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Prognostic value of urine dipstick proteinuria on mortality after acute ischemic stroke

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ABSTRACT

Background and aims: Proteinuria is a marker of kidney disease and a strong risk factor for cardiovascular diseases including stroke. This study was aimed at investigating the prognostic value of proteinuria measured by urine dipstick in patients with acute ischemic stroke.
Methods: This *post-hoc* analysis of a prospective cohort study included 3404 consecutive patients who had been admitted for acute ischemic stroke between November 2005 and June 2013. Proteinuria was defined as a trace or more of protein on a urine dipstick test routinely performed at admission. Date and cause of death until December 31, 2013 were collected. We investigated the association of proteinuria with all-cause mortality, cardiovascular mortality (defined as ICD-10 codes I00–I99), and non-cardiovascular mortality.
Results: Proteinuria was present in 12.8% of the 3404 patients. During the mean follow-up period of 3.56 ± 2.22 years, there were 681 cases of all-cause mortality (460 cardiovascular deaths and 221 non-cardiovascular deaths). Multivariate Cox regression analysis showed that the presence of proteinuria was an independent risk factor for all-cause mortality (adjusted hazard ratio [HR] 1.69, 95% confidence interval [CI] 1.40–2.04), cardiovascular mortality (adjusted HR 1.65, 95% CI 1.31–2.08), and non-cardiovascular mortality (adjusted HR 1.59, 95% CI 1.13–2.23). Adding proteinuria to the multivariate Cox models moderately improved the model performance for all-cause mortality (integrated area under curve [95% CI]: from 0.800 [0.784–0.816] to 0.803 [0.788–0.818], $p = 0.026$).
Conclusions: Proteinuria, which was detected on a urine dipstick test, was a significant predictor of mortality after acute ischemic stroke.

1. Introduction

The brain and the kidney share many similar anatomic and physiologic characteristics; both are distal end organs with low vascular resistance and exposed to a high volume of pulsatile blood flow [1,2]. On the basis of epidemiologic evidence, kidney disease has been suggested as a nontraditional risk factor for cerebrovascular disease and stroke [3]. Proteinuria is a common laboratory finding in clinical practice, which is primarily used as a diagnostic tool for kidney disease. However, it has been demonstrated that patients with proteinuria are at an increased risk for not only renal failure but also various types of brain diseases including dementia, cerebral small vessel disease, and stroke [4–8]. Therefore, proteinuria may be a useful surrogate marker for brain dysfunction and cerebrovascular disease.

Recent clinical studies in acute stroke patients demonstrated that proteinuria is a valuable prognostic marker for predicting stroke recurrence, poor functional outcome, and hemorrhagic transformation [2,9,10]. However, there are insufficient data for the prognostic value of proteinuria on mortality after acute stroke. The urine dipstick test is a convenient diagnostic tool for assessing proteinuria, as it is easily performed and rapidly interpreted in clinical practice [11]. Despite its wide availability and use in clinical

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practice, there are few studies assessing the prognostic value of urine dipstick test in acute stroke. We investigated whether the dipstick test for proteinuria can provide prognostic information on mortality after acute ischemic stroke.

2. Materials and methods

2.1. Study subjects

This was the *post-hoc* analysis of a prospective cohort study that used the data from a hospital-based registry that prospectively enrolls patients admitted with acute ischemic stroke within 7 days of symptom onset to the Stroke Center at Yonsei University Severance Hospital [12]. The present study included consecutive patients admitted between November 2005 and June 2013. We only included patients with acute ischemic stroke confirmed with brain MRI or CT, and who underwent at least one cerebral angiographic evaluation, including magnetic resonance angiography, computed tomographic angiography, and conventional cerebral angiography, during admission. Patients who experienced stroke while being hospitalized for other illnesses (i.e., in-hospital stroke) and those with histories of malignancy were excluded because these conditions have the potential to be powerful confounders of mortality. We also excluded patients who lacked dipstick urine analysis, data on body mass index, or laboratory findings used as covariates in the analysis. The Institutional Review Board of Severance Hospital, Yonsei University Health System approved this study with waiver of informed consent owing to the retrospective nature and no more than minimal risk to the patients.

2.2. Clinical data collection

We collected the clinical and laboratory data, and these were used as the covariates in the analyses (Table 1). The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation, as follows: $175 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) $\times$ 0.742 (if female) [13]. Additional information for the collected clinical characteristics is provided in the online-only Supplementary Data.

2.3. Proteinuria measurements

The urine dipstick test was performed by using Uriscan Pro II and Uriscan Gen 10 SGL strips (YD Diagnostics, Korea) on admission, which was part of routine care for admitted patients in our hospital throughout the study period. The dipstick reader and strips are known to be reliable for the detection of proteinuria [14]. If patients underwent multiple tests during admission, the first result was used. With an automated urine dipstick analyzer, the degree of proteinuria was interpreted as negative, trace (about 10 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (1000 mg/dL) in accordance with the manufacturer's manual. For the analyses, results were recategorized into negative, trace, 1+, and ≥2+. We also dichotomized the dipstick results into the negative and proteinuria (trace or more) categories.

2.4. Survival data

Date and cause of death were ascertained by using death certificates from the Korean National Statistical Office. Patients who were alive on December 31, 2013 were censored. The cause of death was coded by using the 10th revision of the *International Classification of Disease*, and cardiovascular (CV) death was defined as I00–I99. Other causes of death were considered non-CV death. The causes of death in stroke patients based on the death statistics have been reported to be reliable [15].

2.5. Statistical analyses

Across the four patient groups divided according to the degree of proteinuria (negative, trace, 1+, and ≥2+), clinical characteristics were compared by using Fisher's exact test for categorical variables and one-way analysis of variance or Kruskal-Wallis test for continuous variables. We constructed cumulative incidence curves for all-cause, CV, and non-CV mortalities according to dipstick proteinuria. In survival analysis, CV death and non-CV death were considered as competing risks. The log-rank test was performed to compare differences in the cumulative incidence of all-cause mortality according to proteinuria, and differences in CV mortality and non-CV mortality were assessed by using the Gray's test, which is an extended test applied to compare cause-specific cumulative incidences in the presence of competing risks [16]. The hazard ratio (HR) and 95% confidence interval (CI) for proteinuria were computed by using univariate and multivariate Cox proportional hazard regression models. In the cause-specific Cox regression analyses for CV and non-CV mortalities, the competing risks were treated as censored observations. Variables included in the multivariate Cox models were sex, age, body mass index, hypertension, DM(diabetes mellitus), hypercholesterolemia, current smoking, previous stroke, atrial fibrillation, cerebral artery atherosclerosis, use of thrombolytic treatment, proteinuria, eGFR, hemoglobin, high-sensitivity C-reactive protein (hs-CRP), and National Institutes of Health Stroke Scale (NIHSS) score at admission, which were selected based on prior knowledge and studies on stroke mortality [17–19]. The variables age, body mass index, eGFR, hemoglobin, hs-CRP, and NIHSS score were treated as continuous variables in the models. The proportional hazards assumption for proteinuria was tested by exploring the log(−log(survival)) plot and interaction for follow-up time in a time-dependent Cox regression model, which were found to be satisfactory.

To explore whether the dipstick test for proteinuria can help identify patients who are at an increased risk of mortality, we constructed a time-dependent receiver operating characteristic curve for censored survival data [20]. We compared the global concordance probability (integrated area under the curve, iAUC) of the multivariate Cox models with and without the presence of proteinuria. The iAUC is a weighted average of the AUC across the period of follow-up time and a measure of overall predictive accuracy of the survival model. For the calculation of the 95% CI for iAUC and the difference between the models, a standard bootstrap method with 1000 times resampling was used. We also computed the continuous net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) at the median follow-up time point (3.40 years) to assess the performance improvements in the survival model with proteinuria [21]. All of the statistical analyses were performed by using R software, version 3.2.5, for Windows (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). A two-sided $p < 0.05$ was considered statistically significant. We used the survival, etm, boot, Hmisc, risksetROC, and survIDINRI packages for the survival analyses.

3. Results

3.1. Demographic characteristics

Of the 4386 patients who were registered in the Yonsei Stroke Registry during the study period, we excluded 614 patients with histories of malignancy or in-hospital stroke, 291 patients with