Reperfusion Therapy for Trousseau Syndrome-Related Cerebral Infarction: A Case-Control Analysis of Efficacy and Prognosis

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ABSTRACT

Objective: To evaluate the efficacy and prognostic significance of reperfusion therapy in patients with Trousseau syndrome-related cerebral infarction.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Neurology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China, and The Second Affiliated Hospital of Xiamen Medical College, Xiamen, China, between January 2017 and December 2023.

Methodology: Patients with Trousseau-associated cerebral infarction who were treated at two hospitals were included in the study. Clinical outcomes, including early neurological deterioration, intracranial haemorrhage, in-hospital mortality, 90-day modified Rankin scale (mRS) score, 90-day mortality, initial and discharge National Institutes of Health Stroke Scale (NIHSS) score, and ΔNIHSS (difference between the initial and discharge NIHSS score), were compared between the reperfusion-treated group (n = 9) and the conventionally treated group (n = 23).

Results: Patients who received reperfusion therapy demonstrated significant neurological improvement at discharge, with a statistically significant difference in their ΔNIHSS scores compared to those of the conventionally treated group (p <0.001). No significant differences were observed in early neurological deterioration (11.10% *vs.* 13.00%, p = 1.000), intracranial haemorrhage (33.33% *vs.* 8.70%, p = 0.121), in-hospital mortality (22.20% *vs.* 26.10%, p = 1.000), 90-day mortality (55.60% *vs.* 87.00%, p = 0.076), or 90-day mRS score (p = 0.052) between the two groups.

Conclusion: Despite the high mortality rate within 90 days, reperfusion therapy has the potential to improve the quality of life of surviving cancer patients with Trousseau-associated cerebral infarction.

Key Words: *Trousseau syndrome-related cerebral infarction, Reperfusion therapy, Intravenous thrombolysis, Mechanical thrombectomy, Acute cerebral infarction.*

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INTRODUCTION

Trousseau syndrome (TS) is characterised by the occurrence of cryptogenic thromboembolic events, often preceding or coinciding with the diagnosis of occult visceral malignancies.[1] TS is closely associated with abnormalities such as neoplasm-related coagulation and fibrinolysis.[1] Thromboembolic events in TS can manifest throughout the body, including deep vein thrombosis, pulmonary embolism, and thromboses in atypical sites such as the cerebral vasculature.[2]

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Acute cerebral infarction (ACI) is a common clinical manifestation of TS. Although its symptomatology may resemble that of other aetiologies of cerebral infarction, the underlying pathomechanisms and therapeutic responses may differ significantly.[3] Currently, there is no established diagnostic standard for TS-related cerebral infarction. However, a consensus amongst researchers suggests that a diagnosis of TS may be considered when imaging reveals multiple ACIs in various vascular territories in a patient with a malignant neoplasm, accompanied by a significant increase in D-dimer levels.[4-6]

Intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) are widely recognised as effective reperfusion therapies for ACI. Current guidelines recommend IVT with alteplase within a 4.5-hour window from symptom onset, whilst MT is advised when the IVT time window has elapsed or when IVT is deemed ineffective.[7,8] However, the American Heart and Stroke Association Guidelines for the Early Management of Patients with Acute Ischaemic Stroke, highlight the uncer-

tainty regarding the efficacy and safety of IVT during the acute phase for patients with ACI and concurrent malignant tumours. Moreover, these guidelines do not provide a definitive recommendation for the use of MT in this patient population.[8] Whilst the efficacy of reperfusion therapies for ACI is well-established in the general population, their safety and effectiveness in patients with TS-related cerebral infarction remain largely uncharted territory. The distinctive pathophysiology of TS, characterised by cancer-associated hypercoagulability and potential complications stemming from underlying malignancies, raises significant concerns regarding the applicability of standard reperfusion protocols in this specific patient cohort.

This study aimed to address the knowledge gap by comparing clinical outcomes of reperfusion therapy *versus* conventional treatment in patients with TS-related cerebral infarction. The investigation of this understudied area aimed to provide insights to the efficacy, safety, and prognostic implications of reperfusion therapies in this complex patient population. Findings may inform future clinical decision-making and guideline development for managing acute stroke in patients with TS.

METHODOLOGY

A retrospective multicentred study was conducted to analyse the clinical records of individuals who presented with concurrent neoplasms and cerebral infarction at Zhongshan Hospital of Xiamen University, Xiamen, China, and the Second Hospital of Xiamen Medical College Xiamen, China, from January 2017 to December 2023. Based on stringent inclusion and exclusion criteria, 32 patients were selected for the final analysis and their records were evaluated. The Ethics Committee of Zhongshan Hospital of Xiamen University approved this study with partial exemption from informed consent from the patients (ERC No. xmzsyyky2022-196, Dated: 28th July 2022).

The inclusion criteria were the presence of an active malignancy[9] (diagnosed during hospitalisation following ACI onset or within 6 months before ACI onset and included recurrent or metastatic tumours); radiological confirmation of multifocal acute cerebral infarcts, encompassing both bilateral anterior and posterior circulations, without detectable vascular stenosis on magnetic resonance angiography; and elevated D-dimer levels that exceeded the normal threshold (>0.5 mg/L). The exclusion criteria were age less than 18 years; previous tumour history not fulfilling the criteria for active malignancy; identification of another source for the patient's emboli (e.g., atrial fibrillation); and a prior history of a significant disability. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

This study collected patient demographic data, stroke risk factor data (hypertension, diabetes mellitus, smoking status, dyslipidaemia status, atrial fibrillation status, and prior stroke status), tumour type and stage, neurological score, and neurological score information (National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS)). Additionally, data on treatment (onset-to-needle time, door-to-needle time, onset-to-puncture time, and puncture-to-revascularisation time), imaging findings (findings on post-hospital CT or MRI, bilateral venous ultrasound), and laboratory data (blood biochemistry, routine blood tests, and blood coagulation information) were also collected.

Neurologic function and prognosis were assessed using the initial, 24-hour, and discharge NIHSS scores, along with the ΔNIHSS (the difference between the admission and discharge NIHSS scores). The prognosis was assessed using the mRS at discharge and that at 90 days post-discharge. Early neurologic deterioration was defined as an increase of ≥2 points within 24 hours after therapy.[10] Adverse events included intracranial haemorrhage conversion, in-hospital mortality, and mortality within 90 days.

Treatment strategies were classified into conventional and reperfusion treatments. Conventional treatment typically included antiplatelet therapy (aspirin or clopidogrel), statin therapy (e.g., atorvastatin), and supportive care, such as blood pressure and blood glucose control. Reperfusion treatment comprised intravenous thrombolysis, mechanical thrombectomy, or both, administered within the appropriate time window. All treatment decisions were made by attending physicians based on individual patient conditions and in accordance with current acute ischaemic stroke treatment guidelines.

Statistical analyses were conducted using SPSS 26.0. Continuous variables following a normal distribution were presented as the mean ± standard deviation, while those not conforming to a normal distribution were expressed as the median (interquartile range). Independent samples t-tests and Mann–Whitney U tests were used for normally and non-normally distributed data, respectively. Categorical data were expressed as frequencies and percentages, with group differences assessed using Chi-squared test or Fisher's exact test. A p-value less than 0.05 in a two-sided test was considered to indicate statistical significance.

RESULTS

The mean age of the 32 patients with TS-related cerebral infarction was 70.53 ± 9.02 years, with a range of 51-91 years, and there were 18 males (56.20%) and 14 females (43.80%). The clinical characteristics and laboratory findings of conventionally and reperfusion-treated patients are presented in Table I. A statistically significant difference in the initial NIHSS score ($p = 0.034$) and the ΔNIHSS score ($p < 0.001$) was observed between the reperfusion and conventional therapy groups. However, no statistically significant differences were observed in age, cerebrovascular disease risk factors, laboratory findings, admission and discharge NIHSS scores, or mRS scores at discharge or at 90 days ($p > 0.05$). A detailed comparison between the baseline characteristics and clinical outcomes of the conventionally treated and reperfusion-treated patients is shown in Table I.

In the reperfusion therapy cohort (n = 9), the treatment modalities included mechanical thrombectomy (n = 2), intravenous thrombolysis (n = 4), and bridging therapy (n = 3). All patients

treated with intravenous thrombolysis were administered 0.9 mg/kg of recombinant tissue plasminogen activator (rt-PA). During hospitalisation, two patients died, with one death attributable to neoplastic complications. Within the 90-day post-discharge period, an additional three patients died - two due to neoplastic complications and one due to recurrent cerebral infarction. The treatment and prognostic information of the patients in the group receiving reperfusion therapy is detailed in Table II and III. In the reperfusion therapy cohort, the treatment modalities included mechanical thrombectomy (patients 5 and 6), intravenous thrombolysis (patients 1, 2, 3, and 4), and bridging therapy (patients 7, 8, and 9).

Table I: Clinical characteristics and laboratory findings of conventionally and reperfusion-treated patients.

Variables	Conventional (n = 23)	Reperfusion (n = 9)	p-value
Age (year) [SD]	71.17 ± 8.10	68.89 ± 11.44	0.528
Gender (male), n (%)	14 (60.90)	4 (44.40)	0.453
Hypertension, n (%)	15 (65.20)	5 (55.50)	0.696
Diabetes, n (%)	8 (34.80)	0 (0.00)	0.070
Dyslipidaemia status, n (%)	3 (13.00)	1 (11.11)	1.000
Prior stroke history, n (%)	3 (13.00)	1 (11.11)	1.000
Smoking, n (%)	6 (26.10)	1 (11.11)	0.640
Alcohol, n (%)	4 (17.40)	0 (0.00)	0.303
Systemic metastasis, n (%)	19 (82.60)	5 (55.60)	0.176
White blood cell [IQR]	9.61 (6.93, 13.68)	10.64 (7.63, 11.51)	0.967
Neutrophil [IQR]	7.86 (4.72, 10.04)	8.84 (5.68, 9.39)	0.805
C-Reactive protein [IQR]	37.96 (14.48, 74.97)	25.30 (17.35, 79.89)	0.807
Lymphocyte	1.18 ± 0.45	1.32 ± 0.34	0.399
NLR	8.08 ± 5.01	6.68 ± 3.43	0.448
Triglyceride [IQR]	1.16 (0.89, 1.45)	1.10 (1.03, 1.48)	0.983
Cholesterol	4.17 ± 1.26	4.83 ± 1.13	0.180
HDLC	1.19 ± 0.32	1.16 ± 0.32	0.823
LDL-C	2.77 ± 0.80	3.24 ± 0.81	0.146
D-Dimer	14.02 ± 9.43	9.73 ± 6.17	0.218
Initial NIHSS, [IQR]	7.00 (4.00, 10.00)	12.00 (8.00, 14.00)	0.034
24-hour NIHSS, [IQR]	8.00 (4.50, 11.50)	10.00 (4.00, 14.00)	0.483
Discharge NIHSS, [IQR]	8.00 (4.00, 30.00)	9.00 (1.00, 12.00)	0.805
ΔNIHSS, [IQR]	2.00 (1.00, 2.00)	4.00 (3.00, 6.00)	<.001
Discharge mRS, [IQR]	4.00 (2.00, 5.50)	5.00 (1.00, 5.00)	1.000
Early neurologic deterioration, n (%)	3 (13.00)	1 (11.10)	1.000
Intracranial haemorrhage, n (%)	2 (8.70)	3 (33.33)	0.121
In-hospital mortality, n (%)	6 (26.10)	2 (22.20)	1.000
90-day mortality, n (%)	20 (87.00)	5 (55.60)	0.076
90-day mRS, n (%)	6.00 (6.00, 6.00)	6.00 (4.00, 6.00)	0.052

NLR, Neutrophil-to-lymphocyte ratio; HDLC, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ΔNIHSS, change in NIHSS score (discharge NIHSS minus baseline NIHSS).

Table II: Baseline characteristics and laboratory data of reperfusion-treated patients.

Age / gender	Tumour site	SM	WBC (10^9/L)	NEUT (10^9/L)	LYM (10^9/L)	NLR	CRP (mg/L)	Dimer (mg/L)
67 / M	Liver	N	8.99	6.61	1.68	3.93	18.26	6.20
78 / F	Lung	N	5.68	3.33	1.90	1.75	1.39	0.88
71 / F	Breast	Y	12.61	10.61	1.02	10.40	181.79	19.55
76 / M	Liver	N	11.51	9.39	1.24	7.57	97.17	12.50
58 / F	Lung	Y	7.63	5.68	1.39	4.09	62.61	18.02
77 / M	Nasal	N	10.64	8.84	0.80	10.9	16.45	8.68
51 / F	Uterine	Y	10.69	8.94	1.05	8.51	26.51	8.74
85 / F	Mediastinum	Y	6.71	4.74	1.41	3.36	24.08	3.54
57 / M	Lung	Y	15.29	13.23	1.38	9.59	NA	9.48

M, Male; F, Female; SM, Systemic metastasis; Y, Yes; N, No; NLR, Neutrophils-to-lymphocytes ratio; D-D, D-dimer.

Table III: Data on treatment and prognostic outcomes of reperfusion-treated patients.

ONT (min)	DNT (min)	OPT (min)	PRT (min)	Initial NIHSS	24-hour NIHSS	D-NIHSS	ICH	D-mRS	90d mRS
180	30	NA	NA	5	1	1	Y	1	0
102	42	NA	NA	7	4	0	N	0	0
103	59	NA	NA	12	9	42	N	6	6
204	14	NA	NA	12	10	9	N	5	6
NA	NA	700	15	8	3	1	N	1	6
NA	NA	560	70	12	12	9	N	5	4
120	55	310	115	14	20	11	Y	5	6
112	30	217	104	22	22	42	Y	6	6
70	30	390	50	17	14	12	N	5	4

ONT, Onset-to-needle time; DNT, Door-to-needle time; OPT, Onset-to-puncture time; PRT, Puncture-to-revascularisation time; ICH, Intracerebral haemorrhage; Y, Yes; N, No; D-mRS, Discharge modified Rankin Scale score; 90d mRS, 90 day modified Rankin Scale score.

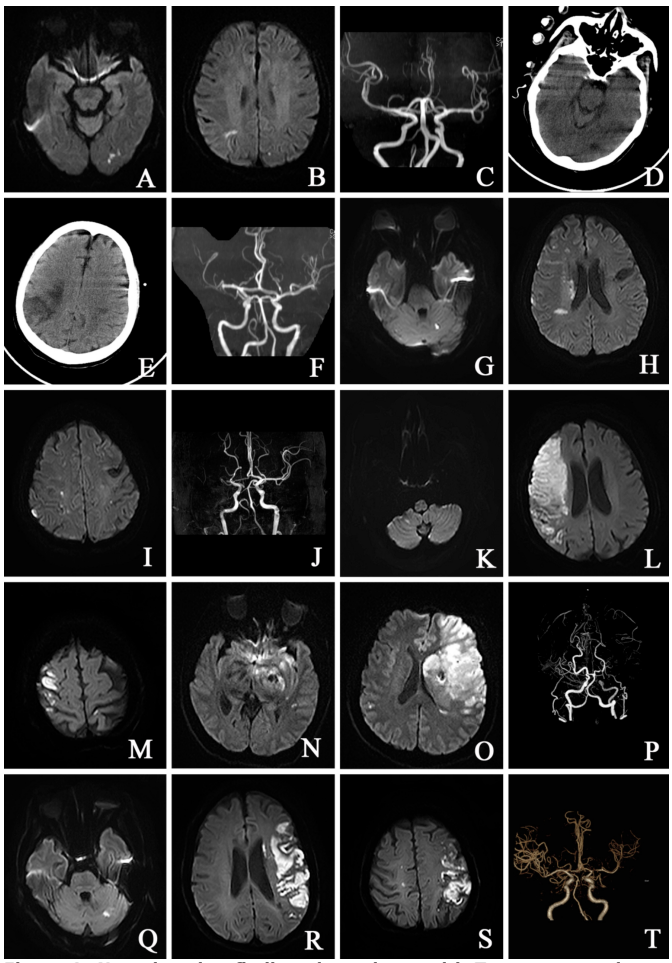

Figure 1: Neuroimaging findings in patients with Trousseau syndrome receiving reperfusion therapy. (A-C) Patient 2, Brain MRI (DWI) and MRA; (D-F) Patient 3, Brain CT and MRA; (Q-T) Patient 4, Brain MRI (DWI) and CTA; (G-J) Patient 5, Brain MRI (DWI) and MRA; (K-M) Patient 8, Brain DWI; (N-P) Patient 9, Brain MRI (DWI) and CTA.

DISCUSSION

This study revealed that patients with TS-related cerebral infarction undergoing reperfusion therapy exhibited a greater 90-day mortality rate (55.60% *vs*. 87.00%, p >0.05) despite a lower in-hospital mortality rate (22.20% *vs*. 26.10%, p >0.05). This increase in mortality is likely not directly linked to the cerebrovascular event itself but rather to the higher incidence of systemic metastasis in patients with malignant neoplasms (55.60% *vs*. 82.60%, p >0.05), along with oncological complications such as interruption of treatment, immunosuppression, advanced malignancy, and organ failure.[11] The higher initial NIHSS scores observed in the reperfusion therapy group may be attributed to the prompt arrival of patients with more severe conditions at the hospital for treatment. Remarkably, despite the elevated 90-day mortality, survivors who underwent reperfusion therapy exhibited substantial neurological amelioration at discharge compared to those receiving solely conventional management and did not experience a significant increase in the risk of haemorrhagic conversion or early neurological deterioration.

Furthermore, this study revealed notable individual variability in the response to intravenous thrombolytic therapy among patients with TS-related cerebral ischaemia. Approximately half of these patients exhibited significant neurological improvement post-thrombolysis, whereas the remaining half did not demonstrate such improvement. An MRI-based radiological assessment revealed that patients with more favourable outcomes from intravenous thrombolysis presented with multiple dispersed small infarcts. In contrast, the efficacy of thrombolysis decreased in patients who had large vessel occlusion in the anterior circulation (Figure 1).

All patients exhibited bilateral cerebral infarction lesions involving both the anterior and posterior circulation. The anterior, middle, and posterior cerebral arteries, along with the main branches of the vertebral arteries, were well displayed in all patients. Occlusion of the main branches due to thrombus was not considered indicative of vessel stenosis.

The variability in therapeutic efficacy may be attributed to the compositional and structural heterogeneity of thrombi.[12,13] Histological analyses of thrombi retrieved after thrombectomy have revealed a common structural characteristic: A core enriched in erythrocytes surrounded by a shell composed of fibrin, von Willebrand factor (vWF), and aggregated platelets, and these thrombi also have variations in the proportions of erythrocytes, platelets, fibrin, and leucocytes.[14-16] The dense fibrin network within the shell acts as a barrier, impeding the diffusion of tissue-type plasminogen activator (rt-PA) and thereby hindering its ability to lyse fibrin in the core, which compromises the thrombolysis efficiency of rt-PA.[13] Furthermore, the presence of various extracellular matrix components, such as vWF, extracellular DNA, and neutrophil extracellular traps, in fibrin-rich thrombi not only enhances the mechanical stability of the thrombus but also decreases its permeability by altering the fibrin structure. These extracellular matrix components increase resistance to thrombolytic agents, making fibrin--dense thrombi significantly less sensitive to rt-PA than erythrocyte-rich thrombi.[17]

Thrombi that are retrieved after thrombectomy in patients with cerebral infarction and concurrent cancer are predominantly composed of fibrin and platelets, and these thrombi have significantly fewer erythrocytes than thrombi from non-cancer patients.[18,19] Fu *et al*. reported that most of these thrombi were white thrombi, primarily consisting of fibrin and platelets.[18] Moreover, Matsumoto *et al*.'s analysis of thrombi from patients with TS-related ACI revealed that fibrin constituted more than 90% of the composition of thrombi in these patients.[19] These findings may explain why more than half of TS patients exhibited no significant improvement in early neurological function following IVT treatment.

However, the current studies on the composition of thrombi retrieved after thrombectomy have limitations. These studies have mainly focused on emboli due to large vessel occlusion, while the characterisation of thrombi components post-small vessel occlusion or following IVT treatment is ambiguous. In a research conducted by Seok *et al*., the plasma levels of D-dimer and the amount of microthrombotic signals in the bilateral internal carotid arteries were measured using transcranial doppler in patients with ACI and concurrent cancer.[20] The results showed that the number of microthrombotic signals in the internal carotid arteries of cancer patients was significantly increased and positively correlated with plasma D-dimer levels.[20] This finding further suggested that cancer may induce a hypercoagulable state, potentially leading to the formation of microemboli and contributing to cerebral infarction secondary to small infarct foci. Whether these microemboli differ significantly in composition from thrombi retrieved post-thrombectomy and whether they are more sensitive to rt-PA warrant further investigation.

This study underscores the significance of reperfusion therapy strategies in patients with TS-related cerebral infarction. Despite the high mortality rate within 90 days, reperfusion therapy is clinically relevant for improving the quality of life of surviving cancer patients.

A major limitation of this study was its retrospective nature, which could introduce potential biases in the data collection and analysis. Additionally, the small sample size restricted the ability to draw firm conclusions about the efficacy of reperfusion therapy for TS patients and the prognosis of these patients. Therefore, future studies with larger cohorts are needed to more accurately assess the impact of reperfusion therapy on TS patients. These studies should also explore the effects of different reperfusion therapy modalities on patient outcomes. Furthermore, the thrombus components associated with small vessel occlusion in TS-related cerebral infarction patients remain underexplored. It is anticipated that advances in thrombus composition imaging techniques will allow for the development of effective alternatives for detailed thrombus composition analysis. By thoroughly examining the thrombus composition in multiple scattered infarcts in patients with TS-related cerebral infarction and implementing targeted preventive measures, it is expected that cerebral infarction induced by a hypercoagulable state in tumour patients will be effectively mitigated.

CONCLUSION

Despite the high mortality rate within 90 days, reperfusion therapy has the potential to improve the quality of life of surviving cancer patients with Trousseau-associated cerebral infarction. Furthermore, there were significant individual differences in the response to intravenous thrombolytic therapy among patients with Trousseau-associated cerebral ischaemia, which may be attributed to the heterogeneity in the thrombus composition and structure in these patients.

ETHICAL APPROVAL:

The Ethical Committee of Zhongshan Hospital of Xiamen University approved this study with partial exemption from informed consent (ERC No. xmzsyyky2022-196, Dated: 28th July 2022).

PATIENTS' CONSENT:

This study primarily involves a retrospective investigation of clinical characteristics of acute cerebral infarction in China's Southeast coastal region. The Ethics Review Committee of Zhongshan Hospital Affiliated to Xiamen University has approved the retrospective collection of clinical data for all acute cerebral infarction patients treated at the hospital until May 2025 (the end date of the government-funded project). This approval explicitly includes patients who received treatment prior to the ethics review. During the ethics approval process, the authors obtained a waiver of informed consent requirements for some patients.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

WG: Acquisition and drafting of the work.
HL: Conception, design of the work, and data analysis.
YZ: Critical revision for important intellectual content, analysis, and interpretation of data for the work.
SL: Critical revision for important intellectual content.
XC: Data collection and critical revision for important intellectual content, analysis, and interpretation of data for the work.
RZ: Approval of the final version to be published.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Varki A. Trousseau's syndrome: Multiple definitions and multiple mechanisms. *Blood* 2007; **110(6)**:1723-9. doi: 10.1182/blood.2006.10.053736.
2. Zhen C, Wang Y, Wang H, Li D, Wang X. Multiple cerebral infarction linked to underlying cancer: A review of trousseau syndrome-related cerebral infarction. *Br J Hosp Med (Lond)* 2021; **82(5)**:1-7. doi: 10.12968/hmed.2020.0696.
3. Kim AS, Khorana AA, Mccrae KR. Mechanisms and biomarkers of cancer-associated thrombosis. *Transl Res* 2020; **225**:33-53. doi: 10.1016/j.trsl.2020.06.012.
4. Tsushima M, Metoki N, Hagii J, Saito S, Shiroto H, Yasujima M, *et al*. D-dimer and c-reactive protein as potential biomarkers for diagnosis oftrousseau's syndrome in patients with cerebral embolism. *J Stroke Cerebrovasc Dis* 2020; **29(2)**:104534. doi: 10.1016/j.jstrokecerebrovasdis.
5. Bao L, Zhang S, Gong X, Cui G. Trousseau syndrome related cerebral infarction: Clinical manifestations, laboratory findings and radiological features. *J Stroke Cerebrovasc Dis* 2020; **29(9)**:104891. doi: 10.1016/j.jstrokecerebrovasdis.2020.104891.

6. Nouh AM, Staff I, Finelli PF. Three territory sign: An mri marker of malignancy-related ischemic stroke (Trousseau syndrome). *Neurol Clin Pract* 2019; **9(2)**:124-8. doi: 10. 1212/CPJ.0000000000000603.
7. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, *et al*. European stroke organisation (ESO) guidelines on intravenous thrombolysis foracute ischaemic stroke. *Eur Stroke J* 2021; **6(1)**:I-LXII. doi: 10.1177/2396987321989865.
8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the american heart association/American stroke association. *Stroke* 2019; **50(12)**:e344-418. doi: 10.1161/ STR.0000000000000211.
9. Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, *et al*. American society of hematology 2021 guidelines for management of venousthromboembolism: Prevention and treatment in patients with cancer. *Blood Adv* 2021; **5(4)**:927-74. doi: 10.1182/bloodadvances.2020003442.
10. Siegler JE, Boehme AK, Kumar AD, Gillette MA, Albright KC, Martin-Schild S. What change in the National Institutes of Health Stroke Scale should define neurologic deterioration in acute ischemic stroke? *J Stroke Cerebrovasc Dis* 2013; **22(5)**:675-82. doi: 10.1016/j.jstrokecerebrovasdis-.2012.04. 012.
11. Aboul-Nour H, Maraey A, Jumah A, Khalil M, Elzanaty AM, Elsharnoby H, *et al*. Mechanical thrombectomy for acute ischemic stroke in metastatic cancer patients: A nationwide cross-sectional analysis. *J Stroke* 2023; **25(1)**: 119-25. doi: 10.5853/jos.2022.02334.
12. Murray V, Norrving B, Sandercock PA, Terent A, Wardlaw JM, Wester P. The molecular basis of thrombolysis and its clinical application in stroke. *J Intern Med* 2010; **267(2)**:191-208. doi: 10.1111/j.1365-2796.2009.02205.x.
13. Krajickova D, Krajina A, Steiner I, Vysata O, Herzig R, Lojik M, *et al*. Fibrin clot architecture in acute ischemic stroke treated with mechanical thrombectomy with stent-retrievers - cohort study. *Circ J* 2018; **82(3)**:866-73. doi: 10. 1253/circj.CJ-17-0375.
14. Brinjikji W, Madalina MO, Dai D, Kallmes DF, Savastano L, Liu Y, *et al*. Mechanisms of fibrinolysis resistance and potential targets for thrombolysis inacute ischaemic stroke: Lessons from retrieved stroke emboli. *Stroke Vasc Neurol* 2021; **6(4)**:658-67. doi: 10.1136/svn-2021-001032.
15. Staessens S, Fitzgerald S, Andersson T, Clarencon F, Denorme F, Gounis MJ, *et al*. Histological stroke clot analysis after thrombectomy: Technical aspects andrecommendations. *Int J Stroke* 2020; **15(5)**:467-76. doi: 10.1177/ 1747493019884527.
16. Staessens S, Denorme F, Francois O, Desender L, Dewaele T, Vanacker P, *et al*. Structural analysis of ischemic stroke thrombi: Histological indications fortherapy resistance. *Haematologica* 2020; **105(2)**:498-507. doi: 10.3324/haematol.2019.219881.
17. Staessens S, Francois O, Brinjikji W, Doyle KM, Vanacker P, Andersson T. Studying stroke thrombus composition after thrombectomy: What can we learn? *Stroke* 2021; **52(11)**: 3718-27. doi: 10.1161/STROKEAHA.121.034289.
18. Fu CH, Chen CH, Lin YH, Lee CW, Tsai LK, Tang SC, *et al*. Fibrin and platelet-rich composition in retrieved thrombi hallmarks stroke withactive cancer. *Stroke* 2020; **51(12)**:3723-7. doi: 10.1161/STROKEAHA.121.034289.
19. Matsumoto N, Fukuda H, Handa A, Kawasaki T, Kurosaki Y, Chin M, *et al*. Histological examination of Trousseau syndrome-related thrombus retrieved throughacute endovascular thrombectomy: Report of 2 cases. *J Stroke Cerebrovasc Dis* 2016; **25(12)**:e227-30. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.041.
20. Seok JM, Kim SG, Kim JW, Chung CS, Kim GM, Lee KH*, et al*. Coagulopathy and embolic signal in cancer patients with ischemic stroke. *Ann Neurol* 2010; **68(2)**:213-9. doi: 10. 1002/ana.22050.