Acute Kidney Injury in Patients with Acute Stroke

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ABSTRACT:

BACKGROUND:

According to world health organization, about 15 million people suffer from stroke worldwide each year. Acute kidney injury complicates 5-7% of acute care hospital admissions and up to 30% of critical care patients. These in turn lead to increase disability, decreased quality of life and disproportionate burden on healthcare resources. Patients admitted for diagnosis and treatment of acute stroke are at high risk of developing acute kidney injury due to comorbid conditions, poor oral intake and exposure to nephrotoxic agents.

OBJECTIVE:

to determine the incidence of acute kidney injury in patients admitted with acute stroke and evaluates associated comorbidities and possible risk factors.

PATIENTS AND METHODS:

in a cross-sectional study, a cohort of 436 patients admitted with acute stroke, (327 with ischemic stroke and 109 with intracerebral hemorrhage) entailed in this study.

Serum creatinine readings using Jaffe method was obtained at first day of insult, after 48 hours and 7 days after onset of stroke, KDIGO criteria was used to define patients who developed acute kidney injury which include elevation of serum creatinine of 0.3 mg\dl or more within 48 hours or 1.5 fold or more increment of baseline serum creatinine within 7 days.

RESULTS:

Acute kidney injury was a common complication in acute stroke population with total incidence 13.5%, with significantly higher incidence in intracerebral hemorrhage group (22.9%) than in ischemic group (10.4%) p=0.000919. The study also show significant sex difference with higher incidence in males than females in ischemic group (13.4% vs 6.7%; p= 0.049) intracerebral hemorrhage group (31.5% vs 12.3%; p=0.0246).

Study also shows significant relation between developing acute kidney injury and history of hypertension in both groups with p=0.00229, and significant relation with diabetes mellitus p=0.009096.

Study shows that there is significant elevation of serum creatinine on consecutive measures between first day and day 7 with p=0.000.

We found that there is significant direct relation between increasing age and incidence of acute kidney injury with p=0.040 in ischemic group and p= 0.015 in intracerebral hemorrhage group.

CONCLUSION:

The incidence of acute kidney injury in acute stroke patients was 13.5% with significantly higher incidence in intracerebral hemorrhage group with significant relation between development of acute kidney injury and being male, has hypertension, diabetes mellitus or advance age.

KEYWORDS: Acute kidney Injury, intracerebral Hemorrhage, ischemic stroke

INTRODUCTION:

A stroke, or cerebrovascular accident, defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the definition of stroke is clinical, and laboratory studies including brain imaging used to support the diagnosis.[1]

In 2013, the Stroke Council of the American Heart Association/American Stroke Association recommended an updated definition that would better reflect current practice.

According to this updated definition:

Ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.

Stroke caused by intracerebral hemorrhage (ICH): Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that not caused by trauma.[2]

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About 85% of strokes are ischemic and 10% are of ICH.[3]

Cerebrovascular disease estimated to account for 7.8 million deaths yearly throughout the world and represents about 13 % of all causes of death.[4]

According to the World Health Organization (WHO), around 15 million people, the world over, suffer from stroke each year. Among these, 5 million are permanently disabled. Four out of five strokes occur in the low and middle income countries who can least afford to manage with the consequences of this disease.[5]

It is therefore, important to note that while the incidence of stroke is dropping in the West, it is probably ominously increasing in Asia. Research has shown that the Middle East region faces a double burden of the disease due to decreasing rates of communicable diseases and the growing rates of non-communicable diseases.[6]

Acute kidney injury (AKI), previously known as acute renal failure, is characterized by the sudden impairment of kidney function resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys.[7]

AKI is not a single disease but rather a syndrome comprising multiple clinical conditions. Outcomes from AKI depend on the underlying disease, the severity and duration of renal impairment, and the patient's renal baseline condition. [8]

AKI is a broad clinical syndrome encompassing various etiologies, including pre-renal azotemia, acute tubular necrosis, acute interstitial nephritis, acute glomerular and vasculitic renal diseases, and acute post-renal obstructive nephropathy.[9]

The development of AKI is the consequence of complex interactions between the actual insult and subsequent activation of inflammation and coagulation. [8]

Risk for disease represents the interaction between susceptibility (i.e., features intrinsic to the patient) and exposure (i.e., the causative factor or factors). Exposures known to produce AKI in susceptible populations include sepsis, ischemia, heart failure, liver disease, major surgery (especially vascular and cardiac), myonecrosis, urinary tract obstruction, and various nephrotoxins.[10]

The traditional paradigm divides AKI into pre-renal, renal, and post-renal causes**.**

Pre-renal uremia may be caused by hypovolemia or a decreased effective arterial volume. Post-renal obstructive renal failure is usually diagnosed by urinary tract dilation on renal ultra-sound. **Intrinsic renal causes** of AKI should be considered under the different anatomic components of the kidney (vascular supply; glomerular, tubular, and interstitial disease.[11]

In the hospital setting, pre-renal uremia and acute tubular necrosis (ATN) account for the majority of AKI cases.[12]

There is growing evidence that sequelae of AKI include poor long-term survival, increased risk of readmissions, worsening of chronic kidney disease, and progression to end-stage renal disease. These in turn lead to increased disability, decreased quality of life, and disproportionate burden on healthcare resources.[13]

AKI defined as **Increase in Serum Creatinine by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours**; or **Increase in Serum Creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/hour for 6 hours**.[9]

Historically, the most common assay for measurement of serum creatinine was the alkaline picrate (Jaffe) assay that generates a color reaction. Chromogens other than creatinine known to interfere with the assay, giving rise to errors of up to approximately 20% in normal individuals. Modern enzymatic assays do not detect non-creatinine chromogens and yield lower serum levels than with the alkaline picrate assays. Until recently, calibration of assays to adjust for this interference was not standardized across laboratories, thereby limiting the estimation of glomerular filtration rate (GFR) from serum creatinine concentrations, especially at higher GFR.[14]

Stroke is a major cause of disability and poor quality of life.[15] The high rates of disability and mortality due to stroke are determined not only by the neurological deficits but also by the associated medical comorbidities as cardiovascular disease, hypertension, diabetes and renal dysfunction.[16]

Data on the association between renal dysfunction and outcome after acute stroke are scarce.[17]

Patients admitted for diagnosis/treatment of stroke are at a high risk of experiencing AKI because of comorbid conditions, and other potential risk factors, including exposure to nephrotoxic medications, dehydration or utilization of hypertonic crystalloid solutions.[13]

Kidney disease might increase the risk of stroke and subclinical cerebral abnormalities, and affect cognitive function, however, the effect of stroke or cerebrovascular disease on renal function has scarcely been explored, which makes the comprehensive description of this two-way interaction more challenging than that of its cardiology counterpart, cardio renal syndrome.[17]

The development of AKI is associated with a significantly increased risk of in-hospital and long-term mortality, longer length of stay, and increased costs.[7] However, data regarding temporal trends of incidence of AKI and its impact on outcomes among patients hospitalized with stroke is limited.[13]

In this study we tried to highlighted the rule of kidney injury in added factor of deterioration of patients with acute stroke by estimation of the incidence of acute kidney injury in patients who admitted for diagnosis and management of acute stroke during their hospital stay as an important prognostic factor in term of morbidly and mortality and to clarify the significant risk factors associated with development of acute kidney injury in patients with acute stroke.

PATIENTS AND METHODS:

Design and settings: This is a cross-sectional study performed in Al-Imamain Al-Khadimain medical city, neurology and medical department, Baghdad Medical city, neurology and medical departments. Patients enrolled between January 1, 2017 and January 1, 2018.

Study population:

Inclusion criteria:

We included a convenience sample of 436 adult patients who diagnosed with acute stroke depending on clinical and radiological findings including 109 (25%) patients with intracerebral hemorrhage (57 males and 52 females) and 327 (75%) patients with ischemic strokes (179 males, 148 females) who admitted in the first day of stroke.

Exclusion criteria:

1. Patient use Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil (Increase Reduced tubular secretion of creatinine) and Keto acids,
2. Patient previously diagnosed with chronic kidney disease or on renal replacement therapy.
3. Patient with baseline estimated-GFR (e-GFR) < 30 ml / min on admission using chronic kidney disease epidemiology collaboration equation.
4. Patients with spinal, cerebral venous infarction and subarachnoid hemorrhage.
5. Patients who did not admitted from first day of their insult.
6. Patients who did not complete the required serial serum creatinine readings for the study.
7. Patients underwent imaging procedures including utilization of contrast agents.

Data collection:

Serum creatinine was measured (using kinetic colorimetric assay based on the Jaffe method) during the first day of admission for all patients using and serial follow up measurements of serum creatinine was taking after 48 hours and day 7 of admission. KDIGO criteria[(9)] for diagnosis of AKI was applied to define patients who developed AKI And accordingly Patients who had elevated follow up creatinine of 0.3mg\dl or more within 48 hours or 1.5 fold increment or more within 7 days from first reading was considered to have AKI .

Statistical analysis:

Statistical analysis was done using **Minitab statistical software version 17**, patients sample was divided into two subgroups; (ischemic stroke group and ICH group), the percentage of subjects who developed AKI in both subcategories (ischemic strokes, ICH) was obtained to determine the incidence.

we compared incidence between ischemic group and ICH using chi square, and p value < 0.05 considered statistically significant and p value >0.05 considered not significant.

The mean serum creatinine for both groups in the three readings were compared to determine if there is significant change of serum creatinine

during the first week of hospitalization using ANOVA test, p value > 0.05 considered significant.

The incidence of AKI in ICH and ischemic stroke in patients who had hypertension was calculated separately in each subgroup, and was compared to patient who did not have hypertension and developed AKI in the same group.

Chi square test used to determine significance of hypertension in the development of AKI in both subgroups (ICH, ischemic) with a p value < 0.05 to be considered significant.

The incidence of AKI in ICH and ischemic stroke in patients who had Diabetes Mellitus (DM) was calculated separately in each subgroup, and was compared to patient who didn't have DM and developed AKI in the same group,and chi square test was used to determine significance of DM as a risk factor to develop AKI in both subgroups(ICH ,ischemic) with a p value < 0.05 to be considered significant.

The incidence of AKI in male patients for both subgroups was calculated separately, and was compared with the incidence of AKI in females patients in each subgroups using chi square test and p value <0.05 considered significant.

Both subgroups (ICH, ischemic) was subdivided into five age groups separately, incidence of AKI in each age group was calculated, using Paerson correlation test to determine relation between age and incidence of AKI in both subgroups (ICH , Ischemic) and p value < 0.05 considered significant.

RESULTS

We included 436 patients, admitted with definite diagnosis of acute stroke. Patients were divided into two subgroups, Ischemic stroke group (327) patients (75%) with (179 males, 148 females) average age was 66.6± 9 years with range (42-87 years), Intra cerebral hemorrhage (109) patients (25%) with (57 males, 52 females) , and the average age 64.6 ± 9.6 years with range (43 -87) years.

The mean baseline serum creatinine (day zero) was 0.908 mg/dl for ischemic group, 0.95 mg/dl, for (day 2) serum creatinine mean was 0.927 mg/dl in ischemic patients and 1.037 mg/dl in ICH group, for (day 7) serum creatinine mean readings was 0.988 mg/dl in ischemic patients and 1.117 mg/dl in ICH patients. Figure (1) and (2)

For all subjects included in this study, there were 59 patients who developed AKI, (34 patients in Ischemic group: 24 males, 10 females) and (25 in ICH group: 18 males and 7 females). All of them fallen within first stage AKI according to KDIGO criteria (i.e.: increased s. creatinine ≥ 0.3 mg/dl or 1.5-1.9 fold from baseline).

The overall incidence of AKI for total population in this study was 13.5 % of hospitalized patients. The incidence of AKI in ischemic group was 10.4 % of hospitalized patients, and for ICH group the incidence was 22.9% of patients. Incidence in both subgroups (ischemic and ICH) were compared to each other and the difference (p value = 0.000919) was statistically significant between both subgroups.

Regarding sex distribution, the incidence of AKI within ischemic group for male sex 13.4 %, and for females in same subgroup 6.7%, and the difference in incidence between both groups found to be statistically significant with p value= 0.0498. For ICH subgroups, the incidence of AKI was 31.5% for male sex, and 12.3% for females, the difference was also statistically significant (p value= 0.0246).For total population, male sex found to be significantly related for AKI incidence with p value= 0.004688.

Incidence of AKI in Hypertensive patients for both groups (ischemic 12.4% and ICH 26.9 %) was calculated, and comparison with non-hypertensive patients showed significant correlation between hypertension (HTN) and development of AKI in stroke patients with p value = 0.0419 for ischemic group, p value = 0.0347 for ICH group and for total population p value = 0.00229.

Incidence of AKI in Diabetic patients in ischemic group was 13.7%, and for ICH group was 33.3 % and comparison with non-diabetic subjects in each group showed significant correlation of DM with development of AKI in ischemic group with p value 0.0410, and correlation with ICH group found significant with p value = 03038. For total population the incidence of AKI in diabetic patients was 16.9 %, and the correlation

between DM and development of AKI in stroke patients found to be statistically significant with p value .009096.

The comparison between the mean of serial serum creatinine readings for each subgroups in day zero , second day and day 7 of admission was done using ANOVA test (analysis of variance test) which show significant differences between means p value = 0.000 for both ischemic and ICH groups.

Both groups (ischemic and ICH) was subdivided into 5 categories for each according to age and incidence of AKI was calculated for each age category in both groups individually, with results in ischemic group(table 1).

The relationship between age and development of AKI in each population was tested using Pearson correlation test, this show a direct correlation between age and incidence of AKI (Pearson correlation =0.896) for ischemic arm of study which found statistically significant with p value =0.040.

Similar correlation was also found in ICH arm with direct relation between age and AKI incidence (Pearson correlation =0.946) and p value = 0.015.

Table (1) shows the age distribution and AKI incidence in each age group.

AGE GROUP	Ischemic stroke			ICH			total		
	AKI	Total	incidence	AKI	total	incidence	AKI	total	incidence
40-49	1	6	16.66%	1	15	6.6%	2	21	9.52%
50-59	5	28	17.85%	5	58	8.62%	10	86	11.62%
60-69	8	38	21%	11	115	9.56%	19	153	12.4%
70-79	8	29	27.58%	14	124	11.29%	22	153	14.37%
80-89	3	8	37.5%	3	15	20%	6	23	26.08%
Total	25	109		34	327		59	436	

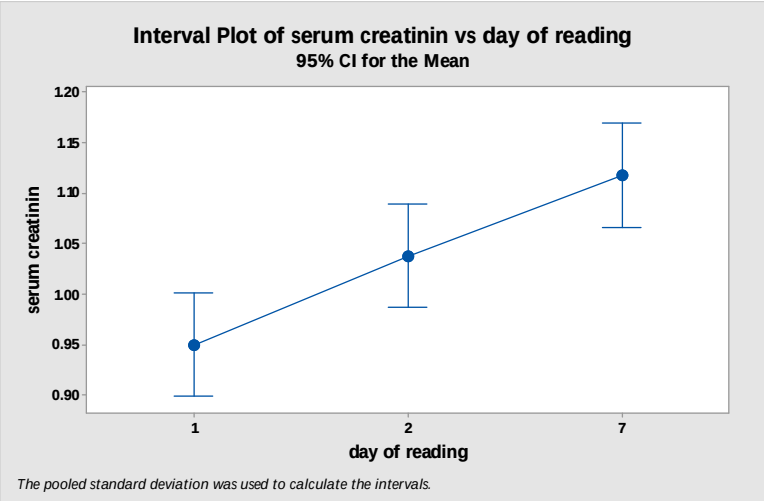

Figure (1) an interval plot graph shows the increment in mean serum creatinine levels on serial readings in ICH patients.

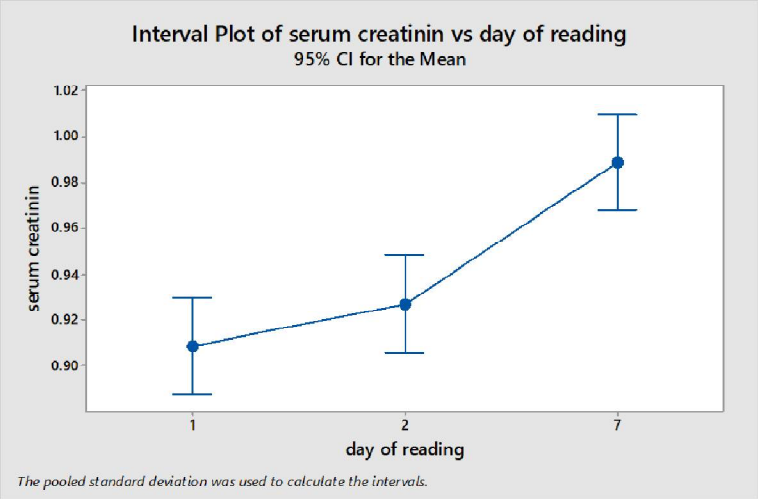

Figure (2) an interval plot graph shows the increment in mean serum creatinine levels on serial readings in ischemic stroke patients.

DISCUSSION:

This study was held to determine the incidence of AKI in acute stroke patients and to evaluate significant associated factors with this serious complication.

The study population consisted of two arms, ischemic stroke arm (75%) and ICH arm (25%), and this was different from global distribution of stroke type (85% for ischemic and 10%) for ICH. [3] This difference could be explained in that the study population was collected from two tertiary centers in Baghdad with referral of ICH cases from other hospitals.

The study shows that AKI is a known complication in acute stroke patients, and 13.5% of study population developed AKI, this result resembles that of AKI incidence in stroke patients reported by Covic A. et al [18] that shows 14.5% of patients had developed AKI but less than that of Khatri M. et al [19] with AKI incidence of 18% may be because the definition of AKI patients, the study depended on serum creatinine levels, and the definition of AKI using declining urine output did not applied due to difficulties in obtaining accurate measures. This may lead to missing cases of AKI who fulfilled the definition of AKI and lead to lower incidence rates than actual incidence.

The incidence of AKI in ICH group was higher than ischemic group (22.9% vs 10.4%) respectively which was also reported by Khatri M. et al [19] (21% vs 14%) and the difference in AKI was statistically significant, there is no clear reason for this difference but it could be attributed to the use of nephrotoxic agents such as mannitol more frequently in ICH patients.[19]

The mean serum creatinine readings was increasing from baseline reading on day zero to the last reading at day 7 of admission in ischemic and hemorrhagic group, this observation was not found in any other studies (graph 1and 2). This elevation in serum creatinine levels on serial measures in acute stroke patients may be explained possibly due to decrease fluid intake due to dysphagia and functional disability in this population, with the concomitant exposure to medications that may lead to renal injury such as antihypertensive and antibiotics that was compensating renal function and with any added factor it lead to renal impairment.

Study shows that incidence of AKI in male gender was significantly higher than females in both ischemic group and ICH group and for total population, this results was similar to what found in both Khatri M. et al [19] and Covic A. et al [18]. Both had found higher incidence of AKI in male sex.

One may argue that the KDIGO criteria are sex-biased in that males, who produce more

creatinine on average than females due to larger muscular mass, are more likely to achieve a certain serum creatinine threshold given an equivalent reduction in glomerular filtration rate. [20]

However, differences in creatinine production appear unlikely to explain the observation that males also have a higher incidence of dialysis-requiring AKI. Although numerous studies have investigated sex differences in progression of chronic kidney disease, few have investigated sex differences in risk of AKI. Further studies needed to confirm this finding and to determine the underlying explanations.[20]

Regarding HTN, the study reveals significant association between HTN and AKI in both arms of the study, these results agreed with results by Girish N.et al.[13] For explanation of this observation, atherosclerosis and long-standing hypertension can lead to hyalinosis and myointimal hyperplasia, causing structural narrowing of the intrarenal arterioles and impaired capacity for renal afferent vasodilation, which in turn affect the capacity of auto regulatory response and the development of prerenal azotemia .[7]

The study also shows significant relationship between DM and development of AKI in ICH and Ischemic arm of the study and in total population ,this results confirmed results from Covic A.et al [18] who found significant association with DM and AKI in stroke population but the study take whole sample without categorizing stroke into ischemic and hemorrhagic. Diabetes Mellitus should be considered a rapid acting risk factor for renal susceptibility to ischemia, its vulnerability increased as consequence to significant microvascular injury and interstitial inflammation.[21]

The study shows that Increasing age was directly associated with increasing incidence of AKI in both ischemic and ICH group and this relation was statistically significant. This results confirmed the results found by Khatri M. et al [19] and Covic A.et al [18] with advanced age as a significant risk factor to develop AKI , this can be explained due to structural and functional changes associated with age that lead to diminished nephron reserve and reduced renal capacity for autoregulation , accumulation of comorbidities (e.g., vascular disease, diabetes, hypertension, CKD), which increases susceptibility to AKI; and increased exposure among the elderly to medications (ACE inhibitors, NSAIDs).[22]

The limitation of the study is that baseline serum creatinine levels prior to development of stroke (before hospitalization) was not available but we study renal function change during acute illness duration where interventions could be attempted to either prevent or treat AKI.

In conclusions; the incidence of AKI in acute stroke patients was 13.5% with significantly higher incidence in ICH group (22.9%) than in ischemic stroke patients (10.4%). There is significant association between patient's age, sex with the development of AKI in stroke patients, with male sex and older age considered significant risk factors. There is a significant association between HTN and DM and the development AKI in stroke patients.

REFERENCES:

1. Wade Smith, et al. Cerebrovascular disease.In: Steve L. Hauser. Harrison's neurology in clinical medicine. Fourth edition .Mc Grow Hill education, New York, 2017:323-325.
2. Sacco RL, et al. American Heart Association Stroke Council. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 July; 44(7):2064-2089.
3. Nicholas Losseff, et al. Stroke and Cerebrovascular Diseases. In: Charles Clarke, et al (Eds). Neurology A Queen Square Textbook. Wiley Blackwell, Second Edition, London, 2016: 133- 135.
4. Allan H. Ropper , et al .Adams and Victor's principles of neurology . Tenth edition. McGraw-Hill education, New York, 2014:778-781.
5. Thrift, A.G., et al. Global stroke statistics. International Journal of Stroke.2014; 9 (1): 6-18.

6. Tran, J., Mirzaei, M., Anderson, L., et al. The epidemiology of stroke in the Middle East and North Africa. Journal of Neurological Science. 2010:295(1-2):38-40.
7. Sushrut S.Waikar, et al. Acute kidney injury .In: J. Larry Jameson, et al .Harrison's Nephrology and acid-Base disorders. Second edition, mc Grow Hill, New York, 2013: 104-115.
8. Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney international. 2012; 81(9):819-825.
9. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Critical care. 2013Feb 4: 17(1):204.
10. Uchino S, Kellum JA, Bellomo R et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294: 813– 818.
11. J. Ashley Jefferson., et al. Pathophysiology and Etiology of Acute Kidney Injury. In: Richard J. Johnson, John Feehally, Jürgen Floege. comprehensive clinical nephrology .fifth edition, Elsevier, Philadelphia, 2015 :802-817.
12. Srisawat N, Kellum JA. Acute kidney injury: Definition, epidemiology, and outcome. Current Opinion Critical Care. 2011;17(6):548-555.
13. Nadkarni GN, et al. Dialysis requiring acute kidney injury in acute cerebrovascular accident hospitalizations. Stroke. 2015 November 1; 46(11):3226-3231.
14. Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine. Nephron, 1992; 62 (3): 249–256.
15. De haan RJ, Limburg M, Vander MeulenJH, Jacobs HM. Quality of life after stroke. Impact of stroke type and lesion location. Stroke.1995 Mar 1:26 (3) 402-408.
16. Theofanidis D, 2015. Management of acute stroke: a debate paper on clinical priorities. a literature review .International Journal of Caring Science. 2015 Jan 1, 8(1): 201-210.
17. Friedman PJ. Serum creatinine: an independent predictor of survival after stroke. Journal of Internal Medicine. 1991 Feb 1; 229(2):175–179.
18. Covic A, Schiller A, Mardare NG, Petrica L, Petrica M, Mihaescu A, Posta N. The impact of acute kidney injury on short-term survival in an Eastern European population with stroke. Nephrology Dialysis Transplantation. 2007 Nov 7;23(7):2228-34.
19. Khatri M, Himmelfarb J, Adams D, Becker K, Longstreth WT, Tirschwell DL. Acute kidney injury is associated with increased hospital mortality after stroke. Journal of Stroke and Cerebrovascular Diseases. 2014 Jan 1; 23(1):25-30.
20. Hsu CY, McCulloch CE, Fan D , Ordonez JD , Chertow GM , Go As .community based incidence of acute renal failure . Kidney international. 2007 july 2:72(2).
21. Patschan D, Müller GA. Acute kidney injury in diabetes mellitus. International journal of nephrology. 2016; 2016.
22. Neesh Pannu, Marcello T0nelli. Epidemiology and prognostic impact of acute kidney injury .In: Richard J. Johnson, John Feehally, Jürgen Floege .comprehensive clinical nephrology. Fifth edition, Elsevier, Philadelphia, 2015: 836-840.