学 位 論 文 の 要 旨

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学　位　論　文　名　Nutritional Status is Associated with non-Cardiovascular Mortality but not with Cardiovascular Mortality in Maintenance Hemodialysis Patients

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論 文 内 容 の 要 旨

INTRODUCTION

The survival rate of patients with dialysis therapy is markedly reduced, compared to the healthy population. Because hemodialysis (HD) therapy is associated with loss of amino acids, maintenance dialysis therapy has been believed to lead to highly catabolic status. In addition, there are many other causes heading to malnutrition, which are tightly linked to inflammation and atherosclerosis. Malnutrition-inflammation-atherosclerosis (MIA) syndrome or malnutrition-inflammation complex syndrome (MICS) has been proposed as a major complication of dialysis patients to reduce survival rate. Malnutrition, sarcopenia, and frailty have been socioeconomic issues in not only chronic kidney disease (CKD) patients but also general aged population, because they are strong risk factors for mortality and hospitalization. Today, this situation is called protein energy wasting (PEW). PEW, which is defined as the loss of somatic and circulating body protein and energy reserves, is usually used for CKD, especially HD patients.

Geriatric nutritional risk index (GNRI), which has been developed as an assessment tool for nutritional status of geriatric population, simply provides nutritional risk for subjects using serum albumin concentration, body weight and height. Recent studies have demonstrated that GNRI is useful for identifying mortality risk of dialysis patients. Mortality rate of HD patients is considerably high especially in younger population. Among this population, cardiovascular (CV) event rates are much higher than those of healthy subjects. Indeed, heart failure is a leading cause of death in Japan and one thirds of patients undergoing dialysis therapy result in CV death. A

recent study shows that CV mortality is associated with nutritional status in incident HD patients. However, it remains uncertain whether or not nutritional status affects CV or non-CV mortality in chronic dialysis patients and if so, to what extent the nutritional status provides an impact on CV or non-CV mortality. To clarify these issues, we conducted a historical cohort study among maintenance HD patients.

MATERIALS AND METHODS

A historical cohort study, which was performed using data from 4 institutes located in Shimane prefecture, started in March 2006 and was completed in March 2013. This study was approved by the institutional review board of Shimane University Faculty of Medicine (study number: 1310) and were conducted in accordance with the Declaration of Helsinki. Patients' background information and data from January to March in 2006 were obtained.

GNRI was calculated by the following formula: GNRI＝14.89×(serum albumin level)＋41.7×(DW/IBW), where DW/IBW=1, if DW>IBW, and abbreviations are as follows: DW; dry weight, and IBW; ideal body weight. In an original study, subjects with GNRI<92 were of high mortality. Thus, the participants were classified into 2 groups (<92 and ≧92) by GNRI to analyze all-cause mortality, CV and non-CV mortalities, and CV events.

In assigned 273 maintenance HD patients, 109 died, 139 survived, and 25 moved or changed the clinic during the study period. CV events, which are called as major adverse cardiovascular events (MACE), were defined by a composite of CV death, non-fatal myocardial infarction, unstable angina, heart failure, stroke, peripheral arterial disease, and sudden death. CV death was shown in 51 patients: 22 (cardiac failure), 17 (stroke), 7 (sudden death), 3 (peripheral arterial disease), and 2 (aortic dissection and aneurysm). The rest was defined as non-CV death.

RESULTS AND DISCUSSION

In 273 HD patients, 46 patients (45.1%) died in those with GNRI<92, whereas 63 patients (36.8%) died in those with GNRI≧92. A Kaplan-Meyer curve showed that the survival rate tends to be lower in 102 patients with GNRI<92, compared to 171 patients with GNRI≧92. In a multivariate Cox proportional hazard analysis, the GNRI was an independent predictor for all-cause mortality with hazard ratio of 0.960 (95% confidence interval: 0.928-0.993, p<0.05) after adjustment with age, gender, dialysis duration, blood access, the presence of diabetes mellitus, serum levels of calcium, phosphate, alkaline phosphatase, parathyroid hormone and C-reactive protein, and drug use of active vitamin D analog and non-calcium containing phosphate binders.

In the Kaplan-Meyer curve and Log-rank test, the CV mortality rate for 7 years was not significantly different between patients with GNRI<92 and those with GNRI≧92 (p=0.531). On the other hand, non-CV mortality was significantly lower in GNRI<92, compared to GNRI≧92

(p=0.008). In multivariate Cox proportional hazard analysis, age, not taking non-calcium-containing phosphate binders, high CRP, and low GNRI were independent predictors of non-CV mortality after adjustment with covariates. In parallel with these findings, there was no significant association between the GNRI and CV events (p=0.429 for Log-rank test).

Taken together, in our historical cohort, the nutritional index GNRI was not statistically associated with future CV events and CV mortality but with non-CV mortality. This suggests that the nutritional status is significantly associated with survival of maintenance HD patients mainly due to non-CV events.

Growing body of evidence suggests that high nutritional risk is a strong predictor of mortality and hospitalization in aged frail people, acute ill patients, and patients undergoing dialysis therapy. Our data showed that about a half of our patients died in 7 years, indicating that the subjects of this study were most likely general dialysis population in Japan. In multivariate Cox proportional hazard analysis, low GNRI was an independent risk factor for all-cause mortality after adjustment with the covariates, which is consistent with the previous reports.

We demonstrated that low GNRI was significantly associated with non-CV death in maintenance HD patients. The mechanism might be explained primarily by altered immune function and the susceptibility to various infectious diseases. Indeed, GNRI was demonstrated to be associated with serum inflammatory markers and to be a significant predictor of PEW status for the elderly HD patients. Inflammatory cytokines stimulate protein degeneration and suppress protein synthesis, leading to malnourished status, which, in turn, leads to impaired immune function, anemia, and skeletal muscle loss as well as bone loss. Then, anorexia, malaise, impaired physical performance and malnutrition may further develop. In this condition, pneumonia, sepsis, decubitus, bone fractures may occur, which affect mortality. Thus, malnutrition may be related directly to non-CV death but not to the incidence of CV event or CV death.

In the present study, we longitudinally followed HD patients for 7 years. Because our dialysis centers/hospitals were located in the countryside, there were a few cases dropped-out from the observation. Shortcomings of this study were small number of patients and a historical cohort study. However, our study population was typical chronic HD patients in our country, based on the baseline characteristics, causes of death, and CV events. Therefore, a multicenter large-scale prospective study should be needed to make findings of this study more certain.

CONCLUSION

We firstly demonstrated a strong relationship of poor nutritional status with non-CV death but not with CV-death and CV events in maintenance HD patients. GNRI may be a good predictor for survival, especially for non-CV mortality, in maintenance HD patients.