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# Association Between Serum Procalcitonin Levels and Functional Outcome in Acute Ischemic Stroke Patient

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**Abstract:**

***Background:*** *Stroke is the second commonest cause of death in developed countries. It is responsible for severe physical disability of a large population. The study was designed to see the association of serum procalcitonin concentration (PCT) with outcome of acute ischemic stroke (AIS) patients.* ***Methods:*** *This study was a prognostic cohort study. A total number of 60 patients, aged 18 years and above, presenting with AIS, from 0 day to 3 days were enrolled in this study. Blood sample was collected for estimation of serum PCT concentration. Modified Rankin Scale (mRS) was done after 1 month of stroke. Unfavorable outcome was defined as mRS>2 and favorable outcome as 0-2.* ***Results:*** *Patients with unfavorable outcome had significant higher serum PCT concentration than patients with favorable outcome (271.82 ± 130.33 vs.128.51 ± 113.91). A positive correlation (r =0.418) was found between mRS score and serum procalcitonin concentration, which was also significant (p<0.001).On logistic regression analysis, higher serum PCT concentration remained independent predictor of unfavorable outcome of AIS patients (p=0.009, Odds Ratio = 1.027).* ***Conclusion:*** *Higher serum PCT concentration is associated with unfavorable outcome of AIS.*

***Key words:*** *Acute ischemic stroke; Serum procalcitonin; Unfavorable outcome; mRS score.*

## Introduction

Stroke is one of the major global health problems. It is the leading cause of adult disability. Mortality from strokes is the second leading cause worldwide[1]. It is the third most common cause of death and the leading cause of adult disability in Bangladesh[2].

Acute stroke is characterized by the rapid appearance (usually over minutes) of a non-convulsive, non-traumatic focal deficit of brain function, most commonly a hemiplegia with or without signs of focal higher cerebral dysfunction (such as aphasia), hemi sensory loss, and visual field defect or brain-stem deficit. Provided that there is a clear history of a rapid-onset focal deficit, the chance of the brain lesion being anything other than vascular is 5% or less[3]. Eighty-five percent of these events are ischemic strokes[4].

The causes of stroke are not fully known, but inflammatory mechanisms play a central role in the pathogenesis and progression of stroke[5]. During the first 3 posttraumatic days 90% of the patients

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exhibited a generalized inflammatory syndrome without infection[6]. Inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) have been identified as predictors of stroke[7]. Serum procalcitonin (PCT)—a marker of septicemia and infection severity[8] has also been proposed as an indicator of systemic inflammatory response in noninfectious situations6,9. Procalcitonin (PCT), a protein comprising 116 amino acids, with a molecular weight of 13 kDa, is a prohormone of calcitonin produced by C-cells of the thyroid gland. But the probable site of PCT production in inflammation are the neuroendocrine cells in the lungs or intestine[10].

Serum PCT levels at admission is associated with stroke severity and lesion volume, and elevated levels could be considered as an independent diagnostic marker for acute ischemic stroke patients[11]. Early and transient release of procalcitonin circulation was observed after severe trauma6, the amount of circulating procalcitonin seemed to be proportional to the severity of tissue injury and hypovolemia, yet unrelated to infection, indicating an inflammation-related induction of procalcitonin9.The highest median procalcitonin level were recorded on days 2 and

3. Higher levels of procalcitonin were independently associated with ischemic stroke risk in amultiethnic, urban cohort[12], and there is a relationship between procalcitonin serum levels and functional outcome in stroke patients[13].

However, to our knowledge, the value of measurement of procalcitonin levels in our population with stroke and the association with stroke have not yet been examined well. Thus, we sought to investigate the association between procalcitonin serum levels and functional outcome in acute ischemic stroke patients.

**Methods:**

This prognostic cohort study was done in the department of neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and department of internal medicine, Dhaka Medical College Hospital, Dhaka from 1st July 2016 to 31st March 2017. Sample size was estimated according to a previous study[13]. Purposive sampling was carried out and 60 Bangladeshi patients of both sexes, aged 18 years and above, presenting with AIS defined according to the World Health Organization criteria (rapidly developing clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin),within first 3 days of presentation (as the highest median procalcitonin level were recorded on days 2 and 3 and confirmed by neuroimaging were included in this study. Exclusion criteria were haemorrhagic stroke, venous stroke, transient ischemic attack, subarachnoid haemorrhage, embolic brain infarction, brain tumours, cerebrovascular malformation, bacterial sepsis (systemic inflammatory response (SIRS) caused by documented bacterial infection. SIRS defined by the presence of two or more-body temperature >38.5°C or <35.0°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or PaCO2<32 mmHg or a need for mechanical ventilation, white blood cell count >12,000/cmm or <4,000/cmm, immature forms >10 percent), and localized bacterial infections [pneumonia (auscultator respiratory crackles combined with at least 1 of the following- temperature 380C, new purulent sputum or positive chest radiograph) , meningitis (characteristic combination of pyrexia, headache and meningism with documented bacterial infection), peritonitis (characteristic abdominal pain, ascites with documented bacterial infection)]. Patients with non- infectious inflammatory stimuli (major burn, severe trauma, acute multi-organ failure, pancreatitis, major abdominal or cardiothoracic surgery), liver or renal diseases (SGPT> 88IU/L, Serum creatinine> 1.5 mg/dl), medullary thyroid carcinoma(Firm thyroid mass, cervical lymph node, raised serum calcitonin level with documented (USG, CT, FNAC) evidence) or other neoplastic diseases were also excluded in this study. Control group included 20 age-matched volunteer of both sexes, had no known diseases and were not using any medication. Prior to commencement, the research protocol was approved by the Institutional Review Board (IRB).

Informed written consent was taken from all subjects. Detailed history was taken and recorded through a structured questionnaire and thorough physical examinations were performed in both groups.

Neurological functions were measured with National Institutes of Health Stroke Scale (NIHSS) [Normal/near normal examination (0-1), Minor stroke (1-4), Moderate stroke (5-15), Moderate/severe stroke (15-20), Severe stroke (>20)]3on admission. A Blood sample (3-4ml venous blood) was taken for serum procalcitonin measurement on admission and was sent to Microbiology department of BIRDEM, Dhaka. Serum procalcitonin was measured by enzyme linked immunosorbent assay (ELISA) method (Biotech-ELA 808).Normal level of serum PCT<0.1ng/ml14.

Clinical outcomes were graded by using the modified Rankin Scale (mRS) after 1 month of stroke. Outcome was divided into unfavorable outcome and favorable outcome. Unfavorable outcome was defined as mRS>2 or death and favorable outcome was defined as 0-2according to Deng et al.13. The mRS score was carried out by the same investigator without any knowledge on the baseline procalcitonin concentration.

**Data processing and data analysis:**

For statistical purposes, Chi-square and Independent t tests were used to compare variables between two groups. Spearman's rank correlation was done to see the association between serum procalcitonin level and outcome after 1 month (based on mRS score). Receiver operating characteristics (ROC) curve was constructed to find out the optimal cutoff value, specificity and sensitivity of the serum procalcitonin level as a test for prognostic evaluation of acute ischemic stroke. Finally, based on the above analyses, theoretical background and specification of statistical modeling, the logistic regression analyses were performed. A p-value of <0.05 was considered as statistically significant. All data were processed using SPSS version-22.0.

**Results**

**Table-I**

*Distribution of the study population by age groups (n=60)*

| Age group (years) | Frequency (n) | Percentage |
|---|---|---|
| 41-50 | 10 | 12.5 |
| 51-60 | 18 | 22.5 |
| 61-70 | 17 | 21.3 |
| 71-80 | 13 | 16.3 |
| >80 | 2 | 2.5 |
| Mean (±SD) | 62.98 (±10.94) | |
| Min-Max | 42-85 | |

The table I showed that the mean age (±SD) of the study population was 62.98 (±10.94) years with a range from 42 to 85. The most frequent age group was 51-60 years representing 22.5% followed by 21.3% in 61-70 year

**Table-II**

*Distribution of the study population by Gender (n=60)*

| Gender | Frequency (n) | Percentage |
|---|---|---|
| Male | 37 | 61.7 |
| Female | 23 | 38.3 |
| Male : Female ratio | 1.6 : 1 | |

Table II shows distribution of patients by gender. Out of all patients, 38.3% patients were female and 61.7% male. Male and female ratio was 1.6:1.

**Table-III**

*Distribution of clinical presentations in study population (n-=60)*

| Clinical presentation | Frequency | Percentage |
|---|---|---|
| Hemiparesis or hemiplegia | 52 | 86.7 |
| Aphasia | 17 | 28.3 |
| Dysarthia | 14 | 23.3 |
| Impaired consciousness | 1 | 1.7 |
| Headache | 2 | 3.3 |
| Vomiting | 4 | 6.7 |
| Visual complains | 3 | 5 |

Table III showed clinical presentation of the study population. It was observed 52 (86.7%) patients had hemiparesis, 17 (28.3%) had aphasia, 14

**Table-IV**

*Distribution of serum procalcitonin level according to stoke severity (by NIHSS) among the study population*

| Group | Serum procalcitoninlevel (pg/L) | Range | P value |
|---|---|---|---|
| Minor stroke | 65.24 (±47.59)# | 11.16 - 125.50 | |
| Moderate stroke | 101.77(±63.52) | 12.70 - 298.80 | |
| Moderate to severe stroke | 240.27 (±127.59) | 119.34 - 460 | 0.003S |
| Severe stroke | 342.35 (±106.45) | 189.39 - 549 | |

S= significant
# mean (±SD)
*p value derived from Kruskal-wallis test

(23.3%) had dysarthia, 4 (7.1%) had vomiting and 3 (5%) had visual complains.

Table IV shows distribution of serum procalcitonin level according to stoke severity (by NIHSS) among the study population. The mean (±SD) value of serum procalcitonin was measured in different categories. The highest increased value of serum procalcitonin was recorded in severe stroke which was 342.35 (±106.45) pg/L in the range of 189.39 to 549 pg/L. It was followed step by step by moderate to severe stroke accounted 240.27 (±127.59) pg/L, 101.77 (±63.52) pg/L in moderate stroke and 64.24 (±47.59) pg/L in minor stroke. The significance of this increasingtrend of serum procalcitonin level from minor stroke to severe stroke i.e. severity was tested by Kruskal-wallis test which was statistically significant (p-value =0.003).

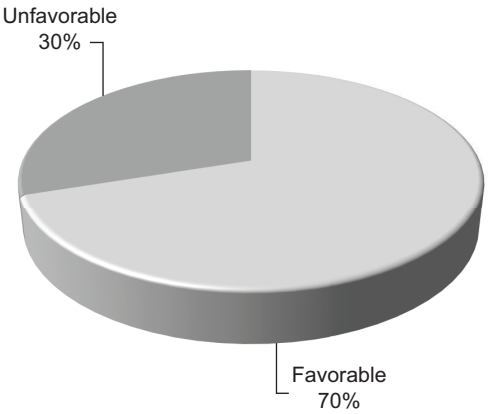


**Fig.-1:** *Pie chart showing the outcome of stroke among the study population according to mRS score (n=60)*

The pie chart showing distribution of the study population according to outcome of stroke based on mRS score. It shows that 70% cases outcome were favorable and 30% cases outcome were unfavorable in this study.

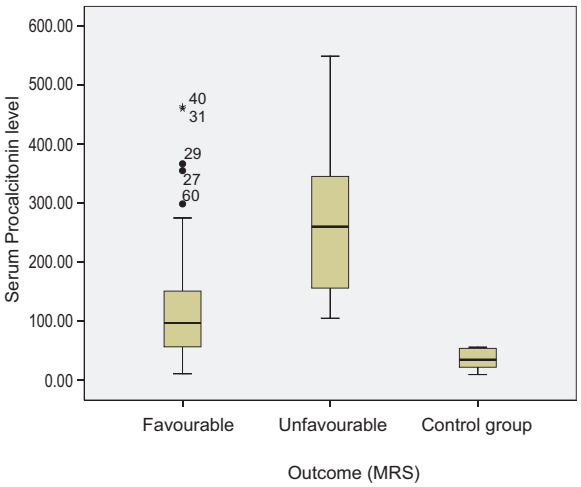


**Fig.-2:** *Box plot showing distribution of serum procalcitonin levels in favorable and unfavorable outcome (according to mRS score) stroke group and control group.*

The Box-plots shows the distribution of serum procalcitonin levels among ischemic stroke patients with favorable and unfavorable outcome compared with control group. It shows that the median value, upper quartile, lower quartile of serum procalcitonin level is more in unfavorable outcome group than favorable outcome group. It is also noticeable that both group of ischemic stroke patients' median value, upper quartile, lower quartile of serum procalcitonin level is more than control group.

**Table-V**

*Mean of Serum procalcitonin level between favorable and unfavorable outcome group*

| Outcome | Serum procalcitonin in pg/L (Mean±SD) | p-value* |
|---|---|---|
| Favorable (n=42) | 128.51±113.91 | |
| Unfavorable (n=18) | 271.82±130.33 | <0.001S |

S= Significant
*p-value derived from independent t test

**Table-VI**

*Comparison of serum procalcitonin in between acute ischemic stroke patients and control group*

| Variables | | Ischemic stroke patient (n=60) | Control group (n=20) | p-value* |
|---|---|---|---|---|
| Serum procalcitonin (Mean±SD) | | 171.50±135.27 | 35.71±16.33 | 0.001s |
| Age (Mean±SD) | | 62.98±10.94 | 61.30±12.06 | 0.563ns |
| Sex | Male | 37 | 10 | |
| | Female | 23 | 10 | 0.118ns** |

S= Significant, ns= not significant
*p-value derived from independent t test
**p-value derived from chi square test

The table V shows the mean value of serum procalcitonin level in favorable and unfavorable outcome group in the study population. The mean value of serum procalcitonin level in unfavorable outcome group were found more than favorable outcome group which is statistically significant (p<0.05).

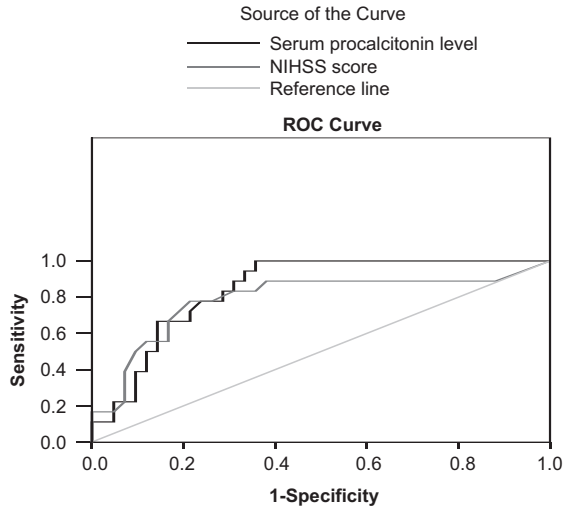


**Fig.-3:** *Receiver operating characteristic (ROC) curves showing the accuracy of serum procalcitonin level and NIHSS score to predict functional outcome of acute ischemic stroke patients*

Receivers operating characteristic (ROC) curves were utilized to evaluate and compare the accuracy of serum procalcitonin level and NIHSS score to predict functional outcome of acute ischemic stroke patients. Graphically it shows that procalcitonin level has greater discriminatory ability as compared to NIHSS score in predicting the outcome.

| Test Variables | Functional outcome | | |
|---|---|---|---|
| | Area under the curve (AUC) | 95% CI | p-value |
| Serum procalcitonin level | 0.85 | 0.75-0.94 | |
| NIHSS score | 0.79 | 0.65-0.93 | <0.001 |

Calculated value of area under the curve (AUC) of ROC showed that serum procalcitonin has more value than NIHSS score which is statistically significant. So it can be concluded that serum procalcitonin is superior than NIHSS score in predicting the outcome of ischemic stroke patients.

Based on the ROC curve, the optimal cut-off value of serum procalcitonin level as an indicator for unfavorable outcome for acute ischemic stroke was estimated to be 208 pg/L which yielded a sensitivity of 66.67% and a specificity of 85.71%.

**Table-VII**

*Comparison of outcome according to the optimal cut-off value (208 pg/L) of serum procalcitonin in the study population*

| Serum procalcitonin level (pg/L) | Outcome | | Total | P value* | OR | 95% CI of OR |
|---|---|---|---|---|---|---|
| | Unfavorable | Favorable | | | | |
| ≤208 | 6 | 35 | 41 | | | |
| >208 | 12 | 7 | 19 | 0.002[S] | 10 | 2.8-35.719 |

S= Significant
*p-value derived from chi square test

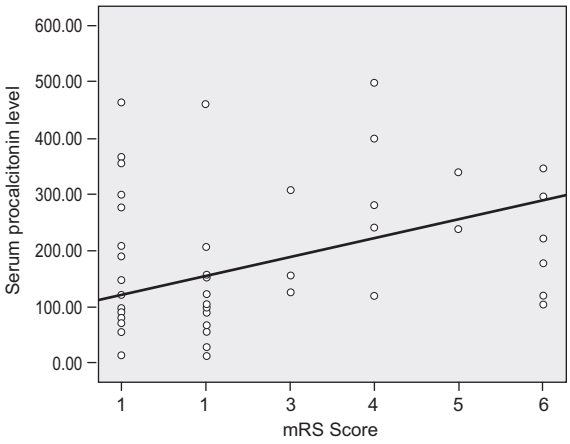


**Fig.-4:** *Correlation between serum procalcitonin level (within 3 days of acute ischemic stroke) and outcome after 1 month (based on mRS score)*

This figure shows correlation between serum procalcitonin level (within 3 days of acute ischemic stroke) and outcome after 1 month (based on mRS score). Spearman rank correlation coefficient test was done. Here we found positive correlation co-efficient (rs=0.418) which is statistically significant (p=0.001).

The table VIII shows the result of logistic regression analysis for prediction of acute ischemic stroke outcome within one month. It revealed that age, raised serum procalcitonin level (within first 3 days of the event) and dyslipidaemia were found independent predictor for acute ischemic stroke outcome within one month. Logistic regression analysis showed statistically significant p- value for these three variables among the others variables in the study population.

**Table-VIII**

*Logistic regression analysis for prediction of acute ischemic stroke outcome within one month (based on mRS score)*

| Variables | p-value | OR | 95% CI for OR | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age | 0.02 | 1.84 | 1.02 | 2.18 |
| Sex | 0.91 | 0.856 | 0.064 | 11.42 |
| Serum procalcitonin level | 0.009 | 1.027 | 1.007 | 1.049 |
| HTN | 0.98 | 0.97 | 0.08 | 11.74 |
| DM | 0.623 | 0.439 | 0.016 | 11.71 |
| Dyslipidaemia | 0.048 | 9.5 | 1.48 | 16.29 |
| Previous vascular event | 0.24 | 5.8 | 0.31 | 11.02 |
| Heart disease | 0.12 | 2.4 | 0.43 | 13.86 |
| Family history of stroke | 0.13 | 7.17 | 0.56 | 19.7 |
| Site of stroke | 0.735 | 1.55 | 0.68 | 1.98 |

**Discussion:**

This current study was done with an aim to find out the association of serum procalcitonin concentration with outcome of ischemic stroke patients.

A total of 60 patients/cases and 20 controls were assessed in this study. The mean (± SD) age of the study population, was found to be 62.98 ± 10.94 years ranging from 42 to 85 years, with a male/female ratio of 1.6: 1. The highest number (22.5%) of the patients was in the 51-60 years age group.In a previous study15 found that the mean (± SD) age was 64.06± 11.238 years with a male/female ratio of 1.9:1. In another study16, found that the mean (± SD) age was 59.97± 12.12 years with a male/female ratio of 1.6:1. Since, both of these studies were conducted on the same population, the results were nearly similar to one another. However, these demographic profiles are likely to vary when the study population is different. Dziedizic et al.,17 and Idicula et al.,18found that mean age of 68 ± 12 and 70.3 ± 14.4 years and a male/female ratio of 0.96:1 and

1.29:1 respectively in European population. These results show that the patients are of older age and the frequency of males and females are nearly equal in European population. In contrast, current study population shows the patients were of relatively younger age and frequencies of male slight higher than female. Higher average life expectancy in European people may explain the older age but explanation of differences in sex is not clear.

In this current study, HTN and DM was found in 71.6% and 35% of patients respectively. According to Saha et al16 HTN was the commonest risk factor (60%) and other common risk factor was (Diabetes mellitus (17%). In another study19,20 HTN and DM was found in 68.38% and21.48% ischemic stroke patients respectively in Poland17. These results suggest that rate of HTN may be similar in various populations, but DM may differ.

The present study observed the association of serum procalcitonin concentration with acute ischemic stroke patients. The mean (± SD) serum procalcitonin concentration was 171.50 (±135.27) pg/L in the present study. Likewise, the mean serum procalcitonin was 0.88ng/L or 880pg/L13 and 0.86ng/L or 860pg/L11 in previous two studies. This may be due to geographical

influences. Patients with unfavorable outcome had significant higher serum procalcitonin concentration than patients with favorable outcome (271.82 ± 130.33 versus128.51 ± 113.91). The serum procalcitonin concentration ranged from 11.16pg/L to 498pg/L and 19 (32%) patientshad serum procalcitonin concentration >208pg/L and 41 (68%) patients had serum procalcitonin concentration <208pg/L.

In current study, serum procalcitonin concentration on admission was highly significant ($p<0.001$) with mRS score after 1 month of stroke. A positive correlation co-efficient ($r =0.418$) was found between mRS Score and serum procalcitonin concentration of the study population, which was statistically significant ($p<0.001$). This study concluded that increase serum procalcitonin concentration associated with unfavorable outcome (mRS score>2) of acute ischemic stroke patients.

In logistic regression analysis for human serum procalcitonin concentration variable that the estimated odds ratio (OR) was 1.027, which means the patients with high serum procalcitonin concentration have odds to have unfavorable outcome and this was significant at a p-value of 0.009. It was observed that lower concentration on admission is more likely to have favorable outcome in acute ischemic stroke than higher serum procalcitonin concentration. On one previous study11 high serum procalcitonin was found to be independently associated with better outcome (OR= 3.12, 95% CI = 1.55-8.06, p =0.0001) and in another one13, higher serum procalcitonin concentration was found to be an independent predictor of unfavorable outcome (OR= 3.45, 95% CI = 2.29-4.77) of ischemic stroke. All of these above mentioned previous studies coincide with the finding of current study.

Overall, in all of the studies including the current one, it can be assumed that serum procalcitonin concentration was either a predictor or was

associated or correlated with functional outcome of acute ischemic stroke.

We acknowledge limitations to our approach as well. Long-term functional outcome beyond one month was not included in this study. Furthermore, the sample size was small and Serum PCT was measured only at admission. Serial measurement of PCT was not done, so dynamic changes of PCT were not assessed. In addition, other ancillary prognostic tools such as MRI or hs-CRP were not seen along with PCT.Conclusions:

In conclusion, our study reveals that higher serum procalcitonin concentration in acute ischemic stroke is independently associated with unfavorable functional outcome. So, it might be considered as an important promising prognostic biomarker for assessing the severity, course and prognosis in early stage of the disease and therefore, active management in acute stage would be helpful in decreasing the risk of unfavorable outcome. Large scale population based studies are needed to elucidate these concerns.

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