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Pathological and neuropathological insights from autopsy in stroke patients across pre-and post-thrombolysis period

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Introduction

Ischemic stroke is a consequence of arterial occlusion in the central nervous system and is one of the leading causes of disability and death worldwide. In 2016, 13.7 million new cases were diagnosed, approximately 87% of which were ischemic in origin. It is estimated that 10–20% of these cases were caused by large vessel occlusion. However, less than 5% of patients with acute ischemic stroke received intravenous thrombolysis (IVT), and fewer than 100,000 mechanical thrombectomies (MT) were performed globally. In Hungary, the incidence of ischemic stroke is 40 per 10,000 inhabitants per years. Timely reperfusion therapy is the cornerstone of effective stroke care**,** requiring early symptom recognition by the general population and first responders, as well as rapid transport to a designated stroke center. Improving the stroke care system and reducing treatment delays are essential for maximizing the effectiveness of reperfusion therapies. Despite advancements in stroke care, WHO data indicate that approximately 5 million patients die from stroke-related causes each year. The cause of death may be hemorrhagic transformation, non-central nervous system (non-CNS) complications (such as pulmonary embolism, pneumonia, or myocardial infarction), or a combination of CNS and non-CNS complications. Since detailed imaging and thorough internal medicine assessment are not always feasible in critically ill stroke patients due to their condition, the frequency of such complications—and the accurate determination of the cause of death—can often only be reliably assessed through both body and brain autopsy. Autopsy represents the final stage of medical practice**,** which not only validates the accuracy of the clinical diagnosis and treatment but also provides valuable information about what occurred between the last clinical evaluation and death. In the past century, the primary purpose of autopsy was to determine the disease that led to death. Today, it also serves as a crucial and reliable tool for evaluating treatment efficacy, detecting adverse effects, and identifying hospital-acquired infections. Autopsy remains the definitive method for confirming the presence or absence of comorbid conditions, and this role continues to be essential today. The COVID-19 pandemic further emphasized the importance of comparing autopsy findings with clinical data, especially in evaluating the efficacy of antiviral and antithrombotic therapies. Due to the initial uncertainties regarding the infectivity of SARS-CoV-2, as well as the limited availability of personnel and personal protective equipment, autopsies of patients who died

from COVID-19 were restricted and primarily focused on pulmonary involvement. During brain autopsy, no significant or acute pathological findings were identified in 65% of cases. In the remaining 35%, hemorrhage and hemorrhagic transformation were the most common complications, and ischemic lesions were also observed in several cases. Histopathological examination revealed that the most frequent microscopic finding was mild to moderate acute hypoxic injury, while severe hypoxic-ischemic damage and focal necrosis were identified less frequently. Mild lymphocytic infiltration with T-cell predominance was commonly observed, and moderate to marked microglial activation was predominantly noted in the brainstem. Autopsy continues to play a significant role in medical education, and even in the advancement of medical science. It allows for the collection of tissue samples from organs that are otherwise inaccessible or difficult to sample in vivo. These autopsy-derived specimens come from their natural in vivo environment—unlike in vitro cell cultures—making them particularly valuable for studying diseases of unclear etiology or pathomechanism, such as various forms of dementia. Despite all these advantages, autopsy rates are declining globally. In the United States and in many European countries, the rate has fallen below 5%. This decline can be attributed to multiple factors: overreliance on the presumed accuracy of in vivo diagnostics, lack of awareness among clinicians about the value of autopsy, a decreasing number of pathologists, and resistance from family members. Unfortunately, this downward trend is also evident in Hungary. This is particularly concerning, as numerous scientific societies and the U.S. Agency for Healthcare Research and Quality (AHRQ) have highlighted the dangers associated with the decreasing number of autopsies.

Literature overview

Definition

According to the World Health Organization (WHO), stroke is defined as “a rapidly developing clinical syndrome of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular origin.” Stroke is classified into two major types: approximately 80% are of ischemic origin, while 20% are hemorrhagic strokes. Within the hemorrhagic category, two main subtypes are distinguished: spontaneous intracerebral hemorrhages (approximately 15%) and non-traumatic subarachnoid hemorrhages (around 5%). Transient ischemic attack (TIA) is also recognized as a separate clinical entity. By definition, it involves transient focal neurological symptoms caused by ischemia of the

brain, spinal cord, or retina, without evidence of acute tissue injury. The occurrence of transient symptoms is an important warning sign, as the risk of a full-blown stroke is highest within the first 48 hours following a TIA.

Risk Factors

The most common causes of ischemic stroke include cerebral infarction resulting from atherothrombotic disease, cardioembolism, and small vessel disease. Less frequent causes involve arterial dissection, vasculitis, prothrombotic states, hematological disorders, mitochondrial diseases, metabolic disturbances, and various genetic syndromes. Classical risk factors include hypertension, diabetes mellitus, hyperlipidemia, smoking, and atrial fibrillation. Other contributing risk factors are obesity, physical inactivity, metabolic syndrome, chronic kidney disease, and systemic inflammatory conditions. It is estimated that 90% of all strokes are preventable and attributable to ten modifiable risk factors.

Ethnicity, Sex, and Age

Stroke is one of the leading causes of death among Americans, but stroke risk varies significantly by race and ethnicity. The risk of a first stroke is nearly twice as high in non-Hispanic Black individuals compared to non-Hispanic Whites, and stroke-related mortality is highest among non-Hispanic Black adults and people of Pacific Islander descent. Women have a higher prevalence and incidence of intracranial aneurysms, as well as a significantly greater frequency of subarachnoid hemorrhage compared to men. Regarding age, the risk of ischemic stroke and transient ischemic attack (TIA) is higher among women under the age of 30, middle-aged men, and becomes approximately equal around the age of 80, after which it shifts again in favor of women over the age of 85. Statistically, women are at greater risk of stroke-related death than men: on average, six out of every ten people who die from ischemic or hemorrhagic stroke are women. Additionally, women are on average 4 to 6 years older than men at the time of stroke onset. Although stroke was traditionally considered a disease of the elderly, data from 2014 indicate that approximately 38% of all stroke patients are younger than 65 years. A correlation has been observed between the rising stroke incidence in younger populations (under 50) and the presence of traditional risk factors more commonly seen in those over 50. Historically, stroke in young adults was generally considered rare or attributed to specific etiologies, such as genetic disorders, vascular malformations, or autoimmune diseases. However, more recent data indicate that “traditional” vascular risk factors—including

hypertension, diabetes mellitus, hypercholesterolemia, smoking, obesity, and physical inactivity—are increasingly prevalent among young adults and play an expanding role in the development of ischemic stroke at a young age. In particular, increased rates of hypercholesterolemia and diabetes have been reported in both men and women aged 35 to 44 years**.**

Diet and Physical Activity

A comprehensive study published in 2019 reported that consumption of folic acid, B vitamins, and adherence to a Mediterranean diet are associated with a reduced risk of stroke. The important role of physical activity in stroke prevention is well established. A 10-year cohort study involving over 16,000 healthy men found that groups with good physical fitness had a 68% lower risk of stroke and mortality compared to those with the poorest fitness levels. The 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend a Mediterranean diet, as well as moderate-intensity physical activity at least four times per week for a minimum of 10 minutes per session, or vigorous-intensity exercise at least twice per week for at least 20 minutes per session, even in patients who have experienced stroke or transient ischemic attack (TIA).

Alcohol and Smoking

According to WHO data, excessive alcohol consumption causes approximately 3 million deaths worldwide each year, while tobacco use is responsible for over 8 million deaths annually, including 1.3 million non-smokers exposed to secondhand smoke. A meta-analysis published in 2014 found that low to moderate alcohol intake (0–20 g/day) significantly reduces the risk of stroke, whereas heavy alcohol consumption significantly increases it. Smoking is an independent, strong, and dose-dependent risk factor for first ischemic stroke, doubling the risk compared to non-smokers. The 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend smoking cessation, and advise reduction of alcohol consumption to no more than two drinks per day for men and one drink per day for women after stroke or transient ischemic attack (TIA).

Hypertension

Hypertension is a global public health issue, with WHO data reporting that approximately 1.28 billion adults aged 30 to 79 worldwide suffer from high blood pressure. A Hungarian study conducted between 2005 and 2018 examined 8,624 overweight and obese children and adolescents, finding the prevalence of hypertension to be 0.8% in the normal-weight population, 8.3% among the overweight group, and 26.7% in the obese group. Lowering blood pressure in hypertensive patients is highly effective in preventing ischemic stroke; a reduction of 10 mmHg in systolic and 5 mmHg in diastolic blood pressure decreases the risk of stroke by 41% and coronary artery disease by 22%. The 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend maintaining blood pressure below 130/80 mmHg following transient ischemic attack (TIA) or stroke.

Hyperglycemia and Diabetes Mellitus

Diabetes mellitus is an independent risk factor for stroke and is associated with poorer outcomes. A meta-analysis published in 2019 reported a diabetes prevalence of 28% among all stroke patients, with 33% in ischemic stroke cases and 26% in hemorrhagic stroke cases. The American Diabetes Association recommends a target HbA1c level of less than 7% for most adults, a goal also supported by stroke management guidelines.

Hyperlipidemia

Elevated lipid levels and their associated complications result from a combination of poor diet, lifestyle, environmental, and genetic factors. Studies indicate that every 1 mmol/L reduction in LDL cholesterol achieved through statin therapy decreases the risk of first stroke by approximately 21%. The recent Treat Stroke to Target (TST) trial reported that ischemic stroke or transient ischemic attack (TIA) patients with an average baseline LDL cholesterol of 3.5 mmol/L who achieved levels below 1.8 mmol/L had a lower risk of cardiovascular events compared to those in the 2.3–2.8 mmol/L group after 3.5 years of follow-up. The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study randomized 4,731 patients with prior TIA (31%) or stroke (ischemic 67%, hemorrhagic 2%) and LDL cholesterol levels between 2.59 and 4.91 mmol/L to atorvastatin doses up to 80 mg. Atorvastatin reduced the risk of recurrent stroke by 16%, but increased the risk of hemorrhagic stroke. Opinions on the hemorrhagic stroke risk associated with statin therapy remain divided. Among 39 lipid-lowering trials including a total of 287,651 participants, lipid-lowering therapy was not associated with a statistically significant increased risk of intracranial hemorrhage (ICH) in both

primary and secondary prevention studies (odds ratio [OR]: 1.12; 95% confidence interval [CI]: 0.98–1.28).

Atrial Fibrillation

The incidence and prevalence of atrial fibrillation (AF) are increasing worldwide, particularly among the elderly, individuals with metabolic syndrome, and patients with high cardiovascular risk. Given that AF significantly contributes to the risk of stroke, heart failure, and all-cause mortality, primary prevention—i.e., preventing the onset of the arrhythmia—is of strategic importance. Primary prevention focuses on managing modifiable risk factors that predispose to AF. The most significant modifiable risk factors include hypertension, obesity, type 2 diabetes mellitus, obstructive sleep apnea (OSA), excessive alcohol consumption, and physical inactivity. According to the INTERAF study, over 70% of AF patients had at least one of these modifiable risk factors. However, this does not imply that no risk factors were present in the remaining nearly 30% of cases underlying the development of atrial fibrillation (AF). Rather, it indicates that no known or modifiable risk factors were identified in these patients. Other, less readily detectable or non-modifiable factors may nonetheless contribute to disease development.

- **Genetic predisposition:** Mutations in genes encoding specific ion channels and structural proteins may independently increase susceptibility to atrial electrical instability.
- **Subclinical or as yet undiagnosed risk factors:** These include conditions such as masked hypertension, latent hyperthyroidism, or mild metabolic disturbances.
- **Structural atrial abnormalities:** Microfibrosis or atrial scarring that has not yet manifested as overt clinical disease but may facilitate the development of AF.
- **Idiopathic atrial fibrillation:** Cases in which no triggering factor can be identified through clinical evaluation, laboratory testing, or imaging studies.

Hypertension is the most important independent risk factor for AF, and adequate control of blood pressure can reduce AF incidence by 20–30%. Similarly, weight reduction and regular physical activity have been shown to decrease the likelihood of developing AF. In the ARREST-AF trial, patients receiving comprehensive lifestyle intervention exhibited lower AF recurrence rates even following ablation therapy. OSA is particularly prevalent in the AF population, and increasing evidence suggests that its recognition and treatment—such as continuous positive airway pressure (CPAP) therapy—may be a crucial component of primary

prevention. Improving health behaviors and implementing early screening strategies are also integral to primary prevention. Risk assessment tools (e.g., Framingham score, QRISK, or newer artificial intelligence-based models) can help identify patients who require closer monitoring for arrhythmia prevention. Digital devices, including smartwatches and mobile ECGs, also play a role in detecting subclinical or paroxysmal AF. In summary, targeted, individualized risk reduction and optimal control of comorbidities can prevent or delay the onset of atrial fibrillation.

Diagnosis

The diagnosis of stroke is based on a detailed medical history, physical and neurological examinations, and imaging studies, while excluding stroke mimics. Subarachnoid hemorrhage (SAH) typically presents with sudden, severe, "thunderclap" occipital headache, whereas ischemic stroke is usually painless, which often delays recognition. According to the Hungarian Stroke Society patient guide, three simple tests aid in stroke symptom recognition (Cincinnati Prehospital Stroke Scale): ask the patient to smile, raise both arms with palms facing upward, and speak by saying a simple sentence. If the patient has difficulty performing any of these tasks, immediate emergency medical assistance is recommended, preventing the loss of approximately 1.9 million neurons per minute. The type of stroke cannot be definitively determined through neurological examination alone; imaging studies are mandatory in all cases. Magnetic resonance imaging (MRI) is not continuously available in most institutions, and local resources typically determine whether MRI or computed tomography (CT) is performed. The minimal stroke imaging protocol consists of non-contrast CT and CT angiography (CTA), with assessment according to the ASPECT score. The ASPECTS (Alberta Stroke Program Early CT Score) is a quantitative topographical CT scoring system used to estimate ischemic severity. It applies to the middle cerebral artery (MCA) territory: including the putamen, caudate nucleus, internal capsule, insula, and the underlying cortex segments M2, as well as the adjacent anterior (M1), posterior (M3), and superior (M4–M6) regions. Each region scores one point, with a maximum of 10 points. Since 2008, the posterior circulation ASPECT (pc-ASPECT) score has been introduced to assess ischemic damage in the cerebellum, thalamus, and occipital lobe, assigning one point per side, and two points each for the pons and midbrain. Computed tomography perfusion (CTP) evaluates the functional status of brain tissue by characterizing cerebral perfusion. CTP improves the diagnostic accuracy of ischemic stroke. Perfusion CT or

diffusion/perfusion MRI allows for extended time-window thrombolysis and thrombectomy in selected cases.

Treatment

Acute management of ischemic stroke

The discovery of thrombolytic agents dates back to the 1930s, but their first use in acute ischemic stroke treatment occurred only in 1958. Optimal patient selection was not possible until the mid-1970s due to the lack of computed tomography (CT) imaging. In 1983, recombinant tissue plasminogen activator (rt-PA) became available through cloned gene expression, but it was only in 1995 that rt-PA was confirmed as an effective treatment for acute ischemic stroke. Between 1989 and 1999, reperfusion therapies were not yet widely implemented in the treatment of ischemic stroke, and early therapeutic strategies were primarily based on antithrombotic agents. The large randomized International Stroke Trial demonstrated that initiation of aspirin therapy (300 mg/day) in acute stroke reduced mortality and the rate of persistent disability, whereas the use of low-molecular-weight heparin was associated with fewer recurrent strokes but an increased incidence of hemorrhagic events. To date, rt-PA remains the only approved thrombolytic agent for ischemic stroke. In Hungary, rt-PA is administered at a dose of 0.9 mg/kg, with 10% given as an initial bolus and the remainder infused intravenously over 60 minutes, with a maximum total dose of 90 mg. The EXTEND-IA TNK study in 2017 compared tenecteplase (0.25 mg/kg, max 25 mg) with alteplase (0.9 mg/kg, max 90 mg) in patients with large vessel occlusion prior to thrombectomy. Tenecteplase was found to be superior, leading to its recommendation in the 2021 European Stroke Organisation (ESO) guidelines. Intravenous thrombolysis reduces disability when administered within 4.5 hours from stroke onset; in selected cases, using perfusion imaging, this window may be extended up to 9 hours. Endovascular thrombectomy reduces disability in patients with large vessel occlusion when performed within 6 hours of symptom onset, or within 24 hours in those selected by perfusion imaging. Several studies demonstrated that patients with low ASPECT scores (<5) can also benefit from thrombectomy, including those with isolated middle cerebral artery, internal carotid artery, and tandem occlusions. A meta-analysis concluded that although the risk of intracranial hemorrhage is higher, complete or partial reperfusion improved 90-day mortality and functional outcomes even in patients with ASPECT scores of 0–4. In cases of basilar artery occlusion, intravenous thrombolysis can be performed within 24 hours of stroke

onset provided there are no contraindications or extensive ischemic injury, regardless of stroke severity.

Acute management of spontaneous, non-traumatic intracerebral hemorrhage

Spontaneous intracerebral hemorrhages (ICH) account for approximately 12–15% of all strokes. Typical and atypical intracerebral hemorrhages arise from different etiologies and mechanisms, with distinct localization, clinical presentations, risk factors, and prognoses. Typical ICH is often a consequence of hypertension and predominantly affects the deep gray matter structures of the brain, such as the basal ganglia and thalamus. Hypertension leads to vulnerability of small cerebral vessel walls, predisposing to hemorrhage. In contrast, atypical ICH more frequently involves cortical regions and is commonly caused by cerebral amyloid angiopathy, tumors, anticoagulant therapy, sinus thrombosis, or other vascular abnormalities such as arteriovenous malformations. Management guidelines are summarized in the 2017 Hungarian Stroke Society protocol and the 2025 European Stroke Organisation (ESO) guidelines. The primary step is to identify and treat the underlying cause. Because elevated blood pressure can exacerbate hematoma expansion, systolic blood pressure should be lowered to 140 mmHg within six hours. Patients with coagulation factor deficiencies or thrombocytopenia require appropriate factor or platelet replacement. A thorough medication history is essential. In patients on vitamin K antagonists, administration of vitamin K and prothrombin complex concentrate (PCC) is recommended; if PCC is unavailable, fresh frozen plasma can be used. For patients treated with dabigatran, idarucizumab is indicated. There is no specific antidote currently available in Hungary for rivaroxaban, apixaban, or edoxaban; thus, PCC is recommended. Protamine sulfate can be administered to patients on heparin. Both hyperglycemia and hypoglycemia worsen outcomes; therefore, blood glucose should be maintained between 4.4 and 6.1 mmol/L. Fever management is important, as elevated body temperature correlates with poor prognosis. Surgical intervention depends on the patient's condition, hemorrhage location, and prognosis. Ventricular drainage is recommended in cases of hydrocephalus. Hematoma evacuation should be considered for lobar hemorrhages exceeding 30 ml in volume and located less than 1 cm deep from the cortical surface. Careful mobilization, physiotherapy, and rehabilitation are integral components of management. Prognosis is largely predicted by the ICH score: 30-day mortality rates are approximately 13% for a score of 1, 26% for a score of 2, 72% for a score of 3, and as high as 97% for a score of 4.

Acute management of non-traumatic subarachnoid hemorrhage

Non-traumatic subarachnoid hemorrhage (SAH) accounts for approximately 3–5% of all strokes. It typically presents with a sudden, severe "thunderclap" headache. In patients presenting with such symptoms, a non-contrast head CT and CT angiography (CTA) should be promptly performed to evaluate for SAH and possible aneurysm. It is important to note that negative imaging does not definitively exclude SAH; therefore, in cases with high clinical suspicion, a lumbar puncture should be performed. A negative cerebrospinal fluid analysis effectively rules out SAH. If SAH is confirmed and no aneurysm is detected on CTA, digital subtraction angiography (DSA) is recommended for further evaluation. In cases of ruptured aneurysm, treatment strategy—endovascular coiling or surgical clipping—is determined by the patient's clinical status and the aneurysm's location.

Pharmacological Secondary Prevention of Ischemic Stroke

Antithrombotic Therapy

Antiplatelet therapy reduces the risk of stroke in patients without cardiovascular disease, but it increases the risk of intracranial hemorrhage. The number needed to treat (NNT) is approximately 241, while the number needed to harm (NNH) is 210. When used for secondary prevention, acetylsalicylic acid had a number needed to treat (NNT) of 1/540 for the prevention of ischemic stroke, while the number needed to harm (NNH) for intracranial hemorrhage was 1/927. For patients with non-cardioembolic ischemic stroke or transient ischemic attack (TIA), initiation of antiplatelet therapy is recommended: aspirin at doses between 50–325 mg or clopidogrel 75 mg. In cases of minor stroke (NIHSS score ≤ 3) or high-risk TIA (ABCD2 score ≥ 4), dual antiplatelet therapy (aspirin plus clopidogrel) is advised to be started within 24 hours and continued for 21 days, followed by monotherapy. The ABCD2 score is based on five clinical parameters easily assessed in emergency settings to stratify TIA risk. Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia, with a rising prevalence worldwide, especially in the aging population. AF is associated with substantial morbidity and increased mortality, particularly due to ischemic stroke, heart failure, and sudden cardiac death. Consequently, both primary and secondary prevention are critical in clinical practice. Risk assessment for AF-related stroke is performed using the CHA_2DS_2-VASc score. A score of 0

in men or 1 in women indicates low risk and generally does not warrant anticoagulation. A score of 1 in men or 2 in women indicates intermediate risk where anticoagulation may be considered. Higher scores recommend anticoagulation. Antithrombotic therapy is a cornerstone of secondary prevention aiming to reduce embolic events, primarily stroke. Direct oral anticoagulants (DOACs)—including apixaban, rivaroxaban, dabigatran, and edoxaban—have demonstrated superior safety and efficacy profiles compared to vitamin K antagonists (VKAs). A meta-analysis involving 42,411 AF patients treated with DOACs and 29,272 patients on warfarin showed that DOACs significantly reduced the risk of stroke or systemic embolism by 19% over a two-year follow-up, and hemorrhagic stroke risk was reduced by 50%. Rate and rhythm control also form essential components of secondary prevention. While rhythm control may not directly reduce mortality or stroke risk in all patients, it can improve quality of life and reduce hospitalizations, particularly in younger symptomatic individuals. A comprehensive secondary prevention approach also includes management of modifiable risk factors such as hypertension, diabetes mellitus, obstructive sleep apnea, and obesity, which not only exacerbate AF progression but are independent risk factors for cardiovascular events. This holistic management approach, integrating lifestyle modification, comorbidity treatment, and psychosocial support, is increasingly emphasized in AF-related stroke secondary prevention. In summary, secondary prevention of AF-related stroke requires a multidisciplinary approach, integrating anticoagulation, rhythm or rate control, and management of comorbidities. Current guidelines stress individualized patient care with long-term follow-up and patient education as key components.

Hemorrhagic Transformation

Hemorrhagic transformation (HT) is a potential complication of acute ischemic stroke, which may occur spontaneously but is particularly significant following reperfusion therapies. Its incidence varies widely in different studies, ranging from 3% to 40%. In our opinion, HT represents the most critical complication associated with acute ischemic stroke. The fear of hemorrhagic transformation notably influences the frequency and decision-making surrounding recanalization treatments.

Pathophysiology

The underlying pathophysiological process is based on the structural and functional disruption of the blood–brain barrier (BBB) and the neurovascular unit. Increased permeability of the BBB allows for the extravasation of blood cells, a process mediated by activated platelets that play a central role in leukocyte recruitment. Subsequently, leukocytes slow down, roll along the activated endothelial surface, and transmigrate through the vessel wall via paracellular pathways. In cases of more severe vascular injury, red blood cells may also escape into the brain parenchyma, where the breakdown of hemoglobin leads to the release and accumulation of free iron. The reactive form of iron induces lipid peroxidation and oxidative stress, resulting in neuronal injury and the development of cerebral edema. Reactive oxygen species generated by iron further increase BBB permeability, promoting continued transmigration of leukocytes and other blood cells, thereby exacerbating neuroinflammatory processes.

Classification

Hemorrhagic transformation (HT) can be classified based on clinical and radiological criteria. Clinically, it is differentiated into symptomatic intracranial hemorrhage (sICH) and asymptomatic intracranial hemorrhage (aICH)**.** By definition, sICH is diagnosed when the NIH Stroke Scale (NIHSS) score worsens by at least 4 points within 36 hours of stroke onset, and the deterioration is attributable to hemorrhagic transformation. The incidence of sICH ranges from 2% to 8%, whereas aICH occurs in approximately 18% of cases following thrombolytic therapy. Radiologically, classification is based on the ECASS II criteria and the Heidelberg Bleeding Classification**.**

Risk Factors

Hypertension, early ischemic changes visible on CT imaging, poor collateral circulation, reperfusion therapy, hyperglycemia, more severe forms of ischemic stroke (indicated by higher NIHSS scores), advanced age, low platelet count, and antithrombotic treatment all increase the risk of hemorrhagic transformation (HT) following acute ischemic stroke. In patients receiving anticoagulation, the HAS-BLED score is used to assess the risk of bleeding.

Domestic and International Status of Autopsy Rates and Diagnostic Discrepancies

Over the past decades, there has been a consistent global decline in the rate of clinical autopsies. In the United States, for example, of the approximately 700,000 patients who died in hospitals in 2018**,** only about 28,000 underwent a postmortem examination. This represents a clinical autopsy rate of just 4%**,** highlighting a significant reduction compared to historical norms. The decreasing number of autopsies has raised concerns regarding the accuracy of clinical diagnoses, as autopsy remains the gold standard for identifying diagnostic errors. To evaluate discrepancies between clinical and autopsy diagnoses, the Goldman criteria are most commonly applied. These criteria categorize discrepancies into major and minor diagnostic errors, based on their potential impact on patient management and survival:

A. Major Diagnostic Discrepancies

- Class I: A significant diagnosis discovered only at autopsy, which, if known before death, could have altered treatment or improved survival.
- Class II: A significant diagnosis identified postmortem, but knowledge of it would not have changed the therapeutic approach or affected the outcome.

B. Minor Diagnostic Discrepancies

- Class III: A diagnosis found only at autopsy, caused by the same pathological process that led to death, but not directly related to the cause of death *and* would not have influenced survival or treatment.
- Class IV: An incidental finding unrelated to the cause of death and without therapeutic or prognostic significance.

These classification systems are essential in auditing the quality of clinical diagnostics and in guiding future improvements in medical education and practice. Despite technological advances in imaging and diagnostics, studies continue to show that clinically significant diagnostic errors persist, particularly in critically ill patients. According to data from the United States National Center for Health Statistics, only 2% of patients who died from stroke in the U.S. underwent autopsy in 2003. A recently published study reported that the frequency of type I diagnostic discrepancies was approximately 9–10%, based on the analysis of 28,000 autopsies. Among critically ill patients, the discrepancies between clinical and autopsy diagnoses are even more pronounced. A meta-analysis focusing exclusively on autopsy findings of patients treated in intensive care units between 1966 and 2011—including 31 studies and a total of 5,863

autopsies—revealed type I discrepancies in 8% of cases and type II discrepancies in 18%, despite the availability of a wide range of diagnostic tools in intensive care settings. According to their hypothesis, approximately 34,000 critically ill patients die annually in the United States due to type I diagnostic discrepancies, assuming that the discrepancy was directly responsible for death. In a study focusing on perioperative cases (213 patients), the discrepancy rate reached as high as 20%. Autopsies conducted in internal medicine departments revealed discrepancies that could have influenced treatment decisions in 10% of cases. Based on six years of autopsy data (334 patients), type I discrepancies were identified in 9.9% of cases, where knowledge of the correct diagnosis in vivo might have affected survival or treatment. Minor discrepancies—those with no impact on survival or therapeutic decisions—were found in 122 patients (36.7%). A review published in *JAMA*, which analyzed 53 studies, estimated that the rate of major clinical errors (those related to the primary cause of death) in an average American institution ranges between 8.4% and 24.4%, while the rate of type I discrepancies (those that would have affected clinical outcome) lies between 4.1% and 6.7%. Hungarian authors have also investigated discrepancies between clinical and autopsy diagnoses. Szende and colleagues analyzed 2,000 autopsies and examined cause-of-death concordance across five disease categories: neoplasms (90.9%), cardiovascular diseases (84.0%), gastrointestinal diseases (82.9%), endocrine-metabolic and immune disorders (55.2%), and respiratory diseases (32.5%). The percentages in parentheses indicate the concordance rates with clinical diagnoses, with the lowest agreement observed in the category of respiratory diseases. In the 697 cases where the underlying disease was a tumor, clinicians failed to recognize the tumor in 61 cases (8.1%) and were mistaken about the primary tumor origin in 130 cases (18.7%). The fact that 43% of admission diagnoses and 19% of clinical diagnoses did not match the disease categories identified at autopsy underscores the importance of postmortem examinations. Similar findings were reported by Swiss authors who compared diagnostic errors before and after 1992 based on autopsies of internal medicine patients. Although the rate of major diagnostic errors decreased over 20 years—from 30% to 7%—it remained high, with discrepancies affecting clinical outcomes found in 2% of patients. A comparable situation is observed in younger patients as well. French researchers evaluated autopsy results of 412 young deceased patients (mean age 27 years, excluding infants) and found poor concordance between clinical and pathological diagnoses regarding both organ-specific diseases and causes of death. Italian authors analyzed data from 879 autopsies performed between 1990 and 2009. They found discrepancies between clinical and autopsy findings in 129 cases (14.7%), of which 69 cases (7.9%) involved major (Class I) discrepancies, where prior knowledge of the findings could

have influenced treatment or survival. Roulson and colleagues published a comprehensive review summarizing their experiences. They examined key studies investigating differences between autopsy and clinical diagnoses over the past three decades. They found that the frequency of major discrepancies between clinical and autopsy diagnoses ranged between 15% and 41%, while discrepancies related to cause of death ranged from 30% to 63%. They compared data from the period 1930-1939 with that from 1975-1977, the latter having a significantly better diagnostic background. The sensitivity for myocardial infarction or coronary thrombosis improved from 26% in 1930-39 to 76%, whereas the sensitivity for pulmonary embolism increased only slightly from 40% in 1934-39 to 44%. The diagnostic sensitivity for tuberculosis was 91% in the 1930s but dropped to 50% in the 1970s. The likely reason for the decreased diagnostic accuracy was that physicians encountered tuberculosis less frequently and were therefore less familiar with its diagnostic criteria. British authors compared 448 clinical discharge summaries with autopsy findings. Combining all cases, the accuracy of the clinical summary (agreement between autopsy-confirmed disease and clinical opinion) was only 47%. Agreement was lowest for cardiovascular causes of death (28%), followed by respiratory causes (pneumonia, embolism) at 51%. The best agreement on cause of death was observed for hemorrhagic and ischemic stroke cases (90%). It should be noted that the authors analyzed data from only a few dozen stroke patients. Swiss authors published a study in *The Lancet* analyzing clinical and autopsy data of 100 randomly selected patients from each of the years 1972, 1982, and 1992. The autopsy rate remained stable around 90%. The proportion of major discrepancies significantly decreased (30% in 1972 to 14% in 1992), but the rate of minor diagnostic discrepancies increased from 23% to 46%. The improved diagnostic accuracy was mainly reflected in better clinical diagnosis of cardiovascular diseases. Specificity (correctly diagnosing healthy individuals as healthy) improved from 85% in 1972 to 97% in 1992 ($p=0.034$). In contrast, the improvement in sensitivity (correctly diagnosing sick patients) was not statistically significant over 20 years (69% vs. 86%, $p=0.061$). Similarly, British authors analyzed data from 108 patients. The clinical detection rates were 24% for pulmonary embolism, 22% for pneumonia, 13% for ischemic heart disease, and 10% for malignant processes. Histopathological examination during autopsy revealed significant new diagnostic information in 5% of patients and less important new findings in 6%. This study also highlighted the importance of complementary histopathological processing. Our observations are unique because, after reviewing publications from recent decades, we found no study presenting clinical and pathological comparisons involving several hundred patients who died exclusively in stroke units. Although CT has 100% sensitivity for diagnosing acute intracerebral

hemorrhage, this high sensitivity is not applicable for subarachnoid hemorrhage, ischemic stroke, or tumor diagnosis when contrast-enhanced CT or MRI is not performed. American authors compared clinical diagnoses with full body autopsy results in only 35 stroke patients and brain autopsy results in 23 stroke patients. Even in this small sample, the rate of major diagnostic discrepancies (class I–II) between autopsy and clinical diagnosis was 6%, and minor discrepancies were 37%. In the 23 brain autopsies, one patient (4%) was clinically diagnosed with cerebral hemorrhage, but autopsy revealed a hemorrhagic glioma. Autopsy techniques and practices have also evolved over recent decades. A recently published article reviewed new autopsy methods, such as minimally invasive autopsy, and highlighted the limitations of these techniques. In virtual autopsy, an optical scanner mounted on a robotic arm maps the contours of the body. This is complemented by postmortem whole-body CT or MRI angiography, and biopsies are performed if necessary. The complex system costs several hundred million forints and is primarily used for forensic investigations. In summary, studies comparing clinical and autopsy diagnoses have shown that respiratory system diseases are the most challenging to diagnose accurately. A few words on the scientific significance of autopsy: French authors confirmed, through the autopsy of 381 stroke patients, that intracranial dolichoectasia and coronary ectasia share a common pathogenesis. Autopsy provides a unique opportunity, especially in the fields of dementia and neurodegenerative diseases, to refine definitive diagnoses and gain insights into pathomechanisms. These findings also draw attention to the fact that, with modern technologies, RNA and DNA as well as immunohistochemical analyses can be performed even on formalin-fixed, paraffin-embedded tissue blocks. Therefore, the thousands of paraffin blocks stored for decades in pathology departments offer opportunities for further research, particularly regarding rare diseases.

Objectives

In our study, we sought to determine whether conventional full-body and brain autopsy can still provide novel diagnostic insights in stroke, a disease in which in vivo diagnosis has been fundamentally transformed by the introduction of CT and MRI. We performed a comparative analysis of two patient cohorts from two distinct 10-year periods.

1. Our first objective was to analyze data from the period **1989–1999**, preceding the era of modern antithrombotic therapy and thrombolysis:

1.1. To assess the frequency of clinically undiagnosed tumors, pneumonia, and thrombotic events.
1.2. By comparing clinical diagnoses with findings established at autopsy, we aimed to identify the proportion of pathological conditions or diagnostic errors that remained unrecognized despite thorough clinical evaluation. This allowed us to evaluate the extent to which conventional full-body and brain autopsy contributed to improving diagnostic accuracy.
1.3. To determine, among patients clinically diagnosed with ischemic stroke, the proportion in whom hemorrhagic transformation (HT) was identified at brain autopsy.

2. As we found no reports in the literature describing large cohorts of deceased stroke patients who had undergone intravenous thrombolysis followed by both brain and full-body autopsy, we analyzed the clinical and pathological data of patients treated with thrombolysis between **2007 and 2017** who subsequently died and underwent autopsy. We addressed the following questions:

2.1. What is the frequency of tumors, pneumonia, and thrombotic events diagnosed exclusively at full-body autopsy?

2.2. What is the frequency of hemorrhagic transformation identified at autopsy in thrombolysed patients?
2.3. Is the immediate cause of death directly attributable to hemorrhagic transformation (e.g., due to cerebral herniation), or is HT more often a complication, with another condition representing the direct cause of death (e.g., pneumonia)?
2.4. What premortem clinical differences can be identified between patients who were HT-positive and HT-negative at autopsy?
2.5. Is the development of hemorrhagic transformation closely related to treatment, occurring predominantly within the first 24 hours following thrombolysis?

The overall aim of our study was to explore the additional diagnostic value provided by autopsy in patients with stroke. In the first patient cohort—representing the era preceding modern neuroimaging and antithrombotic therapies—we were able to analyze the prevalence of clinically unrecognized comorbid conditions, including malignancies, pneumonia, and thrombotic events, and to compare clinical and pathological diagnoses. We also assessed the

frequency of hemorrhagic transformations; however, detailed evaluation was limited due to the restricted availability of advanced imaging modalities at that time.

In the second cohort of thrombolysed patients, our primary focus was on the detection of hemorrhagic transformations, determination of their true incidence, and analysis of risk factors associated with HT. Additionally, we examined the frequency of tumors, pneumonia, and thrombotic events diagnosed exclusively at full-body autopsy.

3. Finally, we compared full-body autopsy findings between the two eras (**1989–1999 vs. 2007–2017**), with particular emphasis on differences in the prevalence of thromboembolic complications, pneumonia, and malignant tumors, as well as on changes in the accuracy of clinical diagnoses.

Patients and Methods

The Stroke Unit of the Department of Neurology at the University of Debrecen was established in 1969, becoming the second such unit in Europe. Since its foundation, the catchment area has remained unchanged, serving the population of Debrecen, which is approximately 220,000 to 230,000 inhabitants. For about fifteen years, acute stroke patients have also been transported to our clinic from a radius of roughly 90 kilometers, provided that the time window and the patient's condition suggest a likely benefit from recanalization therapy. We treat approximately 790 to 840 stroke patients annually. Upon admission, immediate cranial CT and CT angiography are performed, supplemented by perfusion CT if necessary. Acute stroke patients are brought directly to the CT laboratory by ambulance following prior referral, allowing us to gather information on the patient's medical history and medication before arrival. The neurologist examines the patient in the CT laboratory. After the examination, a radiological consultation takes place, and in most cases, the patient's management decision is made at this stage. Subsequently, the patient is admitted to a specialized ward near the CT laboratory for continued care. Body weight is measured using a bed scale, followed by monitoring of blood pressure, pulse, ECG, and oxygen saturation. If the patient's blood pressure exceeds 185/100 mmHg, intravenous urapidil is administered. Blood samples are taken for routine chemical parameters (electrolytes, renal and liver function tests, inflammatory markers, erythrocyte

sedimentation rate), complete blood count, and coagulation parameters, which are processed urgently in the Central Laboratory. Prior to thrombolysis, bedside blood glucose and INR measurements are performed. Treatment is conducted according to the ESO (European Stroke Organisation) protocol. Recombinant tissue plasminogen activator (rt-PA) is administered at a dose of 0.9 mg/kg body weight (maximum 90 mg), with 10% given as a bolus and the remainder infused over one hour. Potential complications are continuously monitored during thrombolysis. On the first day after lysis, patients do not receive antithrombotic therapy. At 24 hours post-treatment, a follow-up CT scan is performed in all patients to exclude hemorrhagic transformation, which is assessed by a radiologist. Thereafter, the patient is transferred to the stroke ward for continued multiparametric monitoring. Severely ill patients remain in the intensive care unit (ICU). If necessary, antipyretics, antibiotics, and antithrombotic therapy are administered, alongside gastric protection and prophylaxis for deep vein thrombosis (DVT).

Brain and Body Autopsy

At our clinic, the autopsy rate remains high, approximately 70–80%, which is attributable to the current applicable regulations. According to Hungarian healthcare law, an autopsy on an inpatient who has died is only waived if neither the clinician nor the pathologist sees any indication for it, the patient did not consent to an autopsy during their lifetime, or the relatives request to forgo the autopsy and the clinician/pathologist agree to this. All of our patients underwent autopsy at the Pathology Institute of our university within 1–3 days after death. Brain autopsies were performed by pathologists or neuropathologists. In addition to examination of thoracic, abdominal, and pelvic organs, the autopsy of both the body and brain included inspection of the carotid and femoral arteries. Brain slicing and any subsequent histological examinations were performed after fixation. The autopsy procedures were conducted in accordance with the institutional standardized operating protocols, which complied with the latest international standards. Our study was approved by the Ethics Committee of the University of Debrecen under protocol number H.0265-2020.

Analysis of Stroke Patients from 1989 to 1999

In this study, we were able to compare data from 534 stroke patients over a 10-year period between 1989 and 1999. The patient cohort was heterogeneous, including both hemorrhagic and ischemic stroke cases. None of the ischemic stroke patients received thrombolysis or thrombectomy during this period. We compared the postmortem brain and body autopsy

findings with the clinical discharge summaries and medical records. The gold standard for diagnosis was the brain autopsy. For comparison between clinical and autopsy diagnoses, the Goldman criteria were applied. Our investigation also aimed to identify whether the general autopsy revealed any non-central nervous system diseases, such as tumors or thromboses, that had not been diagnosed prior to death.

Analysis of Stroke Patients from 2007 to 2017

Our patients were selected from those treated at the Neurology Clinic of the University of Debrecen between 2007 and 2017 who underwent intravenous thrombolysis (IVT); none of the patients received thrombectomy or intra-arterial thrombolysis. During this period, a total of 1,426 IVT procedures were performed. Patients arrived directly to the CT laboratory within 3 to 4.5 hours from symptom onset. After the CT scan and neurological examination, blood samples were taken, and thrombolysis was administered to eligible patients according to the ESO protocol. A follow-up CT was performed the next day to exclude edema and hemorrhagic transformation. The in-hospital mortality rate among the 1,426 patients who underwent intravenous thrombolysis was 11.7%. Of the 167 deceased patients, we were able to compare clinical data with both body and brain autopsy findings in 98 cases (59%). Body autopsies were performed on the day following death, while brain autopsies were conducted after formalin fixation approximately one week later. Brain autopsies were carried out by neuropathologists. Although previous publications subdivided hemorrhagic transformation (HTr) into further categories, we did not apply this classification to either the cranial CT images or the autopsy findings. Hemorrhages, regardless of size, were considered as HTr. We believe that both small parenchymal hemorrhages and larger, confluent hemorrhages can influence the initiation of antithrombotic therapy, promote the development of complications, and worsen patient outcomes.

Statistical Analysis

Statistical analysis was performed using Stata v13 software, the Statistical Package for Social Sciences (SPSS, version 26.0, Chicago, IL), and GraphPad Prism 9.0 (GraphPad Prism Inc., La Jolla, CA). Data normality was assessed with the Shapiro–Wilk test. For comparisons between two independent groups, we used the Student's t-test or the Mann–Whitney U test as appropriate. Differences between categorical variables were evaluated using the χ^2 test or Fisher's exact test when necessary. ROC curves were generated by plotting sensitivity against

1-specificity, and the area under the curve (AUC) was calculated. To determine optimal cutoff values, Youden's J statistic was applied. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated from contingency tables and evaluated using the χ^2 test or Fisher's exact test at statistically optimal cutoffs. Binary logistic regression models were used to identify independent predictors of hemorrhagic transformation (HTr) within the studied patient cohort. Model adjustment was based on the results of univariate statistical analyses of baseline characteristics. The results of logistic regression analysis were expressed as odds ratios (OR) with 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant.

Results

Results of Postmortem Examinations in Stroke Patients Between 1989–1999

Among the 534 cases we examined, systemic malignancies were clinically diagnosed in 26 patients (4.9%), while 8 malignant tumors (1.5%) were identified only during autopsy. Of these eight patients with malignancies diagnosed postmortem, 3 died due to transtentorial herniation caused by parenchymal hemorrhage, while 5 patients died from cardiopulmonary failure, pneumonia, or myocardial infarction. Out of the 534 patients, thromboembolic events—including pulmonary embolism, limb thrombosis, and periprosthetic or periuterine venous plexus thrombosis—were diagnosed in 160 cases either before death or during autopsy. Clinically, thromboembolic events were recognized in 80 patients (15%), whereas in another 80 cases (15%), these were detected only by the pathologist at autopsy. Pneumonia was identified as a complication in 262 cases (49.1%) during clinical management, but in 73 cases (13.6%) it was not included in the final clinical diagnosis. We analyzed whether patient age and sex influenced the likelihood of discrepancies and found that neither age nor sex had a significant effect on the frequency of discrepancies. However, a longer hospital stay reduced the likelihood that pneumonia or thromboembolic events would remain undiagnosed until death. We also examined whether the length of hospital stay influenced the clinical recognition of tumors, thromboembolic events, or pneumonia. Patients whose thromboembolic event or pneumonia was diagnosed clinically during life had a significantly longer hospital stay compared to those whose conditions were identified only by the pathologist at autopsy (median

13.0 [8.0–21.0] vs. 8.0 [5.0–13.0] days for thromboembolic events, and 8.0 [5.0–13.0] vs. 4.0 [2.0–6.0] days for pneumonia).

Results of Brain Autopsies in Stroke Patients Between 1989–1999

In our study, we examined the immediate causes of death. We found that pneumonia and pulmonary embolism were the most frequent causes of death in both ischemic and hemorrhagic transformation groups. Comparison of postmortem neuropathological findings with the last premortem CT scans was possible in 189 ischemic stroke cases. On the last premortem CT scan, only ischemia was reported in 66 patients (34.9%), whereas autopsy confirmed hemorrhagic transformation of the infarction (classified as a Class I diagnostic error). These patients (n=66) had a significantly shorter premortem survival period (6.0 [4.0–10.0] days) compared to those (n=123) in whom autopsy did not confirm hemorrhagic transformation of the infarction (11 [6.0–17.0] days, $p<0.01$). This indicates that hemorrhagic transformation shortened the agonal period. We compared platelet counts between the hemorrhagic transformation group (261.66 G/L, [95% CI 240.70–282.62]) and those in whom autopsy showed only ischemia without hemorrhagic transformation (270.38 G/L, [95% CI 253.33–287.43]) and found no significant difference. No further data were available for comparison of other hemostasis parameters.

Results of Brain and Body Autopsies in Stroke Patients Between 2007–2017

During the ten-year period (2007–2017), our center treated 1426 acute ischemic stroke (AIS) patients with intravenous thrombolysis. The in-hospital mortality rate was 11.7% (n=167 patients). More than half of these deceased patients underwent autopsy, allowing the analysis of 98 cases. During autopsy, two previously undiagnosed malignant tumors (pancreatic adenocarcinoma, neuroendocrine tumor) were discovered, which had not been diagnosed earlier due to poor symptoms. In 15 cases, tumors were documented in the medical history or diagnosed during treatment. Among 15 known cancer patients, hemorrhagic transformation (HTr) was confirmed in 9 cases during autopsy. Four thromboembolic complications (+3 aortic thrombi) and 10 cases of pneumonia were also described, which had not been clinically recognized. Hemorrhagic transformation was found in nearly half of the cases (47%) (46 HTr-positive vs. 52 HTr-negative cases). Less than half of the HTr cases (42%) developed on the first day after intravenous thrombolysis; the majority of HTr cases occurred later, during the

period from the first day until death. In these cases, hemorrhagic transformation or its consequences were often considered the immediate cause of death. Based on the results of brain and body autopsies, herniation was identified as the cause of death in 29 cases (30% of the total population), which was more common in the HTr-positive group, showing a borderline significant trend. In the remaining cases, death was caused by pneumonia, pulmonary embolism, or cardiorespiratory failure. We also analyzed the baseline clinical and laboratory parameters of HTr-positive and HTr-negative patients. Only a few clinical and laboratory parameters showed differences between the two groups at admission:

1. HTr-positive patients had significantly higher lactate dehydrogenase (LDH) levels at admission compared to HTr-negative patients (median: 272, IQR: 217–444 vs. 204, IQR: 176–264 U/L, $p = 0.0011$).
2. HTr-positive patients had significantly lower platelet counts before thrombolysis than HTr-negative patients (median: 184, IQR: 150–227 vs. 223, IQR: 171–264 G/L, $p = 0.0106$).
3. Significantly prolonged prothrombin time (PT) and higher INR values were observed in HTr-positive patients (median: 1.1, IQR: 0.9–1.1 vs. 0.9, IQR: 0.9–1.0, $p = 0.0429$).

We examined whether antithrombotic treatment administered before and after ischemic stroke influenced the risk of hemorrhagic transformation (HTr). There was no significant difference between the HTr-positive and HTr-negative groups regarding various antithrombotic therapy combinations (antiplatelet agents and/or anticoagulants) used prior to thrombolysis (χ^2 test: $p = 0.089$), although bleeding tendency was observed in anticoagulated patients. It should be noted, however, that no platelet aggregation studies were performed. After thrombolysis, no significant difference was found between groups receiving therapeutic or prophylactic anticoagulant treatment concerning the occurrence of HTr ($p = 0.808$). It is important to note that among the 98 cases included, HTr was already detected clinically on the first day following lysis in 20 cases; therefore, more patients in the HTr-negative group received prophylactic anticoagulation for deep vein thrombosis (DVT) prevention. When separately analyzing the 26 cases where HTr was not clinically recognized but confirmed by brain autopsy, and comparing them to the 52 HTr-negative cases, there was no significant association between antithrombotic treatment and bleeding (χ^2 test: $p = 0.945$).

Independent Predictors of Hemorrhagic Transformation

We performed ROC analysis to evaluate the predictive value and diagnostic efficiency of admission test parameters that showed significant differences between groups in univariate statistical analysis for predicting hemorrhagic transformation (HTr). The best ROC area under the curve (AUC) for predicting HTr was for lactate dehydrogenase (LDH): 0.7041 (95% CI: 0.5926–0.8156), with an optimal statistical cutoff of 224 U/L (sensitivity: 64.4%, specificity: 73%). The platelet count AUC was 0.6579 (95% CI: 0.5437–0.7720), with an optimal cutoff of 196 G/L (sensitivity: 66.6%, specificity: 65.1%). This result suggests that a relatively low platelet count (<196 G/L), even within the normal reference range (150–400 G/L), may increase the risk of HTr in AIS patients treated with thrombolysis. The optimal cutoff value for INR based on the Youden index was 1.05. INR provided the best sensitivity (80.7%), although the low AUC indicated that the test overall had weak predictive performance. Using a binary logistic regression model (including age, sex, NIHSS on admission, hypertension, INR ≥1.05, LDH ≥224 U/L, platelet count ≥196 G/L, ASAT, ALT, GGT, creatine kinase, hsCRP, creatinine), only LDH and INR remained significant independent predictors in the examined autopsied cohort:

- LDH (OR: 4.68, 95% CI: 1.57–14.00, p=0.006)
- INR (OR: 6.23, 95% CI: 1.55–25.13, p=0.010)

We also compared patients' blood pressure values during the first 3 days. Higher diastolic (78.1 ± 14.4 vs. 71.1 ± 14.4 mmHg, p=0.02) and systolic (145.4 ± 24.2 vs. 134.3 ± 27.8 mmHg, p=0.049) blood pressures measured on the third day increased the risk of hemorrhagic transformation.

Discussion

The data presented in the following subsections pertain to two distinct study cohorts (1989–1999 and 2007–2017). It is essential to evaluate the results separately, as the investigative

approaches, diagnostic modalities, and clinical care settings differed substantially between the two groups.

Observations in Patients with Malignant Systemic Tumors

In our material, which included autopsy data of 534 patients between 1989 and 1999, malignant tumors were found in 34 cases (6%), of which 24% (8 cases) were diagnosed only at autopsy. In the later period between 2007 and 2017, a total of 17 malignant tumors (17%) were identified, with 2 cases being clinically asymptomatic and revealed solely by pathological examination. The significant difference in tumor incidence between the two periods (6% vs. 17%) can presumably be explained by the older age of patients and improvements in modern diagnostic methods. Hospital treatment costs are rising worldwide, leading each specialty to focus primarily on specialty-specific examinations, which in stroke care primarily means expensive imaging studies. This global trend may result in clinically silent, non-central nervous system tumors remaining undetected in vivo, despite the fact that systemic tumors can provoke ischemia as a paraneoplastic phenomenon by affecting the coagulation cascade. Stroke associated with malignancy most often clinically resembles cardioembolic stroke, with ischemia developing in various vascular territories and frequent cortical localization. According to some observations, malignancy can be diagnosed in 3–5% of patients following ischemic stroke. Others estimate this rate to be higher; Navi and Iadecola report that up to 10% of ischemic stroke patients may be found to have an underlying malignant process. Their observations indicate that the most common tumors in stroke patients are lung, gastrointestinal tract, and breast cancers. Clinically, concurrent malignancy may be suggested by elevated D-dimer, fibrinogen, and C-reactive protein levels, as well as infarcts occurring in various vascular territories. In contrast, our study from 1989 to 1999 found a lower prevalence of malignancy: 4.9% were clinically diagnosed prior to death, while 1.5% were detected only at autopsy. The lower tumor rate in our material is likely explained by the fact that while Navi and Iadecola focused on the frequency of stroke in patients with cancer, our analysis investigated the occurrence of systemic tumors in patients who died as a consequence of stroke. We believe this provides a reasonable explanation for the combined rate of 4.9% + 1.5%. It is important to emphasize that the prevalence and detection of systemic malignant tumors among stroke patients vary significantly across different studies and patient populations. It should be

emphasized that both the frequency of systemic malignancies and their detection rates in patients with stroke can differ substantially across studies and patient populations. Whereas the international literature primarily focuses on stroke risk in cancer patients, our data offer insight into the prevalence of malignant tumors based on autopsy findings in patients who died following stroke.

Thromboembolic Events and Ischemic Stroke

Between 1989 and 1999, thromboembolic complications were diagnosed in 160 out of 534 patients (30%), of which 50% (80 cases) were identified only during autopsy. Between 2007 and 2017, among 98 patients, 12 thromboembolic events occurred, and 7 of these (58%) were detected exclusively through autopsy. Our study indicates that fewer thromboembolic complications occurred during the 2007–2017 period compared to the 1989–1999 period (12% vs. 31%). We believe this reduction in thromboembolic events is associated with the use of more modern antithrombotic medications. A German study reported that between 2005 and 2017, 2,914,546 patients were hospitalized due to ischemic stroke (50.5% female, and 69.3% aged 70 or older). Pulmonary embolism (PE) developed in 0.4% of these patients, and 7.2% died during hospitalization. In ischemic stroke patients, PE significantly increased mortality, with an in-hospital death rate of 28.4% in patients with PE, compared to 7.1% in those without PE. This difference was statistically significant ($P < 0.001$). Sebők and colleagues, in an analysis of 2,125 autopsies, found 272 cases of pulmonary embolism (12.8%). Of these, clinicians recognized only 85 cases (31%), and of the 157 fulminant pulmonary embolisms, only 47 (30%) were clinically identified.

Swedish authors studied the occurrence of thromboembolic cases in autopsy material from surgical, infectious disease, internal medicine, and oncology departments, with a 30-year interval between their investigations. Out of 994 patients, 239 had deep vein thrombosis, and 260 had pulmonary embolism. An interesting observation was that despite the introduction of anticoagulant therapy and early mobilization over the 30 years, the number of thromboembolic findings in autopsies did not decrease in the same admission areas. They explained this relatively stable number by the doubling of patients over 65 years old in their admission area, among whom thromboembolic events are more common, and the beneficial effects of prophylaxis and early mobilization could not compensate for this increase. Brazilian researchers reviewed over 13,000 autopsies between 1995 and 2004. They found fatal pulmonary embolism

in 2.5% (328) of patients. However, in this large patient cohort, only 59 hemorrhagic and 39 ischemic stroke patients were included, and only 20% of the patients received appropriate prophylaxis.

The Relationship Between Time from Admission to Death and Complications

We did not find any previous studies that evaluated the associations between age, sex, and clinicopathological findings, so we were unable to compare our results with other investigations. In our research, we found no age- or sex-dependent differences in the frequency of complications. However, we observed that patients in whom pneumonia or thromboembolic events were not diagnosed premortem had significantly shorter hospital stays. This observation highlights the importance of performing all possible non-invasive examinations in acute stroke patients for the early detection of infections and venous thrombosis. These include imaging studies (chest CT and ultrasound) and laboratory tests (C-reactive protein and D-dimer levels), which enable timely initiation of appropriate therapy. Physicians must consider multiple factors when making therapeutic decisions. Bedridden patients are particularly prone to thromboembolic events, while antithrombotic treatment increases the risk of systemic bleeding and hemorrhagic transformation of ischemic stroke. The prognosis of stroke patients is influenced not only by the severity of ischemic or hemorrhagic transformation but also by complications such as pneumonia and thromboembolic events. These factors significantly affect not only mortality rates but also the chances of recovery among survivors.

Associations Between Hemorrhagic Transformation (HTr) and Thrombolysis

Hemorrhagic transformation (HTr), whether symptomatic or asymptomatic, can occur spontaneously but may also be a consequence of intravenous thrombolysis. Between 1989 and 1999, a comparison of postmortem neuropathological findings and the last premortem CT scans was possible in 189 ischemic stroke cases. In the final premortem CT scans, only ischemia was diagnosed in 66 patients (34.9%), but autopsy confirmed hemorrhagic transformation of the infarct. Between 2007 and 2017, hemorrhagic transformation was found in nearly half (47%)

of the cases. Less than half (42%) of the HTr cases developed within the first day following intravenous thrombolysis, while the majority appeared later, during the period from the first day until death. According to autopsy reports, the incidence of spontaneous hemorrhagic transformation of ischemic stroke varies between 38% and 71%. The reported incidence rates in the literature depend on whether cranial CT findings (13–43%) or symptomatic/asymptomatic cases (0.6–20%) are considered. In a previous clinicopathological study involving 64 ischemic stroke patients, we observed hemorrhagic transformation of the infarct in 38% of the cases. A similar rate (35%) was found in our 534 non-thrombolyzed patients from 1989–1999. Patients with hemorrhagic transformation of the infarct had a shorter survival time until death (6.0 [4.0–10.0] days) compared to ischemic stroke patients without hemorrhagic transformation detected at autopsy (11 [6.0–17.0] days).

According to Jensen et al., intravenous thrombolysis approximately doubled the incidence of hemorrhagic transformation (HR: 2.08 [95% CI, 1.28–3.40]). Pande and colleagues monitored the frequency of hemorrhagic complications in thrombolyzed patients using imaging techniques and found an incidence rate of 36.6%. In the ECASS II trial (involving thrombolyzed patients), the rate of hemorrhagic transformation was 35.6%. The actual incidence of HTr in the above-mentioned studies was likely even higher because the results were based on 24-hour follow-up CT scans, and further cranial CTs were only performed if there was clinical deterioration. Therefore, in asymptomatic HTr patients, if a second cranial CT was not performed for other reasons, the hemorrhagic complication might have gone unnoticed. However, brain autopsy in ischemic stroke patients provides reliable information about the true incidence of hemorrhagic transformation. As previously mentioned, in non-thrombolyzed patients, the frequency of HTr was 35%. It has been shown that rt-PA influences the integrity of the blood-brain barrier (BBB) through multiple mechanisms, including the expression of LRP in endothelial cells, microglia, and astrocytes. It increases plasma kallikrein levels [105] and activates platelet-derived growth factor (PDGF-CC). Shi et al. demonstrated that rt-PA contributes to the worsening of hemorrhagic transformation (HTr) complications by mobilizing immune cells. It enhances the inflammatory response, which further exacerbates tissue damage and increases the likelihood of hemorrhagic transformation after ischemic stroke. In our 2007–2017 study, the incidence of hemorrhagic transformation detected by control cranial CT performed 24 hours after intravenous thrombolysis was only 20%, whereas based on the brain autopsy results of the same patient group, we found a 47% incidence, indicating that 27% of HTr cases occurred later. The 20% incidence detected on the first day does not differ significantly from the observation made

by the ECASS-I study investigators, who found HTr in 48 out of 264 acute ischemic (non-thrombolyzed) stroke patients (18%). A recent multicenter retrospective study involving 32,375 patients reported that the incidence of symptomatic and asymptomatic intracranial hemorrhage following intravenous thrombolysis was 17.5% (95% CI, 17.0–18.0) [108]. Honig et al. reviewed 65 studies analyzing data from a total of 17,259 acute ischemic stroke patients using ECASS-II criteria. The overall incidence of HTr was 27%, with 32% in thrombolyzed patients and 20% in non-thrombolyzed patients. HTr increased the likelihood of unfavorable 90-day outcomes (mRS 5–6), regardless of the type of hemorrhage (HI or PH). Thrombolytic therapy can induce not only space-occupying HTr but also malignant cerebral edema and herniation, which can lead to death. According to our observations, HTr was the direct cause of death in only 30% of cases (through herniation), while the majority of patients died due to other complications, primarily pneumonia.

The Role of INR and Platelet Count in the Development of Late Hemorrhagic Transformation

Our observations show that the 20% incidence of hemorrhagic transformation (HTr) detected within the first 24 hours after thrombolysis increased to 47% at autopsy. This increase cannot be explained by the immediate effect of rt-PA (half-life 4–6 minutes) nor by the prolonged activation of the plasminogen-plasmin system (which may last several hours). Therefore, other factors play a key role in the development of HTr during the period between the 24-hour control cranial CT and death.

According to our results, relatively low platelet counts and prolonged prothrombin index (PI) may increase the likelihood of HTr. Our findings are supported by other researchers' observations: Cheng et al. found an association between low platelet count and the development of HTr in non-atrial fibrillation patients. Domingo et al. reported that patients with lower platelet counts had higher mortality rates compared to those with normal platelet counts following large vessel recanalization. Mustanoja and colleagues studied 636 young patients (median age: 42.9 years) and found no significant association between gender, age, pre-hospital oral anticoagulant, TAG or statin therapy, and blood glucose levels at admission; however, a low platelet count increased the likelihood of hemorrhagic transformation (HTr). Prodan et al. also confirmed that a lower platelet count is associated with early HTr in non-lacunar ischemic stroke patients. Using a binary regression model, only LDH and INR remained independent

predictors in the statistical model. This suggests that while the balance of hemostasis is likely an important factor in the development of HTr, other factors may also play key roles. Since our observations indicate that the vast majority of HTr cases develop between the 24-hour control cranial CT and death, we recommend performing an additional cranial CT before patient discharge regardless of neurological status. The aim is to exclude HTr, as its presence may influence the initiation of antithrombotic therapy. Current European guidelines do not provide strong recommendations for routine platelet count monitoring after acute ischemic stroke or thrombolysis. However, our results suggest that the significance of low platelet count is particularly important. Platelet counts should be monitored more frequently after thrombolysis, and the use of platelet-reducing medications should be avoided. Multicenter, prospective studies could validate the accuracy of our recommendations.

Comparison of the Pre- and Post-Modern Antithrombotic Era

Between the two eras (1989–1999 vs. 2007–2017), not only stroke care but also imaging and laboratory diagnostics have significantly advanced. At our clinic, the Specialized Stroke Unit was established following the relocation in 2007. This unit provides 24-hour multi-parameter monitoring and professional care by specially trained staff using modern equipment, such as bed scales, bedside INR and blood glucose meters, blood pressure and ECG monitoring. Numerous studies have demonstrated that acute care provided in specialized stroke units significantly improves outcomes and reduces mortality. These units, whether functioning as independent departments or as stroke teams within other departments, offer more effective care for stroke patients. A domestic study showed that treatment on a stroke unit favorably influenced disease outcomes; however, the extent of this effect varied among different patient groups. For patients under 60 years of age and those who were self-sufficient before the stroke, survival chances were higher if treated on a stroke unit. However, this form of care did not reduce the proportion of patients requiring hospital care even at the end of the fourth week. Conversely, for patients over 60 years old or those who already needed assistance before the stroke (mRankin $\geq$2), care on the stroke unit more likely enabled discharge within 28 days. The type of care, however, had no significant effect on 28-day mortality rates. During the 1989–1999 period, out of 534 patients, 372 underwent cranial CT scans during treatment. Nowadays, imaging is performed on every patient at admission and multiple times depending on their condition. The availability of CT scans improved significantly after relocating the clinic to the same building as the radiology department, and CT sequencing techniques have also developed.

CTA (CT angiography) was introduced, allowing detection of large vessel occlusions or significant stenosis, and perfusion imaging has become increasingly common. These advances laid the foundation for the use of thrombolysis and thrombectomy, which were not available during the first period. Currently, not only CT but also MRI and other imaging modalities (such as PET-CT) are available, further aiding in accurate diagnosis.

Conclusions

Our observations emphasize the importance of autopsy in an era when, despite all rational considerations, the number of clinical autopsies is dangerously declining. One might assume that advances in clinical diagnostics would reduce discrepancies between clinical and pathological diagnoses, but this is only partially true. According to an article published in 2017 [65], the rate of serious medical errors that affect outcomes or treatment was close to 10%. Similar results were reported by Tejerina and colleagues, who analyzed 834 autopsy reports and found severe (Class I–II) discrepancies in 19% of cases. Wittschieber and colleagues examined more than 1800 autopsy data from Berlin between 1988 and 2008 and found that the frequency of Class I discrepancies decreased significantly from 25.8% in 1988 to 10.7% in 2008, while the frequency of Class II discrepancies increased from 13.7% (1988) to 27% (2008). The combined rate of major discrepancies (Class I + II) dropped from 43% (1988) to 27.1% (2008), but the rate of minor discrepancies (Class III + IV) significantly increased from 16.4% (1988) to 33.0% (2008). Similar observations were recently reported by Erlmeier and colleagues analyzing the experience of two other German hospitals. In 6.6% of cases, the cause of death established by autopsy differed from the clinical opinion. In our own previous observations, hemorrhagic transformation in 38% of 64 cerebral ischemia patients was identified only through autopsy. Analysis of the 2007–2017 patient cohort revealed that while the rate of hemorrhagic transformation (HT) observed within the first 24 hours following thrombolysis was 20%, this proportion increased to 47% at autopsy. This suggests that additional factors contributing to hemorrhage may act in the post-treatment period and are not detectable on the 24-hour follow-up CT scan. Our findings indicate that the risk of HT was most strongly associated with low platelet count, prolonged PT/INR, and elevated LDH levels. Neither antithrombotic therapy prior to thrombolysis nor post-treatment antithrombotic therapy demonstrated a significant association with hemorrhage, although a bleeding tendency was

observed among anticoagulated patients. Higher systolic and diastolic blood pressure values measured on day three were also significantly associated with an increased risk of HT. Since relatives often oppose traditional autopsy for religious or other reasons, new techniques have been developed and introduced, such as postmortem angiography, CT, MRI, endoscopy, virtual autopsy, and needle biopsy. The new postmortem techniques can only provide limited insight into the relationship between complications and the cause of death. These new postmortem examination methods can complement but not replace traditional autopsy. Their widespread use is also hindered by costs. Similar to all retrospective clinical studies, the results of this study should be interpreted considering its strengths and limitations. One major limitation of the study is that it was confined to a single center, which reduced the sample size but ensured uniform patient care and autopsy practices. A second limitation is that autopsy was not performed in 41% of deceased patients at the request of relatives. The data were collected over a 10-year period (2007–2017), and the study focused exclusively on patients who received intravenous thrombolysis, excluding those who underwent mechanical thrombectomy or intra-arterial thrombolysis. Changes in stroke treatment protocols during this period may have influenced the results. Finally, the study did not perform detailed subgroup analyses based on the severity or subtypes of hemorrhagic transformation. Grouping all types of hemorrhagic transformation into one category may have concealed specific factors characteristic of individual subtypes. The most important message of our study is that even in stroke, where diagnosis can be established almost immediately with CT or magnetic resonance imaging (MRI), postmortem autopsy not only reveals concurrent diseases (such as systemic tumors) but can also uncover rarer causes of stroke (e.g., paraneoplasia). It provides a more accurate picture of the incidence of the most common complications (deep vein thrombosis, pulmonary embolism, pneumonia, hemorrhagic transformation) and the direct causes of death. In summary, in a homogeneous stroke population, we demonstrated that traditional body and brain autopsy not only supplies new diagnostic information about clinically undetected systemic diseases but also provides accurate data on therapeutic complications and causes of death. Autopsy remains the ultimate tool for quality assurance even in the 21st century. The old saying, “Mortui docent vivos” (the dead teach the living), remains true.

Summary

Introduction: Ischemic stroke is one of the leading causes of death and disability worldwide. The introduction of reperfusion therapies, including intravenous thrombolysis and mechanical

thrombectomy, has significantly improved treatment options; however, only a small proportion of acute stroke patients receive these interventions. Stroke-related mortality nevertheless remains high, and deaths are often attributable to non–central nervous system (CNS) complications. The quality of stroke care is therefore fundamentally influenced by the extent to which autopsy can provide new information regarding diagnostic errors, unrecognized complications, and the safety of reperfusion therapies. The central question of this dissertation was whether autopsy offers clinically relevant new insights in stroke patients, particularly in relation to the complications of reperfusion therapy.

Methods: This dissertation is based on the analysis of two major datasets: first, the comparison of clinical and autopsy findings in the entire stroke patient population; and second, the investigation of the frequency and risk factors of hemorrhagic transformation (HT) among patients who received reperfusion therapy. By systematically comparing clinical documentation with pathological reports, I examined what additional information autopsy provides regarding comorbidities, complications, and diagnostic discrepancies. In the reperfusion cohort, I conducted a detailed analysis of laboratory parameters, blood pressure trends, and neuroimaging findings, and assessed their association with autopsy-confirmed HT. The results were evaluated in the context of national and international literature, with particular attention to factors that may explain the differences between clinical and pathological recognition.

Results: Our analyses demonstrated that autopsy provides substantial additional information in stroke patients. In the full cohort, we identified a high proportion of clinically unrecognized complications—such as pneumonia, thromboembolism, and malignant tumors—that could potentially have influenced treatment decisions or patient survival. This is consistent with international data, which report major diagnostic discrepancies in approximately 5–10% of cases. In the cohort of patients who received thrombolysis between 2007 and 2017, a marked discrepancy was observed between the 24-hour follow-up CT scan and autopsy findings regarding hemorrhagic transformation (HT): while the early HT rate was 20%, it increased to 47% at autopsy. Elevated LDH levels, prolonged INR, and relative thrombocytopenia significantly increased the risk of HT. Additionally, higher systolic and diastolic blood pressure values measured on day 3 were also associated with an increased likelihood of hemorrhagic complications.

Conclusion: Reperfusion therapy is effective but not without risks. Early detection of hemorrhagic transformation, identification of its risk factors, and the role of autopsy are crucial

for improving the quality of stroke care. Autopsies not only clarify the cause of death but also play an important role in uncovering diagnostic and therapeutic errors.

New Scientific Findings

Thromboembolism, Pneumonia, and Tumors

Changes in Diagnostic Accuracy: 1989–1999 vs. 2007–2017

The clinical accuracy of diagnosing malignant tumors and pneumonia improved in the 2007–2017 cohort compared to 1989–1999:

- **Malignant tumors:** 76% → 88%
- **Pneumonia:** 78% → 88%

In contrast, the clinical recognition of thromboembolic events decreased (50% → 42%).

Longer Hospital Stay Improves Diagnostic Accuracy

Patients in whom thromboembolic events or pneumonia were diagnosed premortem had significantly longer hospital stays than those in whom the conditions were detected only at autopsy.

Hemorrhagic Transformation (HT)

Frequency of HT

In non-thrombolysed patients, the autopsy frequency of HT was 35%. Among thrombolysed stroke patients autopsied between 2007–2017, HT occurred in 47%, with the majority developing beyond the first day post-treatment. These findings support performing a **third cranial CT prior to discharge** in thrombolysed patients.

LDH and INR as Independent Predictors

Autopsy data from 2007–2017 indicate that elevated **lactate dehydrogenase (LDH ≥ 224 U/L)** and **INR (≥ 1.05)** are significant independent predictors of HT following intravenous thrombolysis.

Lower Platelet Count Increases HT Risk

Platelet counts below 196 G/L—even within the normal reference range—were associated with an increased risk of HT (AUC: 0.6579).

Shorter Premortem Interval in HT Cases

In the 1989–1999 ischemic stroke cohort, patients with HT confirmed at autopsy had a significantly shorter time from stroke onset to death compared to those without HT (6 days vs. 11 days).

Neuropathological Findings and Hemorrhagic Transformation

Herniation as the Leading Cause of Death in Thrombolysed HT Patients

Between 2007–2017, **herniation** was the most frequent cause of death among thrombolysed patients with HT (39% vs. 21% in the HT-negative group).

Predictors of Hemorrhagic Transformation

A combined evaluation of **LDH, INR, and platelet count** may serve as a potential marker for predicting HT and warrants further investigation.

Early Recognition of Thrombotic Complications

As more than half of thromboembolic complications are not recognized during treatment, the implementation of **standardized, routine DVT/PE screening protocols** for stroke patients is recommended.

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Registry number: DEENK/446/2025.PL
Subject: PhD Publication List

Candidate: Lilla Hudák
Doctoral School: Doctoral School of Neurosciences
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List of publications related to the dissertation

1. **Hudák, L.**, Kovács, K. B., Bagoly, Z., Szegedi, I., Bencs, V., Lóczi, L., Orbán-Kálmándi, R. A., Péter-Pakó, H., Fülesdi, Z., Busi, B., Nagy, A. C., Perjési-Kiss, B., Oláh, L., Csiba, L.: Clinicopathological Observations in Acute Stroke Patients Treated with Intravenous Thrombolysis.
   J. Clin. Med. 13 (19), 1-11, 2024.
   DOI: http://dx.doi.org/10.3390/jcm13196012
   IF: 2.9
2. **Hudák, L.**, Nagy, A. C., Deliné Molnár, S., Méhes, G., Nagy, K., Oláh, L., Csiba, L.: Discrepancies between clinical and autopsy findings in patients who had an acute stroke.
   Stroke Vasc Neurol. 7 (3), 215-221, 2022.
   DOI: http://dx.doi.org/10.1136/svn-2021-001030
   IF: 5.9

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List of other publications

3. Kovács, K. B., Bencs, V., **Hudák, L.**, Oláh, L., Csiba, L.: Hemorrhagic Transformation of Ischemic Strokes.
   Int. J. Mol. Sci. 24 (18), 1-21, 2023.
   DOI: https://doi.org/10.3390/ijms241814067
   IF: 4.9

4. Varga, E., Ulambayar, B., Szegedi, I., **Hudák, L.**, Kovács, N., Nagy, A. C.: Seasonal patterns in the epidemiology of Bell's palsy in Hungary.
   Front. Neurol. 14, 1-6, 2023.
   DOI: http://dx.doi.org/10.3389/fneur.2023.1188137
   IF: 2.7

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The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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