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MILESTONES OF ACUTE ISCHAEMIC STROKE CARE: REAL-LIFE EVIDENCE ON THE IMPACT OF AI-BASED DECISION-SUPPORT, COVID-19 PANDEMIC AND OF EXTENSION OF THE THERAPEUTIC TIME WINDOWS FOR ACUTE REPERFUSION THERAPIES

PhD thesis

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List of abbreviations:

ACA: anterior cerebral artery

ADC: apparent diffusion coefficient

AHA/ASA: American Heart Association, American Stroke Association

AI: artificial intelligence

AIS: acute ischaemic stroke

ASPECTS: Alberta Stroke Program Early CT Score

BA: basilar artery

COVID-19: Coronavirus disease 2019

CRP: C-reactive protein

CT: Computed Tomography

CTA: Computed Tomography Angiography

CTP: Computed Tomography Perfusion

DALY: disability-adjusted life years

DGT: door-to-groin time

DIT: door-to-imaging time

DNT: door-to-needle time

DWI: Diffusion-weighted imaging

ED: Emergency Department

eGFR: estimated glomerular filtration rate

EMS: Emergency Medical Services

ESO: European Stroke Organisation

EVT: endovascular therapy

FDA: Food and Drug Administration

FLAIR: fluid-attenuated inversion recovery

GRE: gradient echo

ICA: internal carotid artery

ICU: intensive care unit

INR: international normalized ratio

IQR: interquartile range

IVT: intravenous thrombolysis

LVO: large vessel occlusion

MCA: middle cerebral artery

MRI: magnetic resonance imaging

MRP: magnetic resonance perfusion

MT: mechanical thrombectomy

mRS: Modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

NNS: number needed to screen

OECD: Organization for Economic Cooperation and Development

PAD: peripheral artery disease

PCA: posterior cerebral artery

PoC: point of care

PWI: perfusion-weighted imaging

SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

SD: standard deviation

SWI: susceptibility-weighted imaging

TIA: transient ischaemic attack

TOAST: Trial of Org 10172 in Acute Stroke Treatment

TW: time window

WBC: white blood cell count

WHO: World Health Organisation

1. Introduction

Stroke is an increasingly prevalent cause of mortality and disability worldwide (1), contributing to 143 million Disability Adjusted Life Years (DALYs) in 2019 (2). In 2021, the total cost of stroke in 27 EU countries was approximately 110 billion euros, with around 35% attributed to healthcare expenses, 20% to social costs, and 11% to lost productivity due to absence from work (3). This growing healthcare, social, and economic burden is exacerbated by the fact that about 50% of stroke survivors are chronically disabled (4) and only about 40-60%, including those in the younger population, can return to work (5, 6).

Despite the advances in acute stroke reperfusion therapies in recent years, only about 7.3% of acute ischaemic stroke (AIS) patients are treated with intravenous thrombolysis (IVT) and about 2% with endovascular therapy (EVT) in Europe with considerable inter- and intra-country availability differences (7). Still, IVT and EVT are the most efficacious treatment options in AIS, and patient eligibility can determine long-term functional outcomes. Thus, gradually expanding the time windows (TWs) for reperfusion therapies, first for EVT in 2019 (8), then for IVT too in 2021 (9), offered life-changing opportunities for selected patients based on advanced imaging.

Advanced neuroimaging techniques and machine learning-based analysis have revolutionized patient selection for reperfusion therapies, aiming to enhance treatment outcomes and streamline clinical workflows. The interpretation of computed tomography (CT) findings, including early ischaemic changes based on Alberta Stroke Programme Early CT Score (ASPECTS), perfusion- and angiographic data can be inconsistent due to different local expertise and inter-rater variability. Additionally, it is often operationally challenging to coordinate interhospital communication in stroke centres using the drip-and-ship model (10). In this model, there is a primary stroke centre capable of IVT, but not EVT, necessitating secondary transport to another institution for EVT. Artificial Intelligence (AI) models are used to detect ischaemic areas on non-contrast CT scans according to ASPECTS and measure infarct core and penumbra volume - the viable tissue around the irreversibly damaged ischaemic core (11) - on CT perfusion (CTP). Furthermore, it can detect large vessel occlusion (LVO) and calculate collateral scores on CT angiography (CTA) using different machine-learning techniques (10). With the implementation of machine-learning software in the 2010s, there was an improvement in

CT and CTA-based stroke management (12), facilitating faster decision-making and offering enhanced accuracy and efficiency (13).

EVT changed the scene of AIS care in 2015 when multiple trials like MR CLEAN (14), ESCAPE (15), EXTEND-IA (16), REVASCAT (17), SWIFT PRIME (18) and THRACE (19) showed positive results in LVO patient outcomes (20, 21): the number needed to treat to gain at least one point in the modified Rankin Scale (mRS) measuring functional outcome was 2.6 (20). Emphasizing the 'time is brain' principle, the effectiveness of EVT was found to decrease with each passing hour after symptom onset (21). Subsequently, the January 2018 AHA/ASA guidelines recommended EVT up to 6 hours from symptom onset (22).

Perfusion imaging played a key role in the extension of TWs for acute reperfusion therapies. It acquired a pivotal role in the paradigm shift from a strict time-based to a more personal approach, focusing on individual pathophysiology (23). Based on collateral flow assessment, identifying the ischaemic core and the critically hypoperfused yet salvageable brain tissue called the penumbra, helped distinguish between fast and slow progressors (24, 25). This was the basis for the extended TW thrombectomy protocol used in the DAWN and DEFUSE 3 trials (26, 27). In these two landmark trials, evidence showed a clear benefit of EVT within 6 to 24 hours from stroke onset (26, 27). Thus, the American Heart Association/American Stroke Association (AHA/ASA) guidelines were updated (28, 29), and the 2019 European Stroke Organisation (ESO) guidelines (8) were released, recommending the extended TW for EVT up to 24 hours from stroke onset as the standard of care (8). Consequently, the role of CTP and magnetic resonance imaging (MRI) perfusion has become increasingly important for identifying eligible AIS patients for late treatments, who would have otherwise been excluded by standard criteria.

An advantage of MRI, despite its longer acquisition and interpretation time and the need for neuroradiological expertise, is its use in unknown onset strokes. In the WAKE-UP trial (30), IVT was performed in patients with no clear information about onset time or wake-up strokes where MRI showed abnormal signal on diffusion-weighted imaging (DWI) but not on fluid-attenuated inversion recovery (FLAIR) sequence on MRI in the region of the acute stroke (30). This led to the next step, the EXTEND trial (31), which established the basis for the extended TW IVT up to 9 hours from symptom onset based on perfusion

imaging (31). So the updated 2021 ESO IVT guidelines recommend IVT in patients with DWI-FLAIR mismatch in unknown onset ischaemic strokes and also in the extended TW, between 4.5 to 9 hours based on perfusion imaging (CTP or MRI perfusion) (9).

The rapid advancement of AIS care was partly hindered by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic setting foot globally in the dawn of 2020, reaching Hungary in March 2020. The evolving stroke care suffered multiple limitations, including resources for IVT and EVT, the availability of perfusion imaging for extended TW IVT and EVT and transport times (32). While initial reports on the high prevalence and severity of Coronavirus disease 2019 (COVID-19) related AIS worried stroke physicians worldwide at first, eventually, research showed an overall stroke risk of 1.5% associated with COVID-19 (33, 34). Further studies suggested that it is severe COVID-19 infection that is associated with higher stroke risk (35); for example, a study found a 16.7% stroke risk in ICU-treated COVID-19 patients compared to 1% in a milder form of the infection (36). COVID-19, through several pathophysiological mechanisms, increases the risk of ischaemic stroke, such as a proinflammatory immune response that triggers the coagulation cascade, causing endothelial dysfunction that disrupts the blood-brain barrier. This results in a prothrombotic state with thrombotic micro-and macroangiopathy. Other pathomechanisms include downregulating the angiotensin-converting enzyme-2 receptors and creating myocardial injury (37-40). Overall, studies show longer hospitalization, higher in-hospital mortality, and discharge to a destination other than home in COVID-19 AIS patients resulting in an overall worse outcome for patients suffering from both AIS and COVID-19 infection (33, 41).

The Action Plan for Stroke in Europe aspires to treat a minimum of 90% of all stroke patients primarily in a stroke unit, reaching a 95% availability of acute reperfusion therapies, a 15% IVT rate and a more than 5% EVT rate in all countries across Europe by 2030 (42). This is only feasible, if there is a conscious organization of stroke care, keeping account of the true state of current services based on real-life data compared to the constantly progressing research opportunities. This gap can only be filled if real-life data from across Europe is available.

Thus, we aim to provide an overview of data throughout multiple years and eras of stroke care from a university stroke centre in Hungary using MRI routinely as advanced imaging in acute stroke for the first time in the country and still uniquely. In this work, we present four studies spanning six years of AIS care in a primary stroke centre, experiencing stroke protocol changes and the COVID-19 pandemic as an unexpected global healthcare emergency. The studies will be presented in chronological order (*Figure 1.*):

1. AIS care using AI-based decision support
2. Experience on extending the thrombectomy TW
3. The impact of COVID-19 infection on AIS outcome
4. Extending the TW for both thrombolysis and thrombectomy

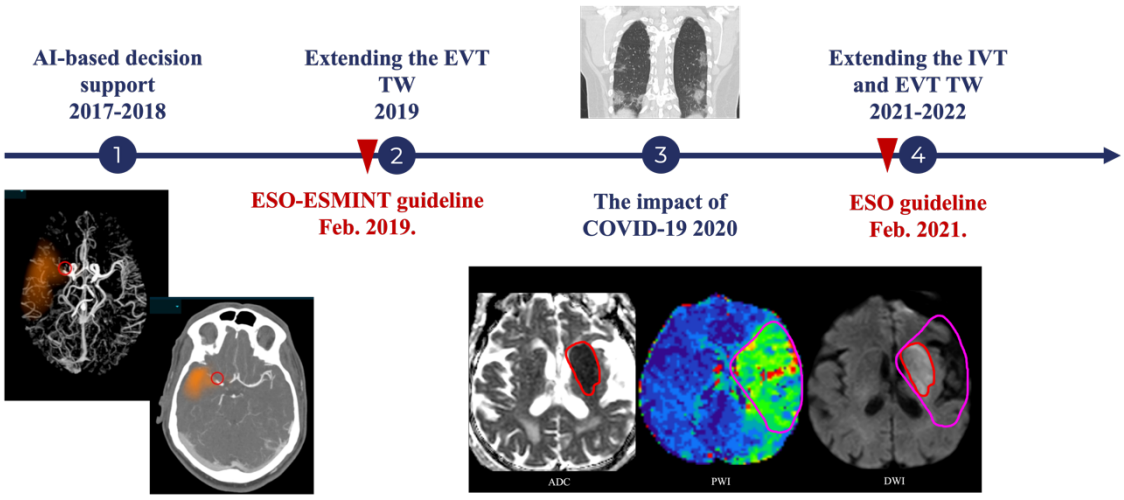

Figure 1. Timeline of the four studies

Following the introduction, the methods and results for each study will be presented individually. Subsequently, each study will be discussed separately, including a section summarizing all the data. Finally, the conclusions and a short summary will be outlined.

Awareness of everyday processes of stroke management helps identify deficiencies and optimize resource allocation. This comprehensive approach is the key to bridging the gap between current practices and future goals set by the stroke community, ultimately improving patient outcomes across Europe.

2. Objectives

Despite substantial improvements in stroke diagnosis and treatment, there is limited information on how AI-driven decision support influences clinical decision-making and patient outcomes in high-volume stroke centres. Additionally, the implications of COVID-19 infection on AIS outcomes, as well as the real-world burden of the extended TW reperfusion strategies, are insufficiently explored, especially in Central Europe.

The real-world data can assist healthcare professionals and management in resource planning across the entire stroke pathway.

We aimed to provide:

1. insight into the effects of AI-based decision support tools on the delivery and outcomes of reperfusion therapies,
2. to assess the impact of COVID-19 infection on the prognosis of AIS patients,
3. to explore the clinical workload and treatment effect of extending reperfusion therapy time windows, as recommended by the periodically changing ESO guidelines in a high-volume primary stroke centre using MRI as advanced imaging.

Our research evaluates different but complementary, timely aspects of stroke management that together provide resilience in an ever-changing environment. It points towards improving stroke care with the emergence of AI, a multidisciplinary approach, and the constant evolution of care provided. By balancing the burden and benefits of widening eligibility criteria based on new research evidence, we aim to enhance patient outcomes and streamline stroke care practices.

3. Methods

All research was conducted at a single centre, Department of Neurology, Semmelweis University, Budapest, Hungary - a primary stroke centre capable of IVT with recombinant tissue plasminogen activator (Actilyse) but not of EVT. EVT was provided in a drip-and-ship model at Semmelweis University, Department of Neurosurgery and Neurointervention, not yet integrated into Semmelweis University network at the time of the studies. This latter comprehensive stroke centre - the only EVT centre in the capital and Central Hungary - used different hospital information and picture archiving systems. This fact made clinical and imaging data transfer a burden to both the sending and receiving parties, overcome in practice by various unorthodox methods. The EVT site is located 8 km away, with an average ambulance transport time of 10-20 minutes (*Figure 2.*).

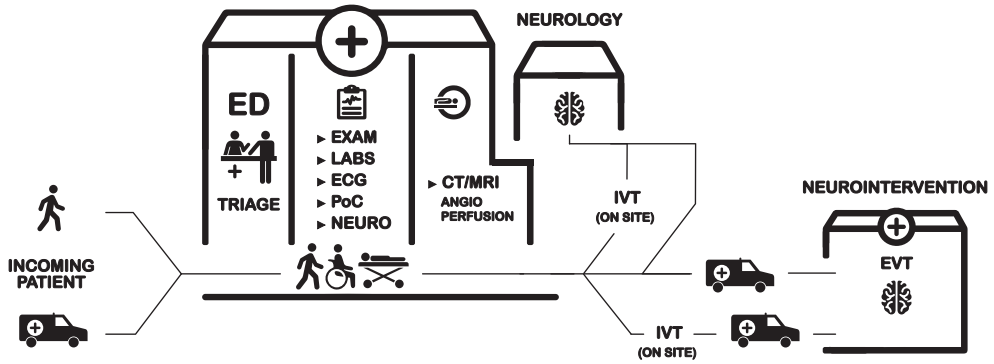

Figure 2. Overview of stroke pathway at Semmelweis University Department of Emergency Medicine (ED), Department of Neurology and Department of Neurosurgery and Neurointervention

PoC: point of care tests

Initial neurological examinations by board-certified neurologists were performed at the Department of Emergency Medicine, Semmelweis University, located on the same plot but in a different building than the Department of Neurology. Some exceptions to this patient pathway were in the COVID-19 era, when the Department of Neurology was

mostly- or solely (between November 2020 and May 2021) involved in COVID-19 care and some in-hospital COVID-19 patients developed acute stroke symptoms.

The data collected were analyzed using appropriate statistical methods after testing for normal distribution. For continuous variables, t-tests and unpaired t-tests were used to compare groups. The Mann-Whitney U test was applied for non-parametric comparisons. Fisher's exact test and chi-square tests were used for categorical variables. Descriptive statistics, including means with standard deviations and medians with interquartile ranges (IQR) and frequencies, were calculated to summarize the basic features of the data. The level of statistical significance was set at $p<0.05$. In tables, significant values are presented in bold.

Table 1. summarizes the methods for the presented studies: study characteristics, patient cohorts, and methodologies across multiple investigations into acute ischaemic stroke management. Methods for the individual studies are described in more detail below.

Table 1. Summary of study setting and reperfusion therapy criteria in the different studies (43-46)

Study	AI based decision-support		Extended EVT TW		The impact of COVID-19 infection on AIS outcome		Extending the TW for both thrombolysis and thrombectomy	
	Control Group	AI Group	Standard EVT TW	Extended EVT TW	non-COVID-19 AIS	COVID-19 AIS	Standard TW Group	Extended TW Group
Sample	Retrospective data of consecutive AIS patients	Retrospective data of consecutive AIS patients	Prospective data of consecutive AIS patients	Prospective data of consecutive AIS patients	Retrospective data of consecutive AIS patients	Retrospective data of consecutive COVID-19 AIS patients	Prospective data of consecutive AIS patients	Prospective data of consecutive AIS patients
Nr. of Patients	398	399	238	199	51	32	IVT:304; EVT: 386	IVT: 231; EVT: 391 (total 777)
Time of the Study	May to December 2017	May to December 2018	1st February 2019 to 31st December 2019	1st February 2019 to 31st December 2019	October 2020	1st March 2020 to 1st May 2021	1st March 2021 to 28th February 2022	1st March 2021 to 28th February 2022
IVT Criteria	presented < 4.5 h, no contraindication, infarct <2/3 MCA territory	Same as control group	N/A	N/A	presented <4.5 h, no contraindications, infarct <2/3 MCA territory	Same as control group	presented <4,5h CT: no contraindication; MRI: core <70 ml, DWI- FLAIR mismatch	presented 4.5-9h infarct core< 70 ml, infarct core ratio > 1.2, penumbra > 10 ml
EVT Criteria	presented <6h, ASPECTS ≥6, ICA, MCA, BA occlusion mRS ≤2	Same as control group	presented <6h, LVO (ICA, M1, M2, A1, P1, BA) and ASPECTS≥6 mRS ≤2	presented 6-24h, NIHSS ≥6, mRS ≤2,core <70 ml, isch./core ratio >1.8, penumbra >15 ml (DEFUSE 3 criteria) ICA, M1, BA occl.	presented <6h, LVO (ICA, M1, M2, A1, P1, BA) and ASPECTS≥6 mRS ≤2	presented <6h, LVO (ICA, M1, M2, A1, P1, BA) and ASPECTS≥6 mRS ≤2	presented <6h, intracranial ICA, M1, M2, A1, P1, BA occlusion (BA only NIHSS >10) mRS ≤2	presented 6-24h, core <70 ml, ischaemia/core ratio >1.8, penumbra >15 ml (DEFUSE 3 criteria) ICA, M1, BA occlusion mRS ≤2
Imaging	CT, CTA without e-ASPECTS analysis	CT, CTA with e-ASPECTS analysis	CT, CTA or in unknown onset MR, MRA	CT, CTA + MRI PWI if LVO (only ICA, M1, BA) and ASPECTS ≥6	CT or MRI, confirmed ischaemia	CT or MRI, confirmed ischaemia,	MRI preferred (DWI, FLAIR, GRE T2*, PWI, MRA) 08-20h, otherwise CT, CTA	MRI (DWI, FLAIR, SWI, postcontrast sagittal T1, PWI, MRA) 08-20h, otherwise CT, CTA
Data Collected	Demographic data, NIHSS, mRS at 90 days, time-to-treatment, collateral flow, imaging outputs	Same as control group	Demographic data, NIHSS, imaging modality, LVO, mRS at 90 days	Demographic data, NIHSS, imaging modality, LVO, mRS at 90 days	Demographic data, NIHSS, TOAST, infarct localization, LVO, mRS at discharge	Demographic data, NIHSS, TOAST, infarct localization, LVO, mRS at discharge	Demographic data, NIHSS, imaging modality, LVO, DIT, DNT, DGT, mRS at 90 days	Demographic data, NIHSS, imaging modality, LVO, DIT, DNT, DGT, mRS at 90 days

3.1. AIS care using AI-based decision support

Between May and December of 2017 and 2018, data from all consecutive patients with AIS admitted to the Department of Neurology at Semmelweis University were retrospectively analyzed. Patients were selected for reperfusion treatment based on international and local guidelines at the time. Briefly, thrombolysis was considered for those presenting within 4.5 hours of stroke onset without haemorrhage or other contraindications, and with hypodensity not exceeding 2/3 of the middle cerebral artery (MCA) territory (43). Thrombectomy eligibility required the absence of haemorrhage, an ASPECTS score ≥6, and LVO in the internal carotid artery (ICA), MCA, or basilar artery (BA) (43). In May 2018, the CE-certified and U.S. Food and Drug Administration (FDA)-approved Brainomix e-Stroke Suite software was implemented and used regularly in acute stroke care (43).

Data collected included age, sex, time-to-treatment, National Institutes of Health Stroke Scale (NIHSS) on admission, and in EVT-treated patients, mRS at 90 days. Non-contrast CT scans and CTA were performed, with e-ASPECTS and e-CTA analysis used to assess ischaemic regions and collateral flow. e-ASPECTS automatically segmented the MCA territory and identified tissue as either ischaemic or normal. It provided outputs such as ASPECTS and acute ischaemic volume; e-CTA outputs included the identification and location of LVO, the ratio of collateral flow compared to the opposite side, and a collateral score ranging from 0 (no flow) to 3 (complete collateral blood supply). Statistical analyses were conducted in R, to evaluate changes in reperfusion therapy, door-to-treatment times, and outcomes (43). Changes in the number of patients receiving reperfusion therapy were characterised using chi-square analysis, and door-to-needle time (DNT) was compared using a Student's t-test (43). Mean DNT was calculated from the data of 44 patients, in 2 patients, IVT time was not documented. Median NIHSS for IVT and EVT groups was analysed with Mann-Whitney U test. Outcome analyses with dichotomised mRS (with 0-2 as good outcome, 0-1 as excellent outcome), using chi-square analysis and for mRS shift using Wilcoxon rank sum test, were performed only for EVT-treated patients. Data are presented as mean with standard deviation for continuous variables, and median with interquartile range (IQR) for ordinal variables (43). This

retrospective review of patient data did not require ethical approval or informed consent in accordance with local guidelines (43).

3.2. Experience on extending the thrombectomy TW

Following the 2019 ESO-ESMINT guidelines, from February 1 to December 31, 2019, all consecutive ischaemic stroke patients admitted within 24 hours of onset were included in the study. Emergency Medical Services (EMS) urgently transported all acute stroke patients with symptom onset within 6 hours to the stroke centre, where the emergency department personnel triaged them as critical (44). It was only in December 2020 that EMS stroke protocol changed and ordered the mandatory transport of suspected stroke patients to stroke centres within 24 hours of symptom onset (47).

During this study, non-invasive angiography was performed routinely in the standard TW for all patients, regardless of stroke severity (except if technically not feasible or allergy to contrast agent), but not for the extended TW (44). Eligibility for EVT in the standard TW included occlusion of the ICA, MCA M1, anterior cerebral artery (ACA) A1 segment or posterior cerebral artery (PCA) P1 segment with ASPECTS ≥ 6 (44).

In the 6–24 hour window, only patients with NIHSS ≥ 6 or fluctuating/brainstem symptoms and premorbid mRS ≤ 2 underwent CTA, and those with ICA, M1 or BA occlusions underwent MRI to identify DWI-PWI mismatch (44). Patients with unknown onset strokes recognized within 4 hours had primarily MRI. In case of DWI-FLAIR mismatch, they were included in the standard, otherwise in the extended TW group. EVT eligibility was determined by DEFUSE 3 criteria (6-16 hours) and simplified DAWN criteria (16-24 hours) (44).

Data collected included time window, age, NIHSS, non-invasive angiography use, presence of LVO, and EVT use. Clinical outcomes (mRS) at 3 months were assessed in treated patients, and the comparisons between the 0–6 and 6–24 hour TWs were made using appropriate statistical tests. The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE-RKEB 17/2020). Because of the observational nature of this study, no informed consent was obtained (44).

3.3. The impact of COVID-19 infection on AIS outcome

We analyzed data from 32 consecutive AIS patients with COVID-19 (March 2020 - May 2021) and 51 non-COVID-19 AIS patients (October 2020) with confirmed ischaemia either on CT or MRI at Semmelweis University Department of Neurology. From March to October 2020, the hospital maintained its Neurology profile while some staff were reassigned to COVID-19 units. From November 2020 to May 2021, it became a COVID-19 hospital, halting acute AIS care. Neurologists provided consultations in other departments. COVID-19 AIS patients had positive SARS-CoV-2 tests within two weeks of stroke onset (45). Pneumonia was assessed on chest CT or X-ray. The COVID-19 infection was classified based on the World Health Organisation (WHO) COVID-19 severity classification (45). October 2020 was chosen as the control period because the second COVID-19 wave was ongoing, but the hospital was not solely dedicated to COVID-19 care (45). Data was collected retrospectively from medical documentation, the analysis included demographics, medical history, stroke characteristics, lab results, hospitalization length, mRS at discharge, in-hospital mortality, and intensive care unit (ICU) transfer (45).

Statistical analysis between patient groups were performed using either paired t-test, unpaired t-test, Mann-Whitney U test, univariable and multivariable logistic regression, linear regression, Chi-squared test, or Fisher's exact test. The variables in the univariable logistic regression were selected based on the clinically most relevant cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipemia, smoking, and other cardiovascular risk factors including history of chronic kidney disease, transient ischemic attack or stroke, ischemic heart disease, peripheral artery disease, and atrial fibrillation) that can affect mortality in AIS patients. The factors with $p<0.1$ in univariable logistic regression were selected for multivariable logistic regression. All analyses were performed using GraphPad Prism version 9 (45).

This study was approved by Semmelweis University Regional and Institutional Committee of Science and Research Ethics (No.: 201/2021). Informed consent was not sought because of its observational and retrospective nature (45).

3.4. Extending the TW for both thrombolysis and thrombectomy

Implementing the February 2021 ESO guidelines from March 2021, we collected data from all AIS or transient ischaemic attack (TIA) patients presenting within 24 hours of symptom onset at Semmelweis University Stroke Centre between March 1, 2021, and February 28, 2022 (46). At this time, the EMS protocol required all suspected stroke patients within 24 hours of symptom onset to be transported to the nearest stroke centre (47). Neurological exams were performed in the ED, with multimodal MRI as the first-choice imaging during working hours (08-20h), otherwise CT and CTA were used (46). For extended TW reperfusion therapies, MRI was needed, but not always feasible due to poor patient condition or unavailability (46).

Reperfusion treatment eligibility followed 2021 ESO guidelines, with specific criteria in the extended TW for IVT and EVT based on advanced imaging results (46). The CT scanner (64-slice Philips Incisive) is in the ED, while the MRI scanner (Philips Ingenia 1.5T) is on another floor, requiring longer transport, including elevator use (46). Standard TW MRI sequences within 4.5 hours included DWI, FLAIR, gradient echo (GRE) T2*, perfusion-weighted imaging (PWI), and contrast-enhanced MRA, with an 8-minute acquisition time. For late TW patients, susceptibility-weighted imaging (SWI) replaced GRE T2* and an additional postcontrast sagittal T1 was included, extending the acquisition time to 12 minutes (46). Postprocessing on the Philips IntelliSpace platform provided core/penumbra volumes within 10 minutes. Infarct core was defined as (apparent diffusion coefficient) ADC < 620 mm^2/s, and critically hypoperfused tissue as Tmax > 6 seconds (46).

IVT criteria included an infarct core < 70 ml, a critically hypoperfused volume/core ratio > 1.2, and a mismatch volume > 10 ml (EXTEND criteria) (46). For EVT, criteria included a core < 70 ml, an ischaemia/core ratio > 1.8, and a penumbra > 15 ml (DEFUSE 3 criteria) (46). Unknown onset strokes within 4 hours were considered for IVT if there was an MRI DWI-FLAIR mismatch and an infarct core < 70 ml (WAKE-UP criteria) (46). Wake-up strokes occurring within 9 hours from the midpoint of sleep with a DWI-PWI mismatch were eligible for IVT (46). Patients received Alteplase 0.9 mg/kg (max 90 mg) for IVT and were considered for EVT if they had LVO - unless contraindicated (46).

Early EVT was indicated for occlusions in the intracranial ICA, MCA M1 and M2, anterior cerebral artery (ACA) A1, PCA P1, and BA. Late EVT was considered for ICA, M1, and BA occlusions based on DEFUSE 3 criteria up to 24 hours for anterior LVO, and for basilar occlusions if NIHSS ≥ 10 and no extensive brainstem damage on DWI-MRI (46).

Data collected included demographics, stroke onset time, NIHSS, imaging modality, door-to-imaging time (DIT), presence and location of LVO, DNT, door-to-groin time (DGT), recanalization rate, EVT complications, and mRS at 90 days in treated patients with any acute reperfusion therapy (46). Detailed mRS at 3 months was available in 102/119 patients in the standard IVT TW, all patients in the extended IVT TW, 26/34 in the standard EVT TW and 12/15 in the extended EVT TW. Mortality data was checked for the patients with unavailable mRS in the national Electronic Health Service Space.

Statistical analysis was conducted between patient groups using either unpaired t-test, Mann–Whitney U test, Fisher's exact test, or Chi-square test. All analyses were performed GraphPad Prism version 9. This study was approved by Semmelweis University Regional and Institutional Committee of Research Ethics (approval no. 123/2019) (46). Patient consent was obtained for off-label Actilyse use in the extended thrombolysis time window (off-label use) (46). For treatment in the standard time window and for data collection without treatment, consent was not obtained because the data were analysed anonymously (46).

4. Results

4.1. AIS care using AI-based decision support

During the May to December period of 2017, 399 patients were admitted. On May 11th, 2018, the AI-based decision support software Brainomix was implemented in acute stroke care. In the corresponding period, we analysed the data of 398 patients, *Table 2*. summarizes the results. Baseline demographics showed no significant difference between the two years (43).

Table 2. Summary of clinical, treatment and outcome data comparing an 11-month period in 2017 to the data of the same period in 2018 aided by AI-decision support. In the indented sections: the data of treated patients with IVT or EVT is listed (43)

	May-Dec 2017	**May-Dec. 2018, AI-support**	**Test**	**p-value**
Number of Cases	399	398	-	-
IVT (% treated)	**46 (11.5)**	**72 (18.1)**	**Chi-square**	**0.009** (56.9% increase)
Age (mean ± SD) years	67.6 ± 13.3	65.1 ± 13.5	Student's t-test	0.3344
Male (%)	45.7	55.6	Chi-square	0.528
NIHSS IVT (median, IQR)	**8 (5–13)**	**6 (3–10.25)**	**Mann-Whitney U**	**0.0460**
Door-to-Needle Time (DNT, median, IQR)	40 (26.25-56)	36 (27.25-54.75)	Mann-Whitney U	0.48
EVT (% treated)	11 (2.8%)	19 (4.8%)	Chi-square	0.13 (72.7% increase)
Age (mean ± SD) years	55.8± 18.1	62.3±15.3	Mann-Whitney U	0.34
Male (%)	6 (54.6%)	10 (52.6%)	Chi-square	0.91
NIHSS EVT (median, IQR)	15 (13.5–18.5)	13 (10–15.5)	Unpaired t-test	0.35
CT-to-Groin Puncture Time (mean ± SD)	174 ± 80.5 min	145 ± 28 min	Student's t-test	0.29 (16.7% decrease)
mRS Excellent Outcome, 0-1 n/n (%)	2/10 (20%)	7/18 (38.9%)	Chi-square	0.55
mRS Good Outcome, 0-2 n/n (%)	6/10 (60%)	11/18 (61.1%)	Chi-square	1

In 2017, among the 46 (11.5%) IVT-treated patients, the median NIHSS was 8 (5-13) and the median DNT was 40 (26.25-56) minutes. Mean DNT was calculated from the data of 44 patients. In 2018, 72 patients (18.1%) were treated with IVT, the median NIHSS was 6 (3–10.25), and the median DNT was 36 (27.25-54.75) minutes (*Table 2.*). This represented a 56.9% increase in the number of patients thrombolyzed compared to 2017 (p = 0.009), with a non-significant decrease in DNT of about 4.5%, *Figure 3* (43).

When comparing EVT, in 2017, 11 patients (2.8%) received EVT, which increased by 16.9%, to 19 (4.8%) in 2018. The mean CT-to-groin puncture time was 174 ± 80.5 min versus 145 ± 28 min (based on data from 17 patients) in 2018, a 16.7% decrease compared to 2017 (p = 0.29), *Figure 3., Table 2* (43).

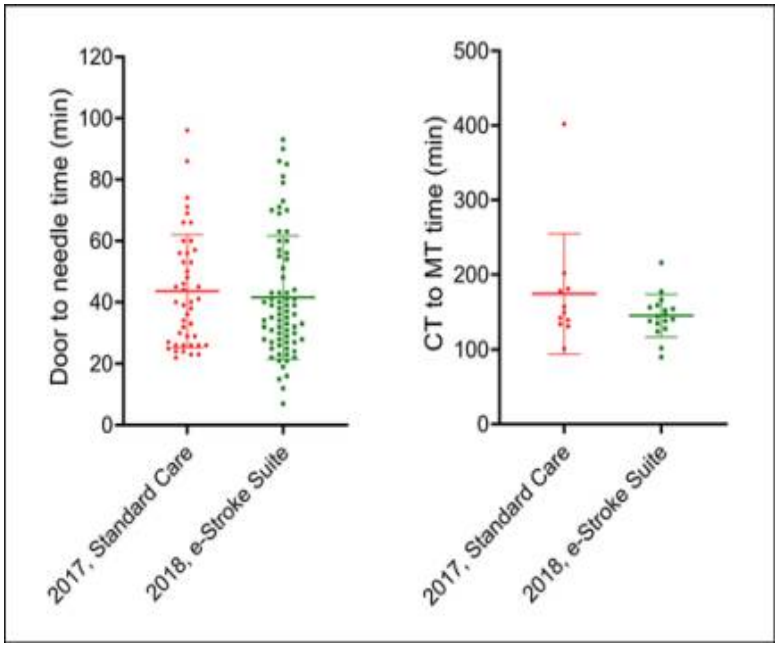

Figure 3. Treatment times for patients in consecutive years for thrombolysis (left) and endovascular therapy (mechanical thrombectomy, MT) (right) (43)

In the EVT group, a good functional outcome (mRS 0–2) was achieved by 6 versus 11 patients in 2018 (p=1). In 2017, 2 patients achieved an excellent outcome (mRS 0–1), compared to 7 patients in 2018 (p=0.55). When examining the mRS shift, there was a trend towards better outcomes in 2018 (p=0.29), *Figure 4., Table 2* (43).

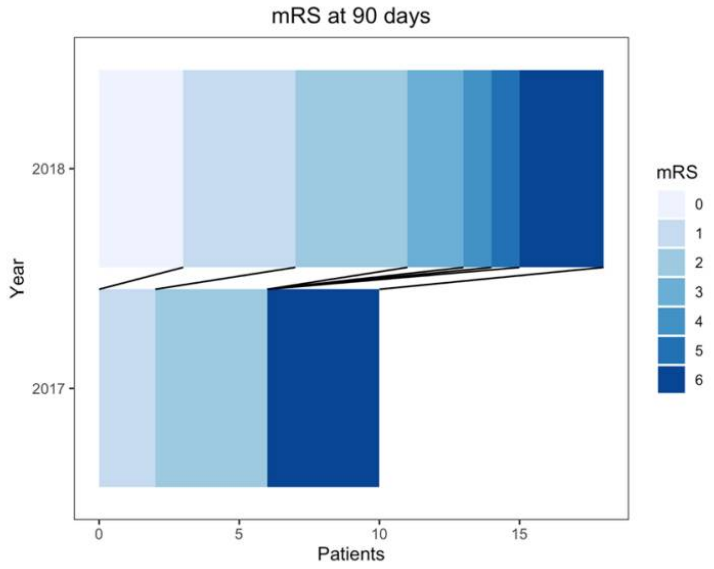

Figure 4. mRS distributions at 90 days following stroke in the EVT cohort, 2017 (control period) and 2018 (with the implementation of AI-based decision support) (43)

4.2. Experience on extending the thrombectomy TW

From February to December 2019, 437 AIS patients were admitted, data is presented in *Table 3*. From the 238 (54.5%) who arrived in the standard (0-6 hours) TW, 92.9% underwent CTA or MRA, 34.5% had LVO and 30 (12.6%) had EVT. Of the EVT group, 11 patients (36.6%) had mRS ≤2 at 3 months (44).

In the extended TW, 199 patients were screened, and with more restrictive imaging criteria, 63.8% underwent CTA or MRA. LVO was diagnosed in 21.1%, and 8 patients (4%) had EVT, while independent functional outcome was achieved in 4 patients (44). Number needed to screen (NNS) was 8 in the standard and 25 in the extended TW (44). Basic demographic data was well balanced between the two groups. NIHSS was more severe in the standard group (median (IQR) NIHSS 6 (4-12) vs 5 (3-8); p = 0.011), where more LVOs were diagnosed (34.5 vs 22.1%; p = 0.0046) and treated (12.6 vs 4%; p = 0.001) *Table 3.* (44).

Table 3. Comparing patients in the standard and extended TW for thrombectomy (44)

	0–6 h	**6–24 h**	**Test**	**p-value**
Number of cases	238	199		-
Male (%)	119 (50%)	99 (49.7%)	Chi-square	0.96
Age (mean, SD) years	70.5 (± 12.4)	70.9 (± 11.7)	t-test	0.744
NIHSS (median, IQR)	**6 (4–12)**	**5 (3–8)**	**Mann-Whitney U**	**0.011**
CTA/MRA (%)	**221 (92.9%)**	**127 (63.8%)**	**Chi-square**	**< 0.001**
LVO (%)	**82 (34.5%)**	**44 (22.1%)**	**Chi-square**	**0.004**
EVT (%)	**30 (12.6%)**	**8 (4%)**	**Fisher's exact test**	**0.001**
EVT in LVO (%)	36.6%	18.3%	Fisher's exact test	0.0415
mRS≤2 at 90 days (%)	11 (36.6%)	4 (50%)	Fisher's exact	0.687
NNS for EVT	8	25	-	-

In the treated patients between the two TWs, age was similar, NIHSS was more severe in the standard TW, and the outcome was worse in early patients (median mRS 4 vs 2.5), but neither result was statistically significant because of the low number of patients (*Table 4*.) (44). Of all 126 LVO strokes, 82 (65.1%) were in the standard TW. Similarly, 30/38 (78.9%) of patients eligible for EVT were in the standard TW (44).

Extending the time window led to an 83.6% rise in emergency clinical screenings, a 57.5% increase in non-invasive angiography, a 26.7% rise in EVT procedures, and a 36.4% improvement in the rate of independent clinical outcomes among treated patients compared to the standard TW (44).

Table 4. Treated patients in the standard and extended TW for thrombectomy (44)

	0–6 h	**6–24 h**	**Test**	**p-value**
Number of EVTs	30	8	-	-
Age (mean, SD) years	68.2 (± 12.2)	69.1(± 14.4)	t-test	0.855
NIHSS (median, IQR)	15 (9–18)	8 (5–15)	Mann-Whitney U	0.086
mRS 90 days (median, IQR)	4 (1–6)	2.5 (0–5)	Mann-Whitney U	0.44
mRS ≤2 number (%)	11 (36.7%)	4 (50%)	Fisher's exact	0.687

4.3. The impact of COVID-19 infection on AIS outcome

The results are summarized in *Table 5* (45).

Table 5. Comparing characteristics of COVID-19 AIS with non-COVID-19 AIS patients (45), significant results are marked in bold, near-significant in italics

Abbreviations: TIA: transient ischaemic attack, PAD: peripheral artery disease, WBC: white blood cell count, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, INR: international normalized ratio. All values are presented as mean ± SD unless otherwise specified.

Data	COVID-19 AIS	Non-COVID-19 AIS	Test	p-value
Demographic data				
Number of patients	32	51		
Age (years)	70.1 (± 12.83)	70.7 (± 14.73)	Mann-Whitney U	0.68
Male sex (%)	21 (65.6%)	32 (62.7%)	Chi-squared	0.79
Medical history				
Diabetes (%)	11 (34.4%)	13 (25.5%)	Chi-squared	0.38
Hypertension (%)	**21 (65.6%)**	**44 (86.3%)**	**Chi-squared**	**0.02**
Hyperlipemia (%)	8 (25%)	18 (35%)	Chi-squared	0.33
Malignancy (%)	3 (9.4%)	7 (13.7%)	Fisher's exact	0.73
Ischaemic heart disease (%)	11 (34.4%)	14 (27.5%)	Chi-squared	0.50
Stroke/TIA (%)	6 (18.8%)	15 (29.4%)	Chi-squared	0.27
PAD (%)	5 (15.6%)	5 (10%)	Fisher's exact	0.32
Chronic lung disease (%)	3 (9.4%)	3 (6%)	Fisher's exact	0.67
Atrial fibrillation (%)	9 (28%)	9 (17.7%)	Chi-squared	0.25
Stroke characteristics				
Admission NIHSS (Median, IQR)	*9 (3-13)*	*4 (2-10)*	*Mann-Whitney U*	*0.06*
LVO (%)	13 (40.6%)	14 (27.5%)	Chi-squared	0.21
Anterior LVO	12/13 (92.3%)	9/14 (64.2%)	Fisher's exact	0.16
Posterior LVO	1/13 (7.7%)	4/14 (25.5%)	Fisher's exact	0.32
Multilocular LVO	0/13	1/14 (7%)	Fisher's exact	>0.99
Acute reperfusion therapy (IVT+EVT)	10 (31.3%)	12 (23.5%)	Chi-squared	0.43
IVT (%)	6 (19%)	6 (11.7%)	Chi-squared	0.37
EVT (%)	4 (12.5%)	6 (12%)	Fisher's exact	>0.99
EVT/LVO (%)	4/13 (31%)	6/14 (43%)	Fisher's exact	0.69
Door to needle time (minutes)	83 ± 35	54 ± 15	Unpaired t	0.17
Door to groin time (minutes)	378 ± 250	310 ± 221	Mann-Whitney U	0.33

Stroke etiology (TOAST)				
Cardiac embolism (%)	11 (34.4%)	16 (31.4%)	Chi-squared	0.77
Small vessel disease	1 (3.1%)	7 (13.7%)	Fisher's exact	0.144
Large artery atherosclerosis	6 (18.8%)	6 (11.8%)	Chi-squared	0.378
Other, determined	0	4 (7.9%)	Fisher's exact	0.156
Undetermined	14 (43.8%)	18 (35.3%)	Chi-squared	0.931
Laboratory findings				
WBC 10^3/µL	9.6 ± 4.3	9.73 ± 3.32	Mann-Whitney U	0.88
Lymphocytes 10^3/µL	**1.54 ± 1.5**	**1.66 ± 0.7**	**Mann-Whitney U**	**0.04**
Thrombocyte 10^3/µL	248.7 ± 86.1	250.2 ± 66.5	Unpaired t	0.92
Hemoglobin g/L	135.3 ± 22.2	142.1 ± 17.2	Mann-Whitney U	0.22
eGFR mL/min/1.73m^3	69.05 ± 21.9	70.16 ± 21	Mann-Whitney U	0.55
CRP mg/L	**59.4 ± 68.4**	**21.89 ± 40.4**	**Mann-Whitney U**	**0.0012**
INR	1.09 ± 0.1	1.08 ± 0.2	Mann-Whitney U	0.16
Outcome				
Hospitalization days	**19.4 ± 17.7**	**9.7 ± 7**	**Mann-Whitney U**	**0.003**
Discharge mRS (Median, IQR)	*4 (1-6)*	*2 (1-4)*	*Mann-Whitney U*	*0.052*
Favorable functional outcome (mRS≤2) (%)	**12 (37.5%)**	**32 (62.8%)**	**Chi-squared**	**0.02**
In-hospital mortality (%)	**10 (31.3%)**	**6 (11.8%)**	**Chi-squared**	**0.02**
Transfer to ICU (%)	4 (12.5%)	1/41 (2.4%)	Fisher's exact	0.16

4.3.1. Demographic data and medical history

There was no significant difference in baseline demographic data and medical history between the COVID-19 AIS and non-COVID-19 AIS groups, except hypertension was significantly more prevalent in the non-COVID AIS group (65.6% vs. 86.3%, p=0.02) (45).

4.3.2. Stroke characteristics

At admission, the median NIHSS (interquartile range, IQR) for the COVID-19 AIS group tended to be higher (9 (3-13) vs. 4 (2-10); p=0.06), though this difference was not statistically significant. The COVID-19 group had a numerically higher LVO rate (40.6% vs. 27.5%; p=0.21), with a greater proportion of anterior circulation LVOs (92.3% vs. 64.2%) (45). Among the COVID-19 AIS group, LVO was more frequently observed

in patients with COVID-19 pneumonia compared to those without (55.6% vs. 23.1%; p=0.139) (45), shown in *Figure 5*.

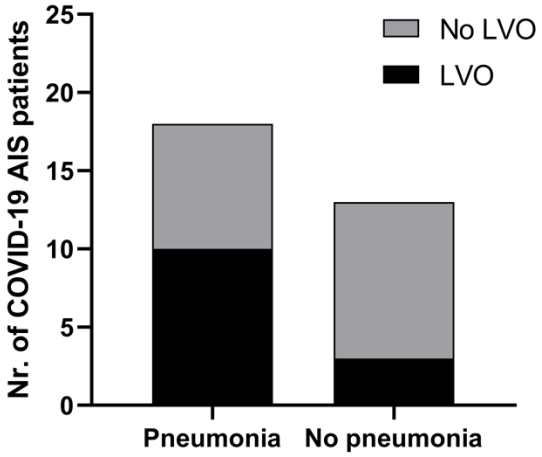

Figure 5. Relation of COVID-19 pneumonia and LVO in COVID-19 AIS patients. COVID-19 AIS patients with pneumonia more often had concomitant LVO (p=0.139) (45).

The percentage of different stroke etiologies based on (Trial of Org 10172 in Acute Stroke Treatment) TOAST criteria were as follows *(Table 5.)*: undetermined strokes were 43.8% in the COVID-19 group and 35.3% in the non-COVID-19 group (45). Cardioembolic strokes accounted for 34.4% and 31.4%, respectively. Small vessel disease was identified in 3.1% of the COVID-19 group and 13.7% of the non-COVID-19 group (45). Large artery atherosclerosis was present in 18.8% of the COVID-19 group and 11.8% of the non-COVID-19 group (45). Other determined causes were found in 0% of the COVID-19 group and 7.9% of the non-COVID-19 group (45). None of these differences were statistically significant (p>0.05) (45).

In our study, 31.3% of COVID-19 AIS patients underwent acute reperfusion therapy. Of these, 19% received IVT and 12.5% received EVT, with no patient eligible for both *(Table 5.)* (45). In the control group, 23.5% were treated with acute reperfusion therapy, with 11.7% receiving IVT and 11.8% undergoing EVT (45). One patient in the control group received both IVT and EVT. The EVT/LVO ratio was 30.8% in the COVID-19 group and 42.9% in the control group (p=0.69) (45). The DNT was longer in the COVID-19 AIS group (83 ± 35 minutes) compared to the non-COVID-19 AIS group (54

± 15 minutes; p=0.17*) (Table 5.).* Similarly, the DGT was longer in the COVID-19 AIS group (378 ± 250 minutes) compared to the non-COVID-19 AIS group (310 ± 221 minutes; p=0.33) (45).

4.3.3. Laboratory findings

In laboratory parameters, lymphocyte count was significantly lower in the COVID-19 compared to the non-COVID-19 AIS patients (1.54 ± 1.5 10^3/μL vs. 1.66 ± 0.7 10^3/μL; p=0.04) and in C-reactive protein (CRP) levels (59.4 ± 68.4 mg/L vs. 21.9 ± 40.9 mg/L; p=0.0012) *(Table 5.)* (45).

4.3.4. COVID-19 severity

Based on the WHO COVID-19 disease severity classification, in our COVID-19 cohort, none of the 32 patients had mild disease, 50% (16/32) had moderate, 37.5% (12/32) had severe, and 12.5% (4/32) had critical COVID-19 severity (45). We assessed clinical characteristics by dichotomizing patients into mild-moderate and severe-critical categories *(Table 6.)*. There was no significant difference in NIHSS (median, IQR) at admission between the mild-moderate and severe-critical groups (9 (5-13.75) vs. 6.50 (2.25-12.5); p=0.30) (45). The number of LVOs was similar in both groups (43.75% (7/16) vs. 40% (6/15); p=0.83). ICU transfers occurred only in the severe-critical group (0% vs. 25% (4/16); p=0.10). Hospitalization duration was slightly longer in the severe-critical group (18.00 (6.75-33.00) days vs. 12.50 (7.50-18.75) days; p=0.39) (45). Mortality was moderately higher in the severe-critical group (37.5% (6/16) vs. 12.5% (2/16); p=0.43). Functional state at discharge was significantly worse in the severe-critical group (mRS 1.5 (1-5) vs 6 (3-6); p=0.014), *Figure 6* (45).

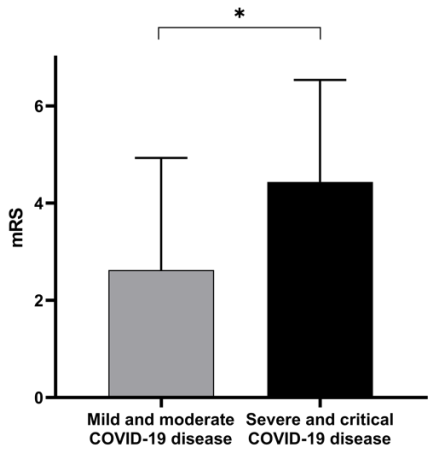

*Figure 6. Association between COVID-19 severity and functional outcome. More severe COVID-19 infection resulted in worse functional outcomes (Discharge mRS 2.6 ± 2.3 vs. 4.4 ± 2.1 Mann-Whitney U; p=0.01). Data are presented as mean ± SD, *p<0.05 (45).*

Table 6. Comparing clinical characteristics of mild-moderate vs. severe-critical COVID-19 AIS patients (45)

Data	Mild-moderate COVID-19	Severe-critical COVID-19	Test	p-value
Admission NIHSS (Median, IQR)	9 (5-13.7)	6.5 (2.2-12.5)	Mann-Whitney U	0.29
LVO (%)	7/16 (43.7%)	6/15 (40%)	Chi-square	0.83
Transfer to ICU	0/16 (0%)	4/16 (25%)	Fisher's exact	0.1
Hospitalization days (Median, IQR)	12.50 (7.5-18.7)	18.00 (6.7-33)	Mann-Whitney U	0.4
In-hospital mortality (%)	2/16 (12.5%)	6/16 (37.5%)	Fisher's exact	0.43
Discharge mRS (Median, IQR)	**1.5 (1-5)**	**6 (3-6)**	**Mann-Whitney U**	**0.01**

4.3.5. Hospitalization and outcome

The length of hospitalization was longer for COVID-19 AIS patients compared to the non-COVID-19 AIS group (19.4 ± 17.7 days vs. 9.7 ± 7 days; p=0.003, *Table 5., Figure 7.A*). A higher proportion of COVID-19 AIS patients were admitted to the ICU (12.5% (4/32) vs. 1.9% (1/41); p=0.16). The median (IQR) discharge mRS was higher in

the COVID-19 AIS group, though the difference was not statistically significant (4 (1-6) vs. 2 (1-4); p=0.052) (45). However, significantly fewer COVID-19 AIS patients achieved a favorable functional outcome (mRS≤2) (12/32 vs. 32/51; p=0.02, *Table 5.*, *Figure 7.B*) (45). In a subgroup analysis of anterior LVO patients, functional outcomes appeared less favorable in the COVID-19 AIS group compared to the non-COVID-19 AIS group (3.8 ± 2.5 vs 2.7 ± 1.9; p=0.22) (45). In-hospital mortality was significantly higher in the COVID-19 AIS population (31.3% (10/32) vs 11.8% (6/51); p=0.02, *Table 5.*, *Figure 7.C*) (45).

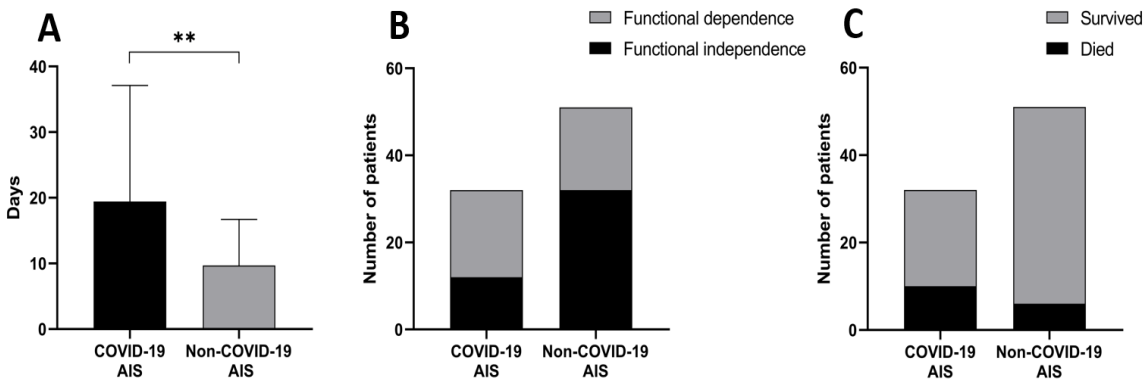

Figure 7. Summarizes the length of hospitalization and outcome results in COVID-19 AIS and non-COVID-19 AIS patients

*(A). The average length of hospitalization. A significant difference in treatment duration can be observed. Data are presented as mean ± SD.**p<0.01. (B). Functional state at discharge. Non-COVID-19 AIS patients showed significantly more favorable functional outcomes (mRS ≤2) than COVID-19 patients; p=0.02 (C). In-hospital mortality rates. There is significantly higher mortality in COVID-19 AIS patients; p=0.02 (45).*

4.3.6. Univariable and multivariable logistic regression analysis

Regarding the full cohort, in univariable logistic regression analysis, significant associations were found between age and mortality (p=0.04, odds ratio=1.05, confidence interval=1.005 to 1.102), NIHSS and mortality (p=0.0007, odds ratio=1.17, confidence

interval=1.07 to 1.29), CRP and mortality (p=0.02, odds ratio=1.010, confidence interval=1.001 to 1.019), and COVID-19 infection and mortality (p=0.0339, odds ratio=3.409, confidence interval=1.122 to 11.18) (45). No significant associations were observed between mortality and diabetes mellitus (p=0.151, odds ratio=2.288, confidence interval=0.72 to 7.116), hypertension (p=0.72, odds ratio=0.792, confidence interval=0.233 to 3.168), hyperlipemia (p=0.236, odds ratio=0.441, confidence interval=0.0943 to 1.54), smoking (p=0.200, odds ratio=0.252, confidence interval=0.013 to 1.421), or other cardiovascular risk factors (p=0.527, odds ratio=1.435, confidence interval=0.476 to 4.639) (45). In multivariable logistic regression analysis, NIHSS was the only independent predictor of mortality (p=0.004, odds ratio=1.156, 95% confidence interval: 1.046 - 1.278), while age, CRP, and COVID-19 infection were not (45).

A sensitivity analysis restricted to patients with an NIHSS range of 5-15, generally considered moderate stroke severity, showed that hypertension remained significantly more common in non-COVID-19 AIS patients (45). There was a significant difference in CRP levels, which were higher in the COVID-19 group, but no significant difference in lymphocyte count. Regarding outcome measures, only hospitalization days were significantly longer in the COVID-19 AIS group. Discharge mRS and in-hospital mortality were numerically worse in the COVID-19 group, although not statistically significant (45). These results indicate that in patients with comparable stroke severity, COVID-19 infection is associated with longer hospitalization time and higher CRP levels, but not with increased mortality (45). Additionally, in both univariable and multivariable logistic regression analyses, NIHSS was the only independent predictor of mortality, while COVID-19 infection was not (45).

4.4. Extending the TW for both thrombolysis and thrombectomy

In the one-year study period, 777 confirmed ischaemic stroke patients were admitted to the ED within 24 h of symptom onset: 304 in the 0-4.5 h TW, an additional 82 in the 4.5-6h TW, in the 6-9h TW 149, and in the 9-24h TW 242 more patients were screened, *Figure 8.* (46). Of all patients, 252 (32.4%) had MRI during working hours (08-20h), while the others had CT-CTA.

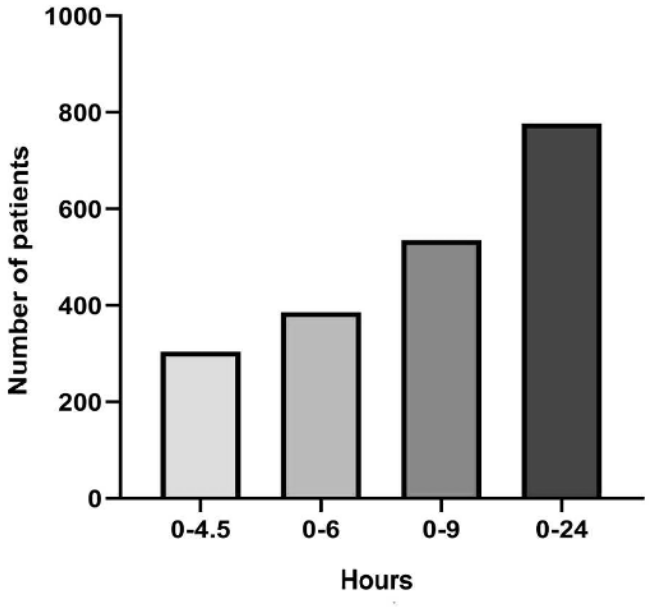

Figure 8. Number of patients presenting in the different TWs, screened with either CT or MRI

4.4.1. Comparing IVT in the standard and extended time window

Clinical data and IVT outcomes for treated patients are presented in *Table 7.* Age, sex, and NIHSS upon admission were similar between the standard and extended TW groups. A significantly higher proportion of patients received IVT in the standard TW (39.1%) compared to the extended TW (6.1%) (46). Overall, to find one treatment-eligible patient, 2 had to be screened in the early period (NNS=2), whereas 9 in the late period (46).

Median (IQR) mRS at 90 days in the IVT group was 3 (1-5) in the standard and 3 (1.75-6) in the extended TW group (p=0.16). Independent clinical outcome (mRS≤2) at 90 days was seen in 49/102 (48.03%) early and 4/14 (28.58%) late-treated patients (*Table 7.)* (46).

Table 7. All patients in IVT TW, in the indented section: clinical data of patients treated with IVT (0-9h) (46)

	Standard (0-4.5 h)	**Extended (4.5-9 h)**	**p (statistics)**
nr. of cases	304	231	-
age mean (SD) years	67.5 (± 14.1)	68.5 (±13.8)	0.28 (Mann-Whitney U)
male (%)	157 (51.6%)	127 (55%)	0.81 (Chi-square)
NIHSS (median, IQR)	5 (2-13)	5 (2-8.25)	0.85 (Mann-Whitney U)
IVT	**119 (39.1%)**	**14 (6.1%)**	**<0.001 (Chi-square)**
age (mean, SD)	68.04 (±11.9)	69.6 (±14.8)	0.66 (Unpaired t)
male (%)	66 (55.4%)	4 (28.6%)	0.08 (Fisher's exact)
NIHSS (median, IQR)	7 (4-13)	8 (4-15)	0.61 (Mann-Whitney U)
mRS 90 days (median, IQR)	3 (1-5)	3 (1.75-6)	0.16 (Mann-Whitney U)
mRS≤2 90 days nr/nr (%)	49/102 (48.03%)	4/14 (28.58%)	0.25 (Fisher's exact)
Mortality rate	25 (21%)	5 (35.71%)	0.21 (Chi-square)
Number needed to screen (NNS)	2	9	-

4.4.2. Comparing EVT in the standard and extended time window

There were no differences in sex, initial NIHSS, and LVO rates between patients in the standard and extended TW groups (*Table 8.*) (46). Patients in the late group were slightly older. IVT was administered before EVT to 27 patients in the early TW and 2 in the late TW. EVT was significantly more common among all patients screened in the standard TW (8.8% vs. 3.8%) (46). Additionally, a higher proportion of LVO patients underwent thrombectomy in the early TW compared to the late TW (38.2% vs. 18.2%). Anterior circulation LVOs were predominant in both TWs (71/89 vs. 61/82, p=0.40). The NNS was 10 in the early TW and 24 in the late TW (46).

Baseline clinical characteristics of treated patients were similar between the standard and extended TW groups. The recanalization rate (TICI ≥ 2b) was equally high in both early and late-treated patients (94% vs. 93%). EVT-related complication rates were not significantly different (4/34 vs. 5/15) (46). An independent clinical outcome (mRS≤2) at 90 days was observed in 38.4% of early-treated patients and 33.3% of late-treated patients (46).

Table 8. All patients in EVT TW, in the indented section: clinical data of patients treated with EVT (0-24h) (46)

		Standard (0-6 h)	Extended (6-24 h)	p (statistics)
number of cases		386	391	-
age mean (SD) years		**67.5 (±14)**	**69.8 (±13.8)**	**0.017 (Mann-Whitney U)**
male (%)		199 (51.6%)	203 (51.9%)	0.91 (Chi-square)
NIHSS (median, IQR)		5 (2-10)	4 (2-8)	0.92 (Mann-Whitney U)
LVO		89 (23.05%)	82 (20.9%)	0.48 (Chi-square)
EVT		**34 (8.8%)**	**15 (3.8%)**	**0.0044 (Chi-square)**
	age (mean, SD)	64.5 (±11.9)	65.3 (±16.4)	0.86 (unpaired t)
	male (%)	18 (52.6%)	8 (53.3%)	0.58 (Chi-square)
	NIHSS (median, IQR)	13 (8-15.25)	12 (8-15)	0.9 (unpaired t)
	LVO location anterior/total (%)	30/34 (88.2%)	11/15 (73.3%)	0.22 (Fisher's exact)
	TICI score ≥ 2b (%)	32/34 (94.1%)	14/15 (93.3%)	0.99 (Fisher's exact)
	complications	4/34 (11,8%)	5/15 (33,3%)	0.109 (Fisher's exact)
	mRS 90 days (median, IQR)	3 (1.75-6)	6 (2-6)	0.43 (Mann-Whitney U)
	mRS 90 days (mean, SD)	3.61 ±2.1	4.2 ±2.4	
	mRS 90 days ≤2 (%)	10/26 (38.4%)	4/12 (33.3%)	0.99 (Fisher's exact)
	Mortality rate (%)	9/34 (26.4%)	7/15 (46.66%)	0.07 (Chi-square)
EVT in LVO patients		**34/89 (38.2%)**	**15/82 (18.2%)**	**0.0009 (Chi-square)**
LVO location anterior/total (%)		71/89 (79.7%)	61/82 (74.4%)	0.40 (Chi-square)
NNS		10	24	-

4.4.3. Comparing treatment times

We compared treatment times (median, IQR) between imaging modalities within the same time window and between different TWs using the same imaging modality (MRI).

CT vs. MRI in IVT: In the standard TW, 119 IVT patients were divided into 38 (31.9%) who had MRI and 81 (68%) who had CT. The DNT was longer for MRI compared to CT: 69 (60-87.25) minutes vs. 60 (47-82) minutes (Mann-Whitney U test: p=0.0405) *Figure 9* (46).

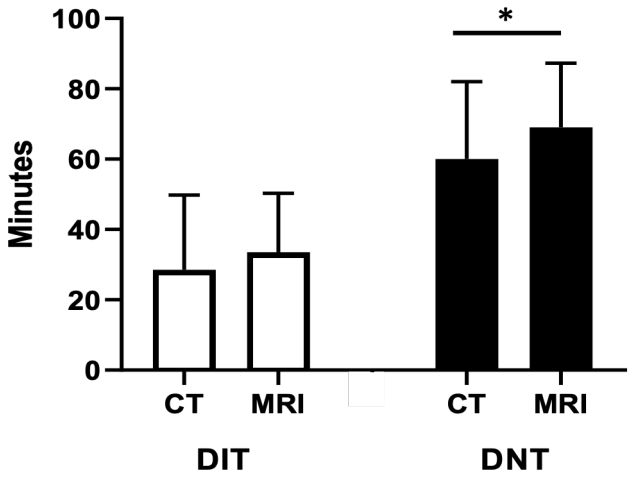

*Figure 9. Standard TW for IVT (0-4.5h) door-to-imaging (DIT) and door-to-needle time (DNT) CT vs MRI; * p=0.0405*

Standard vs. extended IVT with MRI: In the MRI thrombolysis group, 38 patients were treated in the standard TW and 13 in the extended TW. The DNT was significantly longer in the extended group: 111 (74-161.5) minutes vs. 69 (60-87.25) minutes (Mann-Whitney U test: p=0.002) *Figure 10* (46).

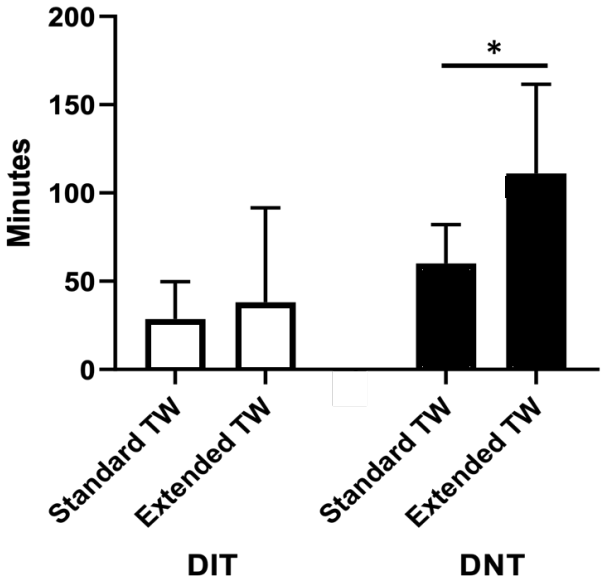

*Figure 10. Door-to-imaging (DIT) and door-to-needle time (DNT)in the IVT TWs with MRI; *p=0.002*

CT vs. MRI in EVT: Of the 34 thrombectomy patients in the standard TW, 13 (38.2%) had MRI and 21 (61.8%) had CT. The DGT was numerically longer for MRI patients compared to CT patients, though not statistically significant: 210 (185-303) minutes vs. 150 (115-220) minutes (Mann-Whitney U test: p=0.0566) *Figure 11* (46).

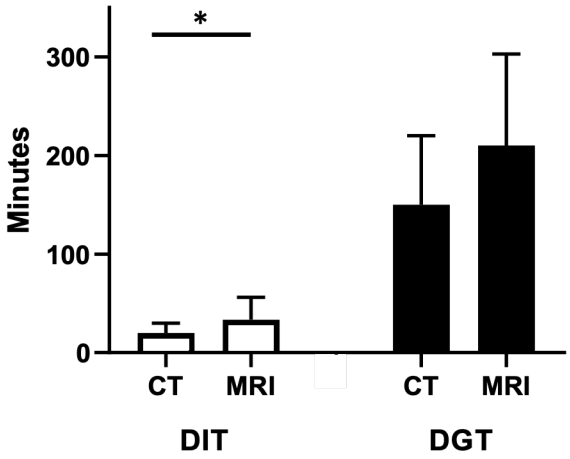

*Figure 11. Standard TW for EVT (0-6h) door-to-imaging (DIT) and door-to-groin time (DGT) CT vs MRI; *p=0.002*

Standard vs. extended EVT with MRI: The DGT using MRI was similar between the standard and extended TWs: 210 (185-303) minutes vs. 229 (161-241) minutes (unpaired t-test: p=0.99), *Figure 12* (46).

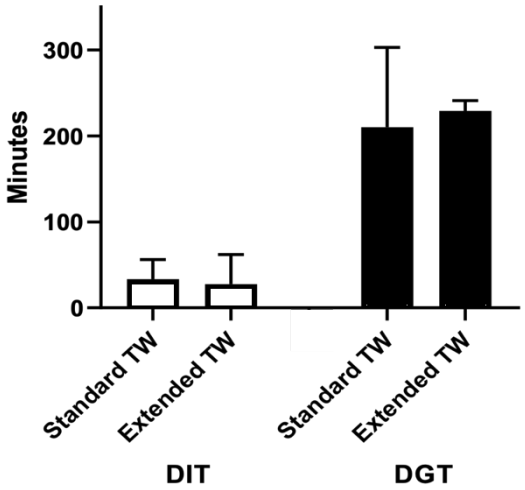

Figure 12. Door-to-imaging (DIT) and door-to-groin time (DGT) in the EVT TWs with MRI

4.4.4. Comparing door-to-imaging times

We compared door-to-imaging times (DIT, median (IQR)) between imaging modalities within the same TW and between different TWs using the same imaging modality (MRI) in treated patients, as well as in all screened patients regardless of whether they eventually received treatment (46).

CT vs. MRI in treated patients**:** In the standard TW for IVT-treated patients, DIT was numerically shorter for CT, though not statistically significant: 28.5 (20-49.75) minutes for CT vs. 33.5 (24.5-50.25) minutes for MRI (Mann-Whitney U test: p=0.28), *Figure 9*. For EVT-treated patients in the standard TW, DIT was significantly shorter with CT compared to MRI: 20 (15-30) minutes for CT vs. 33.50 (26.75-56.25) minutes for MRI (Mann-Whitney U test: p=0.002), *Figure 11* (46).

CT vs. MRI in all screened patients: Among all patients screened within 24 hours, there was no significant difference in DIT between CT and MRI: 73.50 (34-177) minutes for CT vs. 61.00 (38-125) minutes for MRI (Mann-Whitney U test: p=0.12). Among patients screened within 4.5 hours, DIT was also not significantly different between CT and MRI: 42 (24-102) minutes for CT vs. 50 (31-88) minutes for MRI (Mann-Whitney U test: p=0.39) (46).

Standard vs. extended time window in all MRI-screened patients: Among all patients screened with MRI, DIT differed significantly between early and late TWs: 50 (31-88) minutes for the 0-4.5 hour TW vs. 62.5 (37.5-142.8) minutes for the 4.5-9 hour TW (Mann-Whitney U test: p=0.039), *Figure 10.* Respectively, 51 (32.5-102.5) minutes for the 0-6 hour TW vs. 80.5 (42.5-160.8) minutes for the 6-24 hour TW (Mann-Whitney U test: p=0.0022), *Figure 12* (46).

5. Discussion

The adoption of AI-based decision support and extending the TWs have led to expanded eligibility and notable increases in treatment rates. However, these advancements also pose challenges, including the increased clinical and imaging burden and disparities in outcomes due to external factors, like the COVID-19 pandemic, that jeopardize not only patient outcomes but also the overall functioning of the healthcare system.

The findings from this research underscore the complexity and ever-evolving opportunities and challenges that have to be considered when delivering stroke care.

5.1. AIS care using AI-based decision support

Our study showed improved acute reperfusion therapy times and rates with the use of AI-based decision support software, Brainomix e-Stroke Suite. IVT rate showed significant growth compared to the previous year, and EVT rate showed a tendency to be higher although not significant because of the low number of patients (43). We also noticed a drop in imaging-to-groin times, this is in line with international data: a reduction in CT-to-groin time of 20-31 minutes (48, 49) - or, in a more recent study, even 60 minutes (50) with the implementation of AI.

A qualitative aspect of introducing the Brainomix e-Stroke Suite was the opportunity to directly access patient imaging from the EVT hub being part of another hospital since this was an unsolved problem before. Additionally, we found that subjective clinician confidence grew when assessing acute stroke CT imaging (43).

Further advancements in the AI-decision support in acute stroke care are on the way: a recent trend is the AI-based assessment of MRI images for DWI-PWI mismatch (51, 52), aiming to lower inter-rater variability of penumbra assessment and widen the number of eligible patients for IVT. Machine learning algorithms can estimate infarct growth and collateral flow on CT and CTA (53, 54), factors used to select candidates for EVT. Furthermore, AI aids visualization techniques, improving EVT planning, digital subtraction angiography image quality and cerebral aneurysm detection (55). Another

possible implication is AI-interpreted imaging in conjunction with clinical data, such as age, laboratory parameters, and NIHSS, to select patients for acute reperfusion therapies and to give prognostics on clinical outcomes (10, 51, 56, 57). There are multiple methods for estimating patient outcomes in the short term (for example, DWI infarct volume (58) and combined clinical and imaging (56, 57) data) and in the long term (59-62). Even though there are reporting guidelines (63) for medical imaging AI tool developers, reports introducing these usually do not fulfil all requirements (50, 64). Similarly, even if checklists (65, 66) are available for reporting results about AI implementations, no uniform outcome reporting protocol is used across trials for a fair comparison (67).

Despite the broadening usage of AI in acute stroke care and some published benefits such as helping patient selection for treatment, reducing treatment times, enhancing workflow efficiency, and improving patient outcomes, there are many uncertainties and limitations to its use. The black box phenomenon - a term used to illustrate the cryptic nature of the AI methods used - is an important consideration because the end user (stroke clinician) has limited information about what data was used to train the algorithm and how it was tested (64). Thus, clinician trust and confidence in the software varies on one's experience, and false positive results can decrease clinician confidence (68). A new advance is the usage of explainable AI that intends to offer a deeper understanding of the AI processes to provide more trustworthy output (69).

In recent years, there has been an increased number of publicly available data sets in neuroimaging to train AI tools (63), but they still lack diversity, accuracy, and reproducibility (70). Additionally, there are significant gaps in the ethical, legal, data security and cybersecurity frameworks at international, national, and local levels (71, 72), which limits its use.

Implementation of AI-decision-support tools in clinical practice can be a challenge depending on user demand and tool options. There is a trend toward individualized medicine with AI tools integrating various clinical data to aid decision-making. However, there is a fine line between the abundance of data and workflow efficiency (67) - finding the equilibrium between enough clinical data that is easy to input and usable AI prediction is key.

Since 2022, all stroke centres in Hungary have had access to the Brainomix e-Stroke Suite. In the first three months, there was a 20-minute reduction in the door-to-decision and secondary transport initiation times (73).

In this study, with no protocol or infrastructure change, just simply implementing the e-Stroke Suite on CT scanners and managing the administrative task of granting access to selected personnel, led to improved diagnostic and therapeutic outcomes and facilitated imaging transfer between centres (43).

In conclusion, our study demonstrated that the use of AI-decision support software, such as the e-Stroke Suite, significantly improved acute reperfusion therapy times and rates. While there are promising advancements in AI-based tools for stroke care, challenges remain. There is an urgent need for better ethical, legal, and cybersecurity frameworks and better compliance with reporting guidelines, to provide quality evidence for clinical practice. Despite some hurdles, the Hungarian nationwide stroke network shows the potential benefits of AI in improving patient outcomes and workflow efficiency in stroke care.

5.1.1. Limitations

The study was limited by its observational nature. Although the only change in service delivery was the introduction of the e-Stroke Suite, other factors like increased public awareness of stroke and ongoing quality improvements cannot be ruled out as contributors to better stroke care (43). The relatively low number of patients made our study underpowered for statistical significance in some aspects.

5.2. Experience on extending the thrombectomy TW

EVT revolutionized AIS care in 2015, with multiple trials showing positive outcomes for LVO patients up to 6 hours. The advancement of perfusion imaging techniques led to updated guidelines recommending EVT up to 24 hours from stroke onset based on individual pathophysiology and perfusion imaging in 2018-2019. We implemented the new guidelines in 2019 and examined clinical and imaging burden in light of functional outcomes. Since these guidelines were implemented relatively recently,

there are only a few comparable studies based on real-world data. In our study, 45.5% of stroke patients within 24 hours arrived beyond 6 hours (44), a higher number than in other trials (74, 75).

In our cohort, age and initial NIHSS were lower compared to another single-centre study not using perfusion imaging in late patients (75). NIHSS in the standard TW was higher in both studies (75). Favorable functional outcome was found in 30-40% of both standard and extended TW groups (44), equivalent to other studies (75-77).

In the 0–6 hour time window, the rate of LVO was lower compared to another centre (34.5%) (75) but higher than estimated from a retrospective cohort (10.5%) (78).

In the 6–24 hour time window, our study found a similar rate of LVO (22.1%) but a lower rate of EVT (4%) (44) compared to a retrospective analysis (19.6% and 9.2%, respectively) using similar DAWN and DEFUSE 3 criteria (79). In this retrospective analysis, data for non-trial patients was lacking, resulting in a potential selection bias towards LVO patients.

The EVT rate in the extended TW in our study (44) was similar to the eligibility estimates reported by Lee et al. (3.6%) (74). The EVT rate in our patients was significantly lower in the extended TW (4%) compared to the standard time window (12.6%) (44). This difference is due to both a lower rate of LVO (22.1% vs. 34.5%) and a lower rate of EVT in LVO strokes (18.2% vs. 36.6%) (44). Several factors contribute to the reduced LVO rate: (1) a lower utilization of non-invasive angiography (63.8% vs. 92.2%), as patients with mild strokes (NIHSS<6) were not candidates for CTA, potentially overlooking LVOs presenting with mild symptoms; (2) a stricter definition of treatment-eligible LVO (only ICA, M1, and BA); and (3) more severe strokes with higher NIHSS and higher probability of LVO prompting earlier (median 5 vs. 6, $p = 0.011$) ED presentation (44). The lower EVT rate in LVO strokes is due to stricter imaging eligibility criteria beyond 6 hours: higher ASPECTS, smaller core, and demonstration of significant penumbra - that rapidly decreases with time (44). Likewise, milder strokes in the extended TW group resulted in good functional outcomes of about 50% (44), comparable to the DAWN and DEFUSE 3 results (26, 27).

Overall, in our study, the extension of TW for EVT resulted in a larger burden of screening to identify EVT-eligible patients (NNS 25 vs NNS 11 (79) in a retrospective analysis). The extension of the TW led to a smaller increase in treated patients (26.7%)

(44) compared to the 33.3% increase in theoretically EVT-eligible patients from a retrospective single-centre registry analysis (80). We found that the main burden of the extended TW lies in the clinical and imaging screening of patients (ambulance, ED, neurologists, and radiologists) rather than their treatment, due to the smaller proportion of EVT-eligible patients compared to the standard time window. However, a more than 25% increase in EVT rate is clinically important, and screening for late thrombectomy up to 24 hours was shown to be both clinically highly efficacious (26, 27, 81) and cost-effective (82).

5.2.1. Limitations

The primary limitation of our study is its single-centre design and the small number of treated patients, which prevents us from drawing firm conclusions on outcomes. Additionally, the unique design of our study limits the ability to make comparisons with existing literature.

5.3. The impact of COVID-19 infection on AIS outcome

The COVID-19 pandemic unexpectedly hit healthcare systems, and the exact nature and extent of the burden that was going to come was unknown. There was excess strain on medical resources and personnel, trying to cope with the pandemic and usual care at the same time. AIS care suffered a great deal globally. The World Stroke Organization reported severe personnel reorganizing and bed reallocation needs from Neurology and an about 40% drop in the peak COVID-19 period in AIS hospitalizations (83, 84). *Nogueira et al.* reported an 11.5% decrease globally in acute stroke hospitalizations and a 13.3% drop in IVT rates (33). This affected mostly mild and moderate strokes (85). Although EVT rates also declined, they remained relatively stable or even increased compared to overall stroke admissions (33, 86). Similarly, in Hungary, there was a decline in stroke admissions, particularly during the first and second waves. However, the number of reperfusion therapies remained relatively steady, partly due to health emergency measures and changes in patients' social behaviors (87).

In our study, COVID-19 AIS patients had higher initial NIHSS scores and a tendency to have LVOs more frequently, indicating higher stroke severity (45) corresponding to other studies (88-91). More severe neurological deficit was more alarming, thus likely prompting more patients to arrive within the therapeutic time windows (92).

We have seen a higher percentage of acute reperfusion therapies of about one-third in the COVID-19 AIS group (45) compared to both our control group and the COVID-19 AIS group in other large studies (IVT: 18.75% vs. 19.7% *Ntagios et al.,* 4.8% *Mathew et al.,* 13.6% *Shahjouei et al.* and EVT 11.8% vs. 12.1% *Ntaios et al.,* 3.2% *Mathew et al.*, 7.4% *Shahjouei et al*.) (91, 93, 94). One possible explanation is that during the second and third COVID-19 waves (from the end of October 2020 to May 2021), our hospital focused solely on COVID-19 care. As a result, only a few AIS patients, usually thrombolysis candidates, were brought to the centre by mistake (45). The relatively high EVT rate of 12% vs the pre-COVID era 8%, compared to the slightly lower-than-usual IVT rate of 14% vs pre-COVID 26% (95), might be due to stay-at-home measures and fear of hospitalization during the pandemic or in-hospital isolation, causing delays in symptom recognition (45). Additionally, the strict IVT time window of 4.5 hours often passed without the benefit of multimodal perfusion imaging data - which was unavailable in COVID-19 care - leading to IVT being contraindicated, so EVT was more often a feasible treatment option. The lower EVT/LVO ratio in the COVID-19 AIS group can be explained by the worse overall clinical state and prognosis of COVID-19 patients together with the unavailability of EVT on-site, which meant that patients eligible for EVT were selected strictly (45).

It is well documented in systematic reviews and meta-analyses, that more severe COVID-19 infection is linked to more severe strokes (33, 34). A novelty in this regard shown in our study is that patients with COVID-19 pneumonia visible on chest CT or X-ray more often had LVOs (45).

Our data aligns with the consensus in the literature, which suggests that there is no clear correlation between specific risk factors and COVID-19-related stroke. Instead, all risk factors are linked to cardiovascular vulnerability, increasing the chance of both ischaemic stroke and COVID-19 infection, as well as ischaemic stroke as a complication

of COVID-19 (41, 96). The risk factor profile in our study was similar to other studies, with the exception that hypertension was significantly more common in the control group. This can be explained by the high prevalence of hypertension across the nation (97) and distribution of TOAST categories as stroke etiologies in our study, which is consistent with international findings: COVID-19 patients had a higher rate of large vessel disease, a similar percentage of cardioembolism, and a notably lower rate of small vessel disease (91, 94, 98-100).

The most general observation in COVID-19-related stroke, both in our paper and other studies, is the overall worse clinical outcome. COVID-19-related AIS is associated with longer hospitalization time, lower mRS, higher mortality and more frequent discharge to places other than home (41, 93, 94, 101, 102). Our results align with these findings: we observed a two-fold increase in hospitalization duration due to the patients' worse clinical conditions and confinement regulations (45). Additionally, about two-thirds of COVID-19 AIS patients had dependent functional outcomes, and the in-hospital mortality rate was approximately 30%, similar to other studies (34, 41, 91, 93, 98, 99, 103-106). During hospitalization, more COVID-19 AIS patients required ICU transfers than the control group. However, our data indicate a significantly lower transfer rate compared to other cohort studies (41, 93, 107). This discrepancy may be because the majority of patients admitted to our hospital had medium COVID-19 severity (50%). More severe and critical cases were usually directed to Internal Medicine, Pulmonology COVID-19 wards, or ICU. The higher mortality rate in our control group compared to previous data from our hospital (11.8% vs. 7.5% (108)) can be attributed to stay-at-home regulations, fear of the pandemic, and the fact that primarily patients with severe neurological symptoms sought medical help, often too late for acute reperfusion therapy (95).

In some studies, COVID-19 was found to be an independent predictor of AIS (109) and worse outcome (110, 111). However, in our study, logistic regression analysis showed that in univariate testing, the presence of COVID-19 infection is a strong predictor of in-hospital mortality (odds ratio=3.409) but not independent of age, NIHSS, and CRP.

In conclusion, the elderly, with more cerebrovascular risk factors, are susceptible to both COVID-19 infection and AIS alone, as well as to the reciprocal effect of COVID-19 and AIS.

The COVID-19 pandemic tested the resilience of stroke centres, requiring infection control, containment, and deployment measures to keep patients and healthcare providers safe, while still delivering state-of-the-art stroke care. Application of personal protective equipment, strict sterilization requirements, COVID-19 testing before patient transfers on interventions, together with additional safety measures, delayed stroke care (112). A solution option by a site was implementing AI for stroke image analysis to cope with the obstructions caused by the pandemic (113). The number of stroke admissions and IVTs decreased, but EVT rates remained relatively stable (33). This suggests that limited resource availability, fear of hospitalization, containment regulations, and changes in social behaviour collectively shifted the focus to treating severe strokes. The pandemic also brought innovations, such as the expansion of telemedicine, which is a suitable option for clinically mild cases, and the use of wearable Internet of Things (IoT) healthcare devices, which have improved the management of chronic illnesses. The lessons from the COVID-19 pandemic can help in the management of other epidemics or other sudden healthcare emergencies.

5.3.1. Limitations

The most important limitation of this study is the single-centre and retrospective nature of the study. Therefore, we could only assess laboratory tests and other available patient data, and discharge mRS was determined based on medical documentation, not patient interviews (45).

Another important shortcoming is the low number of patients, which led to lower statistical power.

5.4. Extending the TW for both thrombolysis and thrombectomy

A meta-analysis of three randomized controlled trials demonstrated that in patients selected by advanced imaging, initiating IVT between 4.5 and 9 hours after stroke onset improved functional outcomes compared to a placebo (114).
In this study, we immediately implemented the 2021 ESO guideline recommending extended TW IVT and EVT, using MRI as advanced imaging. We found a 101% increase in the number of screened patients within 24 hours of symptom onset for potential reperfusion therapy eligibility compared to the standard TWs.

5.4.1. IVT

Extending the TW from 4.5 to 9 hours resulted in a 75.9% increase in screening burden for potential IVT candidates compared to the standard TW. Additionally, there was an 11.7% increase in the number of actual IVTs performed when combining the standard and extended TWs compared to the standard TW alone (46). The overall IVT rate in the entire cohort was 17.1%, which is comparable to previous data from our center (11.5% in 2017, 18.1% in 2018) (43), but lower than in the pre-COVID era (26% in 2019) (95).

Using MRI as the first-choice imaging instead of CT significantly increased the DNT in the standard treatment window (median 69 vs. 60 minutes). DIT was also longer for MRI in the standard TW, though not significantly. The longer DNT for MRI compared to CT in both TWs is due to extended transportation and interpretation times.
In the late TW DNT was significantly longer compared to the standard TW with MRI (DNT 111 vs 69 minutes), and also DIT was significantly longer in the late IVT IT in all MRI-screened patients (DIT 62.5 vs 50 minutes) compared to early patients; on one hand because of the longer imaging protocol and time-consuming core-penumbra assessment, and on the other hand because of the lower sense of urgency in late patients (46).

Demographic and stroke characteristics were similar in both TWs. Outcome measures were similar, pointing to a slight but non-significant benefit of higher functional independence rate in the standard TW, in accord with the 'time is brain' concept.

There was a 5-fold increase in NNS in the extended TW, which emphasizes the clinical burden of finding a treatable patient. Still, functional outcome at 90 days was

similar in the standard and extended TW group, and independent functional outcome in 48% in early vs 28% in late patients, underscoring the efficacy of extended TW IVT (115, 116).

A promising trend in IVT is administering 0.25 mg/kg tenecteplase beyond the standard TW and in wake-up strokes recognized within 4.5 hours. Randomized clinical trials (117-121) are encouraging, but there is no guideline evidence for its use and the global shortage of tenecteplase limits its use.

5.4.2. EVT

By extending the time window from 6 to 24 hours, we screened twice as many patients. This resulted in a marked increase in potentially treatable LVO patients, and a 44% rise in actual EVTs performed (46). NNS was 2.5 times higher in the extended TW, still a lot lower than the extended TW IVT. The EVT rate across TWs was 6.3%, an increase to 2017-2018 data (2.7% and 4.8%) (43), but a decrease from the pre-COVID era (8% in 2019) (95).

DGT was similar with CT and MRI in the standard TW. Also, DGT was similar in standard and extended TW with MRI. Contrary, DIT was significantly longer with MRI compared to CT in the early TW (33.5 vs 20 minutes) (46). This suggests that severe neurologic deficit is alarming and more straightforward, and CT does provide a significantly faster imaging solution with the relevant data to determine treatment eligibility. The lack of significant difference in DGT between imaging modalities is due to the dilution of the time benefit of CT by the much longer secondary transport time in the drip-and-ship model.

DIT was significantly shorter in early than late TW among all patients screened with MRI (51 vs 80.5 minutes), probably due to a higher sense of urgency in early patients (46).

While EVT rates were similar in the extended TW (3.8% in 2019 vs 4% in 2021), it was lower in the standard TW in our recent trial (12% in 2019 vs 8% in 2021) (43). EVT in LVO was 34.5% in the standard and 22.1% in the extended TW in 2019, and EVT/LVO rate was 36.6% and 18.3%, respectively (43, 46). In 2021, LVO rates were 23.05% in early and 20.9% in late TW, and EVT/LVO rates corresponded with the data from 2019: 38.2% and 18.2%. So, the number of EVTs in LVOs remained steady, while

there was a reduction in LVOs found. This might be explained by the awareness of ambulatory services taking severe strokes to a primary thrombectomy centre, however, no clear regulations were available at the time.

Outcomes seem to have deteriorated since the previous trial where CTA was used before MRI to determine LVO, and MRI was used to assess the penumbra, thus eligibility for EVT (90 days mRS 4 and 2.5 in 2019, mRS 3 and 6 in 2021) (44), but there was a more strict selection criteria for treatment. A favourable functional outcome was achieved by 30-40% in both TWs (46), comparable to other studies (122-125).

Taking into consideration the new, large ischaemic core EVT trials (126-128) and their meta-analysis (129), EVT can be offered up to 24 hours based on CT and CTA with good outcomes. These studies also point out that current guideline-based selection criteria for EVT may be too restrictive (130-132). Offering advanced imaging is still an important option in late IVT patients without severe symptoms indicative of LVO, diagnostic uncertainties and stroke mimics. However, IVT is still recommended before EVT, and extended IVT eligibility depends on advanced imaging. Overall, CT and CTA seem to be enough, more accessible, and cost-effective for straightforward, severe stroke patients, especially aided by AI-decision support software (43, 133).

Working closely with neurointerventionalists, we have already implemented the CT and CTA-based approach in severe strokes.

Our study once again underscores the importance of staying updated with new guidelines, implementing them in practice, and evaluating evidence at a local level. This medical controlling system can help identify shortcomings in our stroke pathway and implement corrective measures. In this rapidly evolving era of stroke care, new trials can quickly influence practice. Therefore, regularly updating local guidelines and pathways is important.

5.4.3. Limitations

The limited availability of MRI (during working hours 08-20 hours) meant that 231 patients within 4.5-9 hours since stroke onset were not considered for IVT due to the lack of perfusion imaging (46).

A few patients were lost to follow-up (with only their vital status available), primarily in the standard time window groups. This is unlikely to affect our favorable results for late-treated patients. The complex patient pathways in the Budapest region explain this: patients from outside our catchment area who are acutely brought to our center due to geographical proximity might be later managed by another healthcare provider.

The single-centre design of this study limits its generalizability; however, it is noteworthy that this was the first centre in Hungary to implement extended time window reperfusion therapies and routinely utilize MRI in hyperacute stroke care (46).

Our study was conducted according to current AHA/ASA and ESO guidelines, yet in the era of the rapid evolution of stroke care and considering the recent large core EVT trials, our results might seem outdated.

5.5. Combined discussion of all studies

Each study highlights different aspects of stroke management, including the implementation of AI-based decision support, the extension of therapeutic TWs, and the impact of the COVID-19 pandemic.

The average number of confirmed AIS patients screened monthly was 57 in the AI study, 39.7 in the extended TW EVT study and 64.75 in the extended TW IVT and EVT study. It is of note that the first study was retrospective, while the latter two were prospective. Across all studies, basic demographic characteristics were similar, with an average age of around 67-71 years, with a slightly higher proportion of males in most groups.

We found that CT and CTA to be more effective in severe strokes, especially when combined with AI support. MRI, although useful for diagnostic uncertainties and stroke mimics, prolonged treatment times, so its usage is recommended in late IVT candidates without severe symptoms suggesting LVO and ambiguous cases.

Stroke severity was highest in treated EVT patient groups (median NIHSS 15 in the standard TW of the extended TW EVT study (44), 13 in the standard and 12 in the extended TW in the last study (46)), followed by the COVID-AIS group with median NIHSS of 9, which was significantly more severe than the control group (median NIHSS

4) (45). Treatment times were the shortest in the first study (mean DNT 42-44 minutes, mean CT-to-groin time 140-170 minutes) (43), where the imaging selection was the least complicated, meaning that all stroke patients started with CT (and CTA if applicable), MRI was only a second imaging if eligible. Also, at that time, the ED was less crowded, with about 30 patients per 12-hour shift (134), making patient pathways faster and easier. The longest treatment times were in the COVID-19 AIS study, mostly in the COVID-19 AIS group (DNT 83 vs 54 minutes) (45). This can be attributed to the strain on the healthcare system caused by the pandemic, including the need for protective equipment, sanitization protocols, and confinement regulations in place at the time, which had a greater impact on patients infected with SARS-CoV-2 compared to the control group.

The gradual increase in treatment times over the years is visible in the last study, with DNT (median 60-69 in the standard TW with CT and MRI, 69-111 with MRI in the standard and extended TW group) and DGT (median 150-210 minutes in the standard TW CT and MRI, median 210-229 minutes with MRI in standard and extended TW) (46). This can be explained by the ever-growing workload of the ED, up to about 100 patients per shift (134), and the relative unavailability of personnel, together with the infrastructure (the need for elevator use for MRI), resulting in increased DIT times for MRI. Additionally, across all studies, there is a noticeable increase in treatment times in the extended TWs, suggesting that beyond the longer imaging processing times, the sense of urgency diminishes as more time elapses since symptom onset.

It is important to consider, that this work focuses only on the workload of confirmed AIS patients in relation to treated ones, but not on the number of all patients screened for possible stroke, which multiplies the clinical and imaging burden.

With higher life expectancy and an ageing society (135), the number of stroke patients will continue to increase (136). Approximately one in seven ischaemic stroke survivors will experience a second stroke after one year (135). This means an increased workload for an already overwhelmed workforce, as the Organization for Economic Cooperation and Development (OECD) report notes a 1.2 million shortage of doctors, nurses and midwives as of 2022 (135). Consequently, organizing stroke pathways requires considerations grounded in real-world data rather than solely relying on trial evidence, while also accounting for local infrastructure and available resources.

6. Conclusions

Keeping up with novel research and implementing new guidelines in everyday practices with the same infrastructure and resources is a constant challenge. While aiming for better patient outcomes, the extra workload and burden of finding eligible patients cannot be disregarded. Our research provides real-world data on multiple landmark changes in stroke care during recent years.

Our first study presented a positive real-world impact of AI-decision support implementation in stroke care, resulting in a significantly higher IVT rate and a trend toward more EVTs and better outcomes. It also filled a gap in logistics, aiding image transfer between our primary stroke centre and the EVT hub.

The second study showed that the expansion of EVT TW with patient selection aided by advanced imaging following CT and CTA resulted in a 25% increase in EVTs performed. This number was lower than the excess burden of screened patients (83.6% compared to the standard TW), with only 22% presenting with LVO-s and only 4% eligible for the intervention. We found better, yet statistically not significant outcome results in the standard TW compared to extended TW, showing the merit of the 'time is brain' concept. Yet, there is an outcome benefit for a reasonable number of patients treated in the extended EVT group.

COVID-19 impacted healthcare systems, and AIS care was no exception. While AIS hospitalizations decreased globally, IVT rates showed a milder drop, and EVT rates were relatively steady (87) in Hungary, similar to other countries (93). Treatment times also suffered significant delays, taking a toll on patients. Yet, the most robust results are the overall worse clinical outcome of COVID-19-infected AIS patients. As shown by our study results, which are in line with international data: stroke severity is higher, hospitalization is longer, functional outcome is worse, and mortality is higher in AIS patients. We found that clinical prognosis seems to further deteriorate with the severity of the COVID-19 infection, while COVID-19 pneumonia showed an association with more LVOs. This underscores the need for a multidisciplinary team to manage these patients with multiple cardiovascular risk factors, as they are vulnerable to both COVID-19 and AIS.

Our last study focused on extending the TWs for both IVT and EVT. We screened 102% more AIS patients within 24 hours during our 12-month study period. IVT rates increased by 11.7%, while there was a 44% rise in EVTs performed. Advanced imaging (MRI) proved to be useful in screening extended IVT candidates, wake-up strokes, stroke mimics and diagnostic difficulties, but in severe strokes CT and CTA seem enough to judge EVT eligibility, especially if IVT is contraindicated.
Further guideline changes are on the horizon considering the success of the recent large ischaemic core clinical trials offering EVT up to 24 hours based on CT and CTA, allowing a large infarct size.

Our four studies demonstrate that early implementation of new guidelines and the impact of emerging technologies on stroke management can help re-evaluate the stroke pathway and clinical workflow. Extended TWs can increase the number of patients eligible for acute reperfusion therapies, which until now are the only medical treatment options to alleviate stroke symptoms. With the ageing population and recurrent strokes, despite the best efforts in secondary prevention strategies, there is an expanding burden of clinical and imaging screening. The organization of stroke care must consider these factors to plan pathways and resources effectively, ensuring optimal care within a resilient system capable of implementing adaptive strategies during future pandemics or healthcare emergencies.

7. Summary

Stroke is a leading cause of mortality and disability worldwide, contributing significantly to the global burden of disease. The economic impact of stroke in the EU is substantial, with high costs related to healthcare, social services, and lost productivity.

Despite advancements in acute stroke therapies, only a small percentage of AIS patients receive IVT or EVT, which are the most effective treatments, only available in the acute phase. The extension of therapeutic TWs broadens eligibility but comes with an increased clinical and imaging screening burden.

Advanced neuroimaging and AI-based decision-support tools help patient selection for these treatments. However, the COVID-19 pandemic has posed additional challenges, highlighting the need for adaptive strategies to maintain effective stroke care.

This research aims to provide insights into the effects of AI-based tools, the impact of COVID-19, and the clinical workload of extended reperfusion therapy time windows, ultimately aiming to improve stroke care and patient outcomes through a multidisciplinary approach.

Our data demonstrated that AI-based decision support can streamline AIS care by facilitating faster decision-making and increasing treatment rates. Extending the EVT time window resulted in a 25% increase in EVT rates and an 83.6% increase in the number of patients screened. The COVID-19 pandemic impacted stroke care, resulting in more severe strokes, longer hospitalization, worse functional outcome and higher mortality rates in the COVID-19 AIS group. Extending both IVT and EVT TWs, using MRI as advanced imaging increased the number of screened patients by 102%. We experienced an 11.7% rise in IVT and a 44% increase in EVT rates, while functional outcomes at 90 days were comparable in the early and late TWs.

Our work highlights the need to stay up-to-date with evolving guidelines and implement them efficiently in clinical practice while continuously evaluating its results at the local level. It is important to assess not only patient outcomes but also the workload and burden associated with it to plan stroke care accordingly. In this era of rapidly advancing stroke care, new trials and research can swiftly impact clinical practices, making it essential to regularly update local guidelines and patient pathways to ensure optimal stroke care.

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9. Bibliography of the candidate's publications

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9.2. Other publication

Gyongyosi, B., Magyar-Stang, R., Takacs, T., Szekely, E., Illes, Z., Nilsson, C., Gyorke, T., Barsi, P., Juhasz, D., Banky, B., Bereczki, D., Honnorat, J., Gunda, B. (2023). Paraneoplastic Kelch-like protein 11 antibody-associated cerebellar and limbic encephalitis caused by metastatic "burned-out" seminoma - A scar(r)y phenomenon. Journal of neuroimmunology, 378, 578073. https://doi.org/10.1016/j.jneuroim.2023.578073

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