplements in hospital. The dose of both supplements was the same (120 ml, four times daily), but the intensive nutritional support contained 240 calories and 11 gm of protein, as against the standard nutritional supplement of 127 calories and 5 gm of protein. Both supplements were accompanied by minerals and vitamins. The nutritional supplements were given within three days of admission, and stopped when patients were discharged from the hospital. The results showed that both study groups gained weight, but those in the intensive supplement group gained weight more than their counterparts in the control group. However, the difference was insignificant (*P* 0.37). Those patients who had received intensive nutritional support did, nonetheless, demonstrate more functional independence and were more able to go as opposed to requiring institutional care. Overall, the study highlights the importance of early intensive nutritional intervention in improving patients' clinical outcomes, and saving health resources.

In another study (124) the nutritional treatment in the intervention group was via energy and protein-rich meals to maintain and improve patients' nutritional status. As some patients had sever dysphagia, the pattern of dietary supply was oral or enteral tube feeding according to the patient's swallowing ability. Total energy requirements were calculated using an appropriate physical activity level factor and a specific nutritional plan was prepared for every individual which included details of the type, amount, and method of feeding. Before hospital discharge the patients were given verbal and written advice to avoid malnutrition, and no patient was subsequently contacted until the three months follow up. The control

group, on the other hand received standard nutritional supplements, again via oral or tube feeding depending upon their swallowing abilities. They did not receive any individual nutritional assessments, plans for monitoring their dietary intake or treatment to deter malnutrition. On contact at the three month follow up stage, unplanned weight loss was reported at ≥5%, and secondary outcomes were recorded via a quality of life score, handgrip strength, and hospital stay. The study's results demonstrated that the intervention group who had individualised, nutritional intakes, and appropriate dietary advice, had less chance of becoming malnourished and losing weight in the three month period afterwards, when compared to the control group. Additionally, there was a significant improvement in handgrip strength and quality of life score compared to the routine care group. The intervention group had significant energy consumption during their hospital stay as compared with the control group, which had no nutritional assessments, monitoring of dietary intake, or other treatment procedures. This limitation might lead to the conclusion that the study provides only weak evidence of the effect of one strategy over another, and thus offers insufficient advice to health policy-makers.

The FOOD trial (3) consisted of 3 RCTs with the same randomisation, data collection, and follow-up systems. Its purpose was to compare between different nutritional management approaches and their clinical outcomes after six months of follow up. In Trial 1, patients who were able to swallow within one month of admission were allocated into two groups as follows: a group with a normal diet and another group with normal diet plus nutritional supports, both groups were monitored until discharge. Patients in Trial 2, who were unable to swallow within seven days of admission, were assigned into two groups as follows: one group given early tube feeding, and a second group given delayed enteral feeding for at least seven days (fluids were given using parenteral fluid as required). In Trial 3, the patients who were unable to swallow within the first month of admission were randomised into two groups, the first being tube-fed using NGT, and the second group being tube-fed using PEG. This trial aimed to determine whether intensive nutritional supplements improve survival and functional outcomes. It concluded that nutritional status is associated with patient outcomes. However, the reports of this trial have been published without clear evidence as to whether this association (between intensive nutritional regimens and outcomes) is present or not. Surprisingly, in the next FOOD trial that was undertaken in 2005 (126), it was revealed that there was no association between intensive nutritional supplements and outcomes. This

evidence might warrant further research about the role of very specific nutritional interventions and the method of feeding in reaching particular clinical outcomes.

Analysis of results of nutritional status effects on clinical outcome

In the Nip et al. paper (120), the nutritional status was assessed using Mini-Nutritional Assessment (MNA) and Body Mass Index (BMI). Accordingly, a small sub-group of patients were identified as malnourished or at risk of malnutrition (according to MNA) and with low BMI. This small study demonstrated that insufficient energy intake throughout hospitalisation was persistently associated with a high risk of malnutrition. Consequently, this study concluded that dietary energy intake predicts rehabilitation outcomes (Appendix D).

The paper by Gomes et al. (121) demonstrated a significant increase in mortality, LOS, and hospitalisation costs with increasing risk of malnutrition (using MUST).

In the Lisa et al. trial (122) both anthropometry measures and BIA were used to assess body composition (body-, fat-and fat-free mass) at baseline, after one week and after three months of admission in study groups. However, how these changes in nutritional status affected the clinical outcomes were not mentioned in this study.

Rabadi et al. (123) found that the comparisons in nutritional status (assessed by body weight, percentage of ideal body weight (%IBW), albumin, pre-albumin and transferrin) of both study groups at admission and discharge were not statistically different. Additionally, there was no mention of the effect of nutritional status on either primary or secondary outcomes.

The Lisa et al. trial (124) demonstrated no significant statistical difference in body mass loss ($\geq$ 5%) between the intervention group and standard group after three months follow-up (P *=0.055)*. However, a post-hoc analysis was conducted as a result of which 38 subjects were excluded from the standard group with dietary recording, which may have affected routine care and improved dietary support in the standard group. Hence, a significant reduction was seen in the proportion of subjects with $\geq$ 5% body mass loss in the intervention group compared with in the standard group (P = 0.032). This analysis supported the evidence that dietary intervention improves weight control when compared with routine care. Relating this finding to functional outcomes, the intervention group who had a low proportion of body weight loss, had a substantially higher QoL score (P = 0.0090) and handgrip strength (P = 0.002) than the control group.

The observational findings from the FOOD trial (3) concluded that the undernourished group had more post-stroke complications than others. Moreover, undernourished subjects were more likely to develop pressure sores, to die, and become dependent than others. In accordance with previous evidence, it was shown that an early nutritional status assessment after a stroke can be considered as an independent predictor of long-term outcome.

In the Geeganage et al. review (125), the authors addressed the effectiveness of intervention procedures on dysphagia and feeding and fluid support on functional outcome and mortality rate in dysphagic patients after a stroke (within 6 months after stroke). The conclusion revealed that swallowing therapy and feeding and fluid supplementation had no effect on case fatality or functional outcome (combined death or dependency). Nevertheless, authors concluded that behavioural and acupuncture interventions were associated with reduced dysphagia, and pharyngeal electrical stimulation was associated with pharyngeal transit time reduction. Furthermore, PEG feeding reduced treatment failures, gastrointestinal bleeding, and had higher albumin level and feed delivery. Nutritional support also improved protein and energy intake, and reduced pressure sores. The diagnosis of undernutrition and risk of malnutrition in these patients was based on BMI, Demiqute index (as alternative to BMI, where measurement of height is impractical, and in old patients, where BMI is unreliable), malnutrition risk, anthropometric (weight, MAC) and biochemical (albumin) measures. However, nutritional status measures were considered as secondary outcomes in this review. Out of 33 studies, only two demonstrated that there was no effect on albumin level after behavioural interventions within six months from stroke onset. In another three studies PEG was associated with high albumin level, whilst in yet another three 3 studies PEG was also associated with high MAC measurements. In respect of looped nasogastric tube (NGT) and conventional nasogastric tube interventions, two studies demonstrated that there was no effect of looped NGT on albumin level. With this in mind, it is important to note that PEG was associated with both higher albumin concentration and MAC values than was NGT. PEG was also associated with reduced treatment failures and gastrointestinal bleeding. Accordingly, both high albumin level and MAC were also associated with reduced gastrointestinal bleeding and treatment failures; hence, they can be used as dependent predictors of clinical outcome

Nutritional status measures in the included studies

All studies assessed nutritional status in participants using one or more of the following: MNA, BMI, MUST score, body weight, MUAC, TSF, AMC, BIA, % IBW, albumin, pre-

albumin, transferrin, Bedside assessment, height, dietary history, and Demiqute index as shown in Appendix F. MNA and BMI were used to assess nutritional status in one study (120), since that defined malnutrition risk according to MAN and BMI results. According to the MNA classification, only 66 (66%) and 28 (74%) of subjects were categorised as at risk of malnutrition (i.e. with MNA score ≥17 and <24) when scored within two weeks of admission and before discharge respectively, whilst at the first assessment, 18 (23%) of patients had BMI values < 20 Kg/m2 compared to 9 (26.5) of the participants assessed before discharge. This study demonstrated that insufficient energy intake accompanied by rising malnutrition risk throughout hospitalisation and energy intake can predict rehabilitation outcomes (changes in mBI [modified Barthel index] scores between the first assessment and discharge, and the index of rehabilitation efficiency). In one study (121) the MUST score was used to evaluate risk of malnutrition, which has already indicated, was associated with increased mortality, LOS, and hospitalisation costs. In another study (122), the MUST score was used to assess nutritional risk status within seven days after admission to recruit eligible patients. Minor modifications were made for elderly participants, namely the cut-off value for BMI was set at ≤ 20 kg/m2. Subjects with at least one marker out of three (BMI, unintentional weight loss, and the effect of acute disease) were included in this study. Anthropometry measures (weight, BMI, MUAC, TSF, AMC), and BIA were conducted to evaluate changes at baseline and after three months. However, neither MUST nor anthropometry measures changes were used to assess their influence on outcomes. In study 123, the authors assessed nutritional status at admission and before discharge using weight, %IBW, albumin, pre-albumin and transferrin. Statistically there were no differences between these measures at admission and at discharge. Moreover, the influence of measures on primary (FIM total score) and secondary outcome (FIM motor and cognitive sub-scores, LOS, 2- and 6-minute timed walk tests and discharge deposition) was unmentioned. The MUST score was used as an indicator of malnutrition risk among patients after a stroke and accordingly 54.1% were identified as being at such risk (124). BMI, TSF and MUAC were also chosen to identify patients as being malnourished at inclusion, and consequently, 19 participants were identified as being undernourished. Interestingly, in this study the intervention group had less weight loss, higher QoL, and handgrip strength than the control group. In the FOOD trial (3), the authors identified patients as undernourished, normal or overweight on the basis of bedside assessment (accurately assessed BMI) or when practical, using weight, height, dietary history or blood tests. With this in mind, nutritional status

assessment after a stroke can be used as an independent predictor of long-term clinical outcome.

Although the nutritional status assessment based on BMI, Demiquet index, nutritional risk score, anthropometric measures and biochemical markers was conducted to assess malnutrition or undernutrition in this review, only nutritional measures (weight, albumin and MAC) were considered as secondary outcomes (125). Taken into consideration, the effects of PEG (as one feeding route) on functional outcome and death in patients with dysphagia, were only associated with high albumin concentration, MAC values, and less post-stroke complications (treatment failures and gastrointestinal bleeding).

Risk of bias within objective measurements

The objective measures adopted in the studies to remove the possibility of bias, were reviewed, from which it was seen that all studies selected objective criteria to assess undernutrition/treatment interventions. In this connection, all studies demonstrated a particularly low risk of bias owing to the use of well-trained and blind analysts (3,120, 122-125). However, some studies were vague about whether analysts were blind to exposure/intervention and clinical outcomes or not (121, 125).

3.1.4 Discussion

This systematic review aimed to assess the effect of nutritional status on clinical outcomes in people after a stroke. Two studies addressed the effectiveness of nutritional status as an independent predictor on the patients' outcome (3, 121). One of these demonstrated that risk of malnutrition (using MUST) is an independent predictor of mortality, LOS, and hospitalisation costs six months after a stroke (121). In the other study it was revealed that people with undernutrition immediately after a stroke are more prone to reduced survival, functional ability, and independency after six months of stroke onset (3). Four of the other studies used nutritional screening tools and/or nutritional assessments to evaluate nutritional status in patients after a stroke to determine the efficiency of nutritional interventions on clinical outcome (120, 122-124). Only one study addressed the effectiveness of intervention for the treatment of dysphagia and nutritional support in patients after a stroke by using nutritional screening tools (125). Clinical outcomes measured in the studies included

mortality (3,121,124), length of hospital stay (3,121,123-125), functional ability (3,120,125), discharge destination (123,125), body composition (122,124), quality of life (124,125), index of rehabilitation efficiency (120), hospitalisation costs (121), total functional measure (123), handgrip strength (124), and post-stroke complications (3).

The paper by Gomes et al. (121), with a relatively large sample size and hence low risk of bias, especially demonstrated that the association between risk of malnutrition and clinical outcome was statistically significant according to the risk grade. That is, the greater the risk of malnutrition, the higher the risk of death, the longer the LOS, and the greater the hospitalisation costs. However, the lack of data regarding body weight change during the six months preceding the follow up, the absence of any information about the percentage or number of participants who were seen by the dietician, and the kind and length of any nutritional treatments that the participants may have received is a shortcoming of the study. Furthermore, there is no information about the percentage of risk of malnutrition on discharge. Hence, further detail is required to see how many patients received nutritional supplements and what the influence of this was on their clinical outcomes.

In the Food Trial Collaboration (3), the researchers also recruited a large sample from a wide range of hospitals in many societies, thereby minimising the possibility of bias, and this trial importantly revealed that people with malnutrition after a stroke are associated with poor clinical outcome. When this relationship was adjusted for other prognostic factors such as age, pre-stroke function, living conditions and stroke severity, it is weakened, but nonetheless, remains statistically significant. In the same trial (3), researchers assessed nutritional status on the basis of their own bedside assessment or, when practical, from a full evaluation that included weight, height, blood tests, and/or dietary intake. The simple bedside assessment of nutritional status conducted by healthcare personnel without clear criteria, precisely matches BMI with accepted inter-observer reliability (unweighted k=0.53 to 0.77) (127). Nevertheless, future studies should assess whether additional intensive nutritional regimens might potentially improve survival and clinical outcomes. This is partially addressed in the Feed or Ordinary Diet (FOOD) study (126), but that study was relatively large, and the majority of patients were normally weighted (92%) meaning that only a small percentage (8%) of people were malnourished, and only this percentage received the intensive nutritional regimens. Therefore, the potential influence of nutritional supplementation on that small portion of the overall sample might be lost statistically by the large percentage of people with normal weight.

Nip et al. (120) demonstrated a significant association between energy intake immediately after admission, and the rate of functional outcome, flagging the importance of nutritional status assessments - Mini-Nutritional Assessment (MNA), BMI, Mid-Arm Circumference (MAC), Triceps Skinfold Thickness (TSF), Calf Circumference (CC), and handgrip strength - taken both in exact time and accurately. However, this was a relatively small study and consequently the results are not capable of wide generalisation. Moreover, the study excluded those patients with cognitive and communication problem and this is seen as a major limitation. At the same time, around 25% of patients did not consume all the food meal provided by the hospital yet did compensate for this by eating non-hospital food. As the study did not gather any information regarding patients' food preferences, it might be assumed that those patients did not like the hospital food and hence ate from other sources, or not all. These questions need to be answered, and therefore, further study is warranted.

In Lisa et al. (122), the study showed, by using specific anthropometry measurements and BIA, that individualised nutrition supplements to patients admitted to hospital after a stroke were associated with good short-term body composition, and less fat loss among females after three months. Additionally, MAC might be used in nutritional status evaluation if BMI is unobtainable, owing to difficulties in establishing weight and height in immobile patients after a stroke. Furthermore, the BIA technique used to assess change in body composition in this study provided a validated and relatively easy and non-invasive approach (103,104, 128). However, BIA may be inaccurate due to selection bias on the basis of exclusion of patients with a cardiac pacemaker or metallic stents (122).

In one trial (123), the authors demonstrated that stroke patients achieved a higher level of motor recovery but no cognitive recovery, and were more likely to go home rather than to institutional care when individualised nutritional support was received during the inpatient rehabilitation period. Body weight was used to assess nutritional status among these patients, and malnutrition was defined as loss of 2.5% or more of body mass within two weeks after the acute stroke. The fact that the intensive nutritional support improved motor function but not cognitive function is interesting yet this point was not taken up, and would seem to demand further investigation. Furthermore, the lack of any caloric count of the intensive nutritional supplements is a shortcoming that might weaken the study's results.

The trial reported by Lisa et al. (124) demonstrated that nutritional risk and being undernourished were assessed by MUST and TSF, MAC, BMI respectively, which are

validated tools for the evaluation of nutritional status in post-stroke patients. Those patients identified at risk of malnutrition or undernourishment were shown to be less likely to lose body weight or become malnourished after three months of admission if they had been given nutritional support than those in the routine nutritional care group. Nevertheless, there was a lack of nutritional assessment and nutritional treatment procedures in respect of the control patients, and this might limit the comparison between study groups.

Geeganage et al. (125) found insufficient evidence of the influence of specific interventions (swallowing therapy, nutritional and fluid support) in patients after a stroke with dysphagia on clinical outcome and death. In that study, the researchers relied BMI, Demiquet index (where BMI was not applicable due to the difficulty of obtaining height and weight measurements in some cases, and also in older people where BMI is less reliable), nutritional risk score, anthropometry, and biochemical measures. However, the quality of the review is called into question by the presence of certain facts, in which respect, further inquiries need to be made. Specifically, the authors excluded 108 studies as there was no control group in these studies, and they merely compared two active treatment patients. Several studies were excluded for their lack of outcome measures symmetry and data. And secondly, a further 38 studies were excluded on the grounds that they were waiting for assessment, and it may be that some of those might have had an effect on the results of the review.

All studies provided robust evidence that being malnourished or at risk of malnutrition can be used as an independent predictor of clinical outcome in patients after a stroke. Indeed, most patients in these studies underwent nutritional status screening or assessment as part of their routine admission procedure; this offers a practical, precise and simple indicator to identify those who are more prone to develop post-stroke complications, and poor outcome.

The results of the present review are subjected to certain caveats. Firstly, the exclusion of non-English articles may imply different findings in other environmental settings that might have the potential to affect the generalisation of the results of the analysis. Secondly, as studies heterogeneous in design, of varied time scales, used different nutritional screening or assessment tools, used different definition of malnutrition, and demonstrated various outcomes, it is hard to make direct comparisons in terms of their accurate incidence of malnutrition, validity, prognostication, and usefulness of the nutritional status screening or measurement tools. Thirdly, some studies recruited only small samples, thereby reducing the possibility of generalisability.

Implications for practice

Most studies demonstrated that nutritional screening and/or assessment tools may be used as independent predictors of clinical outcome, but it remains unclear as to which of these tools is the most effective. Furthermore, it is not apparent from the many studies reported, whether the prevalence of undernutrition or risk of malnutrition in post-stroke patients is high or not by using simple, quick and validated tool.

Implications for research

Further research is therefore needed to discover which type of nutritional screening tool is the most beneficial in the evaluation of nutritional status. Additionally, a focus on the degree of undernutrition in patients after a stroke would be useful. Outcomes from such studies would allow for more targeted nutritional interventions.

In conclusion, most studies in this review showed the significance of deterioration in nutritional status in as much as it appears to strongly influence clinical outcome for the worse. Hence, the review highlights the importance of nutritional screening and/or assessment as a routine procedure at hospital admission. For this to be translated into clinical practice, further studies need to have uniform end points and follow the consensus implementation of a simple, rapid, validated and practicable routine nutritional screening and/or assessment tool. Although in the UK, nutritional screening is already implemented in most hospitals, there remains a need to know the exact incidence of malnutrition using an appropriate and validated tool and whether malnutrition has any impact on clinical outcomes. Additionally, the future use of an accurate and simple method of nutritional screening and/or assessment to identify malnutrition will facilitate the recognition of those at nutrition risk, and be helpful in assessing the benefit of an interventional dietary programme.

CHAPTER 4

The role of Malnutrition Universal Screening Tool (MUST) in determining the risk of malnutrition and predicting clinical outcome in patients after a stroke

4. The role of Malnutrition Universal Screening Tool (MUST) in determining risk of malnutrition and predicting clinical outcome in patients after a stroke

Malnutrition is a major complication often encountered by victims after a stroke in health institutes. Several published studies have been performed to estimate nutritional status in these people using both nutritional screening tools, and nutritional assessment (7, 8). However, in the study by Chai et al. (7) the authors did not report clinical outcomes or look at the risk of being malnourished and having a stroke on clinical outcome. Additionally, in the study by Choi-Kwon et al. (8) published in 1998 biochemical markers and anthropometry were used for the assessment of nutritional status rather than screening of nutritional status. Therefore, these studies fail to decide whether the risk of malnutrition is high in this group of people. Moreover, there is no clear evidence from these studies as to whether the MUST score can be used as a nutritional screening tool and an independent predictor of clinical outcome in the aforementioned people. Our hypothesis is that a high MUST score on admission with stroke is associated with a poorer clinical outcome and longer stays in hospital. Accordingly, in this study we aim to address this issue and clarify whether the MUST score on admission to a large urban teaching hospital in the north west of England is associated with poor clinical outcome and clinical complications or not. If it is, then future early identification of risk of malnutrition in people after a stroke, and rapid nutritional and treatment interventions are likely to become important priorities for the health service in the UK.

4.1 Introduction

The World Health Organisation (WHO) has estimated that stroke has caused approximately 5.7 million deaths all over the world (129). Although stroke mortality has been declining over the past few decades in Western communities, the residual disabilities are become increasingly relevant among these patients (114). Malnutrition has become a paramount residual disability that is commonly seen in patients after a stroke with or without dysphagia. In addition, malnutrition is associated with poor clinical and functional outcome in these people (7, 8). Many published studies have reported that the prevalence of malnutrition in patients after a stroke varies widely from 6.1-62% (15), whilst other studies have reported the

rate ranges from 8 to 49% (10-14). The type of stroke (whether hemorrhage or infarct), evaluation time, existence of stroke complications, and coincidence of chronic disorders all play a major role on this wide variability. However, it seems likely that the most significant cause of this variation is the discrepancy between nutritional screening/assessment tools (14, 16).

To effectively manage this growing issue, routine tests of nutritional status are recommended in all patients who are admitted to hospital to allow appropriate early intervention. There are more than three million individuals in the UK who are potentially at risk of undernourishment (130), yet to date, this continues as an under-perceived and under-treated issue. Additionally, the community health services' expenditure on diseases associated with malnutrition in Britain in 2007 was estimated to be more than thirteen billion pounds annually, of which around 80% was spent in England (130). This is a substantial financial burden for health and social care services, and for the community in general.

Although many traditional nutritional screening and assessment tools are available to provide information about the general aspect of nutritional status, they fail to recognise more specific issues such as the need to accurately establish the risk of malnutrition and the effect of malnutrition when it is present, on clinical outcome. For example, dietary evaluation relies on patient self-report measures, but due to communication problems and inconsistencies in relating information, objective and accurate evaluation is difficult to obtain. Moreover, the body mass index (BMI) presumes a typical fat and muscle distribution, and bioelectrical impedance analysis (BIA) depends on the subject having fasted and his/her internal fluid balance being in equilibrium even though when compared with BMI and self-reporting, BIA is considered the best tool (131). However, there are some international techniques have been developed to screen for malnutrition or risk of malnutrition, and of these, the Malnutrition Universal Screening Tool (MUST) has received most attention. This technique was developed by the multidisciplinary Malnutrition Advisory Group (now called the Malnutrition Action Group) of the British Association of Parenteral and Enteral Nutrition (BAPEN) for use in clinical practice in the UK (132).

The MUST technique has been validated and correlated well with other previously described tools (132). Staff from the Royal College of Physicians, Royal College of General Practitioners, Royal College of Obstetricians and Gynaecologists, Royal College of Nursing, British Dietetic Association and numerous other associations, independent physicians, and

health and social care practitioners have autonomously looked into the advancement of MUST (60), and the MUST score has been assessed in health care settings including hospital wards, outpatient clinics, general practice, the community, and in care homes.

Utilising the MUST to categorise people according to their malnutrition risk has been observed to be simple, fast, reproducible, and reliable. If a patient's height and weight are unobtainable, the MUST can be used as an alternative measure relying on subjective criteria. For example, if patients are unable to stand, recalled height or a surrogate measure using ulna length is used, and pre-illness weight is obtained from the patient or proxy (60). However, healthcare staff who are required to perform nutritional screening using the MUST tool must be properly trained and have developed the skill to do so. That said, favourable results have been observed in respect of individuals self-screening using the MUST score, with screening results similar to those of health experts being obtained (60). Recently, the MUST score technique has become the common nutritional screening test used in Britain and Ireland (133).

The MUST methodology incorporates three independent variables: (1) BMI score, BMI >20.0= 0, BMI 18.5-20.0= 1, BMI < 18.5= 2; (2) Unplanned weight loss in previous 3-6 months, weight loss <5%=0, weight loss 5-10% = 1 and weight loss >10 % = 2; and (3) Acute disease effect score, add a score of 2 in the case where a patient is recently affected by a disease and there was no nutritional intake or likely to be no nutritional intake for more than 5 days. Each variable is scored on a scale of 0, 1, 2, and their total sum used to categorise the risk of malnutrition as low (0), medium (1) and high (≥2) (134) as illustrated in Appendix E. Each of the three variables can independently predict a patient's clinical outcome whilst also showing the variation in importance of each component in relation to the clinical situations. However, together, the three variables are better predictors of clinical outcome than the individual variables (60).

Study Aims and Hypotheses

Given the aim of this study was to test whether the prevalence of undernutrition is high in patients after a stroke, and given the widespread agreement that the MUST tool is useful, it is reasonable to assume that it would be capable of functioning as an independent predictor of clinical outcome in stroke victims, and hence the study will explore the value of the MUST tool in this respect.

4.2 Methods

Study Design

This is a retrospective observational cohort study using the records of patients admitted to the Stroke Unit at Salford Royal Hospital between January 2013 and March 2016, and who had a MUST score calculated for them as part of their routine care.

Study Sample

As indicated, the sample came from the Stroke Unit at the Salford Royal Hospital. This is a large hospital in Pendleton, Salford, England, and is an integrated provider of hospital, society and primary care services, comprising around 750 beds and around 7,000 staff. The hospital provides a comprehensive range of services to the Salford community, as well as specialist services to Greater Manchester, the north west of England, and nationally, meeting the explicit and often complex needs of a wide range of patients. Referrals are accepted from the aforementioned places and from the nearby acute medical hospitals. The sample was all adult patients hospitalised after a stroke (> 18) who were admitted to SRFT and managed on the Stroke Unit between January 2013 and March 2016. These patients were expected to have been assessed and given a MUST score as part of their routine investigation. The sum of the MUST scores obtained for each category related to unplanned weight loss, BMI, the effect of acute disease, and the ability to eat for more than five days, result in an overall risk of malnutrition score, from which participants are categorised in low (score 0), medium (score 1), or high (score ≥2) risk groups. Malnutrition as categories has been defined as being at risk of malnutrition.

In this retrospective observational study, data were collected after matching the Trust's specific Sentinel Stoke National Audit Programme (SSNAP,) and Electronic Patient Records (EPR). The EPR is an electronic record used to store a defined set of key patient data for every patient in Salford Royal Hospital. The National Sentinel Stroke Audit was conducted in 1998 and 1999 by the Stroke Programme at the Royal College of Physicians (RCP), and reported that whilst there were variations in standards across society, much was being done at

local level to change services. The Stroke Improvement National Audit Programme (SINAP) began in 2010 and was soon followed by improvements in intense care and in the recognised areas for improvement (135).

The SSNAP is the only source of stroke data in England, Wales, and Northern Ireland. It categorises data into three groups: the clinical audit, acute organisational audit, and post-acute organisational audit. The clinical audit component gathers a minimum dataset for each patient after a stroke, including acute stroke care, rehabilitation, 6-month follow-up, and outcome measures.

Principally, the aim of the SSNAP is to review patients against the National Clinical Guidelines for Stroke (fourth version, 2010), the Quality Standard for stroke, the Accelerating Stroke improvements measurements, and the National Stroke System. Additionally, it expands on the work of the National Sentinel Stroke Audit, and the Stroke Improvement National Audit Programme (SINAP). Additionally, the SSNAP provides constant, dependable and routine information to benchmark health settings nationally and territorially, to screen progress against a background of change, to help physicians recognise where improvements are required, to push for amendments and celebrate success, and to engage patients so that they ask questions (135).

The RCP has developed an interactive map which allows the domain levels and scores to be represented dynamically, thus enabling comparisons to be made across the different domains of care and also between two hospitals. For example, there are ten domains which can be viewed and contrasted, thereby enabling Salford Royal's SSNAP and any other health services' SSNAP to be compared. Each of these ten domains (including for example, scanning, stroke unit, and thrombolysis) is an important area of care comprising 44 key indicators. Table 4.1 shows the SSNAP comparisons between Salford Royal Hospital, and the Royal London HASU from April to July 2016. SSNAP levels (A, B, C, D, E) showed how much each team had achieved for each domain (A is the top achievement, and E is the bottom). Either patient-centred domain scores (scores are attributed to every team which treated the patient at any point in his/her care) or team-centred domain scores (scores are attributed to the team considered to be most appropriate to assign the responsibility for the measure) were calculated and given an achievement level (A-E) (135). This particular SSNAP comparison shows, for example, that in domain number 4 (specialist assessment) which is comprised of 6 indicators, Salford Royal Hospital achieved a SSNAP score A.

Indicators included: percentage of patients who were seen by a stroke specialist within 24 hours of admission, median time between time of admission and being seen by a stroke consultant, proportion of patients who were evaluated by a nurse trained in stroke management within 24 hours of admission, median time between admission and being seen by a stroke nurse (minutes), percentage of eligible patients who were given a swallow screen within 4 hours of admission, and percentage of eligible patients who were given a formal swallow test within 72 hours of admission. This reflects the speed and precision with which the process of patient management (which included the MUST assessment) occurred within the hospital after admission.

Table 4.1 SSNAP comparison between Salford Royal and Royal London HASU

Domain name	Hospital name	
	Salford Royal	Royal London HASU
SSNAP level:	A	B
SSNAP score (%)	88	77
Domain 1: Scanning level	A	A
Scanning score (%)	96.7	100
Domain 2: Stroke unit level	B	C
Stroke unit score (%)	81.7	72
Domain 3: Thrombolysis level	C	B
Thrombolysis score (%)	66.7	78.2
Domain 4: Specialist assessments level	A	B
Specialist assessments score (%)	91	82.2
Domain 5: Occupational therapy level	A	C
Occupational therapy score (%)	86.4	74.1
Domain 6: Physiotherapy level	B	B
Physiotherapy score (%)	79.1	78.2
Domain 7: Speech and language therapy level	C	B
Speech and language therapy score (%)	58.7	65.2
Domain 8: Multidisciplinary team working level	A	B
Multidisciplinary team working score (%)	86	84.7
Domain 9: Standards by discharge level	A	B
Standards by discharge score (%)	99	85.4
Domain 10: Discharge processes level	A	C
Discharge processes score (%)	98.7	77.9

Ethical approval/study governance

The research ethics office at The University of Manchester has considered this study as a secondary data analysis of an existing dataset. There was no opportunity to seek patients' consent, and accordingly it did not require formal ethical review. The extraction of data has been performed by the Information Technology Department at SRFT using the Electronic Patient Records (EPR). This data was matched with that on the Sentinel Stroke National Audit Programme (SSNAP) database by a member of the clinical team and fully anonymised. The research team had access to the anonymised data only. Therefore, the study has been registered as a clinical audit at the Clinical Audit Department (reference number 2016151) at Salford Royal NHS Foundation Trust. The study is subject to the audit and monitoring regime of the University of Manchester, and conducted in full conformance with the principles of the "Declaration of Helsinki", Good Clinical Practice (GCP), and within the laws and regulations of the country in which the research is undertaken.

Statistical Analysis

The descriptive data is displayed in tables and charts. Statistical analyses were conducted to determine the association between malnutrition risk on admission to and discharge from the hospital, and clinical outcomes (mortality, length of hospital stay, and clinical complications). The multivariable analyses included the following potential confounders and effect modifiers: age, gender, ethnicity, stroke type, stroke severity, and stroke risk factors (congestive heart failure, hypertension, diabetes, atrial fibrillation, previous transient ischemic attack). Multiple regression was used to test the relationship between the nutrition risk categories (MUST score) and clinical outcomes, where MUST was dichotomised according to combined scores, i.e. if it is more than or equal to 3 malnourished or equal to 2 as malnourished compared to the other group. This classification will explain whether the association between being at risk of malnutrition and outcomes is graded and proportional (the greater the risk of malnutrition, the higher the possibility of poorer outcomes). Additionally, the Chi-square test was performed to establish any statistically significant differences between the risk of malnutrition groups and clinical outcomes, since the missing data in the outcomes left very small numbers that are not suitable for multiple regression analysis. The MUST is an independent variable that has been dichotomised and evaluated in relation to outcomes as the dependence variables. Analysis of variance (ANOVA) was used to determine any

confounding variables. All tests carried out were two-sided. Statistical significance was accepted at the 95% confidence interval and any differences were considered significant when the P value was ≤ 0.05.

4.3 Results

During the period from January 2013 to March 2016, 1,101 patients were admitted to, and screened in the Stroke Unit in Salford Royal Hospital. All these patients were included in the study.

However, as the study is a retrospective observational cohort study depending upon the EPR, there were missing data in respect of certain variables at the admission, discharge, and six months follow up stage. For example, certain outcomes (urinary tract infection, pneumonia, and length of hospital stay (LOS)) were missed in 112 (10.1%), 113 (10.2), and 279 (25.3%) patients respectively during their stay in hospital. Other missing data was encountered in type of stroke, since 5 (0.5%) patients did not have this recorded at admission. Moreover there were 8 (5%) patients for whom there was no cause of death recorded. And at the time of discharge, there were 121 (11%) patients for whom there was no indication of their final destination (home, or care facility).

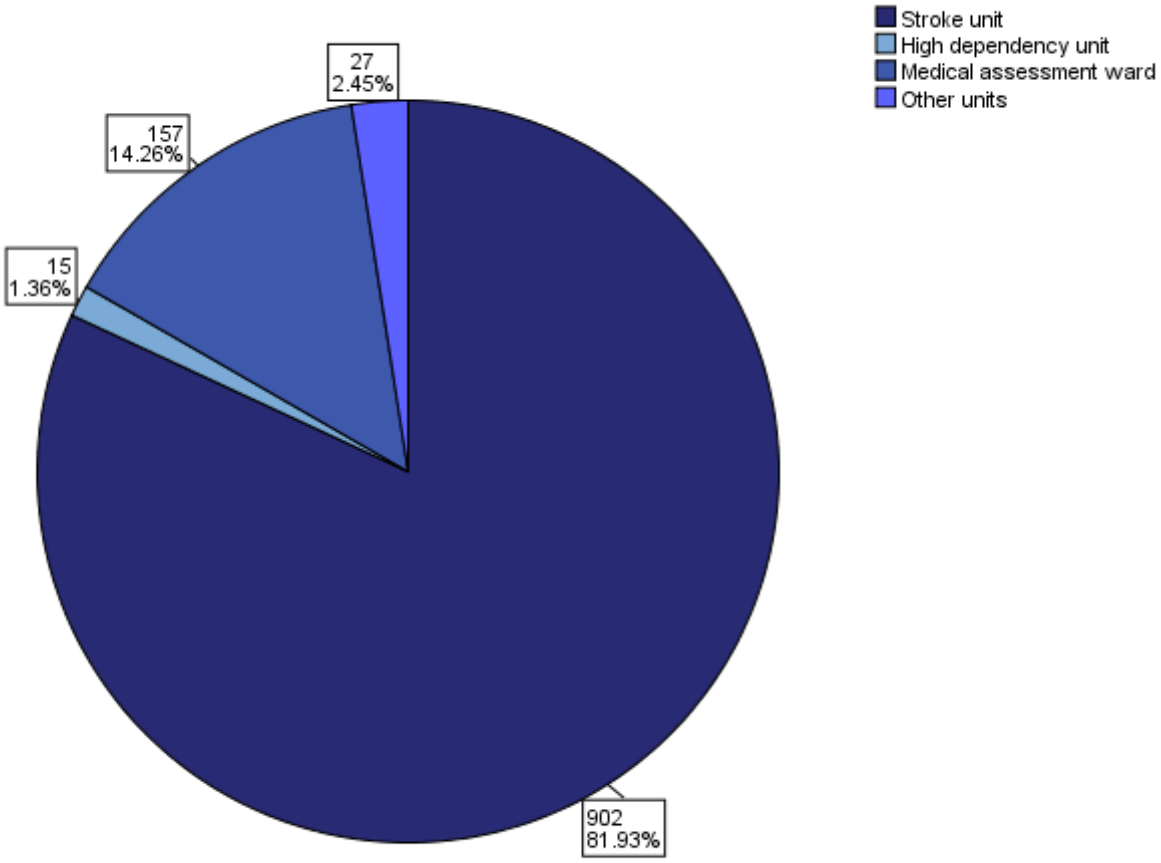
Baseline Characteristics

Table 4.2 Patients' characteristics

Gender n (%)	
Male	539(49)
Female	562(51)
Ethnicity n (%)	
White	1,031 (94)
Non white	70 (6)
Age mean (SD)	73.6 (13.6)
Range (minimum-maximum)	22-102
Congestive heart failure n (%)	
Yes	49 (4.4)
No	1,052 (95.6)
Hypertension n (%)	
Yes	561 (51)
No	540 (49)
Atrial fibrillation n (%)	
Yes	197 (17.9)
No	904 (82.1)
Diabetes mellitus n (%)	
Yes	212 (19.3)
No	889 (80.7)
Transient ischemic attack n (%)	
Yes	219 (19.9)
No	882 (80.1)
Type of stroke n (%)	
Infarction	977 (88.7)
Primary intracerebral haemorrhage	119 (10.8)
Missing	5 (0.5)

The 1,101 patients included in this study had a mean age of 73.6 years, 51% were women, just over half of patients (51%) had a history of hypertension, about one fifth of patients (19.3%) had had diabetes mellitus, almost one fifth (19.9%) had had a previous transient ischemic attack, 17.9% had atrial fibrillation, and a tiny minority (4.4%) had congestive heart failure. The vast majority of patients 977 (88.7%) were diagnosed with ischemic (infarction) stroke, while only 119 patients (10.8%) were diagnosed as having a primary intracerebral haemorrhage. Table 4.2 presents these results.

Figure 4.1 Admission ward for patients where patients were initially admitted



The vast majority of patients were admitted to the Stroke Unit 902 (81.93%). A further 175 patients (14.26%) were admitted to the medical assessment ward, and the remaining patients were admitted to other wards and the High Dependency Unit. Specifically, 27 (2.45%) went to other wards, and 15 (1.36%) went to the HDU, as illustrated in Fig. 4.1.

Malnutrition Universal Screening Tool (MUST) at admission and at discharge from the hospital

Figure 4.2 First Malnutrition Universal Screening Tool (MUST) recorded for patients on admission to the Stroke Unit

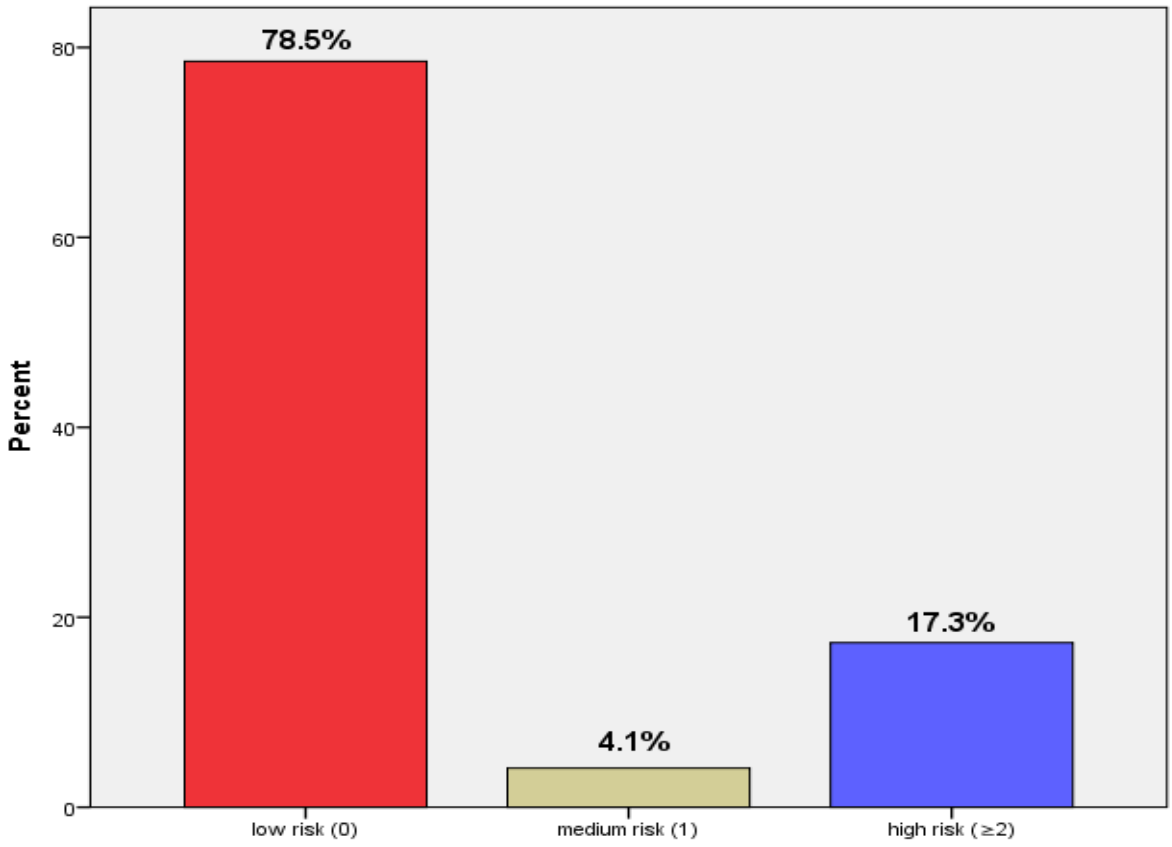


Figure 4.2 shows that at the time of admission the majority of patients 78.5% (n=571) were at low or no risk of malnutrition (MUST score 0). However, 17.3% (n=126) were classified as being at high risk (MUST score ≥ 2), and 4.1% (n=30) were considered to be at medium risk of malnutrition (MUST score 1). To calculate the risk of malnutrition at admission, both the patients at risk of malnutrition (medium) group, and those identified as in the high risk group were added together (30 + 126 = 156) and then the prevalence calculated with respect to the total number of patients who had undergone MUST at hospital admission (n=727). The prevalence of risk of malnutrition at admission was therefore, 21.4%.

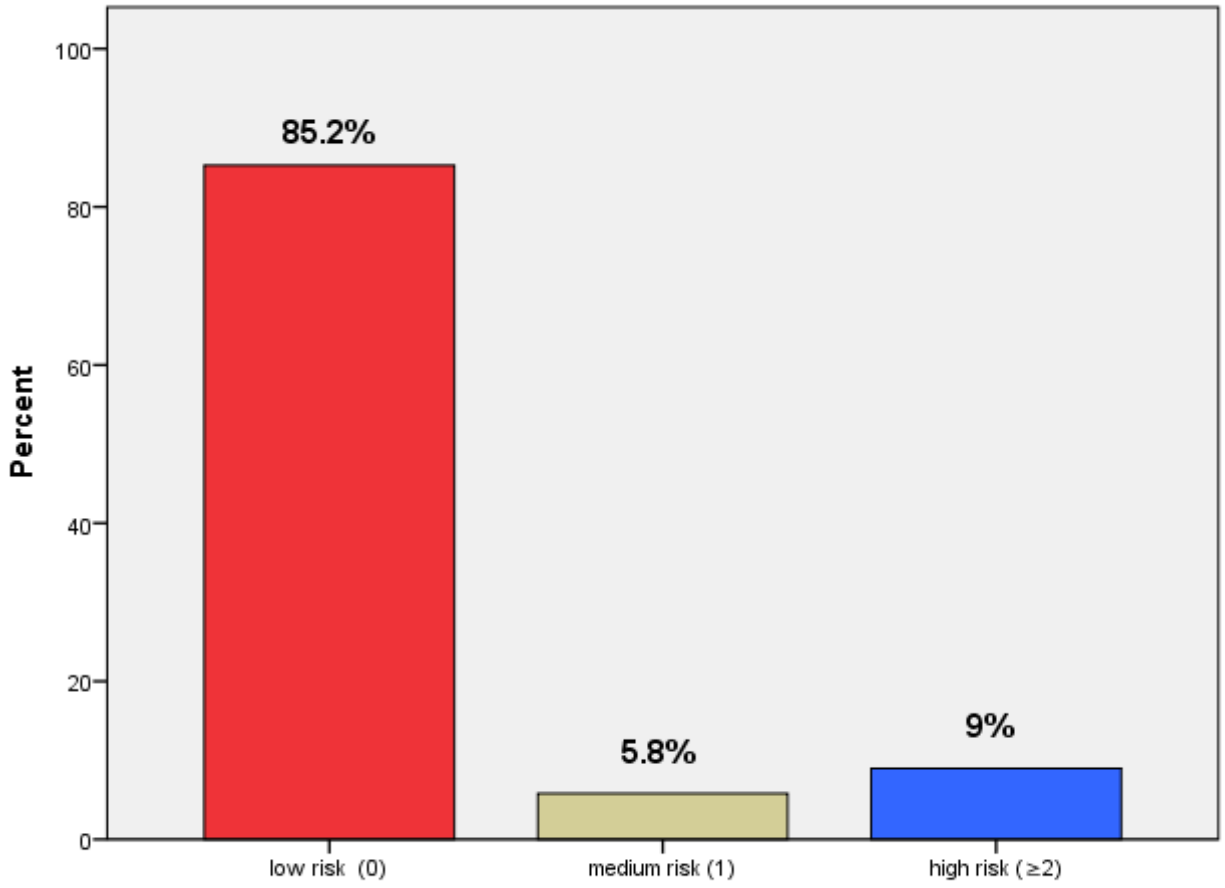
Table 4.3 Comparison of prevalence of malnutrition and risk of malnutrition between this study and other studies

Source	Country	Total number of participants; age (years)	Nutrition screening/assessment method	Malnutrition risk or prevalence in participants	Type of department
This study	The UK	n= 1101; mean age: 73.6 ± 13.6	MUST	Risk of malnutrition 21.4%	Stroke unit
Agarwal et al., 2012 (136)	Australia and New Zealand	*N* = 3122; mean age: 65 ± 18 years	SGA	60% of participants were malnourished	Unknown
Imoberforf et al., 2009 (137)	Switzerland	*N* = 32,837; mean/median age not specified	NRS-2002	Risk of malnutrition in 65–84 year old participants: 22%; in participants aged >85 years: 28%	All patients who were admitted to the departments of internal medicine
Pirlich et al., 2006 (138)	Germany	*N* = 1886; mean age: 62 ± 17 years	SGA	Malnutrition prevalence in: 60–69years: 23%; 70–79 years: 35%; and ≥80years: 55%	Geriatric, surgery, gastroenterology, cardiology, urology, oncology, rheumatology, and gynaecology department
Correia and Campos, 2003 (139)	Latin America	*N* = 9348; mean age: 52 ± 17 years	SGA	Malnutrition prevalence 53%	All departments were included except the obstetric and paediatric units
Waitzberg et al., 2001 (140)	Brazil	*N* = 4000; mean age not specified	SGA	Malnutrition prevalence 53%	All departments were included except the obstetric and paediatric units

MUST, malnutrition universal screening test; NRS-2002, Nutrition Risk Screening 2002; SGA, subjective global assessment.

Table 4.3 illustrates the comparison of malnutrition prevalence between this study and previously published studies that have included other medical conditions. In these studies the frequency of malnutrition in elderly patients ranged from 23 to 60% and the risk of malnutrition from 22 to 28%, whilst in this study the frequency of risk of malnourishment was only 21.4%.

Figure 4.3 Late Malnutrition Universal Screening Tool (MUST) score recorded for patients on discharge from hospital



On the other hand, at the time of discharge from the hospital the majority of patients 85.2% (n=618) were at low or no risk of malnutrition, 9% (n=65) were at high risk of malnutrition, 5.8% (n=42) at medium risk, presented in Figure 4.3.

Table 4.4 Percentages and numbers of patients with their MUST score at admission and at discharge from the hospital

MUST score	First MUST for patients on admission to SU	Last MUST for patients before discharge from hospital
Low risk (0), n (%)	571(78.5)	618(85.5)
Medium risk(1),n(%)	30(4.1)	42(5.8)
High risk (2), n (%)	126(17.3)	65(9)
Total n (%)	727 (66)	725 (65.8)
Missing n (%)	374 (34)	376 (34.2)

SU, stroke unit

Table 4.4 demonstrates that among those patients who were admitted to the Stroke Unit, the majority (571 - 78.5%) were patients at low risk of malnourishment (MUST score 0), 126 (17.3%) had a high risk of malnourishment, and only 30 (4.1%) were at medium risk (MUST score 1). The total number of patients who underwent MUST at hospital admission was 727 (66%), meaning that 374 (34%) had no MUST on admission. By contrast, at the time of discharge from the hospital there was an increase in the number of patients at low risk of malnutrition 618 (85.5%), interestingly the frequency of patients at high risk of malnutrition had declined to just 65 (9%), and 42 (5.8%) of patients were at medium risk. This left a further 376 (34.2%) patients who did not undergo MUST on discharge from the hospital.

Type of interventions in the hospital

Table 4.5 Type of interventions patients received in the hospital

Swallow screening test within 4 hours after admission to hospital n (%)	
Yes	406 (36.9)
No	695 (63.1)
Swallow screening test within 72 hours after admission to hospital n (%)	
Yes	465 (42.2)
No	636 (57.8)
Patients seen by Dietitian n (%)	
Yes	106 (9.6)
No	995 (90.4)
Patients assessed by stroke nurse n (%)	
Yes	1067 (96.9)
No	34 (3.1)
Patients assessed by stroke consultant n (%)	
Yes	1081 (98.2)
No	20 (1.8)
Decision for palliative care within 72 hours of admission n (%)	
Yes	85 (7.7)
No	1016 (92.3)
Out of 85 patients who planned to end their life care (e.g. rapid discharge home to die) at admission n (%)	
Yes	10 (11.7)
No	75 (88.3)
Decision for palliative care at discharge N (%)	
Yes	60 (5.4)
No	843 (76.5)
Missing	198(18.1)
Out of 60 patients who planned to end their life care (e.g. rapid discharge home to die) at discharge n (%)	52 (86.7)
Yes	8 (13.3)
No	

The bedside swallowing test was performed within 4 hours after admission to only 406 patients (36.9%), and within 72 hours after admission to 465 patients (42.2%). According to the SSNAP database (SSNAP Core Dataset 3.1.2), the patient is first identified to determine whether s/he is at a high risk of malnutrition following nutritional screening using MUST. Secondly, if the patient has been identified as being at high risk in this connection, then the date on which the patient was seen by a dietitian is recorded. It was established that 106

patients (9.6%) who had a high risk of malnutrition (high MUST score≥ 2) were seen by a dietitian at admission. Given the retrospective nature of this study, there were many missing data that it was impossible to retrieve either from the EPR or from the SSNAP database. Hence, no local nutrition care policies or local care pathways were found and followed for patients at a high risk of malnutrition. There were 1,067 patients (96.9%) who were seen initially by a stroke nurse on arrival at hospital, and 1,081 patients (98.2%) who were seen by a stroke consultant. The decision for palliative care was made in the first 72 hours in 85 patients (7.7%), and of these patients, only 10 (11.7%) planned to end their life care (for example rapid discharge home to die pathway). The decision to offer palliative care on discharge was made in the case of 60 patients (5.4%) and of these patients, 52 (86.7%) received end-of-life care once discharged home to die, as shown in Table 4.5.

Causes of death in the hospital

Table 4.6 Cause of death inside the hospital

Ischaemic Stroke n (%)	66(42)
Pneumonia n (%)	25 (16)
Spontaneous Cerebral Haemorrhage n (%)	21 (13.4)
Dementia n (%)	5 (3.2)
Lung cancer n (%)	3 (2)
Old Age n (%)	4 (2.5)
Metastatic Carcinoma n (%)	5(3.2)
Coronary Artery Narrowing n (%)	2 (1.2)
Other causes n (%)	18 (11.5)
Missing	8 (5)

The paramount cause of death during patients' stay in the hospital was ischaemic stroke (42%), pneumonia was the second cause of death (16%), Spontaneous Cerebral Haemorrhage was the third killer (13.4%), both dementia and metastatic carcinoma were the fourth causes of death (3.2% for each). Old age accounted for only 2.5%, 2% died as a result of lung cancer, and 1.2% as a result of coronary heart disease. The remaining 11.5% of deaths were due to other causes as demonstrated in Table 4.6.

Figure 4.4 Causes of deaths inside the hospital

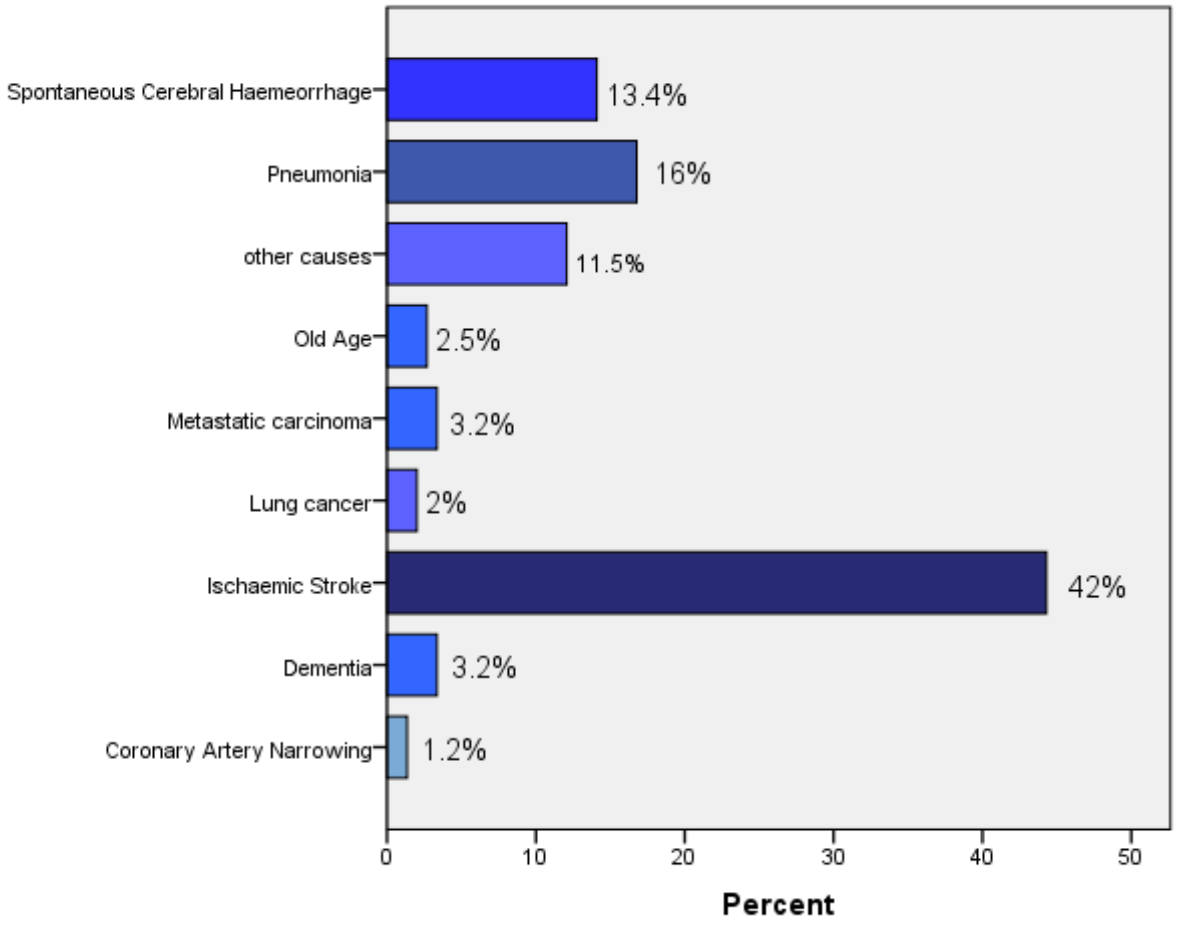


Figure 4.4 also demonstrates the major cause of death inside the hospital as being ischemic stroke (42%), followed by pneumonia as a second cause of death (16%), the third cause of death is spontaneous cerebral haemorrhage (13.4), whereas other causes like dementia (3.2%), metastatic carcinoma (3.2%), old age (2.5%), lung cancer (2%), and coronary artery disease (1.2%) constitute just a minority. Other causes (11.5%) are considered the fourth cause of death (for example cardiac failure, hepatocellular carcinoma, pulmonary embolism, End Stage Renal Failure etc.).

Type of discharge and final destination

Table 4.7 Discharge type and final destination of discharged patients

Care home n (%)	70(6.3)
Died n (%)	157(14.2)
Home n (%)	186(17)
Somewhere else n (%)	2(0.1)
Another hospital n (%)	10(0.9)
Community team n (%)	541(49.3)
Community team, not participate in SSNA* n (%)	7(0.6)
Another hospital, not participate in SSNAP* n (%)	7(0.6)
Missing n (%)	121(11)

*SSNAP, Sentinel Stroke National Audit Programme.

Table 4.7 shows the discharge type and final destination, indicating that the majority of patients 541 (49.3%) were transferred to community teams. Of the others, 186 patients (17%) were discharged home, 157 patients (14.2%) died, 70 patients (6.3%) were discharged to a care home, 10 people (0.9%) were transferred to another in-patient care team, seven patients (0.6%) were transferred to another in-patient care team which was not participating in SSNAP, seven patients (0.6%) were transferred to a community team not participating in SSNAP, and just two patients (0.1%) were discharged to somewhere else.

Outcomes

Table 4.8 Clinical outcome for patients after a stroke

Urinary tract infection n (%)	
Yes	20 (2)
No	969 (98)
Missing	112
Pneumonia n (%)	
Yes	53 (5.4)
No	935 (94.6)
Missing	113
Death in the hospital n (%)	157 (14)
Total death up to six months n (%)	214 (19.4)
Length of stay	
Median, range(min-max)	7 (0-147)
Total n (%)	822 (74.6)
Missing	279

Table 4.8 demonstrates the outcome results, showing that only 20 patients (2%) were diagnosed with urinary tract infection in hospital, and that 112 patients were not investigated in the first seven days following initial admission for stroke to ensure they did not have such infection. Pneumonia affected 53 patients (5.4%), while 113 patients were not investigated to determine whether they had newly-acquired pneumonia in the first seven days following initial admission for stroke. The mortality rate in the hospital was 14% (157 patients), whereas deaths up to six months follow up amounted to 214 patients (19.4%). There were 822 patients (74.6%) whose LOS was recorded, meaning that for 279 patients no such information was available.

Table 4.9 Linear regression showing adjusted analyses for length of stay outcome as the dependent variable and independent variables as MUST (where MUST was dichotomised into not malnourished and at risk of malnourishment compared to high risk) with other confounders

	Unstandardised coefficient (B)	P-Value	95% CI
MUST score	4.428	0.023	0.616, 8.241
Age (years)	-0.015	0.783	-0.120,0.090
Gender	-0.651	0.408	-2.194,0.892
Congestive Heart Failure	6.444	0.078	-0.722,13.610
Hypertension	0.812	0.568	-1.975,3.598
Atrial Fibrillation	3.517	0.068	-0.254,7.288
Diabetes Mellitus	3.201	0.074	-0.313,6.714
Transient Ischemic attack	-1.294	0.440	-4.586,1.997
Severity of stroke	1.489	0.001	1.234,1.744
Type of stroke	3.282	0.203	-1.776,8.341

CI, Confidence interval. R squared change = 0.223

The adjusted analyses of linear regression for length of stay (LOS) as the dependent variable and the independent variables are demonstrated in Table 4.9. The independent variables include: MUST (dichotomised into not malnourished and at risk of malnourishment compared to high risk of malnourishment), age, gender, congestive heart failure, hypertension, atrial fibrillation, diabetes mellitus, transient ischemic attack, severity of stroke, and type of stroke. The association between the MUST score and LOS is statistically significant ($P \leq 0.023$), as also is that between severity of stroke and LOS ($P \leq 0.001$), whereas age, gender, congestive heart failure, and other stroke risk factors (hypertension, atrial fibrillation, diabetes mellitus, transient ischemic attack, and type of stroke) Showed no significant association with LOS.

Table 4.10 Linear regression showing adjusted analyses for length of stay outcome as the dependent variable and independent variable as MUST (where MUST was dichotomised into not malnourished compared to at risk of malnourishment and high risk) with other confounders

	Unstandardised coefficient (B)	P-Value	95% CI
MUST score	3.784	0.033	0.310,7.257
Age (years)	-0.014	0.790	-0.119,0.091
Gender	-0.647	0.411	-2.191,0.897
Congestive Heart Failure	6.581	0.072	-0.591,13.753
Hypertension	0.915	0.519	-1.870,3.701
Atrial Fibrillation	3.546	0.065	-0.227,7.319
Diabetes Mellitus	3.207	0.074	-0.309,6.723
Transient Ischemic attack	-1.256	0.455	-4.551,2.039
Severity of stroke	1.506	0.001	1.254,1.758
Type of stroke	3.375	0.191	-1.686,8.436

CI, Confidence interval. R squared change = 0.222

Table 4.10 shows the adjusted analyses of linear regression for length of stay (LOS) as the dependent variable, and the independent variables, which include: MUST (dichotomised into not malnourished compared to at risk and high risk of malnourishment), age, gender, congestive heart failure, hypertension, atrial fibrillation, diabetes mellitus, transient ischemic attack, severity of stroke, and type of stroke. As seen in the logistic regression shown in Table 3.10, the association between MUST and LOS is statistically significant ($P \leq 0.033$). Severity of stroke also showed a significant relationship with LOS ($P \leq 0.001$). On the other hand, age, gender, congestive heart failure, and other stroke risk factors (hypertension, atrial fibrillation, diabetes mellitus, transient ischemic attack, and type of stroke) show no significant association with LOS.

Table 4.11 Patients with recorded outcomes and their frequency in MUST and Chi-Square test showing the association between outcomes and MUST at admission (where MUST was dichotomised into not malnourished and at risk of malnourishment compared to high risk)

	MUST at admission no = 727		Chi-Square test				
Outcomes	Not Malnourished and at risk no= 601	High risk No= 126	Pearson Chi-Square	Likelihood Ratio	N of Valid Cases	df	P value
Urinary tract infection (UTI) no(%) Total no (20) Missing MUST at admission 374	11 (1.8)	6 (4.7)	-	-	-	-	-
Pneumonia no (%) Total no (53) Missing MUST at admission 374	12 (1.9)	8 (6.3)	40.910[c]	37.790	988	2	0.001
Total infections no (%)	23 (3.8)	14 (11)	-	-	-	-	-
Death at hospital no (%) Total no (157) Missing MUST at admission 374	0 (0)	1 (0.8)	349.161[b]	382.239	1101	2	0.001
Deaths up to 6 months no (%) Total no (214) Missing MUST at admission 374	21 (4.76)	16 (12.6)	286.980[a]	289.029	1101	2	0.001

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 24.49, b. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 17.97, c. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.76.

In Table 4.11 it is seen that of the 727 patients who had MUST performed at admission, 601 patients were placed in the not malnourished and at risk of malnutrition group, and the remaining 126 patients were categorised as patients with a high risk of malnutrition. As percentages, there were more patients who had high risk of malnutrition compared to those

who were not malnourished, and at risk of malnutrition in relation to outcomes. Of the 126 patients with a high risk of malnutrition, six (4.7%) had urinary tract infection, whereas of the 601 patients who had no risk of malnutrition and at risk of malnutrition, only 11 (1.8%) patients had urinary tract infection. Of the 126 patients who had high risk of malnutrition, eight (6.3%) patients had pneumonia, while of the 601 patients who had no risk and at risk of malnutrition, just 12 (1.9%) had pneumonia. Similarly, of the 126 patients who had high risk, 14 (11%) patients had total infections (UTI and pneumonia), compared to 23 (3.8%) patients who had total infections of UTI and pneumonia from the 601 patients in the group of not malnourished and at risk of malnutrition. Among patients who died in hospital, only one (0.8%) died who had high risk MUST. However, in patients who died during the six months follow-up, 16 (12.6%) had high risk MUST compared to 21 (4.76%) who were classified in not malnourished and the at risk group. On other hand, of 20 patients with urinary tract infection, three (15%) had not been given the MUST test on admission, of the 53 patients with chest infection (pneumonia), 33 (62.4%) had missed the MUST assessment on admission, of the 157 patients who died in hospital, 156 (99.4%) had no MUST test on admission, and of the 214 patients who died up to six months follow up, 177 (82.7%) patients had no MUST test at admission.

It can be seen in Table 4.11 that the Chi-Square test rather than regression was performed since the amount of missing data in the main outcomes resulted in very small numbers that were not suitable for any form of multiple regression analysis, and therefore not susceptible to adjustment in relation to the confounders. In this Chi-Square test, there was a significant difference between the MUST scores within the admission groups and total deaths at six months follow up (Chi-Square test, $P \leq 0.001$). In other words, those patients belonging to MUST (high risk) group were more susceptible to death after six months follow up than were those allocated to not malnourished and at risk group. Moreover, the difference is statistically significant (Chi-Square test, $P \leq 0.001$) between both groups for death in hospital, with patients among the high risk group being more prone to death in hospital compared to those in the not malnourished and at risk group. Also in relation to chest infection (pneumonia) as an outcome, the difference between groups (not malnourished and at risk compared group and at high risk group) was statistically significant (Chi-Square test, $P \leq 0.001$).

Table 4.12 Patients with recorded outcomes and their frequency in MUST and Chi-Square test showing the association between outcomes and MUST at admission (where MUST was dichotomised into not malnourished compared to at risk of malnourishment and high risk)

	MUST at admission no = 727		Chi-Square test				
Outcomes	Not Malnourished and at risk no= 601	High risk No= 126	Pearson Chi-Square	Likelihood Ratio	N of Valid Cases	df	P value
Urinary tract infection (UTI) no (%) Total no (20) Missing MUST at admission 374	9 (1.57)	8 (5.1)	-	-	-	-	-
Pneumonia no (%) Total no (53) Missing MUST at admission 374	12 (2.1)	8 (5.1)	39.234[c]	35.513	988	2	0.001
Total infections no (%)	21 (3.67)	16 (10.2)	-	-	-	-	-
Death at hospital no (%) Total no (157) Missing MUST at admission 374	0 (0)	1 (0.6)	349.148[b]	381.810	1101	2	0.001
Deaths up to 6 months no (%) Total no (214) Missing MUST at admission 374	20 (3.5)	17 (10.89)	285.623[a]	286.273	1101	2	0.001

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 30.32, b. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 22.25, c. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 8.37.

In Table 4.12 it is seen that of the 727 patients who underwent the MUST test at admission, 571 were assigned as not malnourished, and 156 were grouped as at risk and at high risk. As

in Table 4.11, as percentages, more patients who had at risk and a high risk of malnutrition compared to those who were not malnourished experienced worse outcomes. Of the 156 patients with a UTI, eight (5.1%) had at risk and high risk of malnutrition, whereas nine (1.57%) were not malnourished. In patients with pneumonia eight (5.1%) patients belonged to the group at risk and high risk of malnutrition, while 12 (2.1%) patients had no risk of malnutrition. In at risk and high risk group, 16 (10.2%) patients had total infections, whereas in the not malnourished group, 21 (3.67%) had a total infections. Of the patients who died in hospital, only one (0.6%) had at risk and high risk MUST score. Of the death in the six month follow up, 17 (10.89%) patients had at risk and high risk MUST scores, compared to 20 (3.5%) patients who had MUST scores showing they were not malnourished. Similarly as displayed in Table 3.10, of 20 patients with urinary tract infection, three (15%) had missed a MUST test at admission, of 53 patients with chest infection (pneumonia), 33 (62.4%) patients had not had a MUST assessment on admission, in respect of the 157 patients who died in hospital, 156 (99.4%) had no MUST test on admission, and of the 214 patients who died up to six months follow up, 177 (82.7%) had no MUST test at admission.

Additionally, as seen in Table 4.12, because the impact of the missing data in these main outcomes negatively affected the remaining (small) numbers, it was not possible to perform any type of multiple regression analysis, and consequently, the Chi-Square test was used for analysis. Moreover, the numbers were too small to run adjust for in relation to the confounding factors. The Chi-Square test revealed a significant difference between MUST at admission for total deaths up to six months follow-up ($P \leq 0.001$), showing therefore, that patients achieving an at risk and high risk MUST score on admission were more susceptible to dying during the following six months of follow up compared to those with no risk of malnutrition on admission. There was also a significant difference (Chi-Square test, $P \leq 0.001$) between the MUST score groups for death whilst in hospital. Namely, patients belonging to at risk and at high risk of malnourishment as predicted by their MUST scores on entry to the hospital were more likely to die while hospitalised than were those in the not malnourished group. In addition, the difference between groups of MUST for pneumonia was also statistically significant (Chi-Square test, $P \leq 0.001$), with patients in at risk and high risk group, being more prone to pneumonia infection compared to patients who had no risk of malnutrition.

4.4 Discussion

This study shows that MUST can be used as an independent predictor of risk of post-stroke complications and negative clinical outcomes in patients after a stroke. Malnutrition has been reported in many studies as an independent prognostic factor of post-stroke complications and poor clinical outcomes among patients after a stroke (13, 48,141). The prevalence of risk of malnutrition among patients after a stroke in this study was 21.4%, which is comparable to previously published studies that show a range from 8 to 49% (10-14, 78), and in other reported studies conducted in other populations from 6.1 to 62% (15). The prevalence of malnutrition (21.4%) in this study is in keeping with the findings of other published studies, and for much the same reasons as those mentioned earlier in the introduction section regarding a wide variation of malnutrition. However, it seems likely that the most important cause of this wide variation is the heterogeneity of nutritional screening or assessment techniques (14, 16). Indeed, Foley et al. (15) pointed to the fact that a wide variety of nutritional screening or assessment tools, a significant number of which have not been validated, may well have promoted the extensive variation in the outcomes associated with patients after stroke. If this claim by Foley et al. is true, then the need for a valid and dependable nutritional assessment and screening method to deepen our understanding of the relationship between stroke and nutritional status is great. In this connection, it is seen that the MUST has already been validated and correlated well with other previously-mentioned techniques (132). For example, in the Stratton et al. study (132), the authors addressed the validity of MUST with other tools tested (MEREC Bulletin tool; Hickson and Hill tool; nutrition risk score; malnutrition screening tool; mini nutritional assessment; short-form mini nutritional assessment tool; subjective global assessment and undernutrition risk score), finding that MUST has good-to-excellent validity with most tools used. Therefore, the prevalence of risk of malnutrition in this study (21.4%), using MUST, can be considered as an accurate and reliable prediction, reflection the real magnitude of risk of malnutrition among these patients.

Several published studies conducted in other hospital units (e.g., geriatric, surgery, gastroenterology, cardiology, urology, oncology, rheumatology, and gynaecology) have determined that the frequency of malnutrition in elderly patients ranged from 23 to 60% and the risk of malnutrition from 22 to 28% (136-140). In this study the prevalence of risk of malnutrition was lower than the prevalence in these studies (21.4 %), as seen in Table 4.3.

Considering the multiplicity of stroke risk factors and other disorders that already co-existed on admission (congestive heart failure, hypertension, atrial fibrillation, diabetes mellitus, and transient ischemic attack), this low prevalence is encouraging. For example, among the 1,101 patients studied, 49 (4.4%) had congestive heart failure, 561 (51%) had hypertension, 197 (17.9%) had atrial fibrillation, 212 (19.3%) had diabetes mellitus, and 219 (19.9%) had previously manifested a transient ischemic attack. This low prevalence might reflect good nutritional care given to the patients prior to hospital admission.

In the present study, the prevalence of medium and high risk MUST scores on admission were 4.1% and 17.3% respectively. This, in general, represented the prevalence of being at risk of malnutrition in the studied population. These results are comparable with those obtained in a previous study conducted in the UK with a population of 543 elderly patients who were screened using MUST (121). In that study, the prevalence of medium risk was 7%, and the prevalence of high risk was 29%. Gomes and his colleagues (121) concluded that patients at high risk were more likely to be older, have had a more severe stroke, have had a haemorrhagic stroke, lived at home without support, had atrial fibrillation, had gastrointestinal pathology, had altered mobility prior to stroke, and had inadequate swallow function on admission to hospital. As this study is retrospective, and owing to lack of data regarding the likely MUST scores for each clinical presentation of patients after stroke on admission, it is impossible to argue and discuss the characteristics of patients at medium or at high risk of malnutrition.

There was an increased proportion of patients who had a low risk of malnutrition at the time of discharge (85.2%) compared with patients who had a low risk of malnutrition on admission (78.5%). Moreover, the frequency of patients who had a high risk of malnutrition was notably decreased compared to the frequency on admission (from 17.3% to 9%), whilst the percentage of patients who had medium risk of malnutrition slightly increased at the time of discharge from the hospital, as demonstrated in Table 4.4. The proportions of patients who had improved or deteriorated at the time of discharge might be the result of many reasons. Firstly, the type, length and method of any feeding that the patients had received during the stay in the hospital might have altered the patients' nutrition status at discharge. Secondly, patients' nutritional status might have changed from low risk to high risk and vice versa at the time of discharge. The researchers involved only had access to the anonymised information, and hence, were unable to follow every participant to determine whether his/her nutritional status was improved or worse at discharge. Additionally, owing to the lack of data about

type, method, and length of any nutritional support that the patients may have received during their stay in the hospital, it was impossible to assess whether any of this may have affected their nutritional status by the time they were discharged.

The association between risk of malnourishment and outcomes was statistically significant and graded, as in case of LOS, the greater the risk of malnourishment, the higher the risk of a longer LOS (where MUST was dichotomised into not malnourished and at risk compared to high risk, and not malnourished compared to at risk and at high risk, and *P* values were 0.023 and 0.033 respectively) as displayed in Tables 4.9 and 4.10. Furthermore, as shown in Table 4.9, the LOS was likely to increase by 4.428 days in the high risk group compared to patients who had low risk and at risk. In the same table (4.9), it is seen that there was 95% confidence that the increases of LOS in patients with high risk were from 0.61 (less than a day) to 8.24 days.

Similarly, in Table 4.10, the LOS was likely to increase by 3.784 days in patients with at risk and at high risk scored as compared with those with low risk scores. Additionally, there was 95% confidence that the increases of LOS in patients with at risk and high risk scores was from 0.31 (less than a day) to 7.257 days.

Furthermore, the difference was statistically significant (Chi-Square test, $P \leq 0.001$) between MUST in the admission group (either not malnourished and at risk group, or just not malnourished group) and MUST in the admission group (high risk or at risk group and high risk group) for death in the hospital. That means the patients who belonged to the high risk group or to high risk and at risk group were more prone to die in the hospital, as shown in Tables 4.11 and 4.12.

Additionally, in our study we found that there was a significant difference between MUST at admission and total deaths at six months follow up (Chi-Square test, $P \leq 0.001$). That is to say, those patients with MUST scores of high risk or at risk and high risk were more likely to have died after six months follow up compared with those with MUST scores showing they were not malnourished and at risk or not malnourished as displayed in Tables 4.11 and 4.12.

In this study, our data showing that post-stroke complications which included urinary tract infection, and pneumonia were more common among high risk and at risk and high risk groups compared to those in the not malnourished and at risk, and not malnourished groups as illustrated in Tables 4.11-4.12.

All these results are consistent with previous studies conducted in other societies. For instance, in a UK study of 543 elderly patients who were recruited and screened for risk of malnutrition using MUST (121). Likewise, the same findings have been reported in another study also conducted in the UK, where 150 elderly inpatients with numerous medical conditions were tested using MUST as nutrition screening tool (142). Additionally, in a study undertaken in Singapore 818 patients who were admitted to different units had their nutritional status evaluated using the Subjective Global Assessment (SGA) (143). In that study, malnourishment was associated with LOS and a fourfold increase in death after one year of follow-up was identified, while in another study performed in the UK (144), high risk of malnourishment in patients was associated with a twofold increase in death and LOS. Although two tests (SGA and MUST) were capable of recognising people with poor outcome, it should be remembered that the SGA technique is a kind of nutrition screening tool requiring well-trained personnel, and that it is simultaneously a time-consuming technique. In contrast, in this study we have used a validated nutritional assessment tool which is simple and quick for non-professionals to use once they have undergone initial training in its application.

The present study also used the MUST method to investigate the overall improvement or deterioration in risk of malnutrition from initial hospital admission to subsequent hospital discharge (Figures 4.2, 4.3, and Table 4.4). However, as this study is retrospective, and suffers from a lack of ongoing data concerning those patients from admission until discharge, it was not possible to determine exact discharge positions. Namely, some patients who were at low risk at admission might have remained the same, or increased their risk, whilst others who were at high risk at admission might have become low risk by discharge. Additionally, the lack of data about the type of nutritional supplementation, route of, and length of diet provided limits any explanation of this improvement or deterioration.

Limitations

Despite the extensive research efforts made in the present study, it was inevitable that there would be certain limitations. One is the fact that the study was performed in a single hospital in Salford in the UK, and hence, the findings cannot be generalised to all other societies since ethnicity and dietary patterns differ tremendously from one society to another. A second shortcoming is the retrospective nature of the study which has already mentioned, resulted in many instances of missing data. Data not available on a patient's record could not be

retrieved from any other source, meaning that information about referrals (e.g. referral to Dietitian) and local care pathways for patients' nutritional care, and follow up, all of which might influenced patients' outcomes, was not included. Moreover, these missing items had an effect on the type of statistical testing that was possible. Regarding post-stroke complications (urinary tract infection), we could not use the Chi-Square test in Tables 4.11 and 4.12 as squares in a cross tab were less than five which might affect the degree of difference. In addition, in the case of death in hospital, and total deaths after six months follow-up, most of patients who died had no MUST test at the time of admission to the hospital (missing data), which may also affect the results. Lack of information regarding the type and route of feeding, as well as the length of any nutritional supply that the patients may have received during the stay in the hospital, was also a shortcoming. Therefore, further research is warranted to evaluate how many patients received nutritional support after being admitted to hospital, and how this was seen to impact upon patients' clinical outcomes.

Strengths

The main advantage of the study is the relative large sample size (1101), which increases its generalisability and improves the study's power to detect an association that is independent of other prognostic factors. In one published study (113) of a small sample size (only 104 patients), it was revealed that malnutrition parameters (triceps skin-fold or mid-arm muscle circumference and serum albumin) were accounted for in 16.3% of patients on admission to hospital, and that this percentage increased to 26.2% after one week. There was also an association between malnutrition after one week and poorer outcome after one month (Barthel Index score ≤ 50 and death), and more post-stroke clinical complications, and longer LOS. However, after adjustment for confounders (age, sex, swallowing ability, stroke severity, and urinary cortisol) these associations were not statistically important. Responding to this limitation, this study has used linear regressions (see Tables 4.9 and 4.10) to test which of the other prognostic (confounders) factors that were adjusted for were the main causes of decreased strength of association between being undernourished and length of hospital stay outcome. The stroke severity was the only factor that weakened this relationship (P≤ 0.001). Although adjusting for stroke severity weakened this association, it remained statistically significant (P≤ 0.023 and 0.033 respectively), and this raises the possibility that the relationship is causal.

This study has included all hospitalised adult patients without imposing limitations concerning age, gender, stroke type, and severity of stroke. Such strategy is especially significant to avoid what is called selection bias, which as has been remarked upon by national registries of strokes (e.g. Registry of the Canadian Stroke Network), indicates that in various studies, the patients recruited only ever account for around half of all eligible participants (145).

4.5 Conclusion

This study shows that being at risk of malnourishment on hospital admission, as recognised by the MUST methodology, can be taken as a predictor of the patient's mortality rate both whilst hospitalised, and at the six months follow up. Hence, as a nutrition screening tool the MUST can be used to independently predict this outcome, as well as other outcomes such as LOS, and post-stroke complications. The importance of using MUST with stroke patients on admission is, therefore, highlighted since without the information this can bring, and the subsequent nutritional interventions, patients are likely to have poorer outcomes. Further research is clearly required to determine whether a particular feeding route and specific type of nutritional support might improve clinical outcomes in these patients.

CHAPTER 5

GENERAL DISCUSSION

5.1 Introduction

Although each chapter in this thesis contains its own discussion, this one collates and summarises the most important findings of the individual chapters and provides an overview of outline of the work contained, acknowledging its limitations. The chapter concludes by offering suggestions for future research, based on the results presented in this thesis, which could usefully explore their potential clinical application.

5.2 Summary of Chapters

Chapter two discussed the background of stroke as a medical condition, and its complications, with an especial focus on malnutrition both in dysphagic and non-dysphagic.. Additionally, it considered the patients prevalence, incidence, and the risk factors of stroke. Nutritional guidelines were discussed in detail, together with the evolution of nutrition screening tools such as the MUST technique, to assist in the management of nutrition. However, there were some gaps in knowledge, like how much malnutrition affect stroke' outcome, the existence of wide variations of prevalence of malnutrition that warranted a valid, reliable, simple and quick screening tool. Therefore, it is advisable to find out the most appropriate technique to screen for malnourishment and to predict its influence on clinical outcomes. This in turn will enable early nutritional intervention to improve outcome and save health resources.

Chapter three produced a systemic review, which discussed the influence of nutritional status on clinical outcomes in people after a stroke, and demonstrated that the current evidence for both the screening or assessment, and management of nutritional problems in stroke is limited with a low evidence base.

Chapter four explored the prevalence of malnutrition in acute stroke patients admitted to a secondary care facility, and whether the MUST tool could be used as an independent predictor of clinical outcome. It was demonstrated that the prevalence of undernutrition as identified in this study's sample, was within the range obtained in previously-published

studies. However, the prevalence of risk of malnutrition was lower than in other studies where patients with medical conditions rather than having had a stroke, were recruited. In contrast to national guidelines, MUST was seen not to have been administered in all newly-admitted patients. This would seem to be a serious omission since it is apparent from the findings that the MUST methodology can provide an independent prediction of certain outcomes (mortality, infection, and length of stay) among patients after acute stroke.

5.3 Overview of discussion points in thesis

5.3.1 Novel findings

In my systematic review presented in Chapter three, I highlighted the importance of nutritional status evaluation being completed as a routine procedure during the hospital admission process, as deterioration in nutritional status is believed to be associated with poorer clinical outcome. Although in the UK, nutritional screening is already applied in most healthcare settings, there remains a major need to accurately measure the prevalence of malnutrition or risk of malnutrition using an appropriate, validated, and clinically applicable test as a prelude to determining whether malnutrition has any influence on patients' clinical outcome.

The first consensus guidelines for using nutritional screening tools to sort out the serious public health problems caused by malnutrition have been developed by the Malnutrition Advisory Group (MAG). Malnourishment is not limited to the developing societies and now is a serious UK health issue, in contrast to the previously popular belief. In fact, malnutrition is usually underestimated and untreated in societies and hospitals, and there is currently no nutrition tool or set of guidelines which may respond to the rigorous criteria designed by the British Dietetic Association, Royal College of General Practitioners, and Scottish Intercollegiate Guidelines Network. The MAG guidelines are scientifically strict, evidence-based, and have been tested in the community (17). On the other hand, NICE has recommended guidance for screening for malnutrition, and the risk of malnutrition both in hospitals and out in the community. This guidance covers: screening for malnutrition and the malnutrition risk, the need for trained healthcare workers to administer the recommendation,

the requirement for all newly-admitted patients to be screened on admission and repeatedly every successive week, for screening to calculate the BMI, percentage of unintended weight loss, and the time over which food intake has been unintendedly reduced or for which there is likely to be no nutritional intake in future. The Malnutrition Universal Screening Tool (MUST) is capable of doing this (146). Hence, the future use of an accurate and validated nutrition screening tool to identify malnutrition will facilitate the recognition of those at risk of malnutrition, and be helpful in assessing the benefits of any dietary or treatment interventional programmes.

Although the MUST has been used in the UK as a nutrition screening technique in most hospitals, the results presented in Chapter four, provide one of the first descriptions of the precise prevalence of risk of malnutrition among patients after acute stroke, and allow for the suggestion that the MUST tool can be used as an independent predictor of clinical outcome with implications for future nutritional management, to be tested. Although the study by Gomes et al. (121) published in April 2016, attempted to focus on the latter issue, this study was already under way.

5.3.2 General Discussion

Malnutrition has become an important residual disability that is commonly seen in patients after a stroke with or without dysphagia. In addition, malnutrition is associated with poor clinical and functional outcome in these people (8, 78). Malnutrition has been defined as a deficiency of important nutrients that include energy, protein, vitamins and minerals such that significant negative effects on an individual's body composition and clinical outcome might well occur (99). The prevalence of malnutrition in stroke patients when admitted to hospital ranges according to the study. For example, it is reported as from 8% and 49% (10-14, 78), from 6.1 to 62% (15), and at 9% in the FOOD trial collaboration (3), whilst in Gomes et al. study (121) the prevalence of at risk was 7% and those at high risk was 29%. This wide discrepancy in prevalence could be attributed to many causes, which include both the nutritional markers and definitions of malnutrition which were different in many studies. For

instance, several studies have addressed nutritional screening or assessment methods using different types of nutritional parameters that include a range of anthropometric and haematological markers (8, 14, 16), whereas others have relied on clinicians' decisions (3) or patient-generated global assessment (13,115). The timing of assessment has also varied in these studies with some evaluations occurring within 24 hours (8, 115), others after 48 hours (13, 14), and yet others seven days after the onset of stroke (3). Additionally, in some studies, people after both ischemic and haemorrhagic strokes were assessed together (13, 14, 16, 47), even though malnutrition occurs more frequently in haemorrhagic compared to ischemic patients (8).

There is a difference between full nutritional assessments for malnutrition or risk of malnutrition and a nutritional screening. Nutritional screening is a quick, general, and often initial assessment of risk of malnutrition which can be performed by nurses, medical or other healthcare workers after a short course of training, to detect significant risk of malnutrition (undernutrition). Subsequent to the initial assessment, the evaluator can institute a definite regime in accordance with the nutrition policy, such as for example, generating simple food plans or referring the patient to a dietitian for advice. Nutritional assessment is a more elaborated, more specific, and more comprehensive assessment of nutritional status by a specialist. It aims to ensure that particular food plans can be actualised, and done so with more frequency for more difficult nutrition issues (17).

Several methods of assessment and screening for both malnutrition and the risk of malnutrition are applied in practice to evaluate body composition and nutritional status. Of these indicators, albumin, prealbumin, and transferrin serum level; body weight; body mass index; triceps skin-folds; and mid-arm muscle circumference have been most widely used (116). However, the strengths and weaknesses of each method need to be acknowledged in the evaluation of the degree of malnutrition, and a combination of more than one marker might be advisable in the absence of one gold standard (15). Currently, the most precise and accurate tools for measuring body composition in medical practice are dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), and computed tomography (CT). However, there are other tools that are more practical and easy to use in healthcare settings and in research (98).

There are more than three million individuals in the UK potentially at risk of undernourishment (130), yet despite this epidemic, undernutrition is both under-perceived

and under-treated. Additionally, the community health services expenditure on diseases associated with malnutrition in the Britain in 2007 was estimated to be more than £13 billion annually, of which around 80% was in England (130). This is a substantial burden not just for individuals, but also for national health and social care settings, and the community in general.

Although several nutritional tools are available in practice to provide information about the general aspect of nutritional status, they fail to recognise more specific issues such as accurate malnutrition assessment, its prevalence and its effect on clinical outcome. For example, dietary evaluation relies on patients self-reporting, but due to communication difficulties and inconsistent recounting, it is difficult to accurately obtain body mass index (BMI) with presumed typical fat and muscle distribution. Additionally, in bed-ridden stroke patients, BMI as a simple and quick measure to assess patient's nutrition is inapplicable in practice sometimes. In these situations, surrogate measures might be used to measure weight and height. For example, in patients who are unable to stand, recalled height, that is, height estimated using a patient's ulna length is used, and also usual weight before the illness or hospital admission can be collected from the patients and/or their relatives, or indeed medical notes can be used. In cases where weight or height are unobtainable, subjective criteria such as a patient's physical appearance (e.g. very thin, thin etc.) could be used, together with a measurement of MUAC < 235 mm to identify individuals with BMI < 20 kg/m2 (62). In the case of bioelectrical impedance analysis (BIA), the subject must have fasted and his/her internal fluid balance must be in equilibrium. That said, when compared with BMI and self-reporting, BIA is considered the best tool (131). However, there are some techniques that have been developed to attempt to unify and simplify nutritional status, and these are increasingly being recommended for use in screening malnutrition internationally. Of these screening tools, the Malnutrition Universal Screening Tool (MUST) has received most attention.

In Chapter three, the systematic review of the literature aimed to comprehensively explore issues relating to the nutritional status of patients after stroke, and the influence of such status on clinical outcomes (length of hospital stay, infections, and mortality rate). All the studies reviewed provided some evidence that being malnourished or at risk of malnutrition can be used as an independent predictor of clinical outcome in patients after a stroke (3, 121). Gomes and colleagues (121) revealed, through the use of the MUST, that risk of malnutrition is an independent predictor of mortality, LOS, and hospitalisation costs six months after a

chronic stroke. In another study (3) it was revealed that people with malnutrition immediately after a stroke are more prone to reduced survival, functional ability, and independency after six months of stroke onset.

Generally, all the included studies in this review provided a reasonable level of evidence that being malnourished or at risk of malnutrition can be used as an independent predictor of clinical outcome in patients after a stroke. Indeed, most patients in these studies underwent nutritional evaluation as part of their routine admission procedure, whereby multiple screening and assessment techniques were used to establish their nutritional status; clearly, the use of these techniques offers a practical, precise, and simple way to identify those who are more prone to develop post-stroke complications, and poor clinical outcomes. However, it remains unclear as to which of these techniques is the most beneficial.

In Chapter four, I reported on my retrospective observational cohort study which revealed that the prevalence of malnutrition among patients after a stroke was 21.4%, which is in keeping with the findings of previously published studies (10-15, 78, 143), albeit in a much larger cohort than previously reported. For example, Foley and colleagues (15) revealed that the prevalence of malnutrition in patients after a stroke varies widely from 6.1-62%, whereas in the Chai et al. study (78), the prevalence of malnutrition in these patients when admitted to hospital ranges from 8% and 49%.

On the other hand, in my study with post-stroke patients, the prevalence of risk of malnutrition was low compared to the prevalence of malnutrition or risk of malnutrition in other reported studies (136-140) that collected patients from other departments (e.g., surgery, geriatric, cardiology, gastroenterology, urology, gynaecology, rheumatology, and oncology). Given the many risk factors of stroke and associated diseases that are potentially operative in stroke patients, the low prevalence of risk of malnutrition in these patients would seem to be encouraging.

Interestingly, my study showed that the MUST, as a nutritional screening tool, has good predictive ability, and can be used as an independent indicator of mortality rate, both in hospital and after six months follow-up, LOS, and post-stroke clinical complications (pneumonia, and urinary tract infection). To further explain the previous point, in this study by using mortality (death in hospital and death after six months follow up), LOS, and post-stroke complications as endpoints, it has been shown that MUST is not simply an abstract method but can be related to real clinical outcomes, and thus has prognostic value when

screening for risk of malnutrition in patients after a stroke. If a patient is defined as at high risk by the MUST screening tool, the implication is that she/he has a higher incidence of death, a higher risk of LOS, and is more prone to post-stroke complications, thereby suggesting that early nutritional interventions should be made since these would be likely to improve their clinical outcomes and ultimately save resources.

In the study by Stratton et al. study (132), where the researchers assessed the validity of the MUST technique together with seven other tools, it was found that MUST has good to excellent validity as a nutritional screening tool.

Gomes et al. (121) have revealed that the greater the risk of malnourishment, the higher the rate of mortality after six months of follow-up (chi-square test, $P<0.001$). This finding was consistent with my finding, where patients with high risk of malnutrition were more prone to die during the six months follow-up compared to those with no risk or being at risk of malnutrition (chi-square test, $P\leq0.001$). In the same study (121), the median number of length of stay in a period of six months was three times higher in patients with a high risk of malnutrition; similarly, in my study I found that the greater the risk of malnutrition, the higher the risk of longer LOS ($P\leq 0.023$ and 0.033).

Additionally, Lim and colleagues (143) have reported that being at risk of malnourishment was associated with longer LOS (6.9 versus 4.6 days) and a four-fold increase in death after one year of follow-up. My findings, in a much larger cohort are in agreement with that study.

Furthermore, in one study conducted in the UK (144) it was found that high risk of malnourishment was associated with a two-fold increase in LOS and mortality rate. Again this reported finding is consistent with that obtained in my study.

In the two studies by Shen et al. (141), and Yoo et al (48), malnutrition was an important independent factor of post-stroke complications and clinical outcome of patients after acute stroke. By comparing my results with those presented by Shen et al. and Yoo et al., it is seen that my findings and theirs are completely consistent.

5.3.3 Implications for Further Research

This thesis has assessed the influence of nutritional status on the clinical outcome of post-stroke people, and has simultaneously evaluated the ability of the Malnutrition Universal Screening Tool (MUST) to determine the risk of malnutrition, and predict clinical outcome in the secondary care setting. However, further research is required to discover which type of nutritional screening tool is the most beneficial in the assessment of nutritional status, and also to establish the exact prevalence of malnutrition among patients after both acute and chronic stroke, in hospital and in the community. BAPEN has recommended the most beneficial way to determine which type of nutrition screening tool most successfully evaluates nutritional status and the precise prevalence of malnutrition or malnutrition risk (17). According to that recommendation, the screening method should be: simple and understandable, rapid to implement, acceptable to both patients and the healthcare team, valid, reliable, and evidence-based. The scoring system of the screening tool should also be incorporated, applicable, and related to different clinical conditions (including patients after a stroke) and healthcare settings, and be relevant to a care policy. The following issues should also be addressed by the screening technique: patient's current weight (using BMI), previous and any likely future change in weight, both of which are linked to nutrition intake and severity of the disease. Objective methods should be applied whenever possible and subjective criteria only used when needed. Moreover, the screening tool should assist rather than replace clinical assessment.

In addition, it would be important to understand that the impact on clinical outcomes could be modified by a more intensive nutritional management intervention (e.g. supplement feeding, greater dietician input, more robust screening, etc.).

In this thesis, I have attempted to answer some of the above mentioned questions by assess the role of the Malnutrition Universal Screening Tool (MUST) in determining the risk of malnutrition and predicting clinical outcome in patients after stroke. Moreover, it has been shown that the MUST is effective in this respect. However, there are some limitations associated with it, one being the high rotation of nursing staff in health care settings, and the lack of training in how to apply the MUST in practice. If the MUST is properly applied, then the problem of missing data would not arise, but certainly in this study, because of the inconsistent application of the MUST methodology, the amount of missing data (e.g. missing MUST test on admission, referral to Dietician, and local care pathways for patients'

nutritional care, and follow up) curtailed the ability to accurately identify patient outcomes, as these outcomes themselves might have been affected by the absence of the required data. Other difficulties associated with the study include being able to obtaining measurements for patients who were immobilised. For instance, obtaining past weight, if not known by the patients or their relatives, was time-consuming as it involved searching through old medical files or contacting care homes or patients' GPs. Likewise, not all details were provided about feeding regimes, and further study might be might be justified in order to explore whether a particular route of feeding and a specific nutritional support might improve clinical outcomes in these patients.

5.3.4 Summary

In summary, the research presented in this thesis provides valuable and novel insights into the role of the MUST technique in recognising patients after stroke who are at risk of malnutrition. It also highlights the importance of the MUST as an independent predictor of post-stroke clinical complications and outcomes. Therefore, the MUST technique presents itself as one that can be effectively used in healthcare settings to help predict risk of malnutrition in patients after a stroke. The consequence is that early nutritional intervention has the potential to improve patients' outcomes and reduce health services costs. While further work is needed to support my contention, my findings do add to the current literature and provide further evidence that malnutrition plays a critical role in influencing health care in the UK.

REFERENCES

[1]. World Health Organization. The global burden of disease. Update 2004. Available at: www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed May 11, 2017.

[2]. Kwan J. Clinical epidemiology of stroke. CME Journal Geriatric Medicine 2001;3(3): 94–8

[3]. FOOD Trial Collaboration. Poor nutritional status on admission predicts poor outcomesafter stroke: observational data from the FOOD trial. Stroke. 2003;34 (6):1450-1456.

[4]. Finestone HM, Greene-Finestone LS, Wilson ES, Teasell RW. Malnutrition in stroke patients on the rehabilitation service and at follow-up: prevalence and predictors. Arch Phys Med Rehabil 1995;76(4):310-6.

[5]. Davalos A, Ricart W, Gonzalez-Huix F, Soler S, Marrugat J, Molins A, et al. Effect of malnutrition after acute stroke on clinical outcome. Stroke 1996;27(6):1028-32.

[6]. Gariballa SE, Parker SG, Taub N, Castleden CM. Nutritional status of hospitalized acute stroke patients. Br J Nutr 1998;79(6):481-7.

[7]. Chai J, Chu FCS, Chow TW, Shum NC. Prevalence of malnutrition and its risk factors in stroke patients residing in an infirmary. Singapore Med J. 2008 Apr; 49(4):290-6. PubMed PMID: 18418520.

[8]. Choi-Kwon S, Yang YH, Kim EK, Jeon MY, Kim JS. Nutritional status in acute stroke: undernutrition versus overnutrition in different stroke subtypes. Acta Neurol Scand. 1998;98(3):187-192.

[9]. Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: Identification and management of dysphagia. Edinburgh: SIGN; 2010. (SIGN publication no. 119). [cited 04 May 2010]. Available from url: http://www.sign.ac.uk

[10]. Axelsson K, Asplund K, Norberg A, Alafuzoff I. Nutritional status in patients with acute stroke. Journal of Internal Medicine. 1988 Jan 12;224(3):217-24.

[11]. Unosson M, Ek AC, Bjurulf P, von Schenck H, Larsson J. Feeding dependence and nutritional status after acute stroke. Stroke 1994; 25:366-71.

[12]. Finestone HM, Greene-Finestone LS, Wilson ES, Teasell RW. Prolonged length of stay and reduced functional improvement rate in malnourished stroke rehabilitation patients. Arch Phys Med Rehabil 1996; 77:340-5.

[13]. Martineau J, Bauer JD, Isenring E, Cohen S. Malnutrition determined by the patient-generated subjective global assessment is associated with poor outcomes in acute stroke patients. Clinical nutrition. 2005 Dec 31;24(6):1073-7.

[14]. Gariballa SE, Parker SG, Taub N, Castleden CM. Influence of nutritional status on clinical outcome after acute stroke. The American journal of clinical nutrition. 1998 Aug 1;68(2):275-81.

[15]. Foley N, Salter K, Robertson J, Teasell R, Woodbury M. "Which reported estimate of the prevalence of malnutrition after stroke is valid?" Stroke. 2009, vol. 40, no. 3, pp. e66–e74.

[16]. Da´valos A, Ricart W, Gonzalez-Huix F, et al. Effect of malnutrition after acute stroke on clinical outcome. Stroke. 1996;27(6):1028-1032.

[17]. BAPEN: the British Association for Parenteral and Enteral Nutrition. Malnutrition and Nutritional Care in the UK – BAPEN [internet]. 2016 [cited 13 June 2017]. Available from: http://www.bapen.org.

[18]. Hatano S . Experience from a multicentre stroke register: a preliminary report. Bulletin of the Wornold Health Organization . (1976)54: 541–53.

[19]. Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) Issued: July 2008 NICE clinical guideline 68 guidance.nice.org.uk/cg68.

[20]. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. Neurology. 2013 Jul 16;81(3):264-72. doi: 10.1212/WNL.0b013e31829bfde3. Review. PMID: 23858408 [PubMed - indexed for MEDLINE] .

[21]. Mathers C, Boerma T, Fat Ma D. The global burden of disease: 2004 update. World Health Organization; Geneva: 2008.

[22]. Scherbakov N, Doehner W. Sarcopenia in stroke—facts and numbers on muscle loss accounting for disability after stroke. Journal of Cachexia, Sarcopenia and Muscle 2011;2(1):5-8. doi:10.1007/s13539-011-0024-8.

[23]. Suiter DM, Easterling CS. Update on current treatment and practice patterns for dysphagia. Top Geriatr Rehabil 2007; 23(3):197-210.

[24]. European Registers of Stroke (EROS) Investigators. Incidence of stroke in Europe at the beginning of the 21st century. Stroke. 2009 May 1;40(5):1557-63.

[25]. Go AS., Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127(1):143-52. Epub 2013/01/04.

[26]. Atlantis, ECASS and NINDs rt-PA study group investigator. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363:768–74.

[27]. Redon J, Olsen MH, Cooper RS, Zurriaga O. Martinez-Beneito, MA.; Laurent, S.; Cifkov, R.; Coca, A.; Mancia, G. Stroke mortality and trends from 1990 to 2006 in 39 countries from Europe and Central Asia: implications for control of high blood pressure. European Heart Journal. 32(11):1424-31, 2011 Jun.[Journal Article. Multicenter Study].

[28]. Warlow C, van Gijn J, Dennis M, et al. Stroke: Practical Management. 3rd ed. Malden, MA: Blackwell; 2008.

[29]. Fieschi C, Fisher M, eds. Prevention of Ischemic Stroke. London: Martin Dunitz; 2000.

[30]. Fernanda M, Marcela C, Julio F, Michelle T. "How Can Diet Influence the Risk of Stroke?," International Journal of Hypertension, vol. 2012, Article ID 763507, 7 pages, 2012. doi:10.1155/2012/763507.

[31]. Adult Treatment Panel III, Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report. Circulation, 106 (2002), pp. 3143–3421.

[32]. Office of National Statistics Population trends. PT 118, table 1.4 (population age and sex). London: 2004, ONS.

[33]. Hickson M. Malnutrition and ageing. Postgraduate Medical Journal. 2006 Jan, 82(963):2-8,.

[34]. Office for National Statistics Living in Britain: results from the 2002 General Household Survey. London: 2004, ONS.

[35]. Kyle U G, Genton L, Hans D, et al. Total body mass, fat mass, fat-free mass, and skeletal muscle in older people: cross-sectional differences in 60-year-old persons. J Am Geriatr Soc 2001. 491633–1640.1640 [PubMed.]

[36]. Baumgartner RN., Stauber P M, McHugh D, et al. Cross-sectional age differences in body composition in persons 60+ years of age. J Gerontol A Biol Sci Med Sci 1995. 50M307–M316.M316 [PubMed].

[37]. Forbes GB, Reina J C. Adult lean body mass declines with age: some longitudinal observations. Metabolism 1970. 19653–663.663 [PubMed]

[38]. Novak LP. Ageing, total body potassium, fat-free mass, and cell mass in males and females between ages 18 and 85 years. J Gerontol 1972. 27438–443.443 [PubMed]

[39]. Ruscin JM, Page RL II, Yeager BF, et al. Tumor necrosis factor-alpha and involuntary weight loss in elderly, community-dwelling adults. Pharmacotherapy 2005;25:313–9 [PubMed] [Ref list].

[40]. Goldeberg, RJ, Kaplan LA, Boucher LJ. Physicians' attentiveness to medication use as etiology of weight loss. Long term care interface 2005;6:20–3.

[41]. Gilmore SA, Robinson G, Posthauer ME, et al. Clinical indicators associated with unintentional weight loss and pressure ulcers in elderly residents of nursing facilities. J Am Diet Assoc 1995;95:984–92 [PubMed]

[42]. Kuczmarski RJ. Need for body composition information in elderly subjects. Am J Clin Nutr 1989. 50(suppl 5)1150–1157.1157 [PubMed]

[43]. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D. Cachexia: a new definition. Clinical nutrition. 2008 Dec 31;27(6):793-9.

[44]. Yeh SS, Schuster MW. Geriatric cachexia: the role of cytokines. Am J Clin Nutr 1999. 70183–197.197 [PubMed]

[45]. Roubenoff R. The pathophysiology of wasting in the elderly. J Nutr 1999. 129(uppl 1)256–9S.9S [PubMed]

[46]. Jeejeebhoy KN. Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. Curr Opin Clin Nutr Metab Care. 2012;15(3):213–219.

[47]. Bouziana SD, Tziomalos K. Malnutrition in patients with acute stroke. Journal of nutrition and metabolism. 2011 Dec 27;2011.

[48]. Yoo SH, Kim JS, Kwon SU, Yun SC, Koh JY, Kang DW. Undernutrition as a predictor of poor clinical outcomes in acute ischemic stroke patients. Archives of neurology. 2008 Jan 1;65(1):39-43.

[49]. Wang J, Luo B, Xie Y, Hu H, Feng L, Li Z. Evaluation methods on the nutritional status of stroke patients. Eur Rev Med Pharmacol Sci. 2014 Dec;18(24):3902-7. PMID: 25555882 [PubMed - in process].

[50]. Mann G, Hankey GJ, Cameron D. Swallowing function after stroke: prognosis and prognostic factors at 6 months. Stroke. 1999;30:744–748. [PubMed]

[51]. Smithard DG, O'Neill PA, Parks C, Morris J. Complications and outcome after acute stroke. Does dysphagia matter? Stroke. 1996;27:1200–1204. [PubMed]

[52]. Smithard DG, Smeeton NC, Wolfe CD. Long-term outcome after stroke: does dysphagia matter? Age Ageing. 2007;36:90–94. [PubMed]

[53]. Paciaroni M, Mazzotta G, Corea F, et al. Dysphagia following Stroke. Eur Neurol. 2004;51:162–167. [PubMed]

[54]. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke. stroke. 2005 Dec 1;36(12):2756-63.

[55]. Carnaby-Mann G, Lenius K, Crary M. Update on Assessment and Management of Dysphagia Post Stroke. Northeast Florida Medicine. 2007;58:31–34.

[56]. World Health Organization: Obesity and overweight: fact sheet N0 311. 2012, http://www.who.int/mediacentre/factsheets/fs311/en/index.html.

[57]. Kuczmarski RJ, Flegal KM. Criteria for definition of overweight in transition: background and recommendations for the United States. Am J Clin Nutr. 2000, 72 (5): 1074-1081.

[58]. Buss J. "Limitations of Body Mass Index to Assess Body Fat." Workplace Health & Safety. 2014, 62(6): 264-264.

[59]. Rothman KJ. "BMI-related errors in the measurement of obesity." Int J Obes. 2008, 32(S3): S56-S59.

[60]. Elia M, Russell C, Stratton R, et al. The "MUST" explanatory booklet—a guide to the "Malnutrition Universal Screening Tool" ("MUST") for adults BAPEN (2003).

[61]. Mudge AM, Ross LJ, Young AM, Isenring EA, Banks MD .Helping Understand Nutritional Gaps in the Elderly (HUNGER): a prospective study of patient factors

associated with inadequate nutritional intake in older medical inpatients Clin Nutr, 30 (2011), pp. 320–325.

[62]. Watterson C, Fraser A, Banks M, Isenring E , Silvester C, Hoevenaars R, et al. Evidence based practice guidelines for nutritional management of malnutrition in adult patients across the continuum of care Nutr Diet, 66 (2009), pp. S1–S34. View Record in Scopus | Citing articles (128)

[63]. Kondrup JE, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clinical nutrition. 2003 Aug 31;22(4):415-21.

[64]. Mueller C, Compher C, Ellen DM. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults JPEN J Parenter Enteral Nutr, 35 (2011), pp. 16–24. CrossRef | View Record in Scopus | Citing articles (183).

[65]. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients Nutrition, 15 (1999), pp. 458–464.

[66]. Sorensen J, Kondrup J, Prokopowicz J, Schiesser M, Krähenbühl L, Meier R, Liberda M. EuroOOPS: an international, multicentre study to implement nutritional risk screening and evaluate clinical outcome Clin Nutr, 27 (2008), pp. 340–349.

[67]. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF) J Gerontol A Biol Sci Med Sci, 56 (2001), pp. M366–M372.

[68]. Wilson MMG, Thomas DR, Rubenstein LZ, Chibnall JT, Anderson S, Baxi A, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents Am J Clin Nutr, 82 (2005), pp. 1074–1081.

[69]. Visvanathan R, Penhall R, Chapman I . Nutritional screening of older people in a sub-acute care facility in Australia and its relation to discharge outcomes Age Ageing, 33 (2004), pp. 260–265.

[70]. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment of nutritional status?JPEN J Parenter Enteral Nutr, 11 (1987), pp. 8–13.

[71]. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: the Mini Nutritional Assessment as part of the geriatric evaluation Nutr Rev, 54 (1996), pp. S59–S65.

[72]. Charney P. Nutrition screening vs nutrition assessment: how do they differ?. Nutrition in Clinical Practice. 2008 Aug;23(4):366-72.

[73]. Young AM, Kidston S, et al. "Malnutrition screening tools: Comparison against two validated nutrition assessment methods in older medical inpatients." Nutrition (2013). 29(1): 101-106.

[74]. Meijers JMM, Vanderschueren MAE, Schols J, Soeters PB, Halfens RJG. Defining malnutrition: Mission or mission impossible? Nutrition, 26 (2010), pp. 432–440

[75]. Nightingale JMD, Walsh N, Bullock ME, Wicks AC. Three simple methods of detecting malnutrition on medical wards / R Soc Med 1996; 89: 144-8.

[76]. Dennis M. Nutrition after stroke. Br Med Bull. 2000;56(2):466-75. Review. PMID: 11092095 [PubMed - indexed for MEDLINE].

[77]. Klipstein-Grobusch K, Redly JJ, Potter J, Edwards CA, Roberts MA. Energy intake andexpenditure in elderly patients admitted to hospital witli acute illness BrJ Nutr 1995, 73. 323-34.

[78]. Jo¨nsson AC, Lindgren I, Norrving B, Lindgren A. Weight loss after stroke: a population-based study from the Lund Stroke Register. Stroke . 2008;39:918 –923.

[79]. Scherbakov N, Dirnagl U, Doehner W. Body weight after stroke, lessons from the obesty Paradox. Stroke. 2011 Dec;42(12):3646-50. doi: 10.1161/STROKEAHA.111.619163. Epub 2011 Sep 29. PMID: 21960580 [PubMed - indexed for MEDLINE].

[80]. World Health Organization. The World Health Report 2002 – Reducing Risks, Promoting Healthy Life. (2002) Geneva: World Health Organization.

[81]. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R & Rayner M. (2012) Coronary Heart Disease Statistics, 2012th edn. London: British Heart Foundation.

[82]. Sousa RM, Ferri CP, Acosta D, Albanese E, Guerra M, Huang Y, Jacob KS, Jotheeswaran AT, Rodriguez JJ, Pichardo GR, Rodriguez MC. Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. The Lancet. 2009 Dec 4;374(9704):1821-30.

[83]. World Health Organization. The Atlas of Heart Disease and Stroke. Geneva (2004): World Health Organization.

[84]. Royal College of Physicians Intercollegiate Stroke Working Party. (2011) National Sentinel Stroke Clinical Audit 2010, Round 7. Public report for England, Wales and Northern Ireland.

[85]. Jonsson AC, Lindgren I, Norrving B & Lindgren A. Weight loss after stroke: A population-based study from the Lund Stroke Register. Stroke (2008) 39, 918–923.

[86]. Stratton R, Green CJ, Elia M. Disease-related malnutrition. An evidence based approach to treatment. CABI Publishing; 2003.

[87]. Norman K, Pichard C, Lochs H, Pirlich M: Prognostic impact of disease-related malnutrition. Clin Nutr 2008, 27: 5–15. 10.1016/j.clnu.2007.10.007.

[88]. Howard P, Jonkers-Schuitema C, Furniss L, Kyle U, Muehlebach S, Ödlund-Olin A, Page M, Wheatley C. Managing the patient journey through enteral nutritional care. Clinical nutrition. 2006 Apr 30;25(2):187-95.

[89]. Perry L, McLaren S. Implementing evidence-based guidelines for nutrition support in acute stroke. Evidence-based nursing. 2003 Jul 1;6(3):68-71.

[90]. Rowat A. Enteral tube feeding for dysphagic stroke patients. Br. J. Nurs. 2015, 24, 138–144. [Google Scholar] [CrossRef] [PubMed].

[91]. Royal College of Physicians. National Clinical Guideline for Stroke, fifth edition 2016; 70-71.

[92]. Wirth R, et al. "Guideline clinical nutrition in patients with stroke." Experimental & Translational Stroke Medicine. (2013) 5(1): 14.

[93]. Takahata H, Tsutsumi K, Baba H, Nagata I, Yonekura M. Early intervention to promote oral feeding in patients with intracerebral hemorrhage: a retrospective cohort study. BMC Neurology. 2011;11:6. doi:10.1186/1471-2377-11-6.

[94]. FOOD Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. The Lancet. 2005 Mar 4;365(9461):764-72.

[95]. Ickenstein GW, Stein J, Ambrosi D, Goldstein R, Horn M, Bogdahn U. Predictors of survival after severe dysphagic stroke. J Neurol 2005, 252 :15106.

[96]. Grant MD, Rudberg MA, Brody JA. Gastrostomy placement and mortality among hospitalized Medicare beneficiaries. JAMA 1998, 279 :1973-6

[97]. Ling CH, de Craen AJ, Slagboom PE, Gunn DA, Stokkel MP, Westendorp RG, Maier AB.Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr. 2011 Oct;30(5):610-5. doi: 10.1016/j.clnu.2011.04.001. Epub 2011 May 8. PMID: 21555168 [PubMed - indexed for MEDLINE].

[98]. Thibault R, Pichard C. The evaluation of body composition: a useful tool for clinical practice. Annals of Nutrition and Metabolism. 2012;60(1):6-16.

[99]. National Collaborating Centre for Acute Care (UK. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition.

[100]. Kotler D, Burastero S, Wang J, Pierson RN. Prediction of body cell mass, fat-free mass, and total body water with bioelectrical impedance analysis: effects of race, sex, and disease. Am J Clin Nutr 1996; 64: 489S–497SS. | PubMed | CAS |

[101]. Schols AM, Wouters EF, Soeters PB, Wester-terp KR: Body composition by bioelectrical-impedance analysis compared with deuteri-um dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 1991; 53: 421–424.

[102]. Thibault R, Le Gallic E, Picard-Kossovsky M, Darmaun D, Chambellan A: Assessment of nutritional status and body composition in patients with COPD: comparison of sev-eral methods (in French). Rev Mal Respir 2010; 27: 693–702.

[103]. Thibault R, L Genton, et al. "Body composition: Why, when and for who?" Clinical Nutrition 2012;. 31(4): 435-447.

[104]. Bolton CE, Ionescu AA, Shiels KM, Pettit RJ, Edwards PH, Stone MD, Nixon LS, Evans WD, Griffiths TL, Shale DJ. Associated loss of fat-free mass and bone mineral

density in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 170: 1286–1293.

[105]. Kyle UG, Bosaeus I, De Lorenzo AD, Deu-renberg P, Elia M, Gómez JM, Heitmann BL, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H, Schols AM, Pichard C, Com-position of the ESPEN Working Group. Bio-electrical impedance analysis. part 1. Review of principles and methods. Clin Nutr 2004; 23: 1226–1243.

[106]. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, Heitmann BL, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H. Bioelectrical impedance analysis—part II: utilization in clinical practice. Clinical nutrition. 2004 Dec 31;23(6):1430-53.

[107]. Jaffrin MY, Morel H: Body fluid volumes measurements by impedance: A review of bioimpedance spectroscopy (BIS) and bioimpedance analysis (BIA) methods. Med Eng Phys. 2008, 30 (10): 1257-1269.

[108]. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, Korth O, Müller MJ, Ellegård L, Malmros V, Kaitwatcharachai C. Body fluid volume determination via body composition spectroscopy in health and disease. Physiological measurement. 2006 Jul 25;27(9):921.

[109]. Kafri M., et al. "Multi-frequency bioelectrical impedance analysis for assessing fat mass and fat-free mass in stroke or transient ischaemic attack patients." Eur J Clin Nutr 2014; 68(6): 677-682.

[110]. Jalalzadeh M, Hajiesmaeili M. "Bio-Electrical Impedance Analysis in Patients with Critical Illnesses." Nephrourol Mon 2017;9(1): e41514.

[111]. Tan BHL, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009; 15: 6973–6979.

[112]. Walston JD. Stroke in older adults. Curr Opin Rheumatol. 2012 Nov;24(6):623-7. Review.PMID: 22955023 [PubMed - indexed for MEDLINE].

[113]. Dufour AB, Hannan MT, Murabito JM, et al. Sarcopenia definitions considering body size and fat mass are associated with mobility limitations: The Framingham Study. J Gerontol A Biol Sci Med Sci. 2012 Epub ahead of print.

[114]. Scherbakov N, Von Haehling S, Anker SD, Dirnagl U, Doehner W. Stroke induced Sarcopenia: Muscle wasting and disability after stroke: Int J Cardiol. 2013 Dec 10;170(2):89-94. doi: 10.1016/j.ijcard.2013.10.031. Epub 2013 Oct 14. Review.PMID: 24231058 [PubMed - indexed for MEDLINE].

[115]. Davis JP, Wong AA, Schluter PJ, Henderson RD, O'Sullivan JD. Impact of premorbid undernutrition on outcome in stroke patients. Stroke. 2004 Aug 1;35(8):1930-4.

[116]. Corrigan M, Escuro A, Celestin J, Kirby D. "Nutrition in the stroke patient," Nutrition in Clinical Practice 2011, vol. 26, no. 3, pp. 242–252.

[117]. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med 2008;6:e1000097. 10.1371/journal.pmed.1000097.

[118]. Fitzner K. Reliability and validity: a quick review. Diabetes Educ..2007;33(5):775-780.

[119]. Critical Appraisal Skills Programme (CASP). CASP Checklists (URL used) Oxford. CASP. 2014.

[120]. Nip W, Perry L, McLaren S, Mackenzie A. Dietary intake, nutritional status and rehabilitation outcomes of stroke patients in hospital. Journal of Human Nutrition and Dietetics. 2011;24(5):460-9.

[121]. Gomes F, et al. Risk of Malnutrition Is an Independent Predictor of Mortality, Length of Hospital Stay, and Hospitalization Costs in Stroke Patients. J Stroke Cerebrovasc Dis. (2016).

[122]. Lisa H, et al. Body composition in older acute stroke patients after treatment with individualized, nutritional supplementation while in hospital. BMC Geriatr. (2010).

[123]. Rabadi MH, Coar PL, Lukin M, Lesser M, Blass JP. Intensive nutritional supplements can improve outcomes in stroke rehabilitation. Neurology. 2008 Dec 2;71(23):1856-61.

[124]. Lisa H, et al. Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: a randomized, controlled trial. Clin Nutr. (2010).

[125]. Geeganage C, et al. Interventions for dysphagia and nutritional support in acute and subacute stroke. Cochrane Database Syst Rev. (2012)

[126] Dennis MS, Lewis SC, Warlow C, et al. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomized control trial. Lancet 2005;365:755–763.

[127]. Mead G, Donaldson L, North P, Dennis M. An informal assessment of nutritional status in acute stroke for use in an international multicentre trial of feeding regimens. Int J Clin Pract. 1998;52:316–318.

[128]. Olde Rikkert MG, Deurenberg P, Jansen RW, van't Hof MA, Hoefnagels WH. Validation of multifrequency bioelectrical impedance analysis in monitoring fluid balance in healthy elderly subjects. J Gerontol A Biol Sci Med Sci 1997, 52(3):M137-41.

[129]. World Health Organization. STEP wise approach to stroke surveillance 2011, [cited 15 December 2016]. Availablefrom:http: //www.who.int/chp/ steps/stroke/ en/index.html.

[130]. Elia M, Russell CA. Combating malnutrition: Recommendations for action: A report from the Advisory Group on Malnutrition led by BAPEN,2009.

[131]. Androutsos O, Gerasimidis K, Karanikolou A, Reilly JJ, Edwards CA. Impact of eating and drinking on body composition measurements by bioelectrical impedance. J Hum Nutr Diet 2014; e-pub ahead of print 26 August 2014; doi:10.1111/jhn.12259.

[132]. Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, King C, Elia M. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool'('MUST') for adults. British Journal of Nutrition. 2004 Nov;92(5):799-808.

[133]. Russell CA, Elia M. Nutrition screening survey in the UK and Republic of Ireland in 2010 .A report by BAPEN,2011.

[134]. Miyata S, Tanaka M, Ihaku D. The prognostic significance of nutritional status using malnutrition universal screening tool in patients with pulmonary tuberculosis. Nutrition Journal. 2013;12:42. doi:10.1186/1475-2891-12-42.

[135]. Royal College of Physicians, Sentinel Stroke National Audit Programme (SSNAP). Retrieved from https://www.strokeaudit.org .Accessed November, 2016.

[136]. Agarwal E, Ferguson M, Banks M, Bauer J, Capra E. Isenring Nutritional status and dietary intake of acute care patients: results from the Nutrition Care Day Survey 2010 Clinical Nutrition, 31 (2012), pp. 41-47, 10.1016/j.clnu.2011.08.002.

[137]. Imoberforf R, Meier R, Krebs P, et al. Prevalence of undernutrition on admission to Swiss hospitals Clinical Nutrition, 29 (1) (2009), pp. 38-41

[138]. Pirlich M, Schütz T, Norman K, et al. The German hospital malnutrition study

Clinical Nutrition, 25 (2006), pp. 563-572, 10.1016/j.clnu.2006.03.005.

[139]. Correia M, Campos A. Prevalence of hospital malnutrition in Latin America: the multicenter ELAN study Nutrition, 19 (10) (2003), pp. 823-825

[140]. Waitzberg D, Caiaffa W, Correia M. Hospital malnutrition: the Brazilian national survey (IBRANUTRI): a study of 4000 patients Nutrition, 17 (7–8) (2001), pp. 573-580.

[141]. Shen HC, Chen HF, Peng LN, Lin MH, Chen LK, Liang CK, Lo YK, Hwang SJ. Impact of nutritional status on long-term functional outcomes of post-acute stroke patients in Taiwan. Archives of gerontology and geriatrics. 2011 Oct 31;53(2):e149-52.

[142]. Stratton L, Kingm C, Stroudm M. "Malnutrition Universal Screening Tool" predicts mortality and length of hospital stay in acutely ill elderly, Br J Nutr, 95 (2006), pp. 325–330 http://dx.doi.org/10.1079/bjn20051622.

[143]. Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clinical nutrition. 2012 Jun 30;31(3):345-50.

[144]. Department of Health.Payment by Results in the NHS—tariff information spreadsheet for 2012 to 2013.Version current 25 March 2013 Available at: https://www.gov.uk/government/publications/confirmation -of-payment-by-results-pbr-arrangements-for-2012-13 Accessed November, 2016.

[145]. Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A, Kapral MK. Impracticability of informed consent in the Registry of the Canadian Stroke Network. New England Journal of Medicine. 2004 Apr 1;350(14):1414-21.

[146]. NICE: National Institute for Health and Care Excellence. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition [internet]. 2017 [cited 24 August 2017].

APPENDICES

Appendix A

Quality Assessment (CASP tool) of Cohort Studies

Questions	Nip et al. (120)	Gomes et al. (121)
1. Did the study address a clearly focused issue?	Yes	Yes
2. Was the cohort recruited in an acceptable way?	Yes	Yes
3. Was the exposure accurately measured to minimise bias?	Yes	Yes
4. Was the outcome accurately measured to minimise bias?	Yes	Yes. N.B: blinding of subjects and assessors toward outcome measurement was unknown.
5. (a) Have the authors identified all important confounding factors? (b) Have they taken account of the confounding factors in the design and/or analysis?	No Yes	Yes Yes
6. (a) Was the follow up of subjects complete enough? (b) Was the follow up of subjects long enough?	No No	Yes Yes
7. What are the results of this study?	Younger age, lower Barthel index and a higher energy intake in the early stages of admission predict the extent and rate of restoration of functional ability by discharge.	There was a highly significant increase in mortality with increasing risk of malnutrition. The LOS and hospitalisation costs increased with increasing risk of malnutrition.
8. How precise are the results?	Confidence intervals unknown	The 95% CIs of different variables that included risk of malnutrition (medium or high), age, severity of stroke, hypertension and heart failure on six months mortality were as follows: 1.59-7.73, 3.23-9.69, 1.02-1.08, 1.05-1.13, 1.3-3.8 and 1.54-6.64, respectively.
9. Do you believe the results?	No	Yes
10. Can the results be applied to the local population?	Yes	Yes
11. Do the results of this study fit with other available evidence?	Yes	Yes
12. What are the implications of this study for practice?	No chance	Has a good chance for clinical practice

Appendix B

Quality Assessment (CASP tool) of Randomised Controlled Studies

Questions	**Lisa et al. (122)**	**Rabadi et al. (123)**
1. Did the study address a clearly focused issue?	Yes	**Yes**
2. Was the assignment of patients to treatments randomised?	Yes	Yes
3. Were all the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
4. Were patients, health workers and study personnel blind to treatment?	Yes	Yes
5. Were the groups similar at the start of the trial?	Yes	Yes
6. Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
7. How large was the treatment effect?	The outcomes were: body, fat and fat-free mass. The primary outcome was clearly specified. The results were found for each outcome.	The outcomes were: total FIM score, motor and cognitive FIM sub-scores, length of stay, 2 and 6-minute walk tests and discharge disposition. The results were found for each above mentioned outcomes.
8. How precise was the estimate of the treatment effect?	There was a strong correlation between MUAC and BMI (95% CI 0.92 to 0.99)	95% CIs were discussed in details on results section.
9. Can the results be applied in your context (or to the local population?)	Yes	Yes
10. Were all clinically important outcomes considered?	Yes, there was no other information I would have liked to see that would have affected the outcome.	Yes
11. Are the benefits worth the harms and costs?	Yes	Yes

Quality Assessment (CASP tool) of Randomised Controlled Studies

Questions	**Lisa H et al. (124)**	**Food Trial Collaboration (3)**
1. Did the study address a clearly focused issue?	Yes	Yes
2. Was the assignment of patients to treatments randomised?	Yes	Yes
3. Were all the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
4. Were patients, health workers and study personnel blind to treatment?	Yes	Yes
5. Were the groups similar at the start of the trial?	Yes	The undernourished group were older and more often lived alone than the other groups before stroke. Although the relationships were adjusted for patient age and living circumstances and this weakened them, they remained statistically significant ($P \leq 0.05$).
6. Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
7. How large was the treatment effect?	Primary outcome: percentage of weight loss was clearly specified. Secondary outcomes: QoL, handgrip strength, length of hospital stay. The intervention group had less weight loss, higher QoL and higher handgrip strength than control group but no difference in length of hospital stay.	The clinical outcomes measured included: post-stroke complications, length of hospital stay, functional ability (modified Rankin Scale (mRS)) and mortality rate. The primary outcome was unspecified. The results were found for each outcome and were mentioned in the text.
8. How precise was the estimate of the treatment effect?	The 95% CI was 1.0-4.2 in handgrip strength different between study groups, 95% CI was 3.3-9.8 in protein intake difference in both study groups and 95% CI was 58-1216 in different daily energy intake in study groups.	The 95% CIs were mentioned in results context.
9. Can the results be applied in your context (or to the local population)?	Yes	Yes
10. Were all clinically important outcomes considered?	Yes	Yes
11. Are the benefits worth the harms and costs?	Yes	Yes

Appendix C

Quality Assessment (CASP tool) of Systematic Review

Questions	**Geeganage et al. (125)**
1. Did the review address a clearly focused question?	Yes
2. Did the authors look for the right type of papers?	Yes
3. Do you think all the important, relevant studies were included?	Yes
4. Did the review's authors do enough to assess the quality of the included studies?	Yes
5. If the results of the review have been combined, was it reasonable to do so?	Yes
6. What are the overall results of the review?	Findings in details on page 49 and 50
7. How precise are the results?	See page 49 and 50
8. Can the results be applied to the local population?	Yes
9. Were all important outcomes considered?	Yes
10. Are the benefits worth the harms and costs?	Yes

Appendix D

Results and Measures of Nutritional Status of Included Studies

Source	No. of patients	Results	Measures	No. or percentage of malnourished or/and at risk of malnutrition patients
Nip et al. (120)	100	Energy intake associated with high malnutrition risk will predict rehabilitation outcomes	Mini-Nutritional Assessment (MNA) and Body Mass Index (BMI)	Malnourished and risk of malnutrition, respectively at admission: 7%, 66% (MNA) Malnourished and risk of malnutrition, respectively at discharge: 13%, 74% (MNA) Low BMI (<20 kg/m2) at admission: 23%. Low BMI at discharge: 26.5%
Gomes et al. (121)	543	Risk of malnutrition was associated with increased mortality, LOS and hospitalisation costs	Malnutrition Universal Screening Tool (MUST)	Low risk of malnutrition at baseline: 64%. Medium risk of malnutrition at baseline: 7% High risk of malnutrition at baseline: 29%
Lisa et al. (122)	124	The effect of changes in nutritional status on the clinical outcome were unmentioned	Anthropometry measures (weight, BMI, MUAC, TSF,AMC), MUST score and BIA	The authors assessed 344 patients; only 124 subjects were included as having malnutrition risk using the MUST
Rabadi et al. (123)	116	The influence of nutritional status on both primary and secondary outcomes was unclear	Body weight, % IBW, albumin, pre-albumin, transferrin	Out of 784 patients only 313 met inclusion and exclusion criteria (these patients who lost at least 2.5% significant weight within two weeks of stroke onset)
Lisa et al. (124)	124	The intervention patients who had less weight loss were associated with higher QoL and handgrip strength than control group.	MUST score, BMI, TSF, MUAC	Risk of malnutrition: 54.1% (using MUST) Undernourished: 19% (using BMI, TSF or MUAC)
Food Trial Collaboration (3)	3012	Early nutritional status assessment after a stroke can be considered as an independent predictor of long-term outcome	Bedside assessment , body weight, height, dietary history and blood tests	Undernourished patients: 279 (9%)
Geeganage et al. (125)	6779	The use of PEG was associated with higher albumin level, MAC measurements and less post-stroke clinical complications	BMI, Demiqute index, malnutrition risk, weight, MAC, albumin level	Not mentioned

Abbreviations: MUAC, mid upper arm circumference; TSF, triceps skinfold thickness; AMC, arm muscle circumference; BIA, bioelectrical impedance analysis; % IBW, percent ideal weight.

Appendix E

Malnutrition Universal Screening Tool (MUST)