学 位 論 文

Associated factors analysis and nomogram development

for post-stroke fatigue after discharge

（脳卒中後疲労の関連因子解明と退院後リスク予測モデルの開発）

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Abstract

Background: Fatigue is a common symptom after stroke and negative impact on patients' social participation and daily activities. It also interferes with their rehabilitation outcomes, including participation in rehabilitation therapy and returns to work. Moreover, post-stroke fatigue (PSF) has been shown to be related to poor quality of life and high mortality. Despite a greater than 50% prevalence of fatigue after stroke, no proven effective PSF treatment exists. Moreover, there are few scales were developed specifically for stroke patients, and healthcare professionals have no tools to predict fatigue which makes it impossible to effectively prevent it.

Aims: The aims of this PhD study were to determine the interactions of associated factors with PSF after discharge home, to develop a nomogram for the individualized prediction of the risk of PSF after discharge, and to compare the effectiveness of non-pharmacological interventions in PSF.

Methods: Firstly, a prospective observational study was conducted to explore the interactions of associated factors with PSF after discharge home. Secondly, to develop a new nomogram to predict the individual probability of PSF after discharge. Finally, a systematic review and network meta-analysis of non-pharmacological interventions for PSF was conducted to compare the effectiveness of non-pharmacological interventions in PSF. This study was approved by the Ethics Committee of the Faculty of Health Sciences, Hokkaido University.

Results: PSF was prevalent in 25.5% of the participants in the acute phase and 29.8% at 1 month after discharge. In total, 17.0% of the survivors had persistent PSF. Persistent PSF is not only associated with depression, insomnia, and lower quality of

life scores, but also with sarcopenia. Pre-stroke SARC-F, acute phase depression, and insomnia not only had direct correlations with acute phase PSF, but also had indirect correlations with PSF after discharge home. Thus, a nomogram was developed based on 95 stroke patients with the predictors included sex, pre-stroke sarcopenia, acute phase fatigue, dysphagia, and depression. The model displayed good discrimination and good calibration. We then developed a web application for convenience in the use of the above nomogram. An online version of our nomogram to assist healthcare professionals and researchers can be accessed at https://yasu2020.shinyapps.io/dynnomapp/. Finally, network meta-analysis based on data from the selected Ten Randomized Controlled Trials (RCTs) indicated that the eight PSF non-pharmacological interventions shared equivalent efficacy, but Community Health Management (CHM), Traditional Chinese Medicine (TCM), and Cognitive Behavioural Therapy (CBT) showed potentially better efficacy.

Conclusions: Persistent PSF is not only associated with depression, insomnia, and lower health-related quality of life (HRQOL) scores, but also with sarcopenia. Acute phase PSF was an independent predictor of PSF after discharge home. In addition, the interaction with acute phase depression and insomnia, and pre-stroke SARC-F had an indirect connection with post-stroke fatigue after discharge home, which remains a separate predictor of acute-phase post-stroke fatigue. These findings indicate that early assessment and management of mental status, sleep problems, and sarcopenia during hospitalization might be an important step in post-stroke rehabilitation and home transition. Despite the significant impact of PSF on the recovery and quality of life of stroke patients, it is only currently measured using general fatigue scales. We developed and internally validated a nomogram to predict the individual probability of PSF after discharge. This nomogram showed satisfactory internal validity and discrimination,

indicating good performance. The nomogram, which has been incorporated into an internet-based tool, also showed good clinical utility and can thus aid physicians, physiotherapists, and nurses in clinical decision-making. Despite the high prevalence of fatigue and its great impact on the outcome in stroke patients, there is currently insufficient evidence to determine a specific pharmacological intervention for PSF. In our systematic review, we found no significant differences among fatigue scores in eight PSF non-pharmacological interventions. Thus, there is an urgent need to recognize PSF, and in future studies, more effective clinical interventions need to be developed.

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Chapter 1: Introduction

The purpose of this PhD study was to analyse the interactions of associated factors with post-stroke fatigue (PSF) after discharge home and determine the impact on stroke survivors. Additionally, was to develop a simple clinical tool for nurses or other healthcare professionals to predict PSF after discharge. Furthermore, compared the effectiveness of non-pharmacological interventions in PSF to provide evidence of effective support for PSF patients. This dissertation has five chapters. Chapter 1 provides an overview of stroke and post-stroke fatigue. Chapter 2, a prospective observational study was conducted to identify the interactions of associated factors with PSF and determine the impact of PSF on the short-term outcomes after stroke. Based on the factors identified as being associated with PSF, Chapter 3 developed and internally validated a new nomogram to predict the individual probability of PSF after discharge. This nomogram showed satisfactory internal validity, discrimination, and clinical utility, indicating good performance. The physicians, physiotherapists, and nurses can use this nomogram as an aid in decision-making, to provide early intervention or a discharge plan to stroke patients during the hospitalization period. To enable nurses or other healthcare professionals to provide more effective interventions to patients with PSF, in Chapter 4, a systematic review and network meta-analysis of non-pharmacological interventions for PSF was conducted to compare the effectiveness of non-pharmacological interventions in PSF. This review suggests that the eight PSF non-pharmacological interventions shared equivalent efficacy, but Community Health Management (CHM), Traditional Chinese Medicine (TCM), and Cognitive Behavioural Therapy (CBT) showed potentially better efficacy. In the future, fatigue needs to be recognized and to develop the more effective clinical intervention. Finally,

Chapter 5 discusses the clinical and research implications of the current study and directions for future research.

This initial chapter (Chapter 1) starts with a brief introduction of stroke, followed by a focus on post-stroke fatigue.

1.1 Overview of stroke

Stroke is the second leading cause of death and the third leading cause of disability in adults worldwide [1]. Stroke is defined as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause (ischemia or hemorrhage) [2]. From the 1950s through the 1970s, stroke was the leading cause of death in Japan. Afterward, stroke is now the third leading cause [3]. With the improvement of stroke care and preventive treatment of cardiovascular risk, the incidence of stroke seems stable and the case mortality has also decreased [4]. On the other hand, post-stroke complications have led to increased mortality and length of hospital stay in acute stroke patients [5].

Medical complications are frequent among individuals who have had a stroke, such as aphasia, pain, depression, or need long-time care are particularly common and usually require specific interventions for their prevention and treatment. Moreover, medical complications can also hinder functional recovery and are associated with poorer functional outcomes after adjusting for stroke severity and age [6]. Some complications, such as dysphagia and pneumonia are often apparent early after stroke onset. Whereas others, such as bedsores, venous thrombosis, and falls, can occur after several days [6]. Additionally, many patients report substantial fatigue after a stroke, which can also cause functional limitations [7]. Fortunately, many complications can

be prevented, or early identification and treatment can effectively improve these complications.

1.2 Post stroke fatigue

1.2.1 Definition of Post-Stroke Fatigue

Fatigue is a common and often debilitating sequela after stroke. Fatigue is also a symptom commonly experienced in the general population. “Nonpathological fatigue” describes a state of general tiredness if it lasts fewer than 3 months and has an identifiable cause, which is related to lifestyle or overexertion and can be ameliorated by rest. In contrast, “pathological fatigue” is experienced in many people with chronic illness, which has a longer duration, is difficult to treat, and can cause severe impairments to an individual’s functional activity and quality of life [8]. PSF is not like typical tiredness, in that it does not always improve with rest. After a stroke, people may lack energy or strength, feel constantly weary or tired, and may not feel in control of their recovery. Although there is no agreement on the definition of PSF. Marleen H. de Groot et al. defined PSF as a feeling of physical tiredness and lack of energy, described as pathologic, abnormal, excessive, chronic, persistent, or problematic [9]. Joanna Lynch et al. defined PSF for community and hospital patients. PSF in Community patients is defined as at least a 2-weeks over the past month when the patient has experienced fatigue, lack of energy, or an increased need to rest every or nearly every day, leading to difficulty in taking part in everyday activities. In Hospital patients, PSF is defined as when the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day since their stroke. Fatigue leads to difficulty in taking part in everyday activities (for inpatients, this may include therapy and may include the need to terminate an activity early due to fatigue) [10].

1.2.2 Measurement of Post-Stroke Fatigue

PSF is commonly measured using general fatigue scales as shown in Table 1, and most scales have been developed for multiple sclerosis or chronic fatigue syndrome [11-22]. The Fatigue Severity Scale (FSS) stood out as the most widely used self-report questionnaire. Fatigue Assessment Scale (FAS) and the Multidimensional Fatigue Inventory were also used in several studies [23]. A previous study has been evaluated fatigue scales for stroke, the FSS was not included due to its poor face validity, but the FAS had the high construct validity and had the best test-retest reliability [24]. The items of FAS cover both mental and physical aspects of fatigue which focuses on severity of fatigue symptoms and its impact on daily life. Moreover, FAS is the only measurement tool that has a cutoff value for stroke patients [25]. However, to date there are few of these scales were developed specifically for stroke patients, and healthcare professionals have no tools to predict fatigue.

Table 1. General fatigue scales.

Scale	Developed By	Target Population	Items
Profile of Mood States—fatigue subscale (POMS)	McNair et al., 1971 [11]	Psychiatric patients	65
Fatigue Severity Scale (FSS)	Krupp et al., 1989 [12]	MS, SLE	9
Fatigue Impact Scale (FIS)	Fisk et al., 1994 [13]	MS, CFS	40
Checklist of Individual Strength (CIS)	Vercoulen et al., 1994 [14]	CFS	24
SF-36 (Vitality subscale)	Ware et al., 1994 [15]	Chronic disease patients	4
Multidimensional Fatigue Inventory (MFI-20)	Smets et al., 1995 [16]	Cancer, CFS, General clinical populations	20
FACIT (Fatigue Scale)	David Cella, et al., 1997 [17]	Chronic Illness	13
Multidimensional Fatigue Symptom Inventory (MFIS)	Stein et al., 1998 [18]	Cancer-related fatigue	6
Brief Fatigue Inventory (BFI)	Tito R et al., 1999 [19]	Cancer-related fatigue	4
Fatigue Assessment Scale (FAS)	Michielsen et al., 2003 [20]	Healthy population Workers	10
Neurological fatigue index-MS (NFI-MS) in stroke	Mills et al., 2012 [21]	MS	23
Detection List Fatigue (DLF)	Nena Kruithof et al., 2016 [22]	Post-stroke fatigue	9

MS: Multiple sclerosis; SLE: Systemic lupus erythematous; CFS: Chronic fatigue syndrome.

1.2.3 Prevalence of Post-Stroke Fatigue

Patients often complain of fatigue after stroke, identified as early as 1999 by Ingles et al. in a study of 181 patients with acute stroke. The Ingles study found that 40% of stroke survivors considered fatigue as one of their most serious sequelae [26]. The previous studies reported that more than half of stroke survivors experienced fatigue across the first two years following stroke [27,28], which is considerably higher than observed 10% to 23% in the general population [29-31]. A previous systematic review and meta-analysis have reported the fatigue prevalence assessed by FSS (total n = 3491), the pooled prevalence estimate was 50% (95% CI 43–57%) and ranged from 25 to 85% [32]. However, the use of different fatigue scales that measure different aspects of fatigue, combined with a lack of consensus on a 'cut-off' value that could be contributing to the reported differences in prevalence.

1.2.4 Factors associated with Post-Stroke Fatigue

Recently, an increasing number of physiotherapists, nurses, and researchers have paid increasing attention to PSF. PSF probably results from complex, poorly understood interactions between biological, psychological, and physical factors.

Biological correlates

Previous studies showed that young stroke survivors had a higher frequency of fatigue compared to older survivors. However, others reported that PSF increased with age. Additionally, PSF was found to be more frequent in females. However, others reported no gender difference. Therefore, the inconsistency in the findings may partially be due to different fatigue definition between genders [33]. Furthermore, Inflammation has been proposed to be other possible causes of PSF. There is cumulative evidence for an inflammatory reaction in acute ischemic stroke, indicating important interactions

between the nervous and immune systems [34,35]. Previous studies found that IL-1 seems to be a predictor of PSF [36,37] which suggested fatigue after stroke could be part of what has been described as inflammation-induced sickness behavior [38].

Psychological and Physical Factors

Psychological factors such as anxiety and depression are associated with PSF. To date, the relationship between fatigue and depression remains controversial. Some studies showed that PSF was not dependent on depression [33,39], while other studies reported a significant relationship between fatigue and depression [40]. Ingles and associates demonstrated that the presence of PSF was independent of the presence of depression. However, the effect of fatigue on functional abilities was mediated by depression [26]. Thus, the association between fatigue and depression may exist but may not be direct. Additionally, sleep problems and post-stroke pain were listed as contributors to fatigue. Appelros demonstrated that fatigue measured 1 year after stroke was associated with both physical disability and sleep disturbance. Post-stroke pain is common among stroke survivors [41], and it predicts long term quality of life and mortality [42]. Appelros found no significant association between pain and fatigue [41], while Naess reported that patients with pain reported higher fatigue scores on the FSS. Notably, patients who reported pain also showed a high frequency of sleep disturbances and depression [29]. Pre-stroke fatigue was also a contributor to PSF [40]. However, a previous study showed that 38% reported pre-stroke fatigue, while 36% of the patients who did not suffer from pre-existing fatigue also complained of PSF [27].

1.2.5 Impact of Post-Stroke Fatigue

PSF interferes with patients' social participation and daily activities. It also has a negative impact on their rehabilitation outcomes, including participation in

rehabilitation therapy and returns to work [43-45]. Moreover, PSF has been shown to be related to poor neurological recovery, functional limitations, decreased quality of life, and high mortality [27]. Many stroke survivors reported that a salient feature of the transition phase is managing fatigue [46]. However, 43% of stroke survivors reported inadequate support to manage their fatigue problems [47]. Thus, frustration is a common response to these changes at 1 month after discharge at home [46]. Although fatigue is a persistent symptom affecting many stroke survivors, PSF is often underrecognized. PSF has recently gained increasing attention and is now evaluated in several guidelines for stroke practice [48-50]. The Canadian stroke best practice guidelines recommended that healthcare professionals should anticipate the possibility of PSF and prepare stroke patients and their families to mitigate fatigue through assessment, education, and interventions throughout the stroke-recovery continuum. Moreover, follow-up healthcare visits of stroke survivors should include periodic screening for PSF after return to the community [50]. However, PSF is only currently measured using general fatigue scales [51], none of these scales were developed specifically for stroke patients, and healthcare professionals have no tools to predict fatigue. Additionally, effective management strategies for PSF are yet to be established [50,52].

1.3 Aims and objectives of the dissertation

1.3.1 Aims

Early identification and effective management for post-stroke fatigue can effectively improve the home transition and quality of life of stroke patients. The aims of this PhD study were to conduct a longitudinal study on post-stroke fatigue to determine the prevalence and the interactions of associated factors. Moreover, develop

a simple clinical tool that nurses and other healthcare professionals can use it to identify acute phase stroke patients at risk for PSF after discharge. Finally, to provide evidence for future effective interventions that systematically search and compare the effectiveness of non-pharmacological interventions in PSF.

1.3.2 The objectives of each chapter of this dissertation

・Chapter 1: to provide an overview of stroke and post-stroke fatigue

・Chapter 2: to determine the prevalence and related factors of post-stroke fatigue

・Chapter 3: to develop a tool for predicting post-stroke fatigue during hospitalization

・Chapter 4: to systematically search and compare the effectiveness of non-pharmacological interventions in post-stroke fatigue

・Chapter 5: to discuss the clinical implication of the current study and directions for future research

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Chapter 2: Associated factors and short-term outcomes of post-stroke fatigue in initial phase of transition from hospital to home: a prospective observational study

2.1 Abstract

Aim: To analyse the interactions of associated factors with post stroke fatigue (PSF) after discharge home and determine the predictors of PSF and their impact on stroke survivors.

Design: A prospective observational study

Methods: A total of 94 patients with acute stroke were recruited between May 2019 - July 2020. The main outcomes were fatigue, depression, insomnia, sarcopenia, and health-related quality of life (HRQOL) and were assessed at admission and 1 month after discharge. Fatigue was measured using the Fatigue Assessment Scale. Depression and Insomnia were assessed using the Hospital Anxiety and Depression Scale-Depression and Insomnia Severity Index, respectively. Sarcopenia was measured using the SARC-F questionnaire, and HRQOL was assessed using the Short Form-8.

Results: Acute phase PSF was an independent predictor of PSF after discharge home. Moreover, the path analysis revealed that this effect is mediated through both the direct effect of acute-phase PSF on PSF after discharge home and through the indirect effect of interaction with pre-stroke SARC-F, acute phase depression, and acute phase insomnia, which remains a separate predictor of acute-phase PSF. In total, 17% of the

survivors had persistent PSF. Persistent PSF was significantly associated with depression, insomnia, sarcopenia, and a lower quality of life scores.

Conclusions: Post-stroke fatigue may occur in the acute phase and persists after discharge, it will not only affect later depression, insomnia, and quality of life, but also sarcopenia.

2.2 Introduction

Fatigue occurring as a consequence of stroke is a common complaint (van der Werf et al., 2001), identified as early as 1999 by Ingles et al. in a study of 181 patients with acute stroke. The Ingles study found that 40% of stroke survivors considered fatigue as one of their most serious sequelae (Ingles et al., 1999). In recent years, 25-85% of patients reported experiencing post-stroke fatigue (PSF) (Cumming et al., 2016), even those with good neurological recovery (Staub et al., 2001; Marsh et al., 2018). These rates exceed fatigue levels in the general population that range only from 10-23% (Lamers et al., 2013; Lerdal et al., 2005; Loge et al, 1998). Unlike normal fatigue resulting from overexertion, PSF is not relieved with normal rest and has been documented to persist chronically in some stroke survivors (Chaudhuri et al., 2004; Barbour et al., 2012; Wu et al., 2015; Duncan et al., 2012).

In community patients, PSF is defined as at least a 2-week period over the past month when the patient has experienced fatigue, lack of energy, or an increased need to rest every or nearly every day, leading to difficulty in taking part in everyday activities. In hospital patients, PSF is defined when the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day since their stroke. Fatigue leads to difficulty in taking part in everyday activities and therapies, or the need to terminate an activity early due to fatigue. (Lynch et al.,2007). PSF not only

interferes with social participation and daily activities, but also has a negative impact on their rehabilitation outcomes, including participation in rehabilitation therapy and return to work (Glader et al., 2002; van de Port et al., 2007; Andersen et al; 2012). Moreover, PSF has been shown to be related to poor neurological recovery, functional limitations, decreased quality of life, and increased institutionalization and mortality (Glader et al., 2002; Choi-Kwon et al., 2005; Naess et al., 2013). PSF is an often neglected but important stroke sequela with far reaching consequences (Lerdal et al., 2009). However, little is known about the underlying mechanism and management of PSF (Aarnes et al., 2020).

Recently, an increasing number of physiotherapists, nurses, and researchers have paid increasing attention to PSF. In 2016, the top 10 published research priorities specific to stroke nursing identified managing fatigue as a top research priority (Rowat et al., 2016). Previous studies have shown that PSF is related to the stroke survivor's gender, age, pre-stroke fatigue, or whether stroke was recurrent or first-ever (Nadarajah et al., 2015; Ponchel et al., 2015). Many studies have demonstrated a strong relationship between PSF and psychological factors such as depression (van der Werf et al., 2001; Lerdal et al., 2011). However, the relationship between fatigue and depression remains controversial due to PSF can also occur in the absence of depression (Ponchel et al., 2015). In addition, sleep problems such as insomnia was listed as the contributors to fatigue (Leppävuori et al., 2002). A previous study showed that fatigue measured 1 year after stroke was associated with both sleep disturbance and physical disability (Appelros et al., 2006). Moreover, poor functional ability related to higher levels of PSF, and functional status was reported to mediate the influence of PSF on HRQOL (Vincent-Onabajo et al., 2014). Furthermore, poor functional capacity seems to be related to the increase of the risk of sarcopenia and reduced muscle strength can also

leads to loss of functional capacity (Dhillon et al., 2014; Oliveira et al., 2019). Despite some studies having shown a strong association between low skeletal muscle mass and fatigue in cancer patients (Bye et al., 2017; Wang et al., 2020), to our best knowledge, muscle loss or sarcopenia was not considered in previous studies on PSF. Muscle wasting is a common complication of stroke, with 42% of stroke survivors having sarcopenia (Su et al., 2020). The impact of muscle weakness after stroke on physical function reduction or disability (Bohannon 2007) indicates that it may also contribute to a reduction in psychological function.

As stroke survivors try to manage and adapt to changes or functional limitations, the rhythm and routines of life after stroke will also change. At the initial phase of transition at discharge from hospital to home, the real consequences of the stroke on daily life become apparent (Beunder et al., 2015). Many stroke survivors reported that a salient feature of the transition phase is managing fatigue (Rittman et al., 2004). However, 43% of stroke survivors reported inadequate support to manage their fatigue problems (McKevitt et al., 2011). Thus, frustration is a common response to these changes 1 month after discharge (Rittman et al., 2004). Moreover, the continuity of care is even more difficult for stroke survivors with language, motor, or visual impairments that substantially hinder telephone contact to schedule and confirm appointments after discharge from the hospital (Broderick et al., 2015). To improve home transition for stroke patients, the outcomes of PSF should be determined after the patient returns home for a period. As such, it is important for healthcare professionals to identify risk factors during hospitalization and manage them in time. A recent study (Lerdal et al., 2013) reported that acute phase fatigue is a significant predictor of later physical health. Thus, the acute phase may represent a critical period for functional recovery. However, studies investigating PSF in the acute phase, such as the first or second week after stroke,

are scarce (Chaudhuri et al., 2004; Schepers et al., 2006). Furthermore, most previous studies were focused on the impact of PSF on the long-term outcomes after stroke (Glader et al., 2002; Andersen et al., 2012; Christensen et al, 2008; Elf et al., 2016), studies investigating PSF in the initial phase of transition from hospital to home are scarce.

2.3 Methods

2.3.1 Aims

This study aimed to investigate the characteristics of PSF from the acute phase to the first month after discharge, analyse the possible predictors and interactions of associated factors towards the PSF after discharge home, and determine the impact of PSF on the short-term outcomes after stroke that included depression, insomnia, sarcopenia, and HRQOL.

2.3.2 Design

This study was a part of the For S (Support System for Stroke Survivors) project. This project is prospective observational study that aims to improve home transition and long-term outcomes for stroke patients during the hospitalization period. This study was a single-center, prospective observational study of data collected between May 2019 and July 2020 at a neurosurgical hospital in Sapporo, Hokkaido, Japan.

2.3.3 Participants

Participants who met the following criteria were included: 1) diagnosis of an acute stroke (the acute onset of focal neurological deficit as a result of underlying cerebrovascular disease, including both ischemic and hemorrhagic stroke); 2) age >30 years; 3) willing to discharge from the hospital to home; and 4) willing to complete the

study. The exclusion criteria were: 1) a Mini-Mental State Exam (MMSE) score of <24 or significant impairments in cognition; 2) severe paralysis, severe aphasia, or communication difficulties; 3) inability to speak Japanese; 4) medically unstable or has planned surgery; 5) had a past or present history of depression or started on antidepressant drug therapy within the past 3 months; 6) taking pharmacological treatments for fatigue; and 7) current participation in other research studies that might affect fatigue or add a significant burden to the participant.

The sample size was anticipated to be achievable in a limited time (18 months) available for recruitment in this study. Multiple linear regression (MLR) is a common statistical analysis in a multivariate model that examines how multiple independent variables are related to one dependent variable. At least one journal now requires a minimum N=5 per group for statistical analyses. Some researchers have been advised to use N=10–20 per predictor (Curtis et al., 2015). Path analysis is an extension of multiple regressions. It goes beyond regression in that it allows for the analysis of more complicated models (Streiner, 2005). Some researchers have been advised to use N=5 or 20 per estimated parameter (Bentler and Chou, 1987; Wolf et al., 2013). Therefore, the sample size calculations based on 5 minimum numbers of cases per independent variable [Sample size, N = (number of predictors) × (5 – 20 cases per variable)]. There were five main outcomes variables were measured in this study that included fatigue, depression, insomnia, sarcopenia, and HRQOL. Thus, we pre-specified measured variables for PSF and found that they should be less than or equal 6 based on previous studies and the current study design. This study purposely selects the 15 cases for each variable, and the total of 90 respondents required in this study fulfils the suggested sample size of Multiple linear regression and path analysis. Considering a 10% dropout rate, the desired sample size to be collected was 99.

2.3.4 Data collection

This study has three stages. The screening stage (screening stroke patients within 2 weeks of admission) involved a review of the electronic medical records along with the nurse manager to pre-determine potentially eligible participants. Then, the nurse manager contacted their attending physician to assess whether they did not meet any exclusion criteria and obtain permission. The second stage involved along with the nurse manager going to the ward to provide a detailed verbal explanation of the study to the eligible participants and obtained informed consent from the patients or their relatives. Finally, the assessment stage was conducted at baseline (acute phase: within 2 weeks after admission) and follow-up (patients came to the hospital for follow-up at 1 month after discharge).

Assessment of PSF and course of PSF

Considering a good feasibility, validity, and reliability in measuring fatigue in stroke patients (Mead et al., 2007). Fatigue was measured using the Fatigue Assessment Scale (FAS), which is a 10-item self-report scale on the different aspects of fatigue, with responses made on a 5-point Likert scale: 1=never; 2=sometimes; 3=regularly; 4=often; 5=always (Michielsen et al., 2003; Cumming et al., 2017). The scale is scored from 10 to 50, with higher scores indicating greater fatigue. FAS is easy to complete and has been established to be a reliable and valid tool for identifying fatigue in various diseases and conditions (Michielsen et al., 2003). FAS has been used in 26 different diseases or conditions, including stroke, neurologic disorders, and sarcoidosis. In addition, FAS is the only fatigue measurement tool that has a cutoff value for stroke patients (Michielsen et al., 2004; Mead et al., 2007; Smith et al., 2008; Hendriks et al., 2018), a score of ≥24 indicating post-stroke fatigue (Cumming et al., 2017).

The course of PSF was classified as follows: no PSF, defined as no fatigue (FAS score <24) at baseline and follow-up; persistent PSF, fatigue (FAS score ≥24) both at baseline and at follow-up; recovered from PSF, with fatigue at baseline but without fatigue at follow-up; and incident PSF, without fatigue at baseline but with fatigue at follow-up.

Demographic, clinical, and stroke characteristics

Demographic characteristics included age, sex, and family composition. Clinical characteristics included medical condition, smoking status, alcohol consumption, body mass index, MMSE score, and Functional Independence Measure score. Stroke characteristics included previous stroke, type of stroke, and length of hospital stay. All data were collected from the electronic medical records.

Assessment of possible pre-stroke risk factors

Pre-stroke sarcopenia was assessed using the SARC-F questionnaire, which is a rapid questionnaire to screen for sarcopenia using self-reported information. The SARC-F is comprising 5 assessment items: strength, assistance walking, rising from a chair, climbing stairs, and falls. (Malmstrom et al., 2013). Patients answered based on their condition before the stroke. The total SARC-F score ranges from 0 to 10 points, a score of ≥4 was classified as having a risk of sarcopenia (Ida et al., 2017), with higher scores indicating higher risk of sarcopenia. Pre-stroke fatigue was assessed using a single-item self-report, and patients who reported fatigue lasting longer than 3 months before the stroke were defined as having pre-stroke fatigue. Data on pre-stroke sleep disorders were collected from electronic medical records.

Assessment of possible post-stroke risk factors and outcomes

The SARC-F questionnaire was used to screen for sarcopenia at follow-up, and patients with a score of ≥4 were classified as having a risk of sarcopenia (Malstrom et

al., 2013; Ida et al., 2017). Depression was assessed at baseline and follow-up using the Hospital Anxiety and Depression Scale- Depression (HADS-D). The HADS-D is a Likert scale composed of 7 items to which patients respond through a 4-point scale (from 0 to 3) referring to overt symptoms (Annunziata et al., 2001), with scores >7 set as a cutoff for classifying depression (Zigmond and Snaith, 1983; Zigmond et al., 1993; Hatta et al., 1998). The HADS-D showed to be a valid instrument to measure the symptom severity of depression in both primary care patients and in the general population (Bjelland et al., 2002). Moreover, the HADS-D as one of the most widely used screening tools for post-stroke depression has superior psychometric properties and clinical utility indices in stroke populations (Burton and Tyson, 2015). Insomnia was assessed at baseline and follow-up using the Insomnia Severity Index (ISI), which is a reliable and valid instrument to detect cases of insomnia in the population (Morin et al., 2011). The ISI is a 7-item scale used to assess sleep quality and insomnia severity over the previous 2 weeks rated on a 0-to-4 scale, and the total score ranges from 0 to 28. A higher score indicates more severe insomnia, with a score of >7 being the cutoff for classifying insomnia (Bastien et al., 2001; Munezawa et al., 2009). Health-related quality of life (HRQOL) was assessed using the Short Form-8 (SF-8) questionnaire at baseline and follow-up. SF-8 is an 8-item tool that is commonly used to assess HRQOL, and has demonstrated acceptable validity and reliability in population studies. Moreover, SF-8 takes less time to complete, appears to be less confusing, therefore, likely to be more acceptable to patients (Gulati et al., 2009). The 8 questions are used to calculate two summary measure scores: physical component score (PCS) and mental component score (MCS), with higher scores indicating better health (Fukuhara and Suzukamo, 2004).

2.3.5 Ethical considerations

This prospective observational study was approved by the Ethics Committee of the Faculty of Health Sciences, Hokkaido University (Reference No 18-82,19-80). All participating patients or their relatives provided informed consent.

2.3.6 Data analysis

Statistical analyses included univariate, multivariate, and path analyses. Continuous variables were presented using means and standard deviations or median and range, whereas categorical variables were presented using frequencies and percentages. Normally distributed continuous variables were analysed using the Student's t-test and a one-way analysis of variance. Meanwhile, non-normally distributed variables were analysed using the non-parametric Mann–Whitney U-test and Kruskal-Wallis with Bonferroni multiple-comparison test. Categorical variables were evaluated using the chi-squared test. Significant variables in the univariate analysis (with p values <0.05) were included in the baseline simple linear regression model. Considering that significant variables at baseline may also affect the results of follow-up, not only the significant variables in the univariate analysis but also the variables in the baseline linear regression were included in the follow-up simple linear regression model. Variables with p values <0.05 in the simple linear regression model were entered into the MLR model to determine the relationships between these predictors and PSF. All statistical analyses were conducted using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA). P values <0.05 were considered significant.

Path analysis, a form of applied regression analysis, was conducted to evaluate hypothetical relationships between variables towards the explanation of PSF after

discharge, using the IBM SPSS Amos 26.0 (IBM Corp., Armonk, NY, USA). The explanatory factors included in the model were selected based on existing literature and our findings (variables with p values <0.05 in the MLR). The total PSF score at follow-up was entered into the model as the main dependent variable. We used path analysis to identify a model that will capture the interactions of fatigue, depression, and insomnia in the acute phase and pre-stroke SARC-F in stroke survivors and, in particular, will help explain how these factors lead to PSF after discharge. Several steps were taken to test the assumptions of the model. If the initial model does not fit the data, the model is modified and retested until an acceptable fit is achieved. The model fit was assessed using the following criteria: 1) chi-square (χ^2) goodness-of-fit statistic (good fit if p>0.05); 2) chi-square degrees of freedom ratio (χ^2/df) (good fit if <3); 3) the Goodness-of-Fit Index (GFI) (good fit if ≥0.9); 4) the Comparative Fit Index (CFI) (good fit if ≥0.9); Tucker–Lewis Index (TLI) (good fit if ≥0.9); normed Fix Index (NFI) (good fit if ≥0.9); and 5) the root mean square error of approximation (RMSEA) (acceptable if from 0.06 to 0.08) (Hu et al., 1999; Hooper et al, 2008; Schreider et al., 2006). The significance of the direct, indirect, and total effects were evaluated with the bootstrap resampling method, with 2000 bootstrap samples and 95% confidence intervals around the standardized estimates. Effects with p<0.05 were considered significant (Preacher and Hayes, 2008). R-square was used to evaluate the variance of each variable explained in the model.

2.3.7 Validity, reliability, and rigour

We selected the assessment scales with good validity and reliability to ensure the high quality of this study, and this questionnaire was checked using a pre-test to establish whether questions are properly worded, clear enough to be easily understood by Japanese patients. Moreover, to ensure that all investigators can understand the

survey instruments thoroughly, and ask questions in a manner that will convey the same message to respondents, we provided with manuals, and all the investigators accepted the training before investigation. As part of the field quality control program, when the investigator was conducting the investigation, a supervisor was present to monitor progress in the investigation and take remedial action where necessary. Further, recheck was conducted after data input to ensure the accuracy of data.

2.4 Results

2.4.1 Patient characteristics

In total, 104 of the 171 stroke patients who were recruited consented to participate in the study (Figure 1). Of them, 94 patients had complete follow-up. The mean patient age was 68.5 (*SD* 10.0) years at baseline, 38% of the patients were women, and 30% were living alone. The median length of hospital stay was 16 days (range, 8–142 days), and the mean FAS scores at baseline and at follow-up were 19.4 (*SD* 6.7) and 18.8 (*SD* 7.2), respectively. The patient characteristics are presented in Table 1.

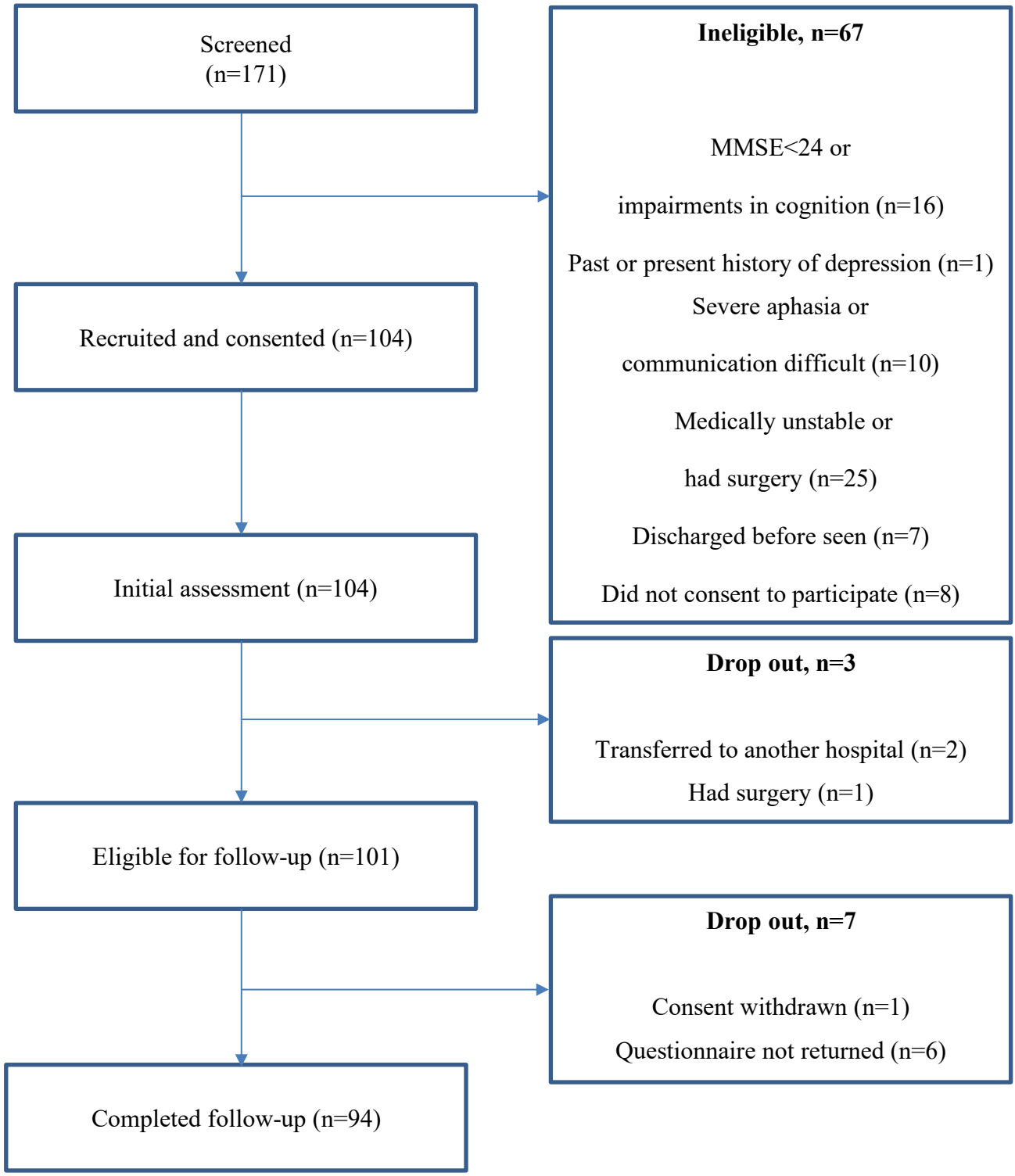

Figure 1. Study recruitment flowchart

Table 1. Patient characteristics at baseline and follow-up

Characteristics	Total n=94	Baseline			Follow-up		
		PSF n=24	No PSF n=70	P-value	PSF n=28	No PSF n=66	p-value
Demographics							
Age, mean years (SD) [c]	68.5 (10.0)	70.0 (10.1)	68.0 (10.0)	0.412	70.6 (7.5)	67.6 (10.8)	0.193
Sex, Female n (%) [a]	36 (38)	14 (58)	22 (31)	0.019*	15 (54)	21 (32)	0.047*
Living alone, n (%) [a]	28 (30)	4 (17)	24 (34)	0.103	6 (21)	22 (33)	0.248
Clinical characteristics							
Hypertension, n (%) [a]	42 (45)	9 (38)	33 (47)	0.412	11 (39)	31 (47)	0.493
Diabetes, n (%) [a]	24 (26)	3 (13)	21 (30)	0.090	5 (18)	19 (29)	0.266
Cancer, n (%) [a]	9 (10)	2 (8)	7 (10)	0.811	3 (11)	6 (9)	0.807
Smoking, n (%) [a]				0.223			0.711
Current	28 (30)	9 (38)	19 (27)		10 (36)	18 (27)	
Former	19 (20)	2 (8)	17 (24)		5 (18)	14 (21)	
Alcohol drinking, n (%) [a]				0.251			0.071
Current	47 (50)	9 (38)	38 (54)		9 (32)	38 (58)	
Former	4 (4)	2 (8)	2 (3)		2 (7)	2 (3)	
MMSE [†], median (range) [b]	28 (25-30)	28 (25-30)	28 (25-30)	0.299	27 (25-30)	28 (25-30)	0.077
BMI, mean (SD) [c]	24.7 (3.9)	24.7 (4.8)	24.7 (3.6)	0.972	24.1 (3.3)	25.0 (4.2)	0.323
FIM at admission							
Total, median (range) [b]	93 (41-126)	89 (41-126)	96 (43-126)	0.267	93 (41-126)	94 (43-126)	0.921
Motor, mean (SD) [c]	62.7 (18.3)	60.4 (19.1)	63.5 (18.0)	0.466	63.9 (19.2)	62.2 (18.0)	0.691
Cognitive, median (range) [b]	33 (16-35)	31 (16-35)	33 (24-35)	0.622	32 (16-35)	34 (22-35)	0.635
Stroke characteristics							
Previous stroke, n (%) [a]	13 (14)	7 (29)	6 (9)	0.029*	4 (14)	9 (14)	0.934
Type of stroke, n (%) [a]				0.037*			0.191
Ischemic	86 (91)	19 (79)	67 (96)		24 (86)	62 (94)	
Hemorrhagic	8 (9)	5 (21)	3 (4)		4 (14)	4 (6)	
Paralysis, n (%) [a]	38 (40)	11 (46)	27 (39)	0.532	12 (43)	26 (39)	0.754
Pre-stroke characteristics							
Pre-stroke fatigue, n (%) [a]	18 (19)	14 (58)	4 (6)	<0.001*	10 (36)	8 (12)	0.008*
Pre-stroke sleep disorder, n (%) [a]	36 (38)	10 (42)	26 (37)	0.694	12 (43)	24 (36)	0.554
Pre-stroke SARC-F, median (range) [b]	1 (0-7)	2 (0-7)	1 (0-5)	0.030 *	2 (0-7)	1 (0-4)	0.137
Post-stroke characteristics							
Depression, n (%) [a]	21 (22)	10 (42)	11 (16)	0.008*	11 (39)	10 (15)	0.010*
Insomnia, n (%) [a]	50 (53)	20 (83)	30 (43)	0.001*	19 (68)	31 (47)	0.063
Fatigue, n (%) [a]	-	-	-	-	16 (57)	8 (12)	<0.001*

[a]: Chi-square test; [b]: Mann–Whitney U test; [c]: t-test; [†]: missing 29, n=65; * Significant association (p<0.05)

Values are shown as means (SD), median (range), or proportions (%).

Abbreviations: BMI, body mass index; FIM, Functional Independence Measure; MMSE, Mini-Mental State Exam; PSF, poststroke fatigue; SD, standard deviation

2.4.2 Prevalence of PSF at baseline and follow-up

In total, 94 stroke survivors were followed up for 1 month after discharge. PSF was prevalent in 25.5% of the patients in the acute phase (baseline) and in 29.8% at 1

month after discharge (follow-up). In total, 61.7% of the stroke survivors did not have PSF at all, whereas 17.0% of the survivors had PSF at both time points. Overall, 8.5% of the survivors had fatigue at baseline but recovered at follow-up, while 12.8% of survivors had no PSF at baseline but had PSF at follow-up.

2.4.3 Factors associated with fatigue at baseline and follow-up

Univariate analysis showed a higher proportion of acute phase PSF in women ($p=0.019$). Previous stroke ($p=0.029$) and hemorrhagic stroke ($p=0.037$) were significantly associated with acute phase PSF. Pre-stroke fatigue ($p<0.001$) and a higher pre-stroke SARC-F score ($p=0.030$) were significantly associated with acute phase PSF. In addition, depression ($p=0.008$) and insomnia ($p=0.001$) were significantly associated with PSF in the acute phase. Meanwhile, female sex ($p=0.047$), previous stroke ($p=0.008$), depression ($p=0.010$), and fatigue ($p<0.001$) at the acute phase were significantly correlated to PSF after discharge home.

2.4.4 Factors associated with FAS score at baseline and follow-up

Univariate regression showed that previous stroke ($\beta=0.21$, $p<0.001$), hemorrhagic stroke ($\beta=0.32$, $p=0.002$), pre-stroke fatigue ($\beta=0.61$, $p=0.041$), higher scores of pre-stroke SARC-F ($\beta=0.32$, $p=0.002$), depression ($\beta=0.47$, $p<0.001$), and insomnia ($\beta=0.47$, $p<0.001$) were significantly associated with higher acute phase FAS scores. Hemorrhagic stroke ($\beta=0.21$, $p=0.048$), pre-stroke fatigue ($\beta=0.36$, $p<0.001$), a higher pre-stroke SARC-F score ($\beta=0.23$, $p=0.027$), fatigue ($\beta=0.66$, $p<0.001$), depression ($\beta=0.42$, $p<0.001$), and insomnia ($\beta=0.28$, $p=0.007$) were significantly associated with higher FAS scores after discharge home. Multiple regression showed that pre-stroke fatigue ($\beta=0.39$, $p<0.001$), higher scores of pre-stroke SARC-F ($\beta=0.16$, $p=0.034$), depression ($\beta=0.21$, $p<0.010$), and insomnia ($\beta=0.19$, $p<0.023$) were

significantly associated with higher acute phase FAS score. The R-square indicated that 50% of the variance in acute phase PSF can be explained by this model. Only the FAS score at the acute phase (β=0.64, p<0.001) was significantly associated with a higher FAS score after discharge home. The R-square indicated that 42% of the variance in PSF after discharge home can be explained by this model (Table 2).

Table 2. Linear regression analyses of the associations between FAS scores at baseline and follow-up

Variables	Baseline				Follow-up			
	Univariate analyses		Multivariate analyses †		Univariate analyses		Multivariate analyses ‡	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	p-value
Sex [a]	0.15 (-0.73-4.84)	0.150			0.17 (-0.57-5.44)	0.113		
Previous stroke [b]	0.21 (7.51-13.05)	<0.001*	0.11 (-0.67-5.05)	0.131	0.06 (-3.00-5.59)	0.551		
Type of stroke [c]	0.32 (2.87-12.21)	0.002*	0.09 (-1.68-5.77)	0.278	0.21 (0.06-10.47)	0.048*	0.06 (-2.90-6.15)	0.477
Pre-stroke characteristics								
Pre-stroke fatigue [d]	0.61 (0.16-7.95)	0.041*	0.39 (3.67-9.61)	<0.001*	0.36 (2.97-10.01)	<0.001*	-0.10 (-5.61-1.97)	0.341
Pre-stroke SARC-F scores	0.32 (0.55-2.29)	0.002*	0.16 (0.06-1.40)	0.034*	0.23 (0.131-2.06)	0.027*	0.01 (-0.78-0.83)	0.945
Post-stroke characteristics								
Depression scores	0.47 (0.52-1.19)	<0.001*	0.21 (0.10-0.69)	0.010*	0.42 (0.46-1.20)	<0.001*	0.16 (-0.03-0.67)	0.075
Insomnia scores	0.47 (0.34-0.76)	<0.001*	0.19 (0.03-0.41)	0.023*	0.28 (0.10-0.60)	0.007*	-0.04 (-0.28-0.18)	0.680
Fatigue scores	-	-	-	-	0.66 (0.54-0.88)	<0.000*	0.64 (0.45-0.94)	<0.001*

* Significant association (p<0.05); †Adjusted R^2: 0.502; ‡Adjusted R^2: 0.419

[a] Sex is coded as female, 1; male, 0

[b] Previous stroke status is coded as previous stroke, 1; first-ever stroke, 0

[c] Type of stroke is coded as hemorrhagic, 1; ischemic, 0

[d] Pre-stroke fatigue status is coded as pre-stroke fatigue, 1; non-pre-stroke fatigue, 0

Abbreviation: CI, confidence interval

2.4.5 Path analysis

We used path analysis to identify a model that will capture the interactions of pre-stroke sarcopenia, depression, insomnia, and fatigue in stroke survivors and, in particular, will help clarify how these factors lead to PSF after discharge home. Based on the existing literature and our findings (variables found to be significantly associated

with FAS score in the multiple linear regression), a model was hypothesized (Figure 2). This initial model had a poor fit: $\chi 2$ / df =5.643, p<0.001, GFI=0.90, CFI=0.818, TLI=0.546, NFI=0.798 and RMSEA=0.219. The model was thus modified and retested until the final model (Figure 3) had an acceptable fit as follows: χ^2 / df=1.482, p=0.205, GFI=0.976, CFI=0.981, TLI=0.953, NFI=0.947, and RMSEA=0.072. As shown in Figure 1, pre-stroke SARC-F (β=0.194, p=0.030), insomnia (β=0.355, p=0.000), and depression (β=0.353, p=0.000) had a significant direct effect on acute phase PSF. Acute phase PSF had a significant direct effect on PSF after discharge home (β=0.579, p=0.001). However, depression (β=0.204, p=0.001), insomnia (β=0.205, p=0.001), and pre-stroke SARC-F (β=0.112, p=0.044) only had an indirect association with PSF after discharge home through acute phase PSF, (Supplementary Tables 1 and 2). The R-square indicated that 43% of the variance in PSF after discharge home can be explained by this model.

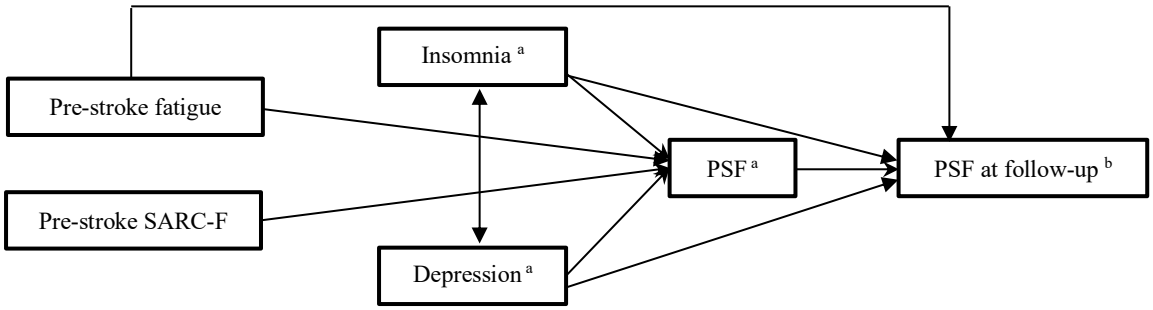

Figure 2. Initial explanatory model of PSF at 1 month after discharge

[a]: measured at admission; [b]: measured at 1 month after discharge; Abbreviations: PSF, poststroke fatigue

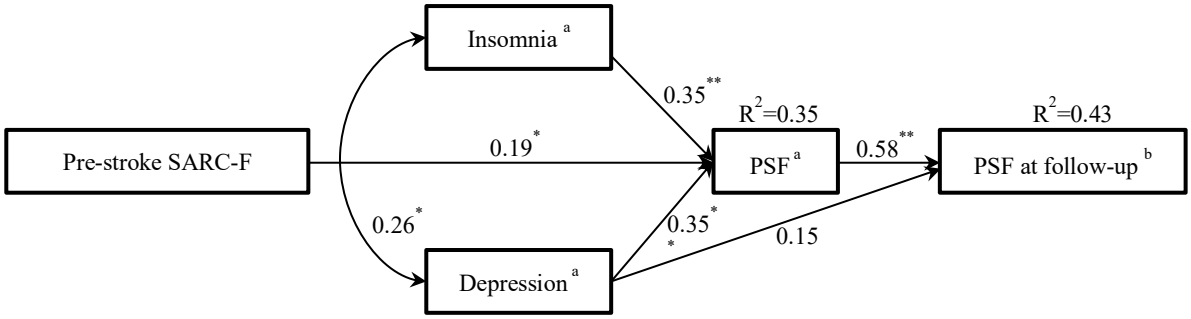

Figure 3. Final version of the path model analysis of PSF at 1 month after discharge

[a]: measured at the acute phase; [b]: measured at 1 month after discharge; *: p<0.05; **: p<0.01

Model fitness: χ^2/df=1.482; p=0.205; GFI=0.976; CFI=0.981; TLI=0.953; NFI=0.947; REMSEA=0.072

Indirect effect: PSF at follow-up<---Pre-stroke SARC-F (β=0.112*)

PSF at follow-up <---Depression at baseline (β=0.204**)

PSF at follow-up <---Insomnia at baseline (β=0.205**)

2.4.6 Impact of post-stroke fatigue on short-term outcomes

The acute phase PSF was significantly associated with fatigue (67% vs 17%; p<0.01), insomnia (71% vs 30%; p<0.01), higher SARC-F scores (2 vs 1; p=0.026), and lower QOL scores (PCS, 48 vs 51; p=0.029; MCS, 46 vs 51; p=0.006) at 1 month after discharge (Supplementary Table 3). Stroke survivors with persistent PSF included a significantly higher proportion of individuals with depression (31% vs 5%; p=0.003), insomnia (81% vs 24%; p=0.001), and sarcopenia (SARC-F score ≥4; 44% vs 9%; p<0.001]) compared with survivors who had no PSF. Moreover, those with PSF showed a significantly higher SARC-F score (3 vs 1; p<0.001) and significantly lower HRQOL scores (PCS, 43 vs 51; p=0.046; MCS, 45 vs 51; p=0.001) compared with survivors who had no PSF (Figure 4). No significant differences were found among the other groups (Table 3).

Table 3. Follow-up outcomes of post-stroke fatigue patients

Variables	No PSF n=58	Persistent PSF n=16	Recovery PSF n=8	Incident PSF n=12	p-value
Age, mean years (SD) [b]	67.9 (10.6)	72.2 (7.7)	65.5 (13.2)	68.4 (7.0)	0.384
Sex, Female n (%) [a]	17 (29)	10 (63)	4 (50)	5 (42)	0.091
Length of hospital stay, median days (range) [c]	16 (8-142)	15 (9-63)	19 (9-64)	20 (10-78)	0.768
FIM at discharge, median (range)					
Total [c]	125 (103-126)	122 (113-126)	126 (124-126)	125.5 (103-126)	0.279
Motor [c]	90 (72-91)	88 (85-91)	91 (89-91)	91 (72-91)	0.120
Cognitive [c]	35 (26-35)	35 (28-35)	35 (35)	35 (31-35)	0.600
Post-stroke characteristics					
(follow-up)					
Depression, *n* (%) [a]	3 (5)	‡5 (31)	0	§4 (33)	0.003*
Insomnia, *n* (%) [a]	14 (24)	‡13 (81)	4 (50)	7 (58)	<0.001*
Sarcopenia (SARC-F≥4), *n* (%) [a]	5 (9)	‡7 (44)	0	5 (42)	0.001*
SARC-F scores, median days (range) [c]	1 (0-5)	‡3 (0-8)	0.5 (0-3)	3 (0-6)	<0.001*
[†]Quality of life, median days (range)					
PCS [c]	51 (31-58)	‡43 (31-52)	50 (33-57)	46 (38-55)	0.038*
MCS [c]	51 (38-58)	‡45 (31-63)	50 (39-55)	46 (35-55)	0.003*

Values are shown as means (SD), median (range), or proportions (%);

a: Chi-square test; b: one-way ANOVA; c: Kruskal–Wallis; * Significant association ($p<0.05$) ; [†]: missing 1, n=93

Kruskal-Wallis with Bonferroni multiple-comparison test

‡ Significant differences between no fatigue versus persistent fatigue.

§ Significant differences between no fatigue versus recovery from fatigue

Abbreviations: FIM, Functional Independence Measure; MCS, mental component score; PCS, physical component score; SD, standard deviation

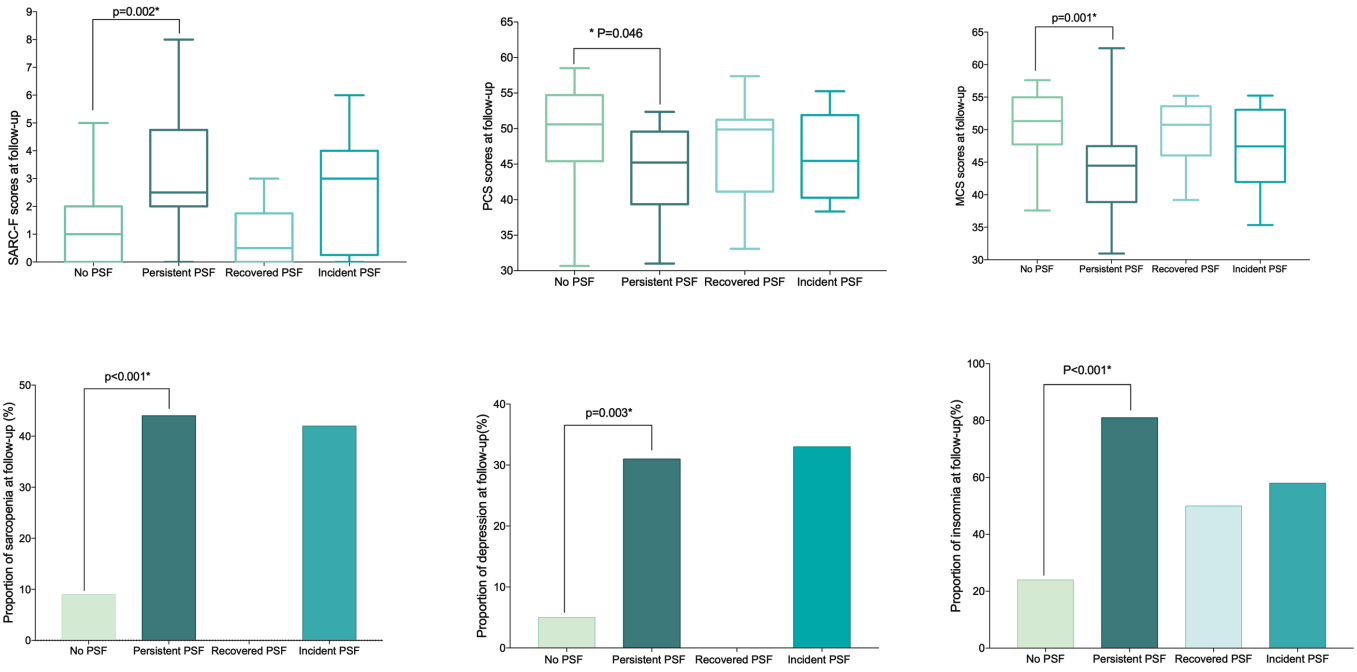

Figure 4. Follow-up outcomes of the patients with post-stroke fatigue

* Adjusted using Bonferroni correction for multiple tests.

2.5 Discussion

This study addressed some evidence gaps regarding the relationships between associated factors and PSF after discharge home. In our study, acute phase PSF was an independent predictor of PSF after discharge, with direct relationships. Acute phase depression, acute phase insomnia, and pre-stroke SARC-F had indirect correlations with PSF after discharge home. This correlation was mediated by acute phase PSF, which also remained a separate predictor of acute phase PSF. In this study, PSF was prevalent in 25.5% and 29.8% of the patients in the acute phase and at 1 month after discharge, respectively. Further, 17.0% of the survivors had persistent PSF, and persistent PSF was significantly associated with depression, insomnia, sarcopenia, and a lower HRQOL score. These findings provide instrumental scientific data that can be used to develop strategies to manage PSF. Further, to the best of our knowledge, this is the first study to report that persistent PSF not only affects depression, insomnia, and lower HRQOL scores, but is also related to sarcopenia.

Our findings in the univariate analyses are consistent with those of other studies (van de Port et al., 2007; Lerdal et al., 2011) that showed a higher proportion of PSF in women than in men. However, several other studies have also reported no sex differences in the incidence of PSF (Naess et al., 2005; Appelros, 2006). In the regression analysis, we found no significant difference in the sex distribution and FAS score between those with and without PSF. In the univariate and multivariate analyses, pre-stroke fatigue was correlated to post-stroke fatigue, consistent with previous findings (Lerdal et al., 2011). There might be numerous potential explanations for this finding, including pre-existing disease, poor health, lifestyle factors, vulnerability to stress, and mental health conditions (Kjeverud et al., 2020).

In line with the findings of previous studies (Kjeverud et al., 2020; Acciarresi et al., 2014), the bidirectional relationship between depression and insomnia played a prominent role in the occurrence of PSF. Although fatigue is a characteristic symptom of depression, PSF and post-stroke depression also share common risk factors, such as functional impairments (MacIntosh 2017). PSF can also occur without depression (Ponchel et al., 2015; De Doncker et al., 2018). Van der Werf et al. (2001) found that only 38% of patients with severe fatigue were also depressed. The current study showed similar findings, with 41.7% and 32.1% of patients with fatigue being depressed in the acute phase and at 1 month after discharge, respectively. Moreover, depression was prevalent in 22.3% of the participants in the acute phase and in 12.8% at 1 month after discharge. A previous study reported that insomnia occurs in 57% of patients in the early months after stroke (Leppävuori et al., 2002). The current study showed similar findings, with 53.2% and 40.4% of patients having insomnia in the acute phase and at 1 month after discharge, respectively.

However, while the prevalence of insomnia was significantly decreased at 1 month after discharge, the prevalence of PSF did not. PSF can occur without depression and/or insomnia. In this study, we found that acute phase PSF had no significant impact on depression after discharge. However, fatigue in the acute phase that continued to discharge was significantly associated with depression after discharge. Thus, early PSF management can not only prevent PSF, but also prevent depression after discharge. Acute phase depression and insomnia had direct associations with acute phase PSF. Additionally, acute phase depression and insomnia also had indirect correlations with PSF after discharge home, with the correlation mediated by acute phase PSF. Collectively, these findings highlight the importance of management of mental and sleep problems during hospitalization in patients with PSF.

A novel finding in our study is that pre-stroke SARC-F score had direct correlations with acute phase PSF and indirect correlations with PSF after discharge home. Some studies have shown that low skeletal muscle mass is strongly associated with fatigue in cancer patients (Bye et al., 2017; Wang et al., 2020). Meanwhile, there have been no studies on stroke patients. Skeletal muscle mass has been reported to be a potential target for reducing fatigue (Neefjes et al., 2017; al-Majid and McCarthy, 2001; Morgado et al., 2016). A potential explanation for this finding is that reduced skeletal muscle mass might induce feelings of tiredness, general weakness, and lack of energy, which may in turn lead to fatigue (Neefjes et al., 2013; Wagner et al., 2004). It is also worth noting that we found that acute phase PSF was associated with a higher SARC-F score after discharge but not with sarcopenia after discharge. However, fatigue in the acute phase that continue to discharge has a significantly impact on sarcopenia after discharge. This may be related to the pre-stroke SARCF score having direct associations with the acute phase PSF. Further, fatigue and low physical function lasted until 1 month after discharge. This ultimately leads to a reduction in physical activity and a decline in the patient's mental and physical function, which may in turn cause muscle loss or sarcopenia. Sarcopenia may then worsen fatigue and lead to decreased activity and social interaction. Moreover, the sequelae of sarcopenia may contribute to frailty, decreased capacity for independent living, and subsequent increase in health care costs (Neefjes et al., 2013; Wagner et al., 2004; Marcell 2003). Further research is needed to better understand the mechanism underlying the association between PSF and sarcopenia.

A previous study with a mean follow-up of 1.5 years reported that 57% of the patients never had PSF, 26% had persistent PSF, 9% had recovered PSF, and 8% had incident PSF (Snaphaan et al., 2011). Similar findings were found in our study despite

a shorter follow-up of only 1 month: 61.7% of the stroke survivors did not have PSF at all, 17.0% of the survivors had persistent PSF, 8.5% of the survivors had recovered PSF, and 12.8% of survivors had incident PSF. This may indicate that long-term PSF is likely to occur 1 month after discharge from the hospital and last for several years. Moreover, fatigue within 2 weeks following stroke was the major risk factor of PSF after discharge. In addition, 17.0% of the stroke survivors had persistent PSF. This indicates that fatigue in the acute phase may last until discharge home, and PSF after discharge is likely to last for several years. PSF itself is not a severe event, but it is the poor outcomes caused by PSF that should be carefully managed. Our findings are similar to those of earlier studies showing that PSF has a significant impact on HRQOL in stroke patients (Tang et al., 2010; Chen et al, 2015; Lerdal et al., 2013; Naess et al., 2006; van de Port 2007). PSF has a significant effect on depression, insomnia, and sarcopenia, and these factors may in turn influence the patient's HRQOL. Previous studies have shown that a markedly impaired QOL in patients with insomnia and sarcopenia (Ishak et al., 2012; Tsekoura et al, 2017). Post-stroke depression in the acute phase of stroke is an independent predictor of QOL in both the acute and chronic phases of stroke (Kim et al., 2018). This study showed that if PSF occurs in the acute phase and persists after discharge, it will affect later depression, insomnia, sarcopenia, and HRQOL. Thus, future research should focus on developing early interventions that improve fatigue before discharge rather than waiting for the fatigue to exert noticeable effects on physical and psychological health.

2.5.1 Limitations

To our knowledge, this is the first study to identify the predictors and short-term outcomes of PSF in the transition from hospital to home. However, this study also has some limitations. First, the results may be influenced by inclusion bias. We excluded

patients with severe paralysis, severe aphasia, communication difficulties, or who were unable to respond to the questionnaire. Thus, most of the severe stroke patients in whom the prevalence of fatigue or sarcopenia is higher may have been lost. In addition, we do not have data on the direct measure of stroke severity, such as the National Institutes of Health Stroke Scale score. Moreover, given that the symptoms of stroke include paralysis and imbalance, we were unable to measure the grip strength and gait speed in all patients. In addition, pre- and post-stroke sarcopenia were only measured using the self-report SARC-F questionnaire, which renders the measure vulnerable to recall bias. Furthermore, the sample size of this study, particularly that of the sarcopenia group, was relatively small. Although the sample size was calculated based on statistical methods, it may also make it difficult to determine if this outcome is a true finding. Thus, studies with larger sample sizes are needed to confirm our findings.

Despite these limitations, the present study has important implications for health professionals and future studies because of the high prevalence of PSF, its adverse effect in stroke survivors, and its importance for rehabilitation and outcomes. PSF is gaining increasing attention and is now evaluated in several guidelines for stroke practice (Eskes et al., 2015; Winstein et al., 2017; Lanctôt et al., 2020). However, research in this area remains scant, and thus, effective treatment modalities and/or management strategies for PSF are yet to be established (Ponchel et al., 2015; Wu et al., 2015). To the best of our knowledge, this is also the first study to analyse the interactions of pre-stroke sarcopenia, acute phase depression, acute phase insomnia, and acute phase fatigue with the occurrence of PSF after discharge home. Moreover, PSF at the acute phase may last until discharge home, and PSF after discharge is likely to last for several years. Thus, health professionals need to pay attention to the subjective experience of PSF in clinical practice and provide timely assessment and

interventions during hospitalization. Our data provide evidence that can be useful for achieving this goal and preventing later perceptible effects on physical and psychological health. In the field of research, this evidence could help clarify the mechanisms of PSF and develop new interventions for its management.

2.6 Conclusions

In this study, 17.0% of stroke survivors had persistent PSF. Persistent PSF is not only associated with depression, insomnia, and lower HRQOL scores, but also with sarcopenia. Acute phase PSF was an independent predictor of PSF after discharge home. In addition, the interaction with acute phase depression, acute phase insomnia, and pre-stroke SARC-F had an indirect connection with post-stroke fatigue after discharge home, which remains a separate predictor of acute-phase post-stroke fatigue. These findings indicate that early assessment and management of mental status, sleep problems, and sarcopenia during hospitalization might be an important step in post-stroke rehabilitation and home transition.

Supplementary Table 1. Path coefficients of the PSF at 1 month after discharge model

Path			Unstandardized estimates	p-value	Critical ratio	Standardized estimates
	<---	Pre-stroke SARC-F	0.839	0.020	2.327	0.194
PSF at baseline	<---	Depression	0.630	<0.001	4.086	0.353
	<---	Insomnia	0.403	<0.001	4.107	0.355
PSF at follow-up	<---	PSF at baseline	0.708	<0.001	8.167	0.646
Insomnia	<-->	Depression	5.372	0.015	2.426	0.260

Abbreviations: PSF, poststroke fatigue

Supplementary Table 2. Percentile 95% CI and p-value of Direct, indirect and total effects

Path		Estimate	Percentile 95% CI	Percentile p-value
Direct effect	PSF at follow-up <--- PSF at baseline	0.579	0.423-0.714	0.001
	PSF at follow-up <--- Depression	0.149	-0.006-0.305	0.063
Indirect effect	PSF at follow-up <---Pre-stroke SARC-F	0.112	0.001-0.236	0.044
	PSF at follow-up <--- Depression	0.204	0.096-0.327	0.001
	PSF at follow-up <--- Insomnia	0.205	0.089-0.326	0.001
Total effect	PSF at follow-up <--- Depression	0.353	0.177-0.516	0.001

Abbreviations: PSF, poststroke fatigue

Supplementary Table 3. Follow-up outcomes of the patients with acute phase post-stroke fatigue

Variables	Total *n* = 94	PSF *n* = 24	No PSF *n* = 70	P-value
Length of hospital stay, median (range) [b]	16 (8-142)	17 (8-130)	16 (8-142)	0.614
FIM at discharge, median (range)				
Total [b]	125 (103-126)	125 (112-126)	125 (103-126)	0.502
Motor [b]	90 (72-91)	90 (83-91)	91 (72-91)	0.253
Cognitive [b]	35 (26-35)	35 (26-35)	35 (27-35)	0.762
Post-stroke characteristics				
（Follow-up）				
Fatigue, *n* (%) [a]	28 (30)	16 (67)	12 (17)	<0.001*
Depression, *n* (%) [a]	12 (13)	5 (21)	7 (10)	0.309
Insomnia, *n* (%) [a]	38 (40)	17 (71)	21 (30)	<0.001*
Sarcopenia (SARC-F≥4), *n* (%) [a]	17 (18)	7 (29)	10 (14)	0.102
SARC-F scores, median (range) [b]	1 (0-8)	2 (0-8)	1 (0-6)	0.026*
[†]Quality of life, median (range)				
PCS [b]	49 (31-59)	48 (31-59)	51 (31-59)	0.029*
MCS [b]	50 (31-63)	46 (31-63)	51 (31-63)	0.006*

Values are shown as means (SD), median (range), or proportions (%).

[a]: Chi-square test; [b]: Mann–Whitney U Test; [†]: missing 1, n=93; * Significant association (P < 0.05);

Abbreviations: FIM, Functional Independence Measure; PSF, poststroke fatigue; SD, standard deviation.

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Chapter 3: Development and internal validation of a nomogram to predict post-stroke fatigue after discharge

3.1 Abstract

Objectives: We aimed to develop and validate a nomogram for the individualized prediction of the risk of post-stroke fatigue (PSF) after discharge.

Materials and Methods: Fatigue was measured using the Fatigue Assessment Scale. Multivariable logistic regression analysis was applied to build a prediction model incorporating the feature selected in the least absolute shrinkage and selection operator regression model. Discrimination, calibration, and clinical usefulness of the predictive model were assessed using the C-index, calibration plot, and decision curve analysis. Internal validation was conducted using bootstrapping validation. Finally, a web application was developed to facilitate the use of the nomogram.

Results: We developed a nomogram based on 95 stroke patients. The predictors included in the nomogram were sex, pre-stroke sarcopenia, acute phase fatigue, dysphagia, and depression. The model displayed good discrimination, with a C-index of 0.801 (95% confidence interval: 0.700–0.902) and good calibration. A high C-index value of 0.762 could still be reached in the interval validation. Decision curve analysis showed that the risk of PSF after discharge was clinically useful when the intervention was decided at the PSF risk possibility threshold of 10% to 90%.

Conclusion: This nomogram could be conveniently used to provide an individual, visual, and precise prediction of the risk probability of PSF after being discharged home.

Thus, as an aid in decision-making, physicians and other healthcare professionals can use this predictive method to provide early intervention or a discharge plan for stroke patients during the hospitalization period.

3.2 Introduction

Post-stroke fatigue (PSF) is a common condition of stroke, even in those with good neurological recovery [1,2]. It can be experienced following a stroke at any point during the recovery process and is likely to persist in the long term. A systematic review indicated that PSF is present in more than one-third of all stroke survivors at any time during the follow-up within 2 years [3]. PSF not only interferes with participation in rehabilitation therapy and daily activities, but also adversely affects patient outcomes and return to work capability [4-6]. Many stroke survivors reported that a salient feature of the transition phase is managing fatigue [7]. However, 43% of stroke survivors reported inadequate support to manage their fatigue problems [8]. Thus, frustration is a common response for these changes at 1 month after discharge at home [7]. PSF has recently gained increasing attention and is now evaluated in several guidelines for stroke practice [9-11]. However, effective treatment modalities and/or management strategies for PSF are yet to be established [12,13].

Previous studies have shown that PSF is related to the stroke survivor's age, sex, or pre-stroke fatigue [14]. Many studies have demonstrated a relationship between PSF and psychological factors such as anxiety and depression [15,16]. However, the relationship between fatigue and depression remains controversial due to PSF can also occur in the absence of depression [12]. In addition, pain and sleep problems such as insomnia were listed as the contributors to fatigue [17,18]. Naess reported that patients with pain reported higher fatigue scores on the Fatigue Severity Scale [19]. A previous

study showed that fatigue measured 1 year after stroke was associated with both sleep disturbance and physical disability [20]. Furthermore, pre-stroke sarcopenia has shown related with functional outcome after a stroke [21]. Therefore, we hypothesized pre-stroke sarcopenia may also affect post-stroke fatigue.

Although fatigue is a persistent symptom affecting many stroke survivors, PSF is often underrecognized. Thus, the Canadian stroke best practice guidelines recommended that healthcare professionals should anticipate the possibility of PSF and prepare stroke patients and their families to mitigate fatigue through assessment, education, and interventions throughout the stroke-recovery continuum. Moreover, follow-up healthcare visits of stroke survivors should include periodic screening for PSF after return to the community [11]. However, PSF is only currently measured using general fatigue scales, such as the Fatigue Severity Scale, Fatigue Assessment Scale (FAS), and Checklist of Individual Strength [22]. None of these scales were developed specifically for stroke patients, and healthcare professionals have no tools to predict fatigue. Additionally, the continuity of care is even more difficult for stroke survivors with language, motor, or visual impairments that substantially hinder telephone contact to schedule and confirm appointments after hospital discharge [23]. Therefore, an early prediction tool of PSF after discharge is essential for anticipating the possibility of PSF and prepare stroke patients to mitigate fatigue.

A nomogram is a simple graphical representation of a predictive model for generating the numerical probability of a disease or an event during the future course of disease [24]. It has been demonstrated to be more reliable than many other systems and has thus been proposed as an alternative or even a new standard [25,26]. Further, a nomogram has the potential to facilitate medical procedures during clinical decision-making.

There is a current trend toward a decreasing length of hospital stay, with a mean hospitalization period of <14 days [27]. To enable the early prevention of PSF after discharge while acknowledging a limited window of in-hospital opportunity, we aimed to develop and validate a nomogram for identifying acute phase stroke patients at risk for PSF after discharge. The ultimate goal was to improve home transition and long-term outcomes for stroke patients during the hospitalization period. Accordingly, we endeavored to develop a simple clinical tool based on acute phase data with which to assess the individual probability of PSF after discharge. The focus was on the predictors available to physicians, physiotherapists, and nurses during hospitalization.

3.3 Methods

3.3.1 Study design and participants

This prospective observational study evaluated participants in the Support System for Stroke Survivors project. Data were collected between May 2019 and July 2020 at a neurosurgical hospital in Sapporo, Hokkaido, Japan. Participants who met the following criteria were included: 1) acute stroke (including both ischemic and hemorrhagic stroke); 2) age >30 years; 3) willing to discharge from the hospital to home; and 4) willing to complete the study. The exclusion criteria were: 1) Mini-Mental State Examination (MMSE) score of <24 or significant impairments in cognition; 2) severe paralysis were included paraplegia and quadriplegia which affects both of arms or/and both of legs. Considering the time or number of physical therapies will increase for stroke patients with severe paralysis that might add the physical burden to the participant; 3) severe aphasia, or communication difficulties; 4) inability to speak Japanese; 5) medically unstable or planned surgery; 6) past or present history of depression or started on antidepressant drug therapy within the past 3 months; 7) taking

pharmacological treatments for fatigue; and 8) current participation in other research studies that might affect fatigue or add a significant burden to the participant.

3.3.2 Demographic, clinical, and stroke characteristics

Demographic characteristics included age, sex, and family composition. Clinical characteristics included MMSE score, Functional Independence Measure (FIM) scores, and medical condition. Stroke characteristics included previous stroke, type of stroke, and length of hospital stay. All data were collected from the electronic medical records.

3.3.3 Assessment of PSF

Fatigue was measured using the Fatigue Assessment Scale (FAS) within 2 weeks from admission (acute phase) and 1 month after discharge. The FAS is a 10-item self-report scale with 10 statements about different aspects of fatigue, is easy to complete, and is a reliable and valid tool to identify fatigue in a range of diseases or conditions [28]. The FAS is used in 26 different diseases or conditions, including stroke, neurologic disorders, and sarcoidosis, with a higher score indicating more fatigue. In addition, it is the only measurement tool that has a cutoff value for stroke [29-32], with a score of ≥24 being the cutoff for classifying PSF [33].

3.3.4 Assessment of possible pre- and post-stroke risk factors

Pre-stroke fatigue was assessed using a single-item self-report and was defined as fatigue lasting longer than 3 months before the stroke. Pre-stroke sarcopenia was assessed using the SARC-F questionnaire, which is a rapid questionnaire to screen for sarcopenia using self-reported information about falls, mobility, and strength (34). Patients answered based on their condition before the stroke. The total score of the SARC-F ranges from 0 to 10 points, and we defined pre-stroke sarcopenia as a score of

≥4 [34,35]. A self-reported dysphagia questionnaire was administered using the 10-item Eating Assessment Tool (EAT-10), which has excellent reliability and validity. An EAT-10 score of ≥3 indicates that a patient is at risk of dysphagia [36,37]. Depression was assessed during the acute phase using the Hospital Anxiety and Depression Scale-Depression (HADS-D), with a score of >7 set as a cutoff for classifying patients at risk of depression [38-40]. The HADS as one of the most widely used screening tools for post-stroke depression has superior psychometric properties and clinical utility indices in stroke populations [41]. Insomnia was assessed during the acute phase using the Insomnia Severity Inventory, which is a 7-item tool for assessing sleep quality and insomnia severity over the previous 2 weeks [42,43]. Higher scores indicate severe insomnia, with a score >7 as a cutoff for classifying the risk of insomnia.

3.3.5 Ethical approval

This study was approved by the Ethics Committee of the Faculty of Health Sciences, Hokkaido University (Reference No 18-82,19-80) and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients or their relatives provided informed consent.

3.3.6 Statistical analysis

Categorical variables were presented using frequencies and percentages; continuous variables were presented using mean and standard deviations and using median and range. The association between acute phase factors and PSF after discharge was assessed using the chi-square test. Statistical analyses in this part were performed using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA). $P<0.05$ was considered statistically significant.

Pre-determined factors with $p \leq 0.20$ in the univariate analyses were entered into the least absolute shrinkage and selection operator (LASSO) analysis to reduce the dimensionality of the data, and the best predictors were identified [44,45]. Features with nonzero coefficients in the LASSO regression model were selected [46]. The features selected in the LASSO regression model were subjected to multivariate logistic regression analysis to develop the nomogram [47]. Nomogram validation consisted of calibration and discrimination. Calibration was performed by plotting the calibration curve to analyse the association between the observed incidence and predicted probability [48]. To quantify the discrimination performance of the nomogram for PSF after the discharge, the concordance index (C-index) was measured. We used 1000 bootstrap resamples for internal validation of the accuracy estimates and to reduce overfit bias [49]. Then, the decision curve analysis (DCA) was used to evaluate the clinical utility of the nomogram based on net benefits at different threshold probabilities in the cohort. Finally, a web application was developed to facilitate the use of the nomogram. Statistical analysis was performed using R version 4.0.2 software (R Foundation, Vienna, Austria).

3.4 Results

3.4.1 Participant characteristics

Of the 171 stroke patients initially identified, 104 stroke patients participated in the study. Among them, 95 patients eventually completed the follow-up and were included in the final analysis. The mean age at the acute phase was 68.5 ±10.0 years, and 38% of them were women. The mean MMSE score was 27.6 ± 1.9, the median FIM score was 93 (range, 41–126), and the median length of hospital stay was 16 days (range, 8–142 days). The mean fatigue (FAS) score at the acute phase was 19.3 ± 6.7

and 18.9 ± 7.2 at 1 month after discharge (follow-up). PSF was prevalent in 25% and 31% of the patients at the acute phase and at 1 month after discharge, respectively.

As shown in Table 1, there were no significant differences in age, sex, clinical, and stroke characteristics between the PSF and no PSF groups (all P>0.05). However, significant differences were found in pre- and post-stroke characteristics between the two groups (all P<0.05).

Table 1. Patient characteristics

Variables	Total n =95	1 month after discharge		P-value
		PSF n =29	No PSF n =66	
Demographics				
Sex (female), n (%)	36 (38)	15 (52)	21 (32)	0.060
Age (years), n (%)				0.494
≤65	27 (28)	6 (20)	21 (32)	
>65	42 (44)	15 (52)	27 (41)	
>75	26 (27)	8 (28)	18 (27)	
Clinical characteristics, n (%)				
Hypertension	42 (45)	11 (39)	31 (47)	0.493
Diabetes	24 (26)	5 (18)	19 (29)	0.266
Cancer	9 (10)	3 (11)	6 (9)	0.807
Stroke characteristics, n (%)				
Previous stroke	13 (14)	4 (14)	9 (14)	0.984
Type of stroke				0.191
Ischemic	86 (92)	25 (86)	62 (94)	
Hemorrhagic	8 (8)	4 (14)	4 (6)	
Paralysis	38 (40)	12 (41)	26 (39)	0.856
Pre-stroke characteristics, n (%)				
Pre-stroke fatigue	18 (19)	10 (35)	8 (12)	0.010*
Pre-stroke sarcopenia	8 (8)	6 (21)	2 (3)	0.004*
Post-stroke characteristics, n (%)				
Dysphagia	27 (28)	13 (45)	14 (21)	0.019*
Depression	22 (23)	12 (41)	10 (15)	0.005*
Insomnia	51 (54)	20 (69)	31 (47)	0.048*
Fatigue	24 (25)	16 (55)	8 (12)	<0.001*

Chi-square test

*P<0.05

3.4.2 Predictors of PSF after discharge

The variables with p≤0.20 in the univariate analysis were sex, stroke type, pre-stroke sarcopenia, pre-stroke fatigue, fatigue, dysphagia, depression, and insomnia. The above eight features were used for the LASSO logistic regression, and five features with non-zero coefficients were subsequently selected (Figure 1A, 1B). The model ultimately included five features: sex, pre-stroke sarcopenia, fatigue, dysphagia, and depression.

3.4.3 Nomogram to predict probability of PSF after discharge

The five features selected using the LASSO logistic regression algorithm were included in the multivariate logistic regression model. The results of the multivariate logistic regression analysis are presented in Table 2. A nomogram was then generated from the multivariate logistic regression analysis (Figure 2A). The C-index for the model before and after bootstrapping was 0.801 and 0.726, respectively. This suggested a nomogram with good discrimination, and the calibration curve of the nomogram showed good agreement between the predicted and actual probabilities in stroke patients in this cohort (Figure 3).

Table 2. Predictive factors of PSF after discharge

Intercept and variable	β	Odds ratio (95% CI)	P-value
Intercept	-2.207	0.110 (0.041-0.253)	<0.001
Sex (Female)	0.681	1.977 (0.641-6.164)	0.232
Pre-stroke sarcopenia	1.960	7.098 (1.082-61.485)	0.048
Fatigue	1.786	5.968 (1.885-19.891)	0.002
Dysphagia	0.318	1.374 (0.413-4.304)	0.591
Depression	1.124	3.078 (0.876-11.237)	0.080

β indicates the regression coefficient; CI, confidence interval

3.4.4 Clinical use

The DCA was performed to evaluate the clinical utility of the nomogram using data from all the 95 patients. Figure 4 shows that if the nomogram predicted a 10% to 90% probability of PSF risk, the nomogram provided additional value relative to the "intervention-all-patients" plan or the "intervention-none" plan, suggesting that the nomogram was clinically useful.

We then developed a web application for convenience in the use of the above nomogram. An online version of our nomogram (Figure 2B) to assist healthcare professionals and researchers can be accessed at https://yasu2020.shinyapps.io/dynnomapp/. The predicted PSF risk probability can be easily determined by inputting the results of acute phase assessment and reading output figure generated by the web application.

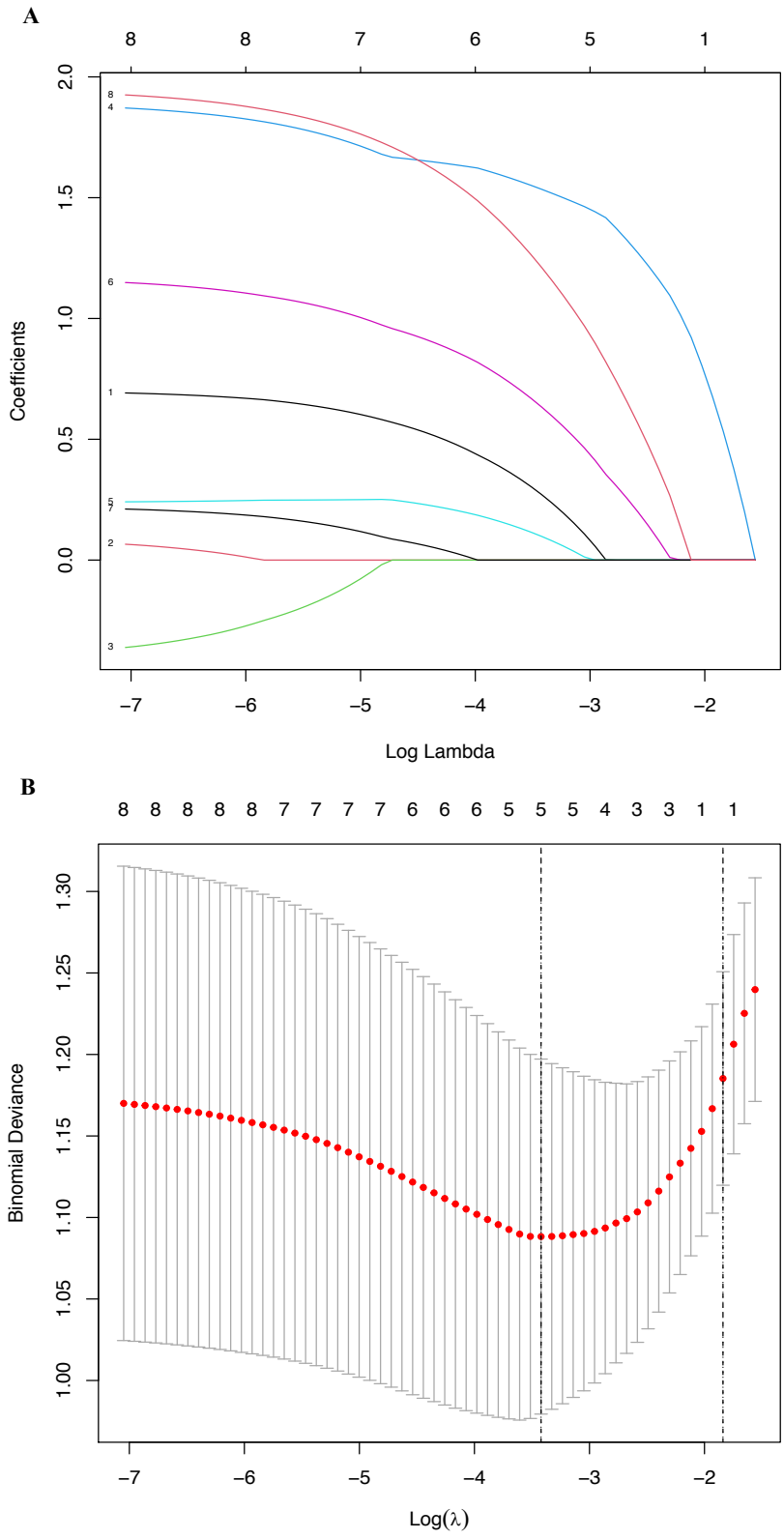
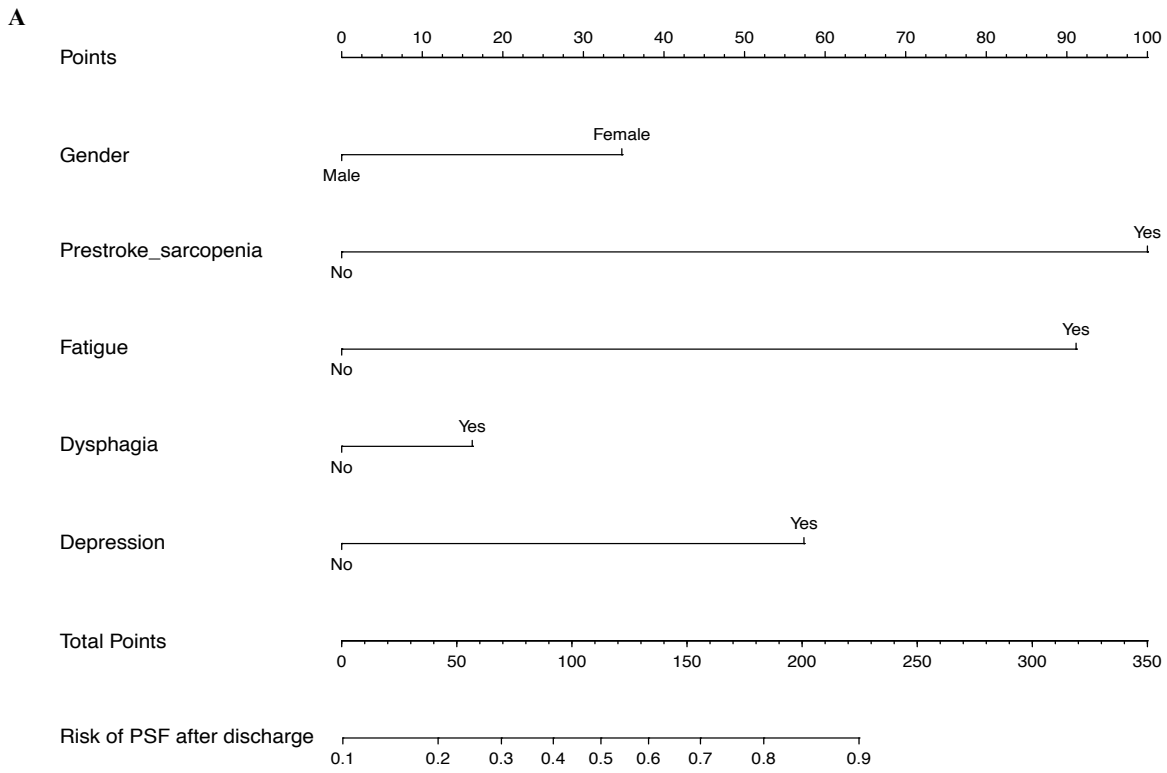


Figure 1. Feature selection using the LASSO logistic regression model.

Notes: (**A**) The LASSO coefficient profiles of the eight features. A coefficient profile plot was produced against the log (lambda) sequence. (**B**) The partial likelihood deviance (binomial deviance) curve was plotted versus the log (lambda). Black dotted vertical lines were drawn at the optimal values by using the minimum criteria (left dotted line) and the 1 SE of the minimum criteria (the 1-SE criteria) to obtain the included feature factors, where optimal lambda resulted in five features with nonzero coefficients.

Abbreviations: LASSO, least absolute shrinkage and selection operator; SE, standard error



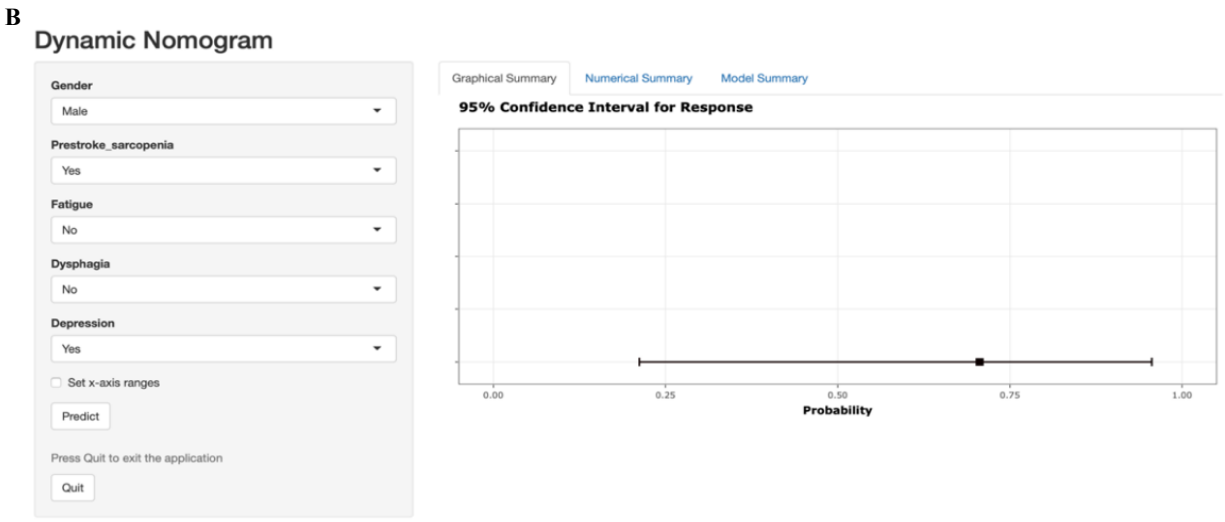


Figure 2. Nomogram predicting the probability of PSF after discharge.

Notes: (A) Nomogram predicting the probability of PSF after discharge using sex, pre-stroke sarcopenia, fatigue, dysphagia, and depression. The probability of PSF after discharge is calculated by drawing a line to the top point axis for each variable. The points for each variable are then summed and located on the total points line, and a vertical line is projected from the total points axis to the bottom predicted probability scale to obtain an individual probability of PSF after discharge. **(B)** Example of a screen from the web application that was developed from the prediction model reported in this study. For example, a male patient (0 point) with pre-stroke sarcopenia (100 points) and acute phase depression (60 points) but no acute phase fatigue (0 points) and dysphagia (0 points) had a total score of 160 points. The PSF after discharge probability would be approximately 70% (95% confidence interval: 20%-96%). This patient would be at high risk of PSF after discharge, and thus early intervention should be considered.

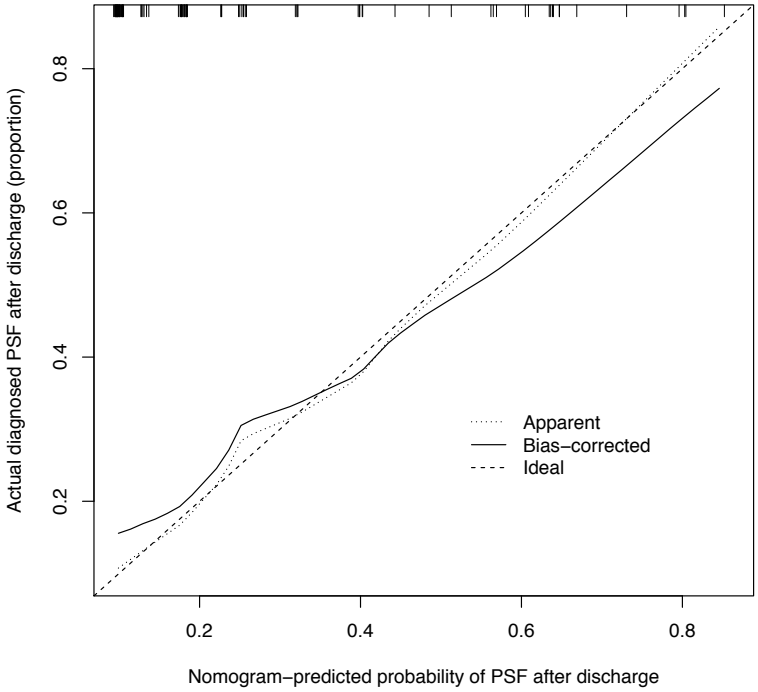


Figure 3. Calibration of our model for predicting PSF after discharge.

The x-axis represents the nomogram-predicted probability, and the y-axis represents the observed rate of PSF after discharge. The dotted line represents the entire cohort (n = 95) and the solid line is bias-corrected by bootstrapping, indicating the observed nomogram performance. Perfect prediction would correspond to the diagonal dashed line.

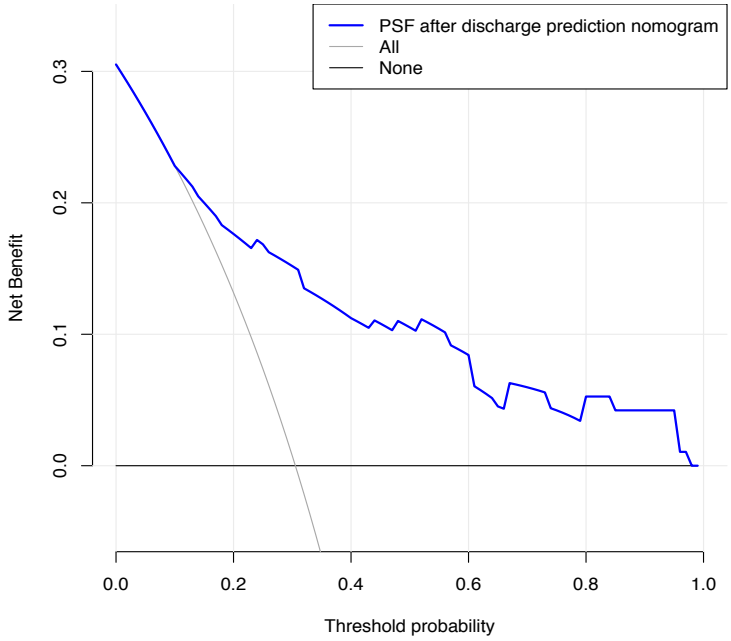


Figure 4. The decision curve analysis (DCA) for the nomogram.

Solid line: Assume the intervention-none, and the net benefit is zero; Grey line: assume intervention-all-patients; Blue line: intervention if the proposed model exceeds a threshold (ranging from approximately 10% to 90%). For example, if your personal threshold probability is 10% (i.e., you would be given intervention if your probability of developing PSF after discharge was greater than 10%), then the proposed nomogram model can be beneficial for making the decision to undergo intervention.

3.5 Discussion

Despite the significant impact of PSF on the recovery and quality of life of stroke patients, it is only currently measured using general fatigue scales. We developed and internally validated a nomogram to predict the individual probability of PSF after discharge by combining sex, pre-stroke sarcopenia, acute phase fatigue, dysphagia, and depression. This nomogram showed satisfactory internal validity and discrimination, indicating good performance. The nomogram, which has been incorporated into an internet-based tool, also showed good clinical utility and can thus aid physicians, physiotherapists, and nurses in clinical decision-making. In recent years, there has been a trend toward a decreasing length of hospital stay, with the current mean duration of hospitalization being <14 days. This nomogram enables the identification of stroke patients at risk for post-discharge PSF within the acute phase of hospital admission, addressing the limited window of in-hospital opportunity for PSF prediction. Several guidelines for stroke practice stipulate that healthcare professionals should anticipate the possibility of PSF, but few have provided a predictive tool based on acute phase data. To our knowledge, this study is the first attempt to establish a predictive nomogram for PSF after discharge based on acute phase data.

In our study, 31% of stroke survivors developed fatigue after discharge. Our results are consistent with those of other studies that reported that 25% to 85% of stroke patients experience PSF [50]. Participants without severe paralysis or severe aphasia, and the median length of hospital stay was 16 days. This result was consistent with a previous study showing that PSF does not appear to be correlated to the severity of stroke and that even mild stroke patients may experience fatigue [17]. Predictive tools for PSF after discharge for acute phase patients and equivocal efficacy of interventions

for PSF are lacking. This prompted us to develop a novel predictive modeling system using nomogram methodology.

Our nomogram showed good discriminative capability, with a high C-index of 0.801. In the univariate analysis, the variables significantly predictive of PSF after discharge were sex, stroke type, pre-stroke sarcopenia, pre-stroke fatigue, fatigue, dysphagia, and depression. Most of these variables have been associated with PSF in previous studies [12,51,16]. However, not all of the variables were significantly associated with PSF after discharge in the multivariate logistic regression analysis. Importantly, a nomogram is a predictive but not an associative model; the criterion for inclusion of a variable is its capability to demonstrably improve the probability that the model will correctly predict PSF after discharge.

Interestingly, to our best knowledge, this study is the first to report that the assessment of pre-stroke sarcopenia has a predictive value for PSF after discharge. Skeletal muscle mass has been reported to be a potential target for reducing fatigue [52, 53], with studies showing that low skeletal muscle mass is strongly associated with fatigue in cancer patients [54,55]. A potential explanation is that reduced skeletal muscle mass might induce feelings of tiredness, general weakness, and lack of energy, which may in turn lead to fatigue [52,56]. However, there have been no studies on stroke patients. Muscle wasting is a common complication of stroke, with 42% of stroke survivors having sarcopenia [22]. The sequelae of sarcopenia may contribute to frailty, decreased capacity for independent living, and subsequent increase in health care costs [57-59]. Thus, if the pre-stroke sarcopenia is not improved in time, sarcopenia may worsen after a stroke. Further research is needed to better understand the mechanism underlying the association between PSF and sarcopenia.

Finally, our nomogram demonstrated calibration curves with little deviation from ideal predictions and a high net benefit in the decision curve analysis. Considering the application of the nomogram, the final and most important point is whether stroke patients need early intervention or additional discharge plans. Our nomogram showed good discrimination and calibration. To prove its clinical utility, we assessed whether the decision based on the nomogram would improve the outcomes of PSF after discharge in stroke patients. Thus, a decision curve analysis was applied. It showed that if a stroke patient had a threshold predicted probability of 10%-90%, the use of the nomogram to predict PSF after discharge was more beneficial than the "intervention-all-patients" plan or the "intervention-none" plan, showing that the nomogram was clinically useful.

The proposed nomogram is innovative in the following aspects. First, to our best knowledge, no nomogram has been previously designed to predict fatigue after discharge in stroke patients. We established a nomogram for these patients to enable individualized screening. Importantly, this nomogram could identify acute phase stroke patients at risk for PSF after discharge and thus enable the early anticipation and prevention of post-discharge PSF. Second, this was the first time that the assessment of pre-stroke sarcopenia was shown to be predictive of PSF after discharge. Finally, decision curve analysis, which is a relatively new approach for analyzing net benefit, was applied to our nomogram, and the results revealed that our nomogram has good clinical utility.

Despite these strengths, some potential limitations should still be considered. First, the results may be influenced by inclusion bias. We excluded patients with severe paralysis, severe aphasia, communication difficulties, or inability to respond to the questionnaire. Thus, most severe stroke patients in whom the prevalence of fatigue is

higher may have been lost. Moreover, the entire cohort originated from one center. Thus, this cohort is not representative of all stroke patients in Japan. Therefore, a multi-center international study should be carried out to further validate the usefulness of our nomogram. Second, pre-stroke sarcopenia was only measured using the self-report SARC-F questionnaire, which renders the measure vulnerable to recall bias. Finally, the sample size of this study was relatively small, although our nomogram had good internal sampling. Further validation of the clinical utility of our nomogram entails the inclusion of stable external data.

3.6 Conclusions

This nomogram enables the identification of acute phase stroke patients at risk for PSF after discharge. This nomogram will be helpful in clinical practice as it enables an easy calculation of individual probability. Physicians, physiotherapists, and nurses can use this nomogram, which has been incorporated into an internet-based tool, as an aid in decision-making and to provide an early intervention or a discharge plan for stroke patients during the hospitalization period. Moreover, it is a valuable tool for patient counseling after discharge.

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Chapter 4: Non-Pharmacological Interventions for Post-Stroke Fatigue: A systematic review and network meta-analysis

4.1 Abstract

Post-stroke fatigue (PSF) is one of the most serious sequelae, which often interferes with the rehabilitation process and impairs the functional recovery of patients. Due to insufficient evidence, it is unclear which specific pharmacological interventions should be recommended. Therefore, in this paper, we compare the effectiveness of non-pharmacological interventions in PSF. A systematic review and network meta-analysis of randomized controlled trials were performed using EMBASE, MEDLINE, CINAHL, Cochrane library, ClinicalTrials.gov, CNKI, and CQVIP, from inception to January 2018, in the English and Chinese languages. RCTs involving different non-pharmacological interventions for PSF with an outcome of fatigue measured using the Fatigue Severity Scale were included. Multiple intervention comparisons based on a Bayesian network are used to compare the relative effects of all included interventions. Ten RCTs with eight PSF non-pharmacological interventions were identified, comprising 777 participants. For effectiveness, most interventions did not significantly differ from one another. The cumulative probabilities of the best non-pharmacological intervention for fatigue reduction included Community Health Management (CHM), followed by Traditional Chinese Medicine (TCM) and Cognitive Behavioral Therapy (CBT). Network meta-analysis based on data from the selected RCTs indicated that the eight PSF non-pharmacological interventions shared equivalent efficacy, but CHM,

TCM, and CBT showed potentially better efficacy. In the future, fatigue needs to be recognized and more accurate assessment methods for PSF are required for diagnosis and to develop more effective clinical intervention.

4.2 Introduction

Fatigue is a common and long-standing complication after stroke. The prevalence of post-stroke fatigue (PSF) ranges from 25% to 85% [1]. The first report of fatigue after stroke, published in 1999, stated that 40% of stroke patients reported fatigue as one of their most serious sequelae [2]. PSF often limits the rehabilitation process and impairs the functional recovery of patients [3], and can also indirectly affect patients' psychological outcomes and quality of life. PSF has also been closely related to prognosis and mortality [4]. As there is currently no specific measurement to identify fatigue and the signs of fatigue are not always obvious to outsiders, it may be difficult to understand how a patient is feeling. Thus, early detection and effective interventions are particularly important. Recently, PSF has gained increasing attention from researchers. The Canadian Stroke Best Practice Recommendations, the first best practice recommendations for PSF, were published in 2015 [5]; further, in 2016, the top 10 published research priorities specific to stroke nursing identified managing fatigue as a top research priority [6]. However, fatigue still does not receive enough attention in patients after stroke, making the management of fatigue in patients after stroke difficult and directly affecting their prognosis.

Pharmacological intervention has been reported to improve PSF, such as Tirilazad Mesylate, Modafinil, and OSU6162. However, there is currently insufficient evidence to determine a specific pharmacological intervention for PSF, and pharmacological management is far from satisfactory. Moreover, there is a lack of systematic nursing

management intervention for PSF [7]. Therefore, evidence-based medicine for PSF patients is required to provide a theoretical basis for prevention, and treatment with targeted health management programs are required to improve the quality of life of patients with fatigue after stroke. In this study, we aim to compare the effectiveness of non-pharmacological interventions for PSF to provide evidence for healthcare providers. Network meta-analyses (NMA), enabling the comparison of multiple interventions to incorporate clinical evidence from both direct and indirect treatment comparisons in a network of treatments and associated trials, is a valuable tool in comparative effectiveness research [8]. To the best of our knowledge, this is the first study using NMA for a multiple intervention comparison of the currently available methods to determine the effectiveness of non-pharmacological interventions in PSF. To provide effective support for stroke patients, it is necessary to first understand the effectiveness of non-pharmacological interventions

4.3 Methods

This systematic review and network meta-analysis was conducted in accordance with the PRISMA statement extension for NMA [9]. We followed a pre-specified protocol registered at PROSPERO (CRD42018105983).

4.3.1 Inclusion and Exclusion Criteria

Only RCTs including outcome using fatigue score measured by FSS were used. We considered that differences in the prevalence of PSF are likely reflected by different measurement tools, in order to minimize the bias induced by the measurement of the outcome. Our inclusion criteria were any outcome of fatigue measurement using FSS, as FSS is a widely accepted and used scale to measure fatigue in stroke populations.

We included any patients diagnosed with ischemic or hemorrhagic stroke, as diagnosed by MRI or CT, and no age or gender limitations were considered. The control group was defined by treatment as usual, including usual treatment, nursing, and rehabilitation, which we called “as usual” (AU). The intervention group was defined as additional provided non-pharmacological interventions based on usual treatment, where non-pharmacological intervention denotes the management of PSF without medications. The outcome was the patient’s degree of fatigue pre- and post-intervention using the FSS scale.

4.3.2 Data Search and Selection

We searched EMBASE, MEDLINE, CINAHL, Cochrane library, ClinicalTrials.gov, CNKI, and CQVIP from inception to Jan. 2018, using the English and Chinese languages, and updated the search to 2019. Our search terms are shown in Table A1. Two reviewers (Y.S. and M.O.) independently read the titles and abstracts identified by the search, then screened the full text manuscripts of potentially relevant references. Any eligibility disagreements were decided by discussing with a third reviewer (M.Y).

4.3.3 Data Extraction and Quality Assessment

Data extraction details included identification of the study, methods of study design, participant characteristics, interventions, outcome measures, and results. Data from baseline and endpoint of fatigue score were included in the results. If results included multiple post-intervention and follow-up scores, we chose the last follow-up score as the endpoint score.

The risk of bias of the included RCTs was assessed based on the Cochrane tool using the Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), with six assessment domains: Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. For each study, the classification of "low risk" was shown in green, "unclear risk" was shown in yellow, and "high risk" was shown in red.

4.3.4 Statistical Analysis

First, a network plot for every intervention was drawn used using the STATA version 14.0 (StataCorp LP. College Station, TX, USA). Second, we conducted pair-wise meta-analyses with a random effects model to synthesize studies comparing the intervention with control (AU). The results were reported as pooled mean difference (MD) with the corresponding 95% confidence interval (CI). Statistical heterogeneity across studies was assessed using a forest plot and the inconsistency statistic (I^2). Statistical significance was regarded as $p < 0.05$. All calculations were performed using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Third, mixed comparisons were carried out on direct and indirect evidence. We conducted Bayesian NMA using the Markov Chain Monte Carlo random effects model in Aggregate Data Drug Information System (ADDIS) version 1.16.8 (Drugis, Groningen, NL). We networked the translated FSS outcomes within studies and specified the relations among the MD across studies making different comparisons, as previously reported. This method combines direct and indirect evidence for any given pair of interventions. We used $p < 0.05$ and 95% CI beyond the null value to assess significance. We also calculated the inconsistency factor (IF) and 95% CI to evaluate the inconsistency of each closed loop, with the IF close to

0. In additional, the random effects variance and inconsistency variance were roughly equal, which is considered to be less inconsistent. Furthermore, we assessed the probability that each intervention was the most efficacious, the second best, the third best, and so on, by calculating the MD of each treatment group, compared with arbitrary common controls, and counting the proportion of iterations of the Markov chain of the MD ranking in treatments.

4.4 Results

Studies were selected by following PRISMA guidelines [8]. Figure 1 presents a flow diagram showing the searching and selection process for this systematic review. This systematic review identified 103 records and, ultimately, included 10 RCTs which compared non-pharmacological interventions in the PSF population. A total of 777 patients from the 10 selected RCTs were included. The population study sizes varied from 15 to 242, median age ranged from 47 to 69 years, and disease duration ranged from 2 weeks to 27 months. The studies were conducted in Australia, the Netherlands, and China, and the publication dates ranged from 2012 to 2018. We updated the search to 2019 and found 4 pharmacological intervention trials that were excluded. The characteristics of each trial are shown in Table A2. Eight non-pharmacological interventions were used for the analyses, and the network plot for each intervention is shown in Figure 2.

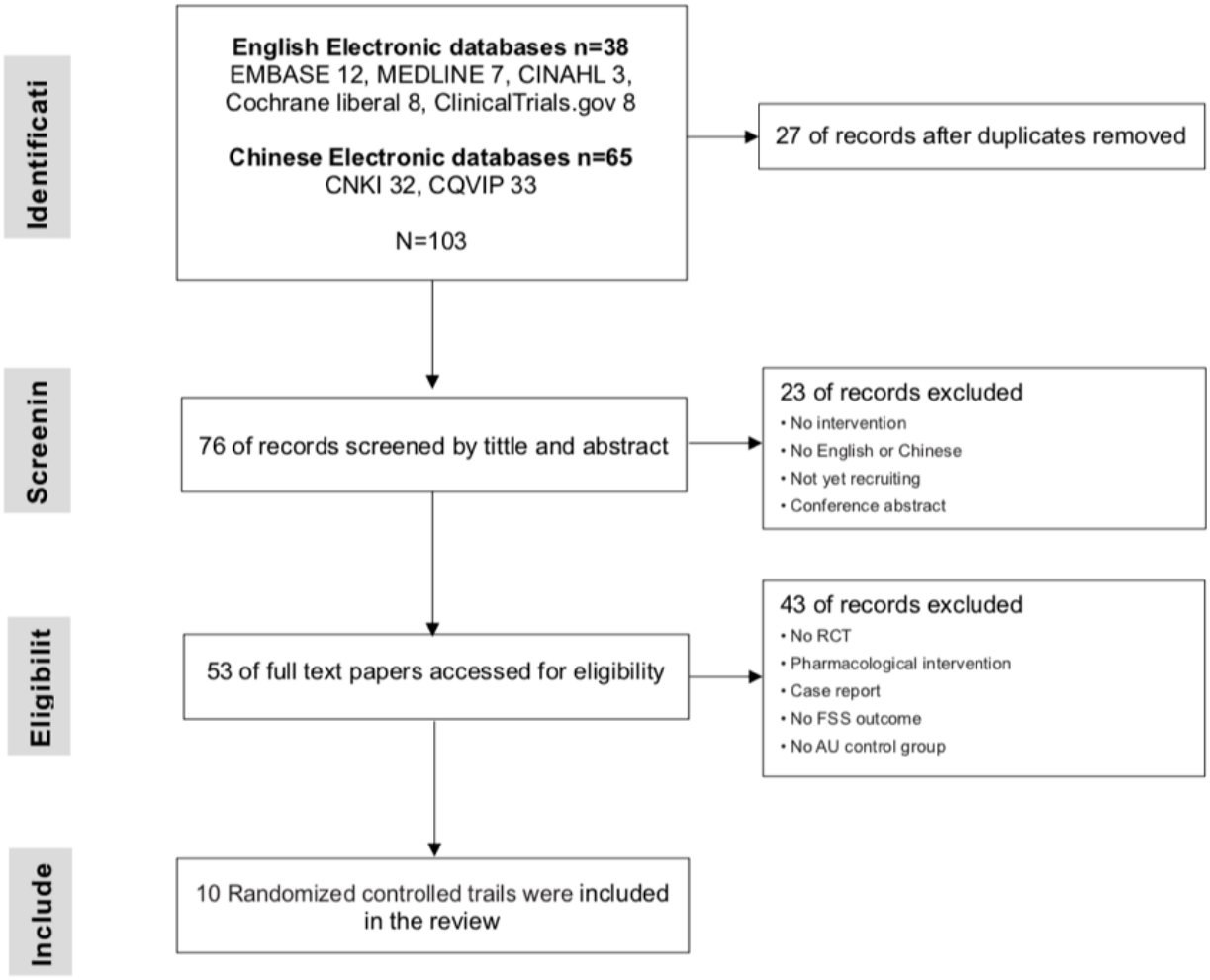

Figure 1. Flow diagram

FSS = Fatigue Severity Scale;

RCT = randomized controlled trails;

AU = as usual (treatment, nursing, rehabilitation, education)

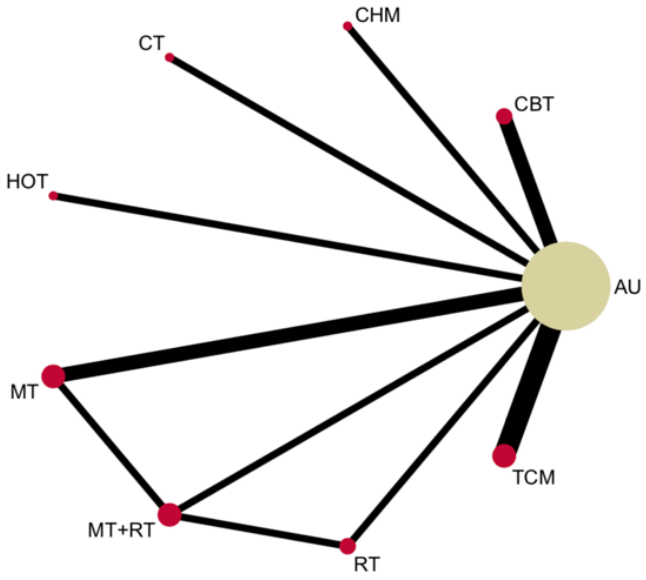

Figure 2. Network plot for each intervention.

The size of the nodes is proportional to the sample size of each intervention and the thickness of the lines proportional to the number of trails available. AU = treatment, nursing, rehabilitation, education as usual; CBT = cognitive behavioral therapy; CHM = community health management; CT = circuit training; HOT = hyperbaric oxygen therapy; MT = music therapy; RT = respiratory training; TCM = traditional Chinese medicine.

4.4.1 Type of Intervention

Community Health Management (CHM)

One study assigned 90 patients to CHM and control (AU) groups at random [10]. The CHM team consisted of 10 nurses, one neurology chief physician, two rehabilitation physicians, and one psychological consultant. The CHM team assessed patients the day before discharge, provided a stroke management manual for patients, and followed up (by telephone) at 1, 2, 5, 8, and 12 weeks after discharge. In the present study, the health management of stroke patients included drug management, fatigue education, community activities, and psychological care. After implementing CHM, the FSS of the CHM group were lower than those of the control group (AU) and pre-intervention. This indicates that conducting community-based post-stroke health

management can effectively prevent the occurrence of PSF, reduce the incidence of PSF, and improve the quality of life in stroke patients.

Traditional Chinese Medicine (TCM)

Three studies showed that TCM intervention could improve fatigue after stroke [11–13]. The first study [11] used acupuncture at Baihui and Sishencong, using 200 rpm for 2 min per needle and leaving the needle for 30 min, once a day for five days a week for a total of four weeks. In the second study [12], moxibustion treatment was combined with intermediate frequency electric acupoint massage for 15 days. Moxibustion treatment combined with massage was performed once per day, which involved selecting acupoints (e.g., Baihui, Shenque, and Zusanli acupoints) for moxibustion, using 3–5 acupoints each time for 15–20 min per acupoint. The third study [13] investigated transcutaneous acupoint electrical nerve stimulation targeting Zusanli, Neiguan, Guanyuan, Pishu, and Qihai acupoints using Han's acupoint stimulator for 30 min, once a day for a total of two weeks.

Cognitive Behavioral Therapy (CBT)

Two studies investigated CBT [14,15]. The intervention by Nguyen et al. [14] used a standardized CBT treatment manual comprised of six modules addressing fatigue over eight individual therapy sessions. Treatment encompassed the psychoeducation CBT framework, reorganization of daily schedules, energy conservation, cognitive restructuring, sleep interventions, strategies for physical and mental fatigue, and review techniques for relapse prevention. The second study [15] included four CBT sessions based on problem solving methods, relaxation training, education, follow-up, and support by telephone. The study concluded that cognitive behavioral intervention based

on problem solving could effectively improve fatigue after stroke, as well as medication compliance to help patients recover.

Respiratory Therapy (RT) and Music Therapy (MT)

Two studies investigated RT and MT [16,17]. The MT-based study [16] included 40 patients with usual nursing and selected the appropriate music and volume, depending on the patient's condition; patients underwent MT for 30 min, once per day for five days a week, for a total of eight weeks. After the intervention, fatigue scores were lower than the AU group and quality of life scores were higher. The other one study [17] included 80 patients divided into four groups: MT, RT, RT + MT, and AU. The RT group received rehabilitation using a breathing exercise for 15 min twice a day, for five days a week; the MT group received rehabilitation using music therapy for 30 min once per day for five days a week; the RT + MT group received both therapies five days a week. After eight weeks of intervention, the RT + MT group had the lowest FSS scores and the AU control group had the highest FSS scores.

Circuit Training (CT)

One study involved 250 patients undergoing CT [18]. The intervention included a 90 min graded task-oriented CT program twice a week over 12-weeks (24 sessions). It included four stages: Warm up (15 min), CT (60 min), evaluation and a short break (10 min), and a group game (15 min). The study found that CT improved walking speed, stair walking, and walking distance, but showed no significant effects in fatigue after stroke; possibly because the patients had low average baseline fatigue and depression levels.

Hyperbaric Oxygen Therapy (HOT)

One study of 62 patients undergoing HOT was found [19]. Patients absorbed pure oxygen once a day for 20 min through a mask, and the procedure was repeated three times with a rest time of 5 min in between. The study showed that, after a four-week intervention, the AU group showed aggravation of PSF; however, the HOT group showed no significant difference in FSS scores.

4.4.2 Assessment of Risk of Bias

We summarize the results of our assessment of the risk of bias for the included studies in Figure 3. All study designs were RCTs, and a high risk of bias was not found in the design of any studies. However, concealment of allocation was difficult to assess in eight studies, due to poor reporting. There were 10 (100%) RCTs with a low risk of bias in random sequence generation and 9 (90%) with a low risk of bias in selective reporting. One RCT showed low risk and high risk of bias in participants and outcome assessment, respectively. Blinding of outcome assessment was difficult to assess in six studies, due to poor reporting. As for incomplete outcomes, five studies had a low risk of bias.

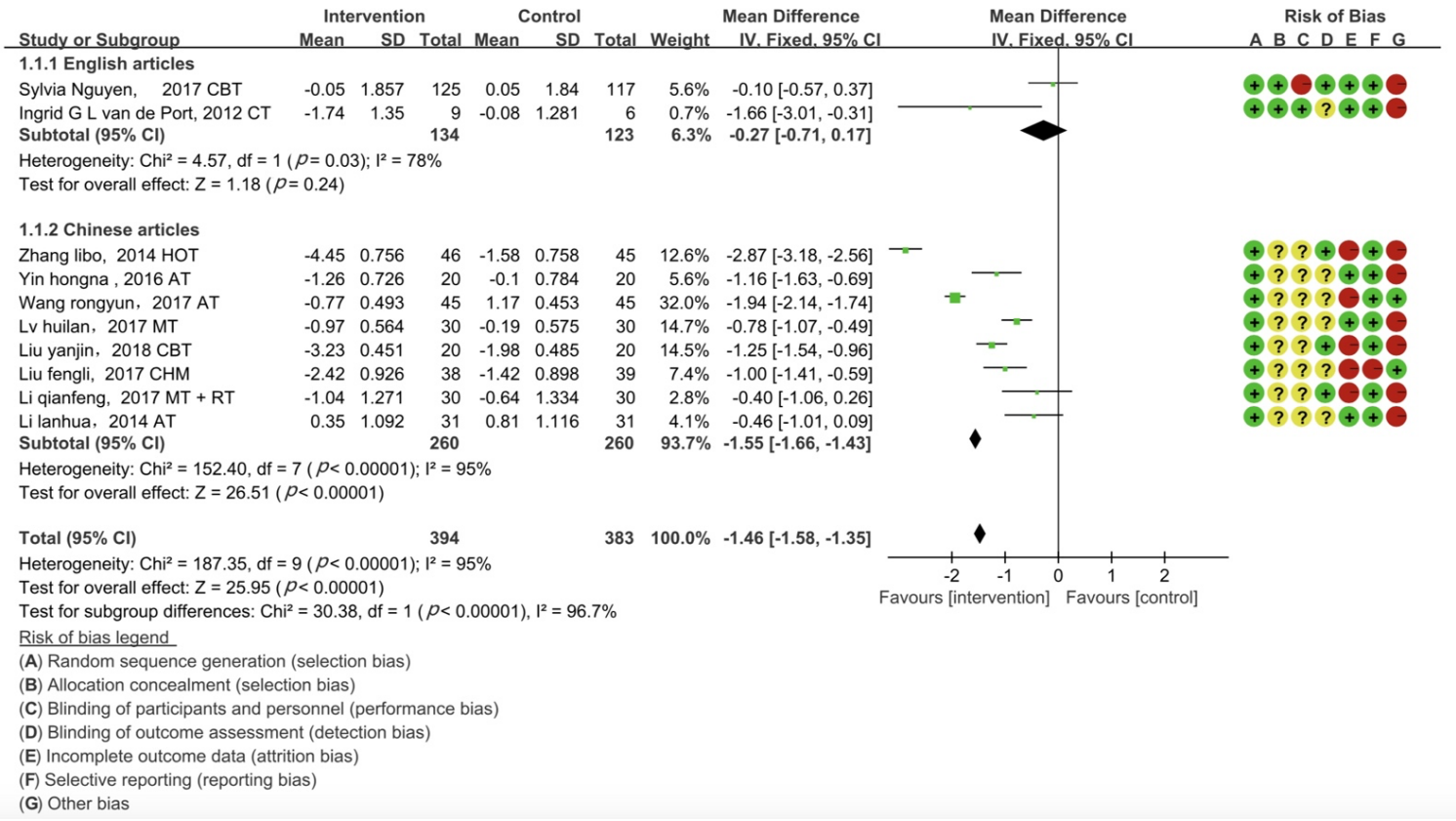

Figure 3. Forest plots and assessment of risk of bias.

Horizontal lines correspond to study-specific MD and 95% CI. The area of the square reflects study-specific weight. The diamond represents pooled results of MD and 95% CI. (1.1.1) Articles in English and (1.1.2) Articles in Chinese. For each study, the selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases were assessed at "low risk" if shown in green, "unclear risk" if shown in yellow, and "high risk" if shown in red.

4.4.3 Pair-Wise Meta-Analysis

Figure 3 summarizes the outcomes, showing that CBT, CHM, HOT, MT, RT, and MT + RT interventions were significantly better than the control treatment (AU). TCM with transcutaneous acupoint electrical nerve stimulation and moxibustion combined with intermediate frequency electric acupoint massage were also significantly better than the control treatment. However, TCM with acupuncture at Baihui and Sishencong acupoints was not significantly different from AU (–0.40 (–1.07, 0.27)). Direct meta-analysis of the English articles' subgroup showed significant heterogeneity between

trials (I^2 = 78%, degrees of freedom (df) = 1, p = 0.03). The Chinese articles subgroup showed significant heterogeneity between trials (I^2 = 95%, df = 7, p < 0.00001).

4.4.4 Network Meta-Analyses for Interventions

We established a network for non-pharmacological interventions in PSF. Table 2 summarizes the results of the network meta-analysis regarding the reduction of fatigue after stroke by FSS. The results show that TCM, CT, CBT, CHM, HOT, MT, RT, MT + RT, and eight PSF non-pharmacological interventions were not statistically different in MD for FSS reduction scores.

We checked for inconsistency, where the IF was 0.00 and 0.66 and, thus, was close to 0 (Figure A1). In addition, the random effects variance (1.28 (0.63, 2.55)) and the inconsistency variance (1.27 (0.64, 2.55)) were roughly equal, which is considered to be less inconsistent.

Table 2. Network meta-analysis for interventions

TCM								
–1.40 (-3.15, 0.35)	**AU**							
–0.27 (-3.05, 2.61)	1.13 (–1.05, 3.42)	**CBT**						
0.46 (–3.02, 3.87)	1.86 (–1.08, 4.87)	0.71 (–3.09, 4.44)	**CHM**					
–1.61 (–5.19, 1.83)	–0.21 (–3.23, 2.81)	–1.34 (–5.20, 2.24)	–2.07 (-6.35, 2.08)	**CT**				
–1.54 (–5.03, 1.83)	–0.16 (–3.20, 2.85)	–1.29 (–5.09, 2.42)	–1.99 (–6.32, 2.15)	0.05 (–4.24, 4.32)	**HOT**			
–0.59 (–3.28, 2.16)	0.80 (–1.30, 2.95)	–0.32 (-3.46, 2.73)	–1.05 (–4.64, 2.68)	1.01 (–2.62, 4.69)	0.96 (–2.65, 4.80)	**MT**		
–0.39 (–3.64, 2.96)	1.02 (–1.83, 3.94)	–0.08 (-3.94, 3.45)	–0.82 (–5.06, 3.27)	1.23 (–2.95, 5.38)	1.17 (–2.92, 5.37)	0.20 (–2.66, 3.03)	**MT + RT**	
–0.61 (–3.87, 2.71)	0.78 (–2.00, 3.63)	–0.35 (–3.98, 3.25)	–1.08 (–5.16, 3.15)	0.99 (–3.09, 5.13)	0.92 (–3.17, 5.10)	–0.03 (–2.85, 2.80)	–0.24 (–3.29, 2.79)	**RT**

The direct and indirect evidence were mixed comparisons. When the entire 95% confidence interval does not contain 0, the MD is statistically significant. TCM: traditional Chinese medicine; AU: as usual (treatment,

nursing, rehabilitation, education); CBT: cognitive behavioral therapy; CHM: community health management; CT: circuit training; HOT: hyperbaric oxygen therapy; MT: music therapy; RT: respiratory training.

4.4.5 Rank Probability of Interventions

Figure 4 shows the ranking, indicating the probability of being the best intervention to reduce fatigue after stroke, followed by the second best, third best, and so on, among all interventions. As lower fatigue is better, Rank 1 is the worst and the higher cumulative probabilities in Rank 9 indicates better intervention effectiveness. Thus, Rank 9 (in which the cumulative probabilities indicated the best non-pharmacological intervention) was CHM (0.41), rank 8 was TCM (0.23), and rank 7 was CBT (0.17). The worst intervention was rank 1, CT (0.35).

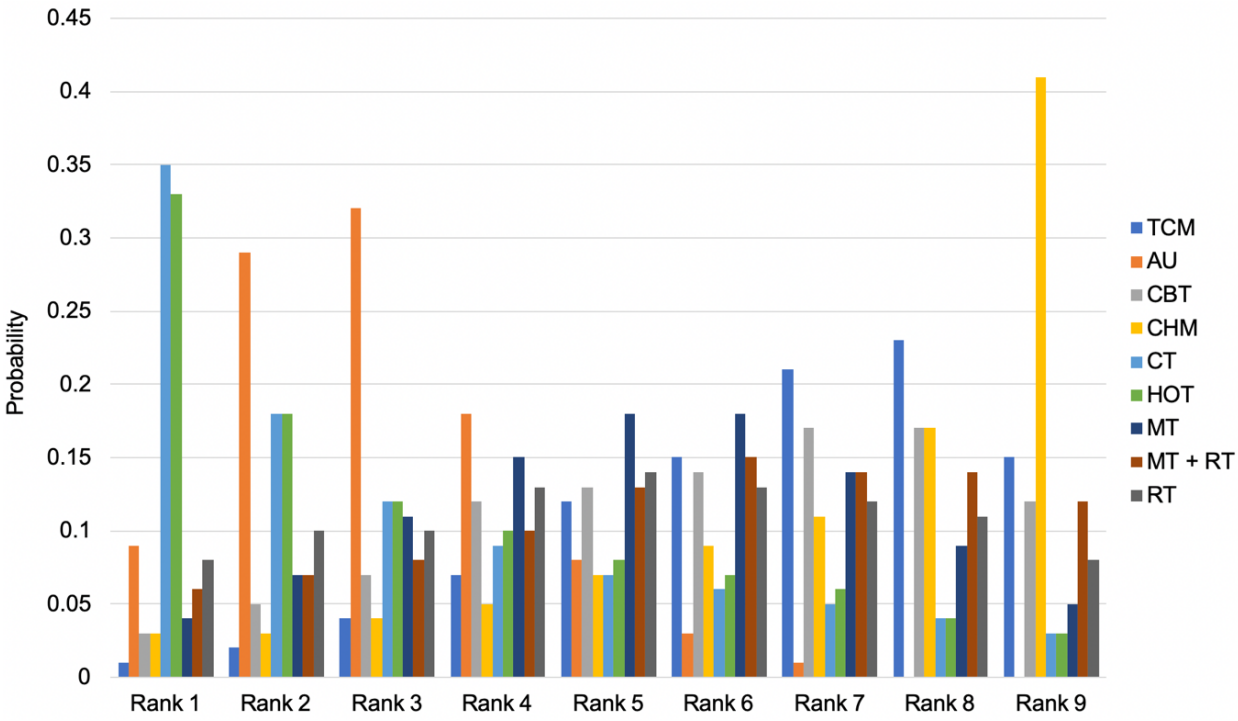

Figure 4. Rank probability of interventions.

TCM: traditional Chinese medicine; AU: as usual (treatment, nursing, rehabilitation, education); CBT: cognitive behavioral therapy; CHM: community health management; CT: circuit training; HOT: hyperbaric oxygen therapy; MT: music therapy; RT: respiratory training.

4.5 Discussion

Despite the fact that most interventions did not significantly differ in effectiveness from one another in this review, the cumulative probabilities indicate that the best non-pharmacological intervention for fatigue reduction was CHM, followed by TCM and CBT. The Canadian Stroke Best Practice Recommendations updated the best practice recommendations for PSF in 2019 [20]. Although there is insufficient evidence to recommend pharmacological or non-pharmacological interventions, stroke survivors who experience PSF should be screened and assessed. First, stroke survivors should be routinely asked about PSF during healthcare visits, following return to the community and at transition points. Second, prior to discharge from a hospital, stroke unit, or emergency department, stroke survivors, their families, and informal caregivers should be provided with basic information regarding the frequency and experience of PSF. Third, stroke survivors who experience PSF should be screened for common and treatable post-stroke comorbidities, as well as medications that are associated with and/or exacerbate fatigue. The results also highlight the importance of CHM.

In this review, many interventions could not be included, as there was no control group. One such intervention was COGRAT, an RCT that compares group cognitive therapy (CO) with a new treatment combining cognitive therapy (CO) with graded activity training (GRAT), called COGRAT [21]. Both treatment groups demonstrated significant improvements in fatigue, but a greater proportion of COGRAT participants achieved clinical improvement. As the COGRAT trial had no AU control group, we could not perform network meta-analysis as it was unclear whether the reduction in fatigue was a result of the physical training or a combined effect with CBT. However, we included studies using CBT without supervised exercise therapy, which showed that CBT may be sufficient for clinically significant and sustained improvements in fatigue

for at least two months post-treatment [14]. Another study which was excluded as there was no AU control group investigated group therapy versus individual task training [22], where no significant differences between groups were found for improvement of fatigue. We also excluded one study which compared fatigue management (FM) with group stroke education (GSE) [23]. FM was comprised of six psychoeducation sessions aimed at alleviating fatigue, which included an overview and introduction to fatigue, fatigue management, sleep/relaxation, exercise and nutrition, mood, and future focus. Although they reported that FM greatly reduced FSS scores, compared with the GSE group, we could not perform network meta-analysis due to the absence of control intervention. We also found another study that used GSE intervention but could not include it, as the design was a quasi-experiment, not RCT [24]. A previous Cochrane review providing a comprehensive review of PSF intervention [25] showed results that were somewhat similar to ours. It included two non-pharmacological interventions, a fatigue education program, and a mindfulness-based stress reduction program; the results indicated that there was no statistically significant benefit of non-pharmacological intervention and that there was insufficient evidence to show the efficacy of any intervention to treat or prevent PSF. Despite the fact systematic reviews and meta-analyses of randomized trials have long been important synthesis tools for guiding evidence-based medicine, to our knowledge, this is the first network meta-analysis enabling the comparison of multiple non-pharmacological interventions for PSF to incorporate clinical evidence. It could provide evidence for healthcare providers to select effective interventions to improve the health management and quality of life of stroke patients.

This review had several limitations: First, article selection was limited to studies in the English and Chinese languages, which may have introduced a language bias and

Ethnic heterogeneity; moreover, the studies were conducted in Australia, the Netherlands, and China, and differences in the prevalence and intervention effectiveness of PSF may be reflected in different countries. However, this study showed good consistency, and more studies are needed to identify the differences among different countries. Second, the sample size and limited data regarding follow-up measurements among the included articles led to an increased heterogeneity between trials. Only two studies had follow-up data, which made a great difference in the result of the endpoint follow-up. However, most previous studies have shown no significant difference in fatigue scores at all time points [26,27]. Third, methodologically, we assessed the risk of bias based on the Cochrane tool, and most trials in this review were judged to be at an unclear or high risk of bias. Thus, we recommend that the results of this study be interpreted with caution. Fourth, we failed to evaluate some important clinical outcomes and comorbidities in PSF patients. In further studies, comorbidities should be considered and assessed. Furthermore, in order to minimize the bias induced by the measurement, we only included FSS and may have missed other interventions. Therefore, future large-sample-sized RCTs based on detailed clinical outcomes may optimize the network and multiple-treatment comparison.

4.6 Conclusions

In conclusion, this network meta-analysis showed no significant differences among fatigue scores in eight PSF non-pharmacological interventions. The cumulative probabilities of best non-pharmacological intervention highlighted CHM followed by TCM and CBT. Despite the high prevalence of fatigue and its great impact on the quality of life in stroke patients, the development of treatment remains compromised due to a lack of understanding by health professionals. Thus, there is an urgent need to

recognize PSF, and more accurate assessment methods for PSF need to be developed in order to improve our understanding of its etiology and to develop more effective clinical interventions.

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Appendix A

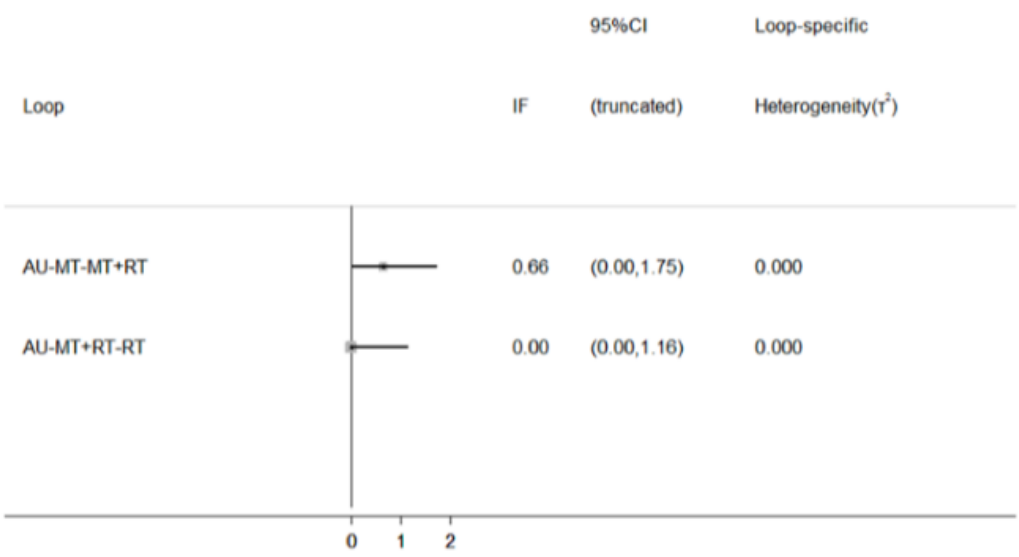

Figure A1. Inconsistency test.

Table A1. MEDLINE search terms.

S1	TI stroke or cerebrovascular accident or cva or cerebral vascular event or cve or transient ischemic attack or tia	89,994
S2	TI fatigue or exhaustion or tiredness or lethargy	24,958
S3	TI fatigue after stroke OR TI post stroke fatigue	99
S4	S1 AND S2	195
S5	AB treatment or intervention or therapy or management or rehabilitation	7,697,803
S6	TI controlled clinical trial or randomized controlled trail or randomized or placebo or randomly or trial or groups	478,666
S7	S3 OR S4	195
S8	S5 AND S6 AND S7	7

Table A2. Characteristics of all involved studies.

Author/Year	Country	Type of Stroke	Intervention	N			Mean Age (Years)		Time		*p*-Value	
				Gender (Male)	Intervention	Control	Intervention	Control	Post-Incident Stroke	Endpoint	Baseline vs. Post	Baseline vs. Follow-Up
Ingrid G L van de Port, 2012	Netherlands	Ischemic and Haemorrhagic	CT	162	CT = 125	AU = 117	56	58	N/A	24 weeks	>0.05	>0.05
Sylvia Nguyen, 2017	Australia	Ischemic and Haemorrhagic	CBT	11	CBT = 9	AU = 6	47	51	27 months	16 weeks	<0.05	<0.05
Lv Huila, 2017	China	Ischemic and Haemorrhagic	MT	24	MT = 20	AU = 20	62	62	2.28 months	8 weeks	<0.05	N/A
Yin Hongna, 2016	China	Ischemic and Haemorrhagic	TCM	33	AT = 30	AU = 30	62	62	2.95 months	4 weeks	<0.05	N/A
Wang Rongyun, 2017	China	Ischemic and Haemorrhagic	TCM	45	AT = 38	AU = 39	67	67	2 weeks	2 weeks	<0.05	N/A
Li Lanhua, 2014	China	Ischemic and Haemorrhagic	TCM	51	AT = 46	AU = 45	51	51	27days-20 months	4 weeks	<0.05	N/A
Liu Vanjin, 2018	China	Ischemic and Haemorrhagic	CBT	N/A	CBT = 30	AU = 30	N/A	N/A	N/A	8 weeks	<0.05	N/A
Li Qianfeng, 2017	China	Ischemic	MT RT MT+RT	47	MT = 20 RT = 20 MT + RT = 20	AU = 20	57	57	N/A	8 weeks	<0.05	N/A
Liu Fengli, 2017	China	Ischemic and Haemorrhagic	CHM	43	CHM = 45	AU = 45	47	49	N/A	12 weeks	<0.05	N/A
Zhang Libo, 2014	China	Ischemic and Haemorrhagic	HOT	N/A	HOT = 31	AU = 31	N/A	N/A	N/A	4 weeks	<0.05	N/A

FSS: Fatigue Severity Scale; CT: circuit training; AU: treatment, nursing, rehabilitation as usual; CBT: cognitive behavioral therapy; MT: music therapy; TCM: Traditional Chinese Medicine; RT: respiratory training; CHM: community health management; HOT: hyperbaric oxygen therapy; N/A: not available; there are two p values in the table, the first is FSS scores of baseline vs post and the second is FSS scores of baseline vs follow-up, and only two studies had follow-up data.

Chapter 5: Dissertation Discussion

5.1 Summary of my dissertation

The purpose of this dissertation was to explore the associated factors of PSF and develop a nomogram for the prediction of PSF after discharge. Furthermore, compared the effectiveness of non-pharmacological interventions in PSF to provide evidence of effective support for PSF patients. This section is a summary of the work that I have done for this PhD study. In the following sections, I will discuss the clinical and research implications of the current work and directions for future research.

The first stage of this dissertation was to conduct a prospective observational study to explore the associated factors of PSF. Additionally, to identify the interactions of associated factors with PSF after discharge home and determine the impact of PSF on the short-term outcomes after stroke.

The next stage was to develop the nomogram to predict the probability of PSF after discharge. This nomogram showed satisfactory internal validity, discrimination, and clinical utility, indicating good performance. The physicians, physiotherapists, and nurses can use this nomogram, which has been incorporated into an Internet-based tool, as an aid in decision-making, to provide early intervention or a discharge plan to stroke patients during the hospitalization period. In order to enable nurses or other healthcare professionals to provide more effective interventions for patients with PSF.

The third stage was conducted a systematic review and network meta-analysis to compare the effectiveness of non-pharmacological interventions in PSF. This review

suggests that the eight PSF non-pharmacological interventions shared equivalent efficacy, but CHM, TCM, and CBT showed potentially better efficacy.

In summary, this dissertation has presented the process of developing a nomogram for PSF and identified evidence to compare the effectiveness of non-pharmacological interventions in PSF.

The limitation of this study was that the results may be influenced by inclusion bias. We excluded patients with severe paralysis, severe aphasia, communication difficulties, or who were unable to respond to the questionnaire. Thus, most of the severe stroke patients in whom the prevalence of fatigue is higher may have been lost. In addition, we do not have data on the direct measure of stroke severity, such as the National Institutes of Health Stroke Scale score. Moreover, given that the symptoms of stroke include paralysis and imbalance, we were unable to measure the grip strength and gait speed in all patients. Thus, self-report SARC-F questionnaire was used to measure sarcopenia. In addition, pre-and post-stroke sarcopenia were only measured using the self-report SARC-F questionnaire, which renders the measure vulnerable to recall bias. Furthermore, the sample size of this study, particularly that of the sarcopenia group, was relatively small. Finally, the sample size of this current study is not large enough, although our nomogram had a good internal sampling. Thus, studies with larger sample sizes are needed to confirm our findings and further validation of the clinical utility of our nomogram entails the inclusion of stable external data.

5.2 Implications for clinical practice and research

PSF is gaining increasing attention and is now evaluated in several guidelines for stroke practice. However, research in this area remains scant, and thus, effective

treatment modalities and/or management strategies for PSF are yet to be established. To the best of our knowledge, this is the first study to analyse the interactions of pre-stroke sarcopenia, acute phase depression, acute phase insomnia, and acute phase fatigue with the occurrence of PSF after discharge home. Moreover, PSF at the acute phase may last until discharge home, and PSF after discharge is likely to last for several years. Thus, our data provide evidence that can be useful for achieving this goal and preventing later perceptible effects on physical and psychological health. In the field of research, this evidence could help clarify the mechanisms of PSF and develop new interventions for its management.

This is also the first study to develop a nomogram to predict fatigue after discharge in stroke patients. Importantly, this nomogram could identify acute phase stroke patients at risk for PSF after discharge and thus enable the early anticipation and prevention of post-discharge PSF. Further, the nomogram which has been incorporated into an internet-based tool, I believe it will be helpful in clinical practice as it enables an easy calculation of individual probability. Physicians, physiotherapists, and nurses can use this nomogram, as an aid in decision-making and to provide early intervention or a discharge plan for stroke patients during the hospitalization period. Last, it also could provide evidence for healthcare providers to select effective interventions to improve the health management and quality of life of stroke patients.

5.3 Future directions

Therefore, in the next stage, we will base this evidence to develop effective interventions to manage PSF. Moreover, to predict the PSF, future studies with larger sample sizes are needed, which is essential to ensure the external validity of the

nomogram. Furthermore, to measure PSF, considering few scales were developed specifically for stroke patients, we will develop a stroke-specific fatigue scale.

5.4 Conclusions

The prospective study indicated that persistent PSF is associated with sarcopenia. Acute phase PSF was an independent predictor of PSF after discharge home. Additionally, the interaction with acute phase depression and insomnia, and pre-stroke sarcopenia had an indirect connection with post-stroke fatigue after discharge home, which remains a separate predictor of acute-phase post-stroke fatigue. These findings indicate that early assessment and management of mental and sleep problems during hospitalization might be an important step in post-stroke rehabilitation and home transition. Thus, we based this evidence developed and internally validated a nomogram to predict the individual probability of PSF after discharge. The nomogram, which has been incorporated into an internet-based tool, also showed good clinical utility and can thus aid physicians, physiotherapists, and nurses in clinical decision-making. Finally, the systematic review and network meta-analysis indicted that CHM, TCM, and CBT showed potentially better efficacy. Thus, this PhD study not only can help healthcare professionals to predict PSF but also provide evidence to select effective interventions to manage the PSF.

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List of Research Achievements

1. Full publications

- **Su, Y.;** Asamoto, M.; Yuki, M*.; Saito, M.; Hasebe, N.; Hirayama, K.; Otsuki, M.; Iino, C. Predictors and short-term outcomes of post-stroke fatigue in initial phase of transition from hospital to home: a prospective observational study. J Adv Nurs. 2020;10.1111/jan.14731.
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- **Su, Y.;** Yuki, M*.; Otsuki, M. Prevalence of stroke-related sarcopenia: A systematic review and meta-analysis. J Stroke Cerebrovasc Dis, Vol. 29, 2020: 1050921
- **Su, Y.;** Yuki, M*.; Otsuki, M. Non-Pharmacological Interventions for Post-Stroke Fatigue: Systematic Review and Network Meta-Analysis. J. Clin. Med. 2020, 9, 621.
- **Su, Y.;** Yuki, M*.; Hirayama, K.; Sato, M.; Han, T. Denture Wearing and Malnutrition Risk Among Community-Dwelling Older Adults. Nutrients 2020, 12, 151.
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2. Conference presentations

- **Su Y,** Yuki M., Hirayama K. The effect of insomnia on Dynapenia and Health-Related Quality of Life in stroke patients: A prospective study. The 40th Annual Conference of Japan Academy of Nursing Science. 2020.12.
- **Su Y,** Hirayama K, Izutsu M, Han TF, Yuki M. Association between depression and frailty among community-dwelling older adults - The CBAN study. The 39th Annual Conference of Japan Academy of Nursing Science. 2019.12.
- **Su Y,** Izutsu M, Hirayama K, Han TF, Yuki M. Prevalence of Sarcopenia in Japanese community-dwelling older adults: according to EWGSOP2. 5th Asian Conference for Frailty and Sarcopenia at Taipei. 2019.10.
- **Su Y,** Hirayama K, Izutsu M, Han TF, Yuki M. Association between wearing denture and malnutrition risk among community-dwelling older adults in Japan. The 11th International Association of Gerontology and Geriatrics Asia/Oceania Regional Congress. 2019.10.
- **Su Y,** Izutsu M, Han TF, Hirayama K, Yuki M. Does denture wearing improve nutritional status among community-dwelling older adults-The CBAN study-The 4th FHS International Conference. 2019.7.
- **Su Y,** Yuki M.1-year incidence and outcomes of post-stroke sarcopenia in older patients. MIRAI Workshops 2019 Ageing and Innovation (Tokyo) Nominated Researcher.2019.6.
- **Su Y,** Izutsu M, Hirayama K, Yuki M. How to prepare from caregiver turn to surrogate decision maker for people with dementia: An integrative review. 14th

International Congress of the European Geriatric Medicine Society (Berlin, Germany) 2018.10.

- **蘇 雅,** 結城 美智子，平山憲吾，井筒深紅．AWGS2 を用いた非サルコペニア地域在住高齢者におけるフレイルの有症率及び関連要因， 日本老年医学会．2020.8.
- **蘇 雅,** 結城 美智子，平山憲吾，浅元美津子，齋藤健，長谷部尚子，飯野智恵子． 急性期脳卒中患者における入院前サルコペニアと入院時の心身状態との関連． 日本リハビリテーション栄養学会学術集会．2019.11.
- **蘇 雅,** 結城 美智子，平山憲吾，井筒深紅，韓天放．地域高齢者におけるサルコペニアに関連する危険因子の検討：EWGSOP2 の診断基準を用いて．日本老年医学会．2019.6.

3. Awards

- 令和 2 年 8 月 18 日「北海道大学大学院保健科学院研究奨励賞」を受賞

4. Funding

- 公益財団法人 在宅医療助成 勇美記念財団「在宅医療研究への助成」
  2019 年 3 月～2020 年 3 月
  研究代表， 907 千円
- 公益財団法人 フランスベッド・メディカルホームケア研究・助成財団 研究助成
  2020 年 6 月～2021 年 3 月
  研究代表，500 千円
- 公益財団法人 ファイザーヘルスリサーチ振興財団 国内共同研究
  2020 年 12 月～2021 年 11 月
  研究代表，1000 千円