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Association between frailty and its individual components with the risk of falls in patients with schizophrenia spectrum disorders

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ABSTRACT

Frailty is common among older people who carry an increased risk for poor outcomes, including falls, physical disabilities, infections, and mortality. However, the prevalence of frailty and the prognostic influence of frailty status are poorly understood in adults with schizophrenia. The present study aimed to assess the predictive ability of frailty and its individual components for the risk of falls in patients with chronic schizophrenia. Frailty status was assessed at baseline by using Fried frailty criteria after the enrollment of 561 patients with chronic schizophrenia. The patients were followed up for 18 months, and the outcome of the study was the incidence of falls. The mean age of the patients was 53.8 years, and a total of 35.3% were females. One-quarter (25.3%) of patients received typical antipsychotics. The prevalence of frailty was 10.2% at baseline. During follow-up, 40 patients (7.1%) experienced falls. Frailty status was associated with increased susceptibility to falling with an unadjusted hazard ratio of 5.27 (95% confidence interval: 2.75–10.10) and a hazard ratio of 4.65 (95% confidence interval: 1.88–11.54) after multivariate adjustment. Among the components of frailty, the most significant association was observed between low physical activity and falls ($p < 0.05$). In conclusion, frailty is highly prevalent in patients with chronic schizophrenia and is associated with the risk of adverse clinical events. Further studies are needed to explore the mechanisms underlying the relationship between schizophrenia and frailty in an attempt to develop an appropriate treatment plan for improving clinical outcomes for these patients.

1. Introduction

Schizophrenia is a severe mental disorder that affects more than 21 million people worldwide (World Health Organization, 2016a). Patients with schizophrenia are known to be at high risk for premature death. There is a 10- to 20-year life expectancy reduction in patients with schizophrenia (Hjorthoj et al., 2017). The increase in mortality rates in patients with schizophrenia was primarily a consequence of a high burden of cardiovascular disease and other conditions commonly associated with aging among these patients (Correll et al., 2017; Vancampfort et al., 2016; Vancampfort et al., 2015). Although controversy still exists, several researchers have suggested that schizophrenia might be a syndrome of accelerated aging (Kirkpatrick et al., 2008; McKinney et al., 2017; Polho et al., 2015). Biomarkers of oxidative stress and inflammation were increased in patients with schizophrenia compared to the general population, and this finding has been postulated to explain the accelerated aging hypothesis (Okusaga, 2014). Accordingly, age-related physiological changes and their clinical consequences, such as frailty and disability, may be more common than is generally appreciated among schizophrenic patients.

Recently, a growing body of evidence has suggested that oxidative stress might play a role in the development of frailty, which is an age-related clinical manifestation (Soysal et al., 2017). Frailty is characterized as a multidimensional syndrome of decreased physiological reserve and poor response to stressors that results from cumulative declines across multiple physiological systems and leads to increased susceptibility to morbidity and mortality (Clegg et al., 2013; Fried et al., 2001; Soysal et al., 2017). Several approaches have been developed to identify frailty in vulnerable individuals (Fried et al., 2001; Rockwood et al., 2006). A simple and well-validated criterion, proposed by Fried et al. (2001), defines frailty as the presence of three or more of the following abnormalities: slow walking speed, weakness, unintentional weight loss, low physical activity, and exhaustion. Patients with various chronic illnesses, as well as the elderly, are at increased risk of frailty (Afilalo

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et al., 2014; Ness et al., 2013; Onen and Overton, 2011). Frail patients are more likely to have adverse outcomes, including falls, hospitalization, progress of underlying disease, disability, and death (Bartley et al., 2016; Morley, 2013). Based on the Fried frailty criteria, the prevalence of frailty among people older than 65 years in the general population was estimated to be about 7% to 16% (Fried et al., 2001). However, few studies to date have examined the prevalence and impact of frailty among patients with chronic schizophrenia.

People with schizophrenia suffer from multiple comorbid disorders, engage in less physical activity, have reduced bone mass, and take antipsychotics, all of which are potential risk factors for falls and increase the risk for subsequent fractures (Stubbs et al., 2015b). Falls and fracture are a significant health concern among patients with schizophrenia because of related diminished quality of life, impairment, and mortality. Therefore, the aims of this study were to investigate the prevalence of frailty by using the Fried criteria and to assess whether frailty or its individual components can predict the incidence of falls in patients with chronic schizophrenia.

2. Methods

2.1. Participant population

Between January 1 and January 31, 2013, we recruited 582 long-term, hospitalized, stable adults aged 20 or older who fulfilled the DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder in Yuli Hospital. Participants were excluded from this study if their data was missing on all five of the frailty components, if they suffered from acute psychosis that required admission to an acute psychiatric ward, or if they incurred a surgical or medical condition that required an acute referral. Finally, 561 patients who fulfilled all study criteria were included and followed up for 18 months until June 30, 2014. This study was approved by the institutional review board of Yuli Hospital, Ministry of Health and Welfare, Hualien, and carried out according to the Declaration of Helsinki. All patients provided written informed consent prior to participation in this research.

2.2. Study design

For all subjects, clinical assessments and laboratory tests were performed after they were recruited in the study. The history of falls in the preceding six months prior to study entry was obtained from the medical record. A Charlson comorbidity index (CCI) score was calculated for each patient to determine the severity of comorbidity, and a higher score represented a greater burden of comorbid conditions (Quan et al., 2011). Medication data were collected, and no major modifications were made in psychotropic agents during the study period. The dose equivalence of antipsychotics, anticholinergics, benzodiazepines, and mood stabilizers was compared by use of the defined daily dose (DDD) method (Whocc.no, 2017). Types of antipsychotics were categorized into typical antipsychotics and atypical ones. Patients concurrently using typicals and atypicals were categorized as atypicals users.

2.3. Measures and variables

2.3.1. Characteristics of frailty

In the present study, frailty was defined on the basis of a modification of the frailty phenotype that was originally proposed by Fried et al. (2001). Fried's definition consists of five major domains that include weight loss, weakness, exhaustion, slowness, and low activity. Weight loss was defined as inadvertent loss of ≥10 pounds in the prior year. Weakness was determined according to a quintile of the handgrip strength adjusted for body mass index (BMI) and gender. Self-reported exhaustion was identified by two questions from the Center for Epidemiologic Studies Depression Scale. Slow gait speed was defined as the slowest quintile adjusted for gender and height, in a 15-foot timed walking test. Low physical activity was defined as performing daily leisure activities at less than once a week (i.e., walking less than 1 h per week) (Bartali et al., 2006). Frailty was identified by the presence of three or more of the five components.

2.3.2. Primary outcomes

The primary endpoint was the occurrence of falls from the time of inclusion. A fall was defined as an event that results in an individual coming to rest unintentionally on the ground, floor, or other lower level (World Health Organization, 2016b).

2.4. Statistical analysis

The baseline characteristics of the study patients are presented based on presence or absence of frailty status. Baseline characteristics are presented as means ± standard deviation (SD) for continuous and normally distributed data and frequencies (percentages) for categorical variables. Student *t*-tests were used for comparing continuous variables, whereas Pearson's χ^2 tests or Fisher exact tests were used for comparing categorical variables, as appropriate. The cumulative probability of the patients being fall-free was examined by the Kaplan-Meier method, and the log-rank test was used to assess differences between groups. Dates of censoring occurred at the time of last contact or on June 30, 2014.

The association between the occurrence of falls and the different risk factors was first examined by calculating hazard ratios (HRs) with the univariate Cox proportional hazard model. Any variables with a p value of <0.05 in univariate analysis, as well as conventional risk factors for falls among the general population, were entered in the multivariate Cox regression model. Because the ratio of events per independent variable was small, the accuracy and precision of hazard ratios of the variables might be affected in our multivariable models, which resulted in biased estimation of significance (Peduzzi et al., 1996). Therefore, a propensity score adjustment was used to reduce confounding variables which might result in a biased estimate of the effect of frailty and its individual components (Cepeda et al., 2003). The propensity score for frailty status was estimated using a logistic regression model with the independent variables being age, sex, CCI, smoking, duration of hospitalization, history of falls, type of antipsychotics, DDD of antipsychotics, anticholinergics, benzodiazepines and mood stabilizers, hemoglobin, and albumin. For predicting the likelihood of having individual frailty components, the propensity scores were estimated as a function of the above-mentioned covariables and the other four criteria of frailty. Other covariates were tested in the propensity score model and found to have no impact on the overall results. A p value of <0.05 was considered to be statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (version 20.0; SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Clinical characteristics and frailty status

The baseline characteristics of all participants and the distribution of the Fried criteria used to define frailty status are summarized in Table 1. The mean (± SD) age of the patients was 53.8 (±9.7) years, and a total of 35.3% were females. Rates of antipsychotic prescription were as follows: clozapine, 32.8%; risperidone, 20.7%; sulpiride, 15.3%; amisulpride, 6.3%; haloperidol, 6.1%; flupentixol, 3.6%; zotepine, 2.7%; olanzapine, 2.3%; chlorpromazine, 2.3%; aripiprazole, 1.2%; clotiapine, 1.2%; and quetiapine, 1.2%. Of those patients, 57 (10.2%) patients met the criteria for frailty status. For patients with age < or ≥65, the prevalence of frailty was 8.1% (41/504) and 28.1% (16/57), respectively.

There were no statistically significant differences in the gender, comorbidities, BMI, age of onset of schizophrenia, or

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