

# Endovascular mechanical thrombectomy for the treatment of stroke in University Hospital of Split : our experience

---

**Rasouli, Pezhman**

**Master's thesis / Diplomski rad**

**2021**

*Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj:* **University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet**

*Permanent link / Trajna poveznica:* <https://um.nsk.hr/um:nbn:hr:171:171682>

*Rights / Prava:* [In copyright](#) / [Zaštićeno autorskim pravom.](#)

*Download date / Datum preuzimanja:* **2024-09-01**



*Repository / Repozitorij:*

[MEFST Repository](#)



**UNIVERSITY OF SPLIT  
SCHOOL OF MEDICINE**

**PEZHMAN RASOULI**

**ENDOVASCULAR MECHANICAL THROMBECTOMY FOR THE  
TREATMENT OF STROKE IN UNIVERSITY HOSPITAL OF SPLIT:  
OUR EXPERIENCE**

**DIPLOMA THESIS**

**Academic year:**

**2020/2021**

**Mentor:**

**Assist. Prof. Krešimir Dolić, MD, PhD**

**Split, September 2021**

# TABLE OF CONTENTS

1. INTRODUCTION .....	1
1.1. Stroke .....	2
1.1.1. Definition.....	2
1.1.2. Epidemiology .....	3
1.1.3. Etiology and Pathophysiology.....	4
1.1.4. Diagnosis .....	6
1.1.5. Treatment.....	7
1.2. Acute ischemic stroke .....	8
1.2.1. General overview .....	8
1.2.2. Brain vascular anatomy and segments .....	9
1.2.3. Imaging of acute ischemic stroke.....	12
1.2.3.1. Non-contrast CT .....	13
1.2.3.2. CT angiography.....	15
1.2.3.3. CT perfusion.....	16
1.2.3.4. Magnetic resonance imaging.....	18
1.3. Endovascular mechanical thrombectomy.....	21
2. OBJECTIVES .....	25
3. SUBJECTS AND METHODS .....	27
4. RESULTS .....	30
4.1. Descriptive statistics of the sample .....	31
4.2. Correlation of mRS outcomes after 3 months with variables .....	35
4.3. Correlation of EMT and mRS outcomes .....	37
5. DISCUSSION.....	38
6. CONCLUSIONS.....	42
7. REFERENCES .....	44
8. SUMMARY .....	51
9. CROATIAN SUMMARY .....	53
10. CURRICULUM VITAE.....	55

# **ACKNOWLEDGEMENT**

Firstly, I would like to express my foremost gratitude to my mentor, Assist. Prof. Krešimir Dolić, MD, PhD, for his consistent support and guidance throughout my thesis and Department of Radiology for supporting me with the collection and analyzing the data for my thesis.

I would also like to thank my family specially my parents and my brother Parham, for always being there for me with their continuous love and encouragement, supporting me throughout this journey.

And finally, Nikolina, for being the driving force over these past years, without whom this journey would have been unimaginable and far more difficult.

# LIST OF ABBREVIATIONS

ACA - Anterior cerebral artery

ACOM - Anterior communicating artery

ADC - Apparent diffusion coefficient

AHA/ASA - American Heart Association/American Stroke Association

AIS - Acute ischemic stroke

ASPECTS - Alberta Stroke Program Early CT Score

BA - Basilar artery

BI - Barthel Scale/Index

CBF - Cerebral blood flow

CBV - Cerebral blood volume

CCA - Common carotid artery

CT - Computerized tomography

CTA - CT angiography

CTP - CT perfusion

DWI - Diffusion weighted imaging

ECA - External carotid artery

EMT - Endovascular mechanical thrombectomy

FLAIR - Fluid attenuated inversion recovery

GOS - Glasgow Outcome Score

ICA - Internal carotid artery

IVT - Intravenous thrombolysis

LVO - Large vessel occlusion

MCA - Middle cerebral artery

mRS - Modified Rankin Scale

MRA - Magnetic resonance angiography

MRI - Magnetic resonance imaging

MTT - Mean transit time

NCCT - Non-contrast CT

NIHSS - National Institutes of Health Stroke Scale

PCA - Posterior cerebral artery

PWI - Perfusion weighted imaging

RCT - Randomized controlled trials

rtPA - Recombinant tissue plasminogen activator

SICH - Symptomatic intracranial hemorrhage

TIA - Transient ischemic attack

TICI - Thrombolysis in cerebral infarction

TTP - Time to peak

VA - Vertebral arteries

WHO - World Health Organization

## **1. INTRODUCTION**

## **1.1. Stroke**

### **1.1.1. Definition**

Over the past decade, the definition of stroke has been modified and significant progress has been acquired in its treatment and prevention. According to the World Health Organization (WHO), stroke was defined as “abruptly developed clinical signs of focal or global interference of cerebral function, lasting more than 24 hours or leading to death and presumed to have vascular origin”. This definition was published in 1970 which was mainly focused on clinical symptoms, and it is currently regarded as obsolete by the American Heart Association/American Stroke Association (AHA/ASA) owing to major progress in the diagnosis of nature, onset, and clinical picture of stroke. Additionally, new imaging techniques have been crucial factors with regards to the mentioned progress (1,2).

In 2009 AHA/ASA published a clarified definition for transient ischemic attack (TIA) which was distinguished from classic stroke mainly by absence of acute cerebral infarction in addition to spontaneous resolution of symptoms within 24 hours in most cases. The most recent definition of stroke which was introduced by AHA/ASA in 2013 is “an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction” where infarction is defined as cell death caused by ischemia which can be diagnosed either by clinical symptoms persisting more than 24 hours, radiologically or pathologically (2).

Stroke has been classified into two main categories: ischemic and hemorrhagic. Ischemic stroke is the most common type of stroke. It is caused by blockage of blood flow to the brain because of arterial obstruction whereas hemorrhagic stroke is a result of vascular rupture or anomalous vascular structure. Brain tissue damage is the primary ramification of both types which can lead to disability or mortality. Although in ischemic areas of brain secondary bleeding can develop, the number of hemorrhagic stroke cases originally starting as ischemic strokes have not been documented (3,4).



### 1.1.2. Epidemiology

Based on multiple factors mainly because of crucial improvements in the prevention and management of stroke in the last decade, epidemiological data in this field can face changes every year. After cardiovascular disease and before cancer, stroke is the second leading cause of mortality worldwide while it is the first leading cause of morbidity and long-term disability in developed countries (5). Mortality caused by stroke has declined in developed countries as well as in many developing countries in the recent years. In comparison with hemorrhagic stroke, ischemic stroke has almost four times higher global burden since it approximately accounts for 80% of cases worldwide (6).

Furthermore, age is the most important factor in the dramatic increase in stroke risk followed by hypertension and diabetes which are the primary modifiable factors. It has been stated that after reaching the age of 55, the risk of stroke can have an exponential increase of 2-fold every ten years (5). Although people at any age can potentially suffer from stroke, 95% of cases occur in individuals of 45 years of age and older whereas more than 65% of these cases include people older than 65. It has been claimed that age is a major factor for the mortality outcome of stroke. Within the first year after stroke, mortality rate has been approximately 20% while long-term disability can be probable in more than 50% of surviving patients. Proximal large artery obstruction has been the substantial element leading to disability burden in about 25% to 50% of cases. It is worth noting that although 60% of mortality from a stroke takes place in females; males have a 25% more tendency than females to suffer from a stroke attack during their lifetime (7,8).

In Croatia, as a developed country stroke has been the second leading cause of death and disability in 2019. It is also stated that tobacco consumption has been the main modifiable risk factor for population in this country followed by hypertension in the same year. Mortality because of stroke in Croatia has shown a slow decline in the past years while it is worth mentioning that Mediterranean diet has been found to have a substantial protective effect against stroke by decreasing the risk of stroke more than 50% (9,10).

### 1.1.3. Etiology and Pathophysiology

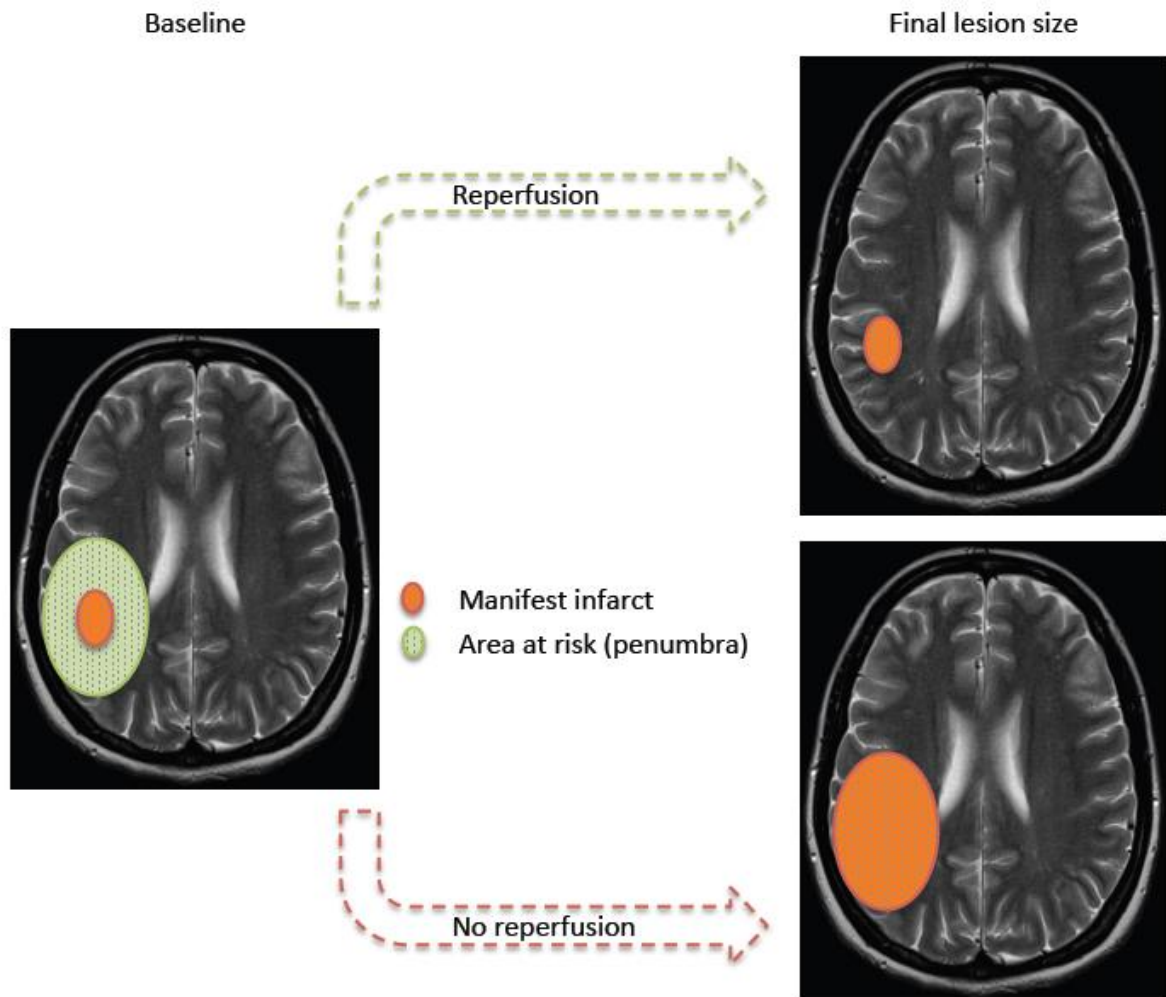
Brain cells have a great demand for oxygenated blood and glucose because of very high metabolic activity. About 20% of total oxygen supply and 15% of cardiac output are consumed during general cerebral function. Thus, parenchyma in this region is very susceptible to blood supply disruptions which can lead to hypoxia, ischemia, and infarction if it is not managed urgently (11).

Furthermore, the pathophysiology of stroke is rather complex since several different mechanisms have been involved in this process. Although ischemic and hemorrhagic strokes are distinguished in the manner of resulting pathophysiological cascades, both types ultimately can lead to brain tissue injury if left untreated in a short period (11,12).

Ischemic stroke is categorized as global and focal ischemias. Focal ischemia is the most common type concerning acute cases of ischemic stroke. Global ischemia is caused by a decline in cerebral perfusion pressure primarily due to cardiovascular failure and reduced systolic blood pressure under 50 mmHg such as in the case of a cardiac arrest or shock where severe hypotension can be considered as the main issue. In case of focal ischemia, it occurs as normal blood flow to a region of the brain has been disrupted mainly as a consequence of vascular occlusion and increased cerebral vascular resistance (12).

In the case of complete occlusion of blood flow, the function of cells in the brain is ceased in 60-90 seconds. Additionally, irreversible infarction of cerebral cells can occur in 4-10 minutes which can be prolonged up to about 4 hours when the occlusion is not complete. In the presence of glucose and oxygen deprivation caused by disruption of blood flow, several processes take place leading to the initiation of ischemic cascade while the most crucial role belongs to anaerobic metabolism of brain cells and production of neurotoxic substances such as lactic acid and excessive amount of glutamate in addition to free radicals which are causative agents for tissue damage and necrosis. Additionally, ischemia and necrosis can lead to cytotoxic cerebral edema in the affected area which can lead to increased intracranial pressure and compression of brain tissue inside the cranium (12,13).

The ischemic region of brain before the occurrence of irreversible infarction is referred to as ischemic penumbra which is the area at risk, suffering from reversible ischemic attack and it can be saved by proper reperfusion within a limited time (Figure 1) (12).



**Figure 1.** Infarct core and ischemic penumbra.

Source: <https://openarchive.ki.se/xmlui/handle/10616/45342>

The main causative factors leading to ischemic stroke include thromboembolic events, and atherosclerosis. It has been claimed that thromboembolism is a consequence of events leading to factors included in the Virchow's triad (stasis of blood flow, hypercoagulability state, and endothelial damage) while atherosclerosis is primarily dependent on lifestyle and diet (11).

In the case of hemorrhagic strokes pathological factors underlying the stroke events are the main classification elements. These factors include aneurysm rupture, cerebral bleeding caused by hypertension, rupture of arteriovenous fistula, and drug-induced cerebral hemorrhage. Additionally, it is worth mentioning that ischemic strokes can also deteriorate into cerebral hemorrhagic events. The overriding mechanism of brain injury is caused by the increased intracranial pressure which is resulted from the production of hematoma and consequently compression of cerebral parenchyma. Additionally, elevated intracranial pressure can disrupt blood flow to the brain and lead to tissue ischemia and infarction (14).

#### 1.1.4. Diagnosis

Clinical signs and symptoms of acute stroke include severe headache, muscle paralysis (generally on one side of the body in the face and arm), and speech difficulties if the dominant hemisphere is affected. These symptoms along with anamnesis, physical and neurological examination of the patient have been the primary step in the diagnosis and estimating the extent of severity and location of the stroke to date. Underlying causes of stroke are the main factors in the determination of suitable treatment. Thus, diagnosis and confirmation of etiology have been a remarkably crucial step in this manner which is mainly to distinguish ischemic stroke from hemorrhagic events and other possible factors. Neuroimaging is the method of choice to confirm the cause and region of the stroke while CT scan (generally used without contrast enhancement) and to a smaller extend MRI scan are the most widely used techniques for this purpose (15,16).

#### 1.1.5. Treatment

After clarification of the underlying cause of stroke, proper treatment can be applied for the best outcome. The main treatment options available for hemorrhagic stroke are supportive care and neurosurgical procedures if it is required. Although thrombolysis was the only treatment option in the case of ischemic stroke for a long time, in the recent years mechanical thrombectomy has been proven to have high safety and efficacy and it is a standard treatment option at present. Stroke rehabilitation is considered as the last resort in all stroke patients where other treatment options have been unsuccessful (13,14).

In this thesis the focus will be on acute ischemic stroke and mechanical thrombectomy as the treatment option.

## **1.2. Acute ischemic stroke**

### 1.2.1. General overview

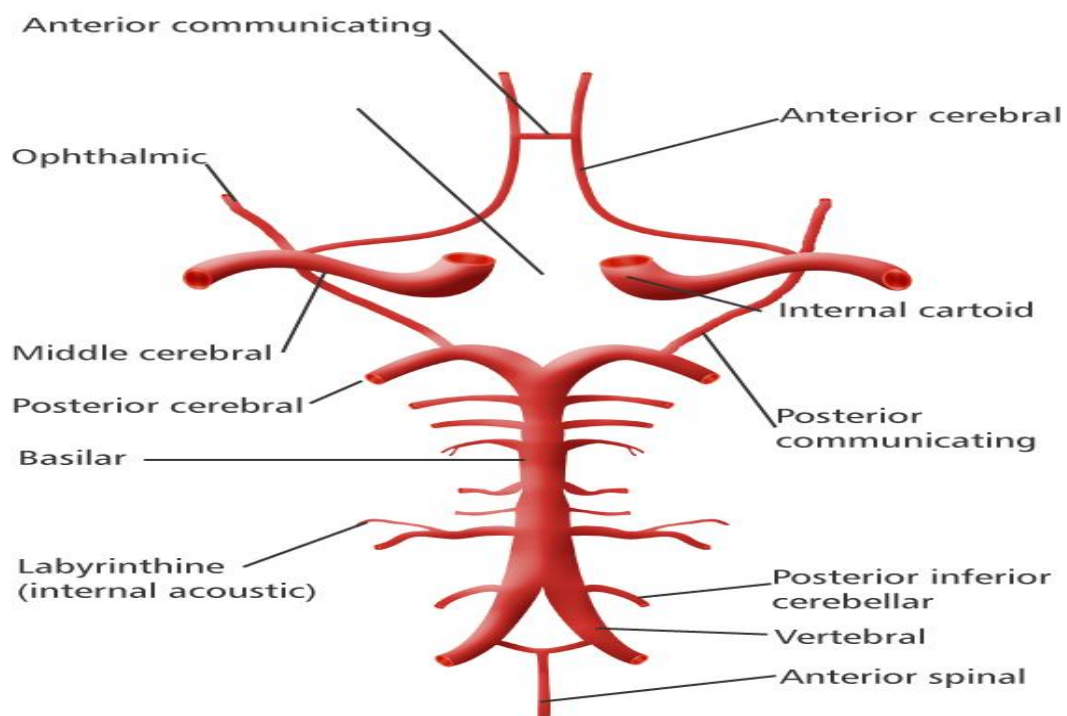
Acute ischemic stroke (AIS), as the most frequently observed type of stroke, covers about 80% of all cases globally. The main cause of AIS is the reduction or complete blockage of blood flow to a part of brain caused by a clot. The primary factors determining the severity and outcomes of stroke are the size of occluded artery, location of occlusion (proximal or distal part of the artery) and the segment of brain affected by this occlusion. Radiological imaging techniques are used as the main helpful tool in recognition of these factors (15).

Prompt reperfusion of the ischemic area in the shortest conceivable time is of utmost importance for the best prognosis in stroke patients. Although the time needed for the development of infarction in everyone can be different, there is a limited time window between the onset of symptoms and treatment for favorable outcomes. Therefore, the treatment needs to be done as quickly as possible. It has been claimed that the best outcomes for the patients are mostly obtained in a time window up to 6 hours from the symptoms' onset. A very commonly used expression in the case of stroke patient says, "Time is brain" and every elapsing minute without treatment can lead to a loss of approximately 1.8 million neurons (17,18).

Additionally, scaling tools (widely used ones are: mRS, NIHSS, GOS, BI and ASPECTS) have been employed for assessment of severity and prognosis of stroke. In the clinical settings, a combination of several scales is used for stroke patients' evaluation. The NIHSS is used for early and repeated evaluation of the patient to establish the severity and prognosis of the stroke, while the BI is mainly employed as the rehabilitation planning tool if required. Furthermore, the mRS and GOS scales are useful tools for assessing the extent of disability and functional outcomes that can provide useful data for the selection of patients for further interventions. The ASPECTS is the main scoring method used for early ischemic changes in brain CT imaging. Lastly TICI scoring is used to assess the degree of recanalization after intervention (19).

### 1.2.2. Brain vascular anatomy and segments

In general blood flow to the brain is separated into two segments namely the anterior and posterior circulation based on the main artery supplying these segments. The anterior circulation includes anterior cerebral artery (ACA) and middle cerebral artery (MCA), both being branches of the internal carotid artery (ICA). The ICA in turn is arising from the common carotid artery (CCA), just like the external carotid artery (ECA). The posterior circulation consists of the posterior cerebral artery (PCA) which originates from the basilar artery (BA) that is formed by the merging two vertebral arteries (VA) (Figure 4). BA together with VA comprise the vertebrobasilar system. The brain consists of left and right hemispheres and consequently, all mentioned arteries have a left and a right branch except for BA which is just a single central artery. All main arteries of anterior and posterior circulations of the brain together with communicating arteries between them collectively create a communicating network at the base of the brain called the circle of Willis (Figure 2). It is worth mentioning that anatomical variation of brain vasculature between individuals is a common phenomenon (20).

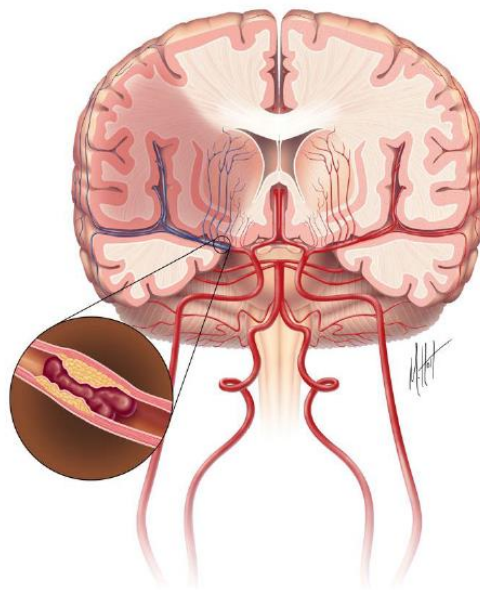


**Figure 2.** Circle of Willis.

Source: <https://meducation.net/resources/21390-Circle-of-Willis-Isolated-Labeled>

Acute ischemic strokes are not common in the territory involving the ACA. However, it has been claimed that many infarcts in this arterial territory can be underdiagnosed as a result of silent strokes. The ACA is generally divided into five segments including proximal part (A1), ascending part (A2, A3) and horizontal part (A4, A5). The most prominent feature of ACA is the vigorous anastomotic complex which can be a reason for uncommon cases of stroke and infarcts in this arterial territory. Additionally, an occlusion of the ACA proximal to the anterior communicating artery (ACOM) may not lead to stroke in anterior territory (A1 segment of ACA) because the ACOM will still provide blood to the affected side from the contralateral side which is not the case if there is an occlusion distal to ACOM (21).

The MCA is the largest cerebral artery that receives direct blood flow from ICA and supplies a big territory in the cerebrum which is the most common arterial territory involving pathological and stroke events in the brain. The MCA is generally divided into M1, M2, M3 and M4 as the distal progression. Furthermore, M1 segment can be subdivided into proximal M1 including lenticulostriate perforating arteries (perfuse the basal ganglia specifically lentiform nucleus) and distal M1 which spares these perforators. Thus, it has been stated that AIS involving proximal M1 subsegment leads to worse outcomes in comparison with distal M1 strokes since the internal capsule which is running through the basal ganglia can be infarcted resulting in a hemiparesis or hemiplegia and thus leading to major morbidity of the patient (Figure 3) (22,23).



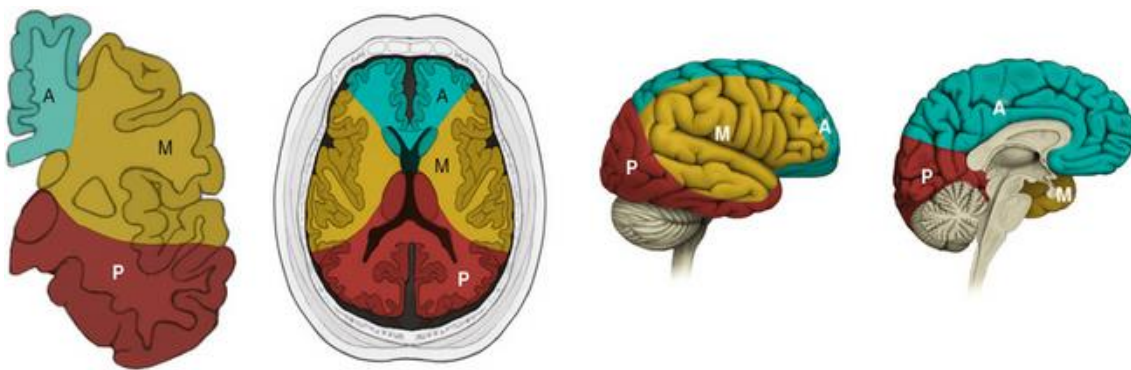
**Figure 3.** Right MCA occlusion (right proximal M1 subsegment occlusion)

Source: <http://www.strokecenter.org/patients/about-stroke/ischemic-stroke/>



PCA infarctions account for about 5-10% of all AISs. The PCA is mainly divided into deep territory including P1 and P2 segments as well as superficial territory consisting of P3 and P4 segments. Although there is a low fatality rate as a result of PCA strokes, it has been emphasized that long-term cognitive and behavioral related dysfunctions are underrated (24).

Lastly, it is worth mentioning that symptoms of AIS observed in different stroke patients have a direct and explicit correlation to the arterial territory influenced by the stroke as well as distal brain segments affected by the vascular occlusion (25-27).



**Figure 4.** Arterial territories of the brain.

A = ACA territory, M = MCA territory, P = PCA territory.

Source: <https://radiologykey.com/clinical-anatomical-syndromes-of-ischemic-infarction/>

### 1.2.3. Imaging of acute ischemic stroke

In the last three decades, imaging techniques have been the remarkably critical constituent of diagnostic assessment and selection of stroke patients for further acute therapies. The significance of neuroimaging role has been emphasized even more by the accomplished progress in the management of AIS in recent years. Noteworthy is the fact that based on evidence the decision was made to extend the time window for treatment to 24 hours in the guidelines for selected patients in late 2017. Moreover, for the inclusion patients of 24 hours treatment, advanced neuroimaging methods including CT perfusion and MRI were added to the standard protocol in early 2018. These recommendations were issued for improving the decision-making process as well as outcomes for the AIS patients while expanding the role of neuroimaging in scope and sophistication (28).

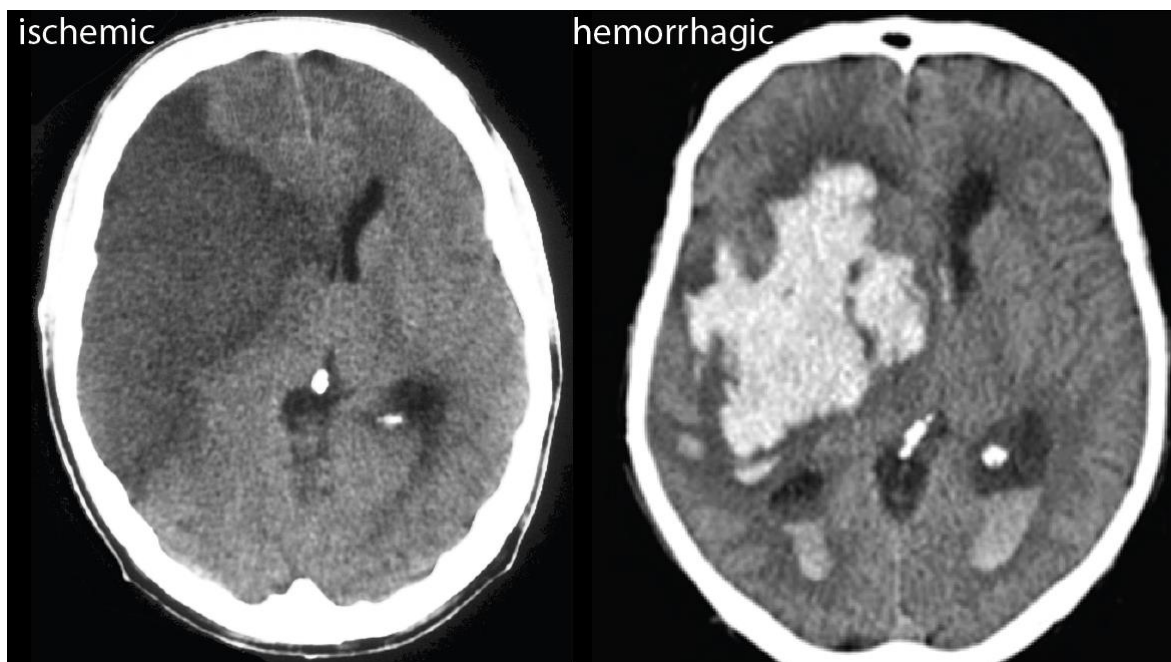
The main preliminary goal of imaging in patients with stroke symptoms in acute settings is to differentiate AIS and cerebral hemorrhage along with the exclusion of other causes such as the brain tumor which can mimic stroke-like symptoms. This is done to determine available therapeutic options for each case since there is a substantial difference between the management of stated disorders. Furthermore, there are other significant data which can be acquired by imaging including the extent of ischemic cerebral tissue that can be salvageable, the location of the obstructed vessel, and an approximate volume of the brain tissue which is irreversibly injured or infarcted (29).

Multimodal CT and MRI are the primary neuroimaging tools used to obtain comprehensive diagnostic information and noninvasive assessments of patients which can be selected for suitable treatment options in the acute settings. Multimodal CT is the main protocol of choice in most stroke centers worldwide. This is due to its availability, shorter scanning time and low cost compared to MRI. Multimodal CT consists of three different modalities including non-contrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP). It is worth noting that both CT and MRI protocols in the case of AIS patients are primarily based on the mismatch concept and penumbra volume estimation (29,30).

### 1.2.3.1. Non-contrast CT

NCCT, as the first imaging modality acquired in multimodal CT protocol, is a remarkably critical step for patients with sudden onset of stroke symptoms primarily to exclude intracranial hemorrhage as well as stroke mimics such as tumors or infections before application of thrombolytic and/or thrombectomy therapy for AIS (Figure 5). Additionally, important information about early ischemic changes, early infarct identification signs (such as hypoattenuation, the disappearance of grey-white matter distinction and obscuration of the lentiform nucleus) and exclusion of large acute infarction in the brain can be also obtained by NCCT (Figure 6). Moreover, in some cases, it is possible to observe the thrombus as a hyperattenuating structure so-called “dense artery sign” (Figure 7). However, NCCT is not able to clearly distinguish between infarcted tissue and penumbra which is considered as a significant disadvantage of this imaging technique (30,31).

Early ischemic changes in NCCT can be quantitatively assessed by ASPECTS scoring system for the estimation of stroke severity in the case of MCA involvement while it has been also adapted for posterior circulation strokes recently (30).



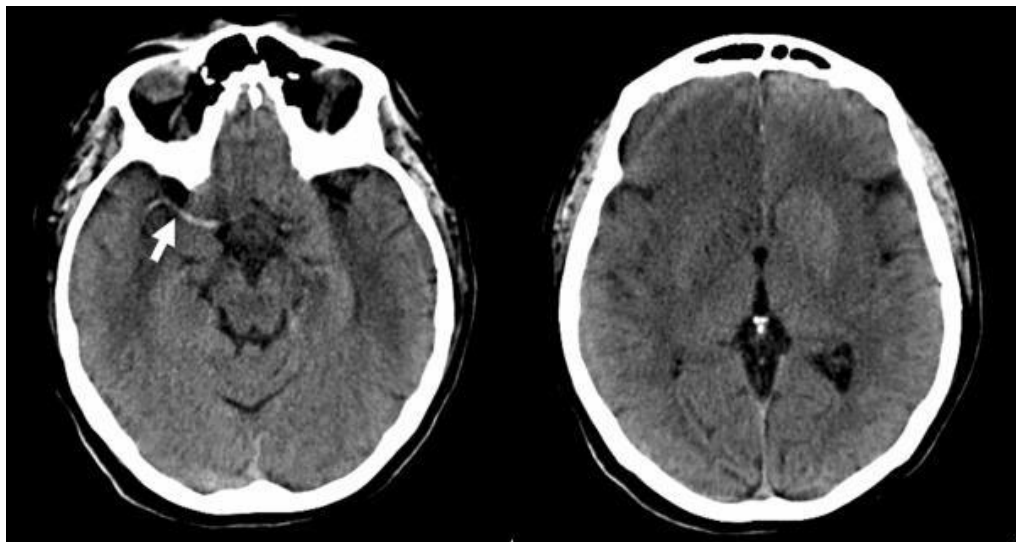
**Figure 5.** Ischemic stroke (left picture) and Hemorrhagic stroke (right picture) CT images

Source: <https://ysjournal.com/can-artificial-intelligence-tell-the-difference-between-ischemic-and-hemorrhagic-stroke/>



**Figure 6.** Hypoattenuation in CT. Appearance of hypoattenuation within 6 hours from onset of stroke symptoms is very specific indicator of infarction.

Source: <https://radiologyassistant.nl/neuroradiology/brain-ischemia/imaging-in-acute-stroke#ct-early-signs-of-ischemia-hemorrhagic-infarcts>

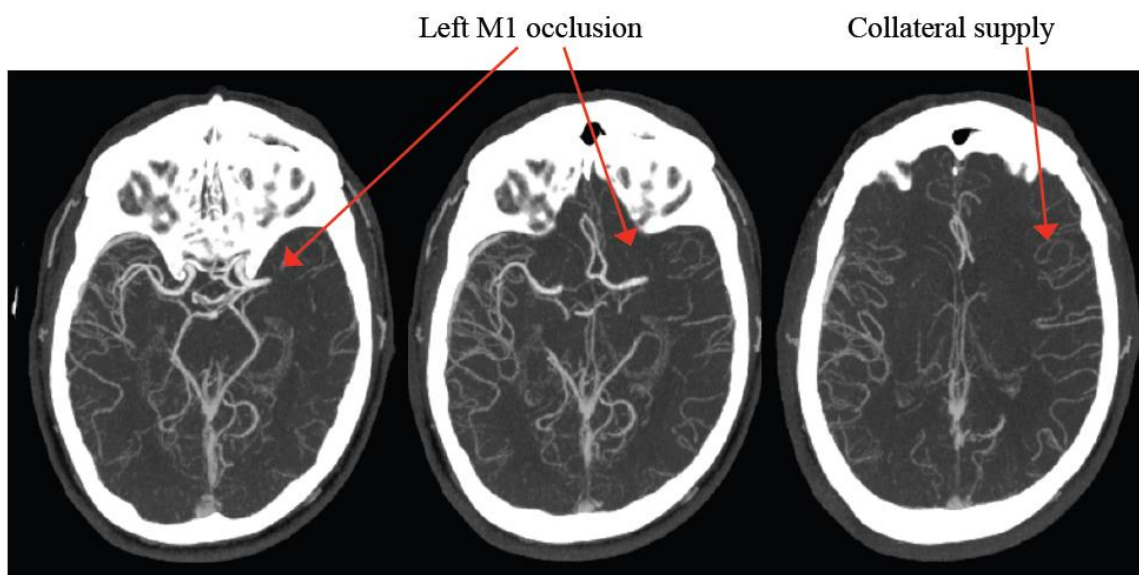


**Figure 7.** NCCT. Dense artery sign in right MCA (left picture), obscuration of right lentiform nucleus and loss of grey-white matter differentiation as a result of MCA occlusion (right picture).

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2965616/>

### 1.2.3.2. CT angiography

CTA is considered as the second modality obtained in multimodal CT protocol which is CT imaging during rapid intravenous injection of contrast media in an optimized fashion. CTA images are acquired in the arterial phase and can provide a thorough picture of intracranial as well as extracranial circulations in a few seconds from aortic arch up to vertex of the skull including the circle of Willis and all collateral circulations (Figure 8). This technique helps locating the exact site and extent of occlusion which is one of the main factors in further planning for therapeutic interventions such as thrombectomy (30,32).



**Figure 8.** CT angiography. Occlusion in M1 territory of left MCA (left and middle pictures). Collateral circulation beyond the occlusion which is an important factor in preservation of cerebral tissue from ischemic damage (right picture).

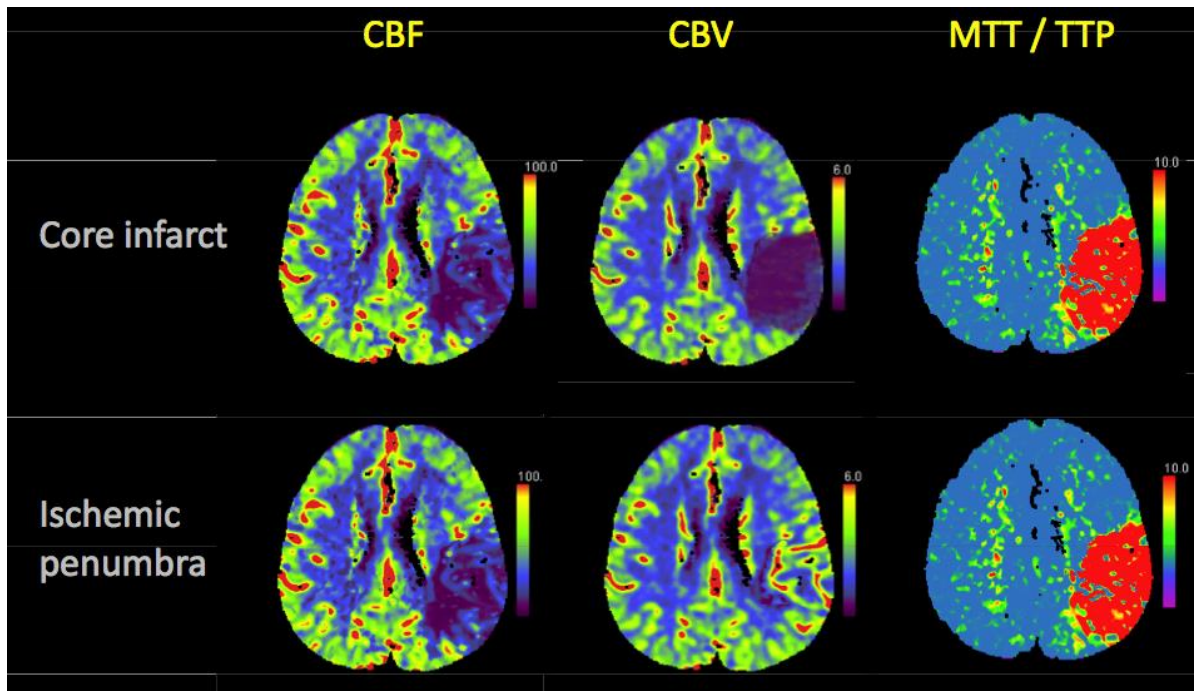
Source: <https://openarchive.ki.se/xmlui/handle/10616/45342>

### 1.2.3.3. CT perfusion

CTP is the third and last component of multimodal CT protocol which is a dynamic imaging method based on repeatedly scanning of brain sections after rapid administration of intravenous contrast. This modality aids distinguishing between irreversibly damaged parenchyma (infarct core) and salvageable ischemic tissue (penumbra). This is done based on cerebral hemodynamics including amount and speed of blood flow to discrete cerebral territories. It is also used in patient selection for reperfusion therapy and prediction of prognostic outcomes (33,34).

Cerebral hemodynamics can be evaluated by four most used parameters including cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP) which is sometimes used instead of MTT. Mathematically CBF equals CBV divided by MTT. MTT is defined as the average amount of time it takes for blood to transit through a given cerebral region which is the most sensitive parameter for the evaluation of abnormalities in blood flow. The reduced total CBV to less than 30% of the normal value is considered as the most specific parameter for the detection of irreversibly injured tissue or infarct core (32,35).

The concept of cerebral vascular autoregulation is the main factor in the demarcation of infarct core and penumbra. In infarcted areas, both CBF and CBV parameters are reduced with prolonged MTT value because of deficit or complete loss of autoregulation ability (CBV/MTT matched deficit indicative of infarct core). However, in the ischemic area at risk (penumbra) which is the target tissue for reperfusion therapy, CBV parameter is normal or increases while CBF parameter decreases due to prolonged MTT value (CBV/MTT mismatch is indicative of ischemic penumbra) (Figure 9). The main reason for the maintained CBV value is that autoregulation of brain is intact in penumbra area, and it will lead to dilation of collateral blood vessels as a result of decreased CBF in that region of the brain (35,36).



**Figure 9.** CTP map. On the top row from left to right, decreased CBF and CBV with prolonged MTT all on the left hemisphere (CBV/MTT matched deficit indicative of infarct core). On the bottom row from left to right, decreased CBF and normal CBV with prolonged MTT all on the left hemisphere (CBV/MTT mismatch is indicative of ischemic penumbra).

Source: <https://radmd.wordpress.com/ctp/>



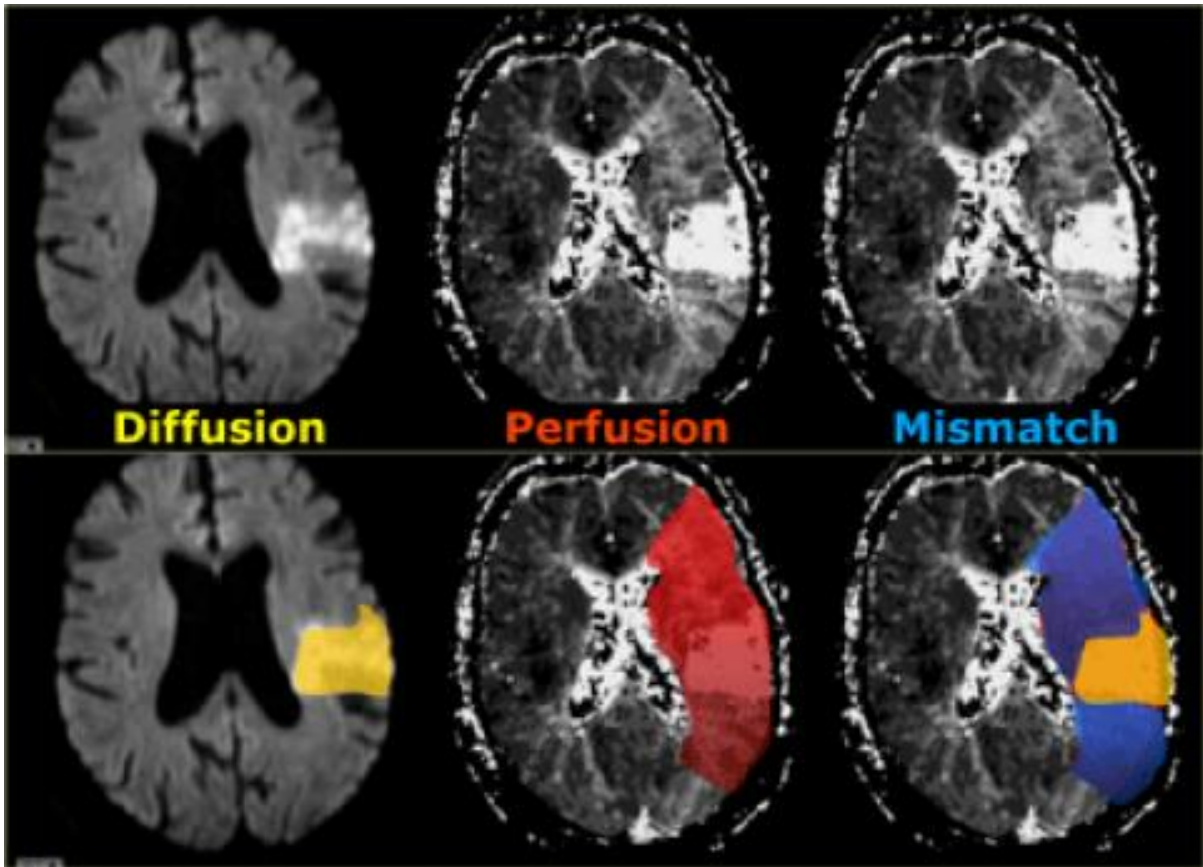
#### 1.2.3.4. Magnetic resonance imaging

Although CT scan is the method of choice in most stroke centers due to short imaging time and availability, there has been a progressive increase in MRI usage for diagnostic and management purposes in recent years. Diffusion-weighted imaging (DWI) is the greatest advantage of MRI and is the most sensitive method for imaging of stroke which provides a superior ability to evaluate the infarct core while perfusion-weighted imaging (PWI) of MRI is comparable to CTP. Additionally, MRI has been a valuable tool for the assessment of posterior stroke cases since the evaluation of ischemic changes of the brainstem in CT imaging can be problematic due to small neuroanatomic structures surrounded by the large osseous anatomy, mainly the petrous bone and clivus of the occipital bone (37,38).

DWI is a T2 weighted based imaging which measures the motion of water molecules in all cells. Infarction of neuronal cells leads to an intracellular collection of water and subsequently results in disruption of water diffusion. This will lead to the detection of these cells as injured cells. Apparent diffusion coefficient (ADC) images also called ADC maps are used together with DWI which can specify diffusion more clearly by the elimination of T2 weighting. MTT or TTP perfusion maps can be obtained by PWI which can be employed as a helpful tool in the detection of ischemic penumbra in a similar fashion as CTP. The ischemic penumbra is defined as the DWI/PWI mismatch in the MRI imaging (Figure 10). This means, DWI reflects irreversibly damaged brain tissue while PWI reflects brain tissue with decreased perfusion, i.e., the difference between DWI and PWI is equal to the penumbra, if DWI and PWI are equal in size and localization, there is no mismatch and thus there is no penumbra to be rescued (Figure 11) (32,37).

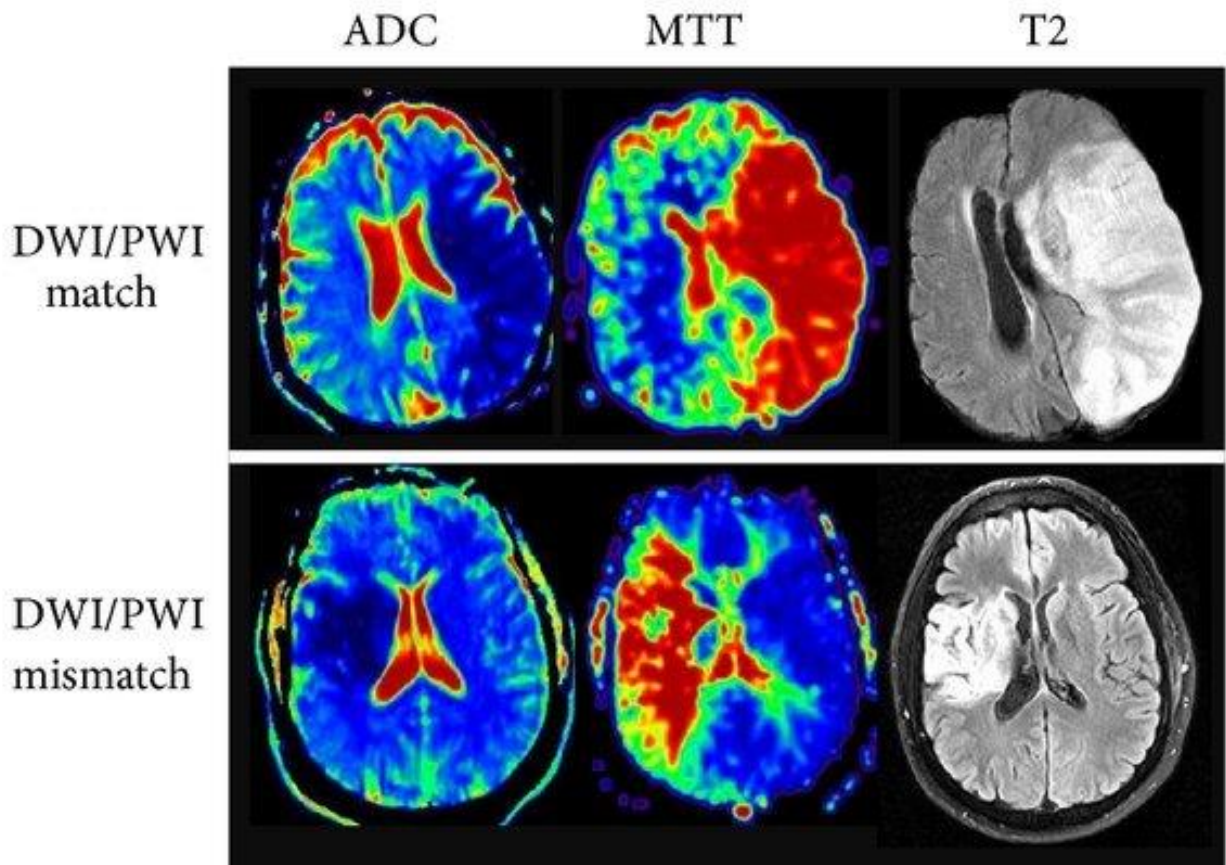
Furthermore, there are other imaging sequences included in multimodal MRI protocol for AIS which are frequently used and have high diagnostic and prognostic values in most of the cases. T2 weighted together with fluid-attenuated inversion recovery (FLAIR) images are very useful tools for diagnostic purposes in acute settings (Figure 11). They are also used in the assessment of older brain infarctions. FLAIR sequence is specifically very sensitive in the detection of acute and subacute intracranial hemorrhages. Additionally, magnetic resonance angiography (MRA) is the method that can be used together with other MRI sequences for detailed virtualization of vasculature in MRI protocol. MRA can be also a valuable diagnostic technique in the detection of uncommon cases that lead to AIS such as dissection of carotid or vertebral artery, fibromuscular dysplasia, and thrombosis in the venous system (32,38).





**Figure 10.** MRI images. DWI (yellow), PWI (red), DWI/PWI mismatch or ischemic penumbra (blue).

Source: <https://radiologyassistant.nl/neuroradiology/brain-ischemia/imaging-in-acute-stroke#ct-early-signs-of-ischemia-hemorrhagic-infarcts>



**Figure 11.** MRI images. DWI (left column), PWI (middle column), T2 weighted images (Right column). On the top row there is DWI/PWI match (complete infarction without obvious penumbra) while on the bottom row there is DWI/PWI mismatch (penumbra is present).

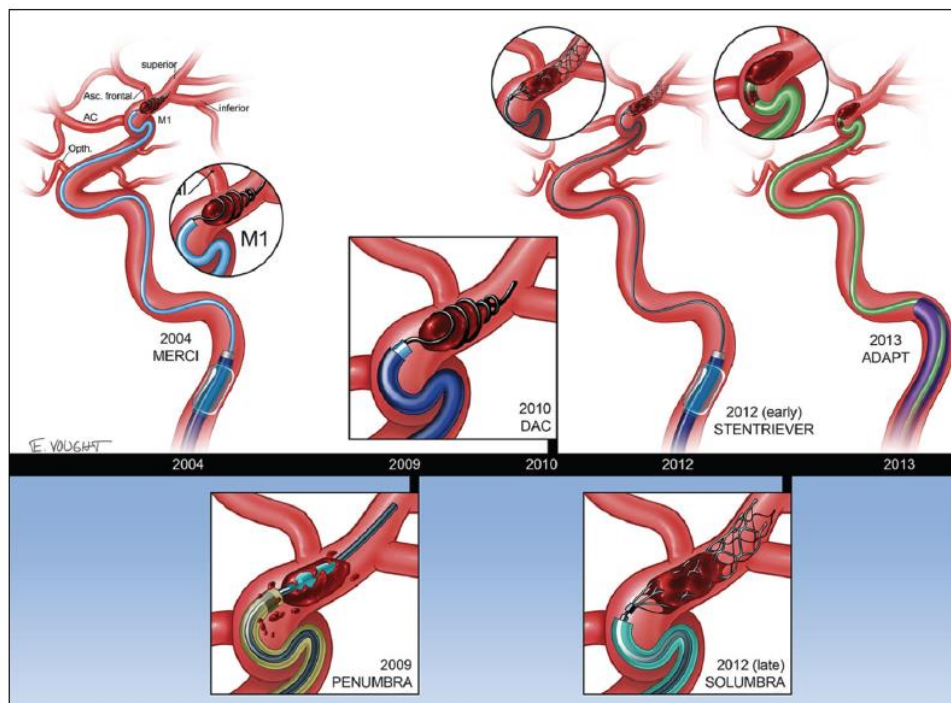
Source: [https://www.researchgate.net/publication/237200938\\_The\\_potential\\_roles\\_of\\_18F-FDG-PET\\_in\\_management\\_of\\_acute\\_stroke\\_patients](https://www.researchgate.net/publication/237200938_The_potential_roles_of_18F-FDG-PET_in_management_of_acute_stroke_patients)

### **1.3. Endovascular mechanical thrombectomy**

Endovascular mechanical thrombectomy (EMT) is a minimally invasive therapeutic option for AIS through which blood clot is removed with the help of specialized instruments (mainly in the form of catheters) designed for this purpose. They are inserted through the femoral artery in the groin area to restore the blood flow in the occluded blood vessel. Although there has been significant progress since the approval of intravenous thrombolysis (IVT) for the treatment of AIS at the end of 20<sup>th</sup> century, the turning point in this field was the year 2015 when the superiority of EMT was demonstrated based on research. There were five randomized controlled trials (RCT) published during 2015 as well as one more RCT published during 2016 which led to the approval of EMT as the gold standard therapy for the patients with large vessel occlusion (LVO) in proximal anterior circulation (39).

As shown in Figure 12, the evolution of EMT devices was started by approval of first-generation thrombectomy devices in the early 2000s as a result of limitations and hemorrhagic incidences of IVT therapy (40). The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) retriever was the first EMT device which is a helical coil formed head known as corkscrew head attached to the distal end of a long thin wire that was used to engage the thrombus by the corkscrew head and remove it as a block. There was a 48% revascularization rate obtained by application of MERCI within the 8 hours from the onset of stroke symptoms in patients who were not suitable for IVT therapy. Furthermore, there was declined mortality and improved outcomes in patients treated with MERCI (41,42). The second generation of EMT devices was introduced in the late 2000s which was called the penumbra aspiration system. This device is based on the extraction of thrombus by active aspiration concurrently with maceration of blood clot into fragments with a separator attached to the distal end of a catheter. Although an 82% revascularization rate was achieved with this method which was superior to MERCI, the outcomes were not adequate and there was a relatively high complications rate while it was applied during the same 8-hour window as MERCI (41,43). This was followed by the first version of DAC (Distal Access Catheter) in 2010 which was primarily designed as a combination of MERCI and active aspiration of penumbra system to remove the thrombus as a block while aspiration was used to minimize emboli and optimization of vector during extraction (44). In the early 2012 third generation of EMT devices was established which is considered as a revolutionary development in the field of AIS management. These devices were designed as fully retrievable stent attached to a

highly flexible microcatheter and they were called stent retrievers (stentriever). The first stent-based device was Solitaire which was later followed by Trevo with a slight change in the design of the stent. However, both devices' function is based on the engagement of stent and extraction of thrombus captured by the stent as a block with no or few iatrogenic emboli (41). The superiority of revascularization rate and favorable clinical outcomes in comparison with MERCI method was proved based on RCT studies for both Solitaire and Trevo (45,46). Later in 2012 SOLUMBRA technique was employed which combines Solitaire and penumbra aspiration methods to achieve the minimization of losing thrombus while retrieving the stent through the vessel (41). ADAPT (A Direct Aspiration First Pass Technique) as the newest generation of EMT method was introduced in 2013. It is fundamentally based on the direct aspiration of thrombus with the largest caliber of catheter possible that can be accommodated in an occluded vessel. This technique was a technologically developed form of penumbra aspiration catheter with larger diameters that could provide an aspiratory field almost as large as caliber of thrombus block. It has been claimed that adequate revascularization was achieved in 66% of cases using direct aspiration alone while this rate was elevated to 89% where stent retriever was used as adjuvant therapy to ADAPT (41,47).



**Figure 12.** Timeline of EMT devices' evolution.

Source: <https://evtoday.com/articles/2016-feb/adapt-a-direct-aspiration-first-pass-technique?c4src=archive:feed>

Although EMT devices are developing and improving constantly, currently stent retriever method is considered as the gold standard for the treatment of AIS patients with acute LVO in anterior cerebral circulation including ICA (in both intracranial and extracranial occlusion) and MCA (primarily M1 and M2 segments). It has been claimed that EMT is also an effective therapy in the case of vertebrobasilar occlusion. Additionally, it has been suggested that EMT might lead to favorable outcomes in selected AIS patients with occlusion of ACA (mainly A1 and A2 segments), PCA (mainly P1 and P2 segments) according to new AHA/ASA guidelines (48-50).

After diagnosis of AIS and exclusion of intracranial hemorrhage, the first line of acute treatment is IVT in eligible patients and recombinant tissue plasminogen activator (rtPA) is the medicine used for this purpose. However, patients in cases such as being on anticoagulant therapy, having severe uncontrolled hypertension or having a recent major surgery are ineligible for IVT. Although the best time window that can lead to the most favorable outcome is 3 hours from the onset of stroke symptoms, it can be prolonged up to 4.5 hours without an increased relative risk of symptomatic intracranial hemorrhage (SICH) which is regarded as the most common and catastrophic complication of IVT therapy. Moreover, the severity of stroke (larger infarction volume or previous ischemic stroke findings) correlates to SICH secondary to IVT (51,52). Distal occlusions are most likely to have the best response to IVT since thrombus is smaller because of the smaller diameter of the distal cerebral vasculature. However, in the proximal LVO the probability of complete reperfusion with IVT alone is remarkably low and EMT is considered as the most effective option for selected patients in these cases (53,54).

Furthermore, evidence suggests that in both eligible and ineligible patients for IVT, EMT is a safe and effective method that will lead to favorable reperfusion rate as well as reduced long-term disability and mortality rate in the case of AIS that is resulted from LVO (55). Based on the guidelines the optimal time for EMT to achieve the most beneficial outcome is 6 hours from the onset of stroke symptoms for selected patients with the help of radiological imaging and scoring scales such as NIHSS and ASPECTS for evaluation of stroke severity. Ideally, EMT is performed within 90 minutes in the case of IVT application and optimal reperfusion needs to be achieved in less than 60 minutes from the start of the interventional procedure. Additionally, according to new EMT guidelines, the time from the onset of stroke symptoms can be prolonged up to 24 hours for carefully selected patients

based on the evidence of substantial salvageable tissue (big penumbra) and small infarct core obtained by advanced imaging techniques such as CTP and MRI (mainly PWI and DWI) and fulfilment of other evaluation criteria. Presentation of large infarctions in radiological imaging (ASPECTS score 0-4) is considered as the most important exclusion criteria for EMT (50,56,57). AIS caused by distal occlusion can also be included in exclusion criteria in most of the cases. However, it has been claimed that EMT might be effective in the treatment of distal vasculature occlusion for carefully selected patients. This, however, requires further investigation (58). It has been claimed that although old age is not an exclusion criteria or effective factor on the efficacy of treatment with EMT, it has a remarkable correlation with the outcome as an independent predictor (59). Moreover, SICH and distal emboli are considered as the most common EMT complications in clinical practice while arterial dissection, perforation of vasculature and puncture site complications are less common (60).

Wake-up strokes are defined as waking up from sleep with symptoms of stroke and unknown time of onset. In this case, there are no clear guidelines, and the treatment is primarily based on radiological findings and evaluation of ischemic damage according to scoring scales for each patient. According to data from recent studies prolongation of the time window for IVT from 4.5 hours up to 9 hours in the selected wake-up stroke patients with salvageable ischemic tissue can lead to better functional outcomes and less neurological deficits with reduced infarcted tissue volume. However, this prolongation of time window can increase the risk of SICH after IVT application. Additionally, it has been suggested that patients with unknown time of symptoms' onset who have been last seen asymptomatic up to 24 hours of admission to a stroke center can be eligible for EMT based on findings of advanced radiological imaging methods (61,62).

Lastly, it is worth noting that both IVT and EMT therapeutic options are substantially time-dependent procedures and best outcomes can be achieved in the minimum time window from the onset of stroke symptoms as feasible (52).

## **2. OBJECTIVES**

The aim of this study was to publish the results obtained from AIS patients who were treated by EMT in University Hospital of Split and compare them with newly published results from other stroke centers worldwide. Additionally, we intended to investigate effectiveness and efficiency of EMT as the golden standard treatment for AIS as well as impact of different EMT related time factors on the neurological outcome of stroke patients.

### **Hypothesis**

1. EMT will lead to favorable neurological outcomes in patients with AIS.
2. The whole process is time dependent and there is a correlation between various time factors and mRS outcomes of patients with AIS.

The primary outcome was to evaluate the effectiveness of EMT on neurological outcomes (mRS) up to 3 months after discharge of patients from hospital.

The secondary outcomes were the probable impact of age, different time factors, selected modifiable comorbidities, degree of recanalization and IVT as well as NIHSS on neurological outcomes after discharge of patients from hospital.



### **3. SUBJECTS AND METHODS**

The presented research is a retrospective type of study conducted during period of 12 months (from January 2020 till end of December 2020) based on the data obtained from the patients with AIS who were admitted to University Hospital of Split for EMT intervention. All interventions were conducted in University Hospital of Split department of radiology KBC Firule, and data were obtained accordingly. This study was approved by the Ethics Committee of the University Hospital of Split.

The data were recorded from 48 patients who were eligible for EMT during this 1-year period. The inclusion and exclusion criteria used for selection of patients for this research were based on the recent recommendations of European Stroke Organization (ESO).

The inclusion criteria:

1. AIS patients with LVO (anterior circulation or basilar artery) who received IVT with 4.5 hours and administered to hospital within 6 hours from the onset of symptoms.
2. AIS patients who were not eligible to receive IVT therapy cause of ongoing anticoagulant therapy or recent surgical intervention.
3. NIHSS score more than 9 (up to 3 hours from the onset of symptoms) or more than 7 (between 3 to 6 hours from onset of symptoms) and ASPECTS score more than 6 with a volume of infarct less than 70 ml.

The exclusion criteria:

1. Patients with stroke as a result of intracranial hemorrhage or other causes.
2. Radiological findings which are indicative of large infarcted tissue (ASPECTS score between 0 to 5 and infarct volume more than 70 ml).

TICI scoring system was used to indicate the degree of the blood vessel recanalization and TICI score ranges from 0 to 3. TICI scores of 2b and 3 are considered as successful recanalization. For neurological outcome measurement mRS score was used which ranges from 0 to 6. In this method scores of 0, 1 and 2 are regarded as favorable outcome while mRS score of 6 is interpreted as death of the patient. NIHSS was used to measure the severity of a stroke. Also, ASPECTS score was used for CT scan scoring.

Additionally, the two most common comorbidities found in AIS patients namely diabetes and hypertension were included in this study.

EMT techniques which were employed in this study were either aspiration thrombectomy alone or together with stent retriever method based on the location of occlusion and factors involving patients' general conditions.

MedCalc software (MedCalc software, Mariakerke, Belgium) was used for statistical analysis of the data. Descriptive statistics, Kendall's correlation test, and t test were used in our study. Statistical significance was set at ( $P < 0.05$ ).

## **4. RESULTS**

#### 4.1. Descriptive statistics of the sample

(N=48)

After analyzing the data extracted from subjects' clinical reports, they were summarized and presented in Tables 1, 2 and 3. The data which were not available to us were written as "missing" in the tables.

The following results are presented in Table 1, Table 2, and Table 3. We enrolled 48 patients in our study. Median baseline NIHSS score was 15 (IQR: 13-18; 95% CI: 14-17). The median age of the patients was 77 years (IQR: 71-83 years; 95% CI: 76-80). While most of the subjects (64%; 95% CI: 50%-76%) whose data were available to us had hypertension, only 12% (95% CI: 5%-24%) of all patients had diabetes. 51% of all patients with non-missing data had atrial fibrillation (95% CI: 37%-65%).

Total occlusion was present in 8% of all patients (95% CI: 3%-19%). The occlusion site was MCA (M1+M2) and basilar artery in 74% and 10% (95% CI for basilar artery occlusion: 5%-21%) of all patients respectively. M1 (Tandem) occlusion was present in 2% of all cases (95% CI: 0%-9%). 42% (95% CI: 29%-56%) of all patients received IVT. Only 17% (95% CI: 8%-29%) of all patients received IVT in the primary stroke center (other clinic record). The median time from the onset of the symptoms till start and end of the intervention was 216 (IQR: 167-298 min; 95% CI: 183-262) and 286 (IQR: 231-390 min; 95% CI: 245-332) minutes respectively. In general, two types of EMT technique were used; aspiration method in 52% (95% CI: 38%-66%) of patients and aspiration with stent retrieval in 44% (95% CI: 30%-58%) of them and the rest was unsuccessful (4%; 95% CI: 1%-13%). The median duration of EMT intervention was 57 minutes (IQR: 31-72 min; 95% CI: 34-64). Super selective catheterization of the occluded vessel was not feasible in 13% (TICI=0; 95% CI: 5%-24%). Successful revascularization was achieved in 60% (TICI 2b and TICI 3) of all patients. Anticoagulant therapy at discharge was given to only 30% (95% CI: 18%-44%) of subjects whose data were available to us. The median NIHSS score at the end of hospitalization was 10 (IQR: 3-16; 95% CI: 4-13).

After 3 months 38% of subjects whose data were non-missing showed good functional outcomes (mRS 0-2). mRS score of 4 and 5 were 5% (95% CI: 1%-14%) and 17% (95% CI: 8%-30%) of non-missing data respectively. 40% (95% CI: 27%-56%) of the patients whose data were available to us died after 3 months (mRS=6). These data were "missing" for 6 patients (12.5% of total N).

**Table 1.** Descriptive table of the patients' data (N=48) [Part 1]

	Median	IQR*	95% CI for Median
Age (years)	77	(71-83)	(76-80)
Duration of intervention (min)	57	(31-72)	(34-64)
NIHSS at admission	15	(13-18)	(14-17)
NIHSS at discharge	10	(3-16)	(4-13)
Time from onset of symptoms till end of intervention (min)	286	(231-390)	(245-332)
Time from onset of symptoms till start of intervention (min)	216	(167-298)	(183-262)

Data are presented as general numbers

\* Interquartile range

**Table 2.** Descriptive table of the patients' data (N=48) [Part 2]

		Count	Valid N	95% CI for Valid N	of total N
Anticoagulant therapy at Discharge	No	33	(70)	(56-82)	(2.1)
	Yes	14	(30)	(18-44)	
	#*	1			
Atrial fibrillation	No	23	(49)	(35-63)	(2.1)
	Yes	24	(51)	(37-65)	
	#	1			
Diabetes	No	42	(88)	(76-95)	
	Yes	6	(12)	(5-24)	
Hypertension	No	17	(36)	(24-50)	(2.1)
	Yes	30	(64)	(50-76)	
	#	1			
Intravenous thrombolysis	No	28	(58)	(44-71)	
	Yes	20	(42)	(29-56)	
mRS after 3 months	0	9	(21)	(11-35)	(12.5)
	1	3	(7)	(2-18)	
	2	4	(10)	(3-21)	
	4	2	(5)	(1-14)	
	5	7	(17)	(8-30)	
	6	17	(40)	(27-56)	
	#	6			
Other clinic record†	No	40	(83)	(71-92)	
	Yes	8	(17)	(8-29)	

Data are presented as general numbers or as (%)

\*Missing

†Primary stroke center record where IVT is the only treatment option available for AIS patients

**Table 3.** Descriptive statistics of patients' data related to EMT (N=48)

	Count	Valid N	95% CI for Valid N
<b>Degree of recanalization:</b>			
TICI 0	6	(13)	(5-24)
TICI 1	2	(4)	(1-13)
TICI 2A	11	(23)	(13-36)
TICI 2B	3	(6)	(2-16)
TICI 3	26	(54)	(40-68)
<b>Localization:</b>			
CCA&ICA&MCA&ECA	1	(2)	(0-9)
BA	5	(10)	(4-21)
M1	33	(70)	(55-80)
M1(Tandem)*	1	(2)	(0-9)
M1&A1	1	(2)	(0-9)
M1&ICA	1	(2)	(0-9)
M2	2	(4)	(1-13)
Total occlusion†	4	(8)	(3-19)
<b>Technique:</b>			
Aspiration	25	(52)	(38-66)
Aspiration and stent retriever	21	(44)	(30-58)
Unsuccessful	2	(4)	(1-13)

Data are presented as general numbers or as (%)

\*Simultaneous occlusion of cervical ICA and cerebral anterior circulation (usually MCA)

†ICA occlusion



#### **4.2. Correlation of mRS outcomes after 3 months with variables (N=42, 6 data missing)**

The following results are presented in Table 4.

Of all the variables only NIHSS at discharge, time from onset of symptoms till end of intervention and duration of EMT intervention have statistically significant correlation ( $P$  values of all three variables are less than 0.05) with the mRS outcomes after 3 months.

Only NIHSS at discharge is moderately to strongly associated with the mRS outcomes (Kendall's tau 0.707;  $P < 0.001$ ), with a higher number of points on the NIHSS at discharge associated with the more severe outcome. Interestingly, the condition in which the patient was admitted to the hospital, measured recently on the NIHSS scale, was not associated with the severity of mRS outcomes in the patient (Kendall's tau 0.21;  $P = 0.081$ ). Although there is a possibility that the absence of this correlation is due to a relatively small sample (the correlation is significant at the level of  $P < 0.1$ ), it is still clear that NIHSS at discharge is more strongly associated with mRS outcomes than NIHSS at admission.

Regarding temporal components: time from onset of symptoms till start of intervention (EMT), time from onset of symptoms till end of intervention (EMT), and duration of intervention (EMT); mRS outcomes were poorly associated with the time from onset of symptoms to the end of EMT (Kendall's tau 0.295;  $P = 0.023$ ) as well as the duration of EMT (Kendall's tau 0.283;  $P = 0.041$ ) whereas the time from onset of symptoms till start of EMT (Kendall's tau 0.19;  $P = 0.177$ ) was not associated with this outcome.

**Table 4.** Association of different variables with mRS outcomes after 3 months (N=42, 6 data missing)

	Correlation coefficient*	P†	N
Intravenous thrombolysis	0.01	0.947	42
Hypertension	0.04	0.766	42
Diabetes	-0.06	0.653	42
Other clinic record	0.08	0.548	42
Atrial fibrillation	-0.11	0.446	42
Age	0.19	0.117	42
Time from onset of symptoms till start of intervention	0.19	0.177	30
NIHSS at admission	0.21	0.081	42
Duration of intervention	0.283	0.041	31
Time from onset of symptoms till end of intervention	0.295	0.023	35
Anticoagulant therapy at discharge	-0.407	0.004‡	41
NIHSS at discharge	0.707	<0.001	32

Data are presented as general numbers

\*Correlation Kendall's tau\_b

†Kendall's correlation test

‡Although this correlation was found to be statistically significant when all the patients were included, with the exclusion of 10 patients who died in hospital it was found that there was not a statistically significant correlation

### **4.3. Correlation of EMT and mRS outcomes**

As expected, a moderate correlation was found between the EMT and mRS outcomes (Kendall's tau  $-0.36$ ;  $P = 0.007$ ;  $N = 42$ ). A better outcome of the EMT (higher TICI) is associated with a better outcome of mRS (lower mRS).

## **5. DISCUSSION**

EMT gives us the possibility of achieving different degrees of recanalization (TICI 1 to TICI 3) and on some occasions even complete recanalization (TICI 3) of the large blood vessels of the anterior and posterior brain circulations supplying key and large areas of the brain. These crucial brain regions are responsible for not only the maintenance of our functional independence but also our survival. Consequently, since mRS grades the stroke patients based on their survival, degree of disability and dependence in daily activities, we hypothesized that EMT can result in good mRS outcomes after 3 months when it is performed in the required optimal conditions. Indeed, our results support this hypothesis and showed a moderate correlation between outcomes of the EMT and the mRS which was statistically significant. This finding agrees with four RCTs performed in 2015 (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME and REVASCAT Trials), one RCT conducted in 2016 (THRACE Trial) and a few other studies (39,48-50).

All neurons in the human brain demand oxygen and different nutrients supplied by the blood circulating in the vessels of circle of Willis. Any obstruction in the vital brain blood vessels that prevents brain from receiving sufficient blood supply can lead to functional impairment and finally death of the neurons through different pathophysiological mechanisms. While we can save the ischemic penumbra of the brain suffering from reversible ischemic attack by establishing proper reperfusion within a limited time, the infarcted region of the brain is irreversible (12). Thus, two important points can be deduced; firstly, it is evident that the whole process is time-dependent and secondly, for any intervention intended for restoring blood flow in clogged blood vessel, there is always a time window during which neurons can be saved to ensure the complete recovery of stroke patients in the future and different time factors might affect the whole process. During this specific time window, the probability of stopping the infarction volume from increasing and saving the penumbra is higher. Therefore, we can apply these same concepts to the EMT intervention as well. We postulated that the whole process is time dependent and there is a correlation between various time factors and mRS outcomes of patients experiencing AIS episode. We tried to investigate the accuracy of this hypothesis by assessing the correlation between three-time factors including time from the onset of the symptoms till start and end of the intervention and intervention duration with mRS outcomes after 3 months. The intervention duration and the time from onset of symptoms till the end of intervention were found to have poor yet statistically significant associations with the mRS outcomes after 3 months. These correlations support our hypothesis. Similar findings about these associations were found in

several research (63-66). In contrast to the previously stated statistically significant findings about two-time factors, the correlation between the time from onset of symptoms till start of EMT (this parameter roughly estimates the time window for EMT) and mRS outcomes after 3 months was found not to be statistically significant. We believe that the main reason for this insignificance lies in the small sample size, which is the main limitation of our study, because based on guidelines it is well-known that the time window is a really important factor in these kinds of interventions. In other studies, the importance of this time window is emphasized as well (52,53).

Moderate to strong correlation was found between NIHSS AT DISCHARGE and mRS outcomes after 3 months where higher score on the NIHSS AT DISCHARGE was associated with the more severe outcomes. A correlation was found between good functional outcomes at 90 days and NIHSS score  $\leq 10$  at 24 hours after EMT (67).

Interestingly no association between NIHSS AT ADMISSION and mRS outcomes after 3 month was established in our study. It is possible that this absence of correlation is because of relatively small sample. In a different study an association was found between admission NIHSS score and clinical outcome (68).

In our study both diabetes and hypertension as two important modifiable risk factors were found not to be correlated with mRS outcomes after 3 months. However, some studies demonstrated just the opposite (69,70).

In contrary to our study's results which illustrated no significant correlation between the age as a non-modifiable risk factor and mRS outcomes after 3 months, several studies have found significant relationship between these two variables (59,71).

The previously mentioned results about the associations between three important risk factors (diabetes, hypertension, and age) and mRS outcomes after 3 months might have been affected by the small sample size in our study.

Atrial fibrillation, anticoagulant therapy at discharge, intravenous thrombolysis and other clinic record were found not to be associated with mRS outcomes after 3 months in our study.

In addition to our study's small sample size which can be regarded as one of the major drawbacks of this study, there are some other limitations that could have an impact on our study and should be taken into account while trying to interpret our study's results; they include missing data about some of our patients' variables, variation of the experience in performing EMT by different specialists and various intervention success rates in different hospitals.

One of the possible applications of our study's findings about the secondary outcomes like NIHSS AT DISCHARGE can be the development of a new scoring system based on these factors to better prioritize patients for the treatment and predict their outcomes after EMT. We need more research to identify such scoring systems.

Future research can be performed to discover a new special mechanical thrombectomy technique or develop new technological devices to reduce the duration of EMT. In addition, researchers can investigate any possible ways to either extend the time window or decrease the time from the onset of the symptoms till start of the intervention.

Building new strategies to improve the organizational procedures and policies of the hospitals and developing programs to inform patients about the importance of the early admission to the hospital in case of a sudden stroke episode can be considered among some of the ways to decrease the time from the onset of the symptoms till start of the intervention.

## **6. CONCLUSIONS**



1. Our study has shown that outcomes of the EMT and mRS have statistically significant association. While in our study's findings mRS outcomes had poor yet statistically significant correlation with the time from onset of symptoms till the end of EMT as well as the duration of intervention, the time from onset of symptoms till start of intervention was not associated with these outcomes. The small sample size presented in this study might have affected our findings about the correlation between mRS outcomes and time from onset of symptoms till start of intervention.
2. In our study the variables including Age, Hypertension, diabetes, intravenous thrombolysis, other clinic record, atrial fibrillation, NIHSS at admission and anticoagulant therapy at discharge were found not to be correlated with mRS outcomes. The mentioned findings could have been influenced by our small sample size. The association of NIHSS at discharge variable with mRS outcomes was statistically significant.
3. Future studies could be conducted about development of new scoring systems based on different prognostic factors related to EMT, discovering new special mechanical thrombectomy techniques and developing new technological devices which can be useful in this field.

## **7. REFERENCES**

1. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ.* 1980;58(1):113-30.
2. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, 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;44(7):2064-89.
3. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. *Cerebrovasc Dis.* 2009;27(5):493-501.
4. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* 2008;371(9624):1612-23.
5. Donkor ES. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res Treat.* 2018;2018:3238165.
6. Kalaria RN, Akinyemi R, Ihara M. Stroke injury, cognitive impairment and vascular dementia. *Biochim Biophys Acta.* 2016;1862(5):915-25.
7. Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. *Continuum (Minneapolis, Minn).* 2017;23(1, Cerebrovascular Disease):15-39.
8. Rennert RC, Wali AR, Steinberg JA, Santiago-Dieppa DR, Olson SE, Pannell JS, et al. Epidemiology, Natural History, and Clinical Presentation of Large Vessel Ischemic Stroke. *Neurosurgery.* 2019;85(suppl\_1):S4-S8.
9. Healthdata.org [internet]. University of Washington: Institute for Health Metrics and Evaluation; c2019 [cited 2020 Nov 17]. Available from: <http://www.healthdata.org/croatia?language=41>.
10. Spence JD. Nutrition and stroke prevention. *Stroke.* 2006;37(9):2430-5.
11. Kumar V, Abbas AK, Aster JC. Robbins basic pathology. 9th ed. Canada: Elsevier Saunders; 2012.
12. Rubattu S, Giliberti R, Volpe M. Etiology and pathophysiology of stroke as a complex trait. *Am J Hypertens.* 2000;13(10):1139-48.
13. Frizzell JP. Acute stroke: pathophysiology, diagnosis, and treatment. *AACN Clin Issues.* 2005;16(4):421-40; quiz 597-8.
14. Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. *Prog Neurobiol.* 2010;92(4):463-77.
15. Hasan TF, Rabinstein AA, Middlebrooks EH, Haranhalli N, Silliman SL, Meschia JF, et al. Diagnosis and Management of Acute Ischemic Stroke. *Mayo Clin Proc.* 2018;93(4):523-38.

16. Yew KS, Cheng EM. Diagnosis of acute stroke. *Am Fam Physician*. 2015;91(8):528-36.
17. Saver JL. Time is brain--quantified. *Stroke*. 2006;37(1):263-6.
18. Maurer CJ, Egger K, Dempfle AK, Reinhard M, Meckel S, Urbach H. Facing the Time Window in Acute Ischemic Stroke: The Infarct Core. *Clin Neuroradiol*. 2016;26(2):153-8.
19. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5(7):603-12.
20. Krishnaswamy A, Klein JP, Kapadia SR. Clinical cerebrovascular anatomy. *Catheter Cardiovasc Interv*. 2010;75(4):530-9.
21. Matos Casano HA, Tadi P, Ciofoaia GA. Anterior Cerebral Artery Stroke. Treasure Island (FL): StatPearls Publishing; 2020.
22. Nogles TE, Galuska MA. Middle Cerebral Artery Stroke. Treasure Island (FL): StatPearls Publishing; 2020.
23. Behme D, Kowoll A, Weber W, Mpotsaris A. M1 is not M1 in ischemic stroke: the disability-free survival after mechanical thrombectomy differs significantly between proximal and distal occlusions of the middle cerebral artery M1 segment. *J Neurointerv Surg*. 2015;7(8):559-63.
24. Cereda C, Carrera E. Posterior cerebral artery territory infarctions. *Front Neurol Neurosci*. 2012;30:128-31.
25. Berman SA, Hayman LA, Hinck VC. Correlation of CT cerebral vascular territories with function: I. Anterior cerebral artery. *AJR Am J Roentgenol*. 1980;135(2):253-7.
26. Berman SA, Hayman LA, Hinck VC. Correlation of CT cerebral vascular territories with function: 3. Middle cerebral artery. *AJR Am J Roentgenol*. 1984;142(5):1035-40.
27. Hayman LA, Berman SA, Hinck VC. Correlation of CT cerebral vascular territories with function: II. Posterior cerebral artery. *AJR Am J Roentgenol*. 1981;137(1):13-9.
28. Rudkin S, Cerejo R, Tayal A, Goldberg MF. Imaging of acute ischemic stroke. *Emerg Radiol*. 2018;25:659-72.
29. Lin MP, Liebeskind DS. Imaging of Ischemic Stroke. *Continuum (Minneapolis)*. 2016;22:1399-423.
30. Ledezma CJ, Wintermark M. Multimodal CT in stroke imaging: new concepts. *Radiol Clin North Am*. 2009;47(1):109-16.
31. Wardlaw JM, Mielke O. Early signs of brain infarction at CT: observer reliability and outcome after thrombolytic treatment--systematic review. *Radiology*. 2005;235(2):444-53.

32. Birenbaum D, Bancroft LW, Felsberg GJ. Imaging in acute stroke. *West J Emerg Med.* 2011;12(1):67-76.
33. Heit JJ, Wintermark M. Perfusion Computed Tomography for the Evaluation of Acute Ischemic Stroke: Strengths and Pitfalls. *Stroke.* 2016;47(4):1153-8.
34. Bivard A, Levi C, Krishnamurthy V, McElduff P, Miteff F, Spratt NJ, et al. Perfusion computed tomography to assist decision making for stroke thrombolysis. *Brain.* 2015;138:1919-31.
35. Konstas AA, Goldmakher GV, Lee TY, Lev MH. Theoretic basis and technical implementations of CT perfusion in acute ischemic stroke, part 1: Theoretic basis. *AJNR Am J Neuroradiol.* 2009;30(4):662-8.
36. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke.* 2006;37(4):979-85.
37. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol.* 2006;60(5):508-17.
38. Leiva-Salinas C, Wintermark M. Imaging of acute ischemic stroke. *Neuroimaging Clin N Am.* 2010;20(4):455-68.
39. Boyle K, Joundi RA, Aviv RI. An historical and contemporary review of endovascular therapy for acute ischemic stroke. *Neurovasc Imaging.* 2017;3(1).
40. Grigoryan M, Qureshi AI. Acute stroke management: endovascular options for treatment. *Semin Neurol.* 2010;30(5):469-76.
41. Spiotta AM, Chaudry MI, Hui FK, Turner RD, Kellogg RT, Turk AS. Evolution of thrombectomy approaches and devices for acute stroke: a technical review. *J Neurointerv Surg.* 2015;7(1):2-7.
42. Katz JM, Gobin YP. Merci Retriever in acute stroke treatment. *Expert Rev Med Devices.* 2006;3(3):273-80.
43. Clark W, Lutsep H, Barnwell S, Nesbit G, Egan R, North E, et al. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke.* 2009;40(8):2761-8.

44. Kalia JS, Zaidat OO. Using a distal access catheter in acute stroke intervention with penumbra, merci and gateway. A technical case report. *Interv Neuroradiol.* 2009;15(4):421-4.
45. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet.* 2012;380(9849):1241-9.
46. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet.* 2012;380(9849):1231-40.
47. Gory B, Armoiry X, Sivan-Hoffmann R, Piotin M, Mazighi M, Lapergue B, et al. A direct aspiration first pass technique for acute stroke therapy: a systematic review and meta-analysis. *Eur J Neurol.* 2018;25(2):284-92.
48. 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;43(4):455-60.
49. Sang HF, Yin CG, Xia WQ, Huang H, Liu KQ, Chen TW, et al. Mechanical Thrombectomy Using Solitaire in Acute Ischemic Stroke Patients with Vertebrobasilar Occlusion: A Prospective Observational Study. *World Neurosurg.* 2019;128:e355-e361.
50. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2019;50(12):e344-e418.
51. Cheng NT, Kim AS. Intravenous Thrombolysis for Acute Ischemic Stroke Within 3 Hours Versus Between 3 and 4.5 Hours of Symptom Onset. *Neurohospitalist.* 2015;5(3):101-9.
52. Tawil SE, Muir KW. Thrombolysis and thrombectomy for acute ischaemic stroke. *Clin Med (Lond).* 2017;17(2):161-5.
53. Seners P, Turc G, Maier B, Mas JL, Oppenheim C, Baron JC. Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. *Stroke.* 2016;47(9):2409-12.
54. Menon BK, Al-Ajlan FS, Najm M, Puig J, Castellanos M, Dowlathshahi D, et al. Association of Clinical, Imaging, and Thrombus Characteristics With Recanalization of

- Visible Intracranial Occlusion in Patients With Acute Ischemic Stroke. *JAMA*. 2018;320(10):1017-26.
55. Sallustio F, Koch G, Alemseged F, Konda D, Fabiano S, Pampana E, et al. Effect of mechanical thrombectomy alone or in combination with intravenous thrombolysis for acute ischemic stroke. *J Neurol*. 2018;265(12):2875-80.
56. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke. *J Neurointerv Surg*. 2019;1136(10).
57. Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke*. 2016;11(1):134-47.
58. Sweid A, Head J, Tjoumakaris S, Xu V, Shivashankar K, Alexander TD, et al. Mechanical Thrombectomy in Distal Vessels: Revascularization Rates, Complications, and Functional Outcome. *World Neurosurg*. 2019;130:e1098-e1104.
59. Goyal M, Menon BK, van Zwam WH, Dippel DW, 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;387(10029):1723-31.
60. Balami JS, White PM, McMeekin PJ, Ford GA, Buchan AM. Complications of endovascular treatment for acute ischemic stroke: Prevention and management. *Int J Stroke*. 2018;13(4):348-61.
61. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendzus M, et al. Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet*. 2019;394(10193):139-47.
62. Jadhav AP, Aghaebrahim A, Jankowitz BT, Haussen DC, Budzik RF, Bonafe A, et al. Benefit of Endovascular Thrombectomy by Mode of Onset: Secondary Analysis of the DAWN Trial. *Stroke*. 2019;50(11):3141-6.
63. Enomoto Y, Uchida K, Yamagami H, Imamura H, Ohara N, Sakai N, et al. Impact of Procedure Time on Clinical Outcomes of Patients Who Underwent Endovascular Therapy for Acute Ischemic Stroke. *Cerebrovasc Dis*. 2021;50(4):443-9.

64. Hassan AE, Shariff U, Saver JL, Goyal M, Liebeskind D, Jahan R, et al. Impact of procedural time on clinical and angiographic outcomes in patients with acute ischemic stroke receiving endovascular treatment. *J Neurointerv Surg.* 2019;11(10):984-8.
65. 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;40(4):252-9.
66. Ozdemir O, Giray S, Arlier Z, Baş DF, Inanc Y, Colak E. Predictors of a Good Outcome after Endovascular Stroke Treatment with Stent Retrievers. *ScientificWorldJournal.* 2015;2015:403726.
67. Wirtz MM, Hendrix P, Goren O, Beckett LA, Dicristina HR, Schirmer CM, Dalal S, Weiner G, Foreman PM, Zand R, Griessenauer CJ. Predictor of 90-day functional outcome after mechanical thrombectomy for large vessel occlusion stroke: NIHSS score of 10 or less at 24 hours. *J Neurosurg.* 2019;20:1-7.
68. Jiang S, Fei A, Peng Y, Zhang J, Lu YR, Wang HR, et al. Predictors of Outcome and Hemorrhage in Patients Undergoing Endovascular Therapy with Solitaire Stent for Acute Ischemic Stroke. *PLoS One.* 2015;10(12):e0144452.
69. Lu GD, Ren ZQ, Zhang JX, Zu QQ, Shi HB. Effects of Diabetes Mellitus and Admission Glucose in Patients Receiving Mechanical Thrombectomy: A Systematic Review and Meta-analysis. *Neurocrit Care.* 2018;29(3):426-34.
70. Mouchtouris N, Al Saiegh F, Valcarcel B, Andrews CE, Fitchett E, Nauheim D, et al. Predictors of 30-day hospital readmission after mechanical thrombectomy for acute ischemic stroke. *J Neurosurg.* 2020;1;134(5):1500-4.
71. Daou B, Chalouhi N, Starke RM, Dalyai R, Hentschel K, Jabbour P, et al. Predictors of Outcome, Complications, and Recanalization of the Solitaire Device: A Study of 89 Cases. *Neurosurgery.* 2015;77(3):355-60; discussion 360-1.



## **8. SUMMARY**

**Objectives:** To evaluate the effectiveness of endovascular mechanical thrombectomy in acute ischemic stroke patients. Time dependency of whole process and correlation of different intervention related time factors with the mRS outcomes after 3 months were investigated as well.

**Subjects and Methods:** A sample of 48 patients was chosen from University Hospital Split over a time span of 1 year (from January 2020 till end of December 2020) based on specific and predefined inclusion and exclusion criteria. The extracted data from patients' medical records were analyzed by different statistical tests. mRS was used to measure the degree of disability or dependence in the daily activities for stroke patients. For severity of the stroke measurement NIHSS was used. TIC1 scoring system was used to indicate the degree of blood vessel recanalization in our study.

**Results:** Our results demonstrated a statistically significant association between endovascular mechanical thrombectomy and mRS outcomes. Of all the variables only NIHSS at discharge, endovascular mechanical thrombectomy duration and time from onset of the symptoms till the end of intervention were found to be correlated with mRS after 3 months in our results.

**Conclusions:** A statistically significant association has been shown between endovascular mechanical thrombectomy and mRS outcomes in our study. Time from onset of symptoms till the end of intervention and duration of intervention were correlated with mRS after 3 months and both associations were statistically significant. However, time from onset of symptoms till start of intervention was not found to be correlated with mRS after 3 months which could be due to impact of small sample size on our study.

## **9. CROATIAN SUMMARY**

## **Endovaskularna mehanička trombektomija u liječenju moždanog udara u Kliničkom bolničkom centru Split: naše iskustvo**

**Ciljevi:** Procijeniti učinkovitost endovaskularne mehaničke trombektomije u bolesnika s akutnim ishemijskim moždanim udarom. Također je ispitana vremenska ovisnost cijelog procesa i korelacija različitih vremenskih faktora povezanih s intervencijom s ishodom mRS -a nakon 3 mjeseca.

**Materijali i Metode:** Uzorak od 48 pacijenata odabran je iz KBC Split u vremenskom rasponu od 1 godine (od siječnja 2020. do kraja prosinca 2020.) na temelju specifičnih i unaprijed definiranih kriterija uključivanja i isključivanja. Izvučeni podaci iz medicinske dokumentacije pacijenata analizirani su različitim statističkim testovima. mRS je korišten za mjerenje stupnja invaliditeta ili ovisnosti u dnevnim aktivnostima za pacijente s moždanim udarom. Za težinu mjerenja moždanog udara korišten je NIHSS. TICI sustav bodovanja korišten je za označavanje stupnja rekanalizacije krvnih žila u našem istraživanju.

**Rezultati:** Naši rezultati pokazali su statistički značajnu povezanost između endovaskularne mehaničke trombektomije i ishoda mRS-a. Od svih varijabli, samo je NIHSS pri otpustu, trajanje endovaskularne mehaničke trombektomije i vrijeme od pojave simptoma do kraja intervencije bili u korelaciji s mRS -om nakon 3 mjeseca u našim rezultatima.

**Zaključak:** U našem istraživanju pokazana je statistički značajna povezanost između endovaskularne mehaničke trombektomije i ishoda mRS -a. Vrijeme od pojave simptoma do kraja intervencije i trajanje intervencije bili su u korelaciji s mRS-om nakon 3 mjeseca, a obje ove veze bile su statistički značajne. Međutim, utvrđeno je da vrijeme od pojave simptoma do početka intervencije nije povezano s mRS-om nakon 3 mjeseca, što bi moglo biti posljedica utjecaja male veličine uzorka na našu studiju.

## **10. CURRICULUM VITAE**

## Personal Data

**Name and Surname:** Pezhman Rasouli

**Date of Birth:** September 20<sup>th</sup>, 1989, Tabriz, Iran.

**Citizenship:** Iranian

**Email:** [pezhman.ra@gmail.com](mailto:pezhman.ra@gmail.com)

## Education

**2013-2021:** Medicine, University of Split School of Medicine, Split, Croatia.

**2010-2013:** Biomedical science, University of Tasmania (UTAS), Tasmania, Australia.

**2006:** Obtained the high school diploma.

## Language Skills

**Turkish** (mother tongue)

**Farsi** (mother tongue)

**English** (fluent)

**Croatian** (basic)