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# Exploring the Association Between Serum Neurogranin, Nardilysin, and Ischemic Stroke: A Case-Control Study Conducted in the Emergency Department

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** Ischemic stroke (IS) is a major cause of mortality and disability worldwide. Rapid and accurate diagnosis in the emergency department (ED) is crucial for improving outcomes. Neurogranin (Ng), a postsynaptic protein involved in synaptic plasticity, and Nardilysin (NRDC), a metallopeptidase with neuronal functions, have been linked to various neurological disorders. This study examines their potential diagnostic and prognostic value in IS.

**Material/Methods:** This prospective case-control study was carried out in a high-volume ED between June and October 2023. A total of 44 IS patients and 44 healthy controls, matched for age and sex, were included. Serum levels of Ng and NRDC were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analyses involved receiver operating characteristic (ROC) analysis to assess diagnostic value and comparisons of biochemical parameters between groups.

**Results:** Ng levels were significantly higher in IS patients compared to controls (281.12±32.12 pg/mL vs 265.71±24.54 pg/mL, *P*=0.01), with moderate diagnostic accuracy (area under curve=0.624). Elevated Ng levels were associated with intensive care unit admission (311.50±46.13 pg/mL, *P*=0.023). NRDC levels showed no significant differences between groups or clinical outcomes. Biochemical parameters, including elevated urea and creatinine and reduced hemoglobin levels, showed the systemic impacts of IS.

**Conclusions:** Ng may have a limited role as a biomarker in IS diagnosis, while its potential prognostic value requires further validation. NRDC did not show significant utility in this study. Larger studies incorporating additional biomarkers are needed to determine whether Ng can provide clinical insights into IS diagnosis and prognosis.

**Keywords:** Biomarkers • Diagnosis • Emergency Medicine • Neurogranin • Stroke

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## Introduction

Ischemic stroke (IS) is a leading cause of long-term mortality and disability globally, with a growing incidence due to an aging population [1,2]. The prompt identification and management of IS in the emergency department (ED) is crucial, as early intervention can significantly improve patient outcomes [3]. However, the complex pathophysiology of IS, which involves endothelial dysfunction, reduced nitric oxide bioavailability, platelet activation, and neuronal injury, presents challenges in effectively diagnosing and predicting the prognosis of affected individuals [4]. In this context, the identification of novel biomarkers that improve the biochemical diagnosis and prognostic assessment of IS has significant clinical relevance.

Neurogranin (Ng) is another protein, consisting of 78 amino acids, predominantly found in pyramidal cells with a granule-like appearance in the hippocampus and cortex [5,6]. Its name reflects its association with these specific cells, and it is recognized for its role in neurosynaptic plasticity, regeneration, and long-term potentiation [7,8]. Due to its involvement in postsynaptic activity, recent research has focused on exploring the connection between Ng and various neurological conditions [5,9]. Ng has been used as a biochemical test for diagnosing and predicting the prognosis of numerous neurological and psychiatric disorders, including neurodegenerative diseases, Alzheimer disease, Parkinson disease, IS, and schizophrenia [5,10]. Additionally, studies have suggested that serum and cerebrospinal fluid (CSF) Ng levels vary in response to diffuse axonal injury, highlighting its potential role as a biomarker in traumatic brain injury models [10]. Moreover, biomarkers like Ng can be analyzed more conveniently than CSF, further emphasizing their significance in studying this group of diseases [5].

N-arginine dibasic convertase, also known as Nardilysin (NRDC), is a metallopeptidase belonging to the M16 family [11,12]. It facilitates the ectodomain shedding of various membrane proteins, including tumor necrosis factor-α and heparin-binding epidermal growth factor, in the extracellular zone [12,13]. Additionally, it regulates transcriptional functions in the nucleus by providing communication between the nucleus and cytoplasm [12,14]. NRDC plays a critical role as a positive regulator in axonal maturation and myelination. Its impact on myelin thickness has been demonstrated in a dose-dependent manner in vivo, showing its potential as a pharmacological target for demyelinating conditions such as multiple sclerosis. Furthermore, NRDC contributes to axonal repair following injury [15]. Evidence from in vivo mouse models also suggests that NRDC helps prevent amyloid plaque formation in Alzheimer disease [16]. These experimental findings underscore NRDC's involvement in a diverse array of neurological disorders [15].

Considering that NRDC and Ng have been investigated in various neurological diseases and found to have significant associations, we hypothesized that these biomarkers might also have a clinical correlation in IS cases, which involve severe neuronal damage. Given their previously established relevance in neurodegenerative and ischemic processes, we propose that NRDC and Ng levels may exhibit meaningful changes in acute IS cases due to neuronal injury. This hypothesis forms the basis of our study, aiming to determine whether these biomarkers could serve as valuable indicators of ischemic cerebrovascular disease.

In this study, we aimed to explore the diagnostic and prognostic potential of Ng and NRDC in IS in the ED. By examining their serum levels in a case-control framework, we assessed their clinical utility in identifying IS and predicting patient outcomes. Understanding the relationship between these biomarkers and IS pathophysiology could provide valuable insights into neuronal damage mechanisms and contribute to the development of novel biochemical tools for improving early diagnosis and risk stratification in acute stroke management.

## Material and Methods

### Ethical Framework, Patient Consent, and Research Center Characteristics

Approval for this study was obtained from the 2nd Ethics Committee of the hospital, where the cases were collected, with approval number E2-23-4178, on May 26, 2023. The researchers provided detailed information about the study to the patients or their legal guardians who were eligible to participate, and informed written consent was obtained from those who agreed. The study was conducted in a tertiary-care, high-volume hospital that serves as a referral center for both medical and surgical emergencies. Patients were admitted through direct emergency visits or transfers via land and air ambulances from surrounding hospitals. This center is fully equipped for stroke management, including advanced imaging modalities and interventional radiology for embolectomy procedures.

### Study Design, Patient Selection, and Diagnosis

This study was designed as a prospective case-control study. The patient and control groups were recruited between June 1 and October 1, 2023. The patient group consisted of individuals diagnosed with IS in the ED, while the control group comprised healthy individuals matched for age and sex.

Patients included in the IS group were those presenting to the ED with an acute neurological deficit. Diagnosis was confirmed through cranial computed tomography (CT) and





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diffusion-weighted magnetic resonance imaging (MRI), demonstrating an ischemic lesion corresponding to the clinical findings. The control group consisted of individuals without any symptoms suggestive of cerebrovascular disease, as confirmed by a detailed neurological examination and the absence of ischemic lesions on neuroimaging.

Participants included in the study were required to be at least 18 years old, provide informed consent, and have no history of chronic neurological or psychiatric disorders. Patients with active infection, malignancy, recent trauma, or pre-existing neurodegenerative diseases that could influence biomarker levels were excluded.

### Biochemical Assessment of Ng and NRDC

For biochemical analysis, 5-mL venous blood samples were collected from all participants into red-capped tubes at the time of admission. The venous blood samples were centrifuged at 1300×g for 10 minutes to separate the serum. The separated serum was aliquoted into Eppendorf tubes and stored at -80°C until further analysis.

Ng and NRDC levels were measured using commercially available ELISA kits in accordance with the manufacturer's protocols. Ng was quantified using an ELISA kit (Fine Test, Wuhan, China; catalog no: EH2396; lot no. H2396H085 E), while NRDC was measured using another ELISA kit from the same manufacturer (catalog no. EH10653; lot no. H10653H085 E). Before analysis, serum samples were diluted 1: 2 with the recommended dilution buffer, as per the manufacturer's instructions.

The 96-well ELISA plates were precoated with anti-Ng and anti-NRDC antibodies. Standard solutions and patient samples were added to the wells, followed by an incubation period. Unbound conjugates were washed away using a buffer, and a biotinylated detection antibody was added to bind with the specific antigen-antibody complexes. After another washing step, horseradish peroxidase (HRP)-streptavidin solution was applied, followed by 3,3',5,5'-Tetramethylbenzidine (TMB) substrate to visualize the enzymatic reaction. The reaction was stopped, and optical density (OD) readings were measured at 450 nm using a microplate reader.

The concentration of Ng and NRDC was determined by comparing OD values to a standard curve, with the detection ranges and assay precision as follows:

- Ng detection range: 78.125-5000 pg/mL, intra- and inter-assay precision <8% and <10%.
- NRDC detection range: 0.313-20 ng/mL, intra- and inter-assay precision <8% and <10%.

To ensure unbiased data collection, the laboratory technician performing ELISA was blinded to the patients' clinical data, imaging results, and group assignments. Similarly, the ED physician responsible for diagnosing patients and interpreting neuroimaging studies was blinded to the biomarker measurements.

### Diagnostic and Prognostic Endpoints

The primary outcome measure was the assessment of Ng and NRDC levels as potential diagnostic and prognostic biomarkers in IS patients. Serum Ng and NRDC levels were evaluated for their ability to differentiate between IS cases and healthy controls. Secondary outcomes included their association with disease severity and the requirement for intensive care unit (ICU) admission.

Additionally, biochemical parameters, such as urea, creatinine, and hemoglobin levels, were analyzed. The study also aimed to assess the diagnostic accuracy of Ng and NRDC through ROC analysis.

### Statistical Analyses

All statistical analyses were conducted using SPSS version 18.0 (IBM, Inc.) and Analyse-it (Analyse-it Software, Ltd). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Comparisons between the IS and control groups were performed using the *t* test or Mann-Whitney U test, as appropriate, while categorical variables were analyzed using Pearson's chi-squared test.

ROC analysis was performed to evaluate the diagnostic performance of Ng and NRDC, with area under the curve (AUC) values and optimal cut-off points determined using the highest likelihood ratio. A $P$ value <0.05 was considered statistically significant.

To ensure the statistical robustness of the findings, post hoc power analysis was performed using the G-Power program. With 44 cases in the IS group and 44 in the control group, at an alpha error of 0.05, the calculated effect size was 0.7069, yielding a study power of 95%.

## Results

### Baseline Characteristics

A total of 44 patients with IS and 44 age- and sex-matched healthy controls were included in the study. Sex distribution was similar between the 2 groups, with no statistically significant difference observed ($P$=0.83). The mean age of IS patients was 71.48±14.19 years, slightly older than that of the





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**Table 1.** Descriptive characteristics of IS patient and control groups comparing Nardilysin and neurogranin values and their comparison with each other.

| | Ng Group (n) | Control Group (n) | *P* value |
|---|---|---|---|
| Sex | | | |
| Female | 23 | 21 | *P*=0.83 |
| Male | 21 | 23 | |
| Age | 71.48±14.19 | 66.52±8.93 | *P*=0.1 |
| BMI | 26.25±4.35 | 24.11±2.12 | ***P*=0.005** |

IS – ischemic stroke; BMI – body mass index.

**Table 2.** Neurological concerns in IS patients whose NRDC and Ng levels were investigated.

| | n (%) |
|---|---|
| Dysarthria | 15 (34%) |
| Right lateral deficit | 14 (31%) |
| Facial asymmetry | 10 (22%) |
| Left lateral deficit | 9 (20%) |
| Confusion | 8 (18%) |
| Visual impairment | 4 (9%) |

IS – ischemic stroke; NRDC – Nardilysin; Ng – neurogranin.

control group (66.52±8.93 years), although the difference did not reach statistical significance (*P*=0.1). The mean body mass index (BMI) was significantly higher in IS patients (26.25±4.35) compared to controls (24.11±2.12; *P*=0.005), suggesting a potential association between higher BMI and IS risk (**Table 1**).

### Neurological Symptoms in IS Patients

The analysis of clinical symptoms in IS patients revealed that dysarthria was the most frequently reported neurological concern, observed in 34% of patients. This was followed by right lateral deficits (31%) and facial asymmetry (22%). Additional symptoms included left lateral deficits (20%), confusion (18%), and visual impairment (9%). These findings indicate the multifactorial neurological involvement in IS, demonstrating the diversity of clinical manifestations (**Table 2**).

### Comparison of Biochemical and Hematological Parameters

Ng levels were significantly higher in IS patients (281.12±32.12 pg/mL) compared to controls (265.71±24.54 pg/mL; *P*=0.01). In contrast, NRDC levels showed no significant difference between groups (6.35±4.13 ng/mL in IS patients vs 6.99±4.16 ng/mL in controls; *P*=0.47) (**Table 3**).

**Table 3.** Comparison of Ng, NRDC, other biomarkers, and blood cell count parameters between IS patients and controls.

| | ISVD-patient Group (n) | Control Group (n) | *P* |
|---|---|---|---|
| Ng (pg/mL) | 281.12±32.12 | 265.71±24.54 | **0.01** |
| NRDC (ng/mL) | 6.35±4.13 | 6.99±4.16 | 0.47 |
| Aspartate amino transferase (U/L) | 36.75 ±34.03 | 25.79±8.19 | **0.04** |
| Alanine amino transferase (U/L) | 29.27±31.52 | 23.11±8.15 | 0.2 |
| Urea (mg/dL) | 47±21.61 | 34.9±14.37 | 0.003 |
| Creatine (mg/dL) | 1.01±0.41 | 0.84±0.21 | 0.02 |
| White blood cells ($\times 10^9$/L) | 7.776±2.414 | 8.423±2.607 | 0.23 |
| Hemoglobin (g/dL) | 12.11±1.79 | 12.99±1.69 | **0.02** |
| Platelet ($\times 10^9$/L) | 244.818±1.051 | 270.272±74.741 | 0.194 |
| Neutrophil ($\times 10^9$/L) | 5.053±1.967 | 5.400±2.335 | 0.45 |
| Lymphocyte ($\times 10^9$/L) | 1.801±798 | 2.181±0.829 | **0.03** |

Ng – neurograninl NRDC – Nardilysin; IS – ischemic stroke.





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**Table 4.** Evaluation and comparison of the prognosis predictive powers of Ng and NRDC in the IS patient group according to hospitalization to intensive care units or other services.

| | Ng | | NRDC | |
|---|---|---|---|---|
| | Mean (standard deviation) | p | Mean (standart deviation) | P |
| Hospitalizated patients in intensive care units (n=5) | 311.5040 (46.1334) | 0.023 | 7.4620 (7.6860) | 0.226 |
| Hospitalizated patients in other services (n=39) | 277.2259 (28.4036) | | 6.2174 (3.6025) | |

Ng – neurogranin; NRDC – Nardilysin; IS – ischemic stroke.

Among other biochemical markers, IS patients exhibited significantly higher levels of aspartate aminotransferase (36.75±34.03 U/L; *P*=0.04), urea (47±21.61 mg/dL; *P*=0.003), and creatinine (1.01±0.41 mg/dL; *P*=0.02) compared to controls. Hemoglobin levels were lower in IS patients (12.11±1.79 g/dL) than in controls (12.99±1.69 g/dL; *P*=0.02). Additionally, lymphocyte counts were significantly lower in IS patients (1.801±0.798×$10^9$/L) compared to the control group (2.181±0.829×$10^9$/L; *P*=0.03) (**Table 3**).

In the IS patient group, Ng levels were significantly higher in individuals admitted to the ICU (311.50±46.13 pg/mL) compared to those hospitalized in other services (277.23±28.40 pg/mL; *P*=0.023). This finding suggests a potential relationship between elevated Ng levels and IS severity, although its prognostic significance remains to be fully clarified. In contrast, NRDC levels did not show a significant difference between ICU admissions (7.46±7.69 ng/mL) and other services (6.22±3.60 ng/mL; *P*=0.226). These results emphasize the potential role of Ng in identifying patients at higher risk of requiring intensive care interventions (**Table 4**).

### Diagnostic Utility of Ng

ROC analysis demonstrated that the Ng levels yielded an AUC of 0.624 (95% CI: 0.508-0.741) for diagnosing IS, reflecting moderate diagnostic accuracy (**Figure 1**).

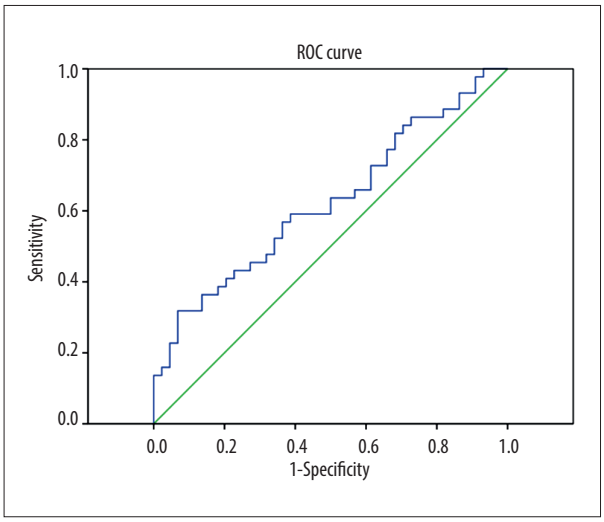


**Figure 1.** The blue curve represents the ROC analysis of Ng levels in differentiating IS patients from controls, with an AUC of 0.624 (95% CI: 0.508-0.741), indicating moderate diagnostic accuracy. ROC – receiver operating characteristic; Ng – neurogranin; IS – ischemic stroke; AUC – area under the curve; CI – confidence interval. *This figure was created by the authors using SPSS version 18.0 (IBM, Inc.) for statistical analysis and visualization.*

## Discussion

This study explored the roles of Ng and NRDC as biomarkers for the biochemical diagnosis and prognosis prediction of IS in ED. Significantly higher Ng levels were observed in IS patients compared to controls, indicating its diagnostic utility. Moreover, the increased Ng levels in patients requiring intensive care suggest a possible association with disease severity. In contrast, NRDC levels did not differ significantly between patient groups or ICU admissions, indicating a limited role in this setting.

Baseline BMI of the study participants revealed a significant association between higher BMI and IS risk. IS patients had significantly higher BMI compared to controls, emphasizing obesity as a modifiable risk factor for cerebrovascular diseases. This result aligns with previous studies identifying weight management as a crucial component of stroke prevention strategies [17]. Furthermore, our finding on similar sex distribution between groups underscores BMI as a more important determinant in the pathophysiological processes underlying IS.

The neurological symptoms observed in IS patients highlight the diverse and multifactorial nature of stroke presentations. Dysarthria was the most common symptom (34%), followed by right lateral deficits (31%) and facial asymmetry (22%). Less frequent but significant symptoms included left lateral deficits (20%), confusion (18%), and visual impairment (9%). This





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variability reflects the involvement of different neural pathways and cortical regions in IS. The findings emphasize the need for improved diagnostic protocols and the potential role of biomarkers like Ng in aiding early recognition and prognosis. Further studies should examine symptom-specific outcomes and their relationship to biomarker levels to optimize management strategies.

ROC analysis has provided an important method to evaluate the role of Ng in diagnosis of IS. The fact that the diagnostic accuracy rate of Ng was found to be at a moderate level in the study (AUC: 0.624, 95% CI: 0.508-0.741) showed that this protein alone could make a limited contribution to diagnosis. However, these results suggest that diagnostic accuracy could be increased if Ng is used in combination with other biomarkers. Considering the critical importance of rapid and effective diagnosis in the ED, evaluation of Ng as a supportive biomarker may be clinically meaningful.

In addition to our findings, several studies have investigated the role of Ng as a biomarker in acute IS. For instance, Kuşdoğan et al evaluated serum Ng levels in acute IS patients admitted within the first 24 hours and found that Ng could serve as a promising diagnostic biomarker, especially within the first 4.5-6 hours. Their study reported that serum Ng levels were significantly higher in acute IS patients compared to controls, with area under the ROC curve values of 0.717, 0.868, and 0.874 for patients admitted during the first 24, 6, and 4.5 hours after onset, respectively. However, Ng did not show significant prognostic value in terms of morbidity and mortality in their cohort [18]. This aligns with our observation of elevated Ng levels in IS patients, suggesting its potential utility in early diagnosis.

Furthermore, De Vos et al analyzed Ng and tau levels in CSF and plasma of acute IS patients. They observed elevated levels of both proteins, indicating that brain injury associated with IS is reflected by increased Ng concentrations in CSF and plasma. This study supports the notion that Ng is released into bodily fluids following neuronal damage, reinforcing its potential as a biomarker for stroke [19].

The prognostic value of Ng became evident as it was found at higher levels in patients requiring intensive care (311.50±46.13 pg/mL; $P$=0.023). This finding shows that Ng may be a marker that can be used not only in diagnostic but also in prognostic processes. However, the fact that NRDC levels did not show a significant difference between IS patients and the control group, as well as between patients in the ICU and other wards, suggests that the relationship of this protein with IS is weak. The fact that NRDC did not make a significant contribution to this study reveals the limits of the value of the protein as a biomarker and points to the need for new research in different patient groups.

In addition to the contribution of Ng in diagnosis and prognosis, the metabolic and hematological effects of IS were also observed through other parameters evaluated in the study. Increased AST, urea and creatinine levels, and decreased hemoglobin and lymphocyte levels in IS patients indicate the systemic effects of the disease. These biochemical changes emphasize that IS should be considered not only a neurological but also a systemic disease.

In light of these findings, more comprehensive studies are needed for the use of Ng in clinical practice. In particular, prospective studies involving different patient groups and combinations with other biomarkers may more clearly reveal both the diagnostic and prognostic value of Ng. Whether NRDC can make an additional contribution to such studies should be evaluated with larger populations. Research in this direction may enable the development of more sensitive and personalized approaches to the management of IS.

### Limitations and Future Studies

Certain limitations, however, should be acknowledged. One major limitation is that our study relied solely on serum biomarker analysis using ELISA, without validation through other methods such as tissue protein or mRNA expression. Due to ethical and practical constraints, we were unable to collect tissue samples from patients, which precluded the use of these techniques. This restricted our ability to confirm that Ng and NRDC are highly specific biomarkers for IS. Additionally, the study did not include CSF analyses, which could have provided additional insights, as prior research indicates stronger biomarker correlations in CSF compared to plasma. Furthermore, infarct-specific data were not included, limiting our ability to comprehensively evaluate the relationship between Ng levels and the severity of IS. These omissions represent areas for further exploration.

Future research should validate these findings in larger, multicenter cohorts and address these limitations. Incorporating complementary validation methods such as tissue protein or mRNA expression analyses, when ethically and practically feasible, would strengthen biomarker specificity. Additionally, including CSF analyses alongside plasma Ng and NRDC measurements and exploring additional biomarkers may enhance diagnostic and prognostic utility. Expanding the scope to include infarct-specific data and investigating dynamic biomarker changes over time could provide a more comprehensive understanding of the clinical relevance of Ng and NRDC in IS management.

## Conclusions

This study identified distinct roles of Ng and NRDC as biomarkers in IS. Plasma Ng levels had a moderate association with its





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clinical relevance, whereas NRDC did not appear to have significant utility. Additionally, higher Ng levels show a moderate correlation with the need for intensive care, suggesting a potential link with stroke severity. While Ng may have a meaningful role in clinical assessment, the utility of NRDC remains limited. Further research with larger patient groups and different methodologies is needed to validate Ng's role and explore its potential integration into stroke management strategies.

**Statement**

This study was conducted without external funding. The researchers personally covered the cost of some laboratory kits.

**Declaration of Figure's Authenticity**

The figure submitted has been created by the authors, who confirm that the image is original, has not been duplicated, and has not been previously published in whole or in part.

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