



Risk of Stroke in Elderly Dialysis Patients

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INTRODUCTION

Stroke is an important health issue in global health care because it is a major cause of morbidity and mortality, and it imposes a significant economic burden on patients (1,2). The risk of stroke varies with a number of factors. Regarding this issue, aging is the most important risk factor for stroke (3). The elderly's vulnerability to stroke is mainly attributable to the increasing incidences of comorbidities such as hypertension and corresponding vascular damage of other organs (4). Chronic kidney disease is also regarded as vascular damage and serves as a major cause of stroke (5). Specifically, end-stage renal disease (ESRD), the worst stage of kidney function, presents a risk of stroke approximately 5 to 10 times greater than normal kidney function (6). In accordance with the relationship between aging, kidney function, and stroke, elderly patients with ESRD deserve to receive the most attention, as the prevalence of both old age and ESRD has continued to increase (7). However, no active strategy to recover kidney function is circumscribed in elderly patients because they are less well suited to kidney transplantation than

their younger counterparts due to their overall poor health status and several comorbidities. In this regard, it is necessary to identify and modify risk factors for stroke in this population before and after the initiation of dialysis, but studies that focus on this important concern are scarce. Regarding elderly patients with ESRD, our previous work revealed that there was a discrepancy in length of survival between 2 dialysis modalities, hemodialysis (HD) and peritoneal dialysis (PD) (8). Both a meta-analysis and Korean results suggest a higher risk of death in elderly patients receiving PD than in those receiving HD. However, no information on the comparison of cardiovascular morbidities between the 2 modalities was provided. Because the dialysis modality acts as an interaction with the patient outcome, we first compared the risks of cardiovascular diseases, including ischemic heart disease and stroke, between HD and PD in elderly Korean patients. Accordingly, HD was a risk factor of stroke compared with PD. Subsequently, we traced factors predicting stroke occurrence using an independent prospective HD cohort from 31 dialysis centers and found 4 factors related with the stroke risk.

Keywords: Cardiovascular Diseases; Aged; Kidney Failure, Chronic; Renal Dialysis; Stroke

their younger counterparts due to their overall poor health status and several comorbidities. In this regard, it is necessary to identify and modify risk factors for stroke in this population before and after the initiation of dialysis, but studies that focus on this important concern are scarce.

Regarding elderly patients with ESRD, our previous work revealed that there was a discrepancy in length of survival between 2 dialysis modalities, hemodialysis (HD) and peritoneal dialysis (PD) (8). Both a meta-analysis and Korean results suggest a higher risk of death in elderly patients receiving PD than in those receiving HD. However, no information on the comparison of cardiovascular morbidities between the 2 modalities was provided. Because the dialysis modality acts as an interaction with the patient outcome, we first compared the risks of cardiovascular diseases, including ischemic heart disease and stroke, between HD and PD in elderly Korean patients. Accordingly, HD was a risk factor of stroke compared with PD. Subsequently, we traced factors predicting stroke occurrence using an independent prospective HD cohort from 31 dialysis centers and found 4 factors related with the stroke risk.

MATERIALS AND METHODS

Data collection from the Korean Health Insurance database

The data on elderly Koreans undergoing dialysis were obtained from the Korean Health Insurance database. The data from all elderly Koreans could be reviewed because Koreans are obliged to register with the national insurance system, which is composed of National Health Insurance and Medical Aid. In total, 35,422 patients with ESRD initiated dialysis between January 2005 and December 2008. From this group, 13,065 elderly patients aged 65 years or older (36.9%) were included in the present analysis.

Baseline parameters, including age, sex, type of insurance, and scale of the hospital (i.e., clinic, hospital or general hospital) were collected after assigning a unique de-identified number to each patient. Comorbidities, such as diabetes mellitus, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, and cancer, were identified by screening the medical history data from the year leading up to the initiation of dialysis therapy based on the International Classification of Diseases 10th revision (ICD-10) (9). Using these covariates, the Charlson comorbidity index (CCI) score for each patient was calculated (10). All patients were divided into 2 groups (HD vs. PD). If patients switched from one modality to the other within 1 month of initiating dialysis, those patients were classified and followed as a changed-modality group as long as no death event occurred within that month. There were no missing data in the variables of the Korean Health Insurance database, but the dataset did not provide detailed information, including biochemical and socioeconomic parameters.

Study patients were followed until kidney transplantation, death, or December 2009. If the dialysis modality changed, the patient was censored. The mortality data were obtained from the Certificate Database (i.e., listing of reasons for changes in eligibility for National Health Insurance or Medical Aid, including death or emigration) as well as through the National Health Insurance Claims Database. The primary outcome was the development of cardiovascular diseases, such as ischemic heart disease and stroke. These conditions were determined using insurance claims recorded in the Korean Health Insurance database.

Data collection from the multicenter cohort of patients with ESRD

To identify the risk factor of stroke in HD, we retrospectively analyzed the Clinical Research Center (CRC) registry for the ESRD cohort, an observational prospective cohort study conducted in Korea. The cohort was established in April 2009 and patients

were enrolled from 31 dialysis centers. A total of 2,208 incidents and 2,991 prevalent patients were recruited until March 2015. Among them, 1,082 patients were 65 years old or older with chronic HD (≥ 3 months). We excluded patients for whom selected information, including laboratory and other parameters, were not available ($n = 102$). Finally, 980 elderly patients receiving chronic HD were analyzed. All of the patients who participated in the study provided informed consent and agreed with examinations in adherence with the study protocol.

Baseline clinical parameters, such as age, sex, dialysis duration, cause of ESRD, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) before HD, comorbidities (e.g., diabetes mellitus, cardiovascular disease including ischemic heart disease, chronic heart failure, stroke, peripheral vascular disease, arrhythmia, chronic lung disease, connective tissue disease, peptic ulcer disease, liver disease, and malignancy), the use of anti-hypertensive drugs (e.g., angiotensin converting enzyme inhibitor, angiotensin receptor blocker, diuretics, beta blocker, and calcium channel blocker), anti-coagulant drugs (e.g., aspirin, warfarin, ticlopidine, and clopidogrel), vitamin D, iron supplements, and erythropoietin-stimulating agents, and the type of vascular access. Using the comorbidity parameters, the CCI score and the Davies index were calculated (10,11). In accordance with the study questionnaire, patients reported the status of the following factors: smoking, current working, presence of spouse, absolute dependence on family or social support (which included both emotional and economic support), educational level, ambulation, visual acuity, and feeding. Laboratory parameters included whole blood cell counts, hemoglobin, calcium, phosphorus, uric acid, albumin, blood urea nitrogen (BUN), creatinine, sodium, potassium, total cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterols, intact parathyroid hormone, ferritin, iron, transferrin saturation, hepatitis B surface antigen, and anti-hepatitis C antibody. The single-pool Kt/V was determined by 2-point urea modeling based on the intradialytic reduction in blood urea and intradialytic weight loss (12).

Elderly patients with HD were followed until dropouts, death, or December 2015. The causes of dropouts included refusal to participate in the study during follow-up, kidney transplantation, and the loss to follow-up. If there were hospitalizations or death, the date and causes were registered at the given institutions. Based on these registrations, we identified the development of stroke-related hospitalizations or deaths as a primary outcome.

Statistical analysis

The data are presented as the means \pm standard deviation for continuous variables and as proportions for categorical variables. The χ^2 test and Student's t-test were used to compare the cate-

gorical variables and continuous variables, respectively. Survival curves were drawn using the Kaplan-Meier method. To compare the survival curves between the groups, the log-rank test was initially applied. To calculate the hazard ratios (HRs) of the outcomes, the Cox proportional hazard model was used, with and without adjustments for the covariates. To identify the risk factors of stroke in the CRC registry, we included age, sex, and parameters with $P < 0.1$ in the univariate analysis in the multivariate model. To prevent co-linearity among significant risk

factors, the backward stepwise selection method was used. A P value of less than 0.05 was considered significant for the estimated HRs. All of the analyses and calculations were performed using SPSS (SPSS version 21.0; IBM, Armonk, NY, USA) and STATA (STATA version 12.0; StataCorp LP, College Station, TX, USA).

Ethics statement

The current study protocol complies with the Declaration of Helsinki and received full approval from the Institutional Review Board at the Seoul National University Hospital (No. 1601-008-729). The CRC registry from a multicenter cohort was approved by the Institutional Review Boards at each center. The Institutional Review Boards are described in the Supplementary 1. All of the patients in the CRC registry provided written informed consent and agreed with the study protocol.

RESULTS

Baseline characteristics of elderly Korean patients receiving dialysis

Table 1 shows the baseline characteristics of elderly Korean patients who began dialysis between January 2005 and December 2008. The mean age was 72.2 years. The number (proportion) of participants in each age category was as follows: 65–69 years,

Table 1. Baseline characteristics of elderly Korean patients undergoing dialysis

Characteristics	Total (n = 13,065)	HD (n = 10,675)	PD (n = 2,390)	<i>P</i>
Age, yr	72.2 ± 5.53	72.4 ± 5.60	71.4 ± 5.12	< 0.001
Male sex, %	54.4	54.8	52.6	0.046
Health security system				0.611
National health insurance	88.8	88.8	89.1	
Medical aid	11.2	11.2	10.9	
Hospital classification				< 0.001
General hospital	93.8	92.6	99.2	
Hospital	2.6	3.0	0.6	
Clinic	3.6	4.4	0.1	
Medical comorbidities, %				
Diabetes mellitus	53.7	53.1	56.5	0.002
Myocardial infarction	6.0	5.2	9.6	< 0.001
Congestive heart failure	19.7	18.6	24.4	< 0.001
Peripheral vascular disease	8.4	8.5	8.0	0.487
Cerebrovascular disease	19.5	20.0	17.4	0.003
Dementia	3.5	3.7	2.8	0.033
Chronic pulmonary disease	23.5	23.9	21.1	0.004
Connective tissue disease	3.3	3.4	3.2	0.702
Peptic ulcer disease	17.5	17.8	16.4	0.102
Liver disease	9.1	9.4	7.6	0.005
Hemiplegia	2.3	2.4	1.6	0.024
Cancer	9.6	10.6	4.9	< 0.001
CCI score	2.7 ± 2.01	2.7 ± 2.04	2.6 ± 1.87	0.007

Statistical differences between dialysis modalities were calculated.

HD = hemodialysis, PD = peritoneal dialysis, CCI = Charlson comorbidity index.

Table 2. Case number and incidence rate (1,000 patient-year) of cardiovascular disease according to the dialysis modality

Outcomes	HD		PD	
	Case	Incidence rate	Case	Incidence rate
Composite cardiovascular disease	2,807 (26.3)	180.4	575 (24.1)	170.7
Ischemic heart disease	1,058 (9.9)	59.3	249 (10.4)	67.1
Stroke	1,994 (18.7)	120.1	381 (15.9)	107.1

Values are presented as number (%).

HD = hemodialysis, PD = peritoneal dialysis.

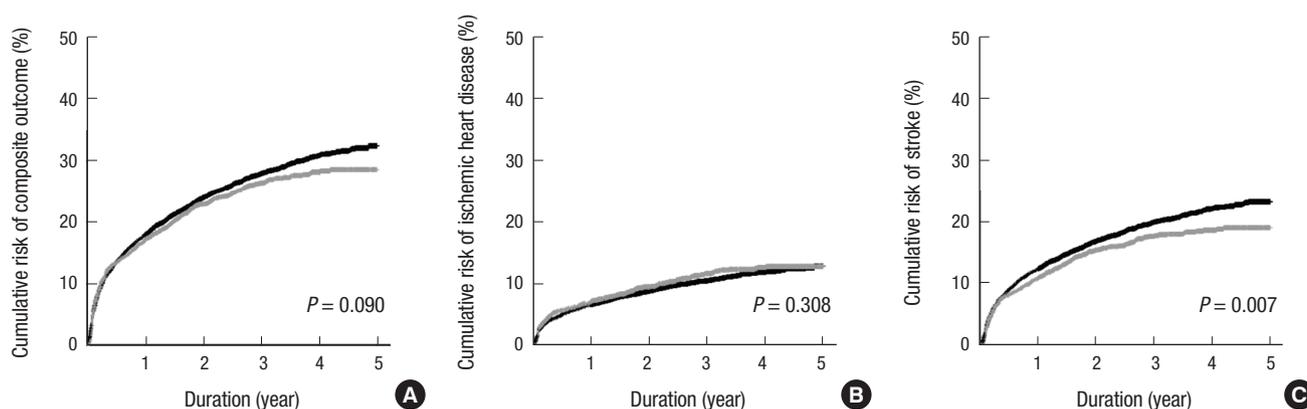


Fig. 1. Cumulative risk of cardiovascular disease according to the dialysis modalities. (A) Composite cardiovascular disease; (B) ischemic heart disease; and (C) stroke. Black and gray lines represent HD and PD, respectively.

HD = hemodialysis, PD = peritoneal dialysis.

4,939 (37.8%); 70–79 years, 6,650 (50.9%); 80–89 years, 1,418 (10.9%); and ≥ 90 years, 58 (0.4%). Comorbidities, such as diabetes mellitus, myocardial infarction, and congestive heart failure, were more frequent in PD than in HD; but, other comorbidities, such as cerebrovascular disease, dementia, chronic pulmonary disease, liver disease, hemiplegia, and cancer, were more common in HD than in PD. The patients were followed for a mean duration of 1.8 ± 1.3 years and a maximum of 5 years.

Cardiovascular disease according to the dialysis modalities

During the follow-up period, cardiovascular disease events occurred in 3,382 patients (25.9%): ischemic heart disease, in 1,307 (10.0%); stroke, in 2,375 (18.2%); and both, in 300 (2.3%). Incidence rates (1,000 patient-year) of cardiovascular disease, ischemic heart disease, and stroke events were 178.7, 60.6, and 117.8, respectively.

Table 2 shows the cardiovascular event number and rates according to the dialysis modality. Fig. 1 shows the crude cumulative rates of cardiovascular diseases in HD and PD patients. The overall rates of cardiovascular diseases did not differ between 2 modalities ($P = 0.090$) (Fig. 1A). When the analysis was conducted separately by the subtype of disease, the rates of ischemic heart disease were similar between 2 modalities ($P = 0.308$) (Fig. 1B), but the rates of stroke differed, as high risk was conferred to HD patients ($P = 0.007$). Subsequently, we adjusted all the covariates (as shown in Table 1) in the comparison analyses (Table 3), and the difference between the 2 modalities remained also significant in terms of stroke, but not ischemic heart disease.

Stroke and subsequent all-cause mortality outcome

Fig. 2 shows the survival curves between the groups with and without stroke. The crude mortality rates of 2 groups were significantly different ($P < 0.001$). When all the variables were adjusted, the HR in the stroke group was 1.24 (1.165–1.327) compared with the non-stroke group ($P < 0.001$). When the analyses were separately conducted by dialysis modality, mortality rates (1,000 patient-year) were 288.3 in HD without stroke, 541.6 in HD with stroke, 314.4 in PD without stroke, and 710.3 in PD with stroke. Compared with the groups without stroke, the adjusted HRs of mortality were 1.19 (1.109–1.282) and 1.63 (1.394–

1.894) in HD and PD with stroke, respectively ($P < 0.001$). These data indicated that the subsequent development of stroke was linked to poor survival of elderly dialysis patients.

Risk factor of stroke in HD

Based on the above relationship between HD and stroke risk of elderly patients, we sought to address which factors were responsible for the high risk of stroke in HD. Because the various clinical and laboratory parameters were not available in the Health Insurance database, we reviewed and analyzed 980 elderly patients with HD, all of whom were recruited between April 2009 and March 2015 from 31 dialysis centers. Their baseline characteristics (e.g., socioeconomic parameters, laboratory findings, and the use of medications) are shown in Table 4. The mean age was 72.0 years. The patients were followed for a mean duration of 2.6 ± 2.1 years and a maximum of 7 years. During the following period, 42 patients (4.3%) had stroke events.

Supplementary Table 1 shows the baseline difference between the stroke and non-stroke groups irrespective of the timeframe

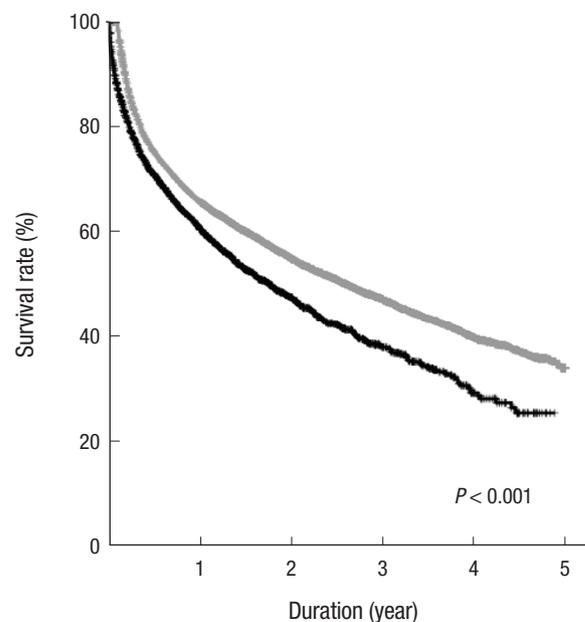


Fig. 2. Survival curves according to the development of stroke events. Black and gray lines represent stroke and non-stroke groups, respectively.

Table 3. HRs of cardiovascular outcomes in the HD group compared with the PD group

Outcomes	Univariate		Multivariate*	
	HR (95% CI)	P	HR (95% CI)	P
Composite cardiovascular disease	1.08 (0.988–1.182)	0.090	1.16 (1.055–1.266)	0.002
Ischemic heart disease	0.93 (0.811–1.069)	0.308	1.13 (0.983–1.302)	0.085
Stroke	1.16 (1.042–1.297)	0.007	1.16 (1.034–1.292)	0.011

HD = hemodialysis, PD = peritoneal dialysis, HR = hazard ratio, CI = confidence interval, CCI = Charlson comorbidity index.

*Adjusted for age, sex, health security system, hospital classification, comorbidities including diabetes mellitus, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, cancer, and CCI score.

Table 4. Risk factors for the risk of stroke in 980 HD patients from 31 dialysis centers

Risk factors	Univariate		Multivariate	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (per 1 yr)	0.99 (0.938–1.053)	0.834	-	-
Male (vs. female)	0.91 (0.496–1.673)	0.764	-	-
Dialysis duration, yr			-	-
< 1	1 (reference)	-		
≥ 1 to < 3	0.52 (0.174–1.525)	0.231		
≥ 3 to < 8	1.60 (0.792–3.245)	0.189		
≥ 8	1.73 (0.684–4.372)	0.247		
Dependence on family support (vs. other)	1.78 (0.956–3.325)	0.069	-	-
Dependence on social support (vs. other)	2.63 (1.400–4.952)	0.003	3.03 (1.572–5.830)	0.001
BMI (per 1 kg/m ²)	0.91 (0.818–1.006)	0.064	-	-
Cardiovascular disease (vs. none)	1.73 (0.943–3.181)	0.077	2.05 (1.069–3.912)	0.031
Visual acuity			-	-
Normal or with glasses	1 (reference)	-		
Mild difficulty	0.64 (0.280–1.444)	0.280		
The blind	2.99 (0.914–9.796)	0.070		
Total cholesterol (per 1 mg/dL)	1.01 (1.000–1.014)	0.044	-	-
LDL cholesterol (per 1 mg/dL)	1.01 (1.003–1.019)	0.006	1.01 (1.004–1.020)	0.003
Calcium channel blocker (vs. none)	1.69 (0.912–3.129)	0.095	-	-
No. of anti-hypertensive drugs (per 1)	1.19 (0.998–1.420)	0.053	1.20 (1.006–1.435)	0.043
Davies index			-	-
0	1 (reference)	-		
1	1.36 (0.491–3.788)	0.551		
≥ 2	2.41 (0.911–6.359)	0.076		

HD = hemodialysis, HR = hazard ratio, CI = confidence interval, BMI = body mass index, LDL = low-density lipoprotein.

of stroke. Compared with non-stroke patients, the patients with stroke had the following characteristics: longer dialysis duration ($P = 0.021$); higher absolute dependence on social support ($P = 0.001$); high LDL cholesterol levels ($P = 0.013$); and use of high number of anti-hypertensive drugs ($P = 0.027$). We additionally grouped the continuous variables according to the tertiles or commonly-used criteria, and determined the relationship with stroke (Supplementary Table 2). As a result, the tertiles of LDL cholesterol significantly discriminated the stroke events ($P = 0.012$), but other continuous variables did not.

Subsequently, we considered the stroke timeframe by applying Cox proportional hazard models to the parameters with $P < 0.100$ in the above analyses (Table 4). Univariate analyses were similar to the previous results shown in Supplementary Tables 1 and 2. However, the multivariate analysis finally determined the independent risk factors of stroke as follows: absolute dependence on social support; a previous history of cardiovascular disease; high LDL cholesterol levels; and the use of a high number of anti-hypertensive drugs. Their corresponding risk curves are shown in Fig. 3.

DISCUSSION

The cardiovascular morbidity and mortality of elderly dialysis patients are important issues due to the high incidence of disease with older age, but older patients' choices for active man-

agement are limited compared with their younger counterparts. The present study firstly addressed the relationship between modality and cardiovascular risk in a subset of elderly Korean ESRD patients. Accordingly, patients who started with HD had a higher risk of subsequent cardiovascular diseases than those who started with PD. In particular, the risk discrepancy was prominent in stroke events, and these events significantly aggravated all-cause mortality of patients. We additionally addressed the risk factors related to stroke in an HD cohort. The results for certain factors (e.g., history of cardiovascular diseases, hypercholesterolemia, and severe hypertensive state) supported previous findings in the literature, while other results (e.g., absolute dependence on social support) provide new information to the knowledge base in this field.

Regarding which modality may be most suitable for elderly patients, a randomized trial that controls for all possible confounders is not feasible (13). The current knowledge is obtained from several observational studies, and there were controversial results regarding the survival benefits between 2 modalities. One meta-analysis of 8 studies published before the year 2000 reported similar mortality results for both modalities (14). Our recent meta-analysis from 15 cohort studies published after the year 2000 preferred HD to PD, particularly in subgroups that had diabetes mellitus, had long dialysis durations (> 1 year), or contained cohorts that began dialysis in the 1990s (8). Nevertheless, studies that have focused on the risk of cardiovascular

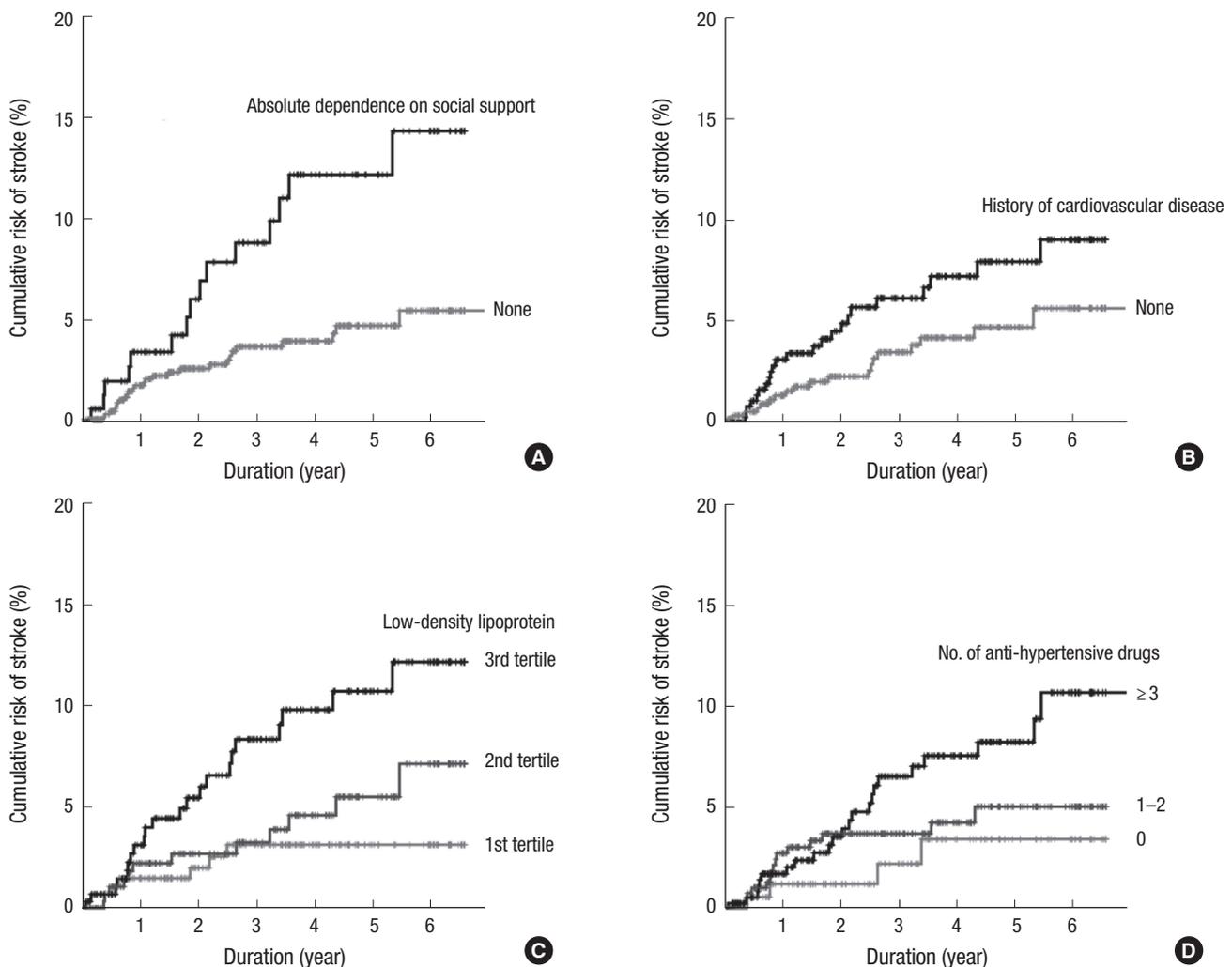


Fig. 3. Risk of stroke depending on the following factors: (A) Absolute dependence on social support; (B) a history of cardiovascular disease; (C) the tertiles of LDL cholesterol levels; and (D) the number of anti-hypertensive drugs used. LDL = low-density lipoprotein.

disease, not all-cause mortality, in the 2 modalities are scarce (15-18). Some studies definitely preferred PD (16,18), but others favored HD (17). Additionally, a study including elderly patients showed that the HD group exhibited worsened cardiovascular parameters (e.g., left ventricular mass index, left ventricular wall thickness, intima media thickness, and intima media area) after 4 years compared with the PD group (16). The present study revealed that the discrepancy of risk was dependent on the type of disease: stroke, not ischemic heart disease, was more common in the HD group than the PD group. Possible mechanisms for the higher presentation of cardiovascular disease in HD include the nature of dialysis regarding rapid loss of residual kidney function and hemodynamic instability compared with PD (19,20). We acknowledge that all of these observational results cannot provide clues regarding the preference between HD and PD. However, these studies, including the present results, may be helpful to raise the awareness of modality

selection, particularly in terms of the characteristics of each modality.

Several traditional and non-traditional factors are responsible for stroke events in dialysis patients (21,22). We identified severe hypertension (i.e., indicated by high number of the anti-hypertensive drugs used) and a previous history of cardiovascular disease as risk factors for stroke in elderly patients receiving HD. In addition to the general mechanism on the relationship between hypertension and stroke (23), HD and hypertension can synergistically increase the stroke risk throughout dialysis-induced ischemia and hemodynamic instability due to ultrafiltration in a short time period (20). Uremic conditions during the non-HD period can further mediate the development of stroke (24). A previous history of cardiovascular disease indicates remnant vascular sequelae and calcification; these vulnerable vessels are also common in the dialysis state or in the elderly population compared with the counterparts (25,26). Thus, the

cardiovascular history can aggravate the risk of stroke in this subset.

Findings on the relationship between hypercholesterolemia and stroke risk supports the current knowledge (27). However, this positive relationship is applied only to the case of ischemic stroke, not hemorrhagic stroke, wherein high cholesterol levels seem to protect the hemorrhagic stroke (28). The higher incidence of ischemic stroke relative to hemorrhagic stroke might be why hypercholesterolemia was selected as a risk factor (29). Unfortunately, the current CRC-ESRD registry did not provide the subtype of stroke; therefore, this limitation may hamper the conclusions about hypercholesterolemia. Particularly, the great concern about lipid-lowering therapy in dialysis patients has not been fully established (30,31).

We found that absolute dependence on social support was strongly associated with stroke risk. This parameter included both emotional and economic supports; thus, the patients who gave a positive answer might have low self-management or low income status. Although subsequent studies will validate our results and their clinical implications, the present results from elderly patients supports the previous concept about the relationship between psychosocial or economic status and the risk of cardiovascular disease (32).

Although the present results are informative, this study has some limitations. The observational study design limits the establishment of any conclusions of causality or underlying mechanisms. Because we primarily considered elderly Korean patients with ESRD, the application of our results to other clinical settings should be performed carefully. Furthermore, other missing or unidentified parameters (e.g., the severity of stroke or the purpose of drug use) could act as confounding factors in the present correlations.

The present study addresses a high risk of stroke in HD and its responsible risk factors in elderly Korean patients with ESRD. Elderly patients with dialysis exhibit a high risk of stroke and subsequent disability or mortality. In this regard, the present study will enrich the present awareness of the elderly patients' vulnerability and form the basis of the future studies to address whether the monitoring and management of factors confirmed here can constitute a strategy to reduce the stroke risk in elderly patients receiving dialysis.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Han SS. Data curation: Han SS, Ryu DR. Formal analysis: Joo KW, Lim CS, Kim YL, Kang SW, Kim YS, Kim DK. Investigation: Han SS, Joo KW, Lim CS, Kim YL, Kang SW,

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SUPPLEMENTARY MATERIALS

Supplementary 1. Institutional Review Boards

Catholic University of Korea, Bucheon St. Mary's Hospital; Catholic University of Korea, Incheon St. Mary's Hospital; Catholic University of Korea, Seoul St. Mary's Hospital; Catholic University of Korea, St. Mary's Hospital; Catholic University of Korea, St. Vincent's Hospital; Catholic University of Korea, Uijeongbu St. Mary's Hospital; Cheju Halla General Hospital; Chonbuk National University Hospital; Chonnam National University Hospital; Chung-Ang University Medical Center; Chungbuk National University Hospital; Chungnam National University Hospital; Dong-A University Medical Center; Ewha Womans University Medical Center; Fatima Hospital, Daegu; Gachon University Gil Medical Center; Inje University Pusan Paik Hospital; Kyungpook National University Hospital; Kwandong University College of Medicine, Myongji Hospital; National Health Insurance Corporation Ilsan Hospital; National Medical Center; Pusan National University Hospital; Samsung Medical Center, Seoul; Seoul Metropolitan Government, Seoul National University, Boramae Medical Center; Seoul National University Hospital; Seoul National University, Bundang Hospital; Yeungnam University Medical Center; Yonsei University, Severance Hospital; Yonsei University, Gangnam Severance Hospital; Ulsan University Hospital; and Wonju Christian Hospital (listed in alphabetical order).

Supplementary Table 1. Baseline characteristics of HD patients in the CRC-ESRD cohort

Characteristics	Total (n = 980)	No stroke (n = 938)	Stroke (n = 42)	P
Age, yr	72.0 ± 5.47	72.0 ± 5.49	71.6 ± 5.05	0.625
Male sex, %	58.4	58.5	54.8	0.628
Dialysis duration, %				0.021
< 1 yr	55.3	55.9	42.9	
≥ 1 to < 3 yr	17.7	18.0	9.5	
≥ 3 to < 8 yr	18.9	18.2	33.3	
≥ 8 yr	8.2	7.9	14.3	
Underlying renal disease, %				0.783
Diabetes	53.2	53.1	54.8	
Hypertension	21.9	22.0	21.4	
Primary glomerulonephritis	6.3	6.4	4.8	
Others	10.0	9.8	14.3	
Unknown	8.6	8.7	4.8	
Smoking status, %				0.275
Never smoker	62.0	61.5	73.2	
Past smoker	31.7	32.1	24.4	
Current smoker	6.2	6.4	2.4	
Work, %	7.1	7.1	7.1	0.997
Spouse, %	80.3	80.4	78.6	0.776
Dependence on family support, %	25.7	25.1	38.1	0.060
Dependence on social support, %	16.4	15.5	35.7	0.001
Education level, %				0.215
Less than high school	52.4	52.9	42.9	
High school	25.0	25.1	23.8	
College and more	22.5	22.0	33.3	
BMI, kg/m ²	22.5 ± 3.22	22.5 ± 3.25	21.7 ± 2.31	0.025
SBP, mmHg	139.7 ± 19.83	139.6 ± 19.67	140.5 ± 23.29	0.785
DBP, mmHg	72.1 ± 12.10	72.1 ± 12.16	71.4 ± 10.65	0.702
Diabetes mellitus, %	59.9	60.0	58.5	0.854
Comorbidities, %				
Cardiovascular disease	41.1	40.5	54.8	0.066
Ischemic heart disease	23.4	23.4	24.4	0.883
Chronic heart failure	11.4	11.1	17.1	0.241
Stroke	13.8	13.5	22.0	0.123
Peripheral vascular disease	8.4	8.1	14.6	0.142
Arrhythmia, %	5.9	5.9	7.3	0.702
Chronic lung disease, %	8.5	8.3	12.2	0.387
Connective tissue disease, %	10.1	10.1	10.0	0.976
Peptic ulcer disease, %	7.0	6.9	9.8	0.478
Liver disease, %	7.0	7.1	4.9	0.592
Malignancy, %	11.0	11.2	4.9	0.202
Ambulation, %				0.737
Normal	74.5	74.4	78.0	
Walk with assistance	17.4	17.5	17.1	
By wheelchair or bed-ridden	8.0	8.2	4.9	
Visual acuity, %				0.079
Normal or with glasses	71.6	71.4	75.6	
Mild difficulty	25.8	26.2	17.1	
The blind	2.6	2.4	7.3	
Feeding, %				0.746
Normal	95.0	94.9	97.6	
Feeding with assistance	4.9	5.0	2.4	
Feeding by tube	0.1	0.1	0	
Modified CCI	6.9 ± 1.98	6.9 ± 1.98	6.9 ± 1.87	0.986
Davies index	1.3 ± 1.00	1.3 ± 1.01	1.5 ± 0.81	0.274

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Supplementary Table 1. Continued

Characteristics	Total (n = 980)	No stroke (n = 938)	Stroke (n = 42)	P
Laboratory finding				
Whole blood cell, \times /mm^3	6.5 \pm 2.45	6.5 \pm 2.46	6.5 \pm 2.34	0.933
Hemoglobin, g/dL	10.7 \pm 1.39	10.7 \pm 1.40	11.0 \pm 1.11	0.215
Calcium, mg/dL	8.6 \pm 0.84	8.7 \pm 0.84	8.5 \pm 0.77	0.413
Phosphorus, mg/dL	4.4 \pm 1.35	4.4 \pm 1.34	4.3 \pm 1.46	0.617
Uric acid, mg/dL	6.9 \pm 1.76	6.9 \pm 1.76	6.7 \pm 1.90	0.452
Albumin, g/dL	3.7 \pm 0.46	3.7 \pm 0.46	3.8 \pm 0.40	0.164
BUN, mg/dL	57.4 \pm 20.78	57.5 \pm 20.81	56.5 \pm 20.24	0.761
Creatinine, mg/dL	7.6 \pm 2.62	7.6 \pm 2.61	8.0 \pm 2.93	0.282
Sodium, mEq/L	137.9 \pm 3.61	137.9 \pm 3.62	138.0 \pm 3.53	0.803
Potassium, mEq/L	4.8 \pm 0.80	4.8 \pm 0.80	4.9 \pm 0.79	0.712
Total cholesterol, mg/dL	153.2 \pm 37.38	152.7 \pm 37.63	163.5 \pm 29.87	0.071
Triglyceride, mg/dL	117.9 \pm 75.12	118.3 \pm 75.81	109.9 \pm 59.05	0.486
HDL cholesterol, mg/dL	42.4 \pm 14.60	42.4 \pm 14.58	42.7 \pm 15.25	0.892
LDL cholesterol, mg/dL	86.9 \pm 31.64	86.3 \pm 31.78	98.8 \pm 26.16	0.013
Intact parathyroid hormone, pg/mL	161.3 \pm 179.21	161.4 \pm 182.00	159.8 \pm 102.39	0.957
Ferritin, ng/mL	299.1 \pm 364.39	297.1 \pm 366.61	340.4 \pm 315.16	0.464
Iron, $\mu\text{g/dL}$	66.9 \pm 34.72	67.0 \pm 34.93	65.6 \pm 30.43	0.810
Transferrin saturation, %	32.1 \pm 24.28	32.1 \pm 24.58	32.2 \pm 17.19	0.986
Positive HBs Ag, %	3.1	3.1	2.4	0.794
Positive HCV Ab, %	3.0	3.0	2.4	0.821
Medications, %				
ACEi or ARB	45.7	45.4	52.4	0.375
Diuretics	39.2	39.3	35.7	0.638
Beta blocker	38.6	38.1	50.0	0.120
Calcium channel blocker	45.6	45.0	59.5	0.064
Aspirin	41.2	41.0	45.2	0.589
Warfarin	2.8	2.7	4.8	0.417
Ticlopidine	5.4	5.2	9.5	0.228
Clopidogrel	14.4	14.1	21.4	0.184
Vitamin D	11.7	11.7	11.9	0.972
Iron	66.1	65.9	71.4	0.458
Erythropoietin-stimulating agent	71.7	71.4	78.6	0.315
No. of anti-hypertensive drugs	2.1 \pm 1.57	2.1 \pm 1.56	2.6 \pm 1.64	0.027
No. of anti-coagulant agents	0.7 \pm 0.75	0.7 \pm 0.75	0.9 \pm 0.65	0.260
Vascular access, %				
Native fistula	65.2	65.2	65.9	0.874
Synthetic graft	19.7	19.9	17.1	
Catheter	15.1	15.0	17.1	
Single-pool Kt/V	1.5 \pm 0.44	1.5 \pm 0.44	1.5 \pm 0.31	0.530

HD = hemodialysis, CRC = Clinical Research Center, ESRD = end-stage renal disease, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, CCI = Charlson comorbidity index, BUN = blood urea nitrogen, HDL = high-density lipoprotein, LDL = low-density lipoprotein, HBs Ag = surface antigen of the hepatitis B virus, HCV Ab = anti-hepatitis C virus antibody, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, K = dialyzer clearance, t = time, V = volume of water a patient's body contains.

Supplementary Table 2. Relationship with the risk of stroke according to the categories of continuous variables

Variables	Categories	Mean value	Stroke, %	P
Age	1st tertile	66.5 ± 1.12	4.5	0.594
	2nd tertile	71.0 ± 1.41	5.0	
	3rd tertile	78.4 ± 3.97	3.4	
BMI, kg/m ²	< 18.5	17.2 ± 1.19	5.1	0.278
	≥ 18.5 to < 25.0	21.8 ± 1.73	4.9	
	≥ 25.0 to < 30.0	26.8 ± 1.33	1.9	
	≥ 30.0	32.5 ± 2.15	0	
BMI	1st tertile	19.2 ± 1.45	5.1	0.454
	2nd tertile	22.2 ± 0.75	4.7	
	3rd tertile	26.0 ± 2.28	3.2	
SBP, mmHg	< 120	109.1 ± 7.17	6.0	0.634
	≥ 120 to < 140	130.9 ± 6.79	3.9	
	≥ 140	158.1 ± 13.06	4.5	
SBP	1st tertile	120.6 ± 9.55	3.9	0.757
	2nd tertile	139.5 ± 4.38	4.5	
	3rd tertile	161.7 ± 12.31	5.0	
DBP, mmHg	< 80	65.3 ± 8.32	4.9	0.337
	≥ 80 to < 90	83.1 ± 4.20	4.2	
	≥ 90	97.6 ± 4.58	0	
DBP	1st tertile	59.1 ± 6.70	4.6	0.663
	2nd tertile	72.1 ± 2.90	5.1	
	3rd tertile	84.9 ± 6.34	3.6	
Modified CCI	1st tertile	4.5 ± 0.63	3.8	0.556
	2nd tertile	6.5 ± 0.50	5.0	
	3rd tertile	9.1 ± 1.36	3.5	
Davies index	0	0	2.5	0.081
	1	1	3.5	
	≥ 2	2.4 ± 0.63	6.0	
Whole blood cell	1st tertile	4.3 ± 0.88	4.0	0.938
	2nd tertile	6.2 ± 0.50	4.2	
	3rd tertile	9.1 ± 2.34	4.6	
Hemoglobin	1st tertile	9.3 ± 1.05	3.4	0.139
	2nd tertile	10.7 ± 0.25	3.4	
	3rd tertile	12.1 ± 0.87	6.1	
Calcium	1st tertile	7.8 ± 0.46	4.7	0.856
	2nd tertile	8.5 ± 0.17	4.5	
	3rd tertile	9.5 ± 0.62	3.8	
Phosphorus	1st tertile	3.0 ± 0.57	5.2	0.463
	2nd tertile	4.3 ± 0.29	3.2	
	3rd tertile	5.8 ± 1.02	4.5	
Uric acid	1st tertile	5.1 ± 0.97	5.4	0.370
	2nd tertile	7.0 ± 0.38	3.1	
	3rd tertile	8.8 ± 1.07	4.4	
Albumin	1st tertile	3.3 ± 0.36	4.0	0.517
	2nd tertile	3.8 ± 0.08	3.5	
	3rd tertile	4.2 ± 0.24	5.3	
BUN	1st tertile	35.6 ± 9.56	3.7	0.747
	2nd tertile	56.1 ± 5.04	4.9	
	3rd tertile	80.5 ± 12.93	4.3	
Creatinine	1st tertile	4.9 ± 1.06	3.7	0.741
	2nd tertile	7.4 ± 0.62	4.3	
	3rd tertile	10.5 ± 1.77	4.9	
Sodium	1st tertile	133.7 ± 2.62	3.7	0.664
	2nd tertile	138.1 ± 0.80	5.1	
	3rd tertile	141.6 ± 1.59	4.0	

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Supplementary Table 2. Continued

Variables	Categories	Mean value	Stroke, %	P
Potassium	1st tertile	4.0 ± 0.36	3.4	0.293
	2nd tertile	4.8 ± 0.19	5.7	
	3rd tertile	5.7 ± 0.51	3.8	
Total cholesterol	1st tertile	116.4 ± 14.83	3.2	0.098
	2nd tertile	149.7 ± 8.05	3.5	
	3rd tertile	193.4 ± 30.33	6.3	
Triglyceride	1st tertile	56.6 ± 15.04	4.7	0.642
	2nd tertile	102.5 ± 13.62	5.3	
	3rd tertile	195.7 ± 81.12	3.7	
HDL cholesterol	1st tertile	29.2 ± 4.98	5.1	0.860
	2nd tertile	40.2 ± 2.89	4.4	
	3rd tertile	58.0 ± 12.74	4.3	
LDL cholesterol	1st tertile	56.1 ± 14.04	2.4	0.012
	2nd tertile	83.8 ± 6.57	4.1	
	3rd tertile	120.7 ± 25.55	7.4	
Intact parathyroid hormone	1st tertile	40.5 ± 21.16	3.5	0.593
	2nd tertile	119.6 ± 25.62	4.5	
	3rd tertile	323.9 ± 229.45	5.2	
Ferritin	1st tertile	76.3 ± 30.20	3.4	0.520
	2nd tertile	205.9 ± 51.84	5.1	
	3rd tertile	615.0 ± 486.79	5.1	
Iron	1st tertile	37.0 ± 9.91	4.2	0.329
	2nd tertile	61.2 ± 6.76	5.9	
	3rd tertile	102.5 ± 36.51	3.4	
Transferrin saturation	1st tertile	17.4 ± 4.64	5.1	0.831
	2nd tertile	28.4 ± 2.93	4.1	
	3rd tertile	50.6 ± 34.22	4.8	
No. of anti-hypertensive drugs	0	0	2.1	0.055
	1–2	1.6 ± 0.50	3.6	
	≥ 3	3.7 ± 0.98	6.1	
No. of anti-coagulant agents	0	0	2.9	0.177
	1	1	5.5	
	≥ 2	2.1 ± 0.40	4.3	
Single-pool Kt/V	1st tertile	1.1 ± 0.38	4.7	0.817
	2nd tertile	1.5 ± 0.05	4.5	
	3rd tertile	1.8 ± 0.38	5.7	

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, CCI = Charlson comorbidity index, BUN = blood urea nitrogen, HDL = high-density lipoprotein, LDL = low-density lipoprotein, K = dialyzer clearance, t = time, V = volume of water a patient's body contains.