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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）

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.