

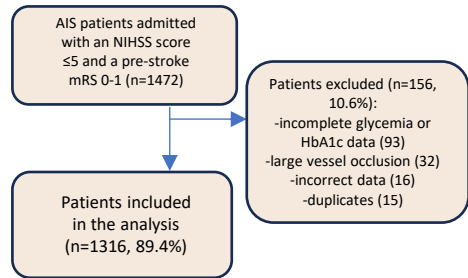
Hemorrhagic transformation and stress hyperglycemia in minor stroke: a causal mediation analysis

Arianna Todesco 1, Francesco Russo 1, Caterina Del Regno 1, Francesco Bax 2,3, Federico Mazzacane 4, Matteo Foschi 5,6
Raffaele Ornello 5, Alessandro Marè 1, Francesco Toraldo 1, Beatrice Del Bello 4, Laura Spigaroli 4, Lucia Pavolucci 6,
Simona Sacco 5, Anna Cavallini 4, Lucio D'Anna 7, Giovanni Merlino 3, Gian Luigi Gigli 1, Mariarosaria Valente 1

- 1 Clinical Neurology, Udine University Hospital and DMED, University of Udine, Udine, Italy
- 2 Hemorrhagic Stroke Research Program, J Philip Kistler Research Center, Department of Neurology, Massachusetts General Hospital and Harvard Medical School 175 Cambridge Street Boston 02114 MA USA
- 3 Stroke Unit, Udine University Hospital, Department of Head, Neck, and Neurosciences, Udine University Hospital, Udine, Italy
- 4 Department of Emergency Neurology and Stroke Unit, IRCCS Mondino Foundation, Pavia, Italy.
- 5 Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy.
- 6 Department of Neuroscience, Neurology Unit, S. Maria delle Croci Hospital, AUSL Romagna, Ravenna, Italy.
- 7 Department of Brain Sciences, Imperial College London, London, UK

Background and aims:

Stress hyperglycemia (SHG) is associated with worse outcomes in minor ischemic stroke. However, there is limited evidence on the underlying causal pathways. Hemorrhagic transformation (HT) has been identified as one of the potential mechanisms, but clear characterization of this relationship is lacking. Therefore, the aim of this study was to investigate whether HT mediates the relationship between SHG and poor functional outcome at 3 months.



Methods

We performed a retrospective analysis of a prospective international cohort of individuals presenting with minor stroke (NIHSS ≤ 5), prestroke-mRS ≤ 1 and no large vessel occlusion, from five centers in Italy and the UK in the period from January 2022 to December 2023. SHG was assessed within 24 hours using the glucose-to-glycated hemoglobin ratio (GAR). HT within 7 days was classified according to the European Cooperative Acute Stroke Study-2 definition in: hemorrhagic infarction (HI-2) or parenchymal hematoma (PH1-2). Causal mediation analysis was used to estimate SHG effect on mRS ≥ 2 and mRS ≥ 4 at 3 months mediated by HT (primary and secondary outcomes). Effect modification of age, diabetes, and C-reactive protein (CRP) was explored.

Results

Among 1,316 patients included, (mean age 69.6 ± 12.7 years; 63.6% males), higher GAR quartiles were associated with mRS ≥ 2 (adjusted-OR 1.72, CI 95% 1.24–2.40, $p=0.001$) and higher HT categories (adjusted-OR 2.32, CI 95% 1.43–3.76, $p=0.001$). A significant proportion (14.8%) of SHG effect on mRS was mediated by HT (Average Causal Mediation Effect = 0.014, CI95% 0.003-0.030, $P=0.003$). The proportion mediated was higher when conditioning to younger age (15.1%~60y vs. 4.0%~80y), higher CRP (9.2%~7 mg/L vs. 7.8%~1 mg/L) and absence of diabetes (9.1% vs. 6.9%). For mRS ≥ 4 , the proportion mediated by HT was higher (23.0%).

Variables / GAR quartiles	Q1 (<15.5)	Q2 (≥ 15.5 & <17.4)	Q3 (≥ 17.4 & <20.2)	Q4 (≥ 20.2)	Total	P
Total, n (%)	309 (23.5)	350 (26.6)	329 (25.0)	328 (24.9)	1316 (100)	0.7
Sex (male), n (%)	180 (58.3)	230 (65.7)	218 (66.3)	209 (63.7)	837 (63.6)	0.2
Age (years), mean (SD)	69.9 (12.6)	69.6 (12.8)	69.3 (12.7)	69.5 (12.9)	69.6 (12.7)	0.6
CRP (mg/L), median (interquartile range)	2.7 (5.1)	1.9 (4.5)	2.5 (5.5)	2.8 (6.6)	2.4 (5.7)	0.4
Type II diabetes, n (%)	46 (14.9)	49 (14.0)	82 (24.9)	125 (38.1)	302 (22.9)	<0.001
Baseline NIHSS, median (IQR)	2 (2)	2 (2)	2 (3)	3 (2)	2 (3)	0.01
mRS at three months, n (%)						
>2	51 (16.5)	55 (15.7)	76 (23.1)	104 (31.7)	286 (21.8)	<0.001
>3	32 (10.3)	26 (7.4)	43 (13.1)	67 (20.4)	168 (12.8)	<0.001
>4	14 (4.5)	11 (3.1)	27 (8.2)	30 (9.1)	82 (6.2)	0.002

1. Krzyz ME, Barakat OJ, Davies IH, et al. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. *Acta Neurol Scand* 2010; 121: 140–150.
2. Merlino G, Russo F, Ornello R, et al. Stress hyperglycemia associated with large vessel occlusion in patients with anterior large vessel occlusion undergoing mechanical thrombolysis. *European Stroke Journal* 2024; 35: 613–622.
3. Imai K, Keele T, Torgler D. A general approach to causal mediation analysis. *Psychol Methods* 2010; 15: 309–334.

Conclusions

In patients with minor stroke, HT significantly mediated the effect of SHG on unfavorable outcome. The mediating effect of HT was greater in patients either ~ 60 y, without diabetes, or with high baseline CRP levels. These initial results might inform patient selection for future interventional studies

