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Serum progranulin as an early diagnostic biomarker in acute stroke

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MAIN POINTS

- PGRN shows diagnostic value within six hours of onset.
- First study comparing PGRN in ischemic vs hemorrhagic stroke.
- PGRN differentiates stroke patients from controls.
- No prognostic association was found for mortality or severity.

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ABSTRACT

Aim: Rapid differentiation between ischemic stroke (IS) and intracerebral hemorrhage (ICH) is crucial for early management. Progranulin, a multifunctional glycoprotein with neuroprotective and anti-inflammatory effects, is involved in neuronal survival and the control of inflammation. Although animal studies suggest a protective role, its diagnostic and prognostic value in acute human stroke remains uncertain. This study aimed to evaluate the diagnostic and prognostic significance of serum progranulin in acute IS and ICH within six hours of onset.

Materials and Methods: Forty-two acute stroke patients and forty-four healthy controls were enrolled. Inclusion criteria were an acute focal neurological deficit, a presentation within six hours, and imaging confirmation of the subtype. Exclusion criteria included prior stroke, trauma, tumors, systemic failure, or major comorbidities. Serum progranulin was measured by ELISA. Statistical analyses included t-tests, Mann–Whitney U tests, ANOVA, chi-square tests, and ROC analyses.

Results: Serum progranulin was significantly higher in stroke patients than in controls (69.6±15.4 pg/mL vs 52.2±18.9 pg/mL; p<0.001). ROC analysis yielded a cut-off value of 53 pg/mL (sensitivity, 64%; specificity, 84%; AUC, 0.778; 95% CI, 0.676–0.861). Progranulin levels did not differ between IS and ICH, nor by severity. No correlations were observed with mortality, ICU admission, or hospital stay; only the Glasgow Coma Scale correlated with clinical outcomes.

Conclusion: An elevated level of progranulin early in stroke supports its potential as a diagnostic biomarker, but it does not distinguish stroke type or predict prognosis. Larger longitudinal studies are needed to clarify its clinical utility.

Keywords: Stroke, Ischemic, Hemorrhagic, Progranulin, Diagnostic

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INTRODUCTION

Cerebrovascular diseases are a group of clinical conditions characterized by sudden onset and potentially life-threatening ischemic or hemorrhagic damage [1]. Cerebrovascular diseases are among the three leading causes of death worldwide. Ischemic stroke (IS) accounts for around 85% of all stroke cases and is associated with serious consequences such as permanent disability, dependency, loss of employment, and social isolation [2]. IS is more common, while intracerebral hemorrhage (ICH) is more severe, with in-hospital mortality rates of 20–30%, and up to 80% of survivors require long-term care [3]. In developed countries, the incidence of stroke is increasing with aging populations, posing a significant economic burden on healthcare systems [4].

While computed tomography (CT) can accurately detect intracerebral hemorrhage, it is relatively to acute, small ISs. However, expensive magnetic resonance imaging (MRI) scanners (especially diffusion-weighted imaging (DWI)) are unsuitable for unstable patients or for those with contraindications, and are available only in specialist hospitals staffed by experienced neuroradiologists. Yet, they have improved stroke detection to approximately 95%. Some may not appear at all [5,6]. Therefore, rapid and accurate diagnosis of patients with suspected stroke, reliable distinction between IS and ICH, the selection of the appropriate patient population for thrombolytic therapy, and the improvement of patient outcomes

are of critical importance [7]. In addition, accurate prognostic evaluation following cerebrovascular events plays a pivotal role across a broad spectrum, from acute treatment decisions and long-term rehabilitation planning to patient and family counseling and the formulation of healthcare policies [8].

Progranulin (PGRN) is a multifunctional glycoprotein that plays an important role in stroke pathogenesis [9]. Thanks to its anti-inflammatory and neurotrophic properties, PGRN supports nerve cell survival and regulates physiological processes, including cell proliferation, wound healing, and nervous system development [10–12]. Primarily expressed by microglia and pyramidal neurons in brain tissue, PGRN exerts a neuroprotective effect by limiting post-stroke inflammation, cell death, and blood–brain barrier damage [13,14]. PGRN promotes the proliferation of neural stem/progenitor cells via PI3K/AKT and MAPK/ERK signaling pathways and supports post-ischaemic recovery by increasing neurogenesis in the subventricular zone [14–16]. Furthermore, it reduces impairments to cognitive function, such as learning and memory disorders, by increasing neuronal differentiation [17]. The suppression of the NF-κB pathway by PGRN and the reduction of oxidative stress and necroptosis play central roles in limiting stroke-induced damage [18]. Given these properties, PGRN stands out as both a biomarker and a potential therapeutic target.

Despite its biological relevance, the clinical significance of PGRN in acute stroke remains incompletely understood. This study aimed to determine the diagnostic and prognostic value of serum PGRN levels measured within the first 6 hours in patients with IS and ICH. This is the first study to compare PGRN levels across subtypes and evaluate PGRN levels in ICH in relation to mortality and prognosis.

MATERIALS AND METHODS

This case-control study included 42 patients with acute stroke who were admitted to the Emergency Department of a tertiary training and research hospital, as well as 44 healthy volunteers. Patients were included if they met the following criteria: sudden-onset focal neurological deficit due to ICH or IS; admission within 6 hours of symptom onset; neurological symptoms during admission; and adequate access to patient information. Patients with a history of stroke, traumatic brain injury, brain tumor, infection, degenerative brain disease, liver failure, kidney failure, chronic heart disease, and acute myocardial infarction were excluded from the study. The Glasgow Coma Scale (GCS) was used to assess neurological status at admission. CT or MRI confirmed the stroke subtype. Up to 2 cc of blood was collected and placed in serum-separating tubes. The tubes were incubated at room temperature for 20 minutes and then centrifuged at 3000 rpm for 15 minutes. The obtained serum was then divided into Eppendorf aliquots of at least 0.3 cc. Eppendorf tubes were labeled and stored at -80°C until analyzed. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Approval was granted by the Clinical Research Ethics Committee of the University of Health Sciences, Sisli Hamidiye Etfal Research and Training Hospital (Approval no: 4825, Date: 08.04.2025). Written informed consent was obtained from all participants.

Sample analysis

Serum PRGN levels were measured using a Human Progranulin ELISA Kit (Elabscience Biotechnology, China). Different standard concentrations were prepared by diluting the lyophilized standard provided with the kit. Following the kit procedure, the absorbance of the examined samples was measured at 450 nm with an EBLX-800 microplate reader (BioTek Instruments, Inc., USA). Concentrations corresponding to absorbance values were calculated using the formula obtained from the standard curve (sensitivity: 37.5 pg/mL, assay range: 62.5-4000 pg/mL, intra-assay CV< 10%).

Statistical analysis

Data distribution was evaluated using the Shapiro–Wilk normality test. Continuous variables are reported as mean ± standard deviation or median with minimum and maximum values, while categorical variables are expressed as counts and percentages. For comparisons between groups, parametric methods(independent-samples t-test or one-way analysis of variance)were applied when distributional assumptions were met; otherwise, nonparametric alternatives (Mann–Whitney U or Kruskal–Wallis tests) were used. Post-hoc analyses were adjusted using the Bonferroni method where appropriate. Associations between categorical variables were examined using the chi-square test or Fisher's exact test, depending on the expected cell counts. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 29.0.2.0; IBM Corp., Armonk, NY, USA).

The discriminative ability of PGRN for patient status was assessed by receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) serving as the primary measure of diagnostic performance. ROC analyses were performed using MedCalc Statistical Software (version 23.2.1).

RESULTS

Descriptive statistics for patient demographic and clinical variables are presented in Table 1. The study groups showed similar baseline demographic characteristics. The median age was comparable between the control and patient groups [59 (28-90) vs 62.5 (13-92) years, p=0.069], indicating no significant age difference. The gender distribution was also similar across groups, with no statistically significant difference (p=0.117).

PGRN levels differed significantly between the groups. The control group had significantly lower mean PGRN levels (52.2±18.9 pg/mL) than the patient group (69.6±15.4

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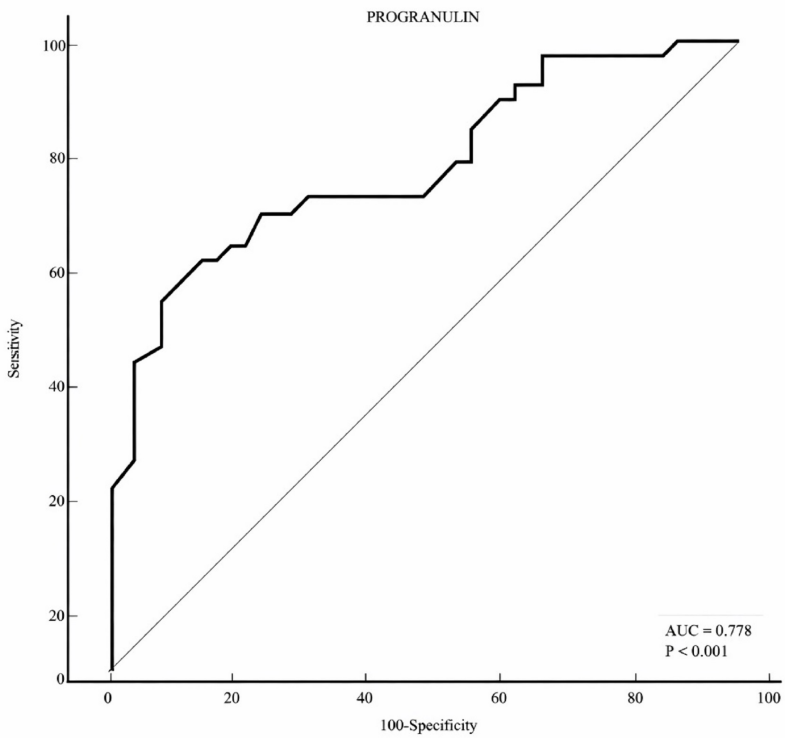

Figure 1. ROC curve analysis demonstrating the diagnostic value of serum progranulin in acute stroke.

Table 1. Demographic data of patients.

Characteristic	n (%)
Gender	
Male	28 (67)
Female	14 (33)
Glasgow Coma Scale	
Mild (<11)	34 (81)
Severe (≥12)	8 (19)
Hypertension	
Yes	12 (29)
No	30 (71)
Diabetes Mellitus	
Yes	6 (14)
No	36 (86)
Atrial Fibrillation	
Yes	4 (10)
No	38 (90)

Table 2. Demographic and biomarker comparison between groups.

	Control (n=44)	Patient (n=42)	p value
Age median (min-max)	59 (28-90)	62.5 (13-92)	0.069
Sex (male/female)	22/22	28/14	0.117
PGRN (pg/mL) mean±SD	52.2±18.9	69.6±15.4	<0.001

PGRN: Progranulin.

pg/mL; p<0.001) (Table 2). For disease detection, PGRN had a cutoff of 53 pg/mL, yielding 64% sensitivity and 84% specificity [AUC = 0.778; 95% CI (0.676 to 0.861)] (Figure 1). There was no correlation between PGRN levels and hospital stay length (42±27 days) or ICU use (12±29 days). Only the GCS score was correlated with length of hospital stay (p=0.019; r=-0.395) and with ICU use (p=0.022; r=-0.385). When we grouped patients as severe or mild (GCS < 11 as severe; GCS ≥ 12 as mild), there was no significant difference in PGRN levels. No significant difference in PGRN levels between IS and ICH was observed (Table 3).

Table 3. Comparison of PGRN according to GCS, mortality, ischemic, and hemorrhagic subtypes.

	PGRN pg/mL
GCS<11 (mild) (n=34)	49.5 (26-110)
GCS≥12 (severe) (n=8)	46 (15-75)
p-value	0.814
Ex (n=8)	43 (26-90)
Survivor (n=34)	56 (15-110)
p-value	0.192
IS (n=22)	47 (31-110)
ICH (n=20)	50 (15-90)
p-value	0.801

PGRN: Progranulin; GCS: Glasgow Coma Scale; IS: Ischemic stroke; ICH: Intracerebral hemorrhage.

DISCUSSION

In this study, we investigated the diagnostic and prognostic significance of serum PGRN levels in patients with acute ischemic or hemorrhagic stroke within the first six hours of symptom onset. Our findings indicate that serum PGRN

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concentrations are significantly higher in stroke patients than in healthy controls, suggesting that PGRN may be an early biomarker of cerebrovascular events. However, PGRN levels did not show a significant association with stroke subtype (ischemic vs. hemorrhagic) or clinical severity and outcome indicators such as mortality, intensive care unit admission, or length of hospital stay. These findings imply that while PGRN reflects an acute response to stroke, its role in prognosis requires further clarification.

Previous studies have reported heterogeneous results regarding the prognostic value of PGRN. Lasek-Bal et al. similarly found elevated serum PGRN levels in the early phase of ischemic stroke, without a significant relationship to patient outcomes [19]. In contrast, Xie et al. demonstrated that increased serum PGRN was independently associated with all-cause mortality in acute ischemic stroke, suggesting a possible prognostic utility [20]. Zhou et al. demonstrated decreased PGRN levels in patients with ICH and in experimental rat models The decrease in PGRN paralleled neutrophil activation and increased proinflammatory cytokines (IL-1β, TNF-α), suggesting that inflammation contributes to early brain injury [12]. This discrepancy may be attributable to differences in study design, sample size, timing of blood sampling, and patient selection criteria. Our study, by including both ischemic and hemorrhagic stroke patients, contributes novel insights into the broader spectrum of cerebrovascular disease. Stroke and traumatic brain injury (TBI) share converging pathophysiological pathways, including acute neuronal injury, neuroinflammation, and microglial activation, suggesting that common inflammatory mediators may be involved across these conditions. In TBI, elevated serum and urine progranulin (PGRN) levels in the early phase have been associated with cortical microglial activation, reflecting an acute neuroinflammatory response [21]. These findings support the biological plausibility that PGRN may also serve as a marker of injury-related inflammatory processes in acute stroke.

Experimental data have consistently shown the neuroprotective and anti-inflammatory roles of PGRN. Animal studies indicate that reduced PGRN levels are associated with increased neutrophil infiltration, blood–brain barrier disruption, and neuronal apoptosis, whereas recombinant PGRN administration mitigates these effects and improves neurological outcomes. These mechanistic findings support the hypothesis that PGRN elevation in human stroke may reflect a compensatory neuroprotective response. However, whether this response is sufficient to influence clinical prognosis remains uncertain [12]. Emerging evidence highlights progranulin as a key regulator of lysosomal function and proteostatic stress, processes that are critically involved in neuronal vulnerability and neuroinflammatory responses across neurological diseases. This mechanistic framework supports the view that altered serum progranulin levels observed in acute stroke reflect injury-related lysosomal and inflammatory pathways [22]. In another study, PGRN was shown to be a multifunctional mediator in ischemic stroke, exerting neuroprotective and anti-inflammatory effects by modulating microglial activation, oxidative stress, apoptosis, and blood–brain barrier integrity [23]. These mechanisms provide a biological rationale for the altered serum levels of progranulin observed in our cohort and support its relevance as a potential biomarker in acute stroke. Interestingly, we did not observe a significant relationship between PGRN levels and either stroke severity (as measured by the GCS) or patient mortality. This lack of association may reflect the complexity of stroke pathophysiology, where multiple inflammatory, vascular, and neurodegenerative pathways interact.

The present study has several strengths, including its prospective design, early sampling within 6 hours of stroke onset, and inclusion of both ischemic and hemorrhagic subtypes. Nonetheless, some limitations must be acknowledged. The relatively small sample size may have limited the power to detect subtle prognostic associations. Moreover, we measured PGRN levels only at a single time point; serial measurements could provide more dynamic insights into temporal changes in this biomarker. Additionally, long-term functional outcomes, such as disability scores and quality of life, were not assessed; their inclusion may have provided a more comprehensive understanding of PGRN's prognostic role.

Limitations

This study has several limitations. First, the relatively small sample size may have limited the statistical power to detect subtle differences, particularly regarding prognostic outcomes. Second, serum progranulin levels were measured at a single time point within the first six hours of symptom onset; therefore, changes over time could not be evaluated. Third, long-term functional outcomes and disability scores were not assessed. Finally, as this was a single-center study, the generalizability of the results may be limited.

CONCLUSION

This study is the first to compare PGRN between IS and ICH and to evaluate its relationship with ICH-related mortality. Elevated serum progranulin levels in the early phase of acute stroke suggest a potential role as a diagnostic biomarker. However, no difference in levels between IS and ICH was observed, and neither was associated with severity or short-term outcomes, indicating limited prognostic value. Further research is required to confirm its clinical utility.

Ethics Committee Approval: Approval was granted by the Ethics Committee of the University of Health Sciences, Sisli Hamidiye Etfal Research and Training Hospital Clinical Research (Approval no: 4825, Date: 08.04.2025).

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