

Evolution of clinicopathological features in patients with and without recanalization therapy before and after the introduction of thrombolysis

Viktor Bencs

bencs.viktor@med.unideb.hu

University of Debrecen

Lilla Hudák

University of Debrecen

Attila Csaba Nagy

University of Debrecen

Dénes Reviczki

University of Debrecen

Márk Kozák

University of Debrecen

Kitti Kovács

University of Debrecen

László Oláh

University of Debrecen

László Csiba

University of Debrecen

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Abstract

Background: Reperfusion therapies have substantially improved outcomes in ischemic stroke, yet their impact on clinicopathological complications observed at autopsy remains insufficiently characterized. This study investigated temporal changes in autopsy findings before and after the introduction of thrombolysis.

Methods: We performed a retrospective cohort study of 916 deceased ischemic stroke patients who underwent complete autopsy at the Department of Neurology, University of Debrecen. Patients from the pre-thrombolysis era (1989–1999; n=477) were compared with patients treated in the reperfusion era (2007–2017; n=439), including non-thrombolized (n=274) and thrombolized (n=165) subgroups. Demographic characteristics and autopsy-confirmed hemorrhagic transformation (HT), thromboembolic complications, pneumonia, and systemic malignancies were analyzed.

Results: Patients who died in 2007–2017 were older than those in 1989–1999 (76.3 ± 10.6 vs. 72.3 ± 12.0 years, $p < 0.001$). HT increased significantly over time, occurring in 18.0% of patients in 1989–1999, 32.1% in the 2007–2017 non-thrombolysis subgroup, and 49.1% in thrombolized patients (both $p < 0.001$). Logistic regression demonstrated significantly higher odds of HT in the later period and in thrombolized patients. In contrast, thromboembolic complications markedly decreased from 39.8% to 11.0% between the two eras ($p < 0.001$), without differences between thrombolized and non-thrombolized patients in 2007–2017. Pneumonia remained highly prevalent across all groups. Systemic malignancies showed a modest increase in the later cohort.

Conclusions: Introduction of modern stroke therapies was associated with a substantial reduction in thromboembolic complications but a marked increase in hemorrhagic transformation, particularly after thrombolysis. These findings emphasize the importance of careful monitoring for HT and individualized antithrombotic management in contemporary stroke care.

Introduction

Stroke remains one of the leading causes of morbidity, mortality and disability worldwide. In 2021, the global prevalence of stroke was 93.8 million, with an incidence of 11.9 million cases. Of all stroke cases, 65.3% were ischemic, 28.8% were intracerebral hemorrhages, and 5.8% were subarachnoid hemorrhages. [1]. Mortality following stroke can be attributed to various neurological or non-neurological causes. Early death is typically due to neurological causes, including cerebral edema, hemorrhagic transformation, epilepsy, delirium, or, in cases of brainstem stroke, failure of circulatory and respiratory centers. Nevertheless, most patients die from post-stroke non-neurological complications: thromboembolic events (such as deep vein thrombosis, pulmonary embolism (PE), and myocardial infarction) and infections, primarily pneumonia. [2] Presence of malignancies is also a significant factor influencing stroke outcomes. In a cohort study, the incidence of pneumonia, PE, and cardiac complications was observed in 47% of stroke patients with mobility limitations, compared to 28% in those without mobility restrictions. [3]. Introduction of reperfusion therapies—including intravenous,

intra-arterial thrombolysis and mechanical thrombectomy—has led to a global decline in stroke-related mortality [4]. Reperfusion therapies became routine in the 2000s, in accordance with the recommendations of the European Stroke Organisation. The frequency of treatment has shown a steady increase, due to more permissive inclusion criteria and advancements in stroke care. An Austrian study reported that, between 2006 and 2018, 18,953 of 103,970 patients with ischemic stroke received recombinant tissue plasminogen activator (rt-PA), with treatment rates rising from 9.9% in 2006 to 21.8% in 2018 [5]. Reperfusion therapy has been available at the Department of Neurology, University of Debrecen, Hungary, since the mid-2000s.

Autopsy remains the reference standard for evaluating the quality of in-hospital care and its related complications. It facilitates the establishment of a definitive diagnosis and provides a means to assess the appropriateness of administered treatments. Nevertheless, despite its pivotal role, the frequency of conventional autopsies has shown a continuous global decline. While autopsy rates in Europe and the United States were approximately 60% several decades ago, they have now decreased to below 5%. [6] Consequently, a substantial proportion of comorbid conditions (e.g., malignancies, systemic disorders), clinically unrecognized complications (e.g., infections, thromboembolic events), and treatment-related adverse effects may remain undiscovered. Although autopsy rates have also declined in our country, they continue to be relatively higher than those reported in Western countries.

Utilizing our relatively high autopsy rate, we conducted a study of patients with ischemic stroke who died at our institution and underwent postmortem examination. This approach allowed us to map how the demographic characteristics and complications of ischemic stroke patients evolved between the pre-thrombolysis era and the era in which thrombolysis became routine, and to determine whether there were meaningful differences in neuropathological and systemic autopsy findings between these periods.

Methods

This study is a retrospective cohort analysis conducted at the University of Debrecen, Department of Neurology, Hungary. We continued our previous observations on stroke-related complications in patients [7, 8] who died and underwent autopsy before the thrombolysis era (between 1989 and 1999), and in patients who died after the introduction of reperfusion therapies (between 2007 and 2017). Our catchment area did not change between the two investigated periods (circa 250 000 people). Cases from 1989 and 1999 were analyzed as a single group, as thrombolysis was not available during this period. The 2007–2017 cohort was subdivided into two groups based on whether desobliteration therapy had been performed. Study groups consisted of patients who were admitted to our clinic due to ischemic stroke, all of whom eventually passed away and underwent autopsy. Design of study and its respective study groups is illustrated on Fig. 1.

Autopsies were performed by pathologists at the Institute of Pathology, while brain autopsies were conducted by neuropathologists in Neuropathology Laboratory of Department of Neurology. Data were collected from the medical records of patients, including clinical diagnoses and corresponding

pathological findings. We recorded patient demographics (age, sex), length of hospital treatment, and whether they received reperfusion therapy. We compared whether hemorrhagic transformation, thromboembolic complications, pneumonia, or extraneural tumors were present during autopsy. The 1989–1999 cohort was compared with the 2007–2017 period's non-thrombolysed subgroup. Furthermore, the two subgroups of the 2007–2017 cohort (non-lysis and lysis group) were compared to assess the impact of intravenous thrombolysis on the occurrence of complications. Statistical calculations were performed using STATA software. Descriptive statistics were calculated for age, sex distribution and length of hospital stay. Multiple logistic regression was conducted to assess the impact of age, gender, and period on complications. The logistic regression analysis reported odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$ for all analyses.

Results

Main characteristics of study population

A total of 916 deceased ischemic stroke patients were included in the study. All patients underwent both general and neuropathological autopsy. The 1989–1999 period included 477 patients, and the 2007–2017 period involved 439 patients without thrombolysis.

The 2007–2017 cohort was divided into two subgroups based on whether reperfusion therapy was performed. Reperfusion therapy was not performed in 274 cases (62.4%), whereas 165 patients (37.6%) received reperfusion treatment. Patients who did not receive thrombolysis either presented beyond the therapeutic time window or had contraindications according to the current applicable guidelines. No reperfusion therapy was available in the 1989–1999 cohort. The proportion of reperfusion therapies is presented in Fig. 2.

The distribution of baseline demographic characteristics was analysed as follows. The 1989–1999 period, during which thrombolysis was not available, was compared with the non-thrombolysed subgroup of the 2007–2017 cohort, as it can be seen on Table 1 (COMPARISON 1). This comparison enables the assessment of temporal changes in study parameters across different decades. In addition, the non-thrombolysed group from 2007–2017 was compared with the thrombolysed group (COMPARISON 2) from the same period, as it can be seen on Table 2, thereby allowing evaluation of differences in variables within a given time frame under different stroke treatment modalities.

Sex distribution in the 1989–1999 period was 55.1% males (263/477) and 44.9% females (214/477), while in the 2007–17 “no-lysis” subgroup consisted of 44.2% males (121/274) males and 55.8% females (153/274).

Using a chi-square test, a significant difference in sex distribution was observed between the two study periods ($p = 0.004$), with a significantly higher proportion of female decedents in the later period.

In the deceased 2007-17 “lysis” subgroup 57.6% of males (95/165) and 42.4% of females (70/165) was observed. Using a chi-square test, significant difference in the sex distribution was observed between 2007-17 “no-lysis” and 2007-17 lysis subgroup ($p = 0.006$), with a significantly higher proportion of male patients who died and received thrombolysis therapy.

Normality of age distribution in the study populations was assessed using Shapiro–Wilk test, which indicated that age was not normally distributed. The mean age in the 1989–1999 group was 72.3 ± 12.0 years (median: 73 years), whereas in the 2007–2017 “no-lysis” subgroup it was 76.3 ± 10.6 years (median: 76 years). Mann–Whitney U testing demonstrated that individuals who died between 2007 and 2017 were significantly ($p < 0.001$) older than those who died between 1989 and 1999. In the 2007-17 “lysis” subgroup mean age was 72.46 ± 10.23 years (median: 74 years). Mann–Whitney U testing demonstrated that the age at death was significantly younger in the “lysis” subgroup compared with the “no lysis” subgroup ($p < 0.001$).

Normality of days in hospital to death in the overall study population was assessed using Shapiro-Wilk test, which indicated that it is not normally distributed.

The mean days in hospital to death in the 1989–1999 group was 13.2 ± 16.0 days (median: 8 days), whereas in the 2007–2017 no lysis subgroup it was 10.90 ± 14.48 days (median: 6.50 days). Mann–Whitney U test demonstrated no significant difference between the two groups in the number of days from hospital admission to death ($p = 0.0983$).

The mean days in hospital to death in the 2007-17 lysis subgroup was 12.9 ± 13.2 days (median: 8 days). Mann-Whitney U test demonstrated no significant difference between the 2007-17 “no lysis” and “lysis” subgroups in the number of days from hospital admission to death ($p = 0.0839$).

Main characteristics of 1989-99 and 2007-17 “no-lysis” group is presented in Table 1. Main characteristics of 2007-17 “no-lysis” and 2007–2017 “lysis” group is presented in Table 2.

Table 1
Comparing main characteristics of 1989-99 and 2007-17 “no lysis” patients

Variable	1989–1999	2007-17 “no-lysis” SUBGROUP	p
Number of deceased patients	477	274	not applicable
Sex	263 (55.1%) male 214 (44.9%) female	121 (44.2%) male 153 (55.8%) female	0.004
Age (mean $\pm$ SD)	72.3 ± 12.0 years	76.3 ± 10.6 years	< 0.001
Days in hospital to death (mean $\pm$ SD)	13.2 ± 16.0 days	10.9 ± 14.5 days	0.0983

Table 2

Comparing main characteristics of the two groups of deceased patients in the period of 2007-17

Variable	2007-17 "no-lysis" SUBGROUP	2007-17 "lysis" SUBGROUP	p
Number of deceased patients	274	165	not applicable
Sex	121 (44.2%) male 153 (55.8%) female	95 (57.6%) male 70 (42.4%) female	0.006
Age (mean $\pm$ SD)	76.3 $\pm$ 10.6 years	72.5 $\pm$ 10.2 years	< 0.001
Days in hospital to death (mean $\pm$ SD)	10.9 $\pm$ 14.5 days	12.9 $\pm$ 13.2 years	0.0839

Hemorrhagic transformation

In the 1989–1999 group, hemorrhagic transformation of ischemic stroke could be found in 18.0% of all cases (86/477).

In the subgroup of non-thrombolized patients in 2007–2017, hemorrhagic transformation was found at autopsy 32.1% of all cases (88/274).

Also, in the same period in 2007–2017, the subgroup of patients who underwent thrombolysis, hemorrhagic transformation was identified at autopsy in 49.1% of all cases (81/165).

Comparing cases from the 1989–1999 period, when thrombolysis was not yet available, a significant increase in the incidence of HT was observed in the non-thrombolysed subgroup of the 2007–2017 cohort ($p < 0.001$).

Furthermore, comparison of the thrombolysed and non-thrombolysed subgroups within the 2007–2017 cohort demonstrated that HT occurred significantly more frequently in patients who received thrombolytic therapy ($p < 0.001$).

The proportion of hemorrhagic transformation is presented in Fig. 3.

Based on logistic regression analysis, the occurrence of hemorrhagic transformation was not significantly associated with age. In contrast, the length of hospital stay showed an inverse relationship with the odds of hemorrhagic transformation, with each additional day associated with a 4.1% reduction in risk. This finding is unlikely to reflect a causal relationship; rather, it suggests that most hemorrhagic transformations develop within the first days following stroke, and if it does not occur early, it is less likely to occur later. The most important predictor of hemorrhagic transformation was the type of group. Compared with the 1989–1999 cohort, patients in the 2007–2017 non-thrombolysed subgroup had 2.10-

fold higher odds of hemorrhagic transformation. Furthermore, compared with the 2007–2017 thrombolysed subgroup, the 2007–2017 non-thrombolysed subgroup showed 56% lower odds of hemorrhagic transformation, suggesting that intravenous thrombolysis represents one of the most important risk factors for the development of hemorrhagic transformation. Results of logistic regression analysis is summarized in Table 3.

Thromboembolic complications

Thromboembolic complications included deep vein thrombosis, pulmonary embolism, and myocardial infarction.

In the 1989–1999 cohort, thromboembolic complications were identified at autopsy in 39.8% of all deceased patients (190/477).

In the 2007–2017 period, in the subgroup of non-lysis patients, thromboembolic complications could be observed at autopsy in 11.0% of all cases (30/274). Comparing the 1989–99 group and 2007–17 no lysis subgroup, by using chi-square test, there is a significant decrease in all cases of thromboembolic complications ($p < 0.001$).

In the 2007–2017 group, the subgroup of lysis patients, thromboembolic complications were identified at autopsy in 12.7% of all cases (21/165). On contrary, the comparison of the lysis and non-lysis subgroups within the 2007–2017 cohort demonstrated that there is no difference in frequency of thromboembolic events between the two subgroups ($p = 0,573$).

The frequency of thromboembolic complications found at autopsy is illustrated in Fig. 4.

Based on logistic regression analysis, the odds of thromboembolic complications were not significantly associated with age or length of hospital stay. A marked decrease in the incidence of thromboembolic complications was observed in the later study period: the odds were reduced by 82% in the 2007–2017 non-thrombolysed subgroup compared with the 1989–1999 cohort. This reduction may be explained by the increasing use of low-molecular-weight heparin (LMWH) and more advanced physiotherapy practices over time. Results of logistic regression analysis is summarized in Table 3.

Pneumonia

In the 1989–1999 cohort, pneumonia was documented at autopsy in 67.9% of deceased patients (324/477). In the non-thrombolysed subgroup of the 2007–2017 period 73.0% of deceased patients had pneumonia in autopsy (200/274). In the thrombolysed subgroup of the 2007–2017 period 79.4% of deceased patients had pneumonia in autopsy (131/165). Comparing cases from the 1989–1999 period, there is no significant difference in the incidence of pneumonia was observed in the non-thrombolysed subgroup of the 2007–2017 cohort ($p = 0.145$) with chi-square test. Comparison of the thrombolysed

and non-thrombolysed subgroups within the 2007–2017 cohort demonstrated that there is no significant difference between frequency of pneumonia between the two subgroups ($p = 0.131$).

Based on logistic regression analysis, the odds of pneumonia were not associated with age, sex or study group. Logistic regression analysis demonstrated a significant association between the occurrence of pneumonia and length of hospital stay, with each additional day associated with an approximately 2% increase in the odds of developing pneumonia. Results of logistic regression analysis is summarized in Table 3.

Table 3

Logistic regression analysis for risk factors of complications of ischemic stroke. *** means $p < 0.001$; ** means $p < 0.01$.

Variable	Hemorrhagic transformation OR (95% CI)	Thromboembolic event OR (95% CI)	Pneumonia OR (95% CI)
Age (years)	1.00 (0.98 to 1.01)	1.00 (0.98 to 1.00)	1.00 (0.99 to 1.02)
Sex (male/female)	0.95 (0.69 to 1.30)	1.30 (0.94 to 1.80)	0.79 (0.59 to 1.08)
Length of hospital stay (days)	0.96 (0.94 to 0.97) ***	1.00 (1.00 to 1.02)	1.02 (1.00 to 1.03) **
DECEASED <i>NON-LYSIS</i> PTS. 1989-99 VS 2007-17 PERIOD	2.10 (1.48 to 3.00) ***	0.18 (0.12 to 0.28) ***	1.28 (0.92 to 1.80)
DECEASED <i>NON-LYSIS</i> PTS. VS <i>LYSIS</i> pts. (2007–2017 PERIOD)	0.44 (0.29 to 0.66) ***	0.84 (0.47 to 1.53)	0.70 (0.44 to 1.11)

Systemic malignancies

The presence of systemic malignancies as a comorbidity is of particular interest, given that paraneoplastic mechanisms — especially hypercoagulability — may contribute to the development of ischemic stroke. In the 1989–1999 cohort, systemic malignancies were documented at autopsy in 8.6% of all deceased patients (41/477).

In the 2007–2017 non-lysis cohort, prevalence of tumors was 14.6% in autopsies (24/165). There was no statistically significant difference in the frequency of tumors between the 89–99 and 07–17 no lysis cohorts (chi-square test, $p = 0.07$). In the 2007–2017 lysis cohort, prevalence of tumors was 8.5% in autopsies (23/274). There was no statistically significant difference between the 07–17 lysis and non-lysis groups based on the chi-square test ($p = 0.059$). Most frequent tumors and changes in the tumor spectrum are illustrated in Table 4.

Table 4
Distribution of tumor types in the two study groups.

Tumor type	Number of tumors in 1989–1999 cohort	Number of tumors in 2007–2017 cohort
lung	15	13
renal	5	4
pancreas	3	8
prostate	2	6
colon	3	6
breast	3	5
thyroid	2	0
esophagus	2	0
small intestines	1	0
hematological	1	2
tongue	1	0
gall bladder	1	0
urinary bladder	1	2
liver	1	3
stomach	0	2
skin	0	1
uterus	0	1
parotid	0	1

Discussion

In the present study, we performed a retrospective cohort analysis to investigate differences in autopsy findings (both cerebral and systemic) across two distinct therapeutic eras. In the earlier period (1989–1999), neither thrombolytic therapy nor modern low-molecular-weight heparin (LMWH)-based antithrombotic treatment was available, whereas both became routine clinical practices in the later period (2007–2017). A significant reduction in thromboembolic events was observed in the later cohort (2007–2017). However, concurrently, there was a marked increase in hemorrhagic transformation (HT) detected at autopsy, including among patients who had not undergone intravenous thrombolysis. The frequency of HT was even higher in patients who received intravenous thrombolytic therapy.

In addition, more systemic tumors were identified at autopsy in the 2007–2017 cohort compared with the 1989–1999 cohort.

In the 2007–2017 period, compared with 1989–1999, the proportion of deceased female patients increased and the patients who died were older. One possible explanation for the former finding is the increasing prevalence of stroke risk factors among women.[9] In addition, the overall life expectancy of the population has increased, which may also explain the higher age observed in our study population. [10] Meta-analyses indicate that women are approximately 13% less likely to receive thrombolysis than men. [11] This disparity may be attributable to the fact that women are, on average, 4–5 years older at the time of stroke onset, and that severe hypertension ($> 185/110$ mmHg) and more severe strokes—both of which constituted contraindications to thrombolysis during the study period—are more prevalent among women. [12] Comparison of age at death between the thrombolized and non-thrombolized groups revealed a significant difference: in the thrombolized group the patients were younger. According to the literature, older patients are less likely to receive thrombolysis due to age limitation in guidelines and old-age comorbidities. [13] In 2009, the American Heart Association/American Stroke Association (AHA/ASA), based on the ECASS III study, extended the therapeutic time window for thrombolysis to 3–4.5 hours. However, the following exclusion criteria were introduced: age > 80 years, NIHSS score > 25 , use of oral anticoagulants, and the coexistence of prior stroke and diabetes mellitus. [14] The 2018 AHA/ASA guidelines permitted the use of thrombolysis within the 3–4.5-hour time window in patients older than 80 years, although with additional restrictions (absence of diabetes mellitus and prior stroke, and NIHSS ≤ 25). [15] The 2019 update of the AHA/ASA guidelines allowed the use of intravenous thrombolysis within the 3–4.5-hour time window irrespective of age. [16] During our study period (2007–2017), a substantial proportion of elderly patients were excluded from thrombolysis based on age. Accordingly, it is not surprising that the mean age of the thrombolized group was significantly lower than that of the non-thrombolized group.

Comparison of autopsy-detected complications across the study groups showed that the frequency of hemorrhagic transformation increased significantly in the later study period (2007–17) even among patients who did not undergo intravenous thrombolysis therapy. To the best of our knowledge, no studies in the literature have investigated temporal trends in the incidence of hemorrhagic transformation at autopsy. Several explanations may be proposed to account for this observation. One of the most important factors may be the routine use of antithrombotic agents before stroke and in the hospital period. In our institute, unfractionated heparin was administered routinely since the mid-1980s, followed by the introduction of low-molecular-weight heparins: nadroparin calcium in 1996, dalteparin in 1999, and enoxaparin sodium in 2005. Based on review of the international literature, in a danish study, the use of oral anticoagulants in the general population increased from 3.8% to 11.1% between 2005 and 2018. Anticoagulant use is also associated with a significantly increased risk of hemorrhagic transformation (OR 2.47) [17, 18]. Advanced age is an independent risk factor for hemorrhagic transformation [19]. This is further supported by the findings of our study, as patients in the 2007–2017 non-lysis cohort were also older compared with those in the 1989–1999 period. With an ageing population, the mean age of stroke

patients has increased, which in itself contributes to a higher risk of hemorrhagic transformation, as previously noted.

With improvements in stroke care, patients with larger infarcts are more likely to survive, and these patients carry a higher risk of hemorrhagic transformation. Larger infarct size and greater stroke severity (as reflected by higher NIHSS scores) are both associated with a significantly increased likelihood of hemorrhagic transformation [20]. Diabetes mellitus is an independent risk factor for early hemorrhagic transformation. The increasing prevalence of diabetes and obesity in the 2000s may also have contributed to the rising incidence of hemorrhagic transformation [21]. Atrial fibrillation (AF) is one of the strongest risk factors for hemorrhagic transformation (OR 2.94) [22]. The prevalence of AF has increased markedly; according to the Framingham Heart Study, over a 50-year period its prevalence rose from 20.4 to 96.2 per 1,000 in men and from 13.7 to 49.4 per 1,000 in women [23]. These findings also imply that the routine use of anticoagulant therapies increased substantially in the 2000s. Based on the results of our study, this trend appears to have a dual effect: on the one hand, it markedly reduces the incidence of thromboembolic complications; on the other hand, in the context of ischemic stroke, it is associated with an increased risk of hemorrhagic transformation.

Beside these, in our study, the incidence of hemorrhagic transformation was significantly higher not only in the non-lysis, but also in the thrombolized group compared with the non-thrombolized group; according to the logistic regression model, thrombolysis was associated with a 66% higher odds. Based on data from the literature, hemorrhagic transformation occurs approximately four times more frequently in patients receiving thrombolysis than in untreated patients, which may be explained by several interrelated pathophysiological mechanisms [24].

Furthermore, an important consideration is that, according to the literature, the timing of hemorrhagic transformation differs markedly between thrombolized cases and spontaneous events. Following thrombolysis, hemorrhagic transformation typically occurs early (< 24 hours), and the median time to symptomatic intracerebral hemorrhage (sICH) is approximately 5–10 hours after treatment [24]. The timing of spontaneous hemorrhagic transformation is considerably more variable and may occur with a substantial delay following stroke onset. In a prospective study, 40% of spontaneous hemorrhagic transformation cases were detected by CT or MRI 4–7 days after symptom onset [25]. In cardioembolic stroke, hemorrhagic transformation exhibits a bimodal distribution: benign forms (petechial hemorrhages) typically occur early (0–3 days), whereas late hemorrhagic transformation (after 9–12 days) almost exclusively presents as severe parenchymal hematoma (PH2) [26]. Although the premortem diagnosis of hemorrhagic transformation has improved, only a fraction of all cases are still recognized in clinical practice. As hemorrhagic transformation directly worsens the outcome, influences the timing of antithrombotic therapy, early diagnosis and appropriate management are crucial for reducing stroke-related mortality. Not only the PH1 and PH2 type of HT, but also the presence of any petechial, asymptomatic HT is a crucial risk factor for clinical worsening if remains undetected and anticoagulation therapy is planned or started to prevent the next ischemic stroke.

Regarding complications, pneumonia was common among deceased patients with ischemic stroke, but its frequency did not show significant increase in the 2007–2017 period. Stroke-related immune dysfunction, reduced mobility, prolonged bed rest, and aspiration all contribute to the development of pneumonia. [2]

In the 2007–2017 period, the prevalence of malignancies showed a slight increase; however, despite improvements in diagnostic infrastructure, the effectiveness of detecting malignancies during the clinical phase did not improve substantially. The most common malignancy in both periods was lung cancer, while the proportion of pancreatic, prostate, and colorectal tumors increased in the second period. In our study, the distribution of malignancies was consistent with findings reported in the international literature. In a cohort of 249 stroke patients with underlying malignancy, Motataianu et al. reported that the most common primary tumor site was the lung, followed by prostate and colorectal cancers, while breast cancer ranked as the fifth most frequent. [27] Malignancies may induce a hypercoagulable state, thereby predisposing patients to the development of ischemic stroke. [28] As the occurrence of malignancies among stroke patients is not uncommon, it is advisable to actively search for signs suggestive of cancer during medical history taking and physical examination, and to request appropriate imaging studies when malignancy is suspected. In cases of previously undiagnosed tumors, this approach may facilitate early detection and allow timely initiation of treatment. Furthermore, if no classical vascular risk factors are identified during the etiological work-up following stroke, tumor-associated hypercoagulability should be considered and excluded as a potential underlying cause.

In Table 5, we summarized our most important observations and possible recommendations based on our results and previous observations.

Table 5

Most important observations from our study, and possible recommendations based on our results and literature

Most important observations from our study	Possible recommendations based on our results and literature
Incidence of hemorrhagic transformation is increasing	Increased attention to the risk factors for hemorrhagic transformation (atrial fibrillation, advanced age, diabetes mellitus, large infarct size, severe stroke as reflected by NIHSS score, pre-stroke antithrombotic therapy, and intravenous thrombolysis).
	Detection of HT is important: in ischemic stroke patients not treated with thrombolysis, a follow-up CT scan is recommended 4–7 days after stroke onset and/or before starting antithrombotic therapy
With the introduction of low-molecular-weight heparin (LMWH), the incidence of thromboembolic complications decreased dramatically, but the frequency of HT increased.	In patients with ischemic stroke and reduced mobility, current stroke guidelines recommend the early initiation of low-molecular-weight heparin (LMWH) or the use of intermittent pneumatic compression devices to prevent thromboembolic complications. But more cautious evaluation of risk/benefit is necessary before antithrombotic/anticoagulation therapy after acute ischemic stroke.
Incidence of pneumonia at autopsy is high among patients with ischemic stroke	Particular attention should be paid to the early diagnosis of infection, as well as to the timely initiation of appropriately selected antibiotics—tailored to the local hospital flora—and administered for an adequate duration, ideally in consultation with an infectious diseases specialist, in order to prevent the selection of multidrug-resistant pathogens.
Ischemic stroke may also occur in the context of an underlying malignancy.	If no classical vascular risk factors are identified during the etiological work-up following stroke, tumor-associated hypercoagulability should be considered and excluded as a potential underlying cause.

Abbreviations

AHA/ASA

American Heart Association / American Stroke Association

CT

computed tomography

ESO

European Stroke Organisation

HT

hemorrhagic transformation

LMWH

low-molecular-weight heparin

NIHSS

National Institutes of Health Stroke Scale

Declarations

Ethics approval and consent to participate

Our work was approved by the relevant local, regional, and institutional research ethics committees (Regionális Kutatásetikai Bizottság (RKEB) (Regional Research Ethics Committee, approval number: 6443-2023), as well as by the national Scientific and Research Ethics Committee of the Medical Research Council (Tudományos és Kutatásetikai Bizottság (TUKEB) (Medical Research Council); approval number: BM/17652-1/2023) and was conducted in accordance with the relevant ethical guidelines and regulations, including the Declaration of Helsinki. As this was a retrospective study and all individuals from whom the data were derived were deceased, obtaining informed consent was not possible and was not required in accordance with the relevant ethical guidelines and applicable Hungarian laws and regulations. Both the local Research Ethics Committee (RKEB) and the national Research Ethics Committee (TUKEB) waived the requirement for informed consent due to the retrospective nature of the study and the use of anonymized data.

Consent for publication

As this was a retrospective study including only deceased individuals, informed consent to participate was waived/not required in accordance with applicable Hungarian regulations and approved by the above ethics committees.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due it contains sensitive patient information, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Conceptualization, L.C., L.O. and V.B.; methodology, L.C., L.O., and V.B.; data curation and preparation, V.B., M.K., K.K., D.R., L.H; statistical analysis, A.N., V.B.; writing—original draft preparation, V.B., A.N., L.C., L.H., M.K. and L.O.; writing—review and editing, V.B., L.C., T.H., K.K., M.K. and L.O.;. All authors have read and agreed to the published version of the manuscript.

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Figures

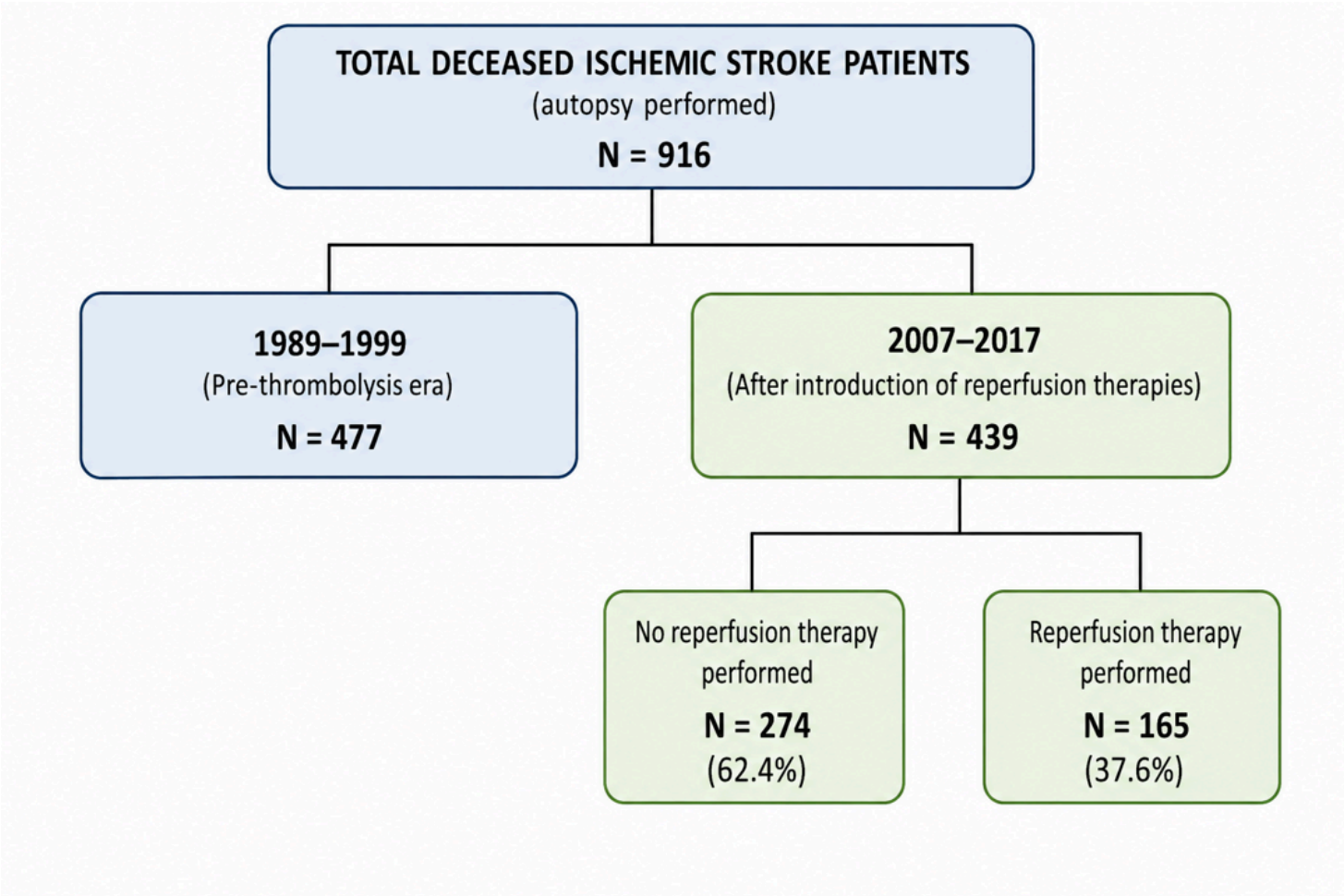


Figure 1

The figure illustrates the fundamental design of the study and its respective study groups.

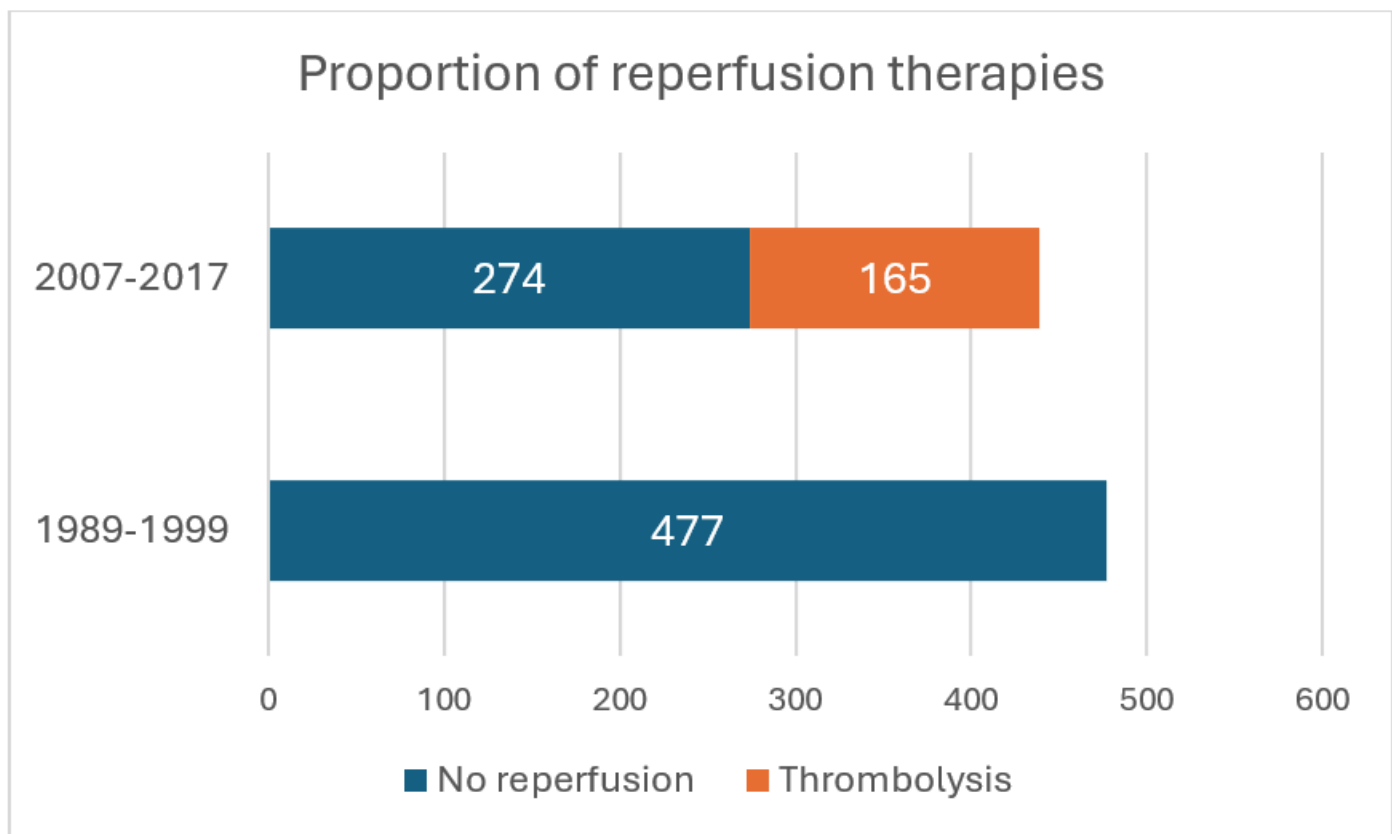


Figure 2

Bar chart shows the proportion of thrombolysis in the two periods.

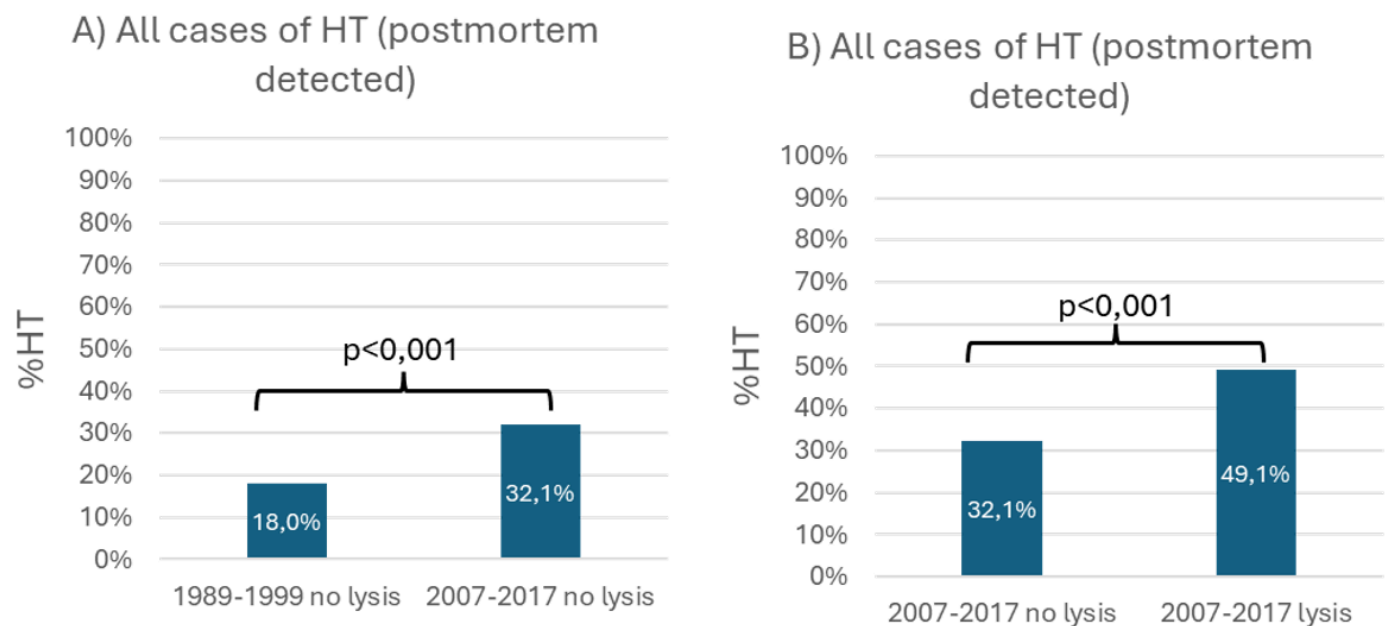


Figure 3

Bar chart diagrams illustrate the frequency of hemorrhagic transformation of the study groups. (p<0.001, chi-square test).

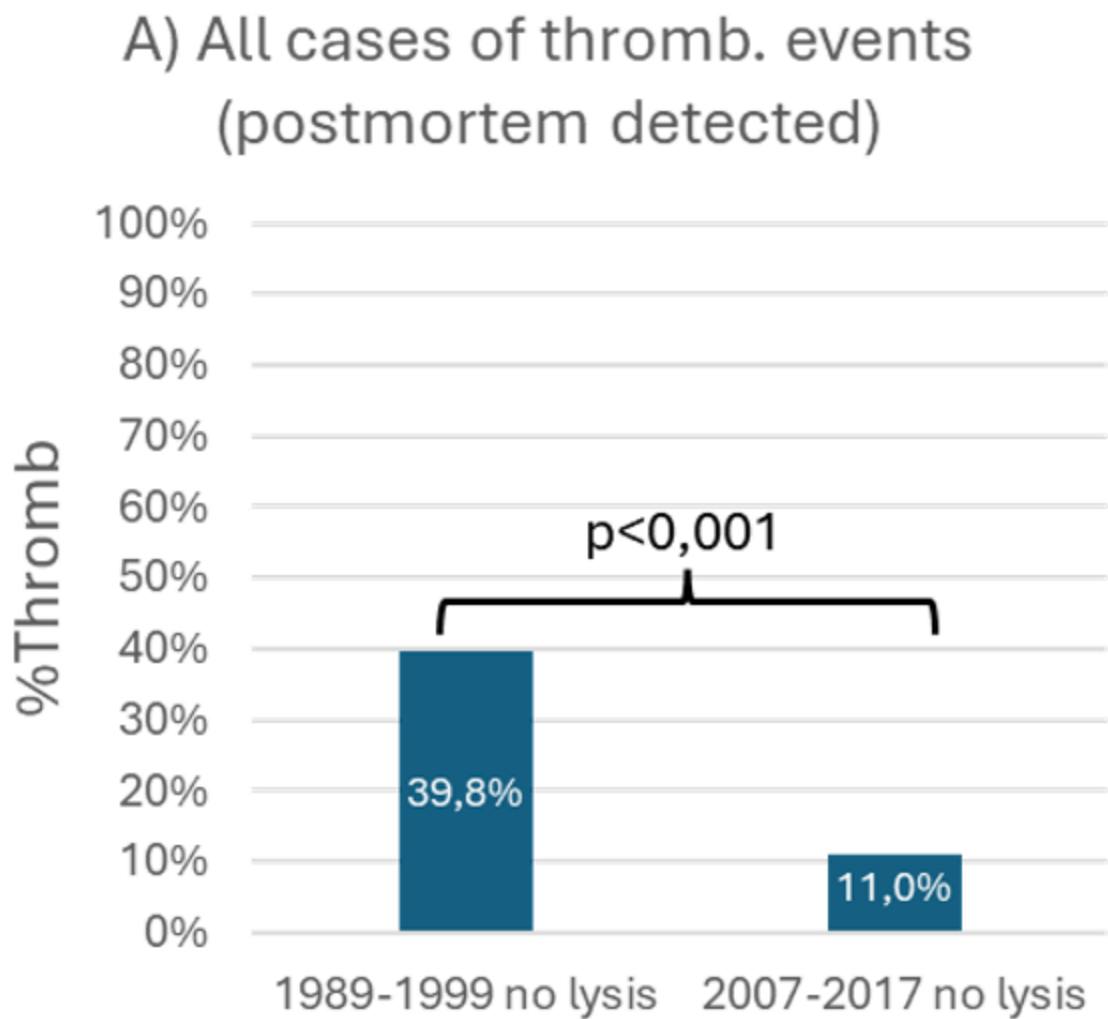


Figure 4

Bar chart diagrams illustrate the frequency of thromboembolic events of the study groups. Diagram A shows significant decrease of prevalence of thromboembolic complications in the later period (p<0,001, chi-square test).