



## A Study On The Correlation Between Serum Cortisol And Severity Of Acute Ischemic Stroke In Patients

**Dr.S. Ashok Kumar**

Professor

Department Of Medicine, Madha Medical College And Research Institute, Kovur, Chennai

**\*Corresponding Author:**

**Dr.S. Ashok Kumar**

Professor, Department Of Medicine, Madha Medical College And Research Institute, Kovur, Chennai

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### Abstract

**Introduction:** There are many clinical variables like symptom severity and advanced age which are identified as potential predictors of outcome in patients with acute stroke. But there is an immense need to detect a biomarker for predicting the outcome of acute stroke. The stress response that occurs after the event of acute stroke causes the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Certain studies have found that increased serum cortisol level in patients with acute stroke is related to larger infarct volume, greater stroke severity, and poor outcome, including death

**Aim And Objective:** To assess the relationship of single serum cortisol levels to the severity of acute ischemic stroke.

**Materials And Methods:** About 50 new cases of acute ischemic stroke patients, within 72 hours of the acute neurological event, who were admitted to the department of medicine, Madha medical college and research institute, kovur, Chennai throughout the year 2020-2021 were included in the study. The study was conducted for 6 months. CT Brain was taken during admission to confirm acute ischemic stroke. NIHSS (National Institute of Health Stroke Scale) scores for all the patients were assessed for severity at the time of admission. Serum cortisol levels were measured the next day early morning. After 15 days, the functional outcome of the patients was assessed using the modified Rankin Scale. The correlation between serum cortisol levels and stroke scales is assessed by Chi-Square Test. All statistical analyses are performed using SPSS (software package used for statistical analysis) package.

**Results:** Of the 50 cases, serum cortisol levels of 23 cases were within normal limits ( $\leq 690$  nmol/L) of which 65.2% had an NIHSS score of less than or equal to 6 and 34.8% of the cases had NIHSS score more than 6. As the NIHSS score of less than or equal to 6 is considered to be a minor stroke, it is obvious from the above findings that most of the cases with normal cortisol levels had no major stroke. The remaining 27 cases had elevated serum cortisol levels. 100% of the cases with serum cortisol levels of more than 690 nmol/L had NIHSS scores above 6. With the p-value of  $<0.001$ , this is found to be statistically significant. As the NIH's score above 6 is considered to be moderate to severe stroke, it is obvious from the above observation that nearly all cases with elevated cortisol levels had moderate to severe stroke. Of the 50 cases, serum cortisol levels of 23 cases were within normal limits ( $\leq 690$  nmol/L) of which 78.3% had MRS score less than or equal to 3 and 21.7% had MRS score more than 3. Since the MRS score is a measure of functional outcome and any score less than or equal to 3 is considered to have a favorable outcome, it is clear from the above findings that most of the cases with normal serum cortisol had a favorable outcome with minimal neurological impairment. And in the remaining 27 cases which had a serum cortisol level of more than 690 nmol/L, 3.7% had an MRS score of less than or equal to 3 and 96.3% had an MRS score of more than 3. With the p-value of  $<0.001$ , this is statistically

significant. Since an MRS score of more than 3 is associated with a bad outcome, most of the cases with elevated serum cortisol had a poor outcome with severe neurological impairment.

**Conclusion:** Among the patients with acute ischemic stroke, high serum cortisol levels at the time of admission correlate with, Clinical severity which is assessed by the National Institute of Health Stroke Scale, and poor prognosis and functional outcome after 15 days which is assessed by Modified Rankin Scale

**Keywords:** Acute ischemic stroke, HPA axis, serum cortisol, clinical severity, Functional outcome, stroke scales

## Introduction

There are many clinical variables like symptom severity and advanced age which are identified as potential predictors of outcome in patients with acute stroke. [1]But there is an immense need to detect a biomarker for predicting the outcome of acute stroke. The period that ensues after the event of acute stroke can be regarded as a reaction to a stressful event. This stress response causes the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system.[2] In an acute stroke, the first measurable alterations are the endocrine changes because of the alteration in HPAaxis.[3] One of the HPA axis-related hormones is cortisol which has a robust circadian rhythm wherein the levels peak typically in the early hours of the day and decline later on. [4]Cortisol has got a significant effect on glucose, fat and protein metabolism, and cardiovascular reactivity. Some studies showed that high serum cortisol levels are associated with very much decreased physical function and an impaired level of consciousness.[5] salivary cortisol levels can be used as a biological marker for identifying patients who are prone to acquiring lower benefits from inpatient rehabilitation services.[6] It is also proved in many studies that, increased cortisol concentrations have been observed in acute ischemic stroke and SAH.[7] Certain studies have found that increased serum and urinary cortisol level in patients with acute stroke is related to larger infarct volume, greater stroke severity, and poor outcome, including death. After the acute event, increased serum cortisol level is significantly associated with the acute confusional state.[8]The primary objective of this study dissertation is to test the hypothesis that increased single serum cortisol level is associated with increased severity of acute ischemic stroke. [9]Though cortisol level has diurnal variations it has

been shown that the normal circadian rhythm of cortisol is suspended during acute stroke and there is no variation of cortisol level in serum throughout the day due to perturbations in the HPA axis.[10]

**Materials And Methods:** About 50 new cases of acute ischemic stroke patients, within 72 hours of the acute neurological event, who were admitted to the department of medicine, Madha medical college and research institute, kovur, Chennai throughout the year 2020-2021 were included in the study. The study was conducted for 6 months. CT Brain was taken during admission to confirm acute ischemic stroke. NIHSS (National Institute of Health Stroke Scale) scores for all the patients were assessed for severity at the time of admission. Serum cortisol levels were measured the next day early morning. After 15 days, the functional outcome of the patients was assessed using the Modified Rankin Scale: Inclusion criteria: Patients in the age group above 18 years, Patients proved to have acute ischemic stroke admitted within 72hrs of onset of a neurological event (by CT Brain - Plain)Exclusion criteria: Age< 18 years, Pregnancy, Liver disease, Patient who are taking following drugs: Immunosuppressants, Steroids, Rifampicin, Phenytoin. serum cortisol levels are compared with NIHSS score and MRS score and levels more than 690nmol/L are considered to be elevated and severity assessed as defined by NIHSS score (score>6) at the time of admission and modified Rankin scale (scale >3) during follow up. Blood samples were taken on the next day morning after admission and serum cortisol levels were measured. The serum cortisol is measured quantitatively using Enzyme Immuno Assay. The principle of the test is based on the competition that is occurring between the unlabelled antigen and the antigen which is an enzyme labeled for limited antibody binding sites on the microwell plates. The unbound materials are removed by

washing and decanting methods. The enzyme-substrate is added. By the addition of a stop solution, the enzymatic reaction is terminated. The microtitre plate reader measures the absorbance. The intensity of the formed color is inversely proportional to the cortisol concentration in the sample. A set of standards are used to plot a standard curve. Through which the amount of cortisol is direct read.5 ml of venous blood is collected into the collecting tube and allowed to clot and centrifuged and the serum layer is removed. Working solutions of the cortisol Horse Radish Peroxidase conjugate and wash buffer is prepared. The required number of microwell strips are removed in a polyclonal antibody-coated microwell plate. 20microlitre of each calibrator, control, and specimen sample is pipetted into the corresponding labeled wells in duplicate.100 microlitre of conjugate working solution is pipetted into each well. Then it is incubated into a plate shaker(around 200rpm) for forty-five minutes at

room temperature. Then the wells are washed with diluted wash buffer and dried.150 microlitre of tetramethylbenzidine substrate is pipetted into each well at intervals of time. Then it is again incubated on a plate shaker at room temperature for 20 minutes.50 microlitre of stop solution is pipetted into the well at timed intervals. Within 20 minutes after the addition of the stop solution, the plate is read on a microwell plate reader at 450nm. Results are calculated using mean optical density and calibrator curve and multiplied by a dilution factor.

**Statistical Analysis:** Mean values of the parameters are calculated by the independent sample – t-test. The correlation between serum cortisol levels and stroke scales is assessed by Chi-Square Test. All statistical analyses are performed using SPSS (software package used for statistical analysis) package. A p-value of less than 0.05 is considered to be statistically significant.

**Results**

**Table: 1. Age Wise Distribution Of Stroke**

AGE IN YEARS	NUMBER OF CASES	PERCENTAGE
31-40	3	6
41-50	4	8
51-60	9	18
61-70	19	38
71-80	11	22
81-90	4	8
<b>Total</b>	<b>50</b>	<b>100</b>

Table :1 The minimum age of the patients is 31 years and the maximum age is 85 years. Among the 50 patients, 6% are in 31-40 years, 8% are in the 41-50 years,18 % in the 51-60 years,38% in the 61-70 years, 22% in the 71-80 years,8% in the 81-90 years.Of the 50 cases , 29 were males and 21 were female i.e.,58 percent were males and 42 percent were females

**Table: 2 . Mean Cortisol Level In Male And Female Cases**

Table:2 Mean cortisol levels in male cases are 631.07 and in female cases are 659.14.

**Table : 3. Number Of Cases With And Without Coronary Artery Disease**

SEX	N	MEAN CORTISOL	STANDARD DEVIATION	STANDARD ERROR OF MEAN
MALE	29	631.07	138.199	25.663
FEMALE	21	659.14	194.324	42.405

	NUMBER OF CASES	PERCENTAGE
CAD	12	24
NON-CAD	38	76
TOTAL	50	100.0

Table :3 Of the 50 cases, coronary artery disease was present in 12 and absent in 38.ie., 24 percent had CAD and 76 percent did not have CAD. Of the 50 cases 13 had systolic BP less than 140mmHg, 37 had systolic BP more than or equal to 140mmHg.ie., 26 percent had normal systolic blood pressure and 74 percent had elevated systolic blood pressure

**Table: 4. Mean Cortisol Level In Cases With And Without Coronary Artery Disease**

CAD	N	MEAN CORTISOL	STANDARD. DEVIATION	STANDARD ERROR OF MEAN
YES	12	612.92	175.944	50.791
NO	38	652.32	159.808	25.924

Table:4 Mean cortisol levels in cases with coronary artery disease are 612.92 and in cases without coronary artery disease are 652.32.

**Table: 5. Number Of Cases With Nihss Score Less Than Or Equal To 6 And Greater Than 6**

	NUMBER OF CASES	PERCENTAGE
NIHSS $\leq$ 6	15	30
NIHSS $>$ 6	35	70
<b>TOTAL</b>	<b>50</b>	<b>100.0</b>

Table:5 Of the 50 cases, 15 had NIHSS score less than or equal to 6 and 35 had NIHSS score more than 6. i.e., 30 % had NIHSS less than or equal to 6 and 70 % had NIHSS more than 6

**Table: 6. Number Of Cases Based On Modified Rankin Scale Less Than Or Equal To 3 And More Than 3**

	NUMBER OF CASES	PERCENTAGE
MRS $\leq$ 3	19	38.0
MRS $>$ 3	31	62.0
<b>TOTAL</b>	<b>50</b>	<b>100.0</b>

**Table:6** Of the 50 cases 19 had a Modified Rankin scale of less than or equal to 3 after 15 days and 31 had a Modified Rankin Scale of more than 3 after 15 days. i.e., 38 percent had MRS $\leq$ 3 and 62 percent had MRS  $>$ 3

**Table: 7. Number Of Cases With Normal And Elevated Serum Cortisol**

	NUMBER OF CASES	PERCENTAGE
SERUM CORTISOL $\leq$ 690nmol/L	23	46
SERUM CORTISOL $>$ 690nmol/L	27	54

<b>TOTAL</b>	<b>50</b>	<b>100.0</b>
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**Table:7** Of the 50 cases, 23 had normal serum cortisol of less than or equal to 690 nmol/L and 27 had elevated serum cortisol of more than 690 nmol/L.ie., 46 percent had normal serum cortisol levels and 54 percent had elevated serum cortisol levels

**.Table:8 Distribution Of Cases Based On Territory Of Infarct**

	<b>NUMBER OF CASES</b>	<b>PERCENTAGE</b>
ACA	6	12.0
MCA	42	84.0
PCA	2	4.0
<b>TOTAL</b>	<b>50</b>	<b>100.0</b>

**Table:8** Of the 50 cases, 6 had infarct in the Anterior cerebral artery territory and 42 had infarct in the middle cerebral artery territory and 2 had infarct in the posterior cerebral artery territory.ie., 12 percent had ACA territory infarct, 84 percent had MCA territory infarct, 4 percent had PCA territory infarct.

**Table: 9. Correlation Of Serum Cortisol Levels And Nihss Score**

<b>NIHSS SCORE ON ADMISSION</b>	<b>SERUM CORTISOL IN NMOL/L</b>			
	<b>&lt;= 690</b>		<b>&gt;690</b>	
	<b>NO OF CASES</b>	<b>PERCENTAGE</b>	<b>NO OF CASES</b>	<b>PERCENTAGE</b>
Less than or equal to 6	15	65.2	0	0
More than 6	8	34.8	27	100
<b>TOTAL</b>	<b>23</b>	<b>100</b>	<b>27</b>	<b>100</b>

Table:9 Of the 50 cases, serum cortisol levels of 23 cases were less than or equal to 690nmol/L, of which 15 cases had NIHSS score of less than or equal to 6 and 8 had NIHSS score of more than 6. Of the cases with serum cortisol of less than or equal to 690nmol/L,65.2% had an NIHSS score of less than or equal to 6 and 34.8% of the cases had an NIHSS score of more than 6. The remaining 27 cases had a serum cortisol level of more than 690 nmol/L and their NIHSS score was above 6. 100% of the cases with a serum cortisol level of more than 6 had an NIHSS score above 6. With the p-value of <0.001, this is found to be statistically significant.

**Table: 10. Correlation Of Serum Cortisol Levels With Modified Rankin Scale**

MRS SCORE	SERUM CORTISOL IN Nmol/L			
	<= 690		>690	
	No Of Cases	Percentage	No Of Cases	Percentage
Less Than Or Equal To 3	18	78.3	1	3.7
More Than 3	5	21.7	26	96.3
TOTAL	23	100	27	100

Table:10 Of the 50 cases, serum cortisol levels of 23 cases were less than or equal to 690nmol/L, of which 18 had an MRS score, which is measured after 15 days, of less than or equal to 3, and 5 had an MRS score of more than 3. Of the cases which had serum cortisol levels less than or equal to 690 nmol/L, 78.3% had MRS score less than or equal to 3 and 21.7% had MRS score more than 3. And in the remaining 27 cases which had serum cortisol levels of more than 690 nmol/L 1 case had an MRS score of less than or equal to 3(3.7%) and 26(96.3%) cases had an MRS score of more than 3. With the p-value of <0.001, this is statistically significant.

**Discussion:** A total of 50 patients were enrolled in the study who were proven to have Acute Ischemic Stroke by CT Brain which was taken at the time of admission. The minimum age of the patients is 31 years and the maximum age was 85 years. Among the 50 patients,38 % of the acute ischemic stroke occurred in the age group of 61 to 70 years. And about 58%were males and 42 % were females. [11]The mean cortisol level was 631.07 in males. The mean cortisol level in females was 659.14Of the 50 cases, 26% were diabetics and 74% were nondiabetics. The mean cortisol level in diabetics was 590.15 7. The mean cortisol level in nondiabetics was 661.38.40 percent were hypertensives and 60 percent were normotensives. The mean cortisol level

in hypertensives was 657.75. The mean cortisol level in normotensives was 632.9324 % had CAD and 76 % did not have CAD. The mean cortisol level in cases with CAD was 612.92.[12] The mean cortisol level in non CAD was 652.32. Of the 50 cases 13 had systolic BP less than 140mmHg, 37 had systolic BP more than or equal to 140mmHg.ie., 26 percent had normal systolic blood pressure and 74 percent had elevated systolic blood pressure. Also, 35 had diastolic BP less than 90 mmHg and 15 had diastolic BP more than or equal to 90 mmHg.ie., 70 percent had normal diastolic BP and 30 percent had elevated diastolic BP Of the 50 cases, 6 had infarct in the Anterior cerebral artery territory and 42 had infarct in the middle cerebral artery territory and 2 had infarct

in the posterior cerebral artery territory. ie., [13] 12 percent had ACA territory infarct, 42 percent had MCA territory infarct, 2 percent had PCA territory infarct. It is clear that the majority of the cases had MCA territory infarct. Of the 50 cases, serum cortisol levels of 23 cases were within normal limits ( $\leq 690$  nmol/L) of which 65.2% had NIHSS scores of less than or equal to 6 and 34.8% of the cases had NIHSS score more than 6 [14]. As the NIHSS score of less than or equal to 6 is considered to be a minor stroke, it is obvious from the above findings that most of the cases with normal cortisol levels had no major stroke. Remaining 27 cases had elevated serum cortisol levels. 100% of the cases with serum cortisol levels of more than 690 nmol/L had NIHSS scores above 6. [15] With the p-value of  $<0.001$  this is found to be statistically significant. As the NIHSS score above 6 is considered to be moderate to severe stroke, it is obvious from the above observation that nearly all cases with elevated cortisol levels had moderate to severe stroke. [16] Of the 50 cases, serum cortisol levels of 23 cases were within normal limits ( $\leq 690$  nmol/L) of which 78.3% had MRS score less than or equal to 3 and 21.7% had MRS score more than 3. Since the MRS score is a measure of functional outcome and any score less than or equal to 3 is considered to have a favorable outcome, it is clear from the above findings that most of the cases with normal serum cortisol had a favorable outcome with minimal neurological impairment. And in the remaining 27 cases which had a serum cortisol level of more than 690 nmol/L, 3.7% had an MRS score of less than or equal to 3 and 96.3% had an MRS score of more than 3. With the p-value of  $<0.001$ , this is statistically significant. [17] Since an MRS score of more than 3 is associated with a bad outcome, most of the cases with elevated serum cortisol had a poor outcome with severe neurological impairment. Also among the 50 cases, 5 cases showed mortality who had elevated serum cortisol ( $>690$  nmol/L) at the time of admission. [18] Similar to the above 2 studies our study also showed a positive correlation between serum cortisol levels and NIHSS score as well as MRS score in predicting the severity of the stroke and the functional outcome, [19] which is found to be statistically significant ( $P < 0.001$ ). Hence it was very clear that acute ischemic stroke was very severe in patients with high serum cortisol levels at the time of admission and also the outcome of the patients after

15 days was poor in patients with high serum cortisol levels. [20]

**Conclusion:** Among the patients with acute ischemic stroke, high serum cortisol levels at the time of admission correlates with, Clinical severity which is assessed by the National Institute of Health Stroke Scale, and Poor prognosis and functional outcome after 15 days which is assessed by Modified Rankin Scale. In humans, the adrenal stress response causes increased blood glucose, catabolism, heart rate, and potentiates ischemic neuronal damage. In acute ischemic stroke, these effects could induce secondary brain damage. Hypothalamic- Pituitary- Adrenal axis alterations are one of the major stress-induced alterations after the event of cerebral ischemia. Cortisol is an independent short-term marker of prognosis of functional outcome and death in patients with acute ischemic stroke even after the correction of confounding factors. Elevated cortisol after the onset of stroke is associated with morbidity, dependency, and mortality. A combined model can however add significant information to the clinical score. Since the early prediction of stroke outcome is very important for therapeutic strategies, serum cortisol level measurement at the time of admission can add significant predictive information to the existing NIHSS score.

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