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# Association of HMGB1 Levels with Stroke Severity and Clinical Outcomes in Ischemic Stroke Patients With and Without Type 2 Diabetes Mellitus

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**KEYWORDS**

Ischemic stroke; HMGB1; Type 2 diabetes mellitus; Stroke severity; Clinical outcomes

**ABSTRACT:**

**Background:** High-mobility group box 1 (HMGB1) is an inflammatory mediator implicated in ischemic stroke and type 2 diabetes mellitus (T2DM); however, its prognostic value in diabetic stroke patients remains uncertain.

**Objective:** To assess the association between serum HMGB1 levels, stroke severity, and clinical outcomes in ischemic stroke patients with and without T2DM.

**Methods:** This multicenter cross-sectional study enrolled adult patients with acute ischemic stroke in Makassar, Indonesia. Serum HMGB1 levels were measured within 24 hours of admission. Stroke severity and functional outcomes were evaluated using the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) at day 1 and day 30. Correlation analyses were performed.

**Results:** Serum HMGB1 levels did not differ significantly between patients with and without T2DM. In patients with T2DM, HMGB1 levels were not associated with NIHSS or mRS scores at day 1 or day 30, nor with fasting blood glucose or HbA1c. Significant improvements in NIHSS and mRS scores were observed at 30 days.

**Conclusion:** Serum HMGB1 levels were not associated with stroke severity or short-term clinical outcomes in ischemic stroke patients with T2DM, indicating limited prognostic utility as a standalone biomarker.

## 1. Introduction

Stroke is an acute neurological syndrome resulting from cerebrovascular injury and remains a leading cause of mortality and long-term disability worldwide. Ischemic stroke accounts for approximately 80–90% of all stroke cases and represents a substantial public health burden, particularly in low- and middle-income countries where most stroke-related deaths and disability-adjusted life years occur [1,2]. Despite advances in acute stroke management, clinical outcomes remain highly variable, highlighting the need for reliable biomarkers that reflect disease severity and prognosis [3].

Type 2 diabetes mellitus (T2DM) is a well-established risk factor for ischemic stroke and is associated with worse post-stroke outcomes, including higher mortality, increased disability, and recurrent stroke risk [4]. Chronic hyperglycemia and insulin resistance contribute to endothelial dysfunction, oxidative stress, and a persistent proinflammatory state, which may exacerbate ischemic brain injury and impair recovery following stroke [5]. However, the molecular mechanisms linking diabetes-related inflammation to stroke severity and outcomes remain incompletely understood [6,7].

High-mobility group box 1 (HMGB1) is a ubiquitously expressed non-histone nuclear protein that functions as a DNA chaperone under physiological conditions [8]. In response to cellular stress, injury, or death, HMGB1 is actively secreted by immune cells or passively released

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from necrotic cells into the extracellular space, where it acts as a damage-associated molecular pattern (DAMP) [9]. Extracellular HMGB1 activates inflammatory signaling through receptors such as the receptor for advanced glycation end products (RAGE) and toll-like receptors (TLR2 and TLR4), amplifying downstream inflammatory cascades [9,10].

In ischemic stroke, HMGB1 is rapidly released from injured neurons within minutes of cerebral ischemia and subsequently from activated astrocytes and microglia, sustaining neuroinflammation during the acute and subacute phases [11,12]. Elevated circulating HMGB1 levels have been associated with infarct expansion, blood–brain barrier disruption, and poorer neurological outcomes [13]. Experimental and clinical studies suggest that HMGB1-mediated signaling contributes to both acute tissue injury and chronic neurodegeneration, although findings in human studies remain heterogeneous, partly due to differences in study design and timing of biomarker assessment [14].

Beyond stroke, HMGB1 plays a significant role in the pathogenesis of T2DM and its vascular complications [15]. Increased HMGB1 levels have been consistently observed in patients with T2DM and are associated with microvascular and macrovascular damage [16]. Hyperglycemia itself can stimulate HMGB1 release, while antihyperglycemic therapies such as metformin have been shown to suppress HMGB1 expression and related inflammatory pathways, supporting its role as a key mediator linking metabolic dysfunction and vascular injury [17].

Given the heightened inflammatory milieu in patients with T2DM, HMGB1 may represent a critical mechanistic link between diabetes and adverse outcomes following ischemic stroke [18]. However, data examining the relationship between HMGB1 levels, stroke severity, and clinical outcomes in ischemic stroke patients stratified by diabetes status remain limited [19]. Therefore, this study aimed to investigate the association between circulating HMGB1 levels, stroke severity, and clinical outcomes in ischemic stroke patients with and without type 2 diabetes mellitus.

## 2. Methods

### *Study Design and Setting*

This study was an analytical observational study with a cross-sectional design conducted to evaluate the association between serum High-Mobility Group Box 1 (HMGB1) levels and stroke severity and clinical outcomes in patients with acute ischemic stroke. The study was carried out at multiple tertiary and teaching hospitals in Makassar, Indonesia, including Dr. Wahidin Sudirohusodo Hospital, Hasanuddin University Hospital, Labuang Baji Hospital, Haji Hospital, Faisal Islamic Hospital, Ibnu Sina Hospital, and Pelamonia Hospital. Patient recruitment was conducted from September 2025 until the required sample size was achieved.

### *Study Population and Sampling*

The study population comprised adult patients with acute ischemic stroke who were hospitalized at the participating centers. Consecutive sampling was applied, whereby all eligible patients meeting the inclusion criteria were enrolled until the minimum sample size was reached.

The minimum sample size was calculated using a correlation-based formula with a two-tailed significance level of 5% ($\alpha = 0.05$), statistical power of 90% ($\beta = 0.10$), and a minimum expected correlation coefficient (r) of 0.40. Based on this calculation, a minimum of 51 participants was required.

### *Eligibility Criteria*

Patients were included if they met the following criteria: (1) diagnosis of acute ischemic stroke with onset within 0–14 days; (2) first-ever stroke; (3) age between 18 and 70 years; (4) willingness to participate and provision of informed consent; and (5) confirmed diagnosis of type 2 diabetes mellitus.

Exclusion criteria included the presence of systemic infection, autoimmune disease, chronic kidney disease, chronic liver disease, chronic heart failure, or malignancy. Patients who did not complete the full study protocol were considered dropouts.

### *Data Collection and Procedures*

Eligible patients were identified during hospitalization and enrolled after informed consent was obtained. Venous blood samples were collected within the first 24

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hours of admission to measure serum HMGB1 levels using enzyme-linked immunosorbent assay (ELISA). Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) at admission, during hospitalization, and at day 30. Clinical outcomes were evaluated using the Modified Rankin Scale (mRS).

***Statistical Analysis***

Data were analyzed using SPSS version 23. Normality of continuous variables was assessed using the Shapiro–Wilk test for sample sizes <50 and the Kolmogorov–Smirnov test for sample sizes ≥50. Correlations between HMGB1 levels and clinical outcomes were analyzed using Pearson or Spearman correlation tests, as appropriate. Comparisons of HMGB1 levels between groups with favorable and unfavorable outcomes were performed using independent t-tests or Mann–Whitney U tests. A p-value <0.05 was considered statistically significant.

***Ethical Approval***

This study received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, Makassar (Approval No. 153/UN4.6.4.5.31/PP36/2026; Protocol No. UH26010070; approval date: 27 January 2026). The study was reviewed under an expedited review process and conducted at Dr. Wahidin Sudirohusodo Hospital, Makassar. Written informed consent was obtained from all participants or their legal representatives prior to study participation. All procedures were performed in accordance with the principles of the Declaration of Helsinki, and standard clinical care was maintained throughout the study period.

## 3. Results

***Respondent Demographics***

Table 1 presents a comparison of demographic, clinical, and laboratory characteristics between ischemic stroke patients with type 2 diabetes mellitus and those without diabetes. No significant difference was observed in age between the two groups (p = 0.630). Sex distribution was also comparable, with no significant differences observed for either males (p = 0.665) or females.

Table 1. Demographic and Clinical Characteristics of the Study Subjects

| Variable | Median With T2DM (n = 67) | Median Without T2DM (n = 22) | P-value |
|---|---|---|---|
| **Age (years)** | 57 | 55.5 | 0.630 |
| **Sex** | | | |
| **Male** | 36 (53.73%) | 11 (50%) | 0.665 |
| **Female** | 31 (46.27%) | 11 (50%) | |
| **HMGB1 (ng/mL)** | 2.21 | 2.45 | 0.524 |
| **NIHSS Day 1** | 5 | 5 | 0.370 |
| **NIHSS Day 30** | 5 | 4 | 0.210 |
| **mRS Day 1** | 2 | 2 | 0.785 |
| **mRS Day 30** | 2 | 2 | 0.760 |
| **Fasting Blood Glucose (mg/dL)** | 183 | 92 | < 0.001** |
| **HbA1c (%)** | 9.30 | 5.47 | < 0.001** |

Data are presented as median or number (percentage). Mann–Whitney U test was used for non-normally distributed variables, and Chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant.

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Serum HMGB1 levels did not differ significantly between the type 2 diabetes and non-diabetes groups ($p = 0.524$). Similarly, no significant differences were found in NIHSS scores on day 1 ($p = 0.370$) and day 30 ($p = 0.210$), nor in modified Rankin Scale (mRS) scores on day 1 ($p = 0.785$) and day 30 ($p = 0.760$). In contrast, significant differences were observed in metabolic parameters, namely fasting blood glucose ($p < 0.001$) and HbA1c levels ($p < 0.001$), with higher values in the type 2 diabetes group, consistent with the underlying disease characteristics.

***Association Between HMGB1 Levels and Clinical Severity in Ischemic Stroke Patients With Type 2 Diabetes Mellitus***

Table 2. Correlation Between Serum HMGB1 Levels and NIHSS Scores on Day 1 and Day 30

| Variable | Spearman's rho (r) | p-value |
|---|---|---|
| HMGB1 vs. NIHSS Day 1 | 0.013 | 0.916 |
| HMGB1 vs. NIHSS Day 30 | −0.018 | 0.884 |

Table 2 presents the results of Spearman correlation analyses between serum HMGB1 levels and NIHSS scores on day 1 and day 30. The analysis showed no significant association between HMGB1 levels and NIHSS scores on day 1 ($r = 0.013$; $p = 0.916$). Likewise, no significant correlation was observed between HMGB1 levels and NIHSS scores on day 30 ($r = −0.018$; $p = 0.884$). These findings indicate that serum HMGB1 levels were not associated with clinical severity during the acute phase or at 30 days of follow-up in patients with ischemic stroke and type 2 diabetes mellitus

***Association Between HMGB1 Levels and Clinical Outcomes in Ischemic Stroke Patients With Type 2 Diabetes Mellitus***

As shown in Table 3, Spearman correlation analysis was performed to evaluate the association between serum HMGB1 levels and functional outcomes measured by the modified Rankin Scale (mRS) on day 1 and day 30. The results demonstrated no significant correlation between HMGB1 levels and mRS scores on day 1 ($r = 0.024$; $p = 0.845$). Similarly, no significant association was observed between HMGB1 levels and mRS scores on day 30 ($r = 0.047$; $p = 0.707$). These findings indicate that HMGB1 levels were not significantly associated with functional outcomes during either the acute phase or the 30-day follow-up period.

Table 3. Correlation Between Serum HMGB1 Levels and mRS Scores on Day 1 and Day 30

| Variable | Spearman's rho (r) | p-value |
|---|---|---|
| HMGB1 vs. mRS Day 1 | 0.024 | 0.845 |
| HMGB1 vs. mRS Day 30 | 0.047 | 0.707 |

***Association Between HMGB1 Levels and Fasting Blood Glucose and HbA1c in Ischemic Stroke Patients With Type 2 Diabetes Mellitus***

Table 4. Correlation Between Serum HMGB1 Levels and Metabolic Parameters (Fasting Blood Glucose and HbA1c) in Ischemic Stroke Patients

| Variable | Spearman's rho (r) | p-value |
|---|---|---|
| HMGB1 vs. Fasting Blood Glucose | 0.059 | 0.635 |
| HMGB1 vs. HbA1c | 0.154 | 0.213 |

As presented in Table 4, Spearman correlation analysis was conducted to assess the association between serum HMGB1 levels and metabolic parameters, namely fasting blood glucose and HbA1c. The results showed no significant correlation between HMGB1 levels and fasting blood glucose ($r = 0.059$; $p = 0.635$). Likewise, no significant association was observed between HMGB1 levels and HbA1c ($r = 0.154$; $p = 0.213$). These findings indicate that serum HMGB1 levels were not associated with glycemic control or metabolic status at the time of assessment.

***Comparison of NIHSS and mRS Scores by Onset in Ischemic Stroke Patients With Type 2 Diabetes Mellitus***

According to Table 5, Wilcoxon signed-rank tests were performed to evaluate changes in NIHSS and mRS

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scores between day 1 and day 30 in patients with ischemic stroke and type 2 diabetes mellitus. Significant differences were observed in both NIHSS scores ($Z = -2.609$; $p = 0.009$) and mRS scores ($Z = -2.608$; $p = 0.009$). These findings indicate a significant improvement in neurological status as well as functional disability after 30 days of follow-up.

Table 5. Comparison of NIHSS and mRS Scores by Onset (Day 1 and Day 30) in Ischemic Stroke Patients With Type 2 Diabetes Mellitus

| Variable | Z value | p-value |
|---|---|---|
| NIHSS Day 1 vs. NIHSS Day 30 | −2.609 | 0.009 |
| mRS Day 1 vs. mRS Day 30 | −2.608 | 0.009 |

## 4. Discussion

This study demonstrated that baseline demographic characteristics and initial clinical profiles were largely comparable between ischemic stroke patients with T2DM and those without diabetes. The primary differences were observed in metabolic parameters, namely fasting blood glucose and HbA1c levels, which were naturally higher in the T2DM group, consistent with the chronic hyperglycemic state characteristic of diabetes. From a biological perspective, HMGB1 is known to function as a DAMP released by necrotic cells and activated immune cells, triggering inflammatory responses through receptors such as RAGE and TLR4, and has therefore been widely implicated as an important mediator in ischemic brain injury [20].

Despite the mechanistic role of HMGB1 in post-ischemic inflammation, the present study did not identify a significant association between HMGB1 levels and either NIHSS or mRS scores at day 1 or day 30. These findings are consistent with several previous reports suggesting that the association between HMGB1 and stroke severity or outcomes may depend on the timing of sample collection, differences in assay methods, and heterogeneity of patient characteristics. While some studies have reported that elevated HMGB1 levels are associated with poorer outcomes, the existing evidence remains inconsistent and should therefore be interpreted with caution [21].

One possible explanation lies in the highly dynamic nature of HMGB1. Its concentration may increase during the very early phase following stroke onset (within hours to days) and subsequently fluctuate in parallel with the evolution of inflammation and reperfusion processes. As a result, a single time-point measurement may fail to capture peak inflammatory exposure or the critical period most relevant to neurological progression. Studies that have assessed HMGB1 serially tend to provide a more accurate depiction of its relationship with infarct size, cerebral edema, and functional outcomes [22].

Moreover, patients with T2DM generally exhibit a higher basal inflammatory state, accompanied by immunometabolic alterations such as increased activation of the RAGE pathway and insulin resistance. In this context, HMGB1 levels may reflect chronic inflammation and metabolic comorbidities rather than acute ischemic injury per se, thereby attenuating the observable association between acute HMGB1 levels and neurological scores. Consistent with this notion, the literature shows variable associations between HMGB1 and glycemic markers such as HbA1c or fasting blood glucose, underscoring the biological complexity of these interactions [17].

The absence of a significant correlation between HMGB1 levels and fasting blood glucose or HbA1c in this study further supports the assumption that HMGB1 is influenced by multiple external factors, including antidiabetic treatment regimens, systemic inflammatory burden, and the presence of other comorbidities. This finding reinforces the notion that HMGB1 may be suboptimal as a standalone biomarker for assessing glycemic control or predicting stroke outcomes in T2DM patients without longitudinal measurements or integration with other inflammatory biomarkers such as IL-6, TNF-α, and C-reactive protein [15].

On the other hand, the significant improvement observed in NIHSS and mRS scores from day 1 to day 30 indicates meaningful neurological recovery within this cohort. These findings suggest that short-term outcomes are likely determined by multifactorial influences, including resolution of cerebral edema, spontaneous or therapeutic reperfusion, quality of acute stroke management, and rehabilitation efforts, thereby limiting the sensitivity of HMGB1 as a single prognostic predictor. Accordingly, future studies are encouraged to integrate clinical

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variables, radiological parameters (such as infarct volume), and panels of inflammatory biomarkers to develop more comprehensive prognostic models [23].

Overall, the findings of this study, together with existing literature, support the biological relevance of HMGB1 in the pathophysiology of both stroke and diabetes. However, to establish HMGB1 as a reliable prognostic biomarker, further research with more robust study designs is required, including serial biomarker measurements, larger sample sizes, careful control of confounding factors such as infection and medication use, and integration of neuroimaging data [13].

## 5. Conclusions

This study found that serum HMGB1 levels were not significantly associated with stroke severity or functional outcomes, as assessed by NIHSS and mRS, during the acute phase or at 30-day follow-up in ischemic stroke patients with type 2 diabetes mellitus. HMGB1 levels were also not correlated with glycemic parameters, including fasting blood glucose and HbA1c, suggesting that HMGB1 may not directly reflect glycemic control or short-term clinical prognosis in this population when measured at a single time point.

Despite the absence of significant associations, patients demonstrated significant clinical and functional improvement over 30 days, indicating that short-term recovery after ischemic stroke is likely driven by multifactorial processes beyond a single inflammatory biomarker. These findings suggest that while HMGB1 has an established biological role in stroke and diabetes-related inflammation, its utility as a standalone prognostic biomarker in ischemic stroke patients with type 2 diabetes mellitus appears limited. Future studies with larger sample sizes, serial HMGB1 measurements, and integration of clinical, radiological, and multimarker inflammatory data are warranted to better clarify the temporal and prognostic significance of HMGB1 in ischemic stroke, particularly in the context of metabolic comorbidities such as type 2 diabetes mellitus.

## 6. Declarations

### *Consent for Publication*

Consent for publication was not required, as this manuscript does not include identifiable personal data or images of study participants.

### *Authors' Contributions*

N was responsible for study implementation, data collection, data analysis, and manuscript preparation. YG and MA conceptualized and designed the study, conducted data analysis, supervised the research process, and critically revised the manuscript. N, YG, and MA contributed to data interpretation and manuscript refinement. All authors (N, YG, MA, FH, AB, and CR) participated in critical review, editing, and approved the final version of the manuscript.

### *Data Availability*

All data supporting the conclusions of this study are included within the manuscript.

### *Conflict of Interest*

The authors declare no conflicts of interest related to this work.

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## References

1. Murphy SJ, Werring DJ. Stroke: causes and clinical features. *Medicine (Abingdon)*. 2020;48(9):561-566. doi:10.1016/J.MPMED.2020.06.002
2. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(7):2064-2089. doi:10.1161/STR.0B013E318296AECA
3. Gkantzios A, Tsiptsios D, Karatzetzou S, et al. Stroke and Emerging Blood Biomarkers: A Clinical Prospective. *Neurology International 2022, Vol 14, Pages 784-803*. 2022;14(4):784-803. doi:10.3390/NEUROLINT14040065
4. Mosenzon O, Cheng AYY, Rabinstein AA, Sacco S. Diabetes and Stroke: What Are the Connections? *J Stroke*. 2023;25(1):26-38. doi:10.5853/JOS.2022.02306

5. Mosenzon O, Cheng AYY, Rabinstein AA, Sacco S. Diabetes and Stroke: What Are the Connections? *J Stroke*. 2023;25(1):26-38. doi:10.5853/JOS.2022.02306

6. Pacinella G, Ciaccio AM, Tuttolomondo A. Molecular Links and Clinical Effects of Inflammation and Metabolic Background on Ischemic Stroke: An Update Review. *J Clin Med*. 2024;13(24). doi:10.3390/JCM13247515

7. Nedosugova L V., Markina Y V., Bochkareva LA, et al. Inflammatory Mechanisms of Diabetes and Its Vascular Complications. *Biomedicines 2022, Vol 10, Page 1168*. 2022;10(5):1168. doi:10.3390/BIOMEDICINES10051168

8. Chen R, Kang R, Tang D. The mechanism of HMGB1 secretion and release. *Experimental & Molecular Medicine 2022 54:2*. 2022;54(2):91-102. doi:10.1038/s12276-022-00736-w

9. Chen R, Kang R, Tang D. The mechanism of HMGB1 secretion and release. *Exp Mol Med*. 2022;54(2):91. doi:10.1038/S12276-022-00736-W

10. Agalave NM, Svensson CI. Extracellular High-Mobility Group Box 1 Protein (HMGB1) as a Mediator of Persistent Pain. *Molecular Medicine 2014 20:1*. 2014;20(1):569-578. doi:10.2119/MOLMED.2014.00176

11. Liu Z, Yang W, Chen J, Wang Q. Circulating HMGB1 in acute ischemic stroke and its association with poststroke cognitive impairment. *PeerJ*. 2024;12(4):e17309. doi:10.7717/PEERJ.17309/SUPP-2

12. Hayakawa K, Qiu J, Lo EH. Biphasic actions of HMGB1 signaling in inflammation and recovery after stroke. *Ann N Y Acad Sci*. 2010;1207(1):50-57. doi:10.1111/J.1749-6632.2010.05728.X;PAGE:STRING:ARTICLE/CHAPTER

13. Li J, Wang Z, Li J, Zhao H, Ma Q. HMGB1: A New Target for Ischemic Stroke and Hemorrhagic Transformation. *Translational Stroke Research 2024 16:3*. 2024;16(3):990-1015. doi:10.1007/S12975-024-01258-5

14. Liu Z, Yang W, Chen J, Wang Q. Circulating HMGB1 in acute ischemic stroke and its association with poststroke cognitive impairment. *PeerJ*. 2024;12(4):e17309. doi:10.7717/PEERJ.17309/SUPP-2

15. Biscetti F, Rando MM, Nardella E, et al. High Mobility Group Box-1 and Diabetes Mellitus Complications: State of the Art and Future Perspectives. *International Journal of Molecular Sciences 2019, Vol 20, Page 6258*. 2019;20(24):6258. doi:10.3390/IJMS20246258

16. Wang H, Qu H, Deng H. Plasma HMGB-1 Levels in Subjects with Obesity and Type 2 Diabetes: A Cross-Sectional Study in China. *PLoS One*. 2015;10(8):e0136564. doi:10.1371/JOURNAL.PONE.0136564

17. Wang Y, Zhong J, Zhang X, et al. The Role of HMGB1 in the Pathogenesis of Type 2 Diabetes. *J Diabetes Res*. 2016;2016:2543268. doi:10.1155/2016/2543268

18. Biscetti F, Rando MM, Nardella E, et al. High Mobility Group Box-1 and Diabetes Mellitus Complications: State of the Art and Future Perspectives. *International Journal of Molecular Sciences 2019, Vol 20, Page 6258*. 2019;20(24):6258. doi:10.3390/IJMS20246258

19. Gu L, Zhou J, Jin Q, et al. Elevated Serum HMGB1 Levels and Their Association with Stroke Risk of Paroxysmal Atrial Fibrillation. *J Inflamm Res*. 2025;18:16957-16965. doi:10.2147/JIR.S568868

20. Chen R, Kang R, Tang D. The mechanism of HMGB1 secretion and release. *Exp Mol Med*. 2022;54(2):91-102. doi:10.1038/S12276-022-00736-W

21. Schulze J, Zierath D, Tanzi P, et al. Severe stroke induces long-lasting alterations of high-mobility group box 1. *Stroke*. 2013;44(1):246-248. doi:10.1161/STROKEAHA.112.676072

22. Nass RD, Wagner M, Surges R, Holdenrieder S. Time courses of HMGB1 and other inflammatory markers after generalized convulsive seizures. *Epilepsy Res*. 2020;162. doi:10.1016/j.eplepsyres.2020.106301

23. Ye Y, Zeng Z, Jin T, Zhang H, Xiong X, Gu L. The role of high mobility group box 1 in ischemic stroke. *Front Cell Neurosci*. 2019;13:426669. doi:10.3389/FNCEL.2019.00127/FULL