

## Association of Hyponatremia with In-hospital Mortality among Patients Hospitalized with Stroke

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### ABSTRACT

**Introduction:** Stroke is the third commonest cause of death. Hyponatremia is most frequently encountered electrolyte disturbance and is associated with increased mortality and morbidity in various diseases.

**Objective:** The present study helped in clarifying the role of hyponatremia at the time of admission on mortality in stroke patients in Pakistan.

**Study:** It was a cohort study, conducted at Medical Unit III, Services Hospital, Lahore, from 07-06-2016 to 06-12-2016.

**Subjects and Methodology:** One hundred and fifty (75 in each group) patients who fulfilled inclusion criteria were enrolled after written informed consent. Sodium levels were measured on admission and patients were divided into two groups i.e., hyponatremic group comprising of  $\text{Na} < 135 \text{ mEq/L}$  and control group with normal sodium levels. All the patients were followed for in-hospital mortality.

**Results:** The mean age of patients was  $63.50 \pm 5.78$  with a median of 40 and a mode 42. Most of the patients (53.3%) were above 60 years old and females (54.6%). Among 75 patients who had hyponatremia, 41 patients died in hospital while 34 were discharged from hospital. Among control group, 20 patients died while 55 were discharged from hospital ( $\text{RR} = 2.05$ ,  $P = 0.001$ ). This showed that there is strong association between hyponatremia and in-hospital mortality.

**Conclusion:** Hyponatremia is strongly associated with in-hospital patients' mortality in patients of stroke.

**Keywords:** Hyponatremia, In-patient Mortality, Stroke.

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## Introduction

Stroke is the third commonest etiology of death and the first major cause of disability in developed and developing countries<sup>1</sup>. It has two types. Ischemic stroke occurs in 85% patients due to blockage of blood flow in one of the vessels supplying the brain. Hemorrhagic stroke occurs in rest of 15% due to rupture of an artery<sup>1,2</sup>. According to World Health Organization estimates, 5.5 million people died of stroke in 2002, with 20% of these deaths occurred in South Asia<sup>1</sup> and the burden of the disease is on rise in South Asian countries (India, Pakistan, Bangladesh, and Sri Lanka)<sup>1</sup>. Large scale epidemiological studies are still needed to determine its exact incidence in Pakistan. An estimated annual incidence, according to Pakistan Stroke Society, is 250/100,000<sup>2</sup>. The younger age at onset of stroke is in keeping with the prevalence of coronary heart disease (CHD) from the Indian subcontinent, which suggest that cardiovascular diseases manifests 10 year earlier in this region<sup>1,2</sup>.

Hyponatremia is the most frequent electrolyte disturbance in patients in intensive care and is associated with increased mortality and morbidity in patients with heart failure, cirrhosis, or chronic kidney disease<sup>3-5</sup>. A one third stroke patients present with preexisting hyponatremia, while majority of these develop during hospital stay<sup>4,5</sup>. A large prospective randomized controlled trial investigating the clinical impact of hyponatremia is the need of the day. Only few studies are available on postoperative neurosurgical patients, traumatic brain injury, and subarachnoid hemorrhage supporting the associations of hyponatremia with increased mortality, longer hospital stay, and raised complications<sup>6,7</sup>.

The rationale of present study was that there is no study from Pakistan which has studied mortality in patients of stroke with hyponatremia. Our study was the first to investigate the frequency of hyponatremia, its associations with clinical attributes, and its influence on mortality in patients with stroke. In addition, there have been few international studies evaluating the impact of hyponatremia on mortality in stroke patients with inconsistent results. But these studies were retrospective. The present study also helped in clarifying the role of admission hyponatremia on mortality in stroke patients in Pakistan which is not currently known.

## Objective

The objective was to determine the association of hyponatremia with in-hospital mortality in patients with stroke.

## Material and Methods

It was a prospective study, carried out at Medical Unit III, Services Hospital, Lahore, from 07-06-2016 to 06-12-2016. Sample size was calculated as non-probability purposive sampling technique to be 150 with 80% power of test, 5% level of significance and expecting percentage of in-hospital patients' mortality in both groups 40.9% among hyponatremic patients' vs. 20% in patients without hyponatremia.

### Inclusion Criteria

- Patient having stroke as per operational definition
- Patients of stroke with hyponatremia (exposed group)
- Patients of stroke without hyponatremia (unexposed group)
- Aged 18 years or older
- Provided informed consent

### Exclusion Criteria

- Not willing to participate in study
- Past history of myocardial infarction or stroke or heart failure as per history and medical record

### Data Collection Procedure and Analysis

One hundred and fifty (75 in each group) medical outpatients who fulfilled inclusion criteria were enrolled at Services Hospital Lahore after written informed consent. The history and physical examination as well as their demographic details were recorded. Sodium levels were measured on admission and patients were divided in two groups depending on the level of sodium. The hyponatremia group comprising patients with Na <135 mEq/L and rest of patients in group with normal sodium levels. All the patients were observed for the in-hospital mortality (as per operational definition). After admission, patients were being treated as per hospital protocol.

Statistical analysis was done on Statistical Package for Social Sciences (SPSS) version 16. Qualitative data like sex, presence of 30 days mortality (yes or no) and frequency of hyponatremia were presented as frequencies and percentages. Quantitative data i.e., age and sodium levels were being presented as means and standard deviations. All the collected data was entered into SPSS and analyzed. Relative risk was calculated to determine the strength of association between hyponatremia and mortality of patients.  $R.R > 1$  was considered as significant. Data was modified for age, gender and type of stroke to deal with modifiers. Post-stratification will be calculated taking  $R.R > 1$  as significance.

## Results

A total of 150 patients were included in the study. Seventy five patients had hyponatremia i.e., serum Na <135 mEq/L while remaining 75 patients had normal sodium (control group). The mean age of patients was 63.50 years with standard deviation of 5.78 with a median of 40 and a mode 42. Most of the patients (53.3%) were above 60 years old. 33.3% patients were between 46-60 years and only 13.3 % patients were below 45 years of age. Among all patients, fifty six (45.4 %) were male and sixty eight (54.6%) were females.

Regarding risk factors of stroke, we have evaluated two major risk factors. It was seen that sixty one patients (40.7%) were having hypertension as a risk factor for stroke whereas thirty six patients (24.0%) were having diabetes mellitus as a risk factor for stroke. Moreover, thirty three patients (22.0%) patients had both hypertension and diabetes as a risk factor for stroke. A small number of patients i.e., 13.3% had other risk factors for stroke like smoking, hyperlipidemia, metabolic syndrome etc. Table 1

Among 75 patients who had hyponatremia, forty one patients (41) died during their stay at hospital while 34 patients improved and were discharged from hospital. Among control group having normal sodium levels, twenty (20) patients died during hospital stay while fifty five (55) improved and discharged from hospital (RR=2.05, P=0.001). This showed that there is strong association between hyponatremia and in-patients mortality. Table 2

Regarding type of stroke was also evident that 103 (68.7%) patients (49 with hyponatremia and 54 without hyponatremia) had ischemic stroke whereas 47 (31.3%) patients (26 with hyponatremia and 21 without hyponatremia) had hemorrhagic stroke. Reason for this is that former is more common than hemorrhagic stroke. Table 3

When we stratified patients among different age groups, it was seen that mortality rate was increased with the increasing age of the patient. Twenty five patients who were hyponatremic and above the age of 60 years died as compared to 9 patients of age >60 but without hyponatremia (RR=2.823). Similarly 12 patients between 46-60 years with hyponatremia died as compared to 7 patients of age 46-60 without hyponatremic patients (RR=1.50). So we can see that with increasing age of the patients, mortality increased. One possible reason for this variation of increased mortality among older age group might be poor body response to the different stimuli and hormones with increasing age. Table 3

When we stratified data according to sex of the patients, it was observed that number of death among female patients with hyponatremia was greater as compared non-hyponatremic female patients i.e., 28 females with hyponatremia dies as compared to 11 who were without hyponatremia and died (RR=2.092). On the other hand, 13 male patients with hyponatremia

died as compared to 9 male patients who were without hyponatremia and died (RR=1.829). One possible reason for this variation was hormonal variation among females making hyponatremia more worsened as compared to males. Table 3

Regarding type of stroke, 22 patients with ischemic stroke and hyponatremia died as compared to 7 patients with ischemic stroke but without hyponatremia (RR=3.463). For hemorrhagic stroke, 19 patients with hemorrhagic stroke and hyponatremia died as compared to 13 patients with hemorrhagic stroke but without hyponatremia. Table 3

**TABLE No. 1: RISK FACTORS FOR STROKE: (n=150)**

<b>Risk Factor</b>	<b>Patients with Hyponatremia</b>	<b>Patients without Hyponatremia</b>	<b>Total patients</b>	<b>Percentage</b>
<b>Hypertension</b>	33	28	61	40.7%
<b>Diabetes Mellitus</b>	15	21	36	24.0%
<b>Hypertension + Diabetes Mellitus</b>	20	13	33	22.0%
<b>Other</b>	7	13	20	13.3%
<b>Total</b>	<b>75</b>	<b>75</b>	<b>150</b>	

**TABLE No. 2: MORTALITY AMONG PATIENTS WITH AND WITHOUT HYPONATREMIA (n=150)**

<b>Hyponatremia</b>	<b>Died</b>	<b>Alive</b>	<b>Total</b>	<b>Relative Risk</b>	<b>P Value</b>
<b>Yes</b>	41	34	75	2.05	0.001
<b>No</b>	20	55	75		

**TABLE No. 3: STRATIFICATION OF PATIENTS ACCORDING TO AGE, GENDER AND TYPE OF STROKE (n=150)**

<b><u>Age (in years)</u></b>	<b>Patients with Hyponatremia</b>		<b>Patients without Hyponatremia</b>		<b>Relative Risk</b>
	<b>Died</b>	<b>Alive</b>	<b>Died</b>	<b>Alive</b>	
<b>≤45</b>	5	4	4	7	1.527
<b>46-60</b>	12	20	7	21	1.500
<b>≥60</b>	24	10	9	27	2.823
<b><u>Gender</u></b>					
<b>Male</b>	13	17	9	29	1.829
<b>Female</b>	28	17	11	26	2.092
<b><u>Type of Stroke</u></b>					
<b>Ischemic Stroke</b>	22	27	7	47	3.463
<b>Hemorrhagic Stroke</b>	19	7	13	8	1.18
<b>Total</b>	<b>41</b>	<b>34</b>	<b>20</b>	<b>55</b>	

### **Discussion**

We enrolled 150 patients, 75 patients had hyponatremia i.e. Serum Na <135 while remaining 75 patients had normal sodium (control group).

When we stratified patients among different age groups, it was seen that mortality rate was increased with the increasing age of the patient; 24 patients who were hyponatremic and above the age of 60 years died as compared to 9 patients of age >60 but without

hyponatremia (RR=2.823). Similarly 12 patients between 46-60 years with hyponatremia died as compared to 7 patients of age 46-60 without hyponatremic patients (RR=1.50). One possible reason for this variation of increased mortality among older age group might be poor body response to the different stimuli and hormones with increasing age. Similar findings of hyponatremia was also observed in the similar age groups in another study as well.<sup>7</sup>

When we stratified data according to sex, it was observed that number of death among female patients with hyponatremia was greater as compared non-hyponatremic female patients i.e. 28 females with hyponatremia dies as compared to 11 who were without hyponatremia and died (RR=2.092). On the other hand, 13 male patients with hyponatremia died as compared to 9 male patients who were without hyponatremia and died (RR=1.829). One possible reason for this variation was hormonal variation among females making hyponatremia more worsened as compared to males. Our result was contradictory to the study published in 2019 where mortality was lower in females.<sup>13</sup>

Regarding risk factors of stroke, we have evaluated two major risk factors. It was seen that sixty one patients (40.7%) were having hypertension, a risk factor for stroke whereas thirty six patients (24.0%) were having diabetes mellitus as a risk factor for stroke. Moreover, thirty three patients (22.0%) patients had both hypertension and diabetes as a risk factor for stroke. A small number of patients i.e. 13.3% had other risk factors for stroke like smoking, hyperlipidemia, metabolic syndrome etc. More or less same results of uncontrolled hypertension as a risk factor was also observed in other area of Pakistan as well.<sup>2</sup> As for as diabetes as a major contributory factor to stroke, it has been established already for the occurrence of stroke and hyponatremia.<sup>10</sup>

Regarding type of stroke, it was evident that 103 (68.7%) patients (49 with hyponatremia and 54 without hyponatremia) had ischemic stroke whereas 47 (31.3%) patients (26 with hyponatremia and 21 without hyponatremia) had hemorrhagic stroke. Reason for this is that former is more common than hemorrhagic stroke. Our results differ from the results described from India where hemorrhagic stroke was more common.<sup>8</sup>

Among 75 patients who had hyponatremia, 41 patients died during their stay at hospital while 34 patients improved and were discharged from hospital. Among control group having normal sodium levels, 20 patients died during hospital stay while 55 improved and discharged from hospital (RR=2.05, P=0.001). This showed that there is strong association between hyponatremia and in-patients mortality. Similar trends of mortality were observed in other studies from all over and hyponatremia had been established as an independent risk factor.<sup>3,4,9,11</sup>

Regarding type of stroke, 22 patients with ischemic stroke and hyponatremia died as compared to 7 patients with ischemic stroke but without hyponatremia (RR=3.463). For hemorrhagic stroke, 19 patients with hemorrhagic stroke and hyponatremia died as compared to 13 patients with hemorrhagic stroke but without hyponatremia. There have been few international studies evaluating the impact of hyponatremia on mortality in stroke patients with inconsistent results<sup>8-11</sup>. There results were consistent with results of our study. Similar results were obtained from one study conducted in Germany. In this study, hyponatremia was found to be an independent predictor of in-hospital mortality in these patients but with 15.6% hyponatremia prevalence and 40.9% mortality<sup>9</sup>. In another study conducted at USA, hyponatremia was found 16% in stroke patients and it was observed that hyponatremia was associated with acute mortality and poor discharge outcome from hospital<sup>11</sup>. In one study recently conducted in India, it was seen that in-hospital mortality of patients was almost double in hyponatremic patient as compared to normonatremic patient. In this study, in-hospital mortality was 40.9% for hyponatremic patients as compared to 21.1% mortality in hospital for normonatremic patient<sup>12</sup>. Therefore, we can say that hyponatremia is a cause of high mortality in hospital in patients of stroke.

There have been few international studies evaluating the impact of hyponatremia on mortality in stroke patients with inconsistent results<sup>8-11</sup>. There results were consistent with results of our study. Similar results were obtained from one study conducted in Germany. In this study, hyponatremia was found the independent predictor of in-hospital mortality in these patients but with 15.6% hyponatremia prevalence and 40.9% mortality<sup>9</sup>. In another study conducted at USA, hyponatremia was found 16% in stroke patients and it was observed that hyponatremia was associated with acute mortality and poor discharge outcome from hospital<sup>11</sup>. In one study recently conducted in India, it was seen that in-hospital mortality of patients was almost double in hyponatremic patient as compared to normonatremic patient. In this study, in-hospital mortality was 40.9% for hyponatremic patients as compared to 21.1% mortality in hospital for normonatremic patient<sup>12</sup>. Therefore, we can say that hyponatremia is a cause of high mortality in hospital in patients of stroke.

## **Conclusion**

Hyponatremia is strongly associated with high mortality in hospitalized patients with stroke.



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