The Egyptian Journal of Hospital Medicine (January 2021) Vol. 82 (4), Page 689-694

The Impact of Acute Kidney Injury on Prognosis and Short-Term Outcome of Acute Ischemic Stroke

Samir Mohamed Attia[1], Mohamed Said Gomaa[2], Hesham Khairy Ismaeil[3], Mahmoud Ahmed Mohamed Eita*[4]
Departments of [1]Vascular Surgery, [2]Neurology Science, [3]Critical Care Medicine and [4]Emergency Medicine and Traumatology, Faculty of Medicine, Mansoura University, Egypt.
***Corresponding author:** Mahmoud Ahmed Mohamed Eita, **Mobile:** (+20) 01004735491,
E-Mail: mahmoudeita64@yahoo.com

ABSTRACT

Background: Stroke is the third leading cause of death and disability globally. After a stroke, neurological deficit leading to dysphagia and physical disability, physiological effects including changes in blood pressure and cerebral salt wasting, as well as investigations and treatments, can all potentially contribute to the development of acute kidney injury (AKI). Furthermore, older, comorbid patients are at greatest risk of AKI.

Objective: To investigate the impact of acute kidney injury on prognosis and short-term outcome of patients admitted for acute ischemic stroke.

Patients and methods: This was a prospective observational study which was carried out on 100 patients that diagnosed with ischemic stroke and arrived to Emergency Hospital, Mansoura University over a year from June 2019 to June 2020.

Results: The average Glasgow coma scale (GCS) among the studied cases was 15. Nearly half of the studied cases developed AKI. The majority of cases were discharged on an Organophosphorus compounds (OPC), while only 29 of which were died. Dead group demonstrated significant increase in serum creatinine after 3 days, AKI development and stay duration more than one week. Demographic characteristics and past history of medical diseases demonstrated insignificant differences among dead and living cases. AKI was demonstrated to be the only significant predator of mortality among the studied cases. AKI was a significant predictor of the survival duration. In contrast, ICU stay and stay duration were not significant predictors of survival.

Conclusion: Patients with acute ischemic stroke were at higher possibility for development of AKI, which was accompanied with worse outcomes.

Keywords: Acute kidney injury, Acute ischemic stroke.

INTRODUCTION

Stroke represents a continuously evolving medical and social problem, being the third leading cause of death after heart disease and cancer in developed countries **(1).** The diagnosis of ischemic stroke is established by a neurologist based on the presence of focal or global signs of cerebral dysfunction lasting more than 24 hours and with no apparent non-vascular cause. In addition, the diagnosis was confirmed by compatible findings of computed tomography or magnetic resonance imaging within 24 to 72 hours after admission, as defined by the World Health Organization criteria**(2).**

Several reports have indicated chronic kidney disease (CKD) to be an additional independent and powerful predictor for stroke outcome. In a cohort study of 2042 patients admitted for stroke, renal indices (serum urea and creatinine, creatinine clearance at admission) remained significant predictors of mortality even after adjustment for a variety of 'classical' risk factors: age, neurological presentation and comorbidities [congestive heart failure (CHF), ischemic heart disease (IHD), hypertension and smoking] **(3).**

AKI was defined by an increase of the serum creatinine in relation to baseline value at admission ≥ 0.3 mg/dL or a rise in the serum creatinine level by 1.5 times or more within the last 7 days after admission, as defined by Kidney Disease Improving Global Outcomes (KIDGO) **(4).** AKI has been a frequent complication after an acute cerebrovascular event, with an overall prevalence around 11.6%. More advanced age, presence of heart failure, diabetes, and ischemic heart disease have been associated with a higher risk of developing AKI after stroke **(5)** and the presence of AKI has been associated to higher mortality risk both in the short-term and long-term after an ischemic stroke**(6).**

Patients with reduced renal function are at high risk for the subsequent development of cardiovascular disease (CVD) including stroke. Although acute stroke is an emergency disease and shares the same atherosclerotic risk factors with ischemic heart disease, the association of renal function and stroke is poorly investigated**(7). MacWalter *et al.* (3)** showed in a larger group of acute stroke patients that mortality was higher among patients with reducedrenal function on admission.

The aim of our present study was to investigate the impact of acute kidney injury on prognosis and

Received:18 /10 /2020
Accepted:6 /12/2020

short-term outcome of patients admitted for acute ischemic stroke.

PATIENTS AND METHODS

This was a prospective observational study, which was carried out on 100 patients that diagnosed with ischemic stroke and arrived to Emergency Hospital, Mansoura University over a year from June 2019 to June 2020.

Inclusion criteria: Aged 18 or older, first-ever ischemic stroke confirmed by a CT and both genders.

Exclusion Criteria: Aged less than 18, pregnancy, previous intracranial hemorrhage, previous ischemic stroke and major surgery within last 6 weeks.

Methods:

I) Full history taking: Personal history and past medical history.

II) Clinical examination:

- **General examination:** Level of consciousness according to Glasgow coma scale (GCS), blood pressure, heart rate respiratory rate, urine output.
- **Neurological examination:** Mental status examination (Glasgow coma scale, intracranial pressure by fundoscopy), cranial nerve examination, motor system, deep tendon reflexes, sensation and cerebellum.

III) Investigations:

- **Laboratory:** CBC, ABG, serum creatinine and INR.
- **Radiology:** CT brain and ECG.

IV) Management:

- **Primary survey and resuscitation:**
  - **A = Airway opening and maintenance of airway.**
  - **B = Breathing and ventilation.**
  - **C = Circulation.**
  - **D = Disability:** neurological status and Glasgow coma scale (GCS).
  - **E = Exposure**: segmental exposure.
- **Secondary survey** (from head to nail examination: head, neck, chest, abdomen, pelvis, lower limb, upper limb) and vital sign (pulse, blood pressure, respiratory rate).

Ethical consideration:

The research approval of the study was obtained from IRB of Faculty of Medicine at Mansoura University before starting the study. The researcher clarified the objective and aim of the study to the subjects included in the study. The researcher assured maintaining anonymity and confidentiality of subjects' data. Every patient signed an informed written consent for acceptance of the operation and the research.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA).

Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) and Fishers exact test were used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation) median, and range.

Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data) and Mann-Whitney test was used to compare the nonparametric data. P value < 0.05 was considered significant.

RESULTS

The age, sex, and medical history are shown in table 1.

Table (1): Age, sex, medical history of the studied cases

	No	%
Sex:		
Male	73	73.0
Female	27	27.0
Age		
Mean±SD	66.61±9.63	
Median (Range)	64.0 (49.0-93.0)	
Medical history:		
Diabetes mellitus (DM)	53	53.0
Hypertension	56	56.0

The blood pressure, laboratory findings and admission to ICU are shown in table 2.

Table (2): Laboratory results and ICU stay among studied groups

	N=100	%
SBP		
Mean±SD	137.20±20.45	
Median (range)	130.0(100.0-200.0)	
DBP		
Mean±SD	82.50±8.33	
Median (range)	80.0 (60.0-110.0)	
Glasgow coma scale (GCS)		
Median (range)	15.0 (12.0-15.0)	
CT brain		
normal	60	60.0
ischemic	40	40.0
Serum creatinine on admission		
Mean±SD	1.022±0.16	
Median (range)	1.0(0.6-1.3)	
Serum creatinine after 3 days		
Mean±SD	1.848±0.83	
Median (range)	1.55(0.9-3.6)	
AKI		
Negative	51	51.0
Positive	49	49.0
ICU stay		
No	46	46.0
Yes	54	54.0
Stay duration more than 10 days		
-ve	47	47.0
+ve	53	53.0

Overall, 29 cases died while the majority of cases (71 cases) were discharged on an OPC (Table 3).

Table (3): Outcome and mortality incidence among studied cases

	N=100	%
Mortality within 10 days		
-ve	71	71.0
+ve	29	29.0
Outcome		
Dead	29	29.0
OPC	71	71.0

Both live and dead cases demonstrated insignificant differences in terms of age, sex, diabetes mellitus (DM) and hypertension (HTN) as shown in table 4.

Table (4): Demographic risk factors affecting mortality incidence among studied cases

	Alive N=71	Died N=29	Test of significance
Age/Years			t=0.60
mean±SD	66.24±9.37	67.52±10.36	p=0.55
Sex	N (%)	N (%)	
Male	55 (77.5)	18 (62.1)	χ^2=2.48
Female	16 (22.5)	11 (37.9)	p=0.116
DM	N (%)	N (%)	
-ve	32 (45.1)	15 (51.7)	χ^2=0.366
+ve	39 (54.9)	14 (48.3)	p=0.545
Hypertension	N (%)	N (%)	
-ve	31 (43.7)	13 (44.8)	χ^2=0.011
+ve	40 (56.3)	16 (55.2)	p=0.915

t:Student t test χ^2=Chi-Square test

There was highly statistically significant increase in dead group compared to live ones as regards serum creatinine after 3 days, AKI development and stay duration more than one week (Table 5).

Table (5): Laboratory results and acute kidney injury affecting mortality incidence among studied cases

	Alive (N=71)	Died (N=29)	Test of significance
SBP	137.04±19.08	137.58±23.85	t=0.120 p=0.905
DBP	81.83±8.67	84.14±7.33	t=1.26 p=0.211
GCS	15.0 (13.0-15.0)	15.0 (12.0-15.0)	z=1.28 p=0.202
CT brain **normal** **ischemic**	 44 (62.0) 27 (38.0)	 16 (55.2) 13 (44.8)	 χ^2=0.397 p=0.529
Serum creatinine on admission	1.04±0.165	0.969±0.149	t=2.11 **p=0.048***
Serum creatinine after 3 days	1.636±0.07	2.37±0.06	t=4.31 **p=0.001***
AKI **negative** **positive**	 48 (67.6) 23 (32.4)	 3 (10.3) 26 (89.7)	 FET=27.015 **p<0.001***
ICU stay **no** **yes**	 9 (31.0) 20 (69.0)	 37 (52.1) 34 (47.9)	 χ^2=3.68 p=0.06
Stay duration more than one week **-ve** **+ve**	 0 (0.0) 29 (100.0)	 47 (66.2) 24 (33.8)	 FET=36.22 **p<0.001***

t:Student t test Z:Mann Whitney U test χ^2=Chi-Square test FET: Fischer exact test. All parameters are described as mean±SD, Median (range), number and percentage. *statistically significant

There were statistically significant increases in dead group compared to live ones as regards duration of AKI development, ICU stay, and stay duration more than one week (Table 6).

Table (6): Factors affecting overall mortality among studied cases

	Median time to death /days (95% CI)	P value
≤65 **Age/Years >65**	8.0 (7.26-8.74) 10.0 (8.19-11.81)	log rank χ^2=2.29 p=0.130
Sex **Male** **Female**	 8.0 (7.14-8.86) 9.0 (7.59-10.40)	 log rank χ^2=1.104 p=0.293
DM **-ve** **+ve**	 9.0 (7.64-10.36) 8.0 (6.98-9.02)	 log rank χ^2=0.019 p=0.891
Hypertension **-ve** **+ve**	 8.0 (6.41-9.58) 9.0 (8.01-9.99)	 log rank χ^2=0.069 p=0.793
CT brain **Normal** **Ischemic**	 8.0 (7.43-8.57) 10.0 (8.88-11.12)	 log rank χ^2=0.024 p=0.877
AKI **Negative** **Positive**	 12.0 (9.85-14.15) 8.0 (7.5-8.5)	 log rank χ^2=30.44 p=0.001*
ICU stay **No** **Yes**	 12.0 (9.65-14.35) 8.0 (7.39-8.61)	 log rank χ^2=8.48 p=0.004*
Stay duration more than one week **-ve** **+ve**	 undefined	 log rank χ^2=14.16 p=0.001*

*statistically significant - AKI was demonstrated to be the only significant predator of mortality among the studied cases (Table 7).

Table (7): Multivariate analysis of factors affecting mortality among studied cases

Predictors	β	p	RR	95.0% C.I. for RR	
				Lower	Upper
Serum creatinine on admission	-4.948	0.005	0.007	0.000	0.223
Serum creatinine after 3 days	0.972	0.191	2.643	0.616	11.345
AKI (+ve)	2.89	0.04*	17.99	1.134	285.38
Stay duration more than one week	21.44	0.99	Undefined		
Constant	1.696	0.328	5.454		

RR: Relative risk

AKI was a significant predictor of the survival duration (Table 8).

Table (8): Cox regression of the predictors affecting median survival duration among studied cases

Predictors	β	p	HR	95.0% CI for HR	
				Lower	Upper
AKI	2.968	0.005	19.449	2.426	155.939
ICU stay	0.161	0.732	1.175	0.468	2.946
Stay duration/ days	-10.677	0.924	0.000	0.000	1.006E91

HR: Hazard Ratio

DISCUSSION

Lima *et al.* [8] conducted a retrospective hospital-based cohort study included patients who had their first ischemic stroke. AKI was defined by an increase of serum creatinine in relation to baseline value at admission ≥ 0.3 mg/dL or a rise in serum creatinine level by 1.5 times the baseline value at any point in the first week after admission.

As regards the demographic distribution of our studied cases, the mean age was 66.61. The majority of cases were male (73%) were males while 27% of which were females. The percentage of DM and HTN were 53% and 56% respectively.

Gadalean *et al.* [6] conducted their study on 45 consecutive stroke patients treated with intravenous recombinant tissue plasminogen activator (iv. rt-PA) (median age = 64 years; 29 male) and 59 age and sex matched controls not eligible for iv. rt-PA have been enrolled in their study. Subjects were followed-up until hospital release or death (median follow up time = 12 days) and the prevalence of AKI was also recorded.

As regards, outcome and mortality incidence among studied cases, 29% of cases died within 10 days, while 71% of which demonstrated complete recovery with hospital discharge. An important note to be considered is the fact that the current study did not allow conclusions concerning a direct causal relation between AKI and the excess mortality in acute ischemic stroke (AIS) patients who had underwent iv. rt-PA.

This came within the global mortality rate in the patients who developed AKI after stroke, which ranged between 42% and 8.4%, being significantly higher as compared to AIS patients without AKI and the in-hospital mortality rates increase in parallel with the severity of AKI [5, 9, 10]. Similarly, **Saeed *et al.*** [10] demonstrated that, patients with AIS with acute renal failure (ARF) had higher rates of in-hospital mortality (8.4% versus 2.9%; P<0.0001) compared with those without ARF. After adjusting for confounding factors, patients with AIS with ARF had higher odds of moderate to severe disability.

As regards the demographic risk factors affecting mortality incidence among the studied cases, there were no significant differences among live and dead cases in terms of age, sex, DM and HTN. Such insignificant differences demonstrated that such parameters were not considered as contributing factors for mortality in the studied cases aiming to signify the actual role of AKI. In terms of, factors affecting overall mortality among studied cases, AKI, ICU stay and stay duration more than one week were considered to be significant factors for overall mortality. On the other hand, age, sex, DM, HTN (SBP and DBP), GCS and CT brain seemed to be insignificant factors for overall mortality. This came in agreement with **Lima *et al.*** [8] who demonstrated that, 30-day mortality was higher in the AKI subgroup compared to non-AKI with highly statistically significant difference (35% vs. 6.2%, p < 0.001). In the same line, **Arnold *et al.*** [11] conducted a meta-analysis study and demonstrated that, mortality in stroke patients who develop acute kidney injury is significantly increased (Odds Ratio 2.45; 95% confidence interval 1.47–4.10), however the reported incidence of AKI after stroke varies widely and is underestimated using coding definitions. In addition, lower baseline renal function was associated with an increased rate of AKI with a subsequent more bad prognosis of ischemic stroke patients as reported by [5, 9, 12].

As regards, multivariate analysis of factors affecting mortality among the studied cases, AKI and serum creatinine on admission seemed to be significant predictors of mortality. Several studied were in agreement with the present study, in which the presence of AKI was independently associated to higher 30-day mortality after ischemic stroke [9, 12, 13].

As regards serum creatinine, **Snarska *et al.* [14]** were in agreement with the current study as they reported that, among patients with ischemic stroke who died, 41,2% had elevated serum creatinine on admission (according to WHO) and among those who survived 15,5% with a highly statistically significant difference ($p<0,001$).

The mechanism that leads to this heavy burden of mortality in patients with AKI is unclear and it is debatable whether AKI is a cause or a consequence of excess mortality. Experimental and observational studies have shown that AKI is an acute systemic disease which induces distant organ injury in lung, brain, liver, intestine, heart and other vital organs **[15, 16].** These systemic phenomena associated with AKI predispose to multiple organ dysfunctions and contribute to the higher mortality observed in patients with AKI. In patients with AIS, AKI could aggravate the neurological lesions. Experimental published data revealed that AKI induced an increased vascular permeability with disruption of the blood-brain barrier, up-regulation of pro-inflammatory cytokines synthesis and granulocyte colony-stimulating factor and increase the microgliosis and neuronal pyknosis **[15, 16].**

On the other hand **Lima *et al.* [8]** did not find such an association when considering stroke severity as in their multivariate analysis they reported that, the presence of AKI and previous ischemic heart disease were a predictor of a higher fatality rate only when the National Institutes of Health Stroke Scale (NIHSS) was removed from the regression model. In addition, higher stroke severity score and age were predictors of a higher fatality rate in both multivariate models. As regards, univariate analysis, they demonstrated that, the predictors related to mortality in 30 days after an ischemic stroke were: presence of acute kidney injury, age, NIHSS score, and previous history of ischemic heart disease.

Thus, the discrepancies between the studies may be due to the fact that, AKI lost predictive strength when considering stroke severity through NIHSS. The NIHSS score has been established as a very important predictor of short and long-term mortality after stroke. There is a graded relationship between an increasing NIHSS score and higher fatality in 30 days after stroke **[17].**

As regards, the predictors affecting median survival duration among studied cases, AKI was a significant predictor of the survival duration. In contract, ICU stay and stay duration were not significant predictors of survival.

CONCLUSION

The current study demonstrated that, patients with acute ischemic stroke were at higher possibility for development of AKI which was accompanied with worse outcomes. In addition, AKI as well as serum creatinine seemed to be important independent predictors of mortality in AIS cases.

REFERENCES

1. **Feigin V, Forouzanfar M, Krishnamurthi R *et al.* (2014):** Global and regional burden of stroke during 1990–2010: Findings from the Global Burden of Disease Study 2010. The Lancet, 383(9913):245-55.
2. **Mittal S, Goel D (2017):** Mortality in ischemic stroke score: A predictive score of mortality for acute ischemic stroke. Brain Circ., 3:29-34.
3. **MacWalter R, Wong S, Wong K *et al.* (2002):** Does renal dysfunction predict mortality after acute stroke? A 7-year follow-up study. Stroke, 33(6): 1630-1635.
4. **Thomas M, Blaine C, Dawnay A *et al.* (2015):** The definition of acute kidney injury and its use in practice. Kidney Int., 87:62-73.
5. **Covic A, Schiller A, Mardare N *et al.* (2008):** The impact of acute kidney injury on short-term survival in an Eastern European population with stroke. Nephrology Dialysis Transplantation, 23(7): 2228-2234.
6. **Gadalean F, Simu M, Parv F *et al.* (2017):** The impact of acute kidney injury on in-hospital mortality in acute ischemic stroke patients undergoing intravenous thrombolysis. PLoS One, 12(10): 589-93.
7. **Damman K, van Deursen V, Navis G *et al.* (2009):** Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. Journal of the American College of Cardiology, 53(7): 582-588.
8. **Lima H, Saibel T, Colato G *et al.* (2019):** The impact of acute kidney injury on fatality of ischemic stroke from a hospital-based population in Joinville, Brazil. Brazilian Journal of Nephrology, 41(3): 323-329.
9. **Khatri M, Himmelfarb J, Adams D *et al.* (2014):** Acute kidney injury is associated with increased hospital mortality after stroke. Journal of Stroke and Cerebrovascular Diseases, 23(1): 25-30.
10. **Saeed F, Adil M, Khursheed F *et al.* (2014):** Acute renal failure is associated with higher death and disability in patients with acute ischemic stroke: analysis of nationwide inpatient sample. Stroke, 45(5): 1478-1480.
11. **Arnold J, Ng K, Sims D *et al.* (2018):** Incidence and impact on outcomes of acute kidney injury after a stroke: a systematic review and meta-analysis. BMC Nephrology, 19(1): 283-88.
12. **Tsagalis G, Akrivos T, Alevizaki M *et al.* (2009):** Long-term prognosis of acute kidney injury after first acute stroke. Clinical Journal of the American Society of Nephrology, 4(3): 616-622.
13. **Kong F, Tao W, Hao Z *et al.* (2010):** Predictors of one-year disability and death in Chinese hospitalized women after ischemic stroke. Cerebrovascular Diseases, 29(3): 255-262.
14. **Snarska K, Kapica-Topczewska K, Bachórzewska-Gajewska H *et al.* (2016):** Renal function predicts outcomes in patients with ischaemic stroke and haemorrhagic stroke. Kidney and Blood Pressure Research, 41(4): 424-433.
15. **Singbartl K, Joannidis M (2015):** Short-term effects of acute kidney injury. Critical Care Clinics, 31(4): 751-762.
16. **Grams M, Rabb H (2012):** The distant organ effects of acute kidney injury. Kidney International, 81(10): 942-948.
17. **Fonarow G, Saver J, Smith E *et al.* (2012):** Relationship of National Institutes of Health Stroke Scale to 30- day mortality in Medicare beneficiaries with acute ischemic stroke. Journal of the American Heart Association, 1(1): 34-39.