RESEARCH ARTICLE

BASELINE RENAL DYSFUNCTION IN ACUTE ISCHEMIC STROKE PATIENTS: PREVALENCE AND IMPACT ON EARLY MORTALITY.

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Manuscript Info	*Abstract*

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Introduction:-

Stroke represents a continuously evolving medical and social problem, being the second leading cause of death globally after ischemic heart disease. It was responsible for 1 in 10 deaths worldwide[1]. Predictors of early mortality identification are considered to be an important issue for clinicians, so that specific therapies and management strategies can be applied to patients at high risk of mortality. However, limited information is available for short-term mortality after acute ischemic stroke [2].

Being a worldwide health problem as it was recorded in up to 15% of the adult population, chronic kidney disease (CKD) was considered a substantial risk for cardiovascular morbidity and mortality.[3] Stroke and CKD share a common cardiovascular risk factors including high blood pressure, smoking, high cholesterol and diabetes. Although CKD had been recognized as a risk factor for stroke with a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2, little is known about the prevalence of renal dysfunction in the setting of ischemic stroke [4].

Although CKD has been shown to be associated with poor early outcome after an acute myocardial infarction[5], there are only few data about the impact of renal dysfunction on mortality in patients suffering from ischemic strokes [6-8]

The aim of the present study was to assess the prevalence of renal dysfunction among acute ischemic stroke patients and its role on the early overall mortality.

Patients and Methods:-

This study was a prospective cohort study conducted on 889 consecutive patients with first ever ischemic stroke who were admitted to Intensive Care Unit (ICU) and stroke unit of Neurology Department as well as ICU of Internal Medicine Department of Zagazig University Hospitals during the period from May 2013 to May 2015. Patients who were hospitalized within 24 hours after symptoms onset with a CT-confirmed diagnosis of stroke were included and followed up for 30 days after admission or at least until death.

The follow-up data were available for 800 (90%) of patients who were included in the present analysis. Informed consents from patients or their relatives about the study were obtained. We excluded patients with neurological deficits due to hemorrhagic brain insult transient ischemic attack (TIA), non-stroke causes (e.g. brain tumor), patients on dialysis, patients with missed data or missed follow-up.

All patients of this study were subjected to the following: detailed medical and neurological history taking from either patients or relatives with stressing on stroke risk factors (especially ischemic heart disease, hypertension, smoking, diabetes) complete general and neurological examination with special emphasis on National Institute of Health Stroke Scale [9] (NIHSS) which was done on admission. Electrocardiography was performed for all patients.

Laboratory investigations were done within 24 hours of admission, including complete blood count, random blood sugar, lipid profile (cholesterol, LDL, HDL, and Triglycerides), liver and kidney function tests, uric acid and electrolytes measurements. Calculation of glomerular filtration rate using The Modification of Diet in Renal Disease (MDRD) Study equation[10] : eGFR (ml/min/1.73 m^2) = 175 x (S.creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female). CKD was defined according to the National Kidney Foundation definition as kidney damage reflected by an estimated GFR of <60 mL/min/1.73 m^2 of body surface area and state that prediction equations have greater consistency and accuracy than serum creatinine in the assessment of GFR. In addition, prediction equations are equivalent or better than 24-h urine creatinine clearance.[11]

All patients were subjected to Computed Tomography (CT) scan of the brain to confirm diagnosis of ischemic stroke. Repeated CT scans were done 48 hours later if the initial scans were normal. All survivors were followed up in outpatient clinics. This is study has been ethically approved by the local ethical committee of our faculty.

Statistical Analysis:-

Collected Data were tabulated and analyzed using IBM, SPSS Version Statistics 20.0 software package[12]. Descriptions of data in the form mean ± standard deviation (SD) for all quantitative variables, and frequency and percentage for all qualitative variables. The independent t-test or chi-square test was used to compare differences between the patient groups with and without renal dysfunction. Significance levels measured according to p value

(probability) where p<0.05 is significant and p<0.001 is highly significant. The associations between renal dysfunction and 30-day mortality were evaluated by multivariate Cox proportional hazards models. In the multivariate analysis, patients with eGFR<60 mL/min/1.73 m^2 were further subdivided into two categories: those with 60>eGFR≥30 and those <30 mL/min/1.73 m^2.

Results:-

The mean age of the 800 ischemic stroke patients was 62.25± 9.7 years (range, 37–86 years) with 424 were males (53%) and 376 were females (47%). According to the eGFR values, we found that 558 patients (69.8%) had normal renal function with eGFR≥60 ml/min/1.73m^2 and 242 of patients (30.2%) had renal dysfunction (eGFR < than 60 ml/min/1.73 m^2). 128 of the studied patients (16%) died within 30-days of stroke onset.

The demographics, clinical and laboratory characteristics of the studied patients were shown in **Table (1).** There was a significant difference between ischemic stroke patients with low and those with normal eGFR regarding most of the studied variables. The stroke severity (NIHSS) was higher in those with impaired than those with normal renal function (13.4±1.42, 8.98±2.75 respectively). Deceased patients were older than survivors and had a higher percentage of IHD, AF, high glucose levels and more renal impairment than survivors (**Table2**). In the multivariate Cox proportional hazard analysis model adjusted for age and sex **(Table 3)**, risk of 30-days mortality was significantly increased in patients with high blood glucose on admission, presence of AF and IHD, GFR < 60 ml/min/1.73 m^2, high NIHSS on admission, and high Uric acid. 30–days mortality risk was increased with 30≤ eGFR< 60 ml/min/1.73 m^2 (HR= 1.7, 95% CI=1.4–2, P=0.002) , eGFR < 30 (HR= 1.9, 95% CI= 1.6- 2.2) , stroke severity (HR= 1.5 , 95% CI=1.3-1.7 , P=0.001) , presence of atrial fibrillation (HR= 1.4 , 95% CI=1.1-1.7 , P=0.007) and IHD (HR= 2.1, 95% CI=1.6- 2.6). **Table (4)** showed predictors of overall mortality after acute ischemic stroke. The risk of mortality was related to age (per 10-year increase), baseline creatinine (per 1mg/dl increase), and NIHSS score (per 5-point increase).

Table 1:- Demographics, clinical and laboratory characteristics of the studied ischemic stroke patients (classified according to estimated Glomerular Filtration Rate , e GFR).

	Patients with eGFR<60 N=242	Patients with eGFR≥60 N=558	Test	P
Age	65.4±10.9	54.8±9.41	t=13.1	**<0.001**
Weight	71.4±5.9	73.5±5.75	t=-4.7	**<0.001**
Smoking, n (%)	54 (22.3)	147 (26.3)	χ^2=1.25	0.26
AF, n (%,)	90 (37.2)	112 (20)	χ^2=25.3	**<0.001**
IHD, n (%)	75 (30.9)	106 (18.9)	χ^2= 13.2	**<0.001**
SBP	160±25.64	150±27.6	t=4.80	**<0.001**
DBP	96.26±14.39	92.4±14.5	t=3.47	**<0.001**
NIHSS	13.4±1.42	8.98±2.75	t= 30.48	**<0.001**
HCT	40.92±4.1	41.78±4	t= 2.75	**<0.05**
Creatinine	2.32±1.3	1.03±0.21	t=15.35	**<0.001**
Urea	49.56±23.9	25.96±4.3	t=15.25	**<0.001**
eGFR	34.9±13.79	80.5±17.05	t= 33.348	**<0.001**
Uric acid	8.5±1.4	5.9±1.3	t=24.6	**<0.05**
Calcium	8.17±0.62	9.19±0.58	t=0.338	NS
Phosphate	3.1±0.61	3.23±0.54	t=2.86	**<0.05**
Serum Albumin	3.17±0.54	3.42±0.57	t=4.874	**<0.001**
Glucose	117.9 ± 68.89	131.9 ± 59.9	t=2.74	**<0.05**
LDL-C	114±17.51	113.74±14.0	t= 0.172	NS
Triglyceride	116.5±44.2	104.6±40.5	t=3.58	**<0.001**
Cholesterol	163.12±51.93	147.52±53.0	t=3.87	**<0.001**
Male-female ratio	79/ 163	200/358	χ^2=0.63	NS
30 -day mortality	48(19.8%)	80(14.3%)	χ^2= 9.6	**<0.01**

SBP: systolic blood pressure; **DPB**: diastolic blood pressure; **LDLC**: low density lipoproteins cholesterol; **HCT**: Haematocrit value ; **eGFR**; estimated glomerular filtration rate; **NIHSS**: National Institutes of Health Stroke Scale; **IHD**: ischemic heart disease ; **AF:** atrial fibrillation.

Table 2:- Comparison between survivors and deceased acute ischemic stroke patients within 30 days of admission.

	Survivors N=672	Deceased N=128	Test	P
Age	57.5±11.8	64.95±9.8	t= 7.61	**<0.05**
Weight	72.1±5.8	72±6.5	t= 166	NS
SBP	156.35±26.7	160±26.19	t= 1.44	NS
DBP	94.7±14.5	96.31±14.46	t= 1.15	NS
Smoking, n (%)	131 (19.5)	21 (16.4)	χ^2=0.8	NS
AF, n (%)	141 (20.98)	35(27.3)	χ^2=5.6	**0.01**
IHD, n (%)	127 (18.89)	32 (25)	χ^2=4.9	**0.02**
NIHSS	7.6±3.1	16.8±2.8	t= 19.718	**<0.001**
HCT	41.16±4.11	41.4±4.17	t= 0.513	NS
Creatinine	1.2±0.3	1.7±0.7	t= 7.943	**<0.001**
eGFR	50.9±26	43±23.8	t= 3.39	**<0.001**
Uric acid	5.7±2.05	8.79±1.65	t= 18.62	**<0.05**
Calcium	9.19±0.6	9.13±0.5	t= 0.813	NS
Phosphate	3.3±0.5	3.3±0.6	t= 0.023	NS
Albumin	3.2±0.5	3.2±0.5	t= 0.800	NS
Glucose	117±56.9	149.95±61.5	t= 5.62	**<0.001**
LDL-C	113.5±16.6	115.9±16.48	t= 1.158	NS
Triglyceride	111.67±43.6	118.35±41.5	t= 1.271	NS
Cholesterol	157.12±53.1	163.23±51.1	t= 1.23	NS

SBP: systolic blood pressure; **DBP**: diastolic blood pressure; **AF**: atrial fibrillation; **IHD**: ischemic heart disease; **NIHSS:** National Institutes of Health Stroke Scale**; HCT**: haematocrit value; **LDLC**: low density lipoproteins cholesterol.

Table 3:- Multivariate Cox proportional adjusted for age and sex hazard analysis determining the effect of different factors on 30 -day mortality of the studied patients .

	Sig.	HR	95% CI	
			Lower	Upper
AF	0.007*	1.4	1.1	1.7
IHD	0.0001**	2.1	1.6	2.6
Glucose	0.040*	1.2	1.0	1.4
60>eGFR≥30	0.002*	1.7	1.4	2
eGFR < 30	0.002*	1.9	1.6	2.2
Uric acid	0.009*	1.6	1.3	1.9
NIHSS	0.001*	1.5	1.3	1.7

AF: atrial fibrillation**; IHD:** ischemic heart disease**; NIHSS:**National Institutes of Health Stroke Scale **;e**GFR: estimated Glomerular filtration rate**.**

Table 4:- Predictors of mortality after acute ischemic stroke.

Variable	OR (95% CI)	P
Age (per 10-year increase)	1.8 (1.4-2.2)	**<0.001****
Baseline creatinine (per 1 mg/dl increase)	1.7 (1.4-2.0)	**<0.001****
NIHSS score(per 5-point increase)	1.6 (1.2- 2.0)	**<0.001****

NIHSS; National Institutes of Health Stroke Scale; **CI**: confidence interval; **OR**: odds ratio.

Discussion:-

Renal dysfunction   is considered a valuable predictor of poor outcomes including mortality in patients with ischemic stroke[13-15] as well as in the general population.[16-17]. Renal function can be roughly assessed by serum creatinine level but more accurately evaluated from estimated glomerular filtration rate (eGFR), which is usually automatically calculated in a clinical setting, based on serum creatinine and basic demographic findings.[18]

From this study, we observed that approximately one-third (30.2%) of the stroke patients had a low eGFR level (eGFR<60 ml per minute per 1.73 m^2). Also, this study showed that patients with renal dysfunction were older, had a higher prevalence of hypertension, a higher NIHSS score and a higher blood glucose level on admission. Similar results were found by Hoshino and colleagues[19] in their study among stroke patients with mild to moderate renal dysfunction. Tsagalis et al.,[20] observed a similar rates (28%) of renal dysfunction in acute stroke patients suggesting a significant prevalence of CKD in stroke sufferers .

Chronic kidney disease was defined as estimated glomerular filtration rate <60 ml/min/ 1.73m^2 according to Yahalom and colleagues [21] who showed in their study that CKD was present in 36% of patients with acute stroke based on MDRD formula and in only 18% if based on Mayo Clinic formula.

 It was postulate that the aetiology for the high prevalence of cerebrovascular disorders in patients with renal dysfunction is enhanced atherosclerosis [22-23]. In patients with CKD, advanced asymptomatic atherosclerosis in the carotid arteries compared with healthy control subjects was observed [24]. Moreover, Preston et al, [25] reported that the increased intima media thickness was directly related with the level of renal dysfunction.

This study showed that early mortality after acute ischemic stroke was quite high and even increased in patients with associated renal dysfunction. This increased risk of mortality appeared to be associated with severity of baseline renal dysfunction.

In this study, the 30-day mortality of all ischemic stroke patients was 16%, whereas it was 14.3% in patients with baseline eGFR $\geq$ 60 ml/min/1.73 m^2. Similar rates were reported from the European Registries of Stroke Collaboration in which 1-month mortality after stroke ranged from 13 to 27% [26]. While a lower rates of 13% were observed by Yahalom and colleagues.[21]

However a lower rate of 10% mortality at 30 -days were reported by De Jong et al., [27] in 998 patients with first-ever cerebral infarction. In addition 5% [28], 7.6% [29] and 8.2% [30] mortality at 30 days after stroke were reported in previous Studies.

The present study revealed that old age, presence of AF, IHD, baseline creatinine, and high uric acid level, low eGFR, higher NIHSS on admission were associated with early mortality. These results were in agreement with previous studies [31-32]

From this study, we observed a higher mortality rates (19.8%) in patients with baseline eGFR<60 ml/min/1.73 m^2 in comparison to those with normal eGFR (14.3%). Also, the severity of impaired kidney function was associated with increased risk of early mortality (odd ratio= 1.7,   95% CI =1.4- 2 , per 1mg/dl increase in serum creatinine). Similarly, Carter et al [33]. showed that serum creatinine level was a strong predictor of mortality in patients with ischemic stroke. Furthermore, other studies showed that low eGFR was associated with a higher in-hospital mortality rates. [3, 34]

Data from Nationwide Inpatient Sample study showed that among 1 million of stroke hospitalizations during the study period,   6.1% had a co- morbid diagnosis of CKD, and 9% of those with CKD died in hospital. Presence of CKD was independently associated with higher odds of dying during stroke hospitalization regardless of stroke type[8].

The association between kidney function and survival following an acute ischemic stroke could be due to shared risk factors underlying vascular diseases including age, diabetes mellitus, hypertension, AF, smoking, coronary artery disease and dyslipedimia. [35] In addition, Ovbiagele [8] stated that hospitalized stroke patients with CKD are less likely to receive evidence-based therapies compared to patients without CKD that contribute to poorer clinical outcomes in these patients. Other reasons for poor early outcomes in stroke patients with compromised kidney function include the association of CKD with conditions that hinder rapid recovery such as oxidative stress, elevated uremic toxins, including plasma dimethylarginine, electrolyte derangements, and procoagulation.[36]

Large sample size could be a point of strength in this study. However, some limitations should be mentioned. The diagnosis of CKD requires the presence of kidney damage for $\geq$3 months. GFR was only estimated   once, meaning that some patients with acute kidney injury may have been misclassified as having CKD. Also, no

differentiation was possible between the different subtypes of ischemic stroke as the localization and extension of ischemic stroke may have prognostic significance. Moreover, our center is a tertiary care center with a large referral base, so patients included may have more severe strokes than patients treated at community hospitals, which may explain higher mortality compared to other studies.

In conclusion, impaired kidney function (assessed by eGFR) was prevalent in patients presented with acute ischemic stroke and associated with increased early mortality. This finding suggests that eGFR can be added to the other known prognostic factors of ischemic stroke and emphasizes the importance of monitoring and proper management of kidney disease in those patients.

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