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Running title: Impact of decreased eGFR on acute stroke

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Abstract

Objective Patients with chronic kidney disease (CKD) are at a high risk for cardiovascular diseases including stroke. However, the characteristics of the stroke subtypes in patients with CKD remain to be determined.

Methods and Patients We investigated the associations between stroke subtypes and estimated glomerular filtration rate (eGFR), and traditional risk factors in 451 (males, 239; mean age, 71.1 y) acute stroke patients at our hospital between 2006 and 2010.

Results The stroke subtype was cardiogenic cerebral embolism in 129 (29%), cerebral hemorrhage in 104 (23%), unclassified cerebral infarction in 65 (14%), lacunar infarction in 65 (14%), subarachnoid hemorrhage in 41 (9%), atherothrombosis in 30 (7%), and transient ischemic attacks in 17 (4%). Among the 451 patients, 134 (30%) had CKD with eGFR <60 mL/min/1.73m^2. Compared with a group without CKD, mean age (75.9 vs. 69.0 years, $P<0.05$), the prevalence of atrial fibrillation (AF) (44% vs. 21%, $P<0.01$) and a history of cardiovascular disease (37% vs. 19%, $P<0.01$) were significantly higher in that with CKD. A comparison of stroke subtypes revealed a significantly higher incidence of cardiogenic cerebral embolism (36% vs. 26%, $P<0.05$) in the group with, than without CKD.

Conclusion We showed the prevalence of CKD in about 30% of acute stroke patients, and those patients were older, had a significantly higher prevalence of AF and a higher rate of cardiogenic cerebral embolism compared with patients without CKD. Thus, strict control of blood pressure and management of AF should be important to prevent stroke among patients with CKD.

Key words: chronic kidney disease, stroke, stroke subtype, estimated glomerular filtration rate

Introduction

Chronic kidney disease (CKD) is a major worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease (CVD), and premature death (1-3). A number of prospective epidemiologic studies have shown that patients with CKD are at increased risk for CVD and stroke, independent of conventional cardiovascular risk factors (4, 5). However, the characteristics of the stroke subtypes in patients with CKD remain to be determined. We therefore evaluated the prevalence of CKD using estimated glomerular filtration rate (eGFR) in the database of patients with acute stroke at our hospital to examine the association between decreased eGFR and stroke and its subtype.

Methods

Patients

We analyzed data from patients who were admitted to Asahikawa Medical University hospital, which is located on the north island of Japan and has 602 beds, within 7 days of stroke onset between March 2006 and February 2010. Age, gender, blood pressures, lipid parameters, conventional cardiovascular risk factors, prior CVD including prior stroke, and medical/surgical treatment before admission were recorded. A history of smoking was defined as > 10 pack-years. Hypertension was defined as fulfilling any of the following criteria: previous hypertension; currently taking antihypertensive medication; or chronically high blood pressure exceeding 140/90 mmHg. Diabetes was defined as: fasting blood sugar ≥ 126 mg/dl; non-fasting blood sugar ≥ 200 mg/dl or HbA1c ≥ 6.5%; or current use of insulin or an oral hypoglycemic agent. Dyslipidemia was defined as: total cholesterol ≥ 220 mg/dl; HDL cholesterol < 40 mg/dl or triglyceride ≥ 150 mg/dl; or current use of an anti-hyperlipidemic medication. CKD was diagnosed with reference to eGFR calculated using the formula of the Japanese Society of Nephrology based on serum creatinine levels at the time of admission, age, and sex: eGFR (mL/min/1.73m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (× 0.739 for females) (6). The study was approved by the ethics committee of our hospital. Before their study entry, written informed consent was obtained from all patients in accordance with the ethical standards laid down in the declaration of Helsinki.

Definition of stroke subtypes

Stroke was classified into ischemic stroke, transient ischemic attacks, subarachnoid hemorrhage (SAH) and intracerebral hemorrhage, and ischemic stroke was further classified according to the criteria of the Classification of Cerebrovascular Disease III

proposed by the National Institute of Neurological Disorders and Stroke of the United States (7) as atherothrombotic infarction, cardiogenic cerebral embolism, and lacunar infarction based on clinical findings, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain. Lacunar infarction is characterized by presentation of focal neurological symptoms and signs, brain image evidence of infarct size ≤15 mm with typical location or unstated size, and no source of cardiac embolism could be identified. Atherothrombotic infarction is characterized by ischemic stroke with brain imaging evidence of infarct size >15 mm, no definite cardioembolic source, moderate to severe arterial stenosis, or infarction of other determined causes. Cardiogenic cerebral embolism required the same criteria of ischemic stroke plus evidence of a possible source of embolus such as valvular heart disease, atrial fibrillation (AF), or history of acute myocardial infarction. A transient ischemic attack is defined as an event with stroke symptoms that lasts less than 24 hours before disappearing without imaging of acute infarction. The infarcts that did not meet any of these criteria or may have had inadequate evaluation such that reasonable diagnostic classification was difficult were categorized as unclassifiable infarction.

Statistical analysis

Statistical analysis was performed using StatView Version 5 Software (Abacus Concepts Inc., Berkeley, California, USA). Values were expressed as mean ± SD. The chi-square test, or Fisher's exact test were used for comparison the baseline characteristics, the prevalence of stroke subtypes and in-hospital mortality between the two groups with and without CKD. Univariate correlation was used for continuous variables. Logistic regression analysis was used to determine valuables closely associated with cardiogenic cerebral embolism. A value of $P<0.05$ was accepted as statistically significant.

Results

The baseline characteristics of the subjects are outlined in Table 1. The mean age of the patients was 71.1 years and 239 men accounted for 53% of the total. The rates of concurrent risk factors for all patients were 91% for hypertension, and 28%, 24%, 20% and 17% for AF, a history of CVD, diabetes, and dyslipidemia, respectively. The details of 109 prior CVD were 46 with ischemic stroke, 6 with intracerebral hemorrhage, 28 with ischemic heart diseases, 10 with chronic heart failure, 9 with valvular heart diseases, 7 with peripheral artery diseases and 3 with abdominal aortic aneurysms.

Figure 1 shows the distribution of eGFR and categories of kidney function (stage 1: GFR ≥ 90; stage 2: GFR 60 to 89; stage 3: GFR 30 to 59; stage 4: GFR 15 to 30; and

stage 5: GFR <15 mL/min/1.73m^2). The prevalence of CKD stages 1 to 5 was 21.3, 49.0, 25.3, 3.1 and 1.3%, representing 96, 221, 114, 14 and 6 patients, respectively (Fig. 1). eGFR distribution was shifted toward lower values in men compared to women. Overall, the prevalence of eGFR <60 mL/min/1.73m^2, that is defined as having complicating CKD, was 29.7%, representing 134 patients (75 men and 59 women) in the stroke patients in our database.

Among the 451 patients, the stroke subtype was cardiogenic cerebral embolism in 129 (29%), cerebral hemorrhage in 104 (23%), unclassified cerebral infarction in 65 (14%), lacunar infarction in 65 (14%), subarachnoid hemorrhage in 41 (9%), atherothrombosis in 30 (7%), and transient ischemic attacks in 17 (4%). Univariate correlations between eGFR or the presence of CKD and various cardiovascular risk factors are listed in Table 2. eGFR correlated significantly and negatively with age, sex, prior CVD, the presence of AF, cardiogenic cerebral embolism, and positively with SAH. Meanwhile, the presence of CKD correlated significantly and positively with age, prior CVD, the presence of AF, cardiogenic cerebral embolism, and negatively with SAH in the univariate correlation analysis.

Compared with the group without CKD (mean eGFR 83.5 ± 17.9 mL/min/1.73m^2), mean age (75.9 vs. 69.0 y, P <0.05), the prevalence of AF (44% vs. 21%, P <0.001), a history of CVD (37% vs. 19%, P <0.001), the use of antiplatelet drugs (20.1% vs. 11.4%, P <0.05) and the use of anticoagulant drug (11.9% vs. 5.7%, P <0.05) were higher in that with CKD (mean eGFR 45.7 ± 13.5 mL/min/1.73m^2). Furthermore, in the prior CVD, the prior ischemic heart diseases and the prior valvular heart diseases were also higher in the group with than without CKD (both P<0.05). There were no significant differences in the prevalence of hypertension, systolic and diastolic blood pressure between groups with and without CKD. Among stroke subtypes, the incidences of cardiogenic cerebral embolism was significantly higher in the group with CKD as compared to that without CKD (36% vs. 26%, P <0.05) (Fig. 2). Meanwhile, the incidences of subarachnoid hemorrhage was significantly lower in the group with CKD as compared to that without CKD (4% vs. 11%, P <0.05) (Fig. 2). We performed the logistic regression analysis to determine whether CKD was closely associated with cardiogenic cerebral embolism. However, the presence of hypertension and AF were independently associated with cardiogenic cerebral embolism (Table 3).

Furthermore, we analyzed the relationship between in-hospital mortality and CKD in the study population. Of the 451 patients, 11 patients died during hospitalization. In these patients, the patients with and without CKD were 6 and 5, respectively. The causes of death were 5 with intracerebral hemorrhage (3 with and 2 without CKD), 6

with cardiogenic cerebral embolism (2 with and 1 without CKD) and 3 with SAH (1 with and 2 without CKD). The rate of in-hospital death tended to higher, but not significantly higher, in the patients with than without CKD (4.5% vs. 1.6%, P=0.068).

Discussion

CKD stages 3–4 is an independent risk factor for ischemic and hemorrhagic stroke, with a relative risk of 1.4 to 2.0 (4, 5). The relative risk of stroke in CKD 5D patients was estimated to be 5–10 times that of the age-matched general population 119 with an overall stroke rate of about 4% per year (8). However, the impact of CKD on acute stroke subtypes in Japan is scarce. Therefore, we retrospectively evaluated the impact of decreased eGFR at the time of admission on stroke and its subtype in the database of Japanese acute ischemic stroke at our hospital. In the present study, we clearly showed the prevalence of CKD in about 30% of Japanese acute stroke patients, and those patients were older, had a significantly higher prevalence of AF and prior CVD and a higher rate of cardiogenic cerebral embolism compared with patients without CKD.

AF is a significant risk factor for ischemic stroke and heart failure events, and is also associated with increased risks of total and cardiovascular death, especially due to stroke (9, 10). Several clinical and population-based studies have shown that the prevalence of AF is independently associated with decreased eGFR and increased levels of urinary albumin (11-13). A recent study reported that decreased eGFR is associated with an increased risk of subsequent new onset AF in a large scale of community-based cohort (14). In the present study, among the 451 patients, the most stroke subtype was cardiogenic cerebral embolism in 129 (29%). Meanwhile, 134 (30%) had CKD with eGFR <60 mL/min/1.73m^2, and those patients were older, had significantly higher prevalence of AF and prior CVD and higher rate of cardiogenic cerebral embolism compared with patients without CKD. The use of antiplatelet and anticoagulation drugs was also higher in the group with than without CKD in parallel with the prior CVD. Furthermore, both eGFR and the presence of CKD were significantly correlated with age, prior CVD, the presence of AF, cardiogenic cerebral embolism and SAH in the univariate correlations. In the logistic regression analysis, the presence of hypertension and AF, but not CKD, were associated with cardiogenic cerebral embolism. However, it might be difficult to evaluate these associations because hypertension and AF are closely associated with CKD. Recently, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study has shown that decreased eGFR increases thromboembolic risk in patients with AF (15). Although it has been revealed that age, systolic blood pressure, left ventricular mass, and left atrial size are related to the incidence of AF (9,

10), there is the possibility that these factors might mediate the association between CKD and AF incidence observed in the present and other studies, because GFR generally decreases with age, and pressure and volume load augmented by renal dysfunction directly increases arterial stiffness, left ventricular mass, and left atrial size (16, 17). Furthermore, increased thromboembolic risk appear to relate to abnormality of procoagulant and inflammatory pathways affected by CKD (1, 18). These findings show that CKD might play a major role in not only arteriosclerosis, but also in the onset of AF and subsequent embolisms. We recently reported that blood pressure control itself is essentially important for preventing AF in the general patient population (19), because poor blood pressure control seemed to have an affect on worsening AF possibly via left ventricular diastolic dysfunction, followed by left atrial overload. Although the clinical dilemma is that bleeding risk increases during warfarin anticoagulation (20), not only strict blood pressure control but also measures to prevent the onset of AF seem important for prevention of stroke in patients with CKD.

We also found that the group with CKD was significantly less prevalent in the SAH than the group without CKD. Previous reports have suggested that CKD might be a strong predictor of cerebral hemorrage including SAH (21, 22). In the present study, the prevalence of SAH in the group with CKD may have been relatively low because the prevalence of cardiogenic cerebral embolism was higher in the group with than without CKD. Further studies with a larger group of patients are needed to examine the possible relationship between the onset of SAH and CKD.

There are some limitations in this study. First, this study is a cross-sectional study, therefore, we could not analyze the long-term prognosis of patients. However, the rate of in-hospital death tended to higher, but not significant, in the patients with than without CKD in the present study as similar as previously reported (2, 4). Second, we did not evaluate the left ventricular systolic/diastolic function and the size of left atrium in all patients. Patients with both heart failure and atrial fibrillation have a high risk of stroke (9, 10), thus it is very important to evaluate the cardiac function in all stroke patients.

In conclusion, the prevalence of CKD was about 30% of acute stroke patients, and those patients had a significantly higher prevalence of AF and a higher rate of cardiogenic cerebral embolism compared with patients without CKD, suggesting that increased left atrial volume is predisposed to AF, followed by stroke caused by cardiogenic cerebral embolism in patients with CKD.

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Figure legends

Fig. 1. Distribution of eGFR and of CKD stages at baseline among the 451 subjects.

Fig. 2. Prevalence of stroke subtypes with and without CKD. Each category was compared using the chi-square test.

Table 1. Baseline Characteristics

	Total	CKD(-)	CKD(+)	P
N	451	317	134	
Age (years)	71.1±12.0	69.0±12.2	75.9±9.9	<0.05
Sex, M/F	239/212	164/153	75/59	NS
Hypertension	409 (91%)	287 (91%)	122 (91%)	NS
Diabetes	91 (20%)	66 (21%)	25 (19%)	NS
Dyslipidemia	75 (17%)	53 (17%)	22 (16%)	NS
Smoking	32 (7%)	27 (9%)	5 (4%)	NS
Prior CVD	109 (24%)	60 (19%)	49 (37%)	<0.001
ischemic stroke	46 (10.2%)	29 (9.1%)	17 (12.7)	NS
intracerebral hemorrhage	6 (1.3%)	3 (1.0%)	3 (2.2%)	NS
ischemic heart diseases	28 (6.2%)	14 (4.4%)	14 (20.5%)	<0.05
chronic heart failure	10 (2.2%)	5 (1.6%)	5 (3.7%)	NS
valvular heart diseases	9 (2.0%)	3 (1.0%)	6 (4.5%)	<0.05
peripheral artery diseases	7 (1.6%)	3 (1.0%)	4 (3.0%)	NS
abdominal aortic aneurysm	3 (0.7)	2 (0.6%)	1 (0.8%)	NS
Atrial fibrillation	127 (28%)	68 (21%)	59 (44%)	<0.001
Systolic BP (mmHg)	168±37	169±37	164±37	NS
Diastolic BP (mmHg)	89±22	90±22	86±22	NS
Pulse pressure (mmHg)	79±29	79±29	79±30	NS
Heart rate (bpm)	78±17	77±16	78±19	NS
Hemoglobin (g/dL)	13.2±1.9	13.4±1.8	12.8±2.0	NS
Total cholesterol (mg/dL)	184±33	180±34	188±32	NS
Triglycerides (mg/dL)	138±96	151±120	125±65	NS
HDL-C (mg/dL)	56±16	53±15	59±16	NS
LDL-C (mg/dL)	107±28	104±26	110±28	NS
Uric acid (mg/dL)	5.3±1.4	5.2±1.4	5.4±1.5	NS
Serum creatinine (mg/dL)	0.87±0.88	0.66±0.16	1.38±1.49	<0.001
eGFR (mL/min/1.73m^2)	72.3±24.1	83.5±17.9	45.7±13.5	<0.001
Previous treatment				
antihypertensive drug	248 (55.0%)	170 (53.6%)	78 (58.2%)	NS
antiplatelet drug	63 (14.0%)	36 (11.4%)	27 (20.1%)	<0.05
anticoagulant drug	34 (7.5%)	18 (5.7%)	16 (11.9%)	<0.05
cardiovascular surgery	19 (4.2%)	11 (3.5%)	8 (6.2%)	NS

pacemaker implantation	9 (2.0%)	5 (1.6%)	4 (3.0%)	NS

Variables are presented as mean±SD, or percentage. CVD; cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate.

Table 2. Univariate correlations between eGFR or presence of CKD and cardiovascular risk factors and each stroke subtype.

	eGFR		CKD (yes =1, no=0)	
	R	P	R	P
Age (years)	-0.296	<0.001	0.262	<0.001
Sex (M=1, F=0)	-0.133	<0.01	0.039	NS
Hypertension (yes =1, no=0)	-0.031	NS	0.008	NS
Diabetes (yes =1, no=0)	-0.004	NS	-0.025	NS
Dyslipidemia (yes =1, no=0)	-0.039	NS	-0.004	NS
Smoking (yes =1, no=0)	0.064	NS	-0.085	NS
Prior CVD (yes =1, no=0)	-0.216	<0.001	0.188	<0.001
Atrial fibrillation (yes =1, no=0)	-0.236	<0.001	0.229	<0.001
cardiogenic cerebral embolism	-0.123	<0.01	0.104	<0.05
unclassified cerebral infarction	0.002	NS	0.037	NS
atherothrombosis	-0.030	NS	0.002	NS
lacunar infarction	0.084	NS	-0.060	NS
transient ischemic attacks	-0.005	NS	-0.001	NS
cerebral hemorrhage	-0.007	NS	-0.010	NS
subarachnoid hemorrhage	0.128	<0.01	-0.121	<0.05

Pearson's univariate correlation coefficients. Each stroke subtype: yes=1, no=0.

Table 3. Logistic regression analysis of the cardiogenic cerebral embolism

	Odds ratio	95% CI	P
Age	0.997	0.975 - 1.019	0.792
Sex	1.031	0.790 - 2.143	0.300
Hypertension	2.020	1.105 - 3.692	0.022
Diabetes	0.410	0.188 - 0.896	0.075
Dyslipidemia	0.597	0.291 - 1.226	1.226
Smoking	1.754	0.688 - 4.473	0.240
Prior CVD	1.127	0.641 - 1.985	0.678
Atrial fibrillation	10.872	6.344 - 18.631	<0.001
CKD (eGFR <60 mL/min/1.73m^2)	1.283	0.733 - 2.248	0.095

CI, confidence interval.

Figure 1

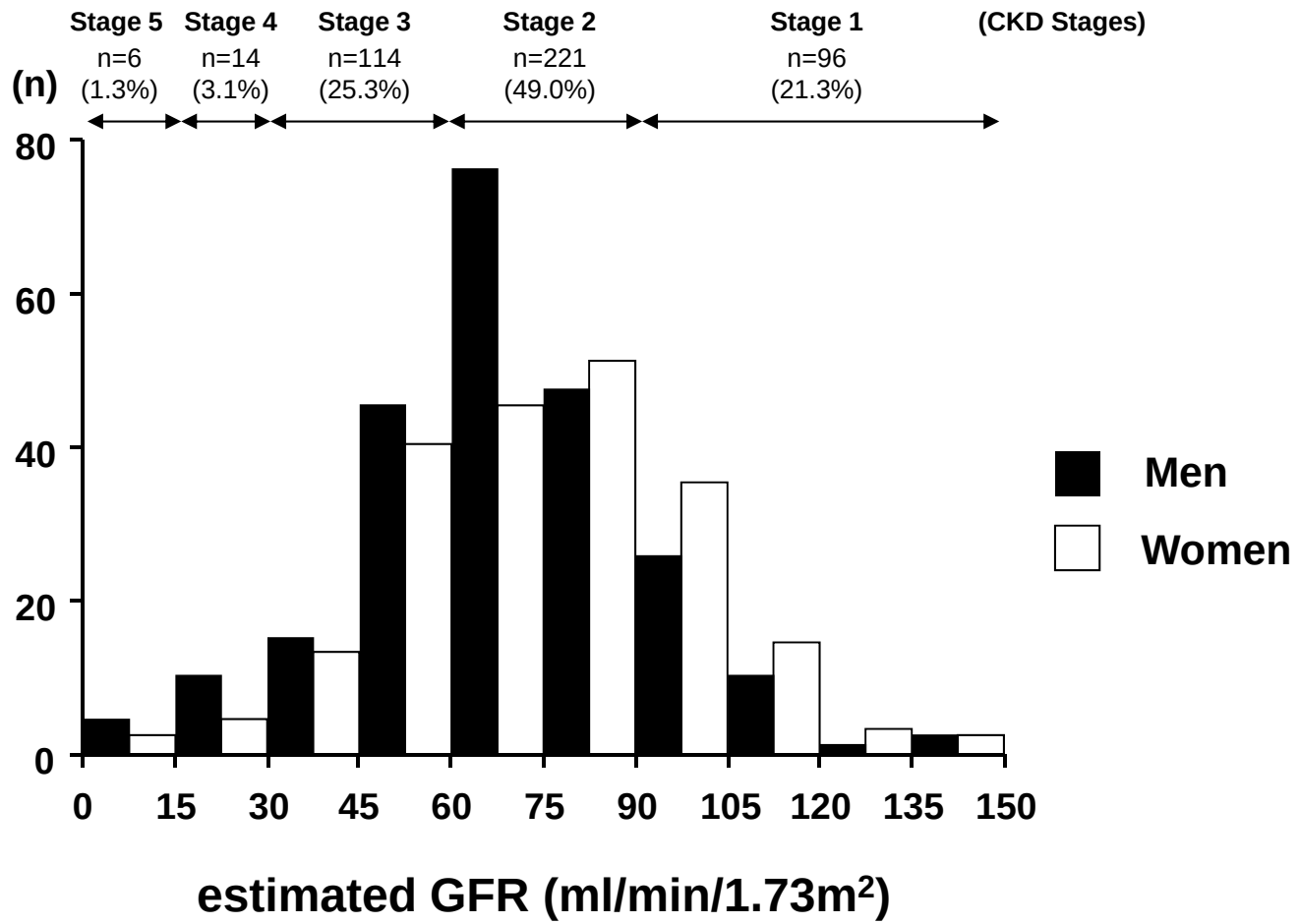

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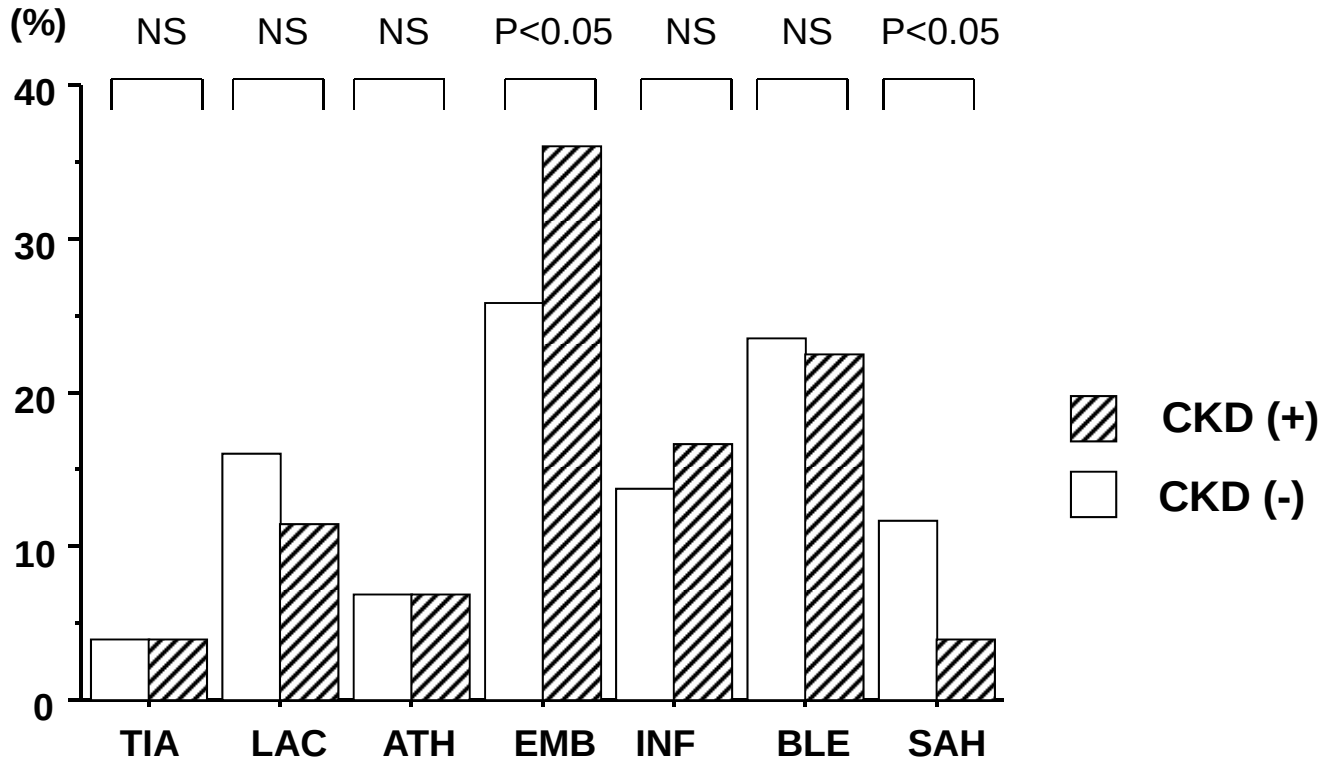
Figure 2



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