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TESI DI LAUREA

'THE ROLE OF WHITE MATTER DISCONNECTION IN STROKE AS A PREDICTOR OF CLINICAL OUTCOME AFTER MECHANICAL THROMBECTOMY'

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ABSTRACT

Rationale: Mechanical thrombectomy is a promising approach to acute treatment in large vessel occlusion (LVO) ischemic stroke. This technique has shown to be safe and effective when performed both in early and late-window trials. Several clinical and mainly volumetric, radiological features are used as prognostic factors for functional outcome and patient eligibility.

However, emerging evidence (1–5) supports the idea that lesion topography is strongly associated with prognosis and functional brain recovery.

The aim of this study is to examine the role of clinical (i.e. mRS and NIHSS) vs. standard volume-based lesion (i.e. ASPECTS, core, penumbra and final lesion volume) vs. topological radiological (i.e. white matter structural disconnection) features, in patients eligible for acute mechanical thrombectomy.

Materials and methods: We selected a group of patients (n=50) who underwent acute mechanical thrombectomy over 47 months, from January 2018 to November 2021, and occurred at the Stroke Unit and Clinica Neurologica of the Hospital of Padova. They were studied with the modified Rankin Scale (mRS) and the National Institutes of Health Stroke Scale (NIHSS) both at admission (pre) and at discharge (post), then, again with the mRS at 90 days from the acute event. The lesions were manually segmented on structural MRI and CT scans using the program ITK-SNAP. Four models were performed through a linear regression analysis. Specifically, we computed a baseline clinical model (M1) based on demographics, pre-stroke mRS and admission NIHSS. Then we added commonly used (standard) radiological parameters of lesion or perfusion damage (core, penumbra, ASPECTS) (M2). Therefore, we added information about the white matter structural disconnection to clinical variables (M3). Finally, we tested a baseline clinical +early recovery model (M4), which included age, pre-mRS, admission NIHSS, and post-mRS.

The lesions were normalized in atlas space and displayed to study their distribution and structural disconnections (SDC).

Results: The mean baseline mRS was 0.48±0.90, while the mean 90-day mRS was 2.18±1.81. The linear regression analysis showed a significant positive correlation

between 90-day mRS and clinical variables (pre-mRS, NIHSS at presentation, post-mRS), while radiological variables (ASPECTS, core, and penumbra volume) did not seem to be associated with functional outcome. The results of the ANOVA analysis showed that, between the four models tested, M4 (including age, pre-mRS, NIHSS at presentation, and post-mRS as independent variables) was the one providing the highest adjusted R-squared [Adj.R-squared=0.614] and explained 62% of the variance in outcome prediction. At a voxel-wise level, we found a significant positive correlation between brain recovery (Delta 90-day mRS-pre-mRS) and damage, affecting predominantly the left corticospinal tract and the corresponding structural white matter disconnection (SDC), which also extended to the cingulum and, bilaterally, to the callosal commissure.

Conclusion: In our sample, acute clinical status represents the most valuable prognostic factor. Interestingly, while radiological (i.e. volumetric and semi-quantitative) features, such as ASPECTS, core, and penumbra volume, did not show any significant correlation with 90-day mRS, structural white matter disconnection and lesion topography, in particular of the left corticospinal tract, were associated with a poorer recovery after endovascular treatment. These results could have important future implications in pre-treatment patients' selection and in post-treatment post stroke rehabilitation.

RIASSUNTO

Razionale: La trombectomia meccanica è un nuovo promettente approccio al trattamento acuto dell'ictus ischemico, associato all'occlusione di uno grosso vaso. Questa tecnica ha dimostrato di essere sicura ed efficace, sia nei trial in finestra precoce che tardiva.

Attualmente vengono utilizzati diversi fattori clinici e radiologici, principalmente volumetrici, per selezionare i pazienti idonei al trattamento e per predire la loro prognosi funzionale.

Tuttavia, le emergenti evidenze (1-5) supportano l'idea che la topografia della lesione abbia una forte associazione con il recupero funzionale cerebrale.

Lo scopo di questo studio è quello di indagare il ruolo delle caratteristiche della lesione ischemica, sia cliniche (mRS ed NIHSS), che volumetriche (ASPECTS, volume di core, penombra e lesione finale) che topologiche (disconnessione strutturale della sostanza bianca) valutate come possibili fattori prognostici, in pazienti elegibili per la trombectomia.

Materiali e metodi: Abbiamo selezionato un gruppo di pazienti (n=50) sottoposti a trombectomia meccanica acuta nell'arco di 47 mesi, da gennaio 2018 a novembre 2021, presso la Stroke Unit e Clinica Neurologica dell'Ospedale di Padova.

Sono stati studiati attraverso la Rankin Scale modificata (mRS) e la National Institutes of Health Stroke Scale (NIHSS) sia al momento del ricovero che alla dimissione e, successivamente, ricontrollati 90 giorni dopo l'evento acuto, tramite mRS. Le lesioni sono state segmentate manualmente su scansioni di RM strutturale e TC utilizzando il programma ITK-SNAP. Sono stati elaborati quattro modelli, attraverso un'analisi di regressione lineare.

In particolare, abbiamo testato un modello basato sulla presentazione clinica di partenza del paziente (M1) che comprendeva età, pre-mRS ed NIHSS all'ammissione. Successivamente, abbiamo aggiunto parametri radiologici, comunemente usati in pratica clinica (ASPECTS, volume di core e penombra), in un secondo modello (M2). In un terzo ulteriore modello (M3) abbiamo aggiunto, alle variabili cliniche, l'informazione riguardante la disconnessione strutturale della

sostanza bianca. Infine, abbiamo testato un modello (M4) che comprendeva età, pre-mRS, NIHSS all'ammissione e post-mRS, valutando anche il recupero precoce. Le lesioni sono state normalizzate nello spazio dell'atlante e visualizzate per studiarne le mappe di distribuzione e disconnessione strutturale (SDC).

Risultati: Il valore medio di partenza di mRS dei pazienti era 0,48±0,90, mentre il valore di mRS medio a 90 giorni era 2,18±1,81.

L'analisi di regressione lineare ha mostrato una correlazione positiva significativa tra il valore di mRS a 90 giorni e le variabili cliniche (pre-mRS, NIHSS alla presentazione, post-mRS), mentre le variabili radiologiche (ASPECTS, volume del core e della penombra) non sembravano essere associate al recupero funzionale del paziente. I risultati dell'analisi ANOVA hanno mostrato che, tra i quattro modelli testati, M4 (che includeva età, pre-mRS, NIHSS alla presentazione e post-mRS come variabili indipendenti) era quello che forniva l'R-quadrato aggiustato più alto [R-quadrato aggiustato=0,614] e spiegava il 62% della varianza nella predizione della prognosi.

A livello di voxel, abbiamo trovato una significativa correlazione positiva tra il recupero cerebrale (Delta mRS a 90 giorni-pre-mRS) ed il danno, che colpiva prevalentemente il tratto corticospinale sinistro e le corrispondenti disconnessioni strutturali della sostanza bianca (SDC), che si estendevano anche al cingolo e, bilateralmente, al corpo calloso.

Conclusione: Nel nostro campione, la presentazione clinica in acuto del paziente rappresenta il fattore prognostico più impattante.

È interessante notare che, mentre le variabili radiologiche (volumetriche e semi-quantitative), come ASPECTS, volume del core e della penombra, non mostravano correlazione significativa con il valore di mRS a 90 giorni, la disconnessione strutturale della sostanza bianca e la topografia della lesione, in particolare a livello del tratto corticospinale sinistro, erano associate ad un più scarso recupero, dopo il trattamento endovascolare.

Questi risultati potrebbero avere importanti implicazioni future, sia nella selezione dei pazienti prima del trattamento che nella riabilitazione dell'ictus post-trattamento.

INTRODUCTION

""Deficit", we have said, is neurology's favourite word–its only word, indeed, for any disturbance of function".

Oliver Sacks

Stroke is a cerebrovascular pathology that has been studied since the epoque of Hippocrates. It is extremely frequent and debilitating, especially in elderly people. Numerous efforts have been made to understand causes and consequences of brain injuries with the goal to identify a treatment that can guarantee good functional recovery.

While traditionally, the relationship between behavioral deficits and locus of injury was studied by anatomical-clinical correlation post-mortem, since the 1970's it has been possible to carry out this correlation in the living brain through computerized tomography (CT) and magnetic resonance imaging (MRI). This has led to the notion of vascular syndromes, i.e., the association between specific behavioral syndrome and the blood vessel involved by the stroke.

In the last 20 years it has been possible through the development of functional and diffusion imaging (functional MRI, fMRI; diffusion weighted imaging, DWI), it has been possible to also study the functional effects of lesion on brain function and white matter structure. These advances have changed our perspective from one in which behavior strictly depend on the function of the damaged brain region/s to one in which even small lesions have widespread effects on brain function through the structural or functional disconnection of brain networks.

On the therapeutic side, major advances have occurred in the last 20 years on the treatment of stroke with the advent of thrombolysis, first, and more recently mechanical thrombectomy. However, the conceptual framework for these interventions is still the idea that post-stroke behavioral deficits depend on the locus of injury, and the adjacent region of hypo-perfusion, so called penumbra, while little attention has been given to the more distributed effects of focal injuries.

In this thesis we explore the relative weight of clinical variables, such as the initial degree of neurological dysfunction or the early recovery, vs. local radiological variables (lesion volume and relative hypoperfusion) vs. distributed (whole brain) white matter alterations in the prediction of long-term clinical outcome.

This thesis is organized into different chapters that describe the background of our study and lead to the explanation of the procedures and results of our experiment.
In the first chapter, I will describe stroke, a complex clinical entity. We concentrate on its acute treatment, specifically, mechanical thrombectomy, which has shown to be safe and effective, providing good functional outcomes. I will review different prognostic factors, fundamental to operate a better selection of patients.
In the second chapter, I will focus on the emerging evidence that focal lesions cause structural and functional disconnection alterations that predict behavioural deficits and stroke recovery.
In the final chapter, I will describe in detail the procedures, materials, results, discussion, and conclusion of our experiment. The principal endpoint of this thesis is to evaluate the predictive power of measures of structural disconnection after mechanical thrombectomy in comparison with other strong prognostic clinical and radiological features, currently used in clinical practice.

PART I. WHAT IS STROKE?

A JOURNEY INTO THE PAST: STROKE IN HISTORY

The history of stroke can be divided into two periods: from the early era to the beginnings of the 19th century and the following period up to the present. Both periods are characterized by different methodical approaches and interpretations(6). Hippocrates in 400 BC was the first to write about medical aspects and the prognosis of stroke. He used the term “apoplexy”, describing a condition characterized by a “sudden abolition of all activities of the mind with the preservation of pulse and respiration”. He also noticed that there were many blood vessels connected to the brain, and he observed that the interruption of the two main large blood vessels could cause loss of consciousness. He named these arteries “carotids”, from the Greek word “κάρος”, which means “deep sleep”(7).

Hippocrates, according to his humoral theory, believed that the interference with blood flow, which is one of the four humours, alongside yellow bile, black bile, and phlegm, would result in apoplexy(8).

His hypothesis was supported, a few hundred years later, by Galen who also believed that the causes of apoplexy were related to humoral aberrations. He described the anatomy of the brain and its blood vessels from dissections of animals, characterizing the “rete mirabile”, a complex of arteries and veins lying very close to each other(9) (Fig.1).

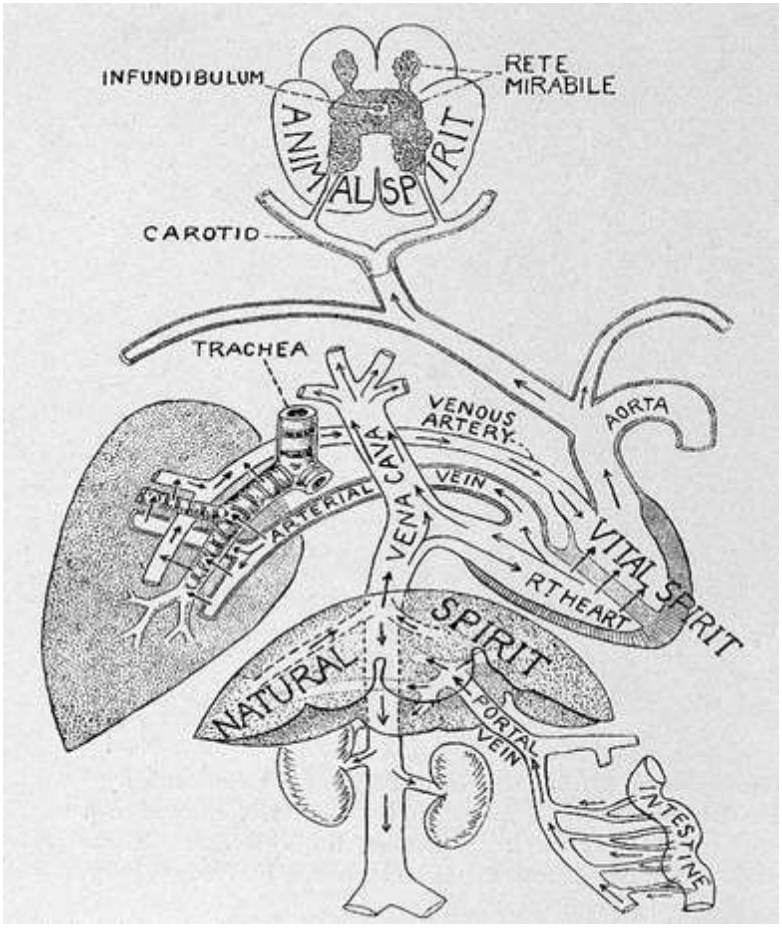

Figure 1

Diagram illustrating Galen's physiological scheme.

Andreas Vesalius (1514-1564), during the 16th century, who was professor of anatomy in Padova, through painstaking anatomical studies, wrote a volume entitled "De Humani Corpis Fabrica", which contained fifteen very detailed diagrams of the brain's neuroanatomy(10) (Fig.2).

In the middle of the 17th century, Johann Jakob Wepfer (1620-1695), who also studied in Padova, examined the brains of patients dying of apoplexy and demonstrated that obstruction of the carotid and vertebral arteries and also brain hemorrhages were important causes of this pathology(8).

In the 18th century, G.B.Morgagni (1682-1771), the founder of anatomical pathology in Padova, shifting attention from anatomy to pathology and clinical presentations, in his work "De Sedibus et Causis Morborum per Anatomen Indagatis", also described cases of intracerebral hemorrhage and noticed that people affected had paralysis on the opposite side of the body. He divided the causes of apoplexy into two principal groups: "sanguineous" and "serous". The

"sanguineous" form was represented by intracranial hemorrhage and the "serous" one was characterized by the presence of normal cerebrospinal fluid. After these observations, apoplexy was considered, predominantly, a vascular disease(11).
This idea was stressed by the discoveries of John Abercrombie, in the early 19th century, and Rudolf Virchow, in the early 20th century. They reclassified the causes of apoplexy as *sanguinea* (hemorrhagic) and *ischaemica*(8).

It was only in the mid-twentieth century when Miller Fisher emphasized the frequent presentations of warnings before the stroke, which he called "transient ischemic attacks". These manifestations were described as "*prodromal fleeting attacks of paralysis, numbness, tingling, speechlessness, unilateral blindness, or dizziness*" that often preceded strokes in patients with carotid artery disease(8).

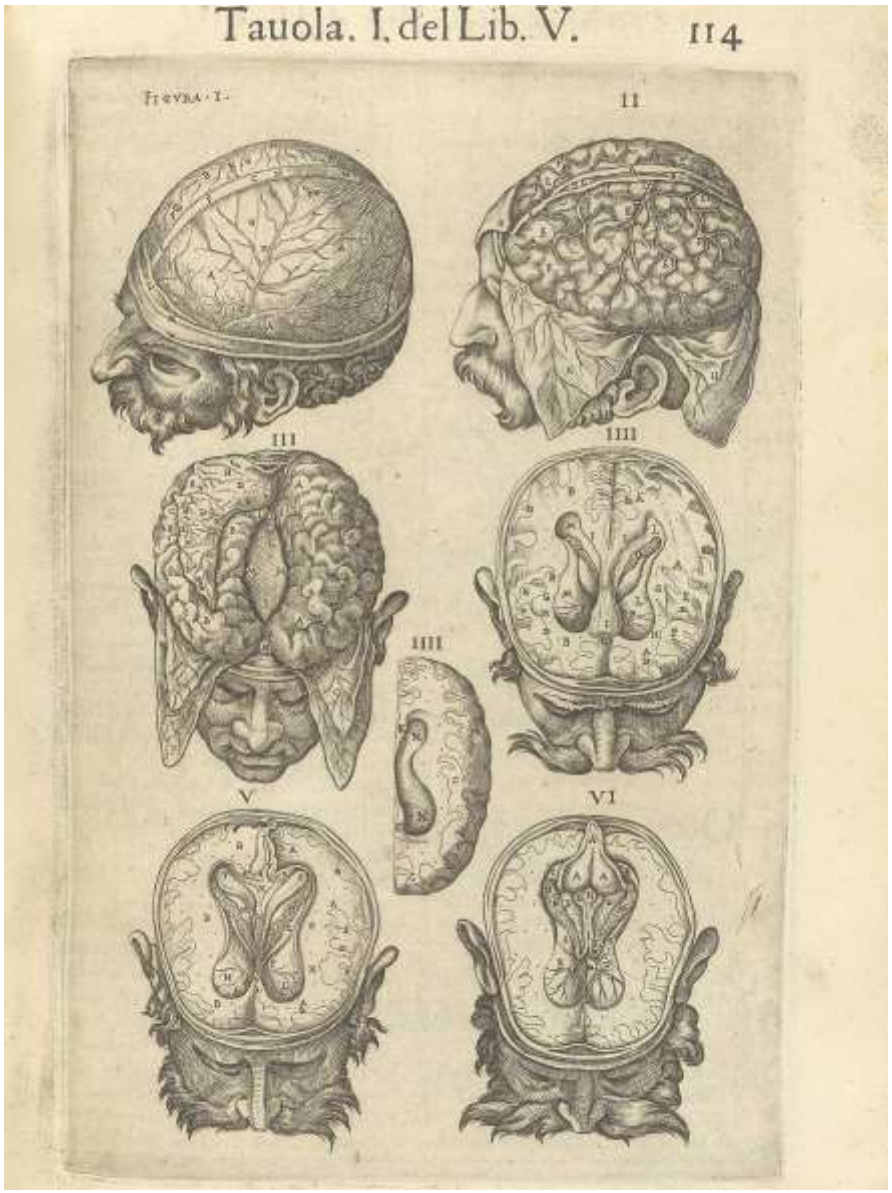

Figure 2

Neuroanatomical illustrations by Andreas Vesalius (1534).

CURRENT DEFINITIONS OF STROKE AND TIA

The International Classification of Diseases (ICD-11), updated in February 2022, divides cerebrovascular diseases into two main categories(12):

- **Intracranial hemorrhage:**
  - Intracerebral hemorrhage;
  - Subarachnoid hemorrhage;
  - Nontraumatic subdural hemorrhage;
  - Nontraumatic epidural hemorrhage.
- **Cerebral ischemia:**
  - Transient ischemic attack;
  - Cerebral ischemic stroke.

In 1970, the World Health Organization defined stroke as "*rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin*"(13). This definition is still in use, but it has been updated by the American Heart Association and American Stroke Association in 2013. The new definition includes silent infarctions (inclusive of cerebral, spinal, and retinal) and silent hemorrhages, to move toward a radiological demonstration of hemorrhage and stroke, even without clinical manifestations(14).

In 1975, the transient ischaemic attack was defined by WHO as "*a sudden, focal neurologic deficit that lasts for less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery*"(13).

In 2002, Easton et al. proposed a new definition of transient ischaemic attack, because the arbitrary period of 24 hours was considered inappropriate and 50% of people affected showed tissue damage. They defined TIA as "*a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction*"(15).

Subsequently, the Stroke Council of the American Heart Association/American Stroke Association removed the "time factor" and in 2009 published the current definition of transient ischaemic attack: "*a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction*"(14).

ISCHEMIC STROKE CLASSIFICATION

A well-structured stroke classification system allows a good selection of patients for epidemiological studies, therapeutic decisions, and outcome predictions. While hemorrhagic strokes could be easily classified, physicians and investigators concentrated their efforts to find two major approaches for ischemic stroke classification: the causative and phenotypic subtyping. Here we present the progressive evolution of ischemic stroke classification during the past decades(16) (Tab. I).

1. Thirty years ago, the first database used for stroke subclassification was the Harvard Cooperative Stroke Registry. Only 3% of patients reported in this database had CT scans, because it was a new imaging technique, still not diffuse. Consequently, the diagnosis was based on clinical information;
2. In 1983, the Oxfordshire Community Stroke Project (OCSP) provided a new clinical classification. It combined clinical features with CT scan findings. This classification has been used in clinical practice for a long time, but it had some limitations, for example, it addressed the outcome but not the causes of stroke;
3. In the 1980s, a group of neurologists at the University of Iowa College of Medicine conducted the Trial of Org 10172 in Acute Stroke Treatment (TOAST), to improve ischemic stroke classification. The TOAST classification was divided into five subtypes of ischemic stroke: 1) large-artery atherosclerosis (LAA); 2) cardioembolism (CE); 3) small-vessel occlusion (SAO); 4) stroke of other determined cause (SOC) and 5) stroke of undetermined cause (SUC). SUC was further subclassified into (1) no cause found or (2) two or more plausible causes found. Despite the TOAST system using more objective criteria for stroke classification, it revealed important limitations; especially in the SUC category, where almost 40% of all strokes with potential multiple etiologies were allocated(17);
4. To take into account new neuroimaging technologies, such as diffusion-weighted magnetic resonance imaging (DWI-MRI) and magnetic resonance angiography (MRA), in 2003, the CCS project was launched. A new classification system was published in 2007, based on TOAST, divided into five major categories, as shown in the table below. This classification aimed to overcome the major limitations of the TOAST system. To resize the

"unclassified" category, they integrated results of diffusion-weighted MRI, CT angiography, magnetic resonance angiography, echocardiography, and Holter monitoring.

The updated CCS system provided both causative and phenotypic stroke subtypes(16);

5. The A-S-C-O-D (Atherosclerosis, Small-vessel disease, Cardiac source, Other cause, Dissection) phenotypic classification was introduced in 2009. This system was aimed to identify the most likely etiology, always considering potential multiple causes. The classification provided three degrees of causality for each category, determined by specific diagnostic tests(18);
6. Moreover, in 2011 the Chinese Ischemic Stroke Subclassification (CISS) system was introduced. It classified stroke into five etiological categories based on TOAST, but the SAO subtype was renominated "penetrating artery disease" (PAD). In conclusion, the CISS classification system was based on both etiological and pathophysiological causes(16).

Currently, the most widely accepted is the TOAST classification, which is still in use in international clinical practice to evaluate the etiology of ischemic stroke, despite its limitations(17).

Characteristics of major etiologic classification systems for ischemic stroke

Publication year	TOAST 1993	CCS 2007	A-S-C-O 2009	CISS 2011
Type of system	Causative	Causative and phenotypic	Phenotypic	Causative
Major subtypes	1. Large artery 2. Cardioembolism 3. Small vessel occlusion 4. Other determined etiology 5. Undetermined etiology	1. Supra-aortic large artery atherosclerosis 2. Cardio-aortic embolism 3. Small artery occlusion 4. Other causes 5. Undetermined causes	1. Atherosclerosis 2. Cardioembolism 3. Small vessel disease 4. Other causes	1. Large artery atherosclerosis 2. Cardiogenic stroke 3. Penetrating artery disease 4. Other etiologies 5. Undetermined etiology
Advantages	Worldwide useSimple, logic and easy to useValidation by independent groupsPredicting prognosis and risk of stroke recurrence	Rules and criteria based on published EvidenceUpdated criteria to stratify cardioembolism into high- and low-risk groupsWeb-based automated version availableReducing the ratio of "undetermined" category	Integration of diagnostic evaluation into the level of confidence for subtype assignmentsClarified diagnostic criteria to identify or rule out a stroke etiologyIntegration of noncausative factors into subtype assignments	Incorporation of the etiology and underlying mechanism into stroke subclassificationCreating a new subtype of PADLarge artery atherosclerosis further subclassified into four categories
Disadvantages	Only moderate inter-rater reliabilityOversized "undetermined" etiologyNot fit to recent advances in diagnostic technology	Depending on the availability of modern diagnostic technologyBased on evidence from diverse studiesAortic arch atherosclerosis belonging to cardio-aortic embolism	Further reliability and validity data needsInterpretation cautiously with the combination of causative and noncausative factorsDepending on the completeness of diagnostic toolsToo many phenotypic subtypes (n = 625) for research studiesToo restrictive definition to diagnose atherosclerosis and small vessel disease	Lacking reliability and validity dataDepends on the availability of brain and vascular imagingFuture imaging technology needed to verify the concept of PAD

Table I- Major etiologic classification systems for ischemic stroke from Chen et al. "Classifying Ischemic Stroke, from TOAST to CISS", 2012.

CEREBROVASCULAR ANATOMY AND PATHOGENESIS

Ischemic stroke is characterized by a deficiency of oxygen and blood supply to the brain due to atherothrombosis of large arteries, cardioembolism, occlusion of small vessels, or other minor causes (according to the TOAST classification mentioned above). To understand the clinical manifestations of stroke, it's important to remind neurovascular anatomy and physiology.

The anterior circulation represents a territory belonging to the carotid arteries and supplies 4/5 of the brain parenchyma(19). The two common carotid arteries, originating from the aortic arch, branch into external and internal carotids. The internal carotid enters the skull and penetrates the cavernous sinus with an S-shaped course. Just outside the cavernous sinus, the ophthalmic artery originates from it and, subsequently, also the other four terminal branches: anterior cerebral artery (ACA), middle cerebral artery (MCA), anterior choroidal, and posterior communicating artery.

The posterior circulation, on the other hand, vascularises 1/5 of the brain parenchyma and is represented by the vertebrobasilar system.

The vertebral arteries (VA) originate from the subclavian arteries, pass through the foramen magnum and join to form the basilar artery at the bulb-pontine level. The posterior-inferior cerebellar arteries (PICA) are collaterals of the intracranial tract of the vertebral arteries.

Finally, the basilar artery runs along the midline, bilaterally forms the two superior cerebellar (SCA) and anteroinferior cerebellar (AICA) arteries, and then bifurcates into the two posterior cerebral arteries (PCA)(20).

The circle of Willis consists of the two ACAs, the anterior communicating artery, the two posterior communicating arteries, and the two PCAs.

The brain receives 20% of cardiac output and its cerebral blood flow typically amounts to 50ml/100g/min. When the flow falls below 20 ml/100 g/min, EEG changes appear, while neuronal death develops below 10 ml/100 g/min(21).

Cerebral blood flow can self-regulate, remaining constant for an average arterial pressure between 60 and 150 mmHg. Self-regulation is due to the variation of

PaCO2, myogenic factors that mediate vasoconstriction or vasodilation, and nervous modulation of vascular tone(22).

When the normal oxygen supply is lacking, the oxygen extraction fraction (OEF) increases, i.e., the brain extracts from the blood supply a higher than normal % of oxygen. Further decreases in blood flow lead to a failure to maintain membrane ion gradients and also an increased release of excitatory amino acids, which causes neurotoxicity.

Early activation of the AMPA receptor determines an accumulation of intracellular water and sodium with cytotoxic edema. While NMDA receptor activation, through an increased free calcium gradient, results in the release of lipases, nucleases, proteases, and free radicals(23).

Recent studies show that oligodendrocytes, due to their large size and low levels of antioxidants, are extremely susceptible to oxidative stress, causing damage to the myelinated bundles and functional disconnections in regions far from the ischemic area(19). Furthermore, increasing evidence suggests that microglial activation has a double function in ischemic stroke: it can promote neural degeneration but also neurogenesis and synaptic recovery(24).

Moreover, numerous studies have demonstrated that ischemia activates mechanisms of programmed cell death, favoring Bcl2, caspases, and HSPs gene expression (23). (Fig.3)

The central part of the ischemic area is called "core" and is composed of non-recoverable necrotic tissue. Around the lesion, however, it is possible to highlight a region called "ischemic penumbra", potentially reversible by re-establishing an adequate blood flow as soon as possible (Time is Brain)(19,25).

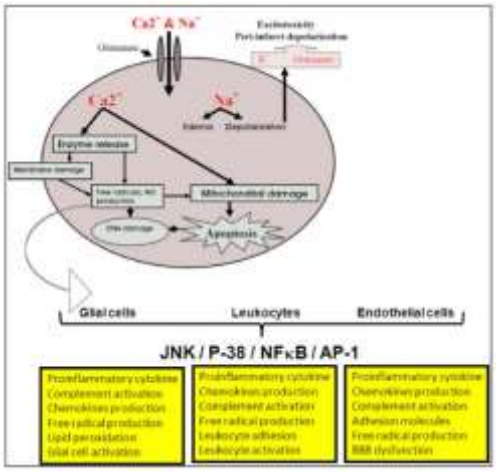

Figure 3

Cellular pathophysiology of ischemic stroke, from Woodruff et al.(2011)(23).

EARLY CLINICAL FRAMEWORK OF ACUTE STROKE

Stroke represents a medical emergency, and it is essential to treat it in the correct therapeutic window to obtain a good outcome, preventing neurological and other clinical complications.

The famous article by JL. Saver, "Time is Brain", quantified the loss of 1.9 million neurons, 14 billion synapses, and 12 kilometers of myelinated fibers for every minute of cerebral ischemia(25). However, there is interindividual variability in the speed of development of tissue damage and in the severity of the clinical manifestations, which is associated with the activation of collateral vessels. This explains, together with the self-regulation of arteriolar vasodilation, the increase in CBF (cerebral blood flow) in response to ischemia(19).

According to ideal management, in hyperacute situations, the patient is admitted to a stroke unit, where he is assisted by medical and paramedical personnel, who is highly specialized in cerebrovascular pathologies(26).

The VIII edition of Italian SPREAD guidelines(27) determines the main goals of early stroke management:

> Define time from symptom onset with an approximation of about 30 minutes, or, in case of an unknown onset/wake-up stroke, evaluate the LKW parameter, e.g. last time the patient was seen in well-being;
> Confirm the vascular nature and the pathogenetic subtype of the focal neurological deficit;
> Evaluate severity and possible spontaneous evolution in worsening or improvement;
> Define the involved arterial territory (anterior or posterior circulation);
> Start treatment acutely to prevent potential medical or neurological complications.

After stabilizing the patient on a hemodynamic level and evaluating his vital parameters, it is necessary to proceed with a targeted anamnesis and clinical examination(26,28).

Neurological examination is usually accompanied by the evaluation of NIHSS (National Institutes of Health Stroke Scale), which is used to determine the current severity of the stroke and its prognosis. This scale (Tab. II) is made up of 15 items

and each one is assigned a score from 0 up to 4, for a maximum of 42 points and a minimum of 0 (patient without deficits, with normal functions)(29,30).

It is also useful to evaluate mRS (modified Rankin Scale), which measures the level of disability or dependence in daily activities before and after a stroke. It represents one of the most important scales in follow-up to predict clinical outcomes. The lower degree (0) is full health, while the higher one (6) indicates the patient's death (Tab.III). Furthermore, after three months from the acute event, a mRS degree of 0-2 correlates with a good prognosis and functional recovery(31).

Category	Score/Description		Date/Time Initials	Date/Time Initials	Date/Time Initials	Date/Time Initials	Date/Time Initials
1a. **Level of Consciousness** (Alert, drowsy, etc.)	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma						
1b. **LOC Questions** (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect						
1c. **LOC Commands** (Open/close eyes, make fist/let go)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect						
2. **Best Gaze** (Eyes open - patient follows examiner's finger or face)	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation						
3. **Visual Fields** (Introduce visual stimulus/threat to pt's visual field quadrants)	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)						
4. **Facial Paresis** (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete						
5a. **Motor Arm - Left** 5b. **Motor Arm - Right** (Elevate arm to 90º if patient is sitting, 45º if supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left					
		Right					
6a. **Motor Leg - Left** 6b. **Motor Leg - Right** (Elevate leg 30º with patient supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left					
		Right					
7. **Limb Ataxia** (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs						
8. **Sensory** (Pin prick to face, arm, trunk, and leg - compare side to side)	0 = Normal 1 = Partial loss 2 = Severe loss						
9. **Best Language** (Name item, describe a picture and read sentences)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute						
10. **Dysarthria** (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near to unintelligable or worse X = Intubated or other physical barrier						
11. **Extinction and Inattention** (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	0 = No neglect 1 = Partial neglect 2 = Complete neglect						
	TOTAL SCORE						

Table II- National Institutes of Health Stroke Scale.

Modified Rankin Scale	
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Table III- modified Rankin Scale.

IMAGING TECHNIQUES

Stroke imaging techniques are numerous and allow obtaining both a rapid primary disease evaluation, useful in the acute phase, and a more accurate characterization of etiology and occlusion site, also monitoring the evolution of parenchymal damage(28).

Three categories of instrumental investigations can be described:

- PARENCHYMA MEASURES (CT and MRI);
- VASCULAR MEASURES (CT and MR angiography, supra-aortic trunks (SAT), and Transcranial (TC) Echo-color-Doppler);
- PERFUSION MEASURES (Perfusion CT and MR, PET and SPECT).

PARENCHYMA MEASURES

CT (Computed Tomography)

This method, without contrast agents, allows making a quick differential diagnosis between ischemic and hemorrhagic stroke. The hemorrhagic infarction appears immediately visible as a hyperdense lesion. In this case, also ventricular compression and midline shift may occur. Subsequently, the hemorrhagic lesion undergoes gradual reabsorption, until a markedly hypodense spot appears(19).

On the contrary, the ischemic lesion is not always visible at the onset but becomes more and more evident as a hypodense area in the following 24 hours(8).

In addition, this examination allows observing early signs of ischemia(19) (in the first hours), including:

> Loss of differentiation between white and grey matter at the insular ribbon level;
> Flattening of the hemispheric sulci;
> Sign of hyperdense middle cerebral artery, due to embolic occlusion;
> Early hypodensity with poorly defined contours, affecting basal ganglia or cortical/subcortical lobar structures.

During the first week after stroke, CT imaging shows edema and hypodensity of the affected area. In the subacute phase, from 1 to 3 weeks, the so-called “fogging phenomenon” can occur: cortex regains near-normal density, and imaging at this time can lead to confusion. This event is caused by the migration of macrophages

and leukocytes into the infarcted tissue, edema reduction, and angiogenesis. Fogging has been demonstrated in around 50% of cases(32).

Finally, beyond 3 weeks, in the chronic phase, a clear focal hypodensity is observed with consensual sulci and ventricles dilatation(19).

Using CT, it is also possible to calculate “The Alberta stroke program early CT score” (ASPECTS). It is used for middle cerebral artery stroke patients and is based on a 10-point topographic score. It has also been adjusted for the posterior circulation. For each region affected, 1 point is deducted from the initial score of 10, evaluating two levels (corona radiata and basal ganglia levels). The analyzed areas are caudate, lentiform nucleus, internal capsule, insular cortex, M1 (anterior MCA cortex), M2 (MCA cortex lateral to insular ribbon), M3 (posterior MCA cortex), M4 (anterior MCA territory, superior to M1), M5 (lateral MCA territory, superior to M2), M6 (posterior MCA territory, superior to M3)(Fig.4) (33).

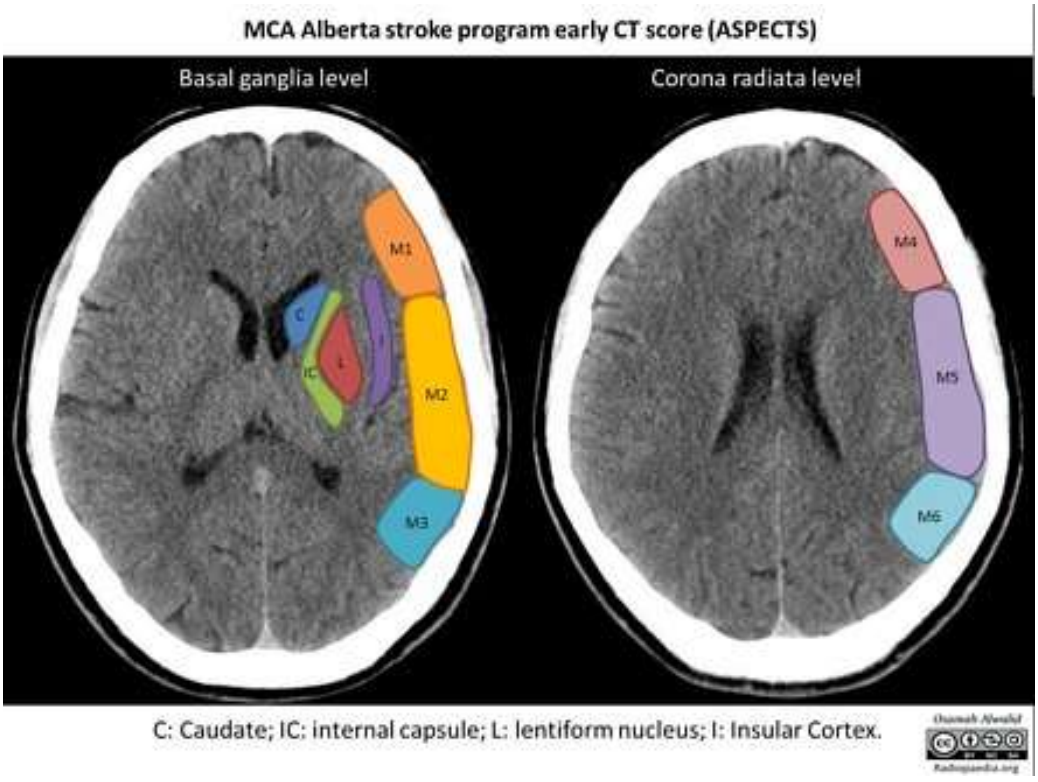

Figure 4

MCA vascular territories evaluated in ASPECT score. C: Caudate; IC: Internal capsule; L: Lentiform nucleus; I: Insular cortex; M1: Anterior MCA cortex; M2: MCA cortex lateral to the insular ribbon; M3: Posterior MCA cortex; M4: Anterior MCA superior territory; M5: Lateral MCA superior territory; M6: Posterior MCA superior territory.

ASPECT score less than or equal to 7 is a poor outcome predictor, at 3 months from onset(34,35). This scoring system has also been adapted for posterior circulation, called pc-ASPECTS. It is always a 10-point scale, in which for each region affected there is a loss of one point. The areas evaluated are thalami, occipital lobes, midbrain, pons, and cerebellar hemispheres(36).

MR (Magnetic Resonance)

The principal MR sequences adopted in acute stroke are represented by FLAIR, DWI, and ADC.

> FLAIR (Fluid Attenuated Inversion Recovery) is a T2-weighted sequence with suppression of the cerebrospinal fluid signal. This sequence allows a significant increase in the sensitivity and specificity of the MR method(28);

> DWI (Diffusion-Weighted Imaging) and ADC (Apparent Diffusion Coefficient) sequences are based on measuring the random Brownian motion of water molecules within a voxel of tissue. Ischemic tissues with cellular swelling exhibit lower diffusion coefficients. Therefore, the ischemic area is hyperintense in DWI and hypointense in ADC(28).

The **PRE-FLAIR study**, published in Lancet Neurology in 2011, has shown that a mismatch between DWI (positive) and FLAIR (negative) can estimate, with a 62% sensitivity, the time from onset of the stroke, which is around the previous 4-5 hours(37) (Fig.5). This result represents the starting point of the subsequent **WAKE-UP trial**, conducted by the same study group, which evaluates the execution of thrombolysis in the aforementioned time window, ensuring a better outcome in patients(38).

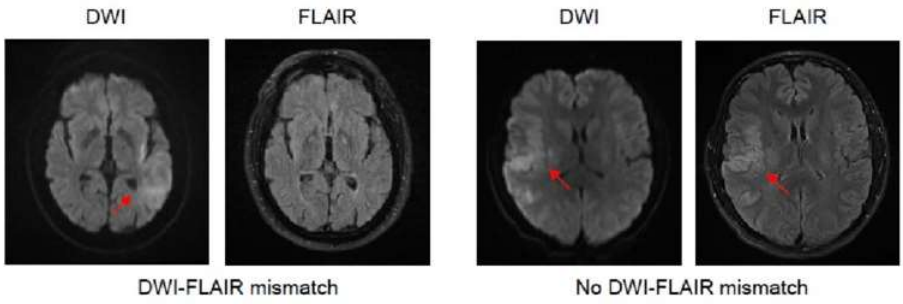

Figure 5

DWI-FLAIR mismatch for the identification of patients with acute ischemic stroke within 4,5 h from symptom onset (PRE-FLAIR study), from Thomalla et al.

DWI: Diffusion-Weighted Imaging; FLAIR: Fluid-Attenuated Inversion Recovery.

VASCULAR MEASURES

CTA (Computed Tomography Angiography)

This method provides good morphological details, uses contrast agents, and studies supra-aortic trunks up to the aortic arch.

MRA (Magnetic Resonance Angiography)

This exam uses the Time of Flight (TOF) technique to visualize flow within vessels, without the need to administer contrast. Moreover, Black-Blood and Fat-Sat sequences study vessels' walls by suppressing blood or fat signals respectively(39). In conclusion, while CTA has greater sensitivity in identifying stenosis/occlusions of cerebral vessels, MRA provides more accurate etiopathogenetic information(28).

Supra-aortic Trunks (SAT) and Transcranial echo-Doppler

These imaging techniques allow a fast, economical, repeatable, or continuous vascular study, even bedside. They evaluate intra and extracranial vessels of small or large dimensions(19).

The vascular anatomic study is possible using the B-mode technique, while a hemodynamic analysis can be performed, using Color and Power Doppler.

This examination allows visualizing the morphological characteristics of the vessels and the presence of atherosclerotic plaques(40) (Fig.6).

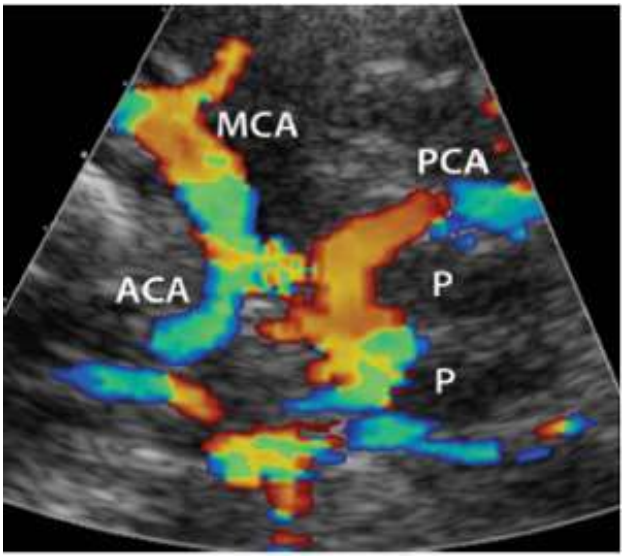

Figure 6

Transcranial echo-Doppler evaluating the Circle of Willis. ACA: Anterior cerebral artery; PCA: Posterior cerebral artery; MCA: Middle cerebral artery; P:Posterior communicating artery.

PERFUSION MEASURES

Perfusion study allows a physiological evaluation of the brain during ischemia.
When cerebral blood flow (normally between 100 and 60 mL/100g/min) falls below 60 mL/100g/min, an asymptomatic and reversible zone of oligemia develops.
The ischemic penumbra, on the other hand, is characterized by a CBF of 22-10 mL/ 100 g/min. At this level, compensatory mechanisms for the reduction of blood flow are arteriolar vasodilation and increased oxygen extraction. This area suffers, but still doesn't have irreversible damage and it can regain vitality after early reperfusion(41).
In conclusion, the infarct core is characterized by a CBF <10 mL/100 g/min (Fig.7). It has a high risk of bleeding and reperfusion is therefore contraindicated, because of irreversible damage(42,43).

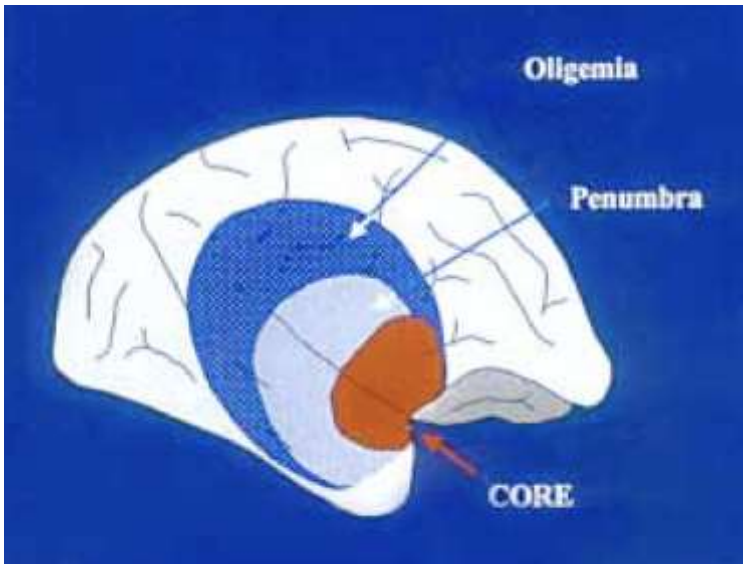

Figure 7

Representation of the three main suffering areas after an ischemic stroke: oligemia, penumbra, and core.

PET (Positron Emission Tomography)

This test is based on radioisotopes that decay by emitting a positron. It represents the gold standard technique for perfusion study and allows the distinction of the three zones of core, penumbra, and oligemia(44).

SPECT (Single Photon Emission Computed Tomography)

This imaging method is based on radioisotopes emitting a single photon, mainly Technetium-99. Compared to PET, it has a lower cost and provides similar information(45).

CT Perfusion

This technique identifies the penumbra and core areas, by injecting a bolus of contrast agents. The dynamic study generally acquires images every second for the first 30-45 seconds and every 2-3 seconds for the next 30-45 seconds(43).

From the time-density curve, CT perfusion maps are obtained, which include different parameters, such as cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT), which corresponds to the average time that red blood cells spend in capillary circulation and Tmax, which reflects the time delay of the contrast bolus arriving in large vessels (Fig.8).

These parameters are related to each other according to the central volume principle: **CBF = CBV / MTT**(46).

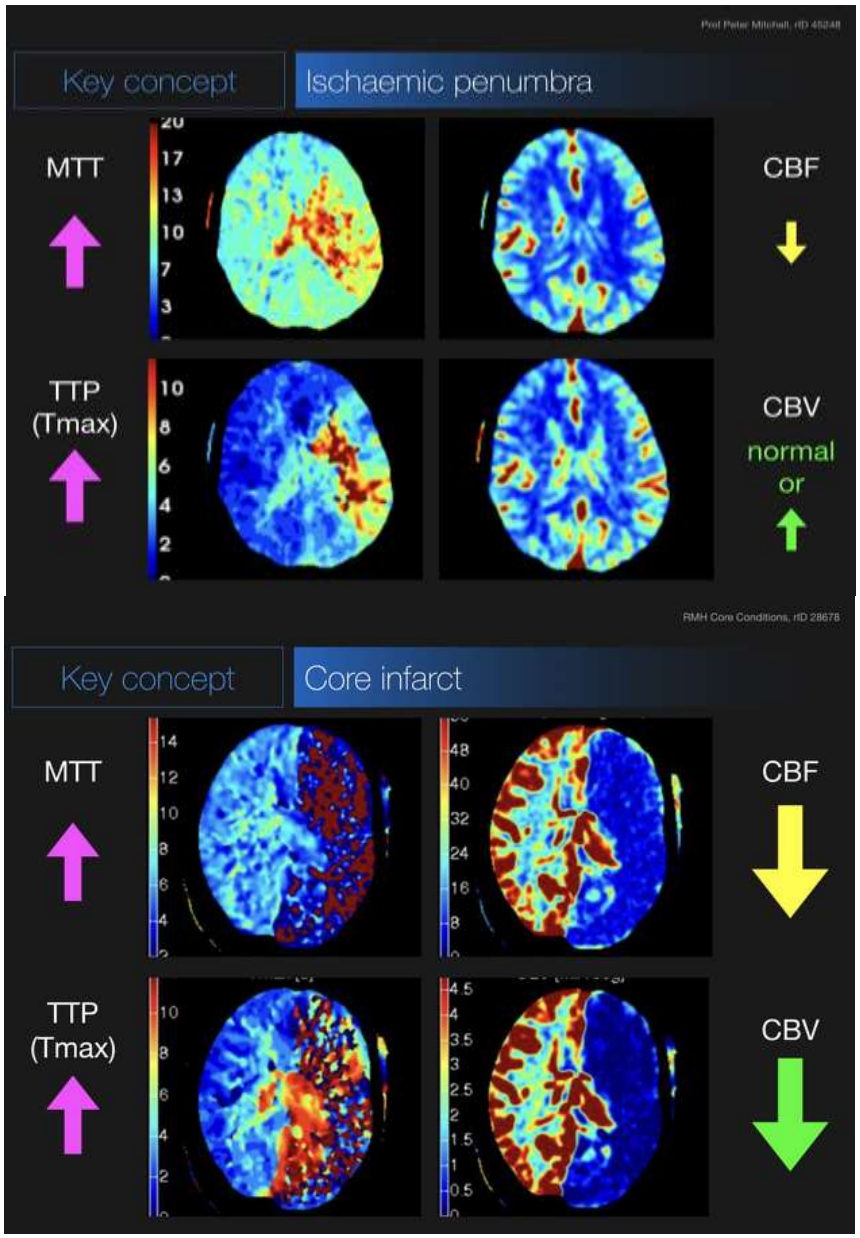

Figure 8

CT Perfusion maps both of the ischemic penumbra and core infarct.

MTT: Mean transit time; CBF: Cerebral blood flow; CBV: Cerebral blood volume; TTP: Time to peak; Tmax: Time to maximum.

MR Perfusion

MR Perfusion maps also have different parameters, such as BV (blood volume), BF (blood flow), MTT (mean transit time), and TTP (time to peak)(47).

It has been postulated that the presence of a mismatch between perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) can be used to select stroke patients who can have a good outcome after reperfusion therapy, within 3 to 6 hours from symptom onset (Alberts et al.)(48) (Fig.9).

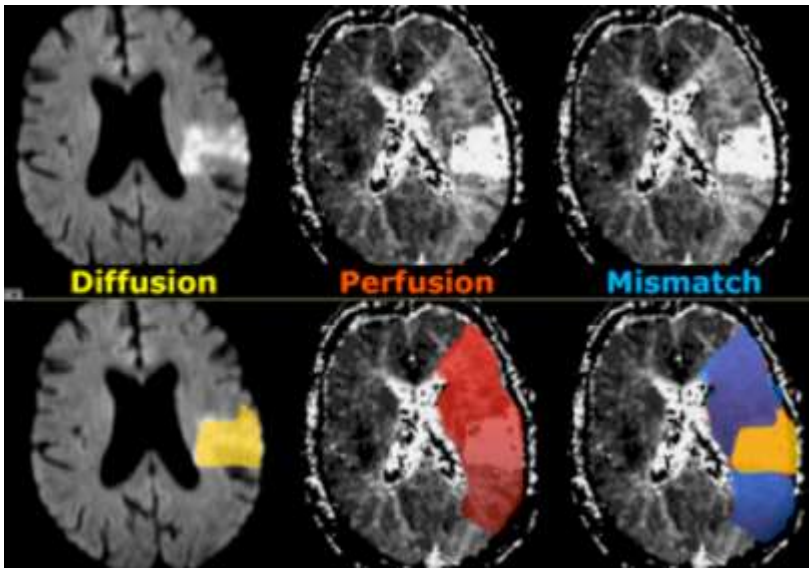

Figure 9

Evaluation of Perfusion/Diffusion mismatch with MR perfusion technique in an ischemic stroke.

ISCHEMIC STROKE THERAPY

Ischemic stroke therapy is divided into several phases.
Four main treatment goals can be identified:
1. In the acute phase, to recanalize the occlusion, depending on the time from symptom onset, it is possible to perform systemic thrombolysis and/or mechanical thrombectomy, if a large vessel is involved;
2. Subsequently, in the subacute phase, for the prophylaxis of early or delayed new events, secondary prevention should be adopted, using a pharmacological or surgical approach;
3. A rapid recognition and management of possible systemic and neurological complications is also necessary, especially during the first 48 hours from onset;
4. In conclusion, as soon as the patient's conditions allow it, an optimal rehabilitation pathway with continuous assistance is indicated(19,28). Therefore, rehabilitation is the most common and the most cost-effective healthcare treatment.

SYSTEMIC THROMBOLYSIS

This reperfusion strategy uses the recombinant tissue plasminogen activator (r-tPA) catalyzing the conversion of plasminogen into plasmin, which can hydrolyze fibrin and fibrinogen. It allows the recanalization of the occluded vessel and the restoration of cerebral flow at the level of the ischemic penumbra(49).
The first multicenter study to demonstrate the efficacy of systemic thrombolysis treatment was the **NINDS** (National Institutes of Neurological Disorders and Stroke) trial, conducted in 1995(50). The protocol involved intravenous administration of r-tPA at a dose of 0.9 mg/kg in patients with ischemic stroke within three hours from the onset, evaluated versus placebo. The results showed in the treated group, compared to controls, an increase of 30% of good outcome patients (mRS 0-1 three months after the acute event).
Meta-analysis studies of different randomized trials (including **NINDS, ECASS I, and II**)(51) have shown that, despite the higher incidence of hemorrhagic transformation, systemic thrombolysis significantly reduces 3-month mortality/disability compared to placebo, if performed within 3 hours from the acute event.

In 2008, a second controlled and randomized placebo trial, **ECASS III** (European Cooperative Acute Stroke Study III) demonstrated the efficacy and safety of the drug up to 4.5 hours from symptom onset, extending the therapeutic window(52).
Subsequently, in 2019, the New England Journal of Medicine published the results of the **EXTEND** trial(53), involving patients with ischemic stroke, out of the therapeutic window, who had salvable penumbra regions, evaluated through perfusion imaging.
This trial resulted in a higher percentage of treated patients with a mRS value of 0-1 after 3 months from the acute event.
Furthermore, many patients with stroke are precluded from thrombolysis treatment because their symptom onset time is unknown. The **PRE-FLAIR** study (Lancet Neurology, 2011)(37) revealed, with a 62% sensitivity, that patients with an acute ischemic lesion detected by DWI-FLAIR mismatch are likely to be in the time window within 4.5 hours from onset.

MECHANICAL THROMBECTOMY

Early-window trials

In early 2015, five independent randomized trials were published (Tab.IV): ESCAPE(54), EXTEND-IA(55), MR CLEAN(56), REVASCAT(57), and SWIFT-PRIME(58). These showed endovascular stroke treatment to be superior, especially associated with intravenous thrombolysis (IVT) versus IVT alone. They analyzed the acute treatment of ischemic stroke caused by the occlusion of a large vessel, such as the proximal middle cerebral artery and distal internal carotid artery. Mechanical thrombectomy (MT) can probably be performed in 4-10% of all stroke patients and it is considered an adjunct, not a replacement for systemic thrombolysis(59).
All these trials demonstrated that patients' age is not an exclusion criterion for EVT and also symptomatic intracranial hemorrhages were not increased in those receiving MT(59).
The mean NIHSS score in these five trials was 17. If the NIHSS score is higher than 11, the probability of occlusion of a large vessel is 3.3 times superior. The emerging data suggested treating patients with an NIHSS score of 9 or above within a time

window of 3 hours, and those with a score of 7 or above within 3 to 6 hours from onset(107).

Moreover, according to these studies' results, thrombectomy seems to lead to a therapeutic benefit in patients with an ASPECTS from 6-7 to 10 and confirmed proximal vessel occlusion(59).

Characteristics of the five randomized trials on mechanical thrombectomy published in 2015

Trial	n: patients: MT/control	IV tPA rate	Groin puncture after symptom onset	Median NIHSS score: MT/control	Vessel occlusion	Recanalization rate: MT	mRS score 0 to 2: control	mRS score 0 to 2: MT	Symptom onset to groin puncture/reperfusion (min)	SICB: MT	SICB: control	NNT (mRS score 0 to 2)
MR CLEAN	233/267	89%	Intra-arterial therapy <6 hours possible	17/18	Distal ICA, M1, M2, A1, A2	59%	19%	33%	260/-	7.7%	6.4%	7
ESCAPE	165/150*[1]	76%	Patient recruitment <12 hours	16/17	ICA + M1, M1, M2	72%	29%	53%	-/241	3.6%	2.7%	4
EXTEND-IA	35/35*[1]	100%	IV <4.5 hours, intra-arterial therapy begun <6 hours, ended <8 hours	17/13	ICA, M1, M2	86%	40%	71%	-/210	0	5.7%	3
SWIFT-PRIME	98/98*[1]	98%	IV <4.5 hours, IA	17/17	ICA, M1	88%	35%	60%	224/252*[2]	0	3.1%	4
REVASCAT	103/103*[1]	73%	Beginning of standard therapy or intra-arterial therapy <8 hours	17/17	ICA + M1, intracranial ICA, M1	66%	28%	44%	269/355	1.9%	1.9%	6

n: Number; MT: Mechanical thrombectomy; tPA: Tissue-type plasminogen activator; ##

VT: Intravenous thrombolysis; IA: Thrombectomy; NIHSS: National Institutes of Health Stroke Scale; ICA: Internal carotid artery; M1: Proximal, horizontal segment of middle cerebral artery; M2: Insular segment of middle cerebral artery following M1; mRS: Modified Rankin Scale; SICB: Symptomatic intracranial bleeding; NNT: Number needed to treat

*Trial halted early due to lack of equipoise

*Time to first deployment of stent retriever

Table IV- Characteristics of the five randomized trials on EVT (2015).

HERMES COLLABORATION: A meta-analysis of results from five randomized trials

This meta-analysis(60) pooled individual patient data from the five previous randomized trials and studied treatment effects across different subgroups of the population.

They analyzed individual data of 1287 patients (634 assigned to the endovascular arm, 653 assigned to the control group). EVT significantly reduced disability at 90 days compared to the control arm.

Moreover, the pooled analysis showed no heterogeneity of effects across different subgroups; 90 day-mortality rates and risk of intracranial hemorrhage did not differ between groups.

In conclusion, timely treatment of patients with acute ischemic stroke caused by a large vessel occlusion can be performed using endovascular thrombectomy and the outcome doesn't depend on their characteristics or geographical location(60).

Late-window trials

In acute ischemic stroke, mechanical thrombectomy is the standard treatment for large vessel occlusion (LVO), within 6 hours from symptom onset. Recent trials have demonstrated also a benefit for wake-up strokes and patients beyond 6 hours from the last known well time.

DAWN TRIAL(61) (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo, 2018) enrolled LVO stroke patients, last known well 6 up to 24 hours earlier and with a mismatch between the severity of clinical damage and the infarct volume, documented on imaging. In conclusion, the mean score on the utility-weighted mRS at 90 days was 5.5 in the thrombectomy group and 3.4 in the control group, thus leading to a better prognosis in patients treated with thrombectomy plus standard care than with standard care alone (Fig.10).

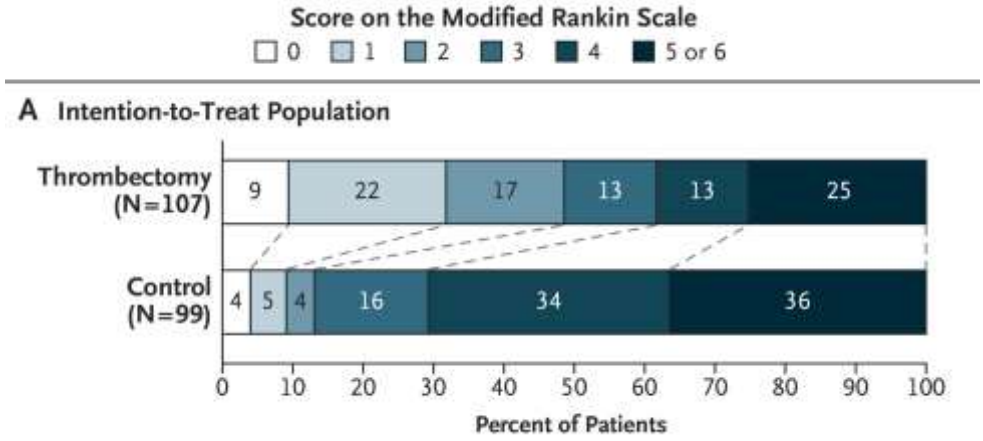

Figure 10

Distribution of scores for disability on the mRS scale among patients in the thrombectomy group and the control arm. The numbers in the bars are percentages of patients who had each score (DAWN trial, 2018).

DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3, 2018) (62) was a multicenter, randomized trial of MT in patients 6 to 16 hours after they were last known well and who had remaining ischemic penumbra tissue on perfusion imaging.

Mechanical thrombectomy plus medical care was associated with a higher number of functionally independent patients at 90 days (Fig.11).

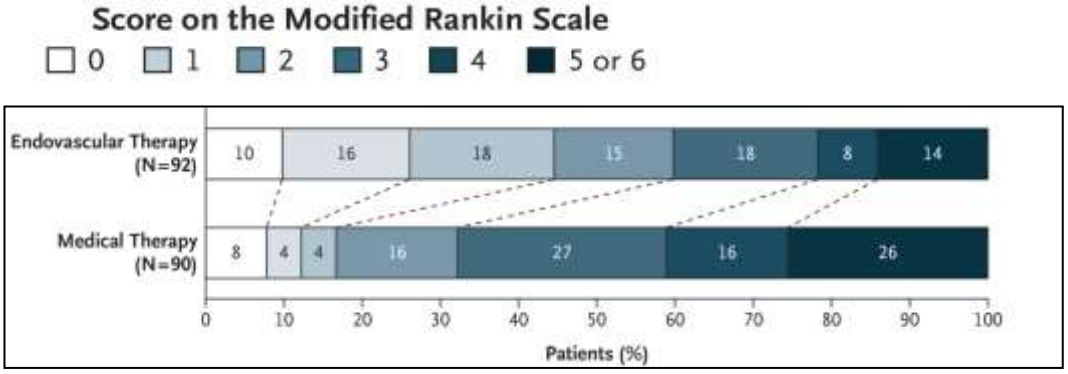

Figure 11

Distribution of scores on the mRS scale at 90 days, both in thrombectomy and control group (DEFUSE 3 trial, 2018).

Following these results, in 2022, the **CLEAR study**(63) (Computerized Tomography for Late Endovascular Reperfusion) was published by Jama Neurology.

They enrolled patients with a proximal anterior circulation stroke, who performed mechanical thrombectomy in the extended window, between 6 to 24 hours from they were last known well.

The principal aim of this study was to compare patients selected by Non-contrast Computed Tomography (NCCT) and CT-angiography with subjects selected by perfusion CT or MRI mismatch, evaluating their 90-day outcome, using the modified Rankin scale (mRS).

They showed that the rate of functional independence at three months after acute onset was comparable between the two groups, with no evidence of a higher risk of symptomatic hemorrhage or death in the NCCT arm (Fig.12).

In this cohort, ASPECTS values were 7-9, thus suggesting that a score of 7 or more was a good outcome predictor and may be considered in patients' selection.

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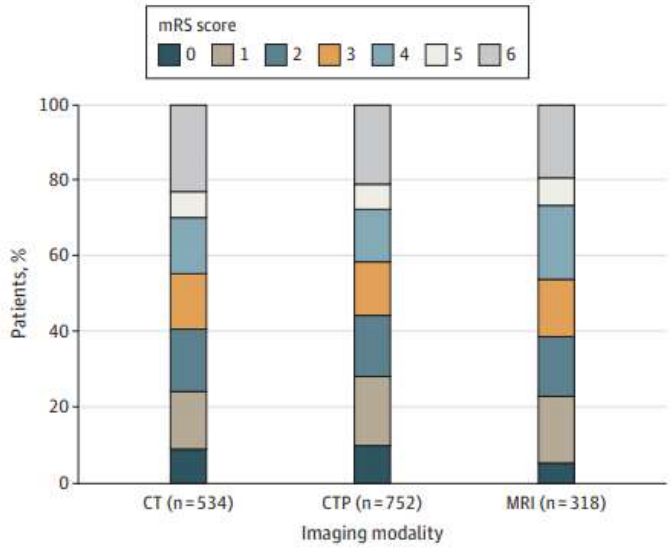


Figure 12

Distribution by imaging modality of 90-day mRS in patients with an acute anterior stroke in the extended window (CLEAR study, 2021).

CT: Computed Tomography; CTP: Perfusion Computed Tomography; MRI: Magnetic Resonance Imaging.

PROGNOSTIC FACTORS

GENERAL STROKE PROGNOSTIC FACTORS

According to the most recent systematic analysis for the Global Burden of Disease Study conducted in 2019, stroke represents the second cause of death (11,6% of total deaths) after cardiovascular ischemic disease. It is also the third cause of disability (5,7% of total DALYs) after neonatal disorders and cardiovascular disease.

It mainly occurs in patients between 65 and 84 years, with a higher risk of post-stroke impairment and disability in elderly male people(64). Age is a significant predictor of 90-day mortality because the incidence of hypertension and atrial fibrillation is high in elderly patients, so their prognosis is poor(65).

The Global Burden of Disease Study (2019) individuated five leading prognostic factors, contributing to stroke DALYs: hypertension and other cardiovascular diseases (i.e. atrial fibrillation and coronary artery disease) (55,5% of all stroke DALYs), high BMI (24,3%), high fasting plasma glucose (20,2%), ambient pollution (20,1%) and smoking (17,6%)(64).

According to ISO-SPREAD guidelines, smoking cessation reduces stroke disability and is therefore indicated in subjects of any age and sex(27).

Moreover, the maintenance of BMI within normal values (18,5-24,9), avoiding an excessive glucose load, and blood pressure values below 130/80 mmHg are indicated(27) to achieve a lower disability rate and a better functional outcome.

Also, other comorbidities, such as chronic kidney disease, neurological history of previous stroke or TIA, migraine, seizures, or psychological history of depression or anxiety are related to poor prognosis and a higher risk of persistent post-stroke disability.

Significant differences in 90-day mortality can be found among the different TOAST subtypes**.** The mortality rate was the highest for the SAO (Small-artery occlusion) subtype (28.57%), followed by the SOC (Stroke of other determined cause) and LAA (large artery atherosclerosis) subtypes (12.5% and 10.21%, respectively)(65).

PRE-ENDOVASCULAR TREATMENT PROGNOSTIC FACTORS

Endovascular therapy (EVT) has emerged as an effective and safe treatment for acute large vessel occlusion stroke. Several pre-intervention prognostic scores for outcomes prediction and patient selection have been validated.

These pre-intervention scores were compared in a recent review (Raza et al., 2018)(66), which included the **PRE score** (Pittsburgh Response to Endovascular therapy), **THRIVE score** (Totaled Health Risks in Vascular Events), **HIAT2 score** (Houston Intra-Arterial Therapy-2) and **SPAN100 score** (Stroke Prognostication using Age and NIHSS) (Tab.V). The results showed a moderate prognostic accuracy in predicting functional 3-month outcomes. PRE and HIAT-2 scores better identified patients most likely to have a clinical benefit from endovascular therapy, using successful reperfusion as the therapeutic goal and 3-month mRS 0–2 as an indicator of good clinical prognosis. Further studies may include collateral imaging or perfusion-based estimation of core and penumbra volumes(66).

Clinical pre-treatment prognostic variables include pre-stroke mRS, stroke severity at onset (measured by NIHSS at admission), and time from onset to revascularization or last known well time if wake up stroke or stroke of unknown onset(67). Moreover, the efficacy to predict functional recovery after endovascular recanalization was assessed for all sub-items of NIHSS, and the consciousness score resulted in being superior to language, gaze, motor, and facial palsy(68).

On the other hand, **radiological pre-treatment prognostic variables** include CT ASPECTS, penumbra volume, and core volume, measured by perfusion CT/MR, and collateral status(69).

CT ASPECTS was incorporated as a categorical variable in the **HIAT-2 score** associated with age, NIHSS, and blood glucose. Overall prognostic accuracy was increased and, subsequently, the **PRE score** was developed by incorporating age, initial NIHSS, and CT ASPECTS as continuous variables. It resulted to be superior to THRIVE and iSCORE and comparable to HIAT-2 score(66).

PRE score	Age (years) + 2 × NIHSS − 10 × ASPECTS
PRE −25 to +49	Highly likely to benefit from successful reperfusion
PRE ≥50	Not likely to benefit despite successful reperfusion
SPAN	Age (years) + NIHSS
SPAN≥100	High-risk group, poor outcomes in general
THRIVE	Points (range 0–9)
NIHSS	
≤10	0
11–20	2
≥21	4
Age	
≤59 years	0
60–79 years	1
≥80 years	2
Comorbidities (HTN, DM, or AFIB)	1 each
THRIVE 6–9	Poor outcome
HIAT	Points (range 0–3)
Age >75 years	1
NIHSS >18	1
Glucose >150 mg/dL	1
HIAT ≥2	Poor outcome after ET
HIAT-2	Points (range 0–8)
Age	
≤59 years	0
60–79 years	2
≥80 years	4
Glucose	
<150 mg/dL	0
≥150 mg/dL	1
NIHSS	
≤10	0
≥10	1
HIAT-2 ≥5	Poor outcome, limited benefit from ET
iSCORE (an online calculator is available at www.sorcan.ca/iscore/)	
iSCORE ≥200	Overall very poor prognosis, not validated for ET
SAD score	Points (range 0–4)
DWI volume	
≤15 mL	0
>15 mL	1
Age	
≤55 years	0
56–69 years	1
70–79 years	2
≥80 years	3

Table V- Comparison of components evaluated in pre-intervention prognostic scores, from Raza et al. (2018).

These prognostic features are the basis of all treatment selection (see Mechanical Thrombectomy chapter) and are therefore fundamental in clinical practice.

POST-ENDOVASCULAR TREATMENT PROGNOSTIC FACTORS

Clinical post-EVT factors, useful to predict the 90-day outcome, are represented by NIHSS and mRS scores at discharge and systemic complications after the procedure, such as pneumonia, urinary infection, IMA, or acute sepsis.

The main **radiological factors** include reperfusion evaluation and lesion infarction. In particular, pathological mechanisms that lead to a lack of post-thrombectomy reperfusion have not been fully clarified yet but there are different possibilities: for example, poor collateral circulation, limited ischemic penumbra, and altered self-regulation of microcirculation(70).

The most used scale is the mTICI (modified Thrombolysis in Cerebral Infarction), which is divided into 4 degrees: 0 = no recanalization; 1 = minimum slow recanalization beyond the initial occlusion; 2 = partial recanalization; the contrast agent passes beyond the initially occluded site but the distal circle is slow or incomplete. There is also another subdivision into mTICI 2a if the revascularized territory is <50% or mTICI 2b if it is ≥50%. In the end, complete recanalization of the artery with a normal filling of all distal branches corresponds to mTICI 3(71).

A revised TICI scale (rTICI) has been proposed, which also distinguishes a 2c degree, in which the recanalization is almost complete, except for the presence of slow flow or small emboli in some distal cortical branches(71).

It has been shown that the outcome of patients with rTICI 2c is similar to those with complete recanalization (rTICI 3) and, therefore, these grades should represent the goal of endovascular treatment, to achieve a good 90-day prognosis(71).

The Heidelberg Bleeding Classification(72) is used to identify possible hemorrhagic infarction after reperfusion.

In their previous studies, Pessin et al. made a distinction between hemorrhagic infarction (HI) and parenchymatous hematoma (PH) after embolic stroke(73).

The European Cooperative Acute Stroke Study (ECASS) protocol (74) adapted pre-existing criteria to define:

- HI 1 as small petechiae along the margins of the infarct;
- HI 2 as more confluent petechiae, without space-occupying effect;
- PH 1 as a clot, not exceeding 30% of the infarcted area and moderate space-occupying effect;

> PH 2 as a clot, exceeding 30% of the infarct volume with significant space-occupying effect.

Class 3, on the other hand, includes intracerebral hemorrhages outside the infarcted tissue or extracerebral intracranial ones, e.g. parenchymal hematoma distant from the affected region, intraventricular, subarachnoid, and subdural hemorrhage (72). A higher score is associated with a more extensive hemorrhagic infarction after EVT and a poorer 90-day prognosis for patients.

PART II. STROKE TOPOGRAPHY PREDICTS BEHAVIOUR

Until the mid-1900s, studies on the relationship between brain lesions and behavioral deficits have suggested that damage to different brain regions produced different behavioral impairments, so specific areas were associated with particular behavioral functions. This association was observed both for sensory and motor systems and for cognitive domains such as language, memory, and attention. The traditional theory emphasizes a pattern of behavioral dysfunction that follows the vascular distribution of the stroke.

STROKE CLINICAL SYNDROMES

A stroke usually occurs with acute neurological deficits. Traditionally, clinical signs and symptoms are attributed to the arterial territory involved (Fig.13). Here we provide a list of the major arteries and vascular territories affected(19).

ANTERIOR CIRCULATION SYNDROMES

Medium cerebral and internal carotid artery stroke

The acute occlusion of these two main arteries causes overlapping clinical manifestations, consisting of severe contralateral hemiparesis, hemi-hypoesthesia, and homonymous lateral hemianopia. Aphasia and apraxia also develop if the dominant hemisphere is involved, while neglect and anosognosia if the non-dominant hemisphere is affected (8,19).

Anterior cerebral artery stroke

Stroke occurring in the anterior cerebral artery region is characterized by motor and sensory symptoms at the level of the contralateral lower limb, behavioral disorders such as abulia and apathy, and transcortical motor aphasia(8,19).

Anterior choroidal artery stroke

The clinical manifestations related to its obstruction are determined by hemiparesis and contralateral hemi-hypoesthesia, homonymous hemianopia, but also by the absence of aphasia, neglect, and cognitive disorders(19).

POSTERIOR CIRCULATION SYNDROMES

Vertebral artery stroke

One of the classic manifestations of VA occlusion is “Wallenberg syndrome”(75), due to a cuneiform infarction of the lateral portion of the bulb.

It is associated with:

• Vertigo, nystagmus, and vomiting for the involvement of the vestibular nuclei;

• Sensory disturbances, ptosis, miosis, enophthalmos (Horner syndrome), and ataxia of the limbs, homolateral to the ischemic area;

• Contralaterally, loss of thermic and pain sensitivity;

• Dysarthria, hoarseness, dysphagia.

Another clinical manifestation associated with VA occlusion is “medial medullary infarction syndrome”(8) determined by:

• Hemiparesis and hemi-hypoesthesia contralateral to the lesion;

• Ipsilateral tongue paralysis.

Basilar artery stroke

The occlusion of its cranial tract causes the “top of the basilar syndrome”, resulting in drowsiness, visual disturbances, hallucinations, and mutism.

If there is the involvement of the collateral branches of the basilar and vertebral artery (SCA, AICA, PICA), cerebellar infarcts may develop, mainly associated with ipsilateral ataxia, dysarthria, and nystagmus.

Furthermore, brainstem infarcts can be associated with alternate syndromes: involvement of cranial nerves or cerebellar peduncles ipsilateral to the lesion and contralateral sensory-motor symptoms(8,19).

Posterior cerebral artery stroke

- Deep infarcts of the proximal PCA: thalamic syndrome (contralateral anesthesia, mild hemiparesis, choreoathetosis of the hand, painful paresthesia), mesencephalic syndrome (ipsilateral ophthalmoplegia and contralateral hemiparesis/ataxia);
- Superficial infarcts of temporal and occipital cortical branches of PCA: contralateral homonymous lateral hemianopia, alexia, anomia, and visual agnosia if the dominant hemisphere is affected(19,76).

Lacunar stroke

Penetrating arteries derive from the middle cerebral artery (lenticulostriate arteries), the anterior choroidal artery, and the posterior cerebral artery (thalamoperforating and thalamogeniculate branches). Their occlusion causes a small lacunar stroke (<1,5 cm), whose clinical symptoms have been divided by Fisher into:

• Pure motor hemiparesis (internal capsule and pons lesions);
• Pure sensory stroke (thalamus involvement);
• Dysarthria syndrome and motor disorders of the hand (internal capsule and pons);
• Ataxic hemiparesis (internal capsule and pons).

Symptoms could begin immediately or develop progressively(77,78)

However, emerging evidence demonstrates that the classic topographic approach has important limitations. In fact, stroke deficits are correlated with functional disconnections in different brain regions, leading to a low-dimensional structure of neurological damage(79,80). As we describe in the next chapter, lesion-symptom mapping approaches have been revolutionized by a new large-scale brain network framework.

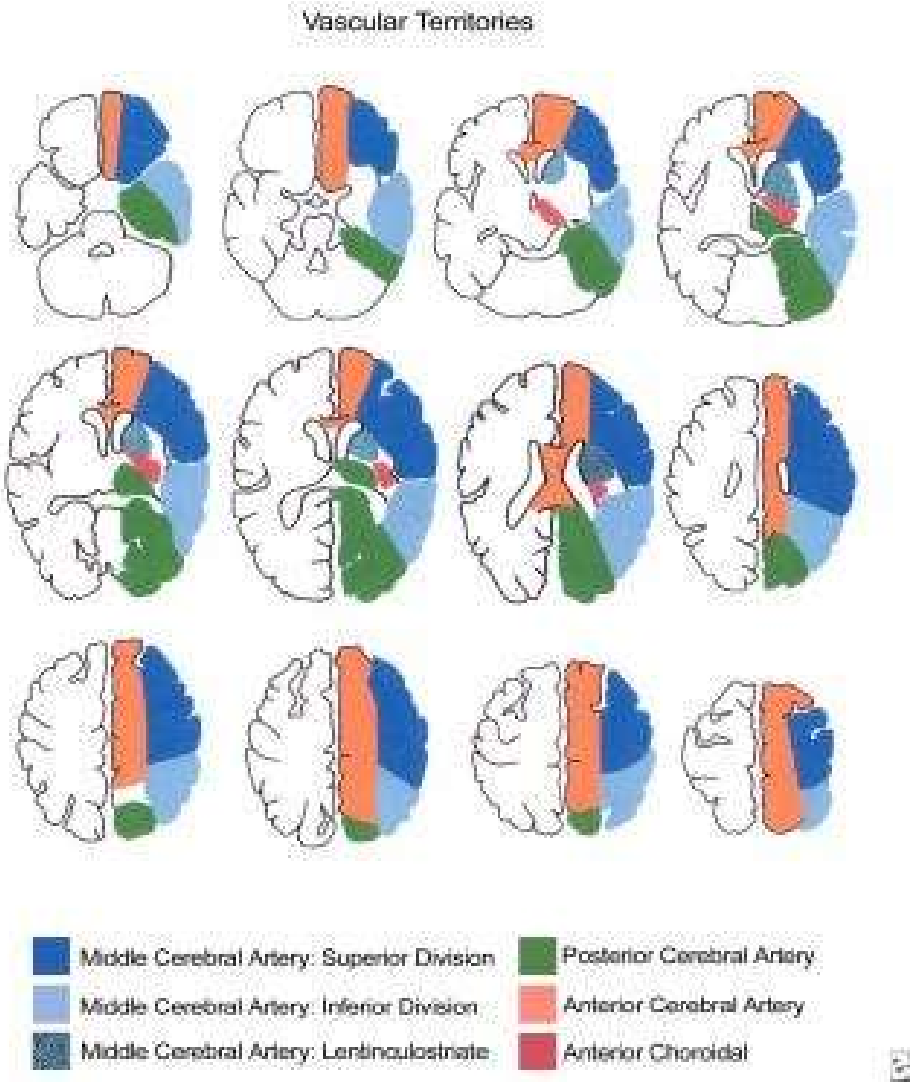


Figure 13

Vascular distribution of anterior and posterior circulation, from Medscape.

BRAIN NETWORKS: FROM LESIONS TO STRUCTURAL AND FUNCTIONAL DISCONNECTIONS

Most stroke patients have less specific behavioural impairments than those described in traditional neuropsychological studies, both within and across domains. For instance, many aphasia patients also show deficits in verbal and spatial memory.

Similarly, patients with left visual field neglect, often show left motor deficits and poorer spatial memory.

These deficits cannot be really explained neither by the locus of injury or the involvement of adjacent regions. Rather they reflect the correlation of different behavioural domains which in turn reflect the correlation among the related neural systems (79–81).

The new emerging picture is that the elementary blocks of cognition are not independent brain areas or individual neurons but networks. The interplay between structural and functional connectivity maintains consistent topology across patients and it can explain many degrees of freedom for context and task-dependent reconfiguration. The application of this knowledge to stroke behavioural alterations is providing fundamental insight into the understanding of many clinical manifestations.

To better acquire this concept, it is important to discuss brain networks for interpreting structural and functional neuroimaging data.

Many studies established the presence of specialized anatomical networks that connect different brain areas, for example, the language system to the frontal cortex.

Several levels of networks can be found: cell-specific metabolic pathways inside a neuron, local connections between neighbouring cells, and large-scale circuits between distant neuronal populations at the cortical or subcortical level.

Both structural and functional networks have been described.

Structural networks

A structural network depends on the anatomical links between neurons, represented by synapses, axons, dendrites, and gap junctions.

A brain area can be described as a subnetwork of a large-scale network, composed of excitatory and inhibitory neurons (nodes) and connecting pathways (edges).
Different neuroimaging techniques have been used to characterize structural nodes, such as anatomical parcellation of the cerebral cortex using the Brodmann atlas; parcellation using structural magnetic resonance imaging (sMRI); automated cortical parcellation based on gyral folding patterns; quantitative cytoarchitectonic and neurochemical maps (82).
The edges connecting brain areas are determined by long-range axonal-fiber pathways.
Three different approaches are used to determine structural network edges. First of all, the autoradiographic tracing in the macaque monkey paved the way for modern neural tractography. Despite this, pathway homology between macaque and human brains is not well defined.
The second method uses diffusion-based magnetic resonance imaging, consisting of diffusion tensor imaging (DTI) (Fig.14) and diffusion spectrum imaging (DSI). These techniques allow determining major fiber tracts of the human brain in vivo, by identifying the density of connections between brain regions. However, this technology has different limitations: lack of gray-matter connections and uncertain measures of connection strength and directionality(83).
The third approach for edge mapping uses local cortical thickness and volume to estimate connectivity.
Both node and edge-mapping identified structural networks across the whole brain or within specific brain areas.

Diffusion imaging techniques allow defining the whole-brain connectome, an ensemble of connections to/from different brain regions(84).
Moreover, this approach accurately localized connectivity fingerprints, i.e. densely connected network communities or modules.

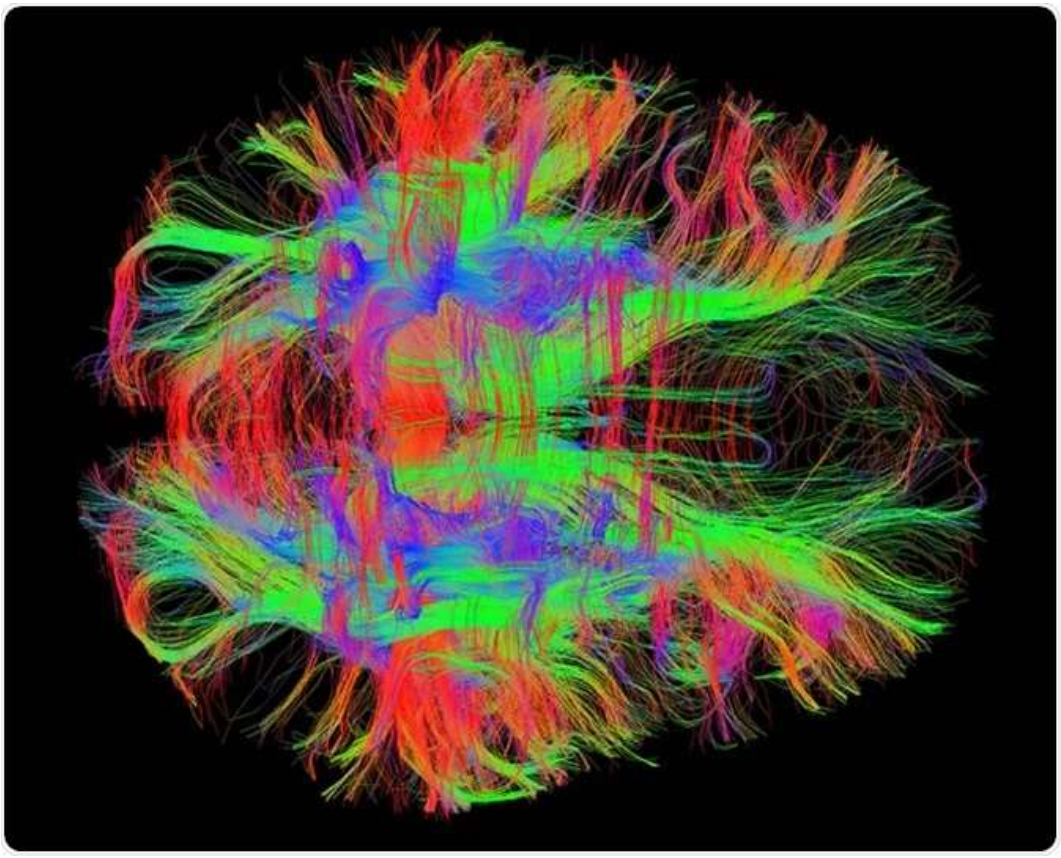


Figure 14

Tractography reconstruction of neural connections through DTI (diffusion tensor imaging).

Functional networks

In functional networks, a node is defined as a specific brain region characterized by elevated metabolism in PET, elevated blood perfusion in functional MRI, or synchronized oscillatory activity in LFP (local field potential). The nodes of a large-scale network can be represented as a group of brain areas activated or deactivated during cognitive functions, such as attention, language, working memory, and motor control(82).

Functional network edges can be identified from time-series data in the time or frequency domain.

To better define functional networks, the measure of resting-state functional connectivity (RSFC) is useful. It shows regional interactions that occur when an explicit task is not being performed.

These studies allow the detection of communities, which are sets of nodes with denser interactions among themselves.

Functional vs structural networks

Many authors have compared patterns of structural and functional connectivity and they found that topology diverges in many ways. It is important to remember that structural networks are based on direct anatomical linkages, while functional connections express the similarity of BOLD or PET signals, also in distant brain regions.

These results could be partially explained by BOLD technique limitations, i.e. uncertain information on the directionality and strength of pathways and by the biases in data acquisition (85).

In the healthy adult brain, highly structurally interconnected areas usually show strong functional connectivity. However, it has been noticed that at the level of the cingulum bundle or fronto-occipital fasciculus, there is no significant association between these two measures in children(86).

These results demonstrate that these connections are dynamic and become stronger with growth.

Furthermore, O'Reilly et al. collected resting-state fMRI data from macaque monkeys before and after the execution of complete sections of the corpus callosum and the anterior commissure. They tested whether the deriving structural disconnection links with a reduction in interhemispheric functional connectivity(87).

This hypothesis was confirmed, but they also reported near-normal functional connectivity between hemispheres in a monkey with the anterior commissure sectioned. This result seems to explain why human callosal agenesis patients have intact, bilateral resting-state functional connectivity, despite the absence of major important commissural fibers.

The authors suggested that the number and directness of structural connections may not be the principal factor in decreasing functional connections.

Moreover, they gave an alternative possible explanation to this phenomenon: the existence of subcortical inputs, especially those from the brainstem, that maintain interhemispheric connections in the absence of structural brain networks.

In conclusion, this study conducted by O'Reilly et al. demonstrated that functional connectivity can dynamically restore interhemispheric coordination after structural injury and disconnection.

THE CONCEPT OF "DIASCHISIS"

Recent lesion studies highlighted the concept of diaschisis, as fundamental for understanding brain function. This term was coined in 1914 by von Monakow to describe the circumscribed neurophysiological changes distant to focal brain damage. Moreover, these changes should be associated with behavioral alterations and recover over time.

Thanks to the development of new imaging techniques, it is now possible to investigate "connectional diaschisis", characterized by changes in structural and functional connectivity between brain regions, far from the lesion.

Connectional diaschisis relates more consistently to the clinical findings, especially after stroke in the motor and attentional networks. Furthermore, it has been shown that remote connectivity changes relate to a better recovery and outcome three months after acute stroke (88).

SUBTYPES OF DIASCHISIS

First of all, it is possible to distinguish between focal and non-focal diaschisis (Fig. 15).

Focal diaschisis

According to von Monakow's definition focal diaschisis is represented by "the presence of remote circumscribed neurophysiological changes directly caused by a focal injury".

It can be in turn subdivided into diaschisis at rest and functional diaschisis.

Diaschisis at rest is considered "a focal decrease in energy metabolism at rest, without stimulation or activation, in anatomically intact brain regions distant from the lesion". Disconnected areas show a reduction in oxygen and glucose metabolism, but recently it has been demonstrated that regions of decreased metabolism do not always correspond to decreased perfusion areas.

The impact of diaschisis drastically changes if the damage is cortical or subcortical. Patients with a subcortical lesion and cortical diaschisis develop behavioral deficits similar to isolated cortical lesions in the same area.

Concerning cortical lesions, different patterns have been studied, but the most investigated is transhemispheric diaschisis. In particular, using standard and high-density EEG, an increase in delta activity and a reduction in alpha frequency in the contralateral hemisphere(89) have been demonstrated, apparently without clinical implications.

In conclusion, while cortical diaschisis after subcortical lesions has a behavioral correlation, it has not been found in cortical diaschisis after cortical lesions.

Functional diaschisis is defined as "an alteration of functional responsiveness of a neural system remote from a lesion when challenged by physiological activation". Obeso et al. (90) first observed an increase in the amplitude of the evoked potentials in the cortex contralateral to the lesion.

It has been shown that absent or reduced response to stimulation can be found distant from the lesion area. For instance, Price et al. (91) reported four patients with damage in the Broca's area with a decreased functional MRI activation in the posterior inferior temporal region, which was intact, during a reading task. The authors called this phenomenon "dynamic diaschisis".

Dynamic diaschisis is considered a subtype of functional diaschisis and is defined as "the context-sensitive effect of focal brain lesion on anatomically intact brain regions distant from the damage".

It has also been demonstrated that an increase in remote excitability can be attributed to the loss of inhibition mediated by the interruption of the transcallosal fibers. This was associated with an impairment in GABA transmission in the contralesional cortex(92). The increase develops a few minutes after stroke and recovers over time. This recovery is associated with a better clinical outcome and can be promoted using transcranial magnetic stimulation (TMS)(93).

Connectional diaschisis

Carrera, Tononi et al. (88) recently coined the term "connectional diaschisis" to describe "a selective change in coupling due to lost afferents from a lesioned node of a defined network".

Several studies have shown how a focal lesion can affect connectivity in functional networks. For instance, using resting-state and seed-based functional measures in humans and animals, a decrease in interhemispheric functional connectivity between cortical regions of the motor network after a subcortical stroke lesion has

been noticed(94). Furthermore, the disruption of interhemispheric connectivity has been also associated with attention deficits in a visual task(94). These alterations correlate with functional impairment immediately after the stroke and tend to normalize over time.

Connectomal diaschisis

The concept of diaschisis has been previously applied to the study of alterations in specific networks distant from the lesion.

Thanks to the new imaging techniques, it is now possible to underline a new subtype of diaschisis: "connectomal diaschisis".

It could be described as "remote changes in the structural and functional connectome, including disconnections and reorganization of subgraphs". However, its clinical interest is still not completely clear and further studies are required for a better comprehension of this novel entity.

The connectome provides a comprehensive map of all neural connections in the brain. It can be defined by a set of nodes and edges, organized following the principle of economy and efficiency. Communities of highly connected nodes can also be found(95).

The connectome can be investigated using structural and functional measures of connectivity such as DTI (Diffusion tensor imaging), which shows structural connectivity, evaluating the diffusion of water molecules for each brain voxel.

This technique can determine white matter connections between grey matter areas. Moreover, diffusion spectrum imaging determines fiber crossing in a singles voxel.

Resting-state functional MRI and electrophysiological measures (such as electroencephalography (EEG) and magnetoencephalography (MEG)) can also be used to determine functional networks. In particular, EEG and MEG have a high temporal resolution, so it is possible to describe over-time alterations.

Connectome models can be based both on structural and functional connectivity. However, structural variability is lower than functional variability, so that two areas can be functionally related, even if there is no direct link between them.

A limit of this approach is that these measures cannot distinguish excitatory and inhibitory synaptic effects or the direction and strength of the relationship between brain areas, thus leading to a difficult comprehension of brain functions after stroke.

The lesions of the cortical midline and the temporoparietal junction represent the widest connectome disruption and alteration of neocortical integrative functions, as shown in a study with the structural monkey CoCoMac database (96).

These studies show that changes in the connectome are not comparable to simple alterations in networks. They represent complex inter-and intra-modular changes providing integration and segregation information.

Remote alterations in the connectome more accurately explain the complexity of behavioral and cognitive deficits, but available imaging techniques are still limited by the number of nodes of the investigated network and by a specific task. Further studies and the development of novel measures will help to better understand the whole connectome function.

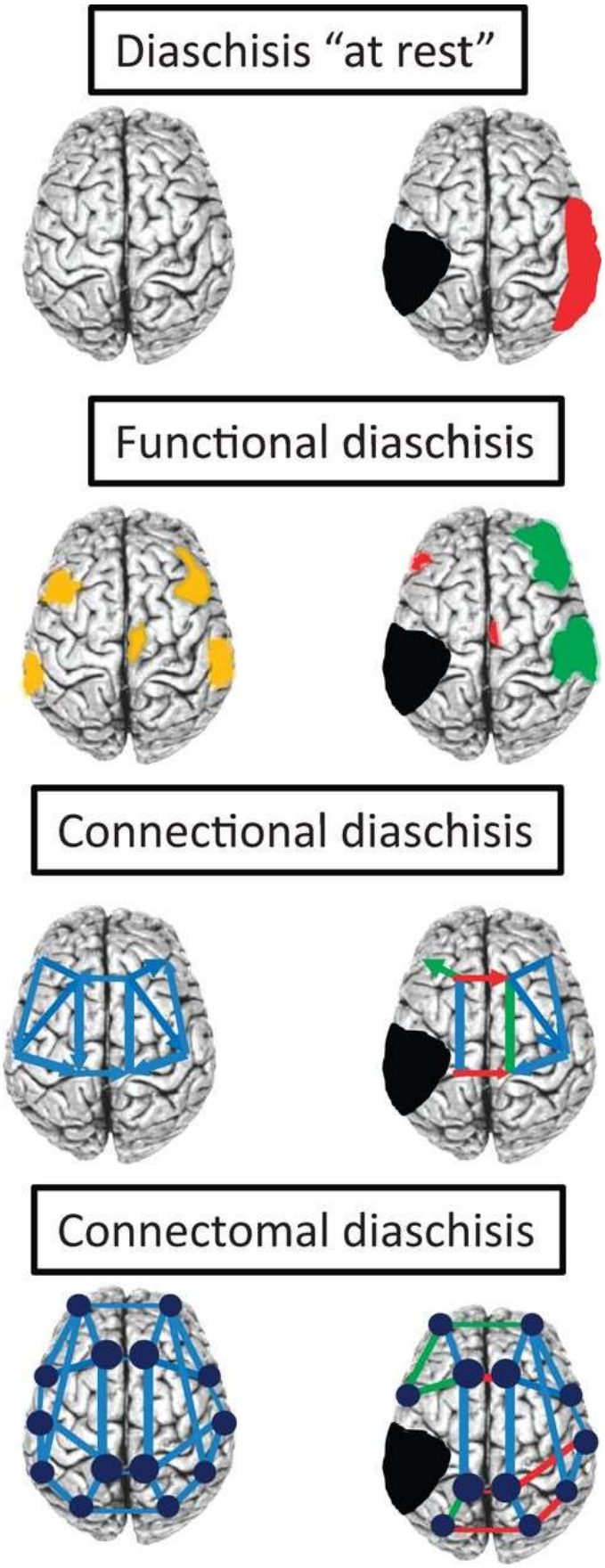


Figure 15

Different subtypes of diaschisis.

FUNCTIONAL DISCONNECTION AND POST-STROKE BEHAVIORAL DEFICITS

Recent evidence shows that stroke structurally damages white matter and subcortical regions much more frequently than the cortex, altering the functional connections between domains.

A study, with a cohort of 132 post-stroke patients, conducted by Siegel et al. (97), measured resting functional connectivity, lesion topography, and behavioral deficits across multiple domains. They got different results: visual and verbal memory deficit was better predicted by FC alterations, visual and motor impairments were better predicted by lesion topography, and attention and linguistic deficits were well predicted by both. Finally, they identified two different phenotypes of post-stroke FC alterations: loss of interhemispheric correlation and an abnormally strong intrahemispheric association between normally segregated regions.

Another study, conducted by Baldassarre et al. (98), measured attention and motor deficits in 44 right hemisphere-damaged patients at 1–2 weeks post-onset. Attention deficits were significantly more correlated with abnormal interhemispheric FC within the dorsal attention network, while motor deficits were significantly more correlated with abnormal interhemispheric FC patterns within motor networks. This result is the evidence that a different topography of FC dysfunction in the structurally normal cortex, after a stroke, generates specific behavioral alterations.

Corbetta et al. (2015) (81)studied a cohort of 132 patients with acute stroke and observed that the 70% of behavioral variability between patients could be summarized by three factors: language and memory deficits (25% of the variance), motor/attention deficits in the right hemisphere (17%) and in the left hemisphere (23%). Furthermore, these three factors explained variability not only in acute conditions but also after 3 and 12 months from the acute phase.

The final hypothesis is that the dysfunction in functional connectivity due to focal damage reduces the variability of neural states both at rest and during tasks, limiting neuronal entropy not only in the affected hemisphere but also in the healthy contralateral one.

Furthermore, Ramsay, Corbetta, et al. (2017)(5) examined the variability of post-stroke recovery in multiple behavioral domains. First-time stroke patients with heterogeneous lesions were analyzed prospectively at 1-2 weeks, 3 months, and 12 months after the acute onset, with structural MRI and neuropsychological assessment. Impairment was described at all timepoints by the aforementioned three correlated factors, which explain 70% of the variability among subjects. The magnitude of recovery was similar across domains, proportional to the severity of initial deficits, and mostly occurred within the first three months.

In particular, this study showed that damage of specific white matter fiber tracts conducted to a poorer recovery across several domains (Fig.16): attention and superior longitudinal fasciculus, language and posterior arcuate fasciculus, and motor and corticospinal tract. They also demonstrated that language and visual memory outcome was worse in lower education patients.

In addition, multiple deficits negatively impacted attention recovery, while spatial memory was acutely associated with attention and motor deficits, but no longer at 3 or 12 months. They showed that, after 12 months, the initial correlation between spatial memory, motor, and attention deficits was not significantly present, thus demonstrating a weakened relationship.

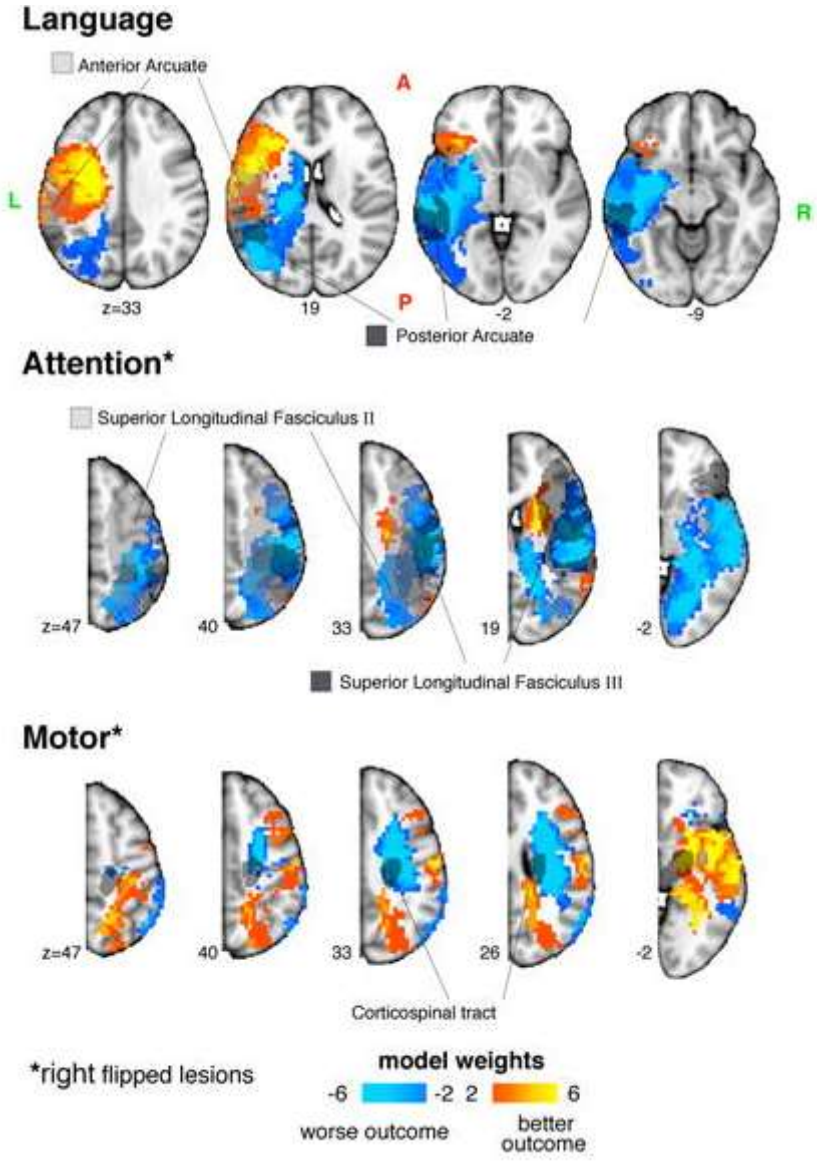


Figure 16

Outcome prediction based on lesion topography.

NEUROMODULATION THERAPY FOR STROKE RECOVERY

Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (DCS) can potentially be exploited for neuromodulation of diaschisis, to obtain a better recovery of clinical functions.

The documented disinhibition of the contralateral hemisphere after a cortical or subcortical motor stroke can be treated by repetitive TMS. The aim is to induce the inhibition of the opposite M1 region e to re-modulate the ipsilesional hemisphere (99).

Several studies on neuromodulation showed no clear benefit on the outcome and the variability between results could be explained by the absence of standard parameters used for inhibition/stimulation, such as frequency and number of pulses(99–101).

In the future, the concomitant use of repetitive TMS and MRI imaging may allow patient-specific treatments for a better recovery of functions.

The validity of the concept of diaschisis will be demonstrated by applying neuromodulation to areas distant from the lesion and observing behavioral and cognitive recovery. This could be an innovative frontier in the treatment of cerebrovascular diseases.

PART III. THE ROLE OF WHITE MATTER DISCONNECTION IN STROKE AS A PREDICTOR OF CLINICAL OUTCOME AFTER MECHANICAL THROMBECTOMY

INTRODUCTION

Mechanical thrombectomy is the frontier of acute treatment in LVO ischemic stroke. This technique has been shown to be safe and effective compared to standard therapy alone, as demonstrated by numerous randomized clinical trials (see ESCAPE(54), EXTEND-IA(55), MR CLEAN(56), REVASCAT(57), and SWIFT-PRIME(58)). These studies essentially demonstrate that reperfusion improves clinical outcomes and prevents infarct growth by salvaging penumbra tissues.

Several clinical factors have been evaluated as possible predictors of good or poor outcome, targeting a mRS score of 0-2 at three months after endovascular treatment. These include the patient's age, pre-stroke mRS, stroke severity at onset (measured by NIHSS), mRS at discharge, time since last known well, and comorbidities (such as diabetes or cardiovascular diseases).

In addition to clinical data, radiological variables were also studied, such as CT ASPECTS values, Heidelberg bleeding classification, TICI reperfusion score, core, penumbra, and final lesion volumes. In particular, a recent study (CLEAR study, 2021)(63) demonstrated the importance of CT ASPECTS in 90-day outcome prediction, after mechanical thrombectomy in the extended window (6 to 24 hours from the last known well time). Results didn't show a significant difference in prognosis between subjects selected by pCT/MRI imaging (DAWN/DEFUSE 3 trials) or by Non-contrast CT and ASPECT scores. In conclusion, they observed that an ASPECT score >7 could be used as a good chronic outcome predictor and may be considered in the selection of patients, eligible for the acute endovascular treatment.

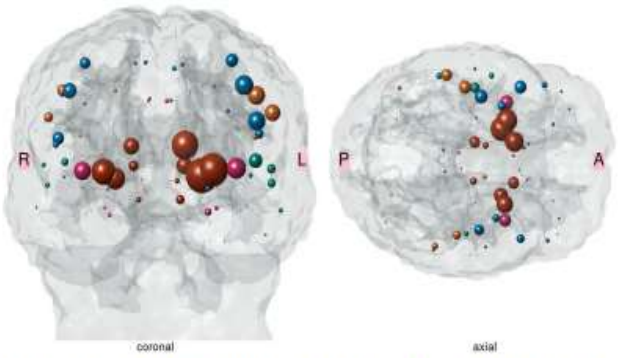
In general, these results substantially elevated the role of early neuroimaging data in defining personalized treatment for stroke. As a result, for example, acute infarct

volume cut-offs, as recognized prognostic factors, are now consistently used in Emergency Rooms and Stroke Units worldwide for acute stroke management protocols(27,102). However, while volumetric data has shown to improve the prediction of recovery after stroke, it only moderately correlates with stroke severity. The impact of infarct volume to estimate outcome resulted in a significantly better correlation with clinical deficit severity when combined with infarct location. In fact, several studies have clearly shown qualitative data on lesion location is crucial to determine post stroke impairment.

Rosso et al. (2014)(1) noted that diffusion-perfusion mismatch volumes are poor predictors of outcome, but that damage to a specific regions of the periventricular white matter and internal capsule may be more predictive.

Corbetta et al. (2015)(81) showed in 132 patients with single stroke that damage to a region of the white matter in the dorsal corona radiata, with many intersecting fibers, leads to deficits across multiple domains of function. Ramsey et al. (2017)(5) showed that damage to different white matter tracts (but not gray matter) improves the long term outcome prediction. For instance, damage to the corticospinal tract improves long-term motor prediction while damage of the temporoparietal white matter improves language prediction. Interestingly, the location of white matter injury increases prediction above a standard model that includes age, education, and acute impairment by only about 5%.

Weaver et al. (2021) demonstrated, in a pooled analysis of 12 acute ischemic stroke cohorts, that infarct location is a potential determinant of PSCI (Post-stroke cognitive impairment) and they identified infarct regions most strongly predictive of impairment: left frontotemporal lobes, left thalamus and right parietal lobe. This study developed the first map of strategic infarct locations associated with the risk of PSCI(2). Following these findings, Schlemm et al. (2021)(3) observed that preserved loss of connectivity, associated with reduction of infarct growth, explained up to 33% of the total effect of alteplase on good clinical prognosis, while prevented infarct growth alone only mediated 8.3% of the clinical effect of thrombolysis on 3-month-mRS (Fig.17).



Pattern and magnitude of structural disconnection induced by acute ischemic stroke lesions prior to randomization illustrated on a three-dimensional template in standard MNI space.

Figure 17

Structural disconnection induced by acute stroke lesions, before the randomization into alteplase and placebo group, on a three-dimensional template, from Schlemm et al. (2021).

In 2022, Regenhardt et al. (4) conducted a cohort study, in which they enrolled 151 patients with LVO ischemic stroke. The average age was 68 years, the median NIHSS score was 16 and 56% of them had a pre-stroke mRS score> 2. They found that lesions affecting white matter tracts had the highest 3-month prognostic power. Therefore, while literature clearly recognizes topography as a strong prognostic factor, this information has yet to be integrated in acute stroke management protocols. To explore this issue, we conducted a study to define the role of different stroke lesion characteristics as prognostic factors after mechanical thrombectomy in comparison to known clinical and radiological variables. We compared the capacity of different linear models to predict post stroke functional outcome, measured by the 90-day mRS.

Specifically, we computed a baseline clinical model based on demographics, pre-stroke mRS and admission NIHSS. Then we added commonly used (standard) radiological parameters of lesion or perfusion damage (core, penumbra, ASPECT). Finally, we added information about the white matter damage computed as a novel overall index of tract disconnection or a voxel-wise analysis of lesion location.

MATERIALS AND METHODS

Study sample

We selected patients who underwent acute mechanical thrombectomy in the Neurology Clinic of the Hospital of Padova from January 2018 to November 2021. The inclusion criteria included:

1. First symptomatic ischemic stroke;
2. LVO eligible for EVT;
3. Anterior circulation stroke.

Exclusion criteria included: (i)Previous stroke based on clinical imaging; (ii) No LVO or not eligible for EVT; (iii) Not available pCT imaging; (iv) Underwent rtPA; (v) Not available acute or follow-up clinical data.

Procedures

We screened a total of N=115 charts. Subjects (n=75) with a first symptomatic LVO ischemic stroke of the anterior circulation were retrospectively recruited, with n=50 meeting post-enrollment inclusion criteria. Figure 18 describes the enrollment flowchart and shows the reasons for exclusion. Subjects were evaluated at admission by experienced neurologists with the National Institutes of Health Stroke Scale (NIHSS) (Tab.II) and the modified Rankin scale (mRS) (Tab.III). For each patient, structural imaging pre-EVT was collected (50 CT and 50 perfusion CT scans).

We also achieved 35 CT and 15 MRI FLAIR scans, performed after acute mechanical thrombectomy. At the discharge, subjects underwent a second clinical examination with NIHSS and mRS.

In conclusion, patients were re-evaluated with mRS at a three-month-follow up and checked out for new events that occurred. Figure 19 illustrates the design of the study.

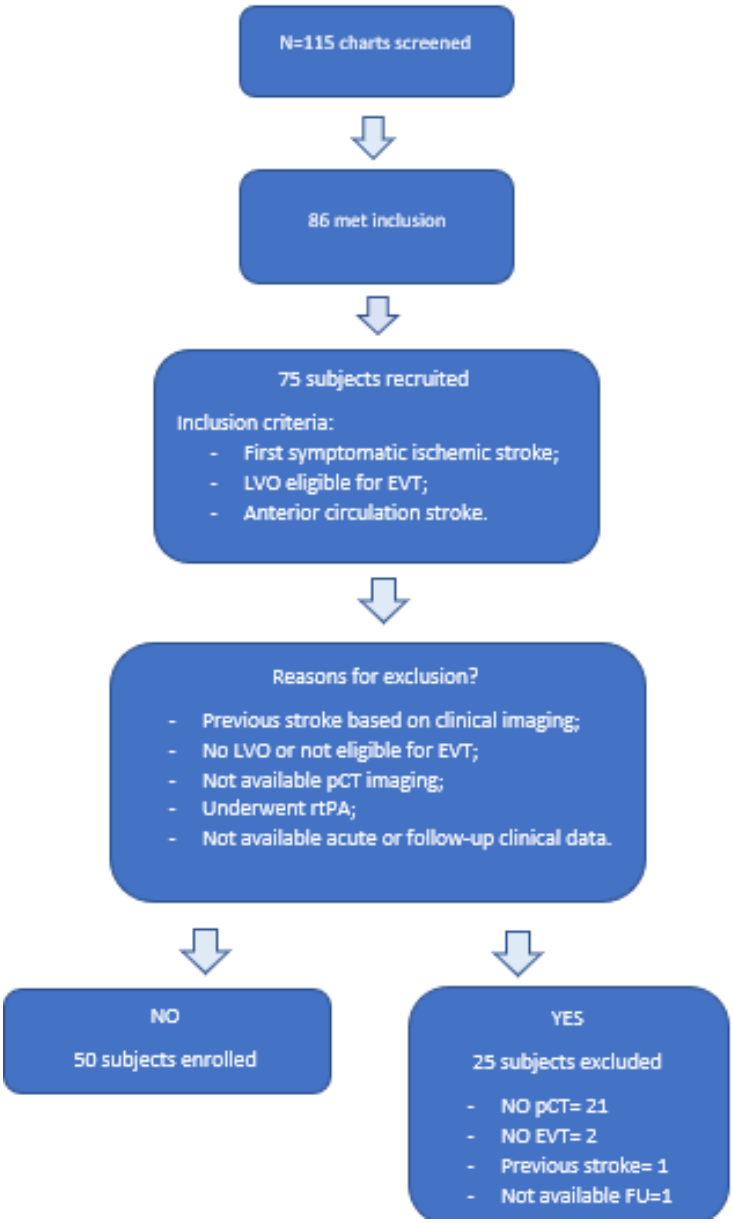


Figure 18

Enrollment flowchart.

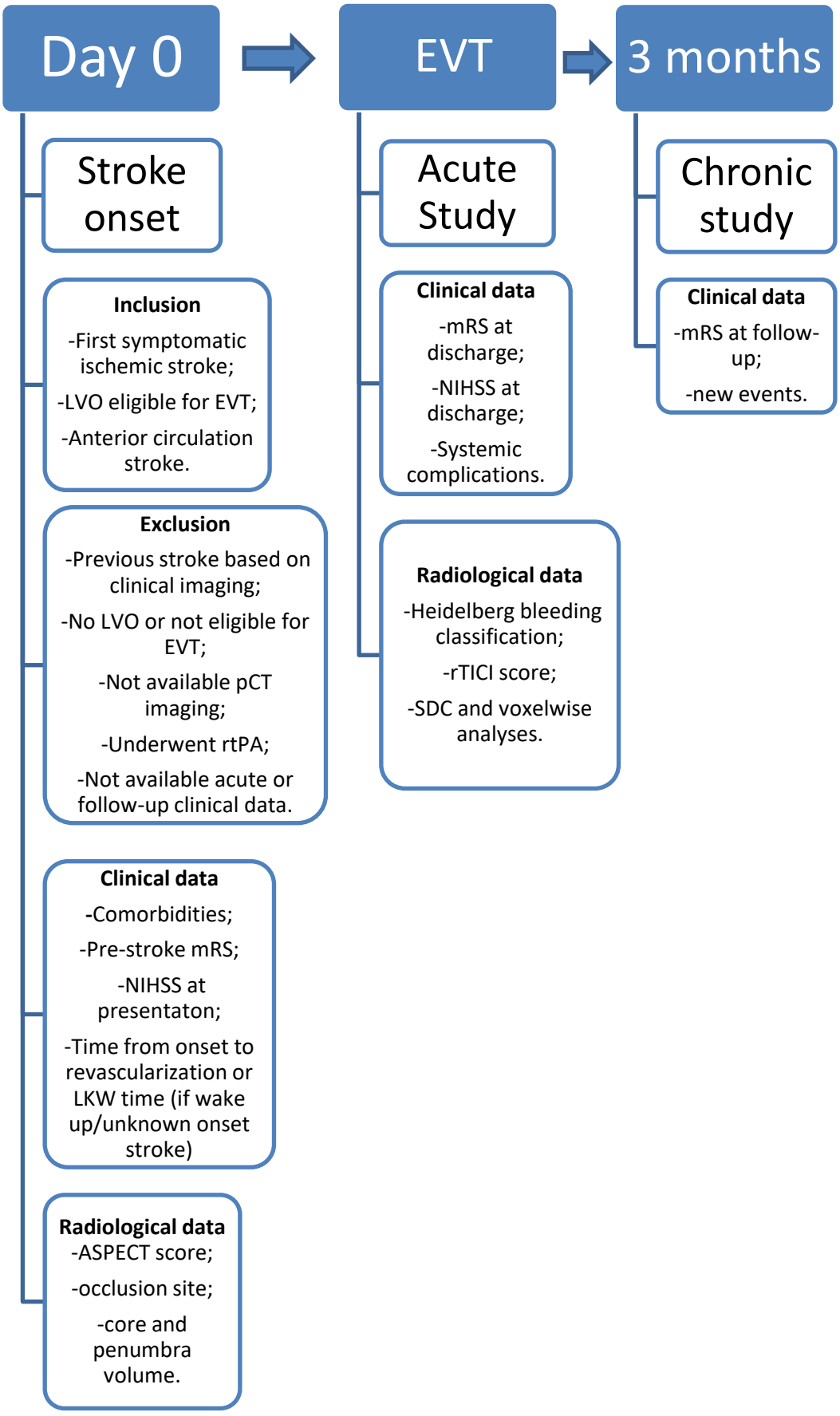


Figure 19

Design of the study.

Measures

Clinical data

All patients were examined by experienced neurologists, using the National Institutes of Health Stroke Scale (NIHSS) (103), which was executed at admission and at the discharge, to evaluate stroke severity. Also, the modified Rankin scale (mRS) (31) was administered at admission, at the discharge, and at the time of follow-up (after three months), to measure the level of disability/dependence in daily activities and to check clinical outcomes. A mRS score of 0-2 was considered compatible with a good prognosis, while a mRS score of 3-6 was associated with a poor outcome.

Also, patients' data were collected to examine the clinical characteristics of the sample: demographics (age at enrolment, gender), stroke risk factors, and comorbidities (cigarette smoking, diabetes, hypertension, coronary artery disease (CAD), atrial fibrillation, neurological, psychological and vision history), time from onset to revascularization or last known well (LKW) time if wake up stroke or stroke of unknown onset.

MRI and CT lesions

Acute structural CT scans were performed at admission and also the Alberta stroke program early CT score (ASPECTS) (Fig.6) (33) was calculated for each subject.

Furthermore, before acute mechanical thrombectomy, patients underwent perfusion CT, to evaluate core and penumbra volumes(46).

After the endovascular treatment, the efficacy of the procedure was examined through the revised Thrombolysis in Cerebral Infarction score (rTICI)(104) to assess the degree of recanalization.

In conclusion, structural MRI and/or CT scans, performed after mechanical thrombectomy, were collected to determine final lesion volumes and topography and to identify a possible hemorrhagic infarction, using the Heidelberg Bleeding Classification (72).

To obtain a voxel-wise analysis of structural lesions, individual DICOM files were transformed into a NIFTI format (MatLab toolbox).

Lesions on structural MRI FLAIR and CT/pCT scans were manually segmented using the ITK-SNAP imaging software system(105) and individually checked by a neurology resident.

CT and MRI segmented brain lesions were drawn onto a standard template, MNI152 brain atlas, using the Advanced Normalization Tools, with a cost function mask approach.

The transformation matrix was finally applied to the lesion masks using a nearest neighbour interpolation approach and resampled to a 1x1x1 mm space.

Linear regression analysis

We first investigated the simple linear relationship between 90-day mRS at follow-up and lesion, penumbra, and core size.

We also compared the same variable to the baseline (NIHSS at presentation and pre-mRS) and to mRS at discharge (post-mRS). We used Spearman's correlation.

Subsequently, we tested 4 different models aimed at investigating the relationship between 90-day mRS and several clinical and radiological stroke lesion characteristics.

Specifically, in a **first model** (**M1**) 90-day mRS was inserted as the dependent variable, while age, pre-mRS, and NIHSS at presentation were inserted as the independent variables. This can be considered a "**baseline clinical model**".

In a **second model** (**M2**), ASPECTS, core, and penumbra volume were added as the independent variables. This can be considered a "**baseline clinical+volumetric model**".

In a **third model** (**M3**) (**baseline clinical +topological model**), structural disconnection (SDC 0.5) was added as the independent variable to age, pre-mRS, and NIHSS at presentation. SDC maps were calculated using the BCB-toolkit(106). In these maps, the value in each voxel takes into account the interindividual variability of tract reconstructions in healthy controls and indicates at each voxel probability of disconnection from 0 to 1 for a given lesion(107). Therefore, this approach indirectly estimates the degree of structural disconnection.

Finally, in a **fourth model** (**M4**) (**baseline clinical model +early recovery)**, 90-day mRS was always inserted as the dependent variable, while age, pre-mRS, NIHSS at presentation, and post-mRS were inserted as the independent variables.

Moreover, to investigate the performance of the four models, we ran a "leave-and-take-one-out analysis". Specifically, we performed the four regressions excluding randomly one subject at each step from the model, computing the corresponding adjusted R squared (variance explained). In total, we performed 20 steps (removing a random subject at each step) and the corresponding values were compared across models through an ANOVA analysis. We then obtained a post-hoc analysis to investigate differences between models, in terms of prediction.

Topological brain analysis

At the voxel-wise level, we investigated brain recovery correlation between the Delta 90-day mRS – pre-mRS with both lesion and SDC maps.

We implemented a nonparametric inference, based on permutations, using FSL randomise(108). Multiple comparisons were corrected across space using family-wise error (FWE) based on permutation testing at a threshold-free cluster enhancement (109). Positive and negative associations between Delta mRS and brain voxels were tested at a TFCE level of $p < 0.025$ corresponding to a two-tailed $p < 0.05$ (randomise correction is only performed on one-tailed tests).

RESULTS

Participants

The study sample had a mean age of 73 years old. There was an equal distribution among the two sexes (male 50%; female 50%).

The most commonly stroke risk factors were hypertension (72% of patients) followed by atrial fibrillation (40%), diabetes (18%), coronary artery disease (14%), and depression (6%) (Tab. VI).

According to the TOAST classification, the most frequent stroke etiology was large-artery atherosclerosis (LAA, 42% of patients), followed by cardioembolism (CE, 38%), stroke of undetermined cause (SUC, 18%), and stroke of other determined cause (SOC, 2%).

In terms of stroke-related clinical variables, before endovascular treatment, the study sample presented a mean NIHSS of 12,38±6,77 at presentation, while the mean pre-mRS was 0,48±0,90. In particular, most patients (94%) had a pre-mRS of 0-2, associated with a good level of functional autonomy at baseline.

Moreover, 62% of subjects presented a left side occlusion, while 38% of them had a right ischemic occlusion.

On the other hand, after mechanical thrombectomy, the mean NIHSS was 5,5±6,16 at the discharge, while the mean post-mRS was 2,82±1,62. Specifically, 42% of subjects had a good functional outcome (mRS 0-2), while 58% of them had a poor prognosis at discharge (mRS 3-6).

After the acute treatment, 52% of patients developed systemic complications, in particular pneumonia (22%), urinary infections (10%), acute sepsis (4%), and ischemic heart disease (2%).

Finally, subjects, rechecked after 94±51 days from the acute event, had a mean mRS of 2,18±1,81 (60% mRS 0-2; 40% mRS 3-6) (Fig.20).

On the other hand, in terms of stroke-related radiological variables, the mean ASPECTS was 8,58±1,31. After mechanical thrombectomy, most of them (72%) achieved complete reperfusion, determined by a revised TICI score of 2C-3, 22% obtained partial reperfusion (rTICI 2A-2B) and 6% failed the procedure (rTICI 0).

Furthermore, according to the Heidelberg Bleeding Classification, 68% of the subjects didn't develop a hemorrhagic transformation of infarcted brain tissues, 18% had an intracerebral hemorrhage (HI1-2), 8% had a parenchymal hematoma (PH1-2) and 6% developed other subtypes of intracranial hemorrhages.

Study sample (n=50)	
Gender	
Female	50,0%
Male	50,0%
Age	
<50	4,0%
50-70	34,0%
>70	62,0%
Risk factors & comorbidities	
Hypertension	72,0%
Atrial fibrillation	40,0%
Diabetes	18,0%
CAD	14,0%
Depression	6,0%

Table VI-Demographics of the study sample.

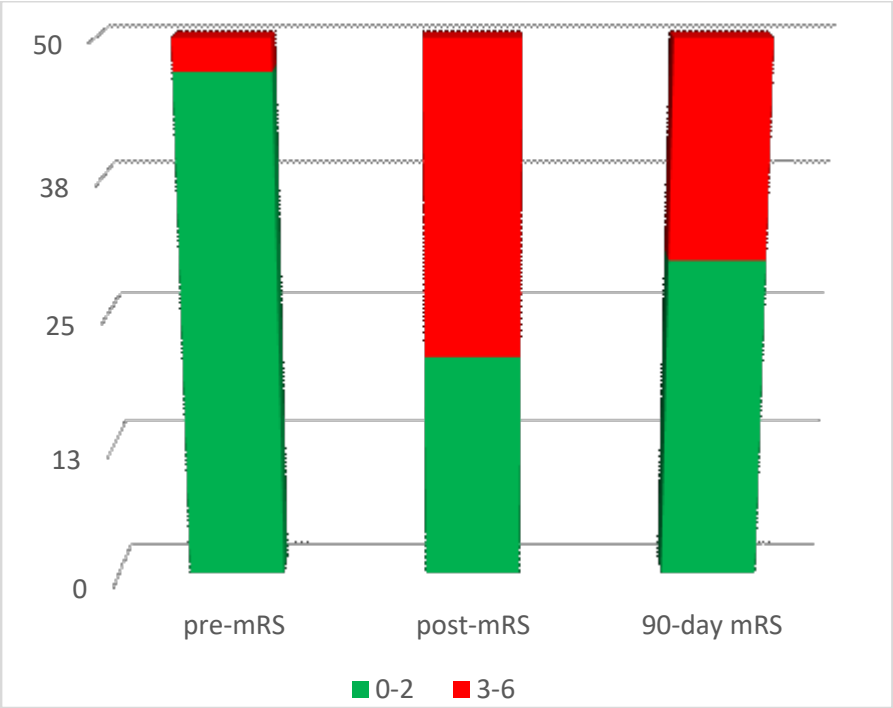


Figure 20

Column chart showing the number of patients with a good mRS value (0-2) and a poor mRS value (3-6) on the total pool of subjects (n=50), evaluated respectively at admission (pre-mRS), at discharge (post-mRS) and at 90-day follow-up.

Anatomy of stroke

We implemented a voxel-wise analysis to generate a precise description of stroke topography. Figure 21 shows a “frequency map” of the overlapping lesions of 43 patients (3 subjects presented negative neuroimaging scans, 2 showed normalization errors, and 2 presented MRI corruption).

This map follows a colorimetric scale, showing in blue the areas in which the sum of the lesions of all subjects is equal to zero, while in red the areas in which the lesions are mostly concentrated.

Segmented lesions included: 30 patients with left hemisphere damage and 13 with a right hemisphere one.

Stroke topography overlapped mainly in the subcortical regions and concentrated in the caudate, internal capsule, lentiform nucleus, and thalamus (accordingly to our previous studies- Corbetta et al. 2015 (81); Bisogno et al. 2021(79)).

Cortical lesions predominantly occurred in the middle cerebral artery territory, especially in the insular cortex, extending to the temporoparietal lobe. Lesions were mainly located in the left hemisphere.

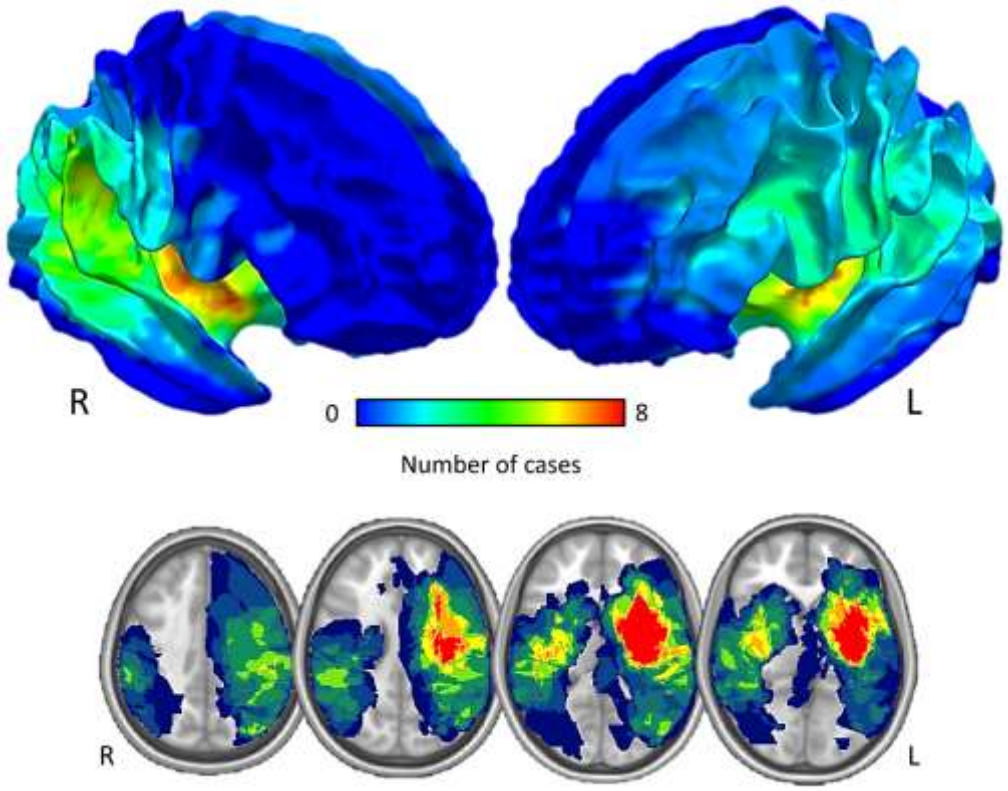


Figure 21

The frequency map shows a predominantly left subcortical distribution of patients' lesions, extending to the temporoparietal cortex.

Linear regression analysis

At first, a linear regression analysis was used to investigate the relationship between 90-day mRS and different stroke clinical and radiological variables, as shown in Figure 22.

We found a positive significant correlation between post-mRS (MRS discharge, in the figure) and 90-day mRS (MRS-Follow Up 90 days, in the figure) [$r=0.706$, $p>0.001$].

A positive significant correlation was also individuated between pre-mRS (MRS acute, in the figure) and 90-day mRS [$r=0.420$, $p=0.005$] and between NIHSS at presentation (NIHSS acute, in the figure) and 90-day mRS [$r=0.649$, $p<0.001$].

Overall these analyses confirm the known relationship between pre-stroke clinical status and degree of acute impairment with long-term clinical outcome.

Next, we analyzed the relationship with radiological lesion variables.

Interestingly, there was no relationship between 90-day mRS and lesion size [$r=0.252$, $p>0.05$], penumbra size [$r=-0.014$, $p>0.05$], core size [$r=0.0001$, $p>0.05$].

Overall these negative findings show that long-term outcome does not strictly depend on the structural lesion damage in line with previous observations about the importance of network disconnection in accounting for clinical impairment(79–81).

In summary, we observed that stroke prognosis depends more on clinical features and is independent of lesion volumetric parameters, collected both before and after the endovascular treatment.

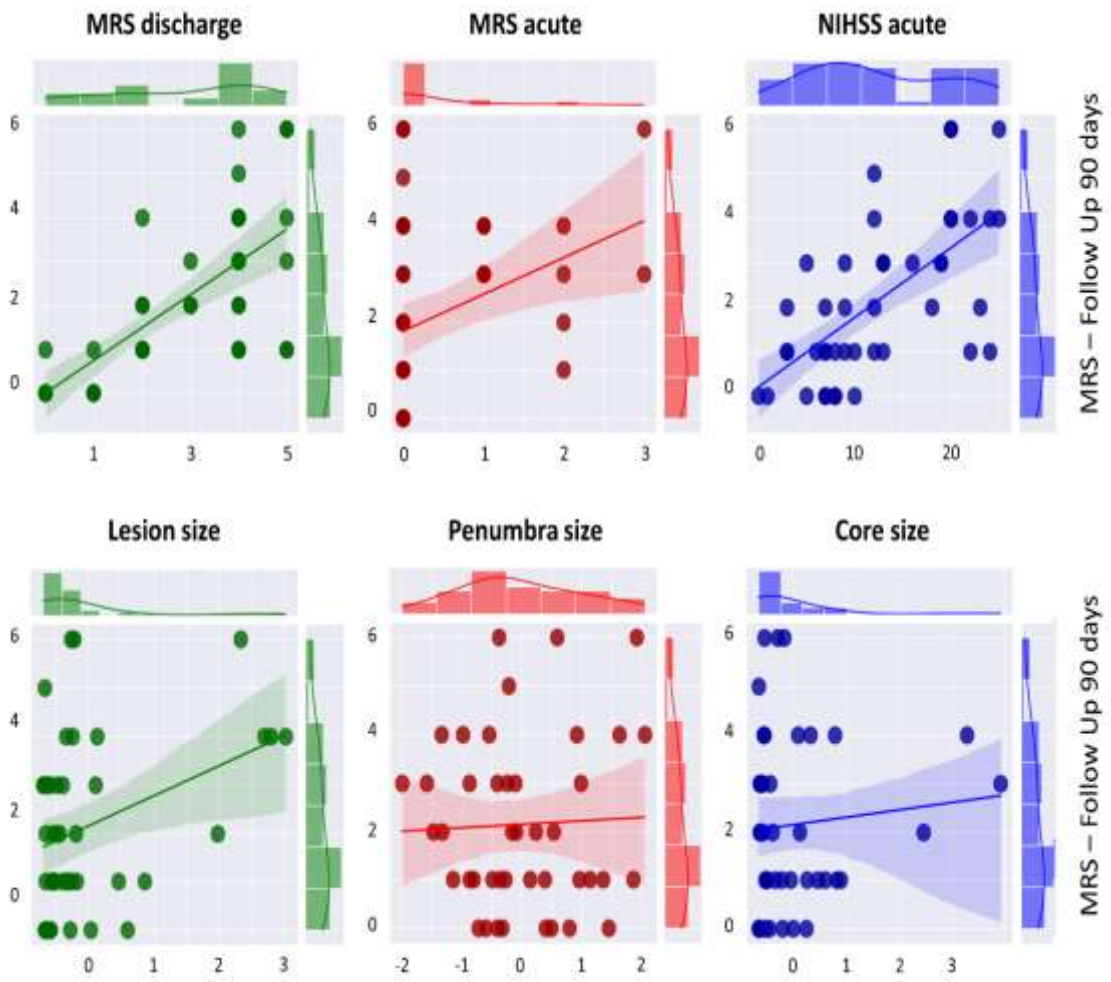


Figure 22

Linear regression scatter plots showing a linear correlation between stroke clinical features (MRS discharge, MRS acute, and NIHSS acute) and MRS-follow up 90 days. They also demonstrate the absence of a linear relationship with volumetric parameters (lesion, penumbra, and core size).

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Next, we evaluated, in multi-regression models, the influence of clinical, lesion, and disconnection variables.

We tested four models, including different combinations of variables, to analyze their power in predicting 90-day mRS, after mechanical thrombectomy.
In the first model (M1), we evaluated the prediction of mRS at 3 months (expressed as explained variance, or R-squared) from the prognostic factors age, pre-mRS, and NIHSS at presentation. The level of prediction was around 52% [R-squared=0.517].
When we added, in the second model (M2), ASPECTS, core, and penumbra volume, the prediction increased to 56% [R-squared=0.559].
In the third model (M3), we added SDC to age, pre-mRS, and NIHSS at presentation, and the prediction of the 90-day mRS was around 54% [R-squared=0,544].
Finally, we created a fourth model (M4), including age, pre-mRS, post-mRS, and NIHSS at presentation and we showed that its level of prediction was around 62% [R-squared=0.624].

Then, we performed an ANOVA analysis, which showed a statistically significant difference between the four models [$F=29,97$, $p<0.001$]. M4 was the model providing the highest adjusted R-squared [Adj.R-squared=0.614], while the other models, respectively M1[Adj.R-squared=0.517], M2[Adj.R-squared=0.504], M3[Adj.R-squared=0.549] presented lower values.
Consequently, we elaborated a post-hoc analysis, to compare the differences between models, in terms of prediction (Tab.VII).

	Group 1	Group 2	Diff	Lower	Upper	p-value
0	M1	M2	0.014	-0.020	0.047	0.679
1	M1	M3	0.032	-0.002	0.065	0.068
2	M1	M4	0.097	0.064	0.131	0.001
3	M2	M3	0.046	0.012	0.079	0.003
4	M2	M4	0.111	0.077	0.144	0.001
5	M3	M4	0.065	0.032	0.099	0.001

Table VII-Post-hoc analysis showing differences between models (M1-M4), in terms of 90-day outcome prediction.

This analysis showed a significant difference [$p<0.05$] between M2 and M3, in terms of explained variance or R-squared. In particular, the third model, based on SDC, seemed to predict 90-day mRS better than the second model, based on ASPECTS, core, and penumbra volume.

Moreover, M4, individually compared to M1, M2, and M3, was always significantly superior [$p<0.001$] in predicting 90-day outcome.

We performed a box plot representation (Fig.23) to provide a graphical summary of these results.

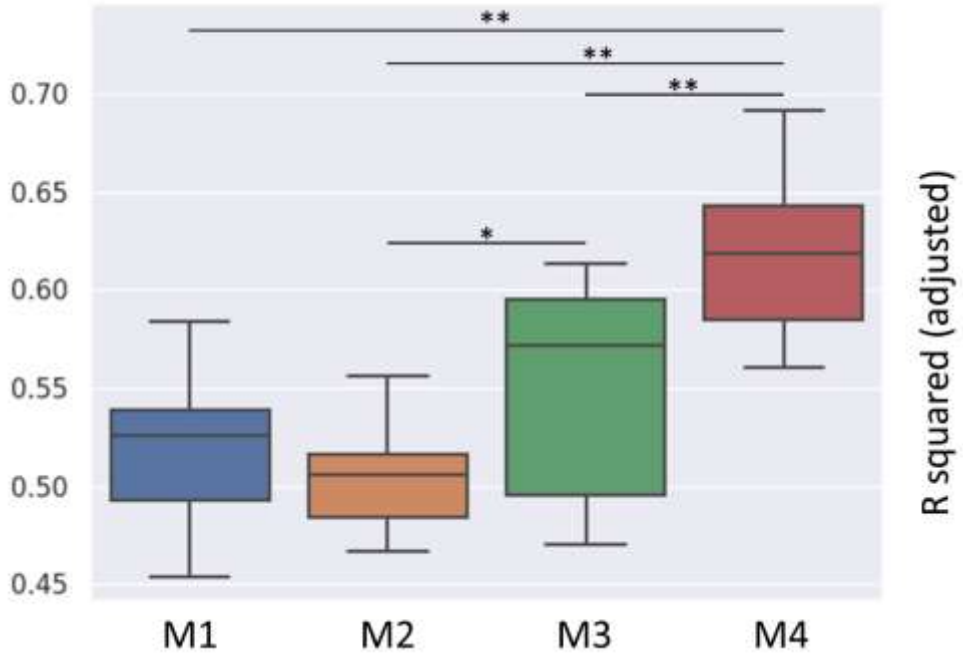

Figure 23

*Box plots showing the distribution of the explained variance or R-squared in four predictive models (M1-M4). Significant differences between models are represented by *marks ($p<0.05$) and **marks ($p<0.001$).*

Topological brain analysis

At the voxel-wise level, we investigated the relationship between brain recovery, expressed as Delta 90-day mRS – pre-mRS, and both lesion distribution and structural disconnection (SDC) maps.

Figure 24 provides a graphical representation of the results.

In conclusion, we found that lesions, affecting predominantly the left corticospinal tract and the corresponding structural white matter disconnections, extending to the cingulum, and bilaterally, through the corpus callosum, were associated with a poor recovery and functional outcome, 90-days after mechanical thrombectomy.

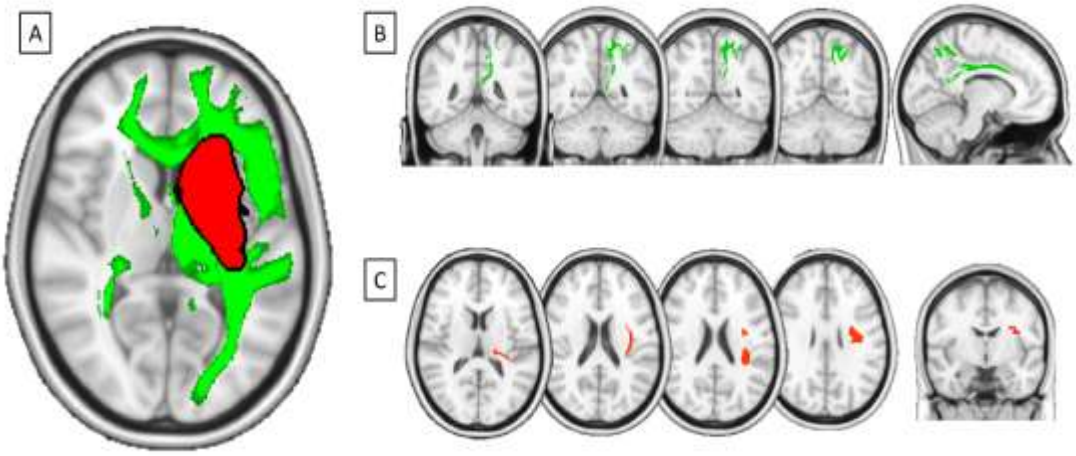

Figure 24

Panel A: individual case, showing the lesion (red) and the corresponding SDC (green).

Panel B and C: results showing voxels positively associated with the Delta 90-day mRS-pre-mRS, respectively in SDC and lesion distribution maps.

DISCUSSION

This study investigated the role of different clinical and radiological stroke characteristics in predicting long-term functional outcome in stroke after acute mechanical thrombectomy. In particular, we focused on stroke volumetric variables (lesion, core, and penumbra size, ASPECTS) and white matter structural disconnection (SDC), compared to clinical features (pre-mRS, post-mRS, and NIHSS at presentation).

Overall, we found that long-term outcome is significantly predicted by the acute level of impairment and pre-stroke function, as well as by information about lesion location. In contrast, volumetric information about the lesion core or penumbra area seem to have a minor role in prediction after endovascular treatment.

Anatomy of stroke

In our study, the stroke topography was predominantly subcortical, concentrated in the caudate, internal capsule, lentiform nucleus, and thalamus, with limited cortical lesions, extending to the insular and temporoparietal cortex. The analysis was based on automatic clustering on the Harvard-Oxford cortical and subcortical maps. These results reproduce Corbetta et al.(81), Bisogno et al.(79), and other prospective clinical sample studies(110,111).In particular, Corbetta et al. observed a predominantly subcortical topography, with only 13% of lesions located in the cortex. Wessels et al.(111) found 14% of cortical lesions, while Kang et al. (110) observed 33% of cortico-subcortical damage and only 16% of cortical impairment. In our sample, lesions were mainly located in the left hemisphere. While this probably reflects the small clinical sample, these findings are in line with Hedna et al. (2013) (112) and Naess et al. (2006) (113) studies. Specifically, Hedna et al. observed that left hemisphere stroke (LHS), in all vascular distributions, was more common than the right one (RHS) (54% vs. 46%, p=0.0073). Furthermore, Naess et al. observed in their study that a total of 98 patients had left hemisphere stroke, while 70 patients had right hemisphere lesions. The physiological basis of this significant difference could be mostly explained by the higher incidence of infarction in the left middle cerebral artery (MCA) territory compared with the right

MCA territory. In conclusion, the lesion distribution in our study (as shown in fig. 21) was similar to that observed in recent prospective studies and can represent the general stroke population.

Characterization of prognostic factors for post stroke outcome prediction

Clinical factors

The results of the linear regression analysis showed a positive significant correlation between 90-day mRS and clinical prognostic factors, pre-mRS, NIHSS at presentation, and post-mRS.

The first model (M1, baseline clinical model),only based on clinical pre-treatment factors (age, pre-mRS, and NIHSS at presentation) explained more than 52% of the variance.

These findings are supported by previous studies, showing the strength of the modified Rankin Scale (mRS) as an outcome predictor.

In particular, ElHabr et al. (114), analyzing a pool of 280 acute ischemic stroke patients, observed that a post-mRS at discharge of 3–5 predicted unfavourable outcomes (90-day mRS 3–6), while a post-mRS of 0-2 predicted favourable outcomes (90-day mRS 0–2).

Moreover, NIHSS has been repeatedly validated as an excellent predictor of patients' outcome. Specifically, Muir et al. (103), studying a cohort of 408 subjects, found that NIHSS at presentation best predicts 3-month outcome, with sensitivity to poor prognosis of 71%, specificity of 90%, and overall accuracy of 83%.

The relationship between the mRS before the stroke and long term outcome suggests that a good clinical status, hence good brain function pre-stroke, is protective of the detrimental effect of a stroke. Also, the degree of acute impairment correlates with long term outcome as more severe deficits acutely correlate with lower outcome. Both of these findings likely reflect the additive effect of recovery mechanisms. Studies (see Krakauer(115)) indicate that recovery of function is proportional to the degree of initial impairment (baseline function in the case of pre-mRS). Most patients recover about 70% of their acute impairment, which

means that a patient with severe deficits will recover to a moderate level, while a patient with mild impairment will recover fully.

Apparently, our results show that the proportional rule accounts also for baseline functional status.

The fourth model (M4) added the discharge mRS to the previous indices, i.e. pre-mRS, post-mRS, and NIHSS at admission.

The model explained more than 62% of the variance and confirmed the importance of patients ʾclinical presentation both before and after mechanical thrombectomy.

In the ANOVA analysis, we found that M4 was the most predictive model and it showed a strongly significant difference ($p<0.001$) with M1, M2, and M3, in the post-hoc analysis.

The relationship 90-day mRS with discharge mRS is consistent with the idea that most recovery occurs in the first few weeks, and that the degree of early recovery relates with long term outcome: the stronger is early recovery, the higher will be the final outcome.

Radiological volumetric indices

We performed a linear regression analysis to evaluate the correlation between 90-day mRS and volumetric parameters: lesion, penumbra, and core size.

We didn't observe a significant relationship, thus suggesting that infarct volume, analyzed both before (core and penumbra dimensions) and after (final lesion size) mechanical thrombectomy, do not relate to patients'3-month outcome.

The second model (M2, baseline clinical +volumetric radiological) tested the previously significant clinical variables, but also added the standard radiological features used in clinical practise (CT ASPECT score, core, and penumbra volumes).

This model explained 56% of the variance, but, according to the post-hoc analysis, there was no significant difference with the first model (M1).

Hence, surprisingly, the addition of ASPECTS, core, and penumbra volume didn't increase significantly the prognostic accuracy of the model.

This negative finding has several implications. First, the volume of the lesion measured in different ways does not relate to the final outcome post-stroke. Interestingly, neither the volume of the lesion pre (perfusion, ASPECT) nor post (final lesion) thrombectomy relate to 3-month functional status hence neurological function. This result may seem surprising if the model of brain-behavior

relationships is based on the localization of function to specific brain regions. This model predicts that larger lesions shall produce more dysfunction. However, a model of brain-behavior relationships based on distributed networks in which functions are distributed across multiple regions would be consistent with our negative findings.

Disconnection of the white matter indices

Based on several recent studies showing the importance of white matter damage and disconnection in stroke (5,79–81), we added an index of white matter disconnection. This index computes in an atlas of white matter connections of healthy subjects the number of white matter connections affected by the lesion. This index is computed voxel-by-voxel and averaged across voxels within the lesion. What is important is that since most connections are distant, i.e. connecting the lesion site with remote regions, this index somehow takes into account the effects of the lesion on the rest of the brain.

Therefore, we tested a third model (M3) (baseline clinical +topological model), to analyze the role of structural white matter disconnection (SDC) as a prognostic factor after EVT, in addition to baseline clinical variables.

This M3 model explained 54% of the 90-day mRS scores and showed, in the post-hoc analysis, a significant difference with the second model (M2).

Our findings suggest that structural white matter disconnection predicts 90-day mRS better than other radiological variables (ASPECTS, core, and penumbra volumes).

These results are in line with different recent studies, which investigated the role of structural disconnection, in predicting 90-day prognosis after the acute treatment (systemic thrombolysis or mechanical thrombectomy).

Rosso et al. (1) observed that disconnections in well-localized regions of the periventricular white matter and internal capsule were associated with poor outcomes after systemic thrombolysis.

Consequently, they found that the impact of structural white matter disconnection on disability was major than the one of core and penumbra volumes.

Moreover, Schlemm et al. (3) demonstrated that treatment with alteplase (r-tPA) reduced both ischemic lesion growth and loss of structural connectivity, measured 22 to 36 hours after stroke. This treatment significantly attenuated structural

disconnection, especially in brain regions involved in motor control and language. Secondly, they observed that prevented loss of connectivity, associated with infarct growth reduction, explained up to 33% of the total effect of alteplase on good clinical prognosis (90-day mRS 0-2), while prevented infarct growth alone only mediated 8.3% of the clinical effect of thrombolysis on 3-month mRS.
Furthermore, Regenhardt et al.(4), using MRI after thrombectomy, have noticed that lesions affecting white matter tracts had the highest predictive power for 90-day mRS.

The role of lesion topography for outcome prediction

We investigated the role of lesion topography and its corresponding white matter structural disconnection, in terms of prediction of brain recovery, represented by Delta 90-day mRS- pre-mRS.
We found that subcortical lesions, in particular the involvement of the left corticospinal tract and its deriving structural disconnection (SDC), which was extended to the cingulum and corpus callosum, were significantly associated with poor recovery, 3 months after the endovascular treatment.
To explain these results, we refer to the well-established mechanism of focal diaschisis, described by Carrera and Tononi (88). Stroke lesions in the white matter can disconnect distant cortical regions, thus causing specific correlated behavioral deficits, associated with a different functional brain recovery.(Corbetta et al.-2015(81); Bisogno et al.-2021(79)).
Moreover, Ramsay, Corbetta, et al. (2017) (95) evaluated post-stroke recovery in multiple behavioral domains.
In particular, they observed that damage of specific white matter tracts determined a poorer recovery across several domains: superior longitudinal fasciculus lesions affected memory recovery, posterior arcuate fasciculus damage influenced language, and corticospinal tract impairment affected motor recovery.
Furthermore, Rosso et al.(1), in a multivariate analysis, demonstrated that the best predictor of outcome was the ischemic damage of the corticospinal tract, which classified patients with 78% of accuracy.
Our findings, in terms of stroke lesion topography and SDC, could be explained by the importance of the corticospinal tract damage after stroke. Motor deficits,

resulting from this lesion, represent the main element of post-stroke disability, affecting almost 50% of the survivors.

The corticospinal tract controls the primary motor activity and is involved in voluntary movements. Moreover, CST (corticospinal tract) damage causes also the alteration of synergistic movements, such as ambulation, and daily activities, thus consistently influencing functional outcome, measured by mRS after three months. Maraka et al.(116) found a significant correlation between the degree of CST damage and the severity of motor impairment in acute, subacute, and chronic phases. They also observed an association between the degree of CST lesions at baseline and motor recovery at follow-up.

Why is lesion topography a better prognostic factor than lesion volume?

As discussed above, lesions of the left corticospinal tract correlate with a poorer 90-day recovery, because they determine consistent motor deficits, affecting the autonomy of the patient in daily activities and ambulation, as measured by mRS. The predominantly left lesion distribution was previously discussed (see "Anatomy of stroke" above). On the other hand, our findings seem to show that lesion volume, both before and after mechanical thrombectomy, is not independently associated with poor outcomes.

The logical explanation of our results, as postulated also by Wu et al. in their study (117), is that if stroke damages behaviourally eloquent regions, we can expect a relevant impact on the patients' 90-day prognosis. While this possibility logically increases with the increase of lesion volume, our results show this only moderately correlates with outcome prediction (118).

The effort in the research of prognostic factors is justified, because it allows, by evaluating the pre-test variables, an easier identification of patients, eligible for mechanical thrombectomy. Our evidence shows that the weight of variables such as ASPECTS, currently used in clinical practice, or core and penumbra volumes, obtained through perfusion CT, is minimal. However, it is fundamental to notice that we only analyzed a sample of patients who met the inclusion criteria for

endovascular treatment (i.e. ASPECTS greater than or equal to 6 and infarct core <70 ml, penumbra area> 15 ml, volume ratio between penumbra and core areas ≥1.8). Despite this, we, interestingly, found that an ASPECTS value of 6 or 10 does not seem to explain patients'90-day functional outcome, after mechanical thrombectomy.

Consequently, remembering that "Time is Brain"(25), it could be useful to opt for a quicker selection of patients, more independent from these radiological criteria, and more oriented on the objective clinical evaluation.

This approach may allow more patients to benefit from the endovascular treatment.

Regarding the role of lesion topography, it shall be a sensitive measure of brain recovery after acute treatment. It could be used, associated with the previously mentioned variables, to implement neuro-stimulation therapies, such as TMS and tDCS, specifically in the areas involved in poor outcomes.

Another interesting finding to discuss is that post-mRS significantly improves prediction. We noticed that some patients, in the acute phase already, recover better than others. This means that, between pre-mRS and post-mRS, during the hospitalization period, something happens that we do not capture with the other lesional variables studied.

These results may reflect a functional reorganization, which varies according to the area concerned (i.e. node versus edge) and, therefore, to lesion topography.

Further studies, evaluating the role of reduced functional connectivity (FDC) after the endovascular treatment, could implement the accuracy of these models.

Moreover, to assess patients' deficits and outcome, we used NIHSS and then mRS, which are not very accurate.

Despite this, topography seems to have a predominant role on volume. We would expect this to be even more relevant, when we use more precise assessments with a greater focus on cognitive domains.

Limitations

The small sample size was an important limitation of our study. The variance explained for each predictive model could be higher with a larger sample. In addition, the retrospective model of the study caused difficulties in collecting data,

especially at the 3-month follow-up. In particular, we focused on the 90-day mRS, which is a strong biomarker of functional motor prognosis, but its implementation with other measures, such as more in-depth functional outcome evaluations (i.e. SIS (Stroke Impact Scale) v3.0(119)), is required, to explore the recovery of other different cognitive domains. Moreover, a study of functional disconnection, based on fMRI, could have better predicted the variance, in the analyzed models.

Further prospective studies, with a larger sample size, are required to overcome these limitations.

CONCLUSION

Mechanical thrombectomy represents an innovative and efficient intervention in acute stroke treatment. Recent studies and the description of valuable prognostic factors have progressively increased the pool of eligible patients. In line with recent works, we investigated in patients, who met the inclusion criteria for the endovascular treatment, how known clinical and radiological features correlate with functional outcome in comparison with lesion topographical data.

We observed that the clinical presentation of patients, both at admission and at discharge, is the most representative prognostic factor. Interestingly, radiological features, in eligible patients, such as ASPECTS, core, and penumbra volume, didn't show any significant correlation with 90-day mRS, while structural disconnection and lesion topography, in particular in the left corticospinal tract, were associated with a poorer recovery after endovascular treatment.

This suggests that lesion topography and the following white matter disconnection are more relevant than lesion volume for functional brain recovery and outcome. We show that acute functional recovery (mRS at discharge) increases our capacity of outcome prediction. This variability is not captured by volumetric lesional data and could be explained by differences in inter-subject functional reorganization following stroke.

These results provide important clinical and theoretical implications. While we only studied eligible patients (according to the most recent randomized controlled trials), these analyses could provide the basis of future prognostic factors for endovascular treatment eligibility. In addition, they define the role of lesion topography as a sensitive measure of brain recovery after acute treatment. Further studies are required to implement neuro-stimulation therapies, such as TMS and tDCS, to normalize connectivity, specifically in the areas associated with a poor outcome. Finally, they reflect the possible role of early functional reorganization following a focal lesion in stroke prognosis.

APPENDIX

Baseline		
Pre-mRS	M= 0,48	σ=0,90
0-2	94,0%	
3-6	6,0%	
NIHSS at presentation	M=12,38	σ=6,77
Discharge		
Post mRS	M= 2,82	σ=1,62
0-2	42,0%	
3-6	58,0%	
NIHSS	M=5,5	σ= 6,16
Follow-up		
Days to FU	M= 94,3	σ=50,56
mRS at FU	M=2,18	σ=1,81
0-2	60,0%	
3-6	40,0%	

Table A1- Stroke-related clinical variables.

Stroke -related radiological variables		
ASPECTS	M=8,58	σ=1,31
Heidelberg Bleeding Classification		
0	68,0%	
HI1-2	18,0%	
PH1-2	8,0%	
3	6,0%	

Table A2- Stroke-related radiological variables.

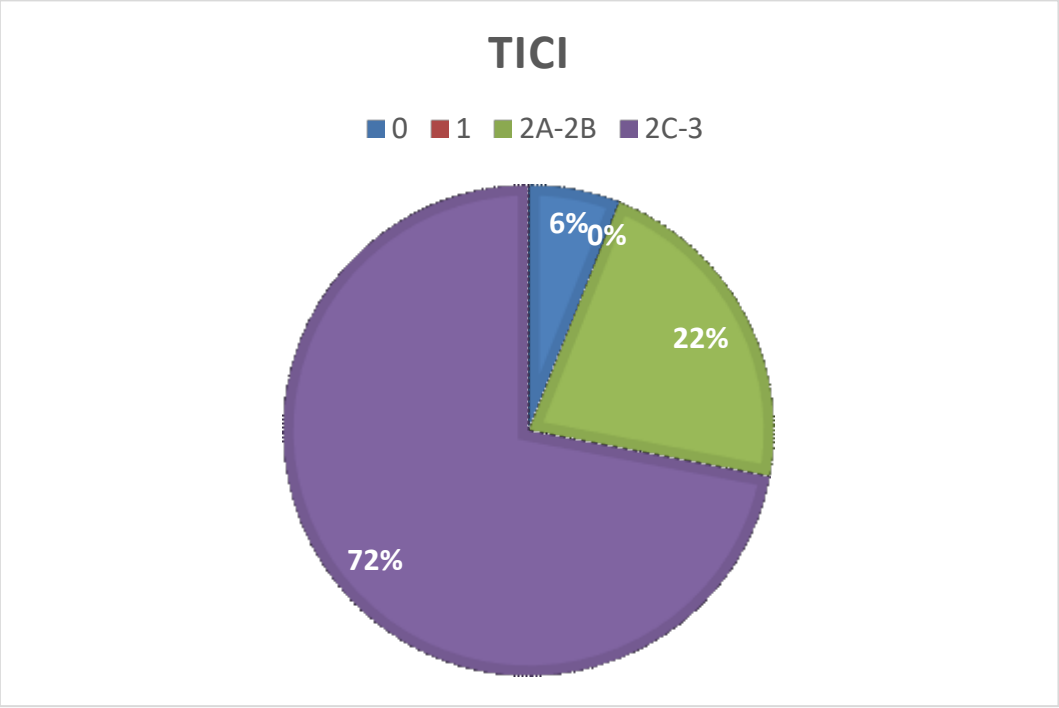

Figure A1

Pie chart showing the percentage distribution of rTICI in the patients' pool (n=50).

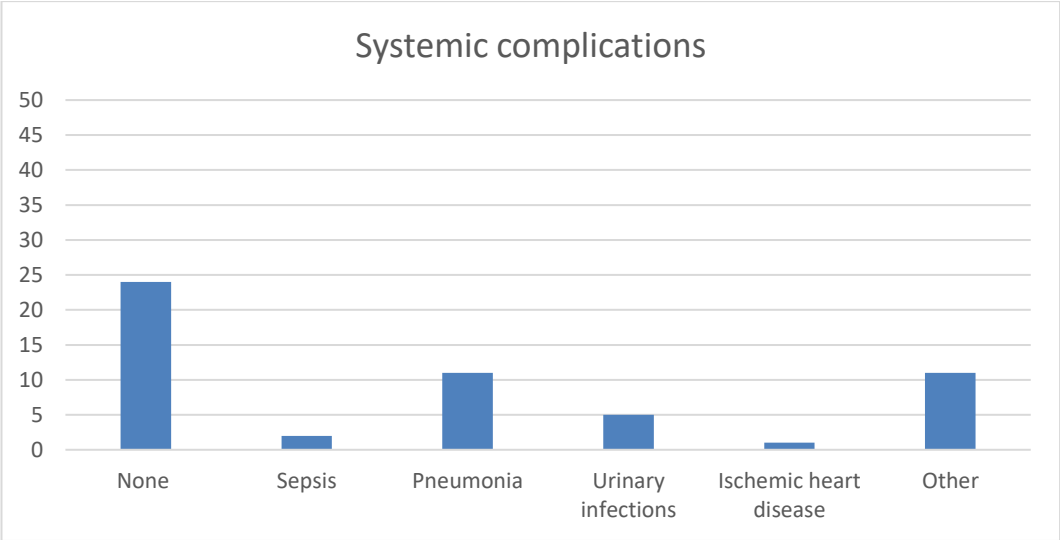

Figure A2

Bar chart showing the number of systemic complications in the patients' pool (n=50).

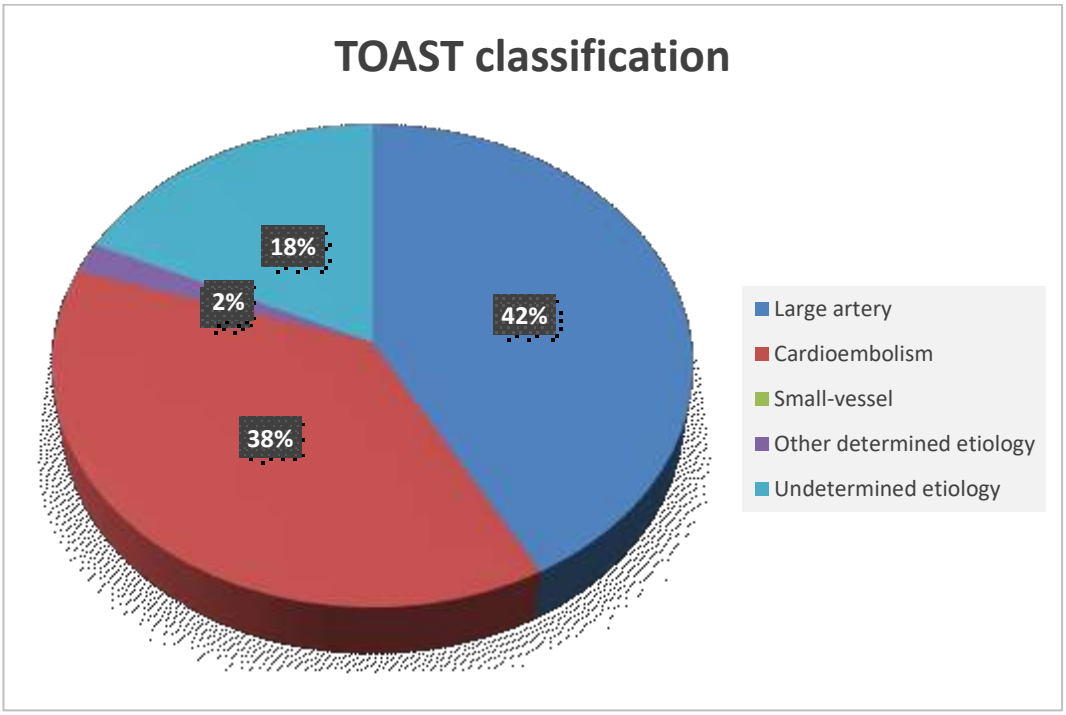

Figure A3

Pie chart showing the percentage distribution of TOAST classification etiologies in the patients' pool (n=50).

```
m = [0.09874801 0.62285687 0.14760899], q = 0.024355785982286715
MODEL 1
                            OLS Regression Results
==============================================================================
Dep. Variable:               mRS_FU90   R-squared:                       0.517
Model:                            OLS   Adj. R-squared:                  0.480
Method:                 Least Squares   F-statistic:                     13.91
Date:                Fri, 17 Jun 2022   Prob (F-statistic):           2.58e-06
Time:                        10:43:44   Log-Likelihood:                -69.353
No. Observations:                  43   AIC:                             146.7
Df Residuals:                      39   BIC:                             153.8
Df Model:                           3
Covariance Type:            nonrobust
==============================================================================
                             coef    std err          t      P>|t|      [0.025
0.975]
------------------------------------------------------------------------------
const                      0.0244      0.415      0.059      0.954      -0.816
0.864
Age_scaled                 0.0987      0.212      0.466      0.644      -0.330
0.527
preMRS                     0.6229      0.244      2.557      0.015       0.130
1.116
NIHSS_at_presentation      0.1476      0.028      5.246      0.000       0.091
0.205
==============================================================================
Omnibus:                        3.181   Durbin-Watson:                   2.165
Prob(Omnibus):                  0.204   Jarque-Bera (JB):                2.211
Skew:                           0.533   Prob(JB):                        0.331
Kurtosis:                       3.316   Cond. No.                         31.8
==============================================================================


m = [-0.09589543  0.57272097  0.15382018  0.35252753  0.32763266 -0.06648989], q =
-3.0232991379671703
MODEL 2
                            OLS Regression Results
==============================================================================
Dep. Variable:               mRS_FU90   R-squared:                       0.559
Model:                            OLS   Adj. R-squared:                  0.485
Method:                 Least Squares   F-statistic:                     7.596
Date:                Fri, 17 Jun 2022   Prob (F-statistic):           2.60e-05
Time:                        10:43:48   Log-Likelihood:                -67.405
No. Observations:                  43   AIC:                             148.8
Df Residuals:                      36   BIC:                             161.1
Df Model:                           6
Covariance Type:            nonrobust
==============================================================================
                             coef    std err          t      P>|t|      [0.025
0.975]
------------------------------------------------------------------------------
```

```
const                    -3.0233      1.867     -1.619      0.114      -6.810
0.763
Age_scaled               -0.0959      0.241     -0.398      0.693      -0.585
0.393
preMRS                    0.5727      0.252      2.275      0.029       0.062
1.083
NIHSS_at_presentation     0.1538      0.029      5.279      0.000       0.095
0.213
ASPECTS                   0.3525      0.215      1.642      0.109      -0.083
0.788
core_scaled               0.3276      0.270      1.215      0.232      -0.219
0.874
penumbra_scaled          -0.0665      0.219     -0.303      0.764      -0.511
0.378
==============================================================================
Omnibus:                        2.400   Durbin-Watson:                   2.182
Prob(Omnibus):                  0.301   Jarque-Bera (JB):                1.499
Skew:                           0.427   Prob(JB):                        0.473
Kurtosis:                       3.330   Cond. No.                         159.
==============================================================================

Notes:
[1] Standard Errors assume that the covariance matrix of the errors is correctly s
pecified.


m = [0.16653055 0.33014524 0.64540134 0.12447788], q = 0.30272632563064716
MODEL 3
                            OLS Regression Results
==============================================================================
Dep. Variable:               mRS_FU90   R-squared:                       0.544
Model:                            OLS   Adj. R-squared:                  0.496
Method:                 Least Squares   F-statistic:                     11.32
Date:                Mon, 20 Jun 2022   Prob (F-statistic):           3.79e-06
Time:                        07:46:17   Log-Likelihood:                -68.120
No. Observations:                  43   AIC:                             146.2
Df Residuals:                      38   BIC:                             155.0
Df Model:                           4
Covariance Type:            nonrobust
==============================================================================
=======
                             coef    std err          t      P>|t|      [0.025
0.975]
------------------------------------------------------------------------------
-------
const                     0.3027      0.449      0.674      0.504      -0.607
1.212
Age_scaled                0.1665      0.213      0.780      0.440      -0.266
0.599
SDC05_scaled              0.3301      0.220      1.497      0.143      -0.116
0.776
preMRS                    0.6454      0.240      2.686      0.011       0.159
1.132
```

```
NIHSS_at_presentation     0.1245      0.032      3.925      0.000       0.060
0.189

m = [0.02662781 0.44126917 0.46644689 0.0967958 ], q = -0.5456376372382783
MODEL 4
                            OLS Regression Results
==============================================================================
Dep. Variable:                mRS_FU90   R-squared:                       0.624
Model:                            OLS   Adj. R-squared:                  0.585
Method:                 Least Squares   F-statistic:                     15.77
Date:                Fri, 17 Jun 2022   Prob (F-statistic):           1.09e-07
Time:                        10:44:11   Log-Likelihood:                -63.957
No. Observations:                  43   AIC:                             137.9
Df Residuals:                      38   BIC:                             146.7
Df Model:                           4
Covariance Type:            nonrobust
==============================================================================
=======
                             coef    std err          t      P>|t|      [0.025
0.975]
------------------------------------------------------------------------------
-------
const                     -0.5456      0.410     -1.332      0.191      -1.375
0.283
Age_scaled                 0.0266      0.191      0.140      0.890      -0.359
0.413
postMRS                    0.4413      0.134      3.293      0.002       0.170
0.713
preMRS                     0.4664      0.223      2.093      0.043       0.015
0.918
NIHSS_at_presentation      0.0968      0.030      3.281      0.002       0.037
0.157
==============================================================================
Omnibus:                        1.720   Durbin-Watson:                   2.193
Prob(Omnibus):                  0.423   Jarque-Bera (JB):                1.652
Skew:                           0.434   Prob(JB):                        0.438
Kurtosis:                       2.590   Cond. No.                         35.6
```

Table A3- Linear regression analysis.

BIBLIOGRAPHY

1. Rosso C, Samson Y. The ischemic penumbra: The location rather than the volume of recovery determines outcome. Current opinion in neurology. 2013 Nov 23;27.

2. Weaver NA, Kuijf HJ, Aben HP, Abrigo J, Bae HJ, Barbay M, et al. Strategic infarct locations for post-stroke cognitive impairment: a pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts. Lancet Neurol. 2021 Jun;20(6):448–59.

3. Schlemm E, Ingwersen T, Königsberg A, Boutitie F, Ebinger M, Endres M, et al. Preserved structural connectivity mediates the clinical effect of thrombolysis in patients with anterior-circulation stroke. Nat Commun. 2021 May 10;12(1):2590.

4. Regenhardt RW, Bonkhoff AK, Bretzner M, Etherton MR, Das AS, Hong S, et al. Association of Infarct Topography and Outcome After Endovascular Thrombectomy in Patients With Acute Ischemic Stroke. Neurology. 2022 Mar 15;98(11):e1094–103.

5. Ramsey L, Siegel J, Lang C, Strube M, Shulman G, Corbetta M. Behavioural clusters and predictors of performance during recovery from stroke. Nat Hum Behav. 2017;1:0038.

6. Karenberg A. Historic review: select chapters of a history of stroke. Neurol Res Pract. 2020;2:34.

7. Tsoucalas G, Papaioannou TG, Karamanou M. The Hippocratic Doctrine of 'the Acute Brain Suffering' as the Brain Stroke. J Stroke Cerebrovasc Dis. 2019 Feb;28(2):412–7.

8. Caplan Louis R. Caplan's stroke. A clinical approach. IV. Saunders Elsevier; 2009.

9. Khuda I, Al-Shamrani F. Stroke medicine in antiquity: The Greek and Muslim contribution. J Family Community Med. 2018;25(3):143–7.

10. Markatos K, Chytas D, Tsakotos G, Karamanou M, Piagkou M, Mazarakis A, et al. Andreas Vesalius of Brussels (1514-1564): his contribution to the field of functional neuroanatomy and the criticism to his predecessors. Acta Chir Belg. 2020 Dec;120(6):437–41.

11. Schutta HS. Morgagni on apoplexy in De Sedibus: a historical perspective. J Hist Neurosci. 2009;18(1):1–24.

12. ICD-11 [Internet]. [cited 2022 Apr 19]. Available from: https://icd.who.int/en

13. Coupland AP, Thapar A, Qureshi MI, Jenkins H, Davies AH. The definition of stroke. J R Soc Med. 2017 Jan;110(1):9–12.

14. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJB, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Jul;44(7):2064–89.

15. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009 Jun;40(6):2276–93.

16. Chen PH, Gao S, Wang YJ, Xu AD, Li YS, Wang D. Classifying Ischemic Stroke, from TOAST to CISS. CNS Neurosci Ther. 2012 Jun;18(6):452–6.

17. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35–41.

18. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). Cerebrovasc Dis. 2013;36(1):1–5.

19. Angelini Corrado, Battistin Leontino. Neurologia clinica. II. Esculapio; 2014. 846 p.

20. Anastasi Giuseppe et al. Anatomia umana. Vol. III. Edi-Ermes; 2010.

21. Nogueira RC, Beishon L, Bor-Seng-Shu E, Panerai RB, Robinson TG. Cerebral Autoregulation in Ischemic Stroke: From Pathophysiology to Clinical Concepts. Brain Sci. 2021 Apr 16;11(4):511.

22. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. Int J Mol Sci. 2020 Oct 15;21(20):E7609.

23. Woodruff TM, Thundyil J, Tang SC, Sobey CG, Taylor SM, Arumugam TV. Pathophysiology, treatment, and animal and cellular models of human ischemic stroke. Mol Neurodegener. 2011 Jan 25;6:11.

24. Qin C, Zhou LQ, Ma XT, Hu ZW, Yang S, Chen M, et al. Dual Functions of Microglia in Ischemic Stroke. Neurosci Bull. 2019 Oct;35(5):921–33.

25. Saver JL. Time is brain--quantified. Stroke. 2006 Jan;37(1):263–6.

26. Herpich F, Rincon F. Management of Acute Ischemic Stroke. Crit Care Med. 2020 Nov;48(11):1654–63.

27. ISO - Italian Stroke Organization [Internet]. [cited 2022 Apr 19]. Available from: http://www.iso-spread.it/index.php?azione=capitoli

28. Seung-Hoon Lee. Stroke revisited: diagnosis and treatment of ischemic stroke. Springer; 2017.

29. Kazi SA, Siddiqui M, Majid S. Stroke Outcome Prediction Using Admission Nihss In Anterior And Posterior Circulation Stroke. J Ayub Med Coll Abbottabad. 2021 Jun;33(2):274–8.

30. Chalos V, van der Ende NAM, Lingsma HF, Mulder MJHL, Venema E, Dijkland SA, et al. National Institutes of Health Stroke Scale: An Alternative Primary Outcome Measure for Trials of Acute Treatment for Ischemic Stroke. Stroke. 2020 Jan;51(1):282–90.

31. Bielewicz JE, Kurzepa J, Kamieniak P, Daniluk B, Szczepańska-Szerej A, Rejdak K. Clinical and biochemical predictors of late-outcome in patients after ischemic stroke. Ann Agric Environ Med. 2020 Jun 19;27(2):290–4.

32. Braileanu M, Weinberg BD, Hu R, Hoch MJ. Appearance of cerebral infarct fogging on CT perfusion. Radiol Case Rep. 2019 Jul;14(7):889–93.

33. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol. 2001 Sep;22(8):1534–42.

34. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000 May 13;355(9216):1670–4.

35. Aviv RI, Mandelcorn J, Chakraborty S, Gladstone D, Malham S, Tomlinson G, et al. Alberta Stroke Program Early CT Scoring of CT perfusion in early stroke visualization and assessment. AJNR Am J Neuroradiol. 2007 Dec;28(10):1975–80.

36. Lu WZ, Lin HA, Bai CH, Lin SF. Posterior circulation acute stroke prognosis early CT scores in predicting functional outcomes: A meta-analysis. PLoS One. 2021;16(2):e0246906.

37. Thomalla G, Cheng B, Ebinger M, Hao Q, Tourdias T, Wu O, et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4·5 h of symptom onset (PRE-FLAIR): a multicentre observational study. Lancet Neurol. 2011 Nov;10(11):978–86.

38. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset | NEJM [Internet]. [cited 2022 Apr 22]. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1804355

39. Boujan T, Neuberger U, Pfaff J, Nagel S, Herweh C, Bendszus M, et al. Value of Contrast-Enhanced MRA versus Time-of-Flight MRA in Acute Ischemic Stroke MRI. AJNR Am J Neuroradiol. 2018 Sep;39(9):1710–6.

40. Boespflug O. [The Doppler test: its practical importance in the study of lesions of the supra-aortic trunks]. Phlebologie. 1978 Dec;31(4):343–53.

41. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. Stroke. 2006 May;37(5):1334–9.

42. Lev MH, Gonzalez RG, Schaefer PW, Koroshetz WJ, Dillon WP, Wintermark M. Cerebral blood flow thresholds in acute stroke triage. Stroke. 2006 Sep;37(9):2202; author reply 2203.

43. Khandelwal N. CT perfusion in acute stroke. Indian J Radiol Imaging. 2008 Nov;18(4):281–6.

44. Heiss WD. PET imaging in ischemic cerebrovascular disease: current status and future directions. Neurosci Bull. 2014 Aug 19;30(5):713–32.

45. Masdeu JC, Brass LM. SPECT imaging of stroke. J Neuroimaging. 1995 Jul;5 Suppl 1:S14-22.

46. Munich SA, Shakir HJ, Snyder KV. Role of CT perfusion in acute stroke management. Cor et Vasa. 2016 Apr 1;58(2):e215–24.

47. Copen WA, Schaefer PW, Wu O. MR Perfusion Imaging in Acute Ischemic Stroke. Neuroimaging Clin N Am. 2011 May;21(2):259–83.

48. Albers GW. Expanding the window for thrombolytic therapy in acute stroke. The potential role of acute MRI for patient selection. Stroke. 1999 Oct;30(10):2230–7.

49. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012 Jun 23;379(9834):2364–72.

50. Tissue Plasminogen Activator for Acute Ischemic Stroke. New England Journal of Medicine. 1995 Dec 14;333(24):1581–8.

51. Hacke W, Brott T, Caplan L, Meier D, Fieschi C, von Kummer R, et al. Thrombolysis in acute ischemic stroke: controlled trials and clinical experience. Neurology. 1999;53(7 Suppl 4):S3-14.

52. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. New England Journal of Medicine. 2008 Sep 25;359(13):1317–29.

53. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. New England Journal of Medicine. 2019 May 9;380(19):1795–803.

54. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015 Mar 12;372(11):1019–30.

55. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015 Mar 12;372(11):1009–18.

56. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. New England Journal of Medicine. 2015 Jan 1;372(1):11–20.

57. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015 Jun 11;372(24):2296–306.

58. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015 Jun 11;372(24):2285–95.

59. Lambrinos A, Schaink AK, Dhalla I, Krings T, Casaubon LK, Sikich N, et al. Mechanical Thrombectomy in Acute Ischemic Stroke: A Systematic Review. Can J Neurol Sci. 2016 Jul;43(4):455–60.

60. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016 Apr 23;387(10029):1723–31.

61. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018 Jan 4;378(1):11–21.

62. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018 Feb 22;378(8):708–18.

63. Nguyen TN, Abdalkader M, Nagel S, Qureshi MM, Ribo M, Caparros F, et al. Noncontrast Computed Tomography vs Computed Tomography Perfusion or Magnetic Resonance Imaging Selection in Late Presentation of Stroke With Large-Vessel Occlusion. JAMA Neurology. 2022 Jan 1;79(1):22–31.

64. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021 Oct;20(10):795–820.

65. Wei W, Li S, San F, Zhang S, Shen Q, Guo J, et al. Retrospective analysis of prognosis and risk factors of patients with stroke by TOAST. Medicine. 2018 Apr;97(15):e0412.

66. Raza SA, Rangaraju S. A Review of Pre-Intervention Prognostic Scores for Early Prognostication and Patient Selection in Endovascular Management of Large Vessel Occlusion Stroke. Interv Neurol. 2018 Apr;7(3–4):171–81.

67. Raoult H, Eugène F, Ferré JC, Gentric JC, Ronzière T, Stamm A, et al. Prognostic factors for outcomes after mechanical thrombectomy with solitaire stent. J Neuroradiol. 2013 Oct;40(4):252–9.

68. Cheng Z, Geng X, Rajah GB, Gao J, Ma L, Li F, et al. NIHSS Consciousness Score Combined with ASPECTS is a Favorable Predictor of Functional Outcome post Endovascular Recanalization in Stroke Patients. Aging Dis. 2021 Apr;12(2):415–24.

69. Costalat V, Lobotesis K, Machi P, Mourand I, Maldonado I, Heroum C, et al. Prognostic factors related to clinical outcome following thrombectomy in ischemic stroke (RECOST Study). 50 patients prospective study. European Journal of Radiology. 2012 Dec 1;81(12):4075–82.

70. Nie X, Pu Y, Zhang Z, Liu X, Duan W, Liu L. Futile Recanalization after Endovascular Therapy in Acute Ischemic Stroke. Biomed Res Int. 2018 May 9;2018:5879548.

71. Coulthard A. Modified treatment in cerebral ischemia (mTICI) score | Radiology Reference Article | Radiopaedia.org [Internet]. Radiopaedia. [cited 2022 Apr 24]. Available from: https://radiopaedia.org/articles/modified-treatment-in-cerebral-ischaemia-mtici-score

72. von Kummer R, Broderick JP, Campbell BCV, Demchuk A, Goyal M, Hill MD, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. Stroke. 2015 Oct;46(10):2981–6.

73. Pessin MS, Teal PA, Caplan LR. Hemorrhagic infarction: guilt by association? American Journal of Neuroradiology. 1991 Nov 1;12(6):1123–6.

74. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke. 1999 Nov;30(11):2280–4.

75. Gasca-González OO, Pérez-Cruz JC, Baldoncini M, Macías-Duvignau MA, Delgado-Reyes L. Neuroanatomical basis of Wallenberg syndrome. Cir Cir. 2020;88(3):376–82.

76. Benke T, Dazinger F, Pechlaner R, Willeit K, Clausen J, Knoflach M. Lesion topography of posterior cerebral artery infarcts. J Neurol Sci. 2021 Sep 15;428:117585.

77. Fisher CM. Lacunar strokes and infarcts: a review. Neurology. 1982 Aug;32(8):871–6.

78. Bailey EL, Smith C, Sudlow CLM, Wardlaw JM. Pathology of lacunar ischemic stroke in humans--a systematic review. Brain Pathol. 2012 Sep;22(5):583–91.

79. Bisogno AL, Favaretto C, Zangrossi A, Monai E, Facchini S, De Pellegrin S, et al. A low-dimensional structure of neurological impairment in stroke. Brain Commun. 2021 Jun 3;3(2):fcab119.

80. Corbetta M, Siegel JS, Shulman GL. On the low dimensionality of behavioral deficits and alterations of brain network connectivity after focal injury. Cortex. 2018 Oct;107:229–37.

81. Corbetta M, Ramsey L, Callejas A, Baldassarre A, Hacker CD, Siegel JS, et al. Common behavioral clusters and subcortical anatomy in stroke. Neuron. 2015 Mar 4;85(5):927–41.

82. Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci. 2010 Jun;14(6):277–90.

83. Fornito A, Zalesky A, Breakspear M. Graph analysis of the human connectome: promise, progress, and pitfalls. Neuroimage. 2013 Oct 15;80:426–44.

84. Contributions and challenges for network models in cognitive neuroscience | Nature Neuroscience [Internet]. [cited 2022 May 18]. Available from: https://www.nature.com/articles/nn.3690

85. Petersen SE, Sporns O. Brain Networks and Cognitive Architectures. Neuron. 2015 Oct 7;88(1):207–19.

86. Supekar K, Uddin LQ, Prater K, Amin H, Greicius MD, Menon V. Development of functional and structural connectivity within the default mode network in young children. NeuroImage. 2010 Aug 1;52(1):290–301.

87. O'Reilly JX, Croxson PL, Jbabdi S, Sallet J, Noonan MP, Mars RB, et al. Causal effect of disconnection lesions on interhemispheric functional connectivity in rhesus monkeys. Proceedings of the National Academy of Sciences. 2013 Aug 20;110(34):13982–7.

88. Carrera E, Tononi G. Diaschisis: past, present, future. Brain. 2014 Sep;137(Pt 9):2408–22.

89. Assenza G, Zappasodi F, Pasqualetti P, Vernieri F, Tecchio F. A contralesional EEG power increase mediated by interhemispheric disconnection provides negative prognosis in acute stroke. Restor Neurol Neurosci. 2013;31(2):177–88.

90. Obeso JA, Marti-Masso JF, Carrera N. Somatosensory evoked potentials: abnormalities with focal brain lesions remote from the primary sensorimotor area. Electroencephalogr Clin Neurophysiol. 1980 Jul;49(1–2):59–65.

91. Price CJ, Warburton EA, Moore CJ, Frackowiak RS, Friston KJ. Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. J Cogn Neurosci. 2001 May 15;13(4):419–29.

92. Mohajerani MH, McVea DA, Fingas M, Murphy TH. Mirrored Bilateral Slow-Wave Cortical Activity within Local Circuits Revealed by Fast Bihemispheric Voltage-Sensitive Dye Imaging in Anesthetized and Awake Mice. J Neurosci. 2010 Mar 10;30(10):3745–51.

93. Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke. 1988 Dec;19(12):1497–500.

94. Carter AR, Astafiev SV, Lang CE, Connor LT, Rengachary J, Strube MJ, et al. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann Neurol. 2010 Mar;67(3):365–75.

95. Sporns O, Tononi G, Kötter R. The Human Connectome: A Structural Description of the Human Brain. PLOS Computational Biology. 2005 Sep 30;1(4):e42.

96. Sporns O, Honey CJ, Kötter R. Identification and Classification of Hubs in Brain Networks. PLOS ONE. 2007 Oct 17;2(10):e1049.

97. Siegel JS, Ramsey LE, Snyder AZ, Metcalf NV, Chacko RV, Weinberger K, et al. Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. Proceedings of the National Academy of Sciences. 2016 Jul 26;113(30):E4367–76.

98. Baldassarre A, Ramsey L, Rengachary J, Zinn K, Siegel JS, Metcalf NV, et al. Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke. Brain. 2016 Jul;139(Pt 7):2024–38.

99. Nowak DA, Grefkes C, Dafotakis M, Eickhoff S, Küst J, Karbe H, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. Arch Neurol. 2008 Jun;65(6):741–7.

100. Kwon Y. The effect of repetitive transcranial magnetic stimulation on patients with dysarthria in subacute stroke. PM and R (var.pagings) [Internet]. 7 [cited 2022 Jun 30];(9 SUPPL. 1). Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01136153/full

101. Du J, Yang F, Hu J, Hu J, Xu Q, Cong N, et al. Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: Evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. Neuroimage Clin. 2019;21:101620.

102. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the

European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). European Heart Journal. 2018 Mar 1;39(9):763–816.

103. Muir KW, Weir CJ, Murray GD, Povey C, Lees KR. Comparison of neurological scales and scoring systems for acute stroke prognosis. Stroke. 1996 Oct;27(10):1817–20.

104. Dargazanli C, Fahed R, Blanc R, Gory B, Labreuche J, Duhamel A, et al. Modified Thrombolysis in Cerebral Infarction 2C/Thrombolysis in Cerebral Infarction 3 Reperfusion Should Be the Aim of Mechanical Thrombectomy: Insights From the ASTER Trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization). Stroke. 2018 May;49(5):1189–96.

105. Yushkevich PA, Yang Gao null, Gerig G. ITK-SNAP: An interactive tool for semi-automatic segmentation of multi-modality biomedical images. Annu Int Conf IEEE Eng Med Biol Soc. 2016 Aug;2016:3342–5.

106. Foulon C, Cerliani L, Kinkingnéhun S, Levy R, Rosso C, Urbanski M, et al. Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. Gigascience. 2018 Mar 1;7(3):1–17.

107. Thiebaut de Schotten M, Ffytche DH, Bizzi A, Dell'Acqua F, Allin M, Walshe M, et al. Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. Neuroimage. 2011 Jan 1;54(1):49–59.

108. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. NeuroImage. 2014 May 15;92:381–97.

109. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage. 2009 Jan 1;44(1):83–98.

110. Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of ischemic lesion patterns on early diffusion-weighted imaging with TOAST stroke subtypes. Arch Neurol. 2003 Dec;60(12):1730–4.

111. T W, C W, A E, I R, S T, E S, et al. Contribution of diffusion-weighted imaging in determination of stroke etiology. AJNR American journal of neuroradiology [Internet]. 2006 Jan [cited 2022 Jun 20];27(1). Available from: https://pubmed.ncbi.nlm.nih.gov/16418352/

112. Hedna VS, Bodhit AN, Ansari S, Falchook AD, Stead L, Heilman KM, et al. Hemispheric Differences in Ischemic Stroke: Is Left-Hemisphere Stroke More Common? J Clin Neurol. 2013 Apr;9(2):97–102.

113. Naess H, Waje-Andreassen U, Thomassen L, Myhr KM. High incidence of infarction in the left cerebral hemisphere among young adults. J Stroke Cerebrovasc Dis. 2006 Dec;15(6):241–4.

114. ElHabr AK, Katz JM, Wang J, Bastani M, Martinez G, Gribko M, et al. Predicting 90-day modified Rankin Scale score with discharge information in acute ischaemic stroke patients following treatment. BMJ Neurology Open. 2021 Jun 1;3(1):e000177.

115. Krakauer JW, Hadjiosif AM, Xu J, Wong AL, Haith AM. Motor Learning. Compr Physiol. 2019 Mar 14;9(2):613–63.

116. Maraka S, Jiang Q, Jafari-Khouzani K, Li L, Malik S, Hamidian H, et al. Degree of corticospinal tract damage correlates with motor function after stroke. Ann Clin Transl Neurol. 2014 Nov;1(11):891–9.

117. Wu O, Cloonan L, Mocking SJT, Bouts MJRJ, Copen WA, Cougo-Pinto PT, et al. Role of Acute Lesion Topography in Initial Ischemic Stroke Severity and Long-Term Functional Outcomes. Stroke. 2015 Sep;46(9):2438–44.

118. Etherton MR, Rost NS, Wu O. Infarct topography and functional outcomes. J Cereb Blood Flow Metab. 2018 Sep;38(9):1517–32.

119. ePROVIDE^{TM} - Online Support for Clinical Outcome Assessments [Internet]. [cited 2022 Jun 24]. Available from: https://eprovide.mapi-trust.org/instruments/stroke-impact-scale2#need_this_questionnaire

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