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Renal Function Predicts Outcomes in Ischemic Stroke and Hemorrhagic Stroke

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Abstract: ***Renal dysfunction has been suggested as risk factor and prognostic factors in cerebrovascular diseases. Regarding the association of renal dysfunction with stroke subtypes, conflicting results have been observed. The aim of this study was to evaluate renal function and the impact of renal function on in-hospital outcomes in hospitalized patients with ischemic and hemorrhagic stroke. We conducted a retrospective cohort study in a sample of 311 hospitalized patients with acute stroke at Department of Neurology, Khmer Soviet Friendship Hospital from January 1, 2020 to June 30, 2021. Mann-Whitney test was used to compare the values of variables between the 2 groups. Multivariate logistic regression was used to identify the independent risk factors for mortality in stroke. In analysis of the impact of severity, variables were standardized for age by arbitrary inclusion of this variable in the model. In addition, for models with a larger number of independent variables, stepwise method was used to eliminate variables (as a criterion for accepting the value of the Wald statistics). Of 311 stroke patients, 52.73% were male and the mean age of 62 years old. There were 84.88% ischemic stroke. The mean serum creatinine on admission in patients with both types of stroke was significantly higher in hemorrhagic stroke. Multivariate analysis showed that independent predictors of severity in patients with ischaemic stroke were: ischemic heart disease or prior myocardial infarction, diabetes, admission glucose and eGFR on admission. Also, multivariate analysis showed that independent predictors of mortality in patients with haemorrhagic stroke were: age and admission glucose. Patients with haemorrhagic stroke, in particular with acute kidney injury during hospitalisation had significantly worse outcomes than patients with ischaemic stroke. Assessment of kidney function is prerequisite to employ the necessary measures to decrease the risk of in-hospital severity among patients with acute stroke. Appropriate approach to patients with renal dysfunction (adequate hydration, avoidance of nephrotoxic drugs, drug dose adjustment etc) should be considered as preventive and therapeutic strategies in the management of acute stroke.***

Keywords: Stroke, Chronic Kidney Disease, Cardiovascular Risk, Renal Function, Hospital Outcomes

1. Introduction

Stroke and chronic kidney disease (CKD) are major health problems worldwide but are usually considered separately. One in every four men and one in every five women will suffer a stroke by 85 years of age. Stroke is the second biggest cause of death and the primary cause of chronic neurological disability world-wide [1]. In the USA, stroke accounted for 5.2% of all deaths and 6–8% (US$66.5 billion) of federal health care spending in direct and indirect medical costs in 2010 [2]. CKD is a similarly large public health challenge which affects around 8% of the population (though >50% of the population aged over 70 years) and accounted for 22% of Medicare expenditure in 2006 [3]. In addition to consuming resources, both stroke and CKD are associated with premature death, falls, dementia and decreased quality of life [4].

Stroke and CKD share common cardiovascular risk factors including high blood pressure, smoking, high cholesterol and diabetes [5]. CKD has also been identified as a risk factor for stroke, with a glomerular filtration rate (GFR) of <60 mL/ min/1.73m2 and albuminuria independently associated with stroke [6]. It remains unc ertain how the magnitude of this increased risk changes as CKD progresses and whether GFR and albuminuria act alone or in combination to modify stroke risk. The aim of this study was to evaluate renal function and the impact of renal function on in-hospital outcomes in patients with ischemic and hemorrhagic stroke who were hospitalized at Department of Neurology, Khmer Soviet Friendship Hospital.

2. Material and Methods

It was a retrospective analysis of prospectively collected data of stroke patients admitted from January 1, 2020 to June 30, 2021. Stroke was diagnosed based on neurological examination and admission computed tomography scan. Serum creatinine was measured on admission and during hospitalization (within 48 hours and more than 7 days -the last before discharge). The method for creatinine measurement was IDMS traceable. The assessment of renal function was based on the glomerular filtration rate estimated by the MDRD equation (Modification of Diet in Renal Disease), the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration). Data on serum creatinine drawn at the time of hospital presentation were collected. Serum creatinine was measured by the clinical chemistry laboratory photometrically using the Jaffe reaction, with a coefficient of variation of 6.4% at the level of 0.7 mg/dl and 2.2% at the level of 5.6 mg/dl. We calculated the eGFR using the abbreviated MDRD equation as follows:

$$eGFR = 186 \times Scr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female})$$

Where *eGFR* is the estimated glomerular filtration rate in milliliters/minute/1.73 square meters, *Scr* is the serum creatinine concentration in milligrams/deciliter and *age* is in years.

2.1 Study Setting and Population

The All patients age equal to or more than 18 years old who admitted to Department of Neurology, Khmer-Soviet Friendship Hospital with first acute stroke. Patients who fulfilled the inclusion and exclusion criteria below were counted into the study. Patients with first acute stroke, with complete medical record and head CT or MRI were in cluded in the study. Those patients experienced an in-hospital stroke or transient ischemic attack, head trauma, brain tumor, and subarachnoid hemorrhage, undergo thrombolysis, history of kidney transplantation, pregnant and lactating women were not enrolled in the study.

The study was based on a questionnaire (case record form) conducted by main investigator. All data will be collected retrospectively from medical records available from hospital admission to discharge. Medical comorbidities, including a history of atrial fibrillation, heart failure, diabetes, coronary artery disease, hypertension, hyperlipidemia, stroke or transient ischemic attack, and smoking within the past year will be abstracted based on documentation in the medical record alone, and assigned binary values. Serum creatinine was measured on admission and during hospitalization (within 48 hours and more than 7 days-the last before discharge). NIHSS scores are measured on admission or estimated retrospectively using data from admission physical exams by a validated method. The method for creatinine measurement was IDMS traceable. The assessment of renal function was based on the glomerular filtration rate estimated by the MDRD equation (Modification of Diet in Renal Disease), the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration)

2.3 Data Analysis

All data were stored in Excel and data entry was carried out with coding and verification. For description of baseline characteristics, number and percentage were used for categorical variables, and mean with standard deviation or median with 25th-75th percentile range were used for continuous variable according to their distribution. Mann-Whitney test was used to compare the values of variables between the 2 groups. The relationships between qualitative variables were assessed using the Fisher's exact test or the Fisher- Freeman-Halton Exact Test (compared the dichotomous variables higher than 2). Multivariate logistic regression was used to identify the independent risk factors for mortality in stroke. In analysis of the impact of severity, variables were standardized for age by arbitrary inclusion of this variable in the model. SPSS Version 22 was used for data analysis, and an alpha of 0.05 was used to determine statistical significance.

2.4 Ethical Consideration

This study was conducted with approval from the committee of Khmer Soviet Friendship Hospital. To avoid having patients' privacy disclosure and to secure patient's confidentiality, there was no any identification of the patients on our case record form and database.

3. Results

3.1 Demographic Data

The demographic data are presented in Table 1. There were 311 subjects enrolled in the study, 164 (52.73 %) were males and 147 (47.27%) were females. There is no significant association among gender group. The median age for the study population was 62 years (SD ±8.67 years) and almost identical. There was an association between hypertension (71.70%), diabetes (63.66%), and atrial fibrillation (11.25%) in this study.

Table 1: Demographic data of sample characteristics

Characteristics	Total Subjects (n=311) No. (%)	Ischemic (n=264) No. (%)	Hemorrhagic (n=47) No. (%)	p-value
Age (years)	62 (±8.67)*	64 (±10.02)	60 (±8.05)	<0.01
Female	147 (47.27)	125 (47.34)	25 (53.19)	0.82
Male	164 (52.73)	139 (52.66)	22 (46.81)	0.78
Hypertension	223 (71.70)	190 (71.96)	38 (80.85)	**0.02****
Diabetes	198 (63.66)	186 (70.45)	12 (29.55)	**0.01****
Atrial fibrillation	35 (11.25)	29 (10.98)	6 (12.76)	**<0.01****
Carotid artery stenosis	21 (6.75)	18 (6.81)	3 (6.38)	0.56
Valvular heart disease	16 (5.14)	14 (5.30)	2 (4.25)	0.27

*Median (IQR). *Statistical significance $p < 0.05$.

3.2 Assessment of Renal Functions

The mean serum creatinine of study population on admission was 1.05mg/dL (±0.67). Among patients with ischaemic stroke the mean serum creatinine was significantly higher compared to patients with haemorrhagic (p<0,01).

At admission 82.8% of patients with ischemic stroke and 89.36% of patients with hemorrhagic stroke had normal serum creatinine (1.2mg/dL in females and 1.4 mg/dL in males, according to WHO). Elevated serum creatinine (p=0.03) occurred more frequents in patients with ischemic stroke. Table 2. Table 3 shows eGFR by CKD-EPI at admission in patient with normal serum creatinine with regard to gender.

Table 2: The mean serum creatinine level and type of stroke

			Stroke	Type of stroke		*p*
				IS	HS	
Serum creatinine at admission	Within normal ranges <1.2 (mg/dL) females <1.4 (mg/dL) males	N	245	203	42	
		%	78.8	82.8	89.36	
	Elevated ≥1.2 (mg/dL) females ≥1.4 (mg/dL) males	N	66	61	5	**0.03**
		%	21.2	23.2	10.6	
Total		N	311	264	47	
		%	100	100	100	

IS (ischemic stroke); HS (hemorrhagic stroke)

Table 3: eGFR by CKD-EPI at admission in patients with normal serum creatinine with regard to gender

Type of Stroke	Gender					
	Total Stroke			Males <1.4 (mg/dL)		Females<1.2 (mg/dL)
	N	eGFR CKD-EPI mL/min/1.73m^2	N	eGFR CKD-EPI mL/min/1.73m^2	N	eGFR CKD-EPI mL/min/1.73m^2
Ischemic	264	72.35 (15.33)	139	80.83 (15.27)	125	65.87 (12.78)
Hemorrhagic	47	80.21 (19.67)	22	86.03 (19.80)	25	15.34 (17.19)
P		**<0.05**		>0.05		**<0.01**

The mean serum creatinine in patients with hemorrhagic stroke was significantly higher than ischemic stroke, 1.30 (±1.09) vs 1.23 (±1.17). There is a significant difference, p<0.05. The eGFR using the CKD-EPI equation on admission in patients with hemorrhagic stroke was significantly higher compared to ischemic stroke (76.62±22.89 ml/ min/1,73m2 vs 72.27 ±25.78 ml/ min/1,73m2 respectively (p<0,05). There were significant differences between eGFR on admission in patients with haemorrhagic stroke depending on the outcome (p<0,05) (Table 4).

Table 4: Kidney function in patients with hemorrhagic and ischemic stroke with regard to outcome

	End of treatment	Ischemic Stroke (N=264)		Hemorrhagic Stroke (N=47)	
		Mean (±SD)	P	Mean (±SD)	P
Creatinine at admission (mg/dL)	Stroke total	1.23 (±1.17)	**<0.05**	1.30 (±1.09)	**<0.05**
eGFR by CKD-EPI at admission (ml/min/1.73m2)	Stroke total	72.27 (25.78)	**<0.05**	76.62 (22.89)	**<0.05**

The eGFR (by CKD-EPI) measured more than 7 days (the last before discharge) of the study population was 67.57 (±24,77) ml/min/1,73m^2. The mean serum creatinine (the last before discharge) in patients with hemorrhagic stroke was 14. (±1.3 mg/dL), p=0.05. There were significant differences in eGFR (using the CKD-EPI equation) measured more than 7 days in patients with ischemic and hemorrhagic stroke, depending on the outcome (p<0.05). Table 5.

Table 5: Kidney function after 7 days of hospitalization in patients with hemorrhagic and ischemic stroke with regard to outcome

	End of treatment	Ischemic Stroke (N=264)		Hemorrhagic Stroke (N=47)	
		Mean SD	P	Mean SD	P
Creatinine >7days (mg/dL)	Stroke total	1.13 (±0.56)	0.08	1.4 (±1.3)	**0.05**
eGFR by CKD-EPI >7days (ml/min/1.73m2)	Stroke total	68.12 (±23.34)	**<0.05**	66.56 (±30.21)	**<0.05**

3.3 Risk Factors for Severity

Multivariate analysis showed that independent predictors of severity in patients with ischemic stroke were: ischemic heart disease or myocardial infarction in the past (P = 0.005; OR = 1.23), diabetes (p = 0.03 ; OR = 1.82), admission glucose (p <0.001; OR = 1.01), and eGFR on admission (p =0.001; OR = 0.98). Table6. Multivariate analysis, the CKD-EPI equations, showed that independent predictors of mortality in patients with hemorrhagic stroke were, age (P=0.1, OR=1.02) and admission glucose (P=0.01; OR=1.82). Table 7.

Table 6: Risk factors for severity in stepwise multivariate regression in ischemic stroke

Parameters	Full model				Model after elimination			
	OR	95%CI		P	OR	95%CI		P
Ischemic stroke								
Age	1.076	0.96	1.04	0.23				
Gender	1.01	0.51	1.75	0.89				
Hypertension	0.76	0.30	2.03	0.61				
Diabetes	1.89	0.98	3.01	**0.05**	1.82	1.01	3.34	**0.03**
Myocardial infarction	1.00	1.01	1.01	**0.001**	1.23	0.12	0.67	**0.005**
Glucose at admission (mg/dL)	0.88	0.89	0.92	**0.001**	1.01	1.00	1.01	**0.001**
eGFR by CKD-EPI*	1.02	0.67	1.56	**0.001**	0.98	0.95	0.98	**0.001**
Creatinine at admission (mg/dL)	1.02	0.67	1.56	0.89				

*eGFR by CKD-EPI at admission (mL/min/1.73m2); OR-odds ratio, CI-coefficient interval

Table 7: Risk factors for severity in stepwise multivariate regression in hemorrhagic stroke

Parameters	Full model				Model after elimination			
	OR	95%CI		P	OR	95%CI		P
Hemorrhagic stroke								
Age	1.02	1.00	1.11	**0.02**	1.06	1.02	1.09	**0.01**
Gender	0.56	0.12	1.67	0.25				
Hypertension	2.57	0.18	2.34	0.20				
Diabetes	1.31	0.24	5.27	0.71				
Myocardial infarction	0.26	0.05	1.30	0.15				
Glucose at admission (mg/dL)	1.35	0.23	5.23	**0.001**	1.02	1.01	1.04	**0.001**
eGFR by CKD-EPI*	1.02	0.98	1.02	0.95				
Creatinine at admission (mg/dL)	1.12	0.52	2.45	0.71				

*eGFR by CKD-EPI at admission (mL/min/1.73m2); OR-odds ratio, CI-coefficient interval

4. Discussion

In our study, we found that 23.2% of ischemic stroke patients and 10.6% of hemorrhagic stroke patients had elevated serum creatinine levels at admission, which is higher than reported in past research. Previous studies [7, 8, 9] have linked elevated creatinine and lower eGFR levels to increased cardiovascular mortality and stroke risk. Renal function, often measured upon hospital admission, is best assessed using eGFR, although variations in age and gender can affect these measurements. Our study noted significant age differences between ischemic (average age 64 years) and hemorrhagic (average age 60 years) stroke patients, while gender distribution did not significantly differ. Multiple studies have demonstrated that a reduced glomerular filtration rate (eGFR) and/or albuminuria significantly increase the risk of stroke independently [8,10,11]. Lee et al. found that patients with a baseline eGFR <60 ml/min/1.73 m² had a 43% higher risk of future stroke [12]. Sweileh et al. identified creatinine clearance, post-stroke complications, and type of stroke as predictors of in-hospital mortality in stroke patients [13]. In our study, chronic kidney disease (CKD) defined as eGFR <60 mL/min/1.73 m² was present in 28.2%-30.8% of stroke patients, similar to findings by Ovbiagele et al [14]. Other studies reported varying prevalence of CKD among stroke patients, with Xu et al. noting 47.7% [15]. Logistic regression indicated proteinuria, hyperglycemia, and anemia as independent risk factors for poor outcomes at 30 days post-stroke. The association between stroke and CKD is well established, but distinctions between stroke subtypes are often not made. Some research indicated that decreased GFR is a stronger risk factor for hemorrhagic stroke [7,11], while others found it linked to ischemic stroke [16]. High albumin/creatinine ratio was associated with both types. Additionally, reduced eGFR during acute stroke was linked to higher 3-year mortality and more acute complications post-discharge. In our study, hypertension was the most common comorbidity, followed by coronary artery disease. Multivariate analysis identified ischemic heart disease, past myocardial infarction, diabetes, glucose levels at admission, and eGFR as independent mortality predictors for ischemic stroke patients, while age and glucose levels were predictors for hemorrhagic stroke patients. Previous studies have also linked reduced creatinine clearance and high serum creatinine to increased mortality post-stroke [17].

Recognizing the limited routine measurement of creatinine during hospitalization for stroke patients, our study explored the impact of kidney function on stroke outcomes, revealing a high prevalence of acute kidney injury (AKI) particularly in hemorrhagic stroke patients. This study, the first of its kind in Poland, found AKI incidences of 20% in hemorrhagic and 8% in ischemic stroke patients. Comparatively, in Romania, the prevalence of AKI in stroke patients was 14.5% [18]. Our findings highlight the severe in-hospital impact of hemorrhagic stroke and emphasize the importance of kidney function assessment for improving stroke patient outcomes, especially in those with ischemic stroke.

5. Conclusion

Patients with haemorrhagic stroke experienced worsening of renal function during hospitalisation and had significantly worse outcomes than patients with ischaemic stroke. Ischaemic heart disease, diabetes, glucose level and renal function were risk factors for mortality in ischaemic stroke, while age and glucose level at admission in haemorrhagic stroke. The assessment of kidney function is prerequisite to employ the necessary measures to decrease the risk of in-hospital severity among patients with acute stroke.However, waiting for a baseline serum-creatinine is an unnecessary delay to emergency reperfusion treatment.

6. Limitation of the Study

A limitation might be that this study was a single-center with short follow-up, but with the same pattern of care. It is acknowledged that our results, although of clear and statistical significance, will need to be validated on a larger populatio.

Conflict of Interest Statement

All authors disclose no conflict of interest related to this submission.

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