Clinical significance and early detection of large vessel occlusion in acute ischemic stroke

PhD Thesis

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Declaration

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- Tárkányi G, Karádi ZN, Csécsei P, et al. Capability of stroke scales to detect large vessel occlusion in acute ischemic stroke - a pilot study. Stroke-skálák képessége nagyérelzáródás detektálására akut ischaemiás stroke-ban – pilot vizsgálat. *Ideggyogy Sz*. 2021;74(3-4):99-103. doi:10.18071/isz.74.0099
- Tarkanyi G, Csecsei P, Szegedi I, et al. Detailed severity assessment of Cincinnati Prehospital Stroke Scale to detect large vessel occlusion in acute ischemic stroke. BMC Emerg Med. 2020;20(1):64. Published 2020 Aug 24. doi:10.1186/s12873-020-00360-9
- Tarkanyi G, Karadi ZN, Szabo Z, Szegedi I, Csiba L, Szapary L. Relationship between leukocyte counts and large vessel occlusion in acute ischemic stroke. BMC Neurol. 2020;20(1):440. Published 2020 Dec 4. doi:10.1186/s12883-020-02017-3
- Tarkanyi G, Tenyi A, Hollos R, Kalmar PJ, Szapary L. Optimization of Large Vessel Occlusion Detection in Acute Ischemic Stroke Using Machine Learning Methods. Life (Basel). 2022;12(2):230. Published 2022 Feb 3. doi:10.3390/life12020230

List of abbreviations

AC	**anterior circulation**	**LOC**	**level of consciousness**
AComm	anterior communicating artery	**LR**	logistic regression
AF	atrial fibrillation	**LVO**	large vessel occlusion
AHA	American Heart Association	**MAP**	mean arterial pressure
AIS	acute ischemic stroke	**MCA**	middle cerebral artery
ASA	American Stroke Association	**mCTA**	multiphase CTA collateral score
ASPECT	Alberta Stroke Program Early CT Score	**ML**	machine learning
AUC	area under the curve	**MRA**	MR angiography
BA	basilar artery	**MRI**	magnetic resonance imaging
CBF	cerebral blood flow	**mRS**	modified Rankin Scale
CCA	common carotid artery	**MSU**	mobile-stroke unit
CI	confidence interval	**MT**	mechanical thrombectomy
CNS	central nervous system	**NCCT**	Non-contrast CT
CPSS	Cincinnati Prehospital Stroke Scale	**NIHSS**	National Institutes of Health Stroke Scale
CT	computer tomography	**NLR**	neutrophil-to-lymphocyte ratio
CTA	CT angiography	**OR**	odds ratio
CTP	CT perfusion	**OSA**	obstructive sleep apnoea
CSC	comprehensive stroke centre	**PC**	posterior circulation
DM	diabetes mellitus	**PComm**	posterior communicating artery
DNT	door-to-needle time	**PSC**	primary stroke centre
DTI	door-to-imaging time	**PSI**	post stoke infection
DWI	diffusion-weighted imaging	**RACE**	Rapid Arterial Occlusion Evaluation
ECA	external carotid artery	**RCT**	randomized-controlled trial
ED	emergency department	**RF**	random forest
EMS	emergency medical service	**ROC**	receiver operating characteristic
ENM	elastic net method	**ROSIER**	Recognition of Stroke in the Emergency Room score
EVT	endovascular thrombectomy	**SBP**	systolic blood pressure
FAST	Face Arm Speech Test	**SD**	standard deviation
FLAIR	fluid attenuated inversion recovery	**sICH**	symptomatic intracranial haemorrhage
HS	haemorrhagic stroke	**SN**	sensitivity
HT	hypertension	**SNN**	simple neural network
ICA	internal carotid artery	**SP**	specificity
IQR	interquartile range	**TIA**	transient ischaemic attack
IVT	intravenous thrombolysis	**UD**	University of Debrecen
LAMS	Los Angeles Motor Scale	**UP**	University of Pécs
LAPSS	Los Angeles Prehospital Stroke Screen	**USZ**	University of Szeged
LASSO	least absolute shrinkage and selection operator	**VA**	vertebral artery
LDL	low-density lipoprotein	**WBC**	white blood cell

1. Basics of acute stroke

Acute stroke is classically defined as the sudden onset of focal neurological deficits attributed to the focal injury of the central nervous system (CNS) as a result of underlying cerebrovascular disease. However, the term 'stroke' implies several conditions with similar clinical presentations but different etiology[1]. About 85% of stroke cases are acute ischemic strokes (AIS) in which occlusion of the cerebral vessels occurs causing ischaemia in the brain tissue and subsequent death of neuronal cells.[1–3] Haemorrhagic strokes (HS) are attributable to a focal collection of blood within the brain parenchyma or ventricular system, while subarachnoid haemorrhage (SAH) refers to bleeding to the subarachnoid space. These conditions account for 10 and 3 percent of the cases, respectively.[2] More broadly the term stroke also includes CNS infarction or haemorrhage caused by cerebral venous thrombosis[1].

Stroke is a leading cause of mortality and disability worldwide with a substantial economic burden.[4] In the European Union about 1.1 million people suffer stroke every year and 460 000 deaths are related to stroke and these numbers will probably increase in the next decades. In 2017 costs related to stroke-care were estimated at €45 billion.[5] Acute stroke is primarily affecting the elderly but can occur in any age and significant differences in incidence are also perceived in terms of sex and race/ethnicity.[6]

1.1. Anatomy of the cerebral vasculature

Uniquely the brain is supplied by four arteries. The anterior circulation territory originates from the two *internal carotid arteries* (ICA) which account for 80% of the blood supply, posterior circulation is made up by the two *vertebral arteries* (VA) that are responsible for the other 20%. There is an extensive collateral network between cerebral arteries and anastomotic connections exist with the extracranial vessels through the skull as well. The anterior circulation of both hemispheres, as well as the anterior and posterior vascular territory is directly connected by communicating arteries, which together forms the *circle of Willis* (Figure 1). These structures can provide sufficient collateral flow to the affected regions in the case of insufficient blood flow due to vascular disease or occlusion.

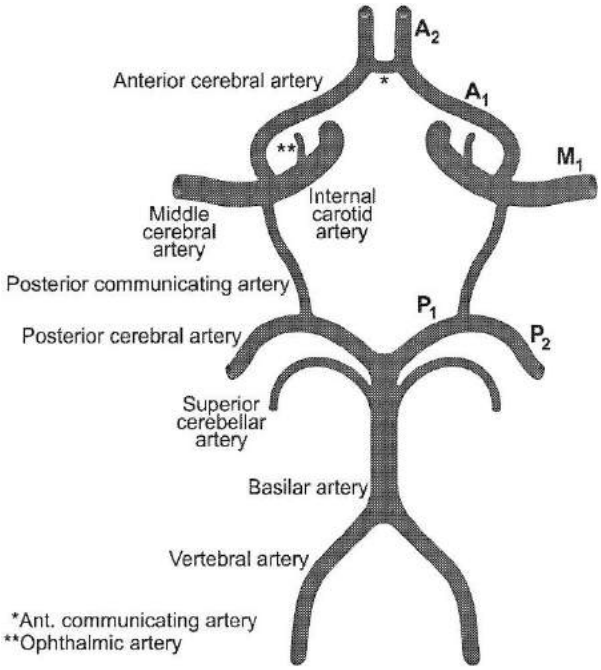

Figure 1. Typical normal polygon configuration of the circle of Willis. M1 indicates main trunk of the middle cerebral artery; A2, postcommunicating part of the anterior cerebral artery; P2, postcommunicating part of the posterior cerebral artery; and Ant., anterior. Reprinted from 'Collateral variations in circle of willis in atherosclerotic population assessed by means of transcranial color-coded duplex ultrasonography' by Hoksbergen et al., 2000, *Stroke.*

1.1.1. Anterior circulation of the brain

The right *common carotid artery* (CCA) originates from the *brachiocephalic trunk*, whilst the left CCA arises from the aortic arch directly. On the neck both CCAs are dividing into two branches, the *external carotid artery* (ECA) and the ICA. The carotid bifurcation is a predilection site for extracranial atherosclerotic plaque build-up. The ECA has many branches supplying the structures of the neck, face and head and plays an important role in the creation of anastomoses between the extra-and intracranial vessels. In contrast ICA normally has no branches extracranially.

In clinical settings a numerical scale is commonly used to divide the ACI into segments following the direction of blood flow and considering surrounding anatomical structures close to the ICA and the compartments through which it travels.[7] Following the cervical portion (C1 segment) the ICA enters the petrous part of the temporal bone through the carotid canal, and extends until the foramen lacerum (petrous segment, C2). That is followed by the segment lacerum (C3), a short, still extradural portion surrounded by periosteum and fibrocartilage. Then the ICA runs surrounded by the cavernous sinus (cavernous segment, C4) where it makes a curve usually called the carotid siphon. The clinoid segment (C5) is another short part which

lasts until ICA crosses the dura mater. Thereafter begins the ophthalmic segment (C6) from which the ophthalmic artery arises, supplying the eye and its muscles, as well as some structures in the nose, face, and meninges. The last segment extends from the origin of the posterior communicating artery (PComm) to the bifurcation of the ICA (communicating segment, C7), where it divides to form the anterior cerebral artery (ACA) and the middle cerebral artery (MCA). An important branch of the C7 section is the anterior choroidal artery, which supplies structures in the prosencephalon, diencephalon, and mesencephalon (Figure 2).

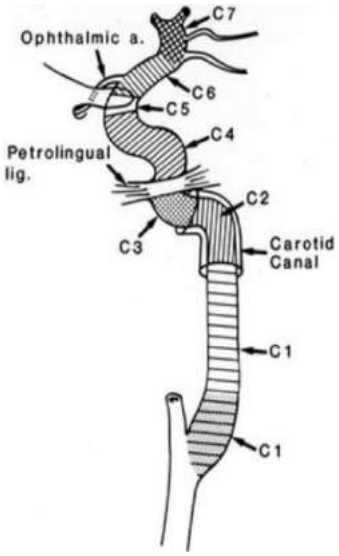

Figure 2. Bouthillier classification of internal carotid artery segments.
Downloaded from https://operativeneurosurgery.com/

The pair of ACAs can also be divided into segments. The first segment (A1) originates from the ICA and extends to the anterior communicating artery (AComm), which connects the two ACAs as a part of the circle of Willis. The medial lenticulostriate arteries are generally considered to arise from this segment, which irrigate the caudate nucleus and the anterior limb of the internal capsule. The A2 segment extends from the AComm to the bifurcation forming the pericallosal and callosomarginal arteries. Recurrent artery of Heubner is the largest perforating branch from the A2 segment, that supplies the head of the caudate nucleus, the medial portion of globus pallidus, the anterior crus of the internal capsule, the anterior hypothalamus, and the nucleus accumbens. The distal part (segment A3) of the ACA is called the pericallosal artery, the most important branch of which are the callosal marginal artery. Its smaller branches are usually considered as the A4 and A5 segments, which often anastomose with the posterior circulation. In general, the ACA is supplying the midline portions of the frontal lobes and superior medial parietal lobes of the brain.

The middle cerebral artery (MCA) is appearing as a continuation of the ICA beyond the origin of the ACA. The MCA is usually subdivided into four segments. The M1 (sphenoidal) segment runs in the Slyvian fissure, then it turns superiorly into the area between the temporal lobe and the insula where it normally divides into two branches. This segment perforates the brain with numerous lateral lenticulostriate arteries, which irrigate the internal capsule, the head and body of the caudate nucleus and the lateral portion of the globus pallidus. The M2 (insular) segment begins at the bifurcation and ascends along the insular cleft before making a hairpin turn at the sulcus of the insula. The M3 (opercular) segment begins at the apex of the hairpin

turn and terminates as the branches reach the lateral convexity of the hemisphere. The M4 (cortical) segments are visible on the lateral convexity of the hemisphere as the arteries arises between the frontal, parietal, and temporal lobes. Generally, the ACM supplies two-thirds of the convexity of brain hemispheres, the surface of the insula and the operculum, as well as the anterior temporal lobes (Figure 3).

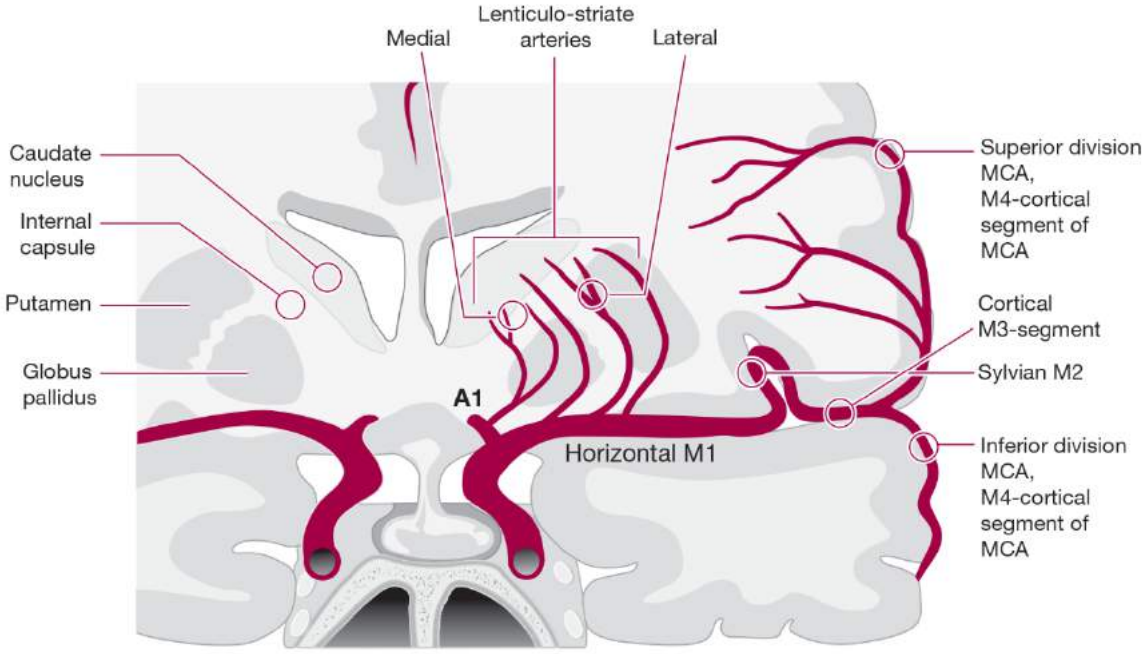

Figure 3. Segments of the middle cerebral artery. Reprinted from 'Stroke' in book: 'Physical Medicine and Rehabilitation Board Review' by Zorowitz et al., 2019, Springer Publishing

1.1.2. Posterior circulation of the brain

Both VAs are originate from the subclavian arteries. The first part (V1) courses superiorly along the muscles of the neck, and subsequently enters the transverse foramen of the 6th cervical vertebra (C6). The second segment (V2) runs upward through the transverse foramens of the C6 to C2 vertebrae. The third segment (V3) starts from C2, whereupon the artery loops the top of the C1 vertebra (atlas) until it enters the skull through the foramen magnum. After the artery pierces the dura the last segment (V4) inclines medialward to the front of the medulla oblongata and subsequently at the lower border of the pons the two VAs merge to form the basilar artery (BA). The V4 segment gives origin for the anterior and posterior spinal arteries (ASA and PSA), perforating branches to the medulla, and the posterior inferior cerebellar artery (PICA). The ASA supplies the anterior portion of the spinal cord, while PICA supplies the inferior part of the vermis and the posterior and medial portions of the cerebellar hemispheres as well as the lateral-dorsal part of the medulla.

The BA ascends in the basilar sulcus of the ventral pons and divides at the junction of the midbrain and pons into the posterior cerebral arteries (PCA). The BA has several small perforating and circumferent branches that supply most of the pons. Besides, two important larger arteries are originating from the BA: the anterior inferior cerebellar artery (AICA) and the superior cerebellar artery (SCA) are supplying parts of the cerebellum, portions of the pons and midbrain, as well as the cochlea and the vestibular apparat (Figure 4).

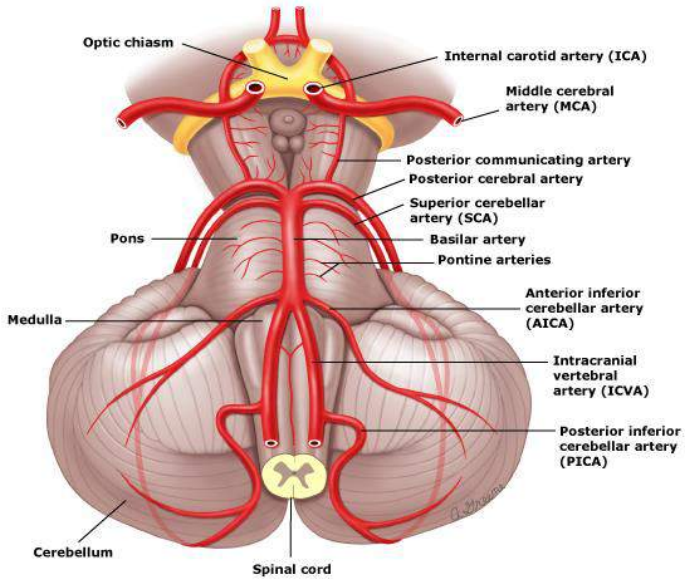

Figure 4. Posterior circulation to the brain. Reprinted from 'Posterior circulation cerebrovascular syndromes' by Caplan LR in: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed March 04, 2022).

The PCAs are the terminal branches of the BA and supply the occipital lobes, the posteromedial part of the temporal lobes and the thalamus. Like others, PCA is also usually divided into segments as follows: the P1 segment lasts until the origin of PComm, the P2 segment travels around the midbrain and terminates as it enters the quadrigeminal cistern, segment P3 courses through the quadrigeminal cistern while it enters the sulci of the occipital lobe in which the P4 segments run.

1.2. Pathophysiology of brain ischaemia

Even though the weight of the human brain is only around 2% of the total body weight (around 1.5 kg), the total cerebral blood flow (CBF) is about 800 mL/min in healthy adults, which is 15-20% of the total cardiac output. This highlights the high metabolic demand of the CNS which is a consequence of the fact that it almost exclusively uses glucose as a sole substrate for energy metabolism. As it is unable to store energy it requires a constant supply of

oxygenated blood containing adequate glucose concentration to maintain its function and structural integrity.[8]

Decreasing CBF gradually causes damage to physiological functions of neuronal cells. Protein synthesis is declined first, and selective gene expression occurs if CBF falls below ~50 mL/100g brain tissue/min. Protein synthesis is supressed when CBF falls under 35 mL/100g/min, however glucose utilisation is only declining below 25 mL/100g/min, when significant ATP depletion already occurs, and this is the value where focal neurological symptoms starting to appear. Anoxic depolarisation occurs at even lower values (<15 ml/100 g/min) indicating the failure of membrane function (Figure 5)[9]. In this case intracellular Ca^{2+} levels increase, triggering a plethora of biochemical pathways promoting apoptosis.

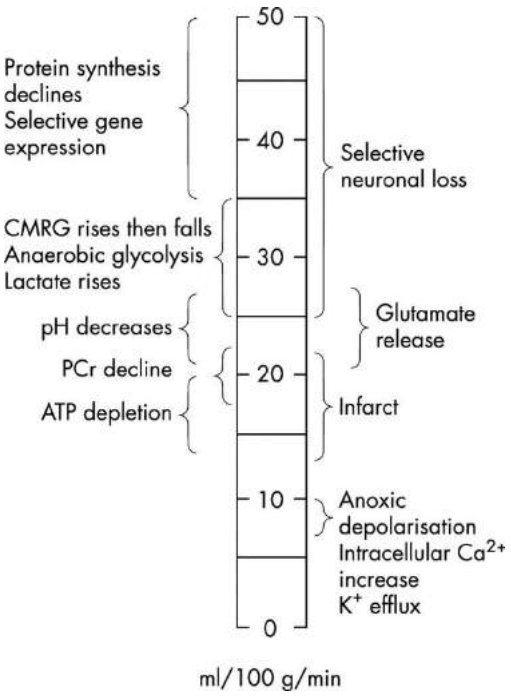

Figure 5. Thresholds of ischaemia for the induction of functional, metabolic, and histological lesions. Exact levels vary slightly in different animal models and also with the duration of ischaemia for certain variables. CMRG, cerebral metabolic rate of glucose; PCr, phosphocreatine. Reprinted from 'Cerebral perfusion and stroke' by Markus HS, 2004, *J Neurol Neurosurg Psychiatry.*

Different territories of the brain are sensitive to ischemic insult to varying degrees. Some areas can tolerate prolonged and greater CBF reductions (e.g. brain stem nuclei), while other regions irreversibly damage even in the case of short-term and small reduction in CBF (for example the neurons of neocortex). Usually, the area with severely impaired CBF and consequential necrosis is surrounded by an area with low CBF (15-40 mL/100g/min) called penumbra.[8] In the penumbra cells are functionally impaired, but their structural integrity is maintained, and if circulation is restored, this area can still potentially be salvageable[10]. Otherwise, apoptosis occurs within a few hours, with the rate of 1.9 million neurons per minute.[3]

To maintain relatively constant CBF over a wide range of systemic blood pressure levels cerebral vessels have complex autoregulatory mechanisms controlled by myogenic, neurogenic, metabolic, and endothelial factors. In general, autoregulation is important to match CBF to the metabolic demand of the brain. When mean arterial pressure (MAP) elevates vasoconstriction of the small cerebral vessels occurs, thus vascular resistance increases. Conversely, a drop in MAP results vasodilatation and decrease of vascular resistance. In healthy adults the optimal range of MAP to maintain sufficient autoregulation is between 60 and 160 mmHg. Changes in

the microenvironment (such as variations in pCO_2 and H^+ levels) also affects the tone of cerebral vasculature. Neurogenic mechanism through an extensive nerve supply to cerebral vessels also regulates vascular tone. Additionally, endothelial factors, such as nitric oxide, may also contribute to autoregulation.

1.3. Risk factors and etiology of acute ischemic stroke

Acute ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery. In the case of thrombotic origin, a thrombus (blood clot) forms locally, within the vessel. In contrast, embolization means that the thrombus forms in another vascular region or in the heart, and subsequently drifts to the cerebral vessels. Eventually, in both cases, the cerebral blood supply is disrupted.

Considering the origin of the clot and the location of the occlusion the commonly used Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria defines 5 major etiological categories: cardioembolic, small-vessel occlusion, large-artery atherosclerosis, other determined origin, and stroke of undetermined etiology.[11] Accordingly, the main risk factors of AIS are the predisposing condition for atherosclerosis and thrombus formation. Atherosclerotic lesion of the cerebral vessels is a significant risk factor for AIS, with a carotid artery stenosis greater than 75% the annual stroke risk is around 10.5%. Ulcerated, echolucent and heterogenous plaques with a soft core represent plaques at high risk for thromboembolism and consequent stroke[12]. Increasing age is the most important non-modifiable risk factor of AIS as stroke incidence doubles each decade past the age of 55 years and half of strokes occur in people older than 75 years. Between the ages of 45 and 75 years AIS is more common among men, thereafter rates are higher in women. Besides race and ethnicity also have associations with the risk of stroke[13].

Numerous modifiable risk factors should also be mentioned. Arterial hypertension (HT) is the most important, which is prevalent in more than half of the population of developed countries. The presence of HT is increasing the risk for AIS three-to fourfold by aggravating atherosclerosis and accelerating heart disease. In general, the association between systolic blood pressure (SBP) and the risk for AIS is linear, consequently the higher the SBP the higher the risk is.[14,15] Diabetes mellitus (DM) is an independent risk factor of AIS, increasing the risk two- to fourfold and contributing to increased morbidity and mortality after stroke. The duration of DM is also associated with the risk of suffering a stroke. Dyslipidaemia is a recognized risk factor for AIS as increasing total cholesterol and low-density lipoprotein (LDL) levels are associated with higher stroke incidence[16]. Atrial fibrillation (AF) is the most common sustained

arrythmia (present in 1% of the general population), the prevalence of which increases with age. As AF is a predisposing factor for intracardiac thrombus formation it is also associated with a substantially increased, around five-to sixfold risk for AIS. Studies have also revealed association between obstructive sleep apnoea (OSA) and stroke, moreover, the severity of OSA is much higher in stroke patients than in controls. Finally, it is very important to highlight that those previously suffered a transient ischaemic attack (TIA), or stroke has a threefold risk for AIS[14,15].

Several unhealthy habits also increase the susceptibility for AIS. Smoking is a major risk factor for cardiovascular diseases and thus AIS. Smokers have a two-to threefold risk for stroke as compared with non-smokers. There is a J-shaped association between alcohol consumption and the incidence of AIS, as light to moderate use is associated with decreased, whereas heavy consumption is associated with a higher AIS risk. The prevalence of obesity is increasing in developed countries, and it is an important predisposing factor for cardiovascular disease. There is some evidence about that regular physical activity can reduce the overall susceptibility for stroke by influencing several risk factors [14,15].

Haemostatic conditions may also contribute to an increased risk of AIS. Elevated haematocrit and haemoglobin levels and increased blood viscosity can be indicators of an increased risk for AIS. Elevated plasma fibrinogen, plasminogen activator inhibitor-1, von Willebrand factor and factor VII levels are also associated with high cardiovascular risks. Antiphospholipid antibodies are markers of increased susceptibility for thrombosis particularly in those younger than 50 years old. In addition, it is worth mentioning that elevated homocysteine levels are also associated with increased AIS rates[14,15].

Hereditary factors also play role in an increased stroke propensity as higher AIS rates can in those with a history of stroke among first-degree relatives, however specific genetic variants are largely unknown. Some inherited diseases (such as familiar dyslipoproteinaemias) are associated with accelerated atherosclerosis, while other disorders cause non-atherosclerotic vasculopathies (e.g. Ehlers-Danlos syndrome, Marfan syndrome, etc.) and thus increases the risk of developing AIS. Besides, several genetic cardiac disorders also predispose for stroke and deficiencies of protein C and S or antithrombin are examples of inherited haematologic abnormalities causing an increased risk for AIS[14,15].

1.4. Diagnosis of acute ischemic stroke

Early recognition of AIS is usually based on the evaluation of distinctive neurological symptoms, the onset of which are rapid, usually developing in seconds. Accurate diagnosis can

be made by using neuroimaging methods, primarily computer tomography (CT) and magnetic resonance imaging (MRI). In addition, further cardiovascular examination may be required to accurately elucidate etiology.

1.4.1. Clinical presentation of acute ischemic stroke

As described earlier the blood supply territories of the brain is well distinguishable, therefore the occlusion of different vessels eventuates different stroke syndromes. The appearance of clinical symptoms is also influenced by the exact location of the occlusion and the degree of collateral circulation. The most affected territory in AIS is the supply area of the MCA, accounting for more than 50% of the cases. This is followed by small-vessel (~13%) and brain stem strokes (~11%). The frequency of involvement of the PCA and ACA are 7 and 5 percent respectively, the remaining 4% of cases are due to cerebellar infracts.[17]

The clinical picture of MCA territory infarctions usually consists contralateral hemiparesis, hemihypaesthesia, homonymous hemianopia, and conjugate ipsilateral eye deviation. Aphasia occurs when the dominant hemisphere is involved, while in the case of non-dominant hemispheric infarction hemineglect can usually be seen. In the case of upper-division MCA occlusions the hemiparesis of the face and arms is more pronounced and expressive aphasia appears. Ischemia of the dominant-hemisphere parietal lobe mainly cause apraxia, alexia, agraphia, acalculia and astereognosis. With lower division MCA-syndromes receptive aphasia is more commonly seen and behavioural disturbances can occur. The occlusion of the M1 segment of the MCA also blocks the lenticulostriate branches causing subcortical infarction that involves the caudate nucleus, the internal capsule, and the putamen. Due to the involvement of these areas in addition to hemiparesis thought disorders, amnesia, behavioural changes, and subcortical aphasia may occur.

The main symptoms of ACA occlusions are contralateral hemiparesis primarily affecting the lower limb and to a lesser extent the upper arm. In addition, hemihypasthesia in a similar distribution, abulia, impaired memory, emotional disturbances, transcortical motor aphasia, conjugate deviation of the eyes towards the lesion and urinary incontinence may develop. Due to the involvement of the corpus callosum anterior disconnection syndrome can occur with left arm apraxia. Besides, the medial part of the parietal lobe could also be affected resulting impaired gnostic functions. In contrast, infarction in the medial lenticulostriate artery territory causes a more pronounced weakness of the face and arm as these arteries supply the portions of the internal capsule.

Occlusions in the vertebrobasilar system can cause various stroke syndromes due to the complex involvement of brainstem-and cerebellar structures. A detailed summary of vertebrobasilar syndromes is presented in Table 1.

Occlusion of the proximal PCA segments cause midbrain, thalamic, and occipitotemporal hemispheric infarctions. Occipital involvement results contralateral homonymus hemianopia with macular sparing, and non-dominant hemisphere infarctions may also cause contralateral visual-field neglect. The involvement of the dominant occipital region and the splenium of the corpus callosum can result alexia, while the damage of the left medial temporal lobe may cause amnesia. The main blood supply of the thalamus comes from different segments of the PCA, therefore PCA occlusions may also cause thalamic syndromes. In case of the thalamogeniculate branch occlusion contralateral hemihypaesthesia occurs, and if the internal capsule is also affected hemiparesis can also be seen. Symptoms of ischaemia caused by the occlusion of the tuberothalamic branches consist neuropsychological disturbances, disorientation, thought disorders, and emotional-facial paresis. Dominant side involvement cause aphasia, while non-dominant side lesions cause neglect. Paramedian branch occlusions cause the triad of decreased level of consciousness, memory loss, and vertical-gaze abnormalities. Dorsal thalamic infarctions are caused by the involvement of the posterior choroideal arteries and characterized by homonymus hemi- or quadrantanopia.

Occlusion of small penetrating arteries usually results in small subcortical or brainstem infarctions with a size up to 15 mm, called lacunes. These cases can be either asymptomatic or present with only very few symptoms as only a small area is affected. The four most recognized lacunar syndromes are pure sensory stroke (involvement of the ventro-posterolateral nucleus of the thalamus), pure motor hemiparesis, ataxic hemiparesis (involvement of the internal capsule or the basis pontis in both cases), and dysarthria-clumsy hand syndrome (involvement of the deep areas of the pons).

It is important to highlight that some other diseases can present with acute onset neurological symptoms similar to AIS. These cases are commonly referred to as stroke mimics, such as post-convulsion hemiparesis, hemiplegic migraine, hypoglycaemia, space-occupying lesions, and CNS infections. The rate of stroke mimics is approximately 15-25% of all stroke suspected cases. In contrast stroke chameleons are manifestations in which the nature and dynamics of the symptoms are primarily do not raise the suspicion for stroke. Often posterior circulation strokes can present as stroke chameleons[18].

Table 1. Vertebrobasilar syndromes

Involved artery	Area of lesion	Symptoms	Notes
Anterior spinal artery	- lateral corticospinal tract - medial lemniscus - caudal medulla (nucleus of hypoglossal nerve)	- contralateral hemiparesis - decreased contralateral proprioception - ipsilateral hypoglossal dysfunction	Medial medullary (Dejerine) syndrome
Posterior inferior cerebellar artery	Structures of the lateral medulla: - nucleus ambiguous (cranial nerves IX, X, XI) - vestibular nuclei - lateral spinothalamic tract, spinal trigeminal nucleus - sympathetic fibres - inferior cerebellar peduncle	- dysphagia, hoarseness, decreased gag reflex - dysarthria - vertigo, nystagmus, nausea - decreased pain and temperature sensation from contralateral body and ipsilateral face - ipsilateral Horner syndrome (ptosis, myosis, enophtalmus, anhidrosis of the face) - ipsilateral ataxia and dysmetria	Lateral medullary (Wallenberg) syndrome
Anterior inferior cerebellar artery	Structures of the lateral pons: - facial nucleus - vestibular nuclei - spinothalamic tract, spinal trigeminal nucleus - sympathetic fibres - middle and inferior cerebellar peduncles - labyrinthine artery	- ipsilateral facial palsy, decreased lacrimation, salivation, and taste from anterior 2/3 of tongue - vertigo, nystagmus, nausea - decreased pain and temperature sensation from contralateral body and ipsilateral face - ipsilateral Horner syndrome (ptosis, myosis, enophtalmus, anhidrosis of the face) - ipsilateral ataxia and dysmetria - ipsilateral sensorineural deafness	Lateral pontine (Millard-Gubler) syndrome
Basilar artery	- structures in the pons, medulla, and lower midbrain - corticospinal and corticobulbar tracts - ocular cranial nerve nuclei, paramedian pontine reticular formation	- quadriplegia; loss of voluntary facial, mouth, and tongue movements - loss of horizontal, but not vertical eye movements	

Adapted from Le, Tao and Bhushan, Vikas. First Aid for the USMLE Step 1 2018, 28th edition. New York: McGraw-Hill Education, 2018.

1.4.2. Stroke scales

As described in the previous chapter, symptoms related to AIS are very heterogenous and the presentation of different territory occlusions may differ significantly. However, to ease the early recognition of AIS, several stroke scales (based on neurological symptom assessment) have been developed and are used routinely.

One of the most commonly used stroke scale is the Cincinnati Prehospital Stroke Scale (CPSS), which examines the presence or absence of three symptoms: upper limb weakness, facial palsy and speech disturbance (including aphasia and dysarthria as well)[19]. Generally, this method can detect stroke with a sensitivity (SN) of 82.46% (95% confidence interval [CI] 74.83-88.09%), while specificity (SP) is only 56.95% (95% CI 41.78-70.92)[20]. The CPSS is proved to be quick and easy-to-use, and reliable, even when used by laymen. Therefore, it is widely applied in public health campaigns for early stroke detection, and frequently used by emergency medical service (EMS) dispatchers and medical staff[21]. However, the CPSS is not able to distinguish between ischaemic and haemorrhagic stroke nor is it able to reliably recognize stroke mimics, consequently it is primarily suitable for screening and triage purposes.

Over recent years, a plethora of other short stroke scales has been developed for various scenarios, such as stroke detection, stroke severity assessment or to discriminate stroke subtypes. Some examples of these are the Face Arm Speech Test (FAST), the Los Angeles Prehospital Stroke Screen (LAPSS), the Recognition of Stroke in the Emergency Room score (ROSIER), and the Los Angeles Motor Scale (LAMS), which also assess symptom severity. These scales generally have moderate to good SN but only low to moderate SP to detect stroke cases[22].

To develop stroke scales with higher accuracy a more detailed and complex, systematic assessment of stroke symptoms was needed. The gold-standard method for stroke recognition and severity assessment is the National Institutes of Health Stroke Scale (NIHSS), which evaluates the severity of 13 different symptoms (Figure 6). The NIHSS has been validated several times and has been shown to be suitable for assessing stroke severity and to predict post-stroke outcomes. This scale was originally developed for use in clinical trials, however, due to its good reproducibility and high inter-rater reliability when performed by trained healthcare providers, it later became widespread in routine clinical use. Currently NIHSS is extensively used for stroke severity assessment, to select suitable patients for acute therapies, and to predict outcomes. However, due to its length and complexity, proper recording requires expertise and sufficient time (about 5-10 minutes). Consequently, its application is subject to

certification, which can be obtained through an online course. For these reasons, the use of NIHSS is primarily suitable for in-hospital settings, and it is rarely used by the EMS prehospitally. It is also important to emphasize that due to the symptoms examined in NIHSS and the scheme of their scoring, left hemisphere strokes are better represented. For similar reasons posterior circulation strokes are usually underrated by NIHSS which is also a significant shortcoming[23].

National Institutes of Health Stroke Scale score	
1a. Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b. Level of consciousness questions: What is the month? What is your age?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly
1c. Level of consciousness commands: Open and close your eyes. Grip and release your hand.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2. Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4. Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5. Motor arm 5a. Left arm 5b. Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement
6. Motor leg 6a. Left leg 6b. Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7. Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8. Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe to total sensory loss
9. Best language	0 = No aphasia; normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia
10. Dysarthria	0 = Normal 1 = Mild to moderate dysarthria 2 = Severe dysarthria
11. Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Total score = 0–42.	

Figure 6. The National Institutes of Health Stroke Scale. Downloaded from https://www.aliem.com/paucis-verbis-nih-stroke-scale/nihstrokescaleedit/.

1.4.3. Neuroimaging in acute ischemic stroke

The initial purpose of brain imaging is the confirmation of acute brain tissue damage and to discriminate haemorrhagic from ischemic lesions. Although MRI can visualize early ischemic changes more accurately than CT, it is not readily available for immediate use in many stroke treating centres, and the duration of MRI examination is also longer. Hence, in routine clinical care, CT remains the primary imaging modality used for the emergent evaluation of AIS.

Non-contrast CT (NCCT) scan is the gold-standard for the detection of intracranial haemorrhage, since blood presents as hyperdense lesions, the density of which decreases continuously over time. In contrast, acute ischemic lesions appear as hypodense territories but are subtle or undetectable in the first few hours after the ictus. Lower density is due to the reduced blood flow and consequential cytotoxic oedema, the extent of which is depends on the severity and duration of ischemia. In addition, the detection of brainstem and cerebellar lesions may be limited due to bone artifacts on CT. Early signs of AIS can be the loss of grey/white-matter differentiation, sulcal effacement and obscuration of the lentiform nuclei. The Alberta Stroke Program Early CT Score (ASPECTS) is a quantitative scoring system that measures the extent of early ischemic changes. The territory of MCA is divided into 10 segments, and 1 point is deducted from the total score for each segment involved. The ASPECTS has good value predicting 3-month functional outcomes, and it is also useful in selecting patients for certain AIS therapies[24].

CT angiography (CTA) of intra-and extracranial vessels can detect the exact location of occlusions and evaluate the extent of collateral circulation. CT perfusion (CTP) is an imaging modality that is based on the repeated acquisition of CT scan slices as the contrast material passes through the cerebral vessels. Based on time-dependent changes in density reflecting tissue perfusion, several parameters can be calculated, such as mean transit time (MTT), time to bolus peak (TTP), and territorial differences in CBF. These data can be used to determine the size of ischemic core and penumbra. Advanced multimodal imaging protocols, including NCCT, CTA, and CTP, are more commonly used to select the most optimal therapeutic modalities for AIS patients. In recent years, software for automated, computerized analysis of CT images have been developed, which are now embedded in routine clinical practice. In addition, online acute stroke image sharing networks operate in several stroke centres[25].

The main advantages of MRI over CT are higher resolution and better visualisation of brainstem and cerebellar structures. Another significant advantage is that the diffusion-weighted imaging (DWI) sequence can depict ischemic area within minutes after the onset of the stroke. In contrast, visible hyperintensity of the ischemic territory on fluid attenuated inversion recovery (FLAIR) imaging appears only hours after the ictus, therefore the assessment of DWI-FLAIR mismatch can be useful to detect those with hyperacute AIS. MR angiography (MRA) and perfusion-weighted imaging methods are also available and are frequently used to select patient-optimized AIS therapies. Another important application of MRI is the recognition of stroke mimics and chameleons.

Additional imaging techniques can be used to clarify the etiology of AIS and to properly set up secondary prevention. Duplex ultrasound examination of the neck arteries is commonly performed to evaluate the degree of atherosclerosis and plaque morphology, occasionally as a supplement for CTA or MRA. Transcranial Doppler ultrasound techniques can be used to examine intracranial arteries, to assess the haemodynamic reserve and to detect microembolic signals. Transthoracic echocardiography is the most commonly used non-invasive tool for cardiac evaluation in AIS patients. The main aim is to detect intracardial thrombi and cardiac conditions which are listed as potential embolic causes. In selected individuals, an oesophageal approach may be required for better visualization of the left atrium. In selected individuals, transoesophageal approach may be needed for better visualisation of the left atrium.

1.5. Acute treatment and clinical management of acute ischemic stroke

The primary goal of AIS treatment is to restore cerebral circulation as soon as possible. The most widely used therapeutic methods, so called reperfusion therapies aim to eliminate the cerebral vessel occlusion. The target of intravenous thrombolysis (IVT) is to dissolve the formed blood clot by promoting thrombolytic processes. In contrast, mechanical thrombectomy (MT), also known as endovascular thrombectomy (EVT), aims to remove the clot directly using endovascular catheter devices.

1.5.1. Intravenous thrombolysis

The history of IVT dates back to the middle of the 20th century. Early attempts were made using streptokinase, urokinase and plasmin, but these proved ineffective, and the rate of intracranial haemorrhagic complications was higher among those treated. An important milestone in the research of more effective and safer thrombolytic agents was in 1983, when the production of recombinant tissue plasminogen activator alteplase became possible. Following promising attempts in acute coronary syndrome treatment, alteplase became the main scope of IVT trials[26].

In the NINDS study, the therapeutic effect and safety of alteplase versus placebo in the treatment of AIS was studied. Only patients with stroke symptoms developing within 3 hours were enrolled. In addition, several criteria were predefined to exclude individuals with high risk for haemorrhagic complications. Therapeutic effect was measured using the changes in NIHSS score and functional outcomes were evaluated 3 months after the ictus. The result showed that treatment with alteplase was associated with better outcomes (OR: 1.7; 95% CI: 1.2 to 2.6), but

no significant difference was observed in mortality rates (17% vs. 21%). However, the rate of symptomatic intracranial haemorrhages (sICH) increased significantly following alteplase treatment (6.4% vs. 0.6%)[27]. Subsequent studies demonstrated a sustained benefit of alteplase in terms of functional outcomes at 6 and 12 months after stroke, and highlighted that the sooner IVT is started, the greater the chance of achieving a good outcome is.

After the NINDS trial routine use of alteplase for IVT became more and more widespread, however, only a few percent of AIS patients received alteplase in the first few years. The main reason for this was that only a small number of patients arrived to an IVT capable stroke centre within 3 hours, and in many cases, the patient slipped out of the 3-hour time frame due to the length of diagnostic tasks. Based on these, multiple randomized-controlled clinical trials (RCT) have investigated whether the time-window of IVT treatment can be extended, hence more patients can receive IVT. The ECASS-3 trial was the first to demonstrate that AIS patients can be safely treated with alteplase up to 4.5 hours after the onset of symptoms. Based on safety concerns, in this RCT several additional exclusion criteria have been defined in this for cases presenting between 3 and 4.5 hours after onset. The results were similar to the findings of the NINDS study, and it was also confirmed that there is an inverse relationship between onset to IVT times and the chances of achieving a good outcome[28]. To date, patient selection criteria for alteplase treatment in the current recommendations are mainly based on the NINDS and ECASS studies[29].

To increase the proportion of AIS patients receiving IVT, several studies have examined the possibility of expanding the time window. The IST-3 study investigated the effectiveness and safety of alteplase when administrated within 6 hours from the onset of symptoms. However, no significant difference in functional outcomes was observed between alteplase and placebo groups. In contrast, the sICH rates were significantly higher among patients treated with alteplase. These results highlight that the risks associated with IVT may outweigh its benefits when applying a 6-hour time-window[30]. A meta-analysis of IVT trials, published in 2014, analysed the relation between onset-to-IVT times and effectiveness of IVT. The results confirmed that the use of alteplase significantly improves the overall odds for achieving a good outcome and earlier treatment associated with bigger proportional benefits. The use of alteplase significantly increase the odds for a good outcome when given within 3 hours (OR 1.75, 95% CI 1.35–2.27) or after 3 hours up to 4.5 hours (OR 1.26, 95% CI 1.05–1.51), but not after 4.5 hours (OR 1.15, 95% CI 0.95–1.40). Based on the cumulated data, the time-point after IVT has more risks than expected benefits is estimated around 5 hours after the onset of AIS[31].

Attempts have also been made to use other thrombolytic agents (such as desmoteplase or tenecteplase) and patient selection criteria to extend IVT time-window, however, most of these studies were unsuccessful. One approach that proved successful was patient selection based on findings on imaging rather than relying on clinical parameters and time-window restrictions. The WAKE-UP trial studied patients in whom the onset of symptoms was unknown (for example symptoms were noticed upon awakening). Patient selection was based on the presence of mismatch on DWI and FLAIR MRI sequences (ischemic signs on the DWI, but not on the FLAIR), which may indicate the onset of symptoms within a few hours. The results proved that IVT can be done effectively and safely in these group of selected patients[32]. Another much studied approach is to select patients for IVT based on the size of salvageable brain tissue, using core-penumbra mismatch assessment based on CTP. The findings of the EXTEND trial were published in 2019, which have proved that IVT can be applied in selected cases with a sufficiently large penumbra up to 9 hours after the onset of symptoms[33].

1.5.2. Endovascular thrombectomy

It can be observed that therapeutic efficiency of IVT is inversely associated with the diameter of the occluded vessel. The rate of complete recanalization after IVT is around 50% in the case of distal MCA occlusions, 30% when a proximal MCA branch is occluded and only 6% in the case of terminal ICA occlusions. A similar association can be observed between the location of LVO and long-term outcomes after AIS[34].

Due to the relative ineffectiveness of IVT, the applicability of endovascular thrombus removal devices for the treatment of AIS cases with radiologically identified large vessel occlusion (LVO) was widely studied in the past two decades, however rudimentary devices failed to show benefit. Finally, in 2015 and 2016 several MT RCTs (MR-CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT) have reported clinical benefits when applying newer-generation devices (stent-retrievers and aspiration devices)[35]. Based on these result, the current guidelines recommend MT to treat appropriately selected AIS patients with LVO. For MT, the generally used time-window (onset to groin puncture) is 6 hours, and primarily the intervention is recommended for patients with ICA and MCA M1 occlusions and an NIHSS score at least 6 points. To prevent haemorrhagic complications patients with extensive early ischemic signs on NCCT (ASPECT score <6) should be excluded. IVT should be performed before MT if the patient is otherwise eligible. Similar to IVT, the earlier MT is started after stroke onset, the greater the chance of achieving a good outcome[29].

Following the first successful RCTs, the possibility of extending eligibility criteria was the main scope of studies. Results have confirmed that stent retrievers are suitable to treat MCA M2 and M3 occlusions within 6 hours, and may be beneficial for selected patients with ACA, PCA, VA and BA LVOs as well. It has also been revealed that MT is applicable in selected patients with ICA and MCA M1 occlusion, but with an NIHSS score <6 or ASPECT score <6. The DAWN and DEFUSE-3 trials investigated the possibility of extending the time window beyond 6 hours (up to 16 hours from onset in the DEFUSE 3 trial and 24 hours in the DAWN trial) in selected cases based on core-perfusion mismatch assessment using an automated imaging software. EVT was associated with better functional outcomes and no significant differences were observed in sICH and mortality rates between the groups[36,37].

1.5.3. Prehospital and early in-hospital management of acute ischemic stroke

As previously described, the key points of AIS treatment are early evaluation of eligibility and initiation of optimal revascularization therapies as soon as possible. In the vast majority of cases, the first observers of symptoms are laymen (usually the patient's relatives), therefore raising public awareness of stroke and its manifestations, the importance of early detection and the urgency of calling EMS in public health programs is crucial[38]. EMS dispatchers should identify stroke suspicious cases based on the reported symptoms, however, this may be challenging due to the heterogeneity stroke presentations (especially posterior circulation strokes). Current guidelines recommend the use of standardized short stroke detection scales for this purpose (for example the CPSS). When stroke is suspected an ambulance should be directed to the scene with no delay[29].

Apart from routine evaluation and stabilisation of the patient, verifying the suspicion of stroke (preferably using stroke scales) and finding out the last seen well time are key components of patient assessment on scene. Obtaining information on medical history about the presence of risk factors, recent surgical procedures, coagulation disorders, presence of AF and concomitant anticoagulation is important and may help to optimize patient pathways. Whenever possible, the time of on-site care should be minimized and patient transportation to the closest stroke centre should started as soon as possible. EMS personnel should notify the receiving hospital indicating that a suspected stroke patient is en route so that the appropriate hospital resources can be mobilized before patient arrival[29,39].

Upon arrival to the emergency department (ED) urgent neurological examination and stroke severity assessment (preferably using the NIHSS) is needed, followed by emergent imaging to differentiate AIS from HS, and to evaluate the extent of ischemic injury and the

status of cerebral circulation. In order to shorten door-to-imaging (DTI) times the patient should be transferred directly to the CT room and then carry out the necessary tasks there in parallel. IVT should started as soon as the diagnosis of AIS is verified, and no exclusion criteria have been identified. Current guidelines recommend aiming to keep DTI under 20 minutes and door-to-IVT (or door-to-needle [DNT]) time under 60 minutes [29]. The acute care of AIS requires the cooperation of many disciplines under significant time pressure. For this reason, adherence to predefined standard operational protocols is critical. Thus, the proportion of those receiving recanalization therapies can be increased and if therapies started as early as possible the chances of achieving good outcomes will increase.

Due to the limited availability of professional and instrumental requirements, most of the stroke centres are only capable to perform IVT. These centres are usually referred to as primary stroke centres (PSC). Centres with capability to perform both EVT and IVT are called comprehensive stroke centres (CSC). However, it is important to emphasize that only a minority of stroke treating hospitals meet the criteria of being a CSC. Unfortunately, transportation between primary and comprehensive stroke-centres is one of the major causes of delayed treatment initiation[40,41].

Regarding patient pathways, two approaches have emerged. According to the first approach, AIS patients should firstly be transported to the nearest IVT-capable PSC. If the presence of an LVO is confirmed, the patient is referred and transported to a CSC for EVT (drip-and-ship approach). In these cases, IVT could be initiated as soon as possible, however, the time spent in the PSC, and the time of transportation can significantly delay the administration of EVT. The second approach is to transport patients with a high likelihood of LVO directly to a CSC (mothership approach). This may slightly delay the start of the IVT due to the longer transportation time, however, the time to EVT administration can be reduced significanlty[42].

To date several prehospital stroke diagnostic methods have been investigated, the main scopes of which were to distinguish between AIS and HS, to exclude stroke mimics, to detect LVO and to assess eligibility for IVT and EVT. In some projects CT scanners were integrated into ambulance units (mobile stroke units [MSU]) to facilitate prehospital diagnosing of AIS. IVT was initiated already in the MSU, thus onset-to-needle times could be reduced significantly, which also resulted in improved long-term outcomes[43]. However, due to cost-effectiveness issues, routine use of MSUs is not widespread yet[44]. Although a plethora of blood-based biomarkers have been studied so far, no individual candidate or multimarker panel has proven to have adequate performance for use in acute clinical settings[45]. Mobile phone

applications to help stroke symptom assessment for non-specialists and teleconsultation facilities are also widely studied and have an emerging role in prehospital stroke care[46].

1.6. Acute ischemic stroke due to large vessel occlusion

Despite some variation in definitions LVO in AIS is commonly referred to as the acute occlusions of the ICA, the VA, the BA and the proximal segments of the MCA, ACA and PCA. LVO is estimated to be present in approximately 20 up to 40% of AIS cases, the reason for this wide range is that different studies applied different LVO definitions[47]. Generally, in the first successful MT trials patients with intracranial ICA and M1 segment MCA occlusions were enrolled. A subset of studies also considered patients with MCA M2, and ACA A1 and A2 occlusions. Subsequent trials also verified the utility of MT to treat posterior circulation LVOs such as VA, BA, PCA P1 and P2 occlusion, and M3 occlusions in the MCA tree. Regarding anatomic location, the majority of LVOs (approximately 70%-80%) occur in the anterior circulation. The term tandem occlusion refers to those cases when both the proximal ICA and MCA is occluded[48].

Four major etiology of LVO development is usually distinguished. LVO can form locally, secondary to intracranial atherosclerosis or an embolism occur from extracranial atherosclerotic plaques. Cardioembolic events related to cardiac diseases can also result LVO development. The most observed predisposing condition to intraatrial thrombus formation is AF, the prevalence of which is higher among LVO patients. Besides, the etiology of LVO sometimes remain unclear (cryptogenic LVO)[48].

In general, stroke severity tends to be significantly higher in the group of patients with AIS due to LVO than those without LVO[49]. The main reason for this is probably that the proximal segments of cerebral vessels are occluded, hence the ischaemia of large cerebral territories occurs. The chances of achieving good functional outcomes are significantly worse in AIS due to LVO than in non-LVO cases, therefore, early recanalization of occluded vessels is warranted[48].

In routine clinical care CTA remains the first-line tool to diagnose LVOs and to evaluate collateral circulation. In some cases, a focal hyperdensity of the MCA can be seen on the NCCT**,** indicating thromboembolic material within the lumen. **(**hyperdense MCA sign). CTP is usually performed together with CTA to assess the size of potentially salvageable brain tissue. MRI modalities can also be used for these purposes, but its availability is limited to certain stroke centres. The gold-standard for cerebral vascular imaging remains conventional catheter-based digital subtraction angiography (DSA), which allows a very accurate visualization of vascular

lesions. However, due to the risks associated with invasive DSA procedures its use for diagnostic purposes has been significantly reduced.

Raising the suspicion of an LVO prehospitally is challenging, however, some stroke scales have moderate-to-good accuracy to predict LVO cases. These scales primarily assess the severity of certain symptoms commonly associated with LVO strokes. However, due to inadequate accuracy, current guidelines do not recommend the routine use of these scales as diagnostic tools, and all AIS patients, regardless of LVO suspicion, should be transported to the nearest stroke centre, commonly a PSC. As described earlier, if the presence of LVO is verified in the PSC, a second transportation is warranted to a CSC for EVT that significantly prolongs onset-to-EVT times. Considering the relative ineffectiveness of IVT, to sufficiently recanalize LVOs, direct transportation of patients with a high likelihood of LVO may be beneficial. The delay in IVT initiation may be compensated or overweighted by the effect of earlier EVT initiation. The RACECAT trial investigated whether applying the mothership versus the drip-and-ship approach to patients with a high likelihood of LVO, assessed using the Rapid Arterial Occlusion Evaluation (RACE) scale, can improve outcomes. However, the results showed no differences in long-term outcomes between the groups, despite a slight reduction in onset-to-EVT times. Nevertheless, it should be noted that only 46% of patients, who were suspected of having an LVO according to the RACE scale, eventually had a confirmed LVO[50].

1.7. Outcomes after ischemic stroke

In most RCTs outcomes are assessed at 90 days after the ictus. The modified Rankin Scale (mRS) is the most widely used scale to evaluate the degree of functional disability and dependence affecting daily activities. This scale consists of seven scores, from 0 to 6, with higher scores indicating greater disability, and points 0 to 2 are generally considered as good functional outcomes. The score of 6 indicates deceased patients[51]. Other scoring systems are often used as well, such as the Barthel scale, the Glasgow Outcomes Scale and scales assessing cognitive functions (e.g. MOCA).

Generally, outcomes after suffering AIS are influenced by many factors. The most noteworthy of these are severity and age at the time of onset. Early ischemic signs, the presence of LVO, poor collateral flow and extensive perfusion deficit are also predictors of worse prognosis. The presence of AIS risk factors and comorbidities are also associated with an increased risk of suffering a poor outcome. Several prognostic scoring systems are available to help estimating prognosis in the acute phase of AIS, such as the Orpington Prognostic Scale and the ASTRAL scoring. It should also be noted that post-stroke complications, such as

suffering a sICH or post-stroke infections (PSI), may significantly worsen the rate of expected improvement[52].

The key factors of improving outcomes after AIS are early initiation of revascularization therapies and treating patients in a dedicated stroke unit. Stroke rehabilitation should be introduced gradually, and a variety of rehabilitation disciplines should be included (e.g., physical therapy, occupational therapy, speech, and language therapy). Secondary prevention is an intensively studied area and plays an important role in reducing the rate of recurrent cerebro-and cardiovascular events, the chance of which is the highest early after AIS[52].

2. Objectives

As there is an increasing need for accurate and reliable methods to detect AIS patients with LVO early on, even by the EMS, the main scope of our research was to examine the effectiveness of currently available tools and to develop new methods for this purpose. The primary objectives of our studies were the following:

- We aimed to measure the accuracy and capability of various stroke scales to detect LVO in AIS. Based on previous results, we expected that various stroke scales can predict LVO in AIS with moderate to good accuracy.

- Since CPSS is one of the most commonly used stroke scale among laymen and EMS, we examined how it could be optimized for LVO detection. We hypothesized that the detailed severity assessment of the symptoms evaluated in CPSS can improve its overall ability to detect LVOs.

- One of our aims was to search blood biomarkers that may be useful to indicate the presence of LVO. Previous studies revealed that peripheral leukocyte counts are associated with stroke severity and the extent of ischemic injury. We hypothesized that leukocyte counts are associated with the presence of LVO as well.

- Finally, we aimed to create complex LVO prediction methods using modern statistical methods. Application of machine learning methods is emerging in the field of creating optimized prediction models. We expected that, using these methods, an optimal subset of variables can be selected and weighted appropriately. We also hypothesized that these models may be superior to currently used stroke scales.

3. Methods

3.1. General settings and ethics

In every presented study, data were prospectively collected and subsequently analysed as a part of the STAY ALIVE Acute Stroke Registry project, the operation of which was funded by the Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2-15-2016-00048). This registry is a prospective, national, hospital-based, multicentre database of acute ischemic stroke patients including the comprehensive stroke centres of three university hospitals in Hungary (University of Debrecen [UD], University of Szeged [USZ], and University of Pécs [UP]), ongoing since November 2017.

The STAY ALIVE Acute Stroke Registry project and related studies were conducted in accordance with the Declaration of Helsinki and was approved by the Hungarian Medical Research Council (35403–2/2017/EKU). Patients who are admitted to one of these stroke centres due to acute ischemic stroke are prospectively screened and enrolled to the registry. Participation is voluntary and written informed consent is obtained from each patient. Detailed data on medical history, on admission parameters, imaging results, interventions, medical investigations, etiology and follow-up data are collected by clinical research administrators and medical doctors. Data are recorded on an electronic case report form and subsequently checked and approved by an assigned trained neurologist and by the chief research administrator. Final approval was made by the head of each department.

3.2. Design of studies and outcomes

Each of the studies presented have cross-sectional, observational design. Baseline data on patient characteristics were obtained retrospectively from the STAY ALIVE Acute Stroke Registry. Patient selection criteria were slightly different for the various studies and will be detailed at the presentation of the particular study.

Generally, our primary outcome of interest was the presence of LVO on the admission CTA scan. According to Rennert et al. unilateral, acute occlusion of the ICA, M1, M2 and M3 segments of the MCA, A1 and A2 segments of the ACA, VA, BA, P1 and P2 segments of the PCA and tandem occlusions were considered[48].

3.3. Statistical analysis

Initial data analysis was performed using SPSS (versions 24.0, 25.0 and 26.0, IBM, New York). Generally, the comparison of continuous variables was performed using t test or Mann-Whitney U test. Normality was assessed using the Shapiro-Wilk test and visually, based on Q-Q plots and histograms. Categorical data were compared using the Pearson X^2 test or Fischer exact test when expected values in any cell was below 5. Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range (IQR) where appropriate. Categorical variables were presented as counts and percentages. Where appropriate 95% CI values were presented. A P value < 0.05 was considered statistically significant. For further analysis, various statistical approaches were used in the different studies. Commonly applied methods were logistic regression analysis to evaluate associations and receiver operating characteristic (ROC) analysis to assess diagnostic accuracy. Study-specific statistical methods are detailed later at the presentation of each study.

4. Results and interpretation of findings

4.1. Capability of stroke scales to detect large vessel occlusion in acute ischemic stroke

Previous studies have demonstrated that multiple stroke scales may be suitable for early identification of AIS patient with LVO. An easy-to-use scale would be also valuable for EMS or ED to ensure appropriate triage of these patients. However, only a minority of these scales have been examined multiple times[53]. Thus, the aim of our study was to assess the ability of various stroke scales to detect LVO in AIS patients.

4.1.1. Study cohort

Patients were admitted up to 4.5 hours after stroke onset to the CSC of UP, Hungary between October 2017 and February 2019. Baseline clinical variables including age, gender, onset-to-admission time, and vascular risk factors were recorded on admission. Neurological symptoms were assessed using the NIHSS on admission. A total of 13 stroke scales were derived from NIHSS items: modified NIHSS (mNIHSS), shortened NIHSS for EMS (sNIHSS-EMS), shortened NIHSS with 8, 5 and 1 items (sNIHSS-8, sNIHSS-5, sNIHSS-1), abbreviated NIHSS (aNIHSS), Cincinnati Stroke Triage Assessment Tool (C-STAT), RACE, 3-Item Stroke Scale (3I-SS), Prehospital Acute Stroke Severity scale (PASS), Vision Aphasia Neglect scale

(VAN), Field Assessment Stroke Triage for Emergency Destination scale (FAST-ED), and Gaze Face Arm Speech Time scale (G-FAST)[53].

4.1.2. Statistical analysis

In addition to the methods presented earlier in Section 3.3 the ability of stroke scale to discriminate the presence of LVO was assessed using ROC analysis. Area under the curve (AUC) was calculated for each variable, an AUC value ≥0.800 were considered as representative of an acceptable discrimination. Optimal cut-off values were calculated using the Youden J index. SN and SP were calculated for different cut-off scores. According to Scheitz et al. we have created two groups according to predefined SN and SP values: a group of scales and cut-off scores with at least 80% SN and 50% and a group with at least 70% SN and 75% SP[54].

4.1.3. Results

During the study period 220 patients were screened. After excluding 40 patients without CTA assessment the data of 180 patients (47.8% female) were evaluated. Ninety-eight patients had LVO (54.4%). Baseline characteristics of the two studied groups (according to the presence of LVO) are shown in Table 1. Patients with LVO tended to have more severe strokes (NIHSS 13 vs. 6; P<0.001) than those without LVO. The proportion of female gender and AF were higher in the LVO group, while DM was more common among non-LVO patients (Table 2).

Table 2. Demography and comorbidities of the cohort according to the presence of LVO

	LVO present (N=98)	LVO absent (N=82)	P value
Age, years, mean (±SD)	68.1 (±11.4)	68.4 (±10.7)	0.860
Sex, female, % (n)	56.1 (55)	37.8 (31)	0.014
NIHSS, median (IQR)	13 (9-17)	6 (3-8)	<0.001
Onset-to-admission time, min, median	150 (110-200)	154 (120-183)	0.608
Smoking, % (n), 48 missing	38.7 (24)	37.1 (26)	0.853
Hypertension, % (n), 10 missing	81.3 (74)	84.8 (67)	0.546
Diabetes mellitus, % (n), 20 missing	20.0 (17)	36.0 (27)	0.024
Hyperlipidaemia, % (n), 45 missing	70.1 (47)	73.5 (50)	0.662
Atrial fibrillation, % (n), 19 missing	35.3 (30)	17.1 (13)	0.009
Coronary artery disease, % (n), 43 missing	32.0 (24)	35.5 (22)	0.667
Chronic heart failure, % (n), 39 missing	16.7 (13)	9.5 (6)	0.217

Abbreviation: LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; TIA, transient ischemic attack.

Receiver operating characteristic curves and AUC values are presented in Figure 7. The highest AUC value was recorded for mNIHSS (AUC: 0.831). The AUC values of NIHSS (0.830), sNIHSS-EMS (0.816), sNIHSS-8 (0.830), sNIHSS-5 (0.826), RACE (0.809) and FAST-ED (0.809) scales were among the highest. Optimal cut-off scores and related SN and SP values are presented in Table 3. A total of 6 scales had a cut-off value with SN of at least 80% and SP of at least 50%, and 5 scales had cut-off values with a least 70% SN and 75% SP (Table 3).

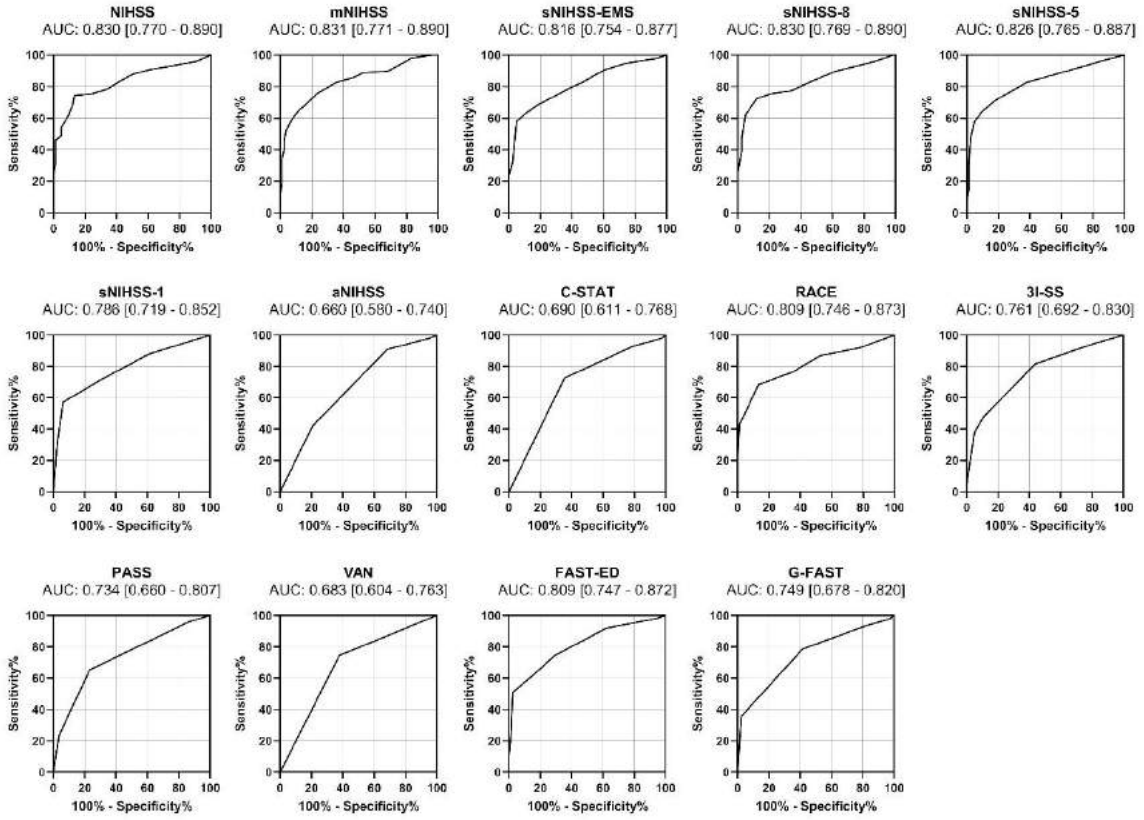

Figure 7. Receiver operating characteristic (ROC) curves analysing the ability of various stroke scales to discriminate large vessel occlusion in acute ischemic stroke: National Institutes of Health Stroke Scale (NIHSS), modified NIHSS (mNIHSS), shortened NIHSS for emergency medical services (sNIHSS-EMS), shortened NIHSS (sNIHSS), abbreviated NIHSS (aNIHSS), Cincinnati Stroke Triage Assessment Tool (C-STAT), Rapid Arterial Occlusion Evaluation (RACE), 3-Item Stroke Scale (3I-SS), Prehospital Acute Stroke Severity (PASS), Vision Aphasia Neglect (VAN), Field Assessment Stroke Triage for Emergency Destination(FAST-ED), Gaze Face Arm Speech Time (G-FAST). Area under the curve (AUC) values and 95% confidence interval are presented. The figure is the author's own work.

Table 3. Diagnostic accuracy of stroke scales according to different cut-off values

Stroke scale	Sensitivity (95% CI)	Specificity (95% CI)
Optimal cut-off value		
NIHSS ≥10	74.5 (64.7-82.8)	86.6 (77.3-93.1)
mNIHSS ≥9	65.3 (55.0-74.6)	87.8 (78.7-94.0)
sNIHSS-EMS ≥10	58.2 (47.8-68.1)	95.1 (88.0-98.7)
sNIHSS-8 ≥7	72.5 (62.5-81.0)	87.8 (78.7-94.0)
sNIHSS-5 ≥5	64.3 (54.0-73.7)	90.2 (81.7-95.7)
sNIHSS-1 ≥3	57.1 (46.8-67.1)	93.9 (86.3-98.0)
aNIHSS ≥2	90.8 (83.3-95.7)	31.7 (21.9-42.9)
C-STAT =3	72.5 (62.5-81.0)	64.6 (53.3-74.9)
RACE ≥5	68.4 (58.2-77.4)	86.6 (77.3-93.1)
3I-SS ≥2	81.6 (72.5-88.7)	56.1 (44.7-67.4)
PASS ≥2	65.3 (55.0-74.6)	76.8 (66.2-85.4)
VAN =1	74.5 (64.7-82.8)	62.2 (50.8-72.7)
FAST-ED ≥5	51.0 (40.7-61.3)	97.6 (91.5-99.7)
G-FAST ≥3	78.6 (63.1-86.2)	58.5 (47.1-69.3)
Cut-off values with sensitivity ≥80% and specificity ≥50%		
NIHSS ≥6	87.8 (79.6-93.5)	50.0 (38.8-61.3)
mNIHSS ≥5	85.7 (77.2-92.0)	53.7 (42.3-64.8)
sNIHSS-EMS ≥5	82.7 (73.7-89.6)	53.7 (42.3-64.8)
sNIHSS-8 ≥4	82.7 (73.7-89.6)	54.9 (43.5-65.9)
sNIHSS-5 ≥3	82.7 (73.7-89.6)	62.2 (50.8-72.7)
3I-SS ≥2	81.6 (72.5-88.7)	56.1 (44.7-67.4)
Cut-off values with sensitivity ≥70% and specificity ≥75%		
NIHSS ≥9	75.5 (65.8-83.6)	75.6 (64.9-84.4)
mNIHSS ≥7	75.5 (65.8-83.6)	76.8 (66.2-85.4)
sNIHSS-8 ≥6	75.5(65.8-83.6)	79.3 (68.9-97.4)
sNIHSS-5 ≥4	71.4 (61.4-80.1)	81.7 (71.6-89.4)
RACE ≥4	71.4 (61.4-80.1)	78.1 (67.5-86.4)

Abbreviation: NIHSS, National Institutes of Health Stroke Scale; mNIHSS, modified NIHSS; sNIHSS-EMS, shortened NIHSS for emergency medical services; sNIHSS, shortened NIHSS; aNIHSS, abbreviated NIHSS; C-STAT, Cincinnati Stroke Triage Assessment Tool; RACE, Rapid Arterial Occlusion Evaluation scale; 3I-SS, 3-Item Stroke Scale; PASS, Prehospital Acute Stroke Severity scale; VAN, Vision Aphasia Neglect scale; FAST-ED, Field Assessment Stroke Triage for Emergency Destination scale; G-FAST, Gaze Face Arm Speech Time scale; LVO, large vessel occlusion.

Values are presented as percentages.

4.1.4. Discussion

The main finding of this study was that multiple stroke scales have good ability to discriminate the presence of LVO in AIS. Currently NIHSS is used as the "gold-standard"

of stroke-severity assessment, and previous results highlighted that it is also among the best in terms of LVO detection, which was also confirmed by our study[49]. However, the complexity, the time-consuming nature, and the need for special training to use NIHSS appropriately may prevent its routine use prehospitally or in the early phase of emergency care.

Short, quick, and easy-to-use stroke scales could be valuable for EMS personal to raise the suspicion of LVO early on. In this regard our results highlighted that some of the shortened versions of NIHSS (sNIHSS-EMS, sNIHSS-8, and sNIHSS-5), and scales that were optimized for prehospital or ED use (RACE and FAST-ED) may have similar diagnostic abilities as NIHSS, while remaining very simple to use or interpret. Modified NIHSS may be a good alternative to NIHSS for quicker stroke severity assessment and LVO detection, however it may be too complex for routine prehospital or ED use. We should emphasize that these scales would still misdiagnose a significant proportion of patients (around 25%), therefore a compromise must be made between high SN and high SP when selecting a cut-off value.

Scales and cut-off values with at least 80% SN and 50% SP (NIHSS ≥6, mNIHSS ≥5, sNIHSS-EMS ≥5, sNIHSS-8 ≥4, sNIHSS-5 ≥3 and 3I-SS ≥2) are good to detect a very high proportion of AIS patients with actual LVO (true positives) at the cost of misdiagnosing almost a half of non LVO patients as LVO suspicious (false positives). By comparison scales with thresholds resulting at least 70% SN and 75% SP (NIHSS ≥9, mNIHSS ≥7, sNIHSS-8 ≥6, sNIHSS-5 ≥4 and RACE ≥4) can reduce the proportion of false positive diagnoses, on the expense of missing higher number of true positive LVO patients. Cut-off values should be selected according to local circumstances considering the capacity of EMS and stroke centres[55,56]. In conclusion NIHSS, mNIHSS, sNIHSS-EMS, sNIHSS-8, sNIHSS-5, RACE, and 3I-SS may be good tools to detect LVO in AIS.

4.1.5. Limitations

The main limitation of our study was its single-centre, observational nature. Besides, we only included patients with AIS, and we did not have data on patients with haemorrhagic strokes and stroke-mimics. Around 18% of screened patients did not undergo CTA assessment (mainly due to minor symptoms or contraindication) that might lead to selection bias. This may also be the reason for slightly higher LVO prevalence rate in our study compared to previous studies (54% vs. 20-40%)[47].

4.2. Detailed severity assessment of Cincinnati Prehospital Stroke Scale to detect large vessel occlusion in acute ischemic stroke

As mentioned earlier CPSS is a simple, three item scale, widely used by EMS. It is easy and quick to learn or perform and has good ability to identify potential stroke patients. Nonetheless, it only has moderate ability to detect AIS patients with LVO, however, important aspect is that CPSS only tests for the presence of three symptoms (facial palsy, upper extremity weakness and speech disturbance), but do not assess the severity of them[19,57,58]. The aim of our study was to examine whether the detailed severity assessment of these items can improve the overall ability of CPSS to detect LVO in AIS patients.

4.2.1. Study cohort

In this study we included consecutive patients with first ever AIS, who were admitted up to 6 hours after symptom onset to the CSC of three university hospitals (UD, USZ and UP) between November 2017 and July 2019. Demographic data, vascular risk factors, baseline clinical variables and time from onset to first assessment in the emergency room were recorded on admission, along with detailed evaluation of the NIHSS.

Based on the 2019 AHA/ASA guidelines for the early management of AIS we have created three groups of LVO patients. In the first group we have included patients with ICA or M1 occlusions as there is a strong recommendation to consider EVT in these patients. In the second group patients with LVO in the more distal segments of the anterior vascular territory (M2, M3 segments of MCA, ACA) were included. The third group included those with LVO in the posterior circulation (VA, BA or PCA). In these cases, the benefit of EVT is uncertain, however it should be considered on a case-by-case basis[29,59]. Patients who did not have CTA scan on admission were excluded.

4.2.2. Scale design

We derived CPSS from four items of NIHSS (item 4: facial palsy, item 5: unilateral upper extremity weakness, item 9: language and item 10: dysarthria), according to Kothari et al. we have combined NIHSS items 9 and 10 to get the speech item of CPSS[19]. We designed a detailed version of CPSS (d-CPSS) derived from the same NIHSS items, but without being converted to bivariate as in CPSS. Detailed scoring criteria are shown in Table 4. The ability of d-CPSS to discriminate an LVO was compared to the ability of CPSS and NIHSS.

Table 4. Detailed scoring of CPSS and d-CPSS compared to NIHSS scores

Severity of symptoms	CPSS	d-CPSS	NIHSS source item and score	
ARM			Item 5: arm motor drift	
No drift for 10 seconds	0	0	0	
Drift, but does not hit bed	1	1	1	
Some effort against gravity	1	2	2	
No effort against gravity	1	3	3	
No movement	1	4	4	
FACIAL PALSY			Item 4: facial palsy	
Normal symmetry	0	0	0	
Minor paralysis	1	1	1	
Partial paralysis	1	2	2	
Complete paralysis	1	3	3	
SPEECH			Item 9: aphasia	Item 10: dysarthria
Normal	0	0	0	0
Mild/moderate aphasia or dysarthria	1	1	1	1
Severe aphasia or dysarthria	1	2	2	2
Global aphasia or anarthic or mute	1	3	3	2
TOTAL	0 - 3	0 - 10		

Abbreviation: CPSS, Cincinnati Prehospital Stroke Scale; d-CPSS, detailed CPSS; NIHSS, National Institutes of Health Stroke Scale.

4.2.3. Statistical analysis

In addition to the methods presented earlier in Section 3.3 Kruskal-Wallis test was used to compare stroke scale scores between multiple groups. Binary logistic regression with enter method was used to assess associations between baseline clinical variables and the presence of LVO. Adjustment was made for potential confounders: variables with $P<0.1$ in the univariable analysis were entered to the multivariable logistic regression model. Stroke scales and symptoms were entered in separate models because of multicollinearity. The ability of scales to detect the presence of LVO and optimal cut-off points was assessed using the ROC analysis. AUC was calculated for each scale and z test was used for comparison. SN, SP, positive and negative predictive values, and accuracy were calculated for different cut-off values.

4.2.4. Results

During the study period 528 patients were screened, 421 (79.7%) of whom underwent CTA imaging. The mean age of the study cohort was 67.2 ± 13.2 years (48.7% female), 183 patients had LVO (43.5%). Baseline demographics and clinical factors of the two studied groups (according to the presence of LVO) are shown in Table 5. On admission CPSS, d-CPSS

and NIHSS scores were significantly higher in those with LVO. The frequency of upper extremity weakness (92.3% vs. 71.8%, P<0.001) and facial palsy (85.8% vs. 69.8%, P<0.001) were higher among LVO patients, but there was no significant difference in the presence of speech disturbance between the groups (77.0% vs. 74.5%, P=0.408). After adjustment for potential confounders (onset-to-assessment time, systolic and diastolic blood pressure, the presence of AF, coronary artery disease and CHF, significant associations were observed between LVO and: (i) known AF (OR: 2.564, P<0.001); (ii) SBP on admission (OR: 0.904 per 10 mmHg increase, P=0.046); (iii) the presence of upper extremity weakness (OR: 5.370, P<0.001); and (iv) the presence of facial palsy (OR: 3.107, P<0.001). Increasing severity of all three symptoms examined in d-CPSS were independently associated with higher odds of LVO presence. Higher CPSS, d-CPSS and NIHSS scores were also associated with increased odds of LVO (Table 6).

Using a ROC analysis, the AUC value of d-CPSS was significantly higher compared to the AUC value of CPSS itself (0.788, 95% CI: 0.743 to 0.832 vs. 0.633, 95% CI: 0.580 to 0.686; P<0.001). The AUC for NIHSS was 0.795 (95% CI: 0.751 to 0.839), which was not significantly different from the AUC for d-CPSS (P=0.510). ROC curves are presented in Figure 8. The optimal cut-off scores to discriminate an LVO were CPSS = 3 (SN: 64.5%, SP: 58.4%), d-CPSS≥5 (SN: 69.9%, SP: 75.2%) and NIHSS≥11 (SN: 64,5%, SP: 87.0%) respectively.

Median NIHSS and d-CPSS scores tended to be higher in patients with LVO in the ICA or M1 segment of MCA compared to those with LVO in the more distal segments of the anterior vascular territory (M2, M3, ACA) (NIHSS: 15 vs. 10, P<0.001; d-CPSS: 7 vs. 5, P=0.001). Patients with ICA or M1 occlusions had higher median NIHSS and d-CPSS scores than patients with posterior circulation LVO (VA, BA, PCA) (NIHSS: 15 vs. 9, P<0.047; d-CPSS: 7 vs. 4, P=0.001). No significant difference in NIHSS and d-CPSS scores were found between the distal anterior territory LVO and posterior LVO groups (P=0.697 and 0.274 respectively). No differences were recorded in CPSS scores between these groups (median score: 3 respectively; P=0.783) (see Figure 9).

4.2.5. Discussion

The main finding of our study is that detailed severity assessment of CPSS items (upper extremity weakness, facial palsy, and speech disturbance) could significantly increase the ability of CPSS to discriminate the presence of LVO in AIS patients.

Table 5. Demography and clinical characteristics of the cohort according to the presence of LVO

	LVO present (N=183)	LVO absent (N=238)	P value
Age, years, median (IQR)	67 (60-78)	69 (58.75-76.25)	0.652
Gender, female, % (n)	52.5 (96)	45.8 (109)	0.175
NIHSS score, median (IQR)	11 (6-16)	6 (4-9)	<0.001
CPSS score, median (IQR)	3 (2-3)	2 (2-3)	<0.001
d-CPSS score, median (IQR)	5 (3-7)	3 (2-4.25)	<0.001
Onset to ER assessment time, min, median (IQR)	80 (58-121.25)	92 (58.75-137.25)	0.053
On admission SBP, mmHg, mean (SD)	159.0 (30.3)	167.8 (29.9)	0.003
On admission DBP, mmHg, mean (SD)	88.2 (16.0)	91.2 (17.1)	0.066
Smoking, % (n), 51 missing	37.0 (57)	31.5 (68)	0.267
Hypertension, % (n), 15 missing	79.5 (140)	79.6 (183)	0.996
Diabetes mellitus, % (n), 19 missing	19.4 (34)	26.0 (59)	0.122
Hyperlipidaemia, % (n), 37 missing	55.7 (93)	55.3 (120)	0.939
Atrial fibrillation, % (n), 23 missing	35.8 (62)	16.9 (38)	<0.001
Coronary artery disease, % (n), 29 missing	25.9 (45)	17.4 (38)	0.042
Chronic heart failure, % (n), 25 missing	14.4 (25)	8.1 (18)	0.047

Abbreviation: LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; CPSS, Cincinnati Prehospital Stroke Scale; d-CPSS, detailed CPSS; ER, emergency room; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

Table 6. Associations between stroke scale scores, symptom severity and LVO (per 1-point increase)

	Univariable analysis (95% CI)	P value	Multivariable analysis (95% CI)	P value
NIHSS score	1.255 (1.196-1.317)	<0.001	1.273 (1.205-1.345)	<0.001
CPSS score	1.970 (1.504-2.580)	<0.001	2.123 (1.567-2.875)	<0.001
d-CPSS score	1.651 (1.485-1.836)	<0.001	1.695 (1.506-1.906)	<0.001
Severity of UEW	2.057 (1.753-2.413)	<0.001	2.045 (1.721-2.430)	<0.001
Severity of facial palsy	1.913 (1.513-2.419)	<0.001	2.133 (1.628-2.795)	<0.001
Severity of SD	2.090 (1.677-2.605)	<0.001	2.299 (1.789-2.953)	<0.001

Abbreviation: LVO, large vessel occlusion; 95% CI, 95% confidence interval; NIHSS, National Institutes of Health Stroke Scale; CPSS, Cincinnati Prehospital Stroke Scale; d-CPSS, detailed CPSS; UEW, upper extremity weakness; SD, speech disturbance.

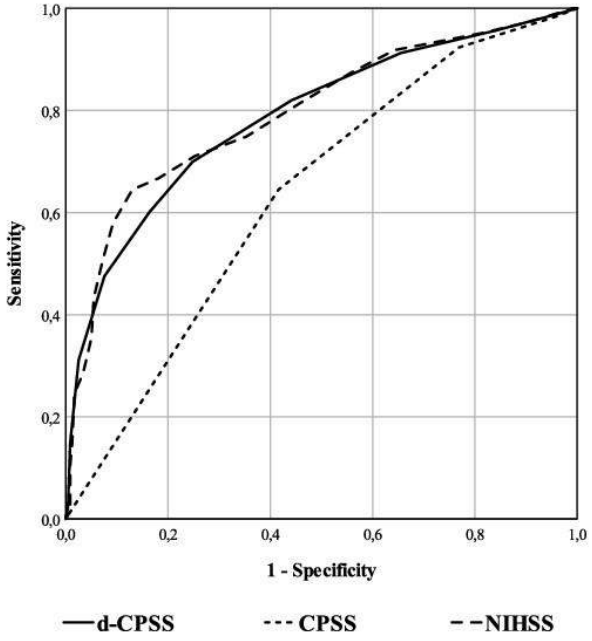

Figure 8. Receiver operating characteristic curves describing the capability of investigated scales to confirm a large vessel occlusion in acute ischemic stroke: Cincinnati Prehospital Stroke Scale (CPSS), detailed CPSS (d-CPSS) and National Institutes of Health Stroke Scale (NIHSS). The figure is the author's own work.

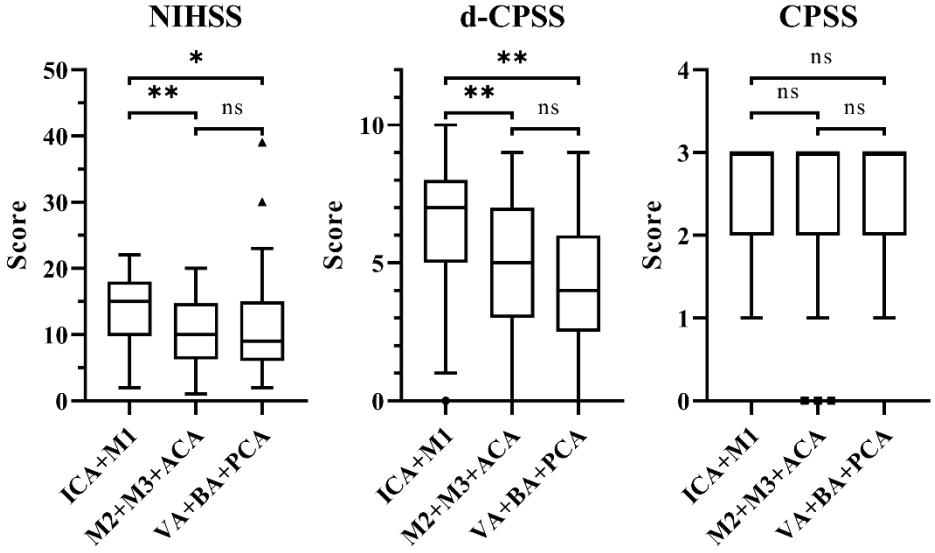

Figure 9. Differences in National Institutes of Health Stroke Scale (NIHSS), detailed CPSS (d-CPSS) and Cincinnati Prehospital Stroke Scale (CPSS) scores between groups according to the location of large vessel occlusion (LVO): proximal LVO in the anterior vascular territory (internal carotid artery [ICA] and M1 segment of the middle cerebral artery [MCA]; n= 118), distal LVO in the anterior circulation (M2 or M3 segments of MCA and anterior cerebral artery [ACA]; n=48) and posterior circulation LVO (vertebral artery [VA], basilar artery [BA] and posterior cerebral artery [PCA]; n=17). Boxes, 25% to 75% interquartile range; central horizontal bars, median; outer horizontal bars, minimum and maximum values excluding outliers (triangle, dot, or square icons). Abbreviation: ns, not significant; *, $p \leq 0.05$; **, $p \leq 0.001$. The figure is the author's own work.

As previously described NIHSS is the gold-standard of stroke severity assessment, and it has good ability to detect LVO[49], however, its complexity, time-consuming nature and the need for a special training can make its application in emergency situations or prehospital environment challenging[60]. Our results suggest that a detailed evaluation of CPSS may have similar capabilities as NIHSS to predict the presence of LVO, nonetheless, both NIHSS and d-CPSS still misdiagnose a significant proportion of stroke patients.

The definition of LVO is heterogenous among studies according to different diagnostic and therapeutic approaches[48]. Endovascular thrombectomy is primarily recommended within 6 hours from symptom onset in cases of ICA or M1 occlusions, however more distal and posterior occlusions might also be treatable using EVT on a case-by-case basis[29]. Perhaps the main aim of prehospital LVO detection is to identify patients who should undergo adequate EVT eligibility screening early on, therefore, the identification of every type of LVO may be useful in this regard.

Our findings are highlighting that stroke severity may be related to the location of LVO as NIHSS and d-CPSS scores tended to be the higher in cases of proximal occlusions (ICA or M1) than in those with more distal or posterior occlusions. This result suggests that it can worth considering proximal LVO in patients with high NIHSS or d-CPSS scores, but it should be noted that posterior LVO may also cause severe strokes, which is also represented by our results (Figure 9). However, this tendency is not noticeable for CPSS, which points out another benefit of detailed severity analysis in d-CPSS.

Over the past few years, attempts have been made to develop new, shorter, and modified LVO detection scales in order to fit them for prehospital use, but only few have been examined extensively yet and only a minority of them have been implemented into the practice of EMS[53]. Since CPSS is one of the most widely used and well-established scales in the field of stroke assessment, it would be obvious to optimize this scale for early LVO detection.

Our results are consistent with previous studies suggesting that certain baseline variables (e.g. known AF, SBP on admission) and the presence of certain symptoms (especially aphasia, negleoct and hemiparesis) are related to the presence of LVO[61,62]. The presence of speech disturbance is not, but its severity was associated with LVO in our study, which highlights how severity assessment may improve stroke scales. Weighting of scale items or adding anamnestic data (such as history of AF) to stroke scales could improve their ability to predict LVO in AIS[62,63].

4.2.6. Limitations

The retrospective analysis of prospectively collected data is the main limitation of our study. Besides, we only examined patients with AIS, and we did not have data on patients with haemorrhagic stroke and stroke-mimics. A significant proportion of screened AIS patients did not have CTA imaging, mainly due to minor symptoms, which may have caused selection bias. The assessment of CTA scans was performed by neuroradiologists as a standard of care, however no inter-rater reliability test was performed which might have led to diagnostic bias. It is important to highlight that we did not prospectively validate d-CPSS in this study.

4.3. Biomarkers for predicting large vessel occlusion: relationship between leukocyte counts and large vessel occlusion in acute ischemic stroke

Despite the amount of biomarker research in the field of AIS so far, only a few markers that are potentially suitable for LVO detection have been identified. Some recent studies have revealed independent associations between protein markers (such as serum troponin and D-dimer) and LVO[64,65]. However, to date, they are not routinely used for screening in the prehospital setting.

Secondary neuroinflammation plays an important role in the pathogenesis of AIS. Ischemic brain damage elicits systematic inflammatory response and cause a time-dependent activation of peripheral immune cells[66]. Leukocyte counts and ratios (such as neutrophil-to-lymphocyte ratio) in peripheral blood proved to have good prognostic value to predict outcomes and post-stroke complications[67,68]. Higher leukocyte counts, especially neutrophil elevation is also associated with increasing severity and larger infarct volumes in AIS[69,70].

Large vessel occlusion tends to cause more severe strokes and place large cerebral territories at ischemic risk[71]. Therefore, the magnitude of peripheral inflammatory response may be related to the presence of LVO, however previous studies did not investigate this context. The aim of our study was to examine the relationship between on admission total and differential leukocyte counts and the presence of LVO in the early phase of AIS.

4.3.1. Study population

AIS patients admitted up to 4.5 hours after symptom onset to the CSC of two university hospitals (UD and UP, Hungary) between October 2017 and October 2019. Blood samples were collected on admission. Total and differential leukocyte counts were measured immediately with an automated hemocytometer (Sysmex XN-1000; Sysmex, Kobe, Japan). We have

recorded demographic data, vascular risk factors, baseline clinical variables, baseline laboratory values, medications at stroke onset and times from onset to sample collection for each patient. On admission stroke severity was assessed using the NIHSS.

Collateral circulation in the anterior vascular territory was evaluated using the multiphase CTA (mCTA) collateral score. Patients were dichotomized into two groups according to good (mCTA 4-5 points) and poor (mCTA 0-3 points) collateral circulation[72]. Evaluation of CTA scan and mCTA collateral score was done by trained neuroradiologist as a standard of care who were blinded to clinical data. Data on early PSIs were recorded considering any type of infection occurred within 72 hours from stroke onset and were at least grade 2 in severity according to Common Terminology Criteria for Adverse Events[73].

Patients without CTA assessment or whose laboratory results were missing due to sampling or measurement errors were excluded. We have also excluded patients who had infection or surgery within 2 weeks prior to the stroke, those who had relevant neurological events (TIA before or seizures after stroke onset), those who take immunomodulatory medications and those with haematological malignancies, as these conditions could influence peripheral leukocyte counts.

4.3.2. Statistical analysis

In addition to the methods described previously in Section 3.3, univariable and multivariable binary logistic regression analysis was performed to assess the associations between leukocyte counts and the presence of LVO, variables with P value ≤0.1 in the univariable analysis were included in the multivariable model. Total white blood cell (WBC) count, each leukocyte subtype counts, and neutrophil-to-lymphocyte ratio (NLR) were entered in a separate model because of multicollinearity. The ability of leukocyte counts to discriminate the presence of LVO was assessed using the ROC analysis, AUC was calculated for each variable. Optimal cut-off values were calculated using Youden J statistics.

4.3.3. Results

During the study period 514 patients were screened, after exclusions the data of 419 patients were analysed (Figure 10). The mean age of the study cohort was 67.7±12.2 years (43.9% female), 167 patients had LVO (39.9%). Demography and baseline characteristics of the cohort are presented in Table 7.

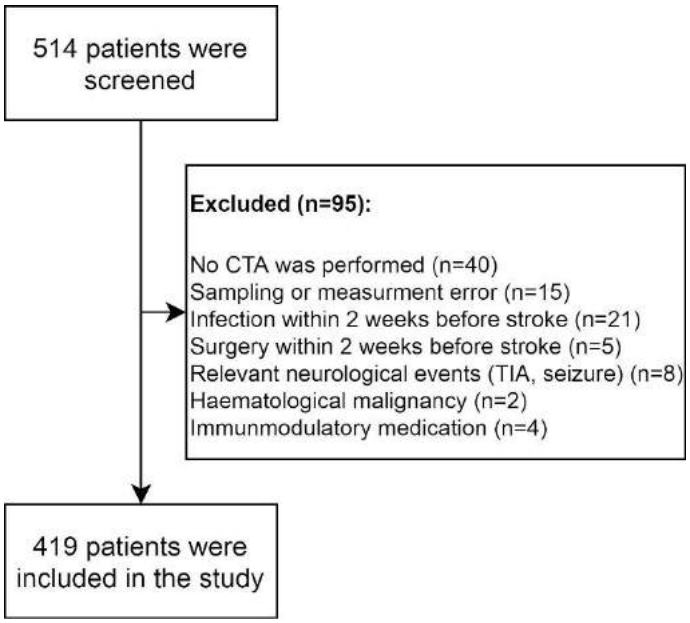

Figure 10. Patient exclusion flowchart. The figure is the author's own work.

Higher total WBC counts were recorded in LVO patients than those without LVO (9.27 x 10^9/L vs. 7.61 x 10^9/L; P<0.001). Regarding major leukocyte subtypes, median neutrophil counts were significantly higher in the LVO group (6.05 x 10^9/L vs. 4.69 x 10^9/L; P<0.001). In contrast, no significant difference was recorded between the groups for the other subtypes (Figure 11). Neutrophil-to-lymphocyte ratio values was slightly higher in patients with LVO (2.83 versus 2.56; P=0.034). Increasing onset to sample times correlated with higher neutrophil counts (Spearman r, 0.175; P<0.001), lower lymphocyte counts (Spearman r, -0.229; P<0.001) and increasing NLR values (Spearman r, 0.275; P<0.001).

Univariable binary logistic regression analysis showed associations between on admission total WBC, neutrophil, lymphocyte, monocyte, and basophil counts and the presence of LVO. After adjustment for potential confounders independent associations were only found between total WBC, neutrophil, lymphocyte, and basophil counts and the presence of LVO (Table 8). There was a trend between increasing NLR values and the presence of LVO in the univariable analysis (OR: 1.079 per 1-point increase, 95% CI: 1.001 to 1.164; P=0.048), but this trend was not present after adjustment for confounders (OR: 1.022 per 1-point increase, 95% CI: 0.924 to 1.131; P=0.672).

Receiver operating characteristic analyses demonstrated moderate ability of total WBC (AUC: 0.667, 95% CI: 0.613 to 0.721; P<0.001) and neutrophil counts (AUC: 0.655, 95% CI: 0.600 to 0.710; P<0.001) to discriminate the presence of LVO. Marginally significant ability was detected for NLR values (AUC: 0.563, 95% CI: 0.505 to 0.621; P=0.030), and the abilities of other leukocyte subtypes to discriminate an LVO were not significant (Figure 12).

Table 7. Demography and clinical characteristics of the cohort according to the presence of LVO

	LVO present (N=167)	LVO absent (N=252)	P value
Demographic characteristics			
Age, years, median (IQR)	68 (61-79)	69 (59-77)	0.258
Gender, female, % (n)	52.1 (87)	38.5 (97)	0.006
Elapsed times			
Onset-to-sample time, min, median (IQR)	83 (55-124)	88 (59-139)	0.313
Sample-to-CTA time, min, median (IQR)	16 (6-25)	12 (5-28)	0.684
Parameters on admission			
NIHSS score on admission, median (IQR)	12 (7-17)	6 (4-8)	<0.001
On admission SBP, mmHg, median (IQR)	158 (140-177)	167 (145-180)	0.004
On admission DBP, mmHg, median (IQR)	85 (78-96)	90 (80-100)	0.004
Body temperature, ^{o}C, median (IQR)	36.4 (36.1-36.5)	36.4 (36.2-36.6)	0.069
Blood glucose, mmol/L, median (IQR)	6.89 (5.90-8.10)	6.43 (5.61-8.35)	0.120
INR, ratio, median (IQR)	1.02 (0.95-1.08)	0.99 (0.94-1.04)	0.003
Vascular risk factors			
Smoking, % (n), 60 missing	39.1 (52)	31.4 (71)	0.139
Hypertension, % (n), 13 missing	81.6 (133)	77.8 (189)	0.352
Diabetes mellitus, % (n), 19 missing	21.4 (34)	30.3 (73)	0.049
Hyperlipidaemia, % (n), 36 missing	50.7 (76)	53.6 (125)	0.568
Atrial fibrillation, % (n), 23 missing	32.9 (52)	17.2 (41)	<0.001
Coronary artery disease, % (n), 33 missing	27.7 (43)	23.4 (54)	0.332
Chronic heart failure, % (n), 23 missing	15.0 (24)	7.6 (18)	0.019
Previous stroke/TIA, % (n), 22 missing	17.6 (28)	25.2 (60)	0.074
Malignancy, % (n), 31 missing	16.4 (25)	9.3 (22)	0.036
Therapy at stroke onset			
Antiplatelet, % (n), 23 missing	40.3 (62)	36.0 (87)	0.388
Anticoagulant, % (n), 28 missing	17.6 (27)	9.7 (23)	0.021
Lipid lowering, % (n), 23 missing	27.7 (43)	22.4 (54)	0.228
Antihypertensive, % (n), 24 missing	72.9 (113)	66.7 (160)	0.190
Antidiabetic, % (n), 24 missing	16.4 (25)	24.0 (58)	0.070

Abbreviation: LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; INR, International Normalized Ratio; TIA, transient ischemic attack.

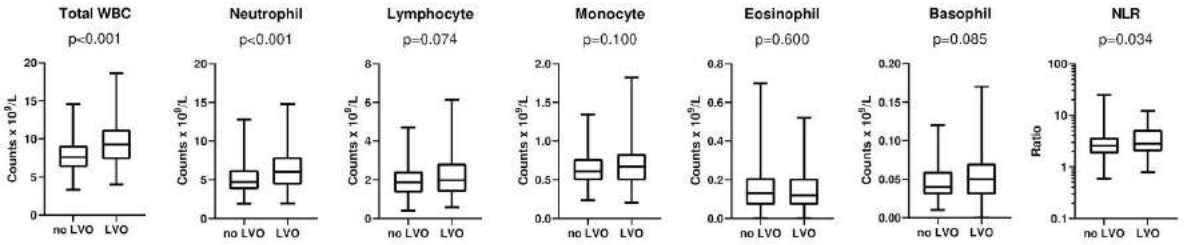

Figure 11. Comparison of admission total white blood cell (WBC) counts, leukocyte subtype counts and neutrophil-to-lymphocyte ratio (NLR) values in acute ischemic stroke according to the presence of large vessel occlusion (LVO). Boxes, 25% to 75% interquartile range; central horizontal bars, median; outer horizontal bars, minimum and maximum values. Statistics: Mann-Whitney *U* test. The figure is the author's own work.

Table 8. Associations between leukocyte counts and the presence of large vessel occlusion in acute ischemic stroke

	Crude OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Total WBC ($1x10^9$/L increase)	1.292 (1.187 to 1.405)	<0.001	1.405 (1.209 to 1.632)	<0.001
Neutrophil ($1x10^9$/L increase)	1.296 (1.181 to 1.421)	<0.001	1.344 (1.155 to 1.564)	<0.001
Lymphocyte ($1x10^9$/L increase)	1.321 (1.064 to 1.641)	0.012	1.631 (1.106 to 2.407)	0.014
Monocyte ($0.1x10^9$/L increase)	1.112 (1.018 to 1.214)	0.018	1.048 (0.903 to 1.217)	0.535
Eosinophil ($0.1x10^9$/L increase)	0.955 (0.807 to 1.131)	0.596	1.043 (0.799 to 1.363)	0.755
Basophil ($0.01x10^9$/L increase)	1.106 (1.024 to 1.194)	0.010	1.296 (1.119 to 1.501)	<0.001

Abbreviation: OR, odds ratio; CI, confidence interval; WBC, white blood cell; L, litre.
* Adjusted to sex, on admission NIHSS score, systolic blood pressure, diastolic blood pressure, body temperature, INR value, the presence of diabetes mellitus, atrial fibrillation, chronic heart failure, previous stroke/TIA, malignancy in patient history and anticoagulant or antidiabetic therapy at stroke onset.

Out of 167 LVO patients 147 (88.0%) had occlusion in the anterior circulation (ICA, M1, M2 and M3 segments of MCA, A1 and A2 segments of ACA). Proximal occlusions (defined as occlusion of ICA or M1 segment of MCA) were found at 105 patients (71.4%). These patients had more severe strokes (median NIHSS score 15 vs. 8; P<0.001) compared to those with more distal occlusions (M2 and M3 segment of MCA, A1 and A2 segments of ACA), but no significant differences were recorded in leukocyte counts. Data on collateral status was available for 145 patients (98.6%). Good collateral circulation was found in 86 patients

(59.3%). Patients with poor collateral circulation had higher NIHSS median scores on admission than those with good collaterals (16 vs. 11; P<0.001), but no significant differences in leukocyte counts were found between the two groups.

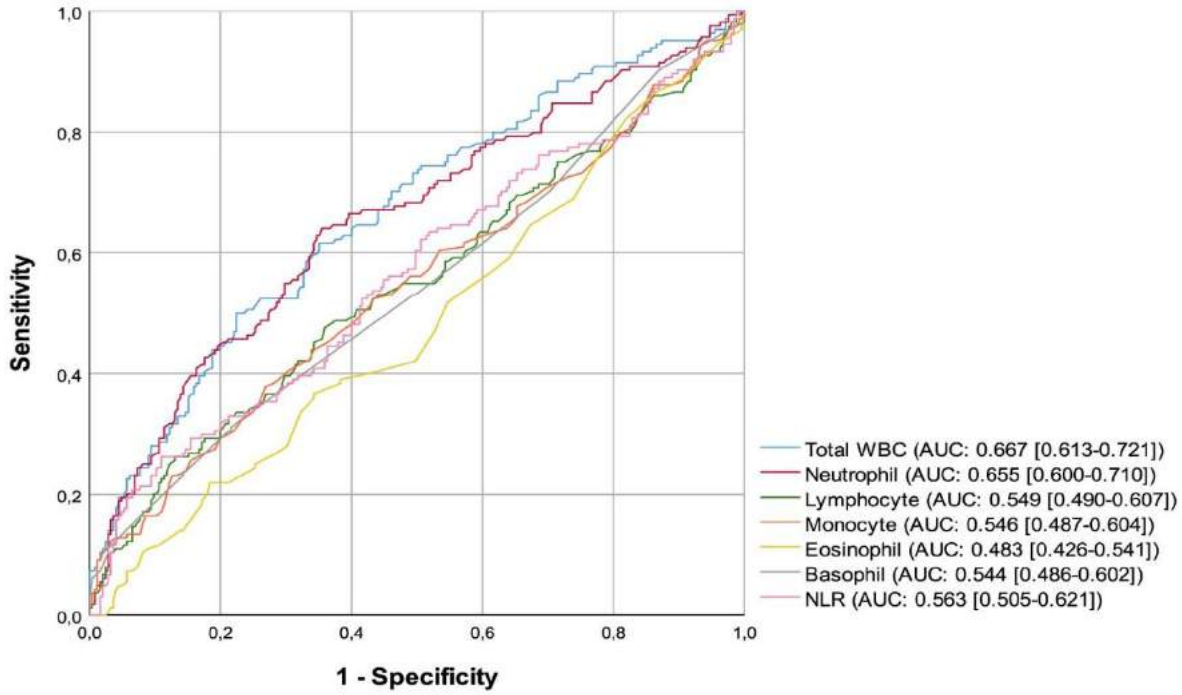

Figure 12. Receiver operating characteristic curves demonstrating the ability of total and differential leukocyte counts to discriminate the presence of LVO in AIS. Area under the curve (AUC) values and 95% confidence intervals are presented.

Twenty patients (12.0%) had LVO in the posterior circulation (VA, BA, P1 and P2 segments of PCA). These patients tended to be younger and had lower median NIHSS scores than patients with LVO in the anterior circulation. Median admission total WBC and neutrophil counts were significantly higher in patients with posterior LVO (8.77 x 10^9/L vs. 10.46 x 10^9/L; P=0.005 and 5.89 x 10^9/L vs. 7.06 x 10^9/L; P=0.010 respectively). Lymphocyte and monocyte counts were slightly higher in posterior LVO patients; however, differences did not reach the significance level.

A total of 100 patients (23.9%) have suffered early post-stroke infections, the majority of which were pneumonia (37%) and urinary tract infections (51%). In the group of non LVO patients on admission neutrophil counts were higher and lymphocyte counts were lower in those with early PSI (5.73 x 10^9/L vs. 4.52 x 10^9/L; P=0.003 and 1.65 x 10^9/L vs. 1.90 x 10^9/L; P=0.037). However, no differences were found in leukocyte counts according to the development of PSI among patients with LVO. No significant differences were recorded in leukocyte counts between the groups of patients with and without hypertension or diabetes.

4.3.4. Discussion

The main finding of our study is that leukocyte counts (especially total WBC and neutrophil) are associated with the presence of LVO in the acute phase of ischemic stroke. Higher total WBC and neutrophil counts could be detected in LVO patients compared to those without LVO, already in the first hours after stroke onset. This highlights the rapid response of systematic inflammatory mechanisms after ischemic brain injury, the extent of which may differ among leukocyte subtypes according to the presence of LVO.

Proinflammatory factors and pathways are activated within minutes after ischemic onset[74]. Neutrophils are the first leukocyte subtype to be upregulated and subsequently infiltrate the ischemic brain tissue[75]. A previous study has reported that neutrophilia is associated with the volume of ischemic tissue in AIS[70]. The presence of LVO can cause blood supply disturbances in large vascular territories and places substantial cerebral areas under ischemic risk, thereby probably increase the magnitude of proinflammatory response. This may explain why higher total WBC counts (mainly due to the increase in neutrophil counts) can be detected in LVO patients compared to those without LVO in AIS.

Our results are consistent with previous studies highlighting the longitudinal changes in leukocyte activation: elevation of neutrophil and decrease in lymphocyte counts over time[76,77]. It should be noted that lymphocytes are recruited in the later stages of ischemic brain injury[78]. In our study no differences were found in baseline lymphocyte counts between LVO and non LVO patients, which may be because lymphocytes have not yet been extensively activated at this early stage of AIS. This may also be the reason why NLR, which is well established in stroke prognosis prediction[68,76,77], hardly differed between the two groups.

Independent associations between increasing counts of neutrophils, lymphocytes and basophils and higher odds of LVO may represent a broad, bi-directional crosstalk between the ischemic brain and the peripheral immune system, which likely affects almost all participants of the immune response quite early after stroke onset. Interestingly in addition to the strong association between neutrophil counts and LVO, association was also found for basophil counts. Basophil leukocytes have unique role in allergic reactions, parasite infections and autoimmune diseases, however, little data are available on their role in acute stroke. Several years ago, a study has raised the role of basophils in stroke, while another study has confirmed the role of mast cells in regulating the blood-brain barrier following cerebral ischemia[79,80]. However, it should be noted that automated analysis of leukocyte subtypes with very low number of cells (eosinophil and basophil counts) might be slightly inaccurate. In addition,

routine hemogram results (which we also used in this study), despite low concentrations, usually only present two decimal places in the numerical values of absolute basophil counts, hence statistical analysis might be somewhat biased.

Raising the suspicion of LVO in AIS early on is crucial to ensure appropriate imaging methods and early transportation of patients to an EVT capable CSC. Hence reliable blood-based biomarkers would be valuable to detect patients with LVO early on. Our results demonstrated that the ability of leukocyte counts to discriminate the presence of LVO are limited on their own. This may be because changes in peripheral leukocyte counts are not specific for brain damage and can be influenced by many other confounding factors.

Interestingly leukocytes did not associate with the size of the occluded vessel and with the status of collateral circulation in the anterior vascular territory. These findings are partly consistent with the result of a previous study by Semerano et al., reporting no significant differences in admission leukocyte counts according to the status of collateral circulation[76]. The interplay between the size of occluded vascular territory and the quality of collateral circulation supplemented by other metabolic and genetic factors are highly related to the size of the core and penumbra within ischemic brain lesions[81,82]. A study by Buck et al. suggests that early changes in peripheral counts are related to the size of bioenergetically compromised brain tissue[70]. Based on our results the magnitude of early peripheral inflammatory response after LVO may not related to the collateral circulation or the size of occluded artery separately. However, the interaction between these factors may affect the size of ischemic core and penumbra, and thus probably the extent of neuroinflammation as well.

A previous study has reported no differences in leukocyte counts between anterior circulation (AC) and posterior circulation (PC) strokes and revealed that NLR values are only correlating with infarct volumes in the AC territory, but not in the PC. However, this study also assessed AIS patients without LVO[83]. The etiology of LVO in the PC and the composition of such thrombi (including the proportion of leukocytes) are different from those of the anterior circulation LVO[84,85]. It should also be noted that the distribution of neuronal and non-neuronal cells is different in the various areas of the human brain[86,87], including the proportion of microglia and astrocytes, which may also influence the extent of neuroinflammation. In our study higher median neutrophil and slightly higher lymphocyte and monocyte counts in the posterior LVO group may be related to these conditions.

The rapidly evolving, new options in the treatment of AIS due to LVO facilitate the need for better understanding the nature of this type of stroke. Reliable blood based LVO biomarkers would be valuable to detect patients with high likelihood of LVO early on. Such a biomarker

could be useful for emergency medical services and emergency department personnel to organize optimal patient pathways and to allocate necessary diagnostic and therapeutic resources as soon as possible. Based on our results leukocyte counts are not sufficiently suitable for this purpose, due to low sensitivity and specificity. However, these findings may warrant further investigation to explore the relationship between LVO and neuroinflammation in details. The scope of further studies could be the interplay between LVO and well-established inflammatory markers such as acute phase proteins, cytokines, cell adhesion molecules, matrix metalloproteinases, damage-associated molecular patterns, markers of oxidative stress, markers of the complement pathway and annexins[66]. Inflammatory markers may also be good candidates to find suitable blood-based biomarkers for early LVO detection[88]. Further, larger scale studies are also needed to examine alterations in neuroinflammation according to the location and the volume of cerebral infarction and ischemic penumbra. A recent study has found that NLR values can be useful biomarkers to predict the occurrence of PSI in AIS patients[89]. Although our result only showed differences in NLR values among non LVO patients and no differences were observed in the group of LVO patients. This highlights that the presence of LVO may affect the prognostic ability of NLR to predict PSI.

As previously discussed, the changes in peripheral leukocyte counts may be epiphenomenal to brain damage. However, previous studies have revealed that higher leukocyte counts in healthy patients are also associated with the increased risk of ischemic stroke events[67,90].

4.3.5. Strengths and limitations

The main strength of our study is the thorough investigation of multiple leukocyte subtypes in a reasonable number of patients from two university centres. However, our study also has some limitations. The observational, cross-sectional design did not allow to assess cause-effect relationship. No assessment of ischemic lesion volume or of the size of ischemic core and penumbra was made on admission. Although we attempted to exclude patients whose leukocyte counts may be affected by other conditions, we cannot be sure that all such patients have been excluded. There is a chance of other, unknown confounding factors that were not considered in this study. No CTA was performed in almost 8% of screened cases (mainly due to minor symptoms or contraindications), which might lead to selection bias. The small number of patients with posterior LVO resulted a probably underpowered subanalysis. Finally, it is important to emphasize that NIHSS may not appropriately assess the spectrum and severity of

PC related neurologic deficits. Therefore, NIHSS scores are usually lower in patients with PC territory strokes than patients with stroke in anterior circulation[91,92].

4.4. Optimization of large vessel occlusion detection in acute ischemic stroke using machine learning methods

As described earlier most of the stroke scales assess symptoms only, however, some other variables (such as AF or SBP) may also have good predictive value. Adding these variables to stroke scales may increase their accuracy to detect LVOs[61,63]. The aim of our study was to comprehensively assess the associations between clinical symptoms, medical history variables, vital parameters, laboratory values and the presence of LVO in AIS, and to develop an optimal combination of them using machine learning tools and methods.

4.4.1. Study Cohort

Consecutive AIS patients presenting up to 4.5 h after symptom onset at the CSC of three university hospitals in Hungary (UD, UP and USZ) were enrolled between November 2017 and July 2019. Data on medical history were collected from past medical documentation and based on personal interview with the patient and relatives upon arrival to the ED when possible. Baseline vital parameters and laboratory values were measured as a part of standard care. On admission, stroke symptoms and severity were assessed using the NIHSS.

4.4.2. Statistical Analysis

Data on 41 variables were collected and used for the modelling task. During pre-processing, variables were excluded from the analysis based on (i) having more than 20% missing values (Body temperature, SpO2), (ii) larger than 0.9 correlation with another variable (Hgb), and/or (iii) near zero variance (Extinction). Rows with missing values were omitted from the analysis. Variables were further processed with Yeo Johnson transformation to reduce skewness in lab variables and variables were centred and scaled to obtain statistical uniformity for machine learning (ML) modelling. Smote resampling was used to balance the sample difference in LVO and non-LVO groups. Grid search was used to select optimal hyperparameter for the models. For final model validation, a randomly selected hold-out test cohort was used consisting of 20% of the patient population. To assess the generalizability of the models a 10-fold cross validation was used.

Four covariate groups were created based on the nature of variables including 6 baseline and demographic variables, 9 medical history variables with yes/no values, 10 laboratory variables with numeric values and 14 symptom-related variables with values on an ordinal scale. The predictive ability of these groups of variables was measured using binary logistic regression analysis and ROC analysis was performed based on probability values.

Feature selection was carried out using least absolute shrinkage and selection operator (LASSO) regression to determine the optimal combination of variables to predict LVO[93]. For further ML modelling, the selected variables were used only as covariates. The performance of three ML models—namely, logistic regression, random forest, and neural network—and elastic net method was compared with each other and with a logistic regression model with NIHSS as the only covariate using area under the ROC curve (AUC) statistic (Figure 13). For neural network modelling, a multi-layer perceptron was used with one hidden layer of four neurons. Analysis was carried out in SPSS (version 26, IBM, New York, NY, USA) and R using the Caret ML library[94,95].

4.4.3. Results

A total of 646 patients were screened during the study period, 526 (81.4%) of whom underwent CTA imaging and were finally included in the analysis (46.2% female). The mean age of the study cohort was 68 ± 13 years; 227 patients had LVO (43.2%). The baseline characteristics of the study cohort and the ability of the variables to distinguish an LVO are presented in Table 9. NIHSS had the best discriminative ability with an AUC of 0.783 (95% CI: 0.742–0.824); the optimal cut-off value of NIHSS to detect an LVO was ≥9 points (sensitivity: 70.9%; specificity: 72.6%). The prevalence of several symptoms and the severity of symptoms were higher among LVO patients (Table 10). The distribution of LVO location was as follows: 54 (23.8%) ICA, 74 (32.6%) MCA M1, 52 (22.9%) MCA M2, 4 (1.8%) MCA M3, 2 (0.9%) ACA, 1 (0.4%) PCA, 12 (5.3%) BA, 11 (4.8%) VA, and 17 (7.5%) tandem occlusions.

Regarding predefined covariate groups, the combination of symptoms had the best ability to discriminate an LVO (AUC: 0.779 on hold-out set and 0.785 after 10-fold cross validation; P<0.001, respectively), followed by medical history (AUC: 0.602 and 0.686; P<0.001), laboratory values (AUC: 0.637 and 0.641; P<0.001) and baseline and demographic parameters (0.599 and 0.567; P<0.001). NIHSS had an AUC of 0.783 and 0.790 after cross validation (P<0.001).

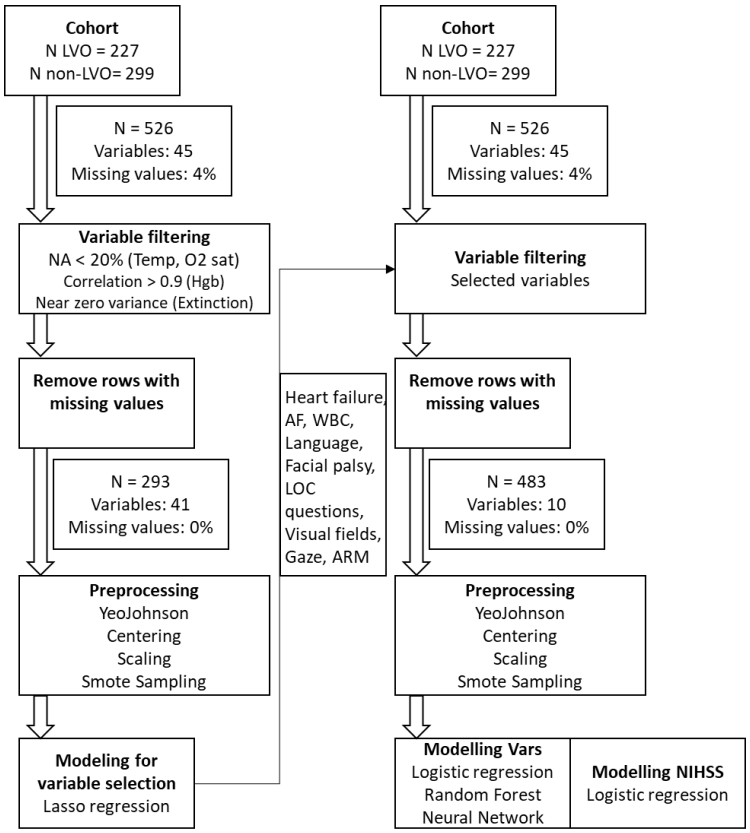

Figure 13. Chart of analysis workflow. The figure is the author's own work.

The results of the covariate group analysis showed that, over a combination of symptoms (NIHSS items), further variables could have potential discriminative power for LVO, especially among the anamnestic and laboratory related variables. Thus, we explored the potential of a mixed-covariate model for discriminate LVO patients using data-driven analysis and a variable selection process (Figure 13).

In the initial dataset, there was a relatively high amount of missing data (4% of the dataset), mainly at random properties and was mainly concentrated in a few variables. Our analysis showed that imputing missing values would negatively affect the performance of the final models, thus, patients with missing values were omitted from the analysis and a two-step approach was followed to maximize sample size for modelling. After preprocessing the dataset, all samples with missing values were omitted (n = 293) and lasso regression was used to select the most predictive variables to LVO. Then, the final data-driven analysis was carried out using the original dataset, filtering only to these selected variables, and omitting patients with missing values (n = 483).

Table 9. Baseline characteristics of the cohort according to the presence of LVO

	LVO present (N=227)	LVO absent (N=299)	P value	AUC (95% CI)
Demographic characteristics				
Age, years, median (IQR)	68 (61-79)	69 (59-77)	0.231	0.524 (0.467-0.582)
Gender, female, % (n)	49.8 (113)	43.5 (130)	0.151	0.530 (0.474-0.587)
Elapsed times				
Onset-to-ER assessment time, min, median (IQR)	83 (58-124)	88 (59-135)	0.110	-
ER assessment-to-CTA time, min, median (IQR)	14 (6-23)	17 (6-32)	0.043	-
Parameters on admission				
NIHSS score on admission, median (IQR)	12 (8-16)	6 (4-9)	<0.001	0.783 (0.742-0.824)
On admission SBP, mmHg, median (IQR)	160 (140-178)	169.5 (145-185)	0.005	0.420 (0.365-0.474)
On admission DBP, mmHg, median (IQR)	86 (78-99)	90 (80-100)	0.034	0.456 (0.401-0.511)
Heart rate, 1/min, median (IQR)	82 (72-93)	80 (71-92)	0.251	0.533 (0.477-0.589)
SpO_2, %, median (IQR)	97 (96-98)	97 (96-99)	0.025	0.447 (0.345-0.550)
Body temperature, ^oC, median (IQR)	36.4 (36.0-36.5)	36.5 (36.2-36.6)	0.008	0.372 (0.270-0.474)
BMI, kg/m^2, median (IQR)	25.78 (23.34-30.12)	26.72 (23.46-31.21)	0.125	0.447 (0.392-0.502)
Laboratory parameters				
Blood glucose, mmol/L, median (IQR)	6.90 (5.91-8.28)	6.50 (5.60-8.30)	0.084	0.548 (0.495-0.602)
INR, ratio, median (IQR)	1.03 (0.96-1.10)	1.00 (0.95-1.05)	<0.001	0.587 (0.534-0.640)
CRP, mg/L, median (IQR)	3.30 (1.50-7.20)	2.98 (1.55-5.80)	0.262	0.540 (0.486-0.595)
WBC, 10^9/L, median (IQR)	8.62 (6.88-10.62)	7.94 (6.55-9.61)	0.005	0.583 (0.530-0.636)
Platelet, 10^9/L, median (IQR)	233.5 (195-271)	224 (186-267)	0.078	0.532 (0.479-0.586)
Haematocrit, %, median (IQR)	40.0 (37.6-42.8)	41.1 (38.0-44.0)	0.034	0.449 (0.396-0.503)
Haemoglobin, g/dL, median (IQR)	138 (126-146)	141 (130-152)	0.005	0.433 (0.380-0.486)
Creatinine, µmol/L, median (IQR)	82 (69-99)	83 (69-101)	0.561	0.485 (0.431-0.539)
BUN, mmol/L, median (IQR)	6.26 (4.80-8.19)	6.10 (4.68-7.63)	0.173	0.527 (0.473-0.581)
AST, U/L, median (IQR)	20 (16-24)	20 (16-25)	0.480	0.476 (0.422-0.530)
ALT, U/L, median (IQR)	15 (11-22)	16 (12-22.5)	0.381	0.466 (0.412-0.520)
Presence of vascular risk factors				
Smoking, % (n)	34.9 (66)	31.4 (85)	0.424	0.517 (0.460-0.574)
Hypertension, % (n)	81.4 (180)	80.4 (234)	0.768	0.496 (0.439-0.553)
Diabetes mellitus, % (n)	21.5 (47)	28.6 (82)	0.069	0.475 (0.418-0.531)
Hyperlipidaemia, % (n)	59.2 (125)	58.3 (161)	0.840	0.495 (0.438-0.552)
Atrial fibrillation, % (n)	35.8 (78)	17.5 (50)	<0.001	0.590 (0.533-0.647)
Coronary artery disease, % (n)	29.6 (64)	21.9 (61)	0.051	0.535 (0.478-0.592)
Chronic heart failure, % (n)	17.9 (39)	8.9 (25)	0.002	0.549 (0.492-0.606)
Previous stroke/TIA, % (n)	21.0 (46)	23.2 (66)	0.564	0.494 (0.438-0.551)
Malignancy, % (n)	15.6 (33)	11.7 (33)	0.217	0.520 (0.462-0.577)

Abbreviation: LVO, large vessel occlusion; AUC, area under the curve; CI, confidence interval; IQR, interquartile range; ER, emergency room; CTA, CT angiography; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; INR, International Normalized Ratio; CRP, C-reactive protein; WBC, white blood cell; BUN, blood urea nitrogen; AST, aspartate-aminotransferase; ALT, alanine-aminotransferase, TIA, transient ischemic attack.

Table 10. Distribution of symptom severity and prevalence as a function of LVO

Symptoms (NIHSS items)	Points			Presence			AUC (95% CI)
	LVO present	LVO absent	P value	LVO present	LVO absent	P value	
1A. Level of consciousness (LOC)	0 (0-0)	0 (0-0)	0.003	12.8%	5.4%	0.003	0.537 (0.487-0.587)
1B. LOC questions	1 (0-2)	0 (0-1)	<0.001	56.4%	33.1%	<0.001	0.638 (0.589-0.686)
1C. LOC commands	0 (0-2)	0 (0-0)	<0.001	47.1%	24.7%	<0.001	0.618 (0.569-0.667)
2. Gaze	0 (0-2)	0 (0-0)	<0.001	46.3%	15.1%	<0.001	0.666 (0.617-0.714)
3. Visual fields	0 (0-2)	0 (0-0)	<0.001	47.6%	21.4%	<0.001	0.632 (0.583-0.681)
4. Facial palsy	2 (1-2)	1 (0-2)	<0.001	85.9%	70.9%	<0.001	0.644 (0.597-0.692)
5. Arm weakness	3 (1-4)	1 (0-2)	<0.001	91.2%	72.6%	<0.001	0.738 (0.695-0.782)
6. Leg weakness	3 (1-3)	1 (0-2)	<0.001	83.3%	64.9%	<0.001	0.717 (0.671-0.762)
7. Limb ataxia	0 (0-0)	0 (0-0)	0.001	7.0%	17.4%	<0.001	0.450 (0.401-0.499)
8. Sensory deficit	0 (0-1)	0 (0-1)	0.688	26.9%	30.1%	0.418	0.492 (0.442-0.542)
9. Language/aphasia	1 (0-2)	0 (0-1)	<0.001	56.8%	37.1%	<0.001	0.634 (0.586-0.683)
10. Dysarthria	0 (0-1)	0 (0-1)	0.893	37.0%	38.1%	0.792	0.497 (0.447-0.547)
11.Extinction/inattention	0 (0-0)	0 (0-0)	0.001	9.7%	2.7%	0.001	0.535 (0.485-0.585)

Abbreviation: LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; AUC, area under the curve; CI, confidence interval.

During feature selection, a total of nine variables were selected for subsequent ML modelling (six symptom variables: language, facial palsy, LOC questions, visual field disturbance, gaze palsy and upper limb weakness; two medical history variables: AF and CHF; and one laboratory value: WBC count. Including the selected variables, four ML tools were applied: random forest (RF), logistic regression (LR), elastic net method (ENM), and simple neural network (SNN). The calculated AUC values on the hold-out set and after 10-fold cross-validation were 0.986 and 0.736 for the RF model, 0.816 and 0.775 for the LR, 0.813 and 0.773 for ENM and 0.808 and 0.772 for SNN.

4.4.4. Discussion

Our study has highlighted that the severity of certain neurological symptoms may have the best ability to predict an LVO, but our results also pointed out that other variables (notably, AF or CHF in medical history and on-admission WBC values) also have good predictive ability.

The clinical presentation of LVO in AIS is highly dependent on the site of occlusion[48]. Currently, NIHSS is the gold-standard for stroke severity assessment and has the best ability to detect LVOs—the previously reported AUC values were similar to our findings[49]. Despite the wide spectrum of symptoms assessed in NIHSS, it still occasionally fails to detect and assess posterior territory strokes appropriately. For short stroke scales, the challenge is to examine the full spectrum of symptoms corresponding to different vascular territory strokes without the process becoming too complicated. The results of a retrospective study suggested that cortical symptoms are better predictors of LVO than motor symptoms, but their combination has the highest accuracy [62]. Our findings showed that upper and lower extremity weakness had the best discriminative abilities, followed by gaze disturbance and facial palsy. However, it should be noted that the majority of the LVO cases in our study involved anterior circulation; therefore, the findings should be interpreted accordingly.

The use of ML methods to optimize prediction models is emerging in the field of stroke research to maximize the predictive performance of variable combinations[96]. Based on the previously mentioned findings, it is not surprising that feature selection using the LASSO method in our study mainly selected symptom variables (motor and cortical symptoms as well) for modelling. The selected symptoms represent a wide spectrum of LVOs in various vascular regions, as they mostly occur in anterior and posterior territory strokes as well. In addition, variables that had a strong association with the presence of LVO in the univariate analysis were selected—notably, AF, CHF, and WBC count. In a recent article by Wang et al. using a similar approach, a set of variables were initially selected based on research in the literature and clinical relevance for subsequent feature selection[96]. In contrast, in our study, we included all variables that were available in adequate quality from a multi-centre registry. However, after feature selection, it appeared in both studies that, although symptoms provide the backbone of the models, other types of variables may be important factors and should be included as well.

Including these variables, all applied ML tools performed well on the full set of data (AUC > 0.800); however, after 10-fold cross validation, the performance of each markedly decreased and the AUC values of three models (RF, LR and ENM) ranged from 0.775 to 0.772; the SNN lagged slightly with an AUC of 0.736. The study by Wang et al. has applied a similar approach to optimize LVO prediction, and their results regarding the performance of ML tools were quite similar. The abilities of stroke scales for LVO detection have also been reported generally around this range in previous retro- and prospective studies[49,53,96].

Over recent years, a plethora of LVO detection methods have been developed and examined. For a tool to be applicable for prehospital use, several criteria must be met, such as

high diagnostic accuracy, easy and fast application, user-friendliness, and cost-effectiveness[97]. The NIHSS may be too complex for routine prehospital use; therefore, the use of shorter scales is warranted at the cost of some reduction in accuracy. It should also be noted that some symptoms are not easily examinable by non-neurologists, such as gaze disturbance and visual field loss, two symptoms that were also selected for modelling in our study and, therefore, may limit prehospital applicability[98]. However, the inclusion of non-symptom variables is not common in LVO scales yet.

Regarding patient history and clinical parameters, a study has found that the history of AF and SBP ≤ 170 mm mmHg are independent predictors of LVO in AIS, and these correlations were also confirmed by our results[61]. There have been some attempts to attach AF to various scales with heterogeneous results. A retrospective analysis has shown no improvement in the accuracy of four broadly used short stroke scales when AF was added as an element[99]. In contrast, another study found that the adding of AF to the Los Angeles Motor Scale (LAMS) could significantly improve its ability to detect LVOs[63]. In addition, several recently created LVO scales include AF as a variable[100,101]. The utility of including SBP in stroke scales is much less studied. A prospective observational study demonstrated that SBP may help to identify patients potentially eligible for EVT[102]. CHF is an independent risk factor of stroke, and other diseases should be considered (such as AF, CAD and valvular disease) that are predisposing factors for CHF and AIS[103]. The association between CHF and the presence of LVO probably represents a wide spectrum of confounding and additive conditions. Therefore, CHF might be interchangeable or be combinable with the aforementioned cardiac diseases. Future studies may use a combined variable containing all predisposing cardiac diseases at once.

Univariate analyses in our study revealed that the strength of associations between most variables and LVO is mild to moderate, the reason for which is probably that associations are affected by many known and unknown confounding factors (e.g., LVO location regarding symptoms). It is also clear that a combination of variables with such specificity cannot exceed a certain accuracy. The study highlighted that machine learning tools are extremely useful to reduce the dimensions of large datasets, and to assess and optimize predictive ability. However, the result should also be approached and interpreted from clinical and practical aspects as well, since the heterogeneity of clinical presentations may limit the clinical utility of these methods.

Molecular biomarkers supporting the clinical care of stroke, especially its classification and objective monitoring, are yet to be available. A better understanding of the biochemical and pathophysiological pathways and processes associated with LVO is needed to identify more specific biomarkers. Screening for a large number of potential biomarkers, i.e., the “omics”

approach, and the combined analysis of multi-omic data, including proteomic, more recently glycomic, and metabolomic data, is a particularly promising solution for identifying new biomarkers. Extended stroke registers and multi-omic databases combining clinical and biomedical data are needed together with data analysis platforms that can facilitate to organize and analyze large amounts of data with modern machine learning methods, to identify new, complex biomarkers that support stroke typing and therapy monitoring[104].

It should also be noted that the definition of LVO is quite heterogenous, and previous studies and clinical trials have used various criteria for LVO classification[48]. Mechanical thrombectomy cannot be performed in some cases that are radiologically considered as cases of LVO. However, from a clinical aspect, the 2019 AHA/ASA stroke guidelines recommend considering MT in a wide spectrum of LVO cases. In the case of distal occlusions (e.g., MCA M2 and M3) and occlusions in the posterior circulation, the decision to indicate MT should be made on a case-by-case basis, weighing the potential costs and benefits[29].

Anterior and posterior circulation territory occlusions and strokes may show quite different clinical appearances and have different predisposing factors[105,106]. The NIHSS also investigates more anterior territory stroke symptoms and, thus, occasionally fails to correctly assess the severity of posterior strokes[107]. Although we aimed to create a universal LVO detection model in our study, we considered all types of LVO. However, for future studies, it may be worthwhile to optimize the prediction of anterior and posterior circulation LVOs separately in a similar way using ML methods, due to the aforementioned differences. Another possible direction is that, after performing a method optimized for anterior circulation LVOs, a method optimized for a posterior circulation LVOs should follow.

4.4.5. Strengths and limitations

The main strength of our study was the comprehensive assessment of real-life, prospectively collected data from multiple centres using novel statistical methods that are not extensively used in medical research yet. However, our study also had some limitations. Firstly, the cross-sectional design only allows to assess associations but not causality. It is important to emphasize that potentially important variables may not have been included to the analyses due to multiple reasons (e.g., a large amount of missing data, or variables were not available in the stroke registry) which could have caused bias. In this study, we used 10-fold cross validation to estimate the generalizability and the true accuracy of the models; however, validation using an external dataset is needed to clinically validate our findings. Finally, ML tools function the best when applied to large datasets (“big-data”), which our dataset did not necessarily match.

5. Summary of novel findings and perspectives

5.1. Summary of novel findings

- Our result highlighted that certain stroke scales may be good tools to predict LVO in AIS. In general, it could be seen that the more complex a scale is, the higher its accuracy is. The NIHSS and mNIHSS had the highest accuracies, however these scales are primary suitable to be used by trained individuals and might be time-consuming to assess. Shorter scales, such as the sNIHSS-EMS, the sNIHSS-8, the sNIHSS-5, the RACE, and the 3I-SS have slightly lower accuracy, but these are considered as easier to use, and more suitable for prehospital application. A significant drawback of using these scales is that that they cannot achieve high specificity and sensitivity simultaneously.

- Our results revealed that detailed severity assessment of symptoms investigated in the CPSS can significantly improve its ability to detect LVO in AIS, while remaining simple to perform. The predictive ability of detailed CPSS reach the ability of the NIHSS.

- Our study demonstrated that increasing admission total WBC and neutrophil counts is independently associated with the presence of LVO in AIS and these markers have moderate abilities to discriminate an LVO. Interestingly median WBC and neutrophil counts were significantly higher in patients with posterior territory LVOs. We also found that the neutrophil-to-lymphocyte ratios are higher in the group of patients who suffer post-stroke infections. However, when the patients were divided into groups according to the presence of LVO, this difference was observable only among non-LVO patients.

- Finally, we applied machine-learning tools to develop an optimal combination of variables for LVO prediction. Our results highlighted that severity assessment of neurological symptoms is the most useful to predict an LVO in AIS, however, other types of variables (certain medical history data, and laboratory values) should also be included to maximize efficiency. However, it is important to emphasize that models based on routine clinical parameters are not able to perform better than a certain level, based on our results they are hardly able to exceed an AUC of 0.8.

5.2. Future perspectives

- As only a minority of short stroke scales is prospectively validated in prehospital settings future studies should focus on testing these scales in this environment. Inter-rater agreement and inter-rater reproducibility should also be assessed.
- More detailed severity assessment of symptoms and proper weighting of variables could be a good perspective of future research and adding items to scales that are strongly associated with LVO could also be beneficial and should be considered.
- Based on our results biomarkers associated with early neuroinflammatory response could be good candidates for LVO detection, which may be worth further research.
- The use of machine learning methods is emerging, and these tools should be used to optimize LVO detection methods, however, to reach maximal performance large scale datasets should be used, the source of which could be comprehensive stroke registries.
- Furthermore, optimal thresholds for LVO detection and prehospital pathways in cases of different likelihoods of LVO should also be clarified according to local circumstances.
- Another interesting scope of future studies could be not only the detection of LVO, but the early recognition of patients potentially eligible for thrombectomy taking other indication criteria (Alberta stroke program early CT score, age, pre-stroke modified Rankin Scale score etc.) into consideration. To determine the true prehospital utility of LVO detection tools all cases of stroke suspicion must also be considered, including patients with HS and stroke mimics as well.

6. References

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CAPABILITY OF STROKE SCALES TO DETECT LARGE VESSEL OCCLUSION IN ACUTE ISCHEMIC STROKE – A PILOT STUDY

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Background and purpose – Rapid changes of stroke management in recent years facilitate the need for accurate and easy-to-use screening methods for early detection of large vessel occlusion (LVO) in acute ischemic stroke (AIS). Our aim was to evaluate the ability of various stroke scales to discriminate an LVO in AIS.
Methods – We have performed a cross-sectional, observational study based on a registry of consecutive patients with first ever AIS admitted up to 4.5 hours after symptom onset to a comprehensive stroke centre. The diagnostic capability of 14 stroke scales were investigated using receiver operating characteristic (ROC) analysis.
Results – Area under the curve (AUC) values of NIHSS, modified NIHSS, shortened NIHSS-EMS, sNIHSS-8, sNIHSS-5 and Rapid Arterial Occlusion Evaluation (RACE) scales were among the highest (>0.800 respectively). A total of 6 scales had cut-off values providing at least 80% specificity and 50% sensitivity, and 5 scales had cut-off values with at least 70% specificity and 75% sensitivity.
Conclusion – Certain stroke scales may be suitable for discriminating an LVO in AIS. The NIHSS and modified NIHSS are primarily suitable for use in hospital settings. However, sNIHSS-EMS, sNIHSS-8, sNIHSS-5, RACE and 3-Item Stroke Scale (3I-SS) are easier to perform and interpret, hence their use may be more advantageous in the prehospital setting. Prospective (prehospital) validation of these scales could be the scope of future studies.

Keywords: *acute stroke, ischemic stroke, large vessel occlusion, stroke scale*

STROKE-SKÁLÁK KÉPESSÉGE NAGYÉRELZÁRÓDÁS DETEKTÁLÁSÁRA AKUT ISCHAEMIÁS STROKE-BAN – PILOT VIZSGÁLAT

Tárkányi G, MD; Karádi NZs, MD; Csécsei P, MD, PhD; Bosnyák E, MD, PhD; Fehér G, MD, PhD; Molnár T, MD, PhD; Szapáry L, MD, PhD
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Háttér és cél – Az elmúlt évek változásai a stroke-ellátásban szükségessé teszik pontos és könnyen használható módszerek kifejlesztését nagyérelzáródás (NÉO) detektálására akut ischaemiás stroke-ban (AIS). Kutatásunk célja számos stroke-skála NÉO detektálására való alkalmasságának vizsgálata AIS-betegek esetében.
Módszerek – Egy hazai stroke-regiszteren alapuló keresztmetszeti vizsgálatot végeztünk, melybe olyan betegeket vontunk be, akik első AIS-jukat szenvedték el, és 4,5 órán belül felvételre kerültek egy komprehenzív stroke-centrumba. Összesen 14 stroke-skála diagnosztikus képességét vizsgáltuk receiver operating characteristic (ROC) analízis segítségével.
Eredmények – A ROC-görbe alatti terület az NIHSS, modified NIHSS, shortened NIHSS-EMS, sNIHSS-8, sNIHSS-5 és Rapid Arterial Occlusion Evaluation (RACE) skálák esetében volt a legmagasabb (>0,800 mindegyik esetben). Összesen hat skála esetében találtunk olyan küszöbértéket, amellyel legalább 80%-os szenzitivitás (SN) és 50%-os specificitás (SP) volt elérhető. Olyan küszöbértéket, amely legalább 70%-os SN-t és 75%-os SP-t biztosított, öt skála esetében találtunk.
Következtetés – Több stroke-skála is alkalmas lehet NÉO detektálására AIS-ban. Az NIHSS és a modified NIHSS elsősorban kórházi felhasználásra alkalmas. Mivel azonban a sNIHSS-EMS, sNIHSS-8, sNIHSS-5, RACE és 3 Item Stroke Scale (3I-SS) skálák rövidebbek és egyszerűbb a felvételük, alkalmazásuk akár prehospitális körülmények között is kivitelezhető lehet. További vizsgálatok szükségesek ezen skálák prospektív (prehospitális) validálásának céljából.

Kulcsszavak: *akut stroke, ischaemiás stroke, nagyérelzáródás, stroke-skála*

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Endovascular thrombectomy (EVT) has been shown to be effective to treat patients with acute ischemic stroke (AIS) caused by large vessel occlusion (LVO), which occurs in 20-40% of cases[1, 2]. Over time, the benefit of EVT decreases, while the chance of complications increases, therefore treatment should be initiated as soon as possible after stroke onset[3, 4]. However, currently only a small proportion of stroke treating hospitals are capable to perform EVT and transportation between primary and comprehensive stroke-centres (CSC) is one of the major causes of delayed treatment initiation[5, 6]. Early detection of LVO is crucial as these patients may benefit from early referral to a CSC and direct transportation to a CSC (bypassing primary stroke centres) may also be beneficial[7].

Previous studies have demonstrated that multiple stroke scales may be suitable for early identification of AIS patient with LVO. An easy-to-use scale would be also valuable for emergency medical services (EMS) or emergency departments (ED) to ensure appropriate triage of these patients. However, only a minority of these scales have been examined multiple times[8]. Thus, the aim of our study was to assess the ability of various stroke scales to detect LVO in AIS patients.

Methods

The study protocol was approved by the Local Ethics Committee at University of Pécs, Faculty of Medicine (35403-2/2017/EKU). Written informed consent was obtained from each patient according to the Good Clinical Practice (GCP) guidelines.

STUDY COHORT

We have performed a cross-sectional, observational study based on a prospectively collected registry of patients with first ever AIS. Patients were admitted up to 4.5 hours after stroke onset to the CSC of University of Pécs, Hungary between October 2017 and February 2019. Baseline clinical variables including age, gender, onset-to-admission time and vascular risk factors were recorded on admission. Neurological symptoms were assessed using the National Institutes of Health Stroke Scale (NIHSS) on admission. A total of 13 stroke scales were derived from NIHSS items: modified NIHSS (mNIHSS), shortened NIHSS for EMS (sNIHSS-EMS), shortened NIHSS with 8, 5 and 1 items (sNIHSS-8, sNIHSS-5, sNIHSS-1), abbreviated NIHSS (aNIHSS), Cincinnati Stroke Triage Assessment Tool (C-STAT), Rapid Arterial Occlusion Evaluation scale (RACE), 3-Item Stroke Scale (3I-SS), Prehospital Acute Stroke Severity scale (PASS), Vision Aphasia Neglect scale (VAN), Field Assessment Stroke Triage for Emergency Destination scale (FAST-ED), and Gaze Face Arm Speech Time scale (G-FAST)[8].

Our outcome of interest was the presence of LVO on the admission CT angiography (CTA) scan, assessed by trained neuroradiologists who were blinded to clinical data. Unilateral occlusion of the internal carotid artery (ICA), the M1, M2 and M3 segments of the middle cerebral artery (MCA), the A1 and A2 segments of the anterior cerebral artery (ACA), the vertebral or basilar artery (VA, BA), the posterior cerebral artery (PCA) and tandem occlusions were considered.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS (version 25.0, IBM, New York). Continuous variables were presented as mean ± standard deviation (SD) or as median and interquartile range (IQR) where appropriate. Categorical variables were presented as counts and percentages. Comparison of continuous variables were performed using *t* test or Mann-Whitney *U* test. Normality was assessed using the *Shapiro-Wilk* test and visually, based on Q-Q plots and histograms. Categorical data were compared using the Pearson χ^2-test. The ability of stroke scale to discriminate the presence of LVO in AIS was assessed using receiver characteristics operating curve (ROC) analysis. Area under the curve (AUC) was calculated for each variable, an AUC value 0.800 were considered as representative of an acceptable discrimination. Optimal cut-off values were calculated using the *Youden J* index. Sensitivity (SN) and specificity (SP) was calculated, for different cut-off scores. According to *Scheitz JF* et al. we have created two groups according to predefined SN and SP values: a group of scales and cut-off scores with at least 80% SN and 50% SP, and a group with at least 70% SN and 75% SP[9]. 95% confidence intervals (CI) were presented where appropriate, $P<0.05$ was considered as statistical significance.

Results

During the study period 220 patients were screened. After excluding 40 patients without CTA assessment the data of 180 patients (47.8% female) were evaluated. Ninety-eight patients had LVO (54.4%). Baseline characteristics of the two studied groups

Table 1. *Demography and comorbidities of the cohort according to the presence of LVO*

	LVO present (N=98)	LVO absent (N=82)	P value
Age, years, mean (±SD)	68.1 (±11.4)	68.4 (±10.7)	0.860
Sex, female, % (n)	56.1 (55)	37.8 (31)	0.014
NIHSS, median (IQR)	13 (9-17)	6 (3-8)	<0.001
Onset-to-admission time, min, median (IQR)	150 (110-200)	154 (120-183)	0.608
Smoking, % (n), 48 missing	38.7 (24)	37.1 (26)	0.853
Hypertension, % (n), 10 missing	81.3 (74)	84.8 (67)	0.546
Diabetes mellitus, % (n), 20 missing	20.0 (17)	36.0 (27)	0.024
Hyperlipidaemia, % (n), 45 missing	70.1 (47)	73.5 (50)	0.662
Atrial fibrillation, % (n), 19 missing	35.3 (30)	17.1 (13)	0.009
Coronary artery disease, % (n), 43 missing	32.0 (24)	35.5 (22)	0.667
Chronic heart failure, % (n), 39 missing	16.7 (13)	9.5 (6)	0.217

LVO: large vessel occlusion, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range

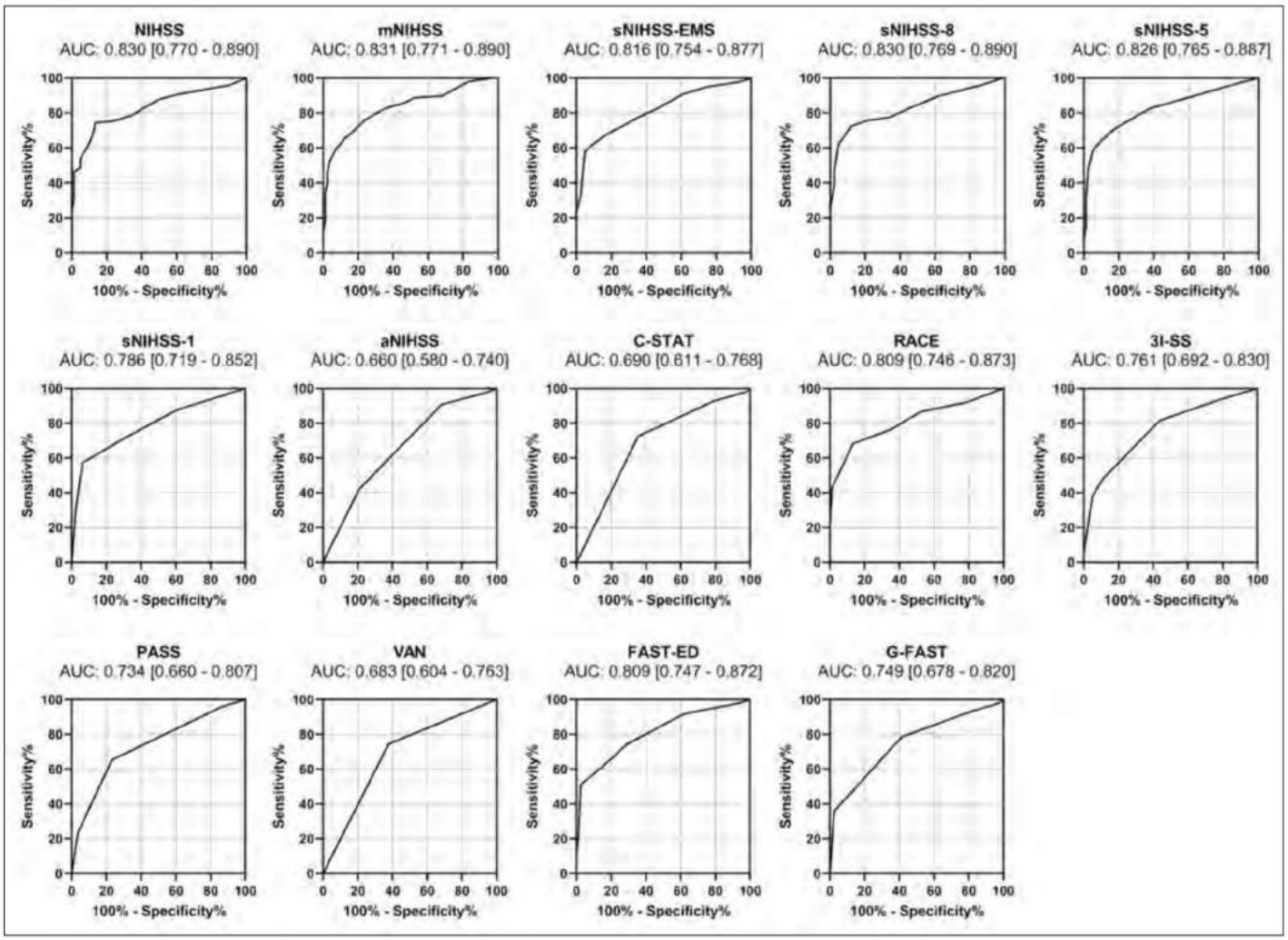

Figure 1. *Receiver operating characteristic (ROC) curves analysing the ability of various stroke scales to discriminate large vessel occlusion in acute ischemic stroke: National Institutes of Health Stroke Scale (NIHSS), modified NIHSS (mNIHSS), shortened NIHSS for emergency medical services (sNIHSS-EMS), shortened NIHSS (sNIHSS), abbreviated NIHSS (aNIHSS), Cincinnati Stroke Triage Assessment Tool (C-STAT), Rapid Arterial Occlusion Evaluation (RACE), 3-Item Stroke Scale (3I-SS), Prehospital Acute Stroke Severity (PASS), Vision Aphasia Neglect (VAN), Field Assessment Stroke Triage for Emergency Destination (FAST-ED), Gaze Face Arm Speech Time (G-FAST). Area under the curve (AUC) values and 95% confidence intervals are presented*

Table 2. *Diagnostic accuracy of stroke scales according to different cut-off values*

Stroke scale	Sensitivity (95% CI)	Specificity (95% CI)
Optimal cut-off value		
NIHSS ≥10	74.5 (64.7-82.8)	86.6 (77.3-93.1)
mNIHSS ≥9	65.3 (55.0-74.6)	87.8 (78.7-94.0)
sNIHSS-EMS ≥10	58.2 (47.8-68.1)	95.1 (88.0-98.7)
sNIHSS-8 ≥7	72.5 (62.5-81.0)	87.8 (78.7-94.0)
sNIHSS-5 ≥5	64.3 (54.0-73.7)	90.2 (81.7-95.7)
sNIHSS-1 ≥3	57.1 (46.8-67.1)	93.9 (86.3-98.0)
aNIHSS ≥2	90.8 (83.3-95.7)	31.7 (21.9-42.9)
C-STAT =3	72.5 (62.5-81.0)	64.6 (53.3-74.9)
RACE ≥5	68.4 (58.2-77.4)	86.6 (77.3-93.1)
3I-SS ≥2	81.6 (72.5-88.7)	56.1 (44.7-67.4)
PASS ≥2	65.3 (55.0-74.6)	76.8 (66.2-85.4)
VAN =1	74.5 (64.7-82.8)	62.2 (50.8-72.7)
FAST-ED ≥5	51.0 (40.7-61.3)	97.6 (91.5-99.7)
G-FAST ≥3	78.6 (63.1-86.2)	58.5 (47.1-69.3)
Cut-off values with sensitivity ≥80% and specificity ≥50%		
NIHSS ≥6	87.8 (79.6-93.5)	50.0 (38.8-61.3)
mNIHSS ≥5	85.7 (77.2-92.0)	53.7 (42.3-64.8)
sNIHSS-EMS ≥5	82.7 (73.7-89.6)	53.7 (42.3-64.8)
sNIHSS-8 ≥4	82.7 (73.7-89.6)	54.9 (43.5-65.9)
sNIHSS-5 ≥3	82.7 (73.7-89.6)	62.2 (50.8-72.7)
3I-SS ≥2	81.6 (72.5-88.7)	56.1 (44.7-67.4)
Cut-off values with sensitivity ≥70% and specificity ≥75%		
NIHSS ≥9	75.5 (65.8-83.6)	75.6 (64.9-84.4)
mNIHSS ≥7	75.5 (65.8-83.6)	76.8 (66.2-85.4)
sNIHSS-8 ≥6	75.5 (65.8-83.6)	79.3 (68.9-97.4)
sNIHSS-5 ≥4	71.4 (61.4-80.1)	81.7 (71.6-89.4)
RACE ≥4	71.4 (61.4-80.1)	78.1 (67.5-86.4)

NIHSS: National Institutes of Health Stroke Scale, mNIHSS: modified NIHSS, sNIHSS-EMS: shortened NIHSS for emergency medical services, sNIHSS: shortened NIHSS, aNIHSS: abbreviated NIHSS, C-STAT: Cincinnati Stroke Triage Assessment Tool, RACE: Rapid Arterial Occlusion Evaluation scale, 3I-SS: 3-Item Stroke Scale, PASS: Prehospital Acute Stroke Severity scale, VAN: Vision Aphasia Neglect scale, FAST-ED: Field Assessment Stroke Triage for Emergency Destination scale, G-FAST: Gaze Face Arm Speech Time scale, LVO: large vessel occlusion.
Values are presented as percentages.

(according to the presence of LVO) are shown in **Table 1**. Patients with LVO tended to have more severe strokes (NIHSS 13 vs. 6; P<0.001) than those without LVO. The proportion of female gender and atrial fibrillation were higher in the LVO group, while diabetes mellitus was more common among non LVO patients **(Table 1)**.

Receiver operating characteristic curves and AUC values are presented in **Figure 1**. The highest AUC value was recorded for mNIHSS (AUC: 0.831). The AUC values of NIHSS (0.830), sNIHSS-EMS (0.816), sNIHSS-8 (0.830), sNIHSS-5 (0.826), RACE (0.809) and FAST-ED (0.809) scales were among the highest. Optimal cut-off scores and related SN and SP values are presented in **Table 2**. A total of 6 scales had a cut-off value with SN of at least 80% and SP of at least 50%, and 5 scales had cut-off values with a least 70% SN and 75% SP **(Table 2)**.

Discussion

The main finding of our study is that multiple stroke scales have good ability to discriminate the presence of LVO in AIS. Currently NIHSS is used as the "gold-standard" of stroke-severity assessment, and previous results highlighted that it is also among the best in terms of LVO detection, which was also confirmed by our study[10]. However, the complexity, the time-consuming nature and the need for special training to use NIHSS appropriately may prevent its routine use prehospitally or in the early phase of emergency care.

Short, quick and easy-to-use stroke scales could be valuable for EMS personal to raise the suspicion of LVO early on. Early referral of patients with high likelihood of LVO to a CSC may be beneficial to ensure appropriate patient transportation pathways and diagnostic methods as soon as possible to reduce stroke-onset to treatment times. Our results highlight that some of the shortened versions of NIHSS (sNIHSS-EMS, sNIHSS-8 and sNIHSS-5), and scales that were optimized for prehospital or ED use (RACE and FAST-ED) may have similar diagnostic abilities as NIHSS, while remaining very simple to use or interpret. Modified NIHSS may be a good alternative to NIHSS for quicker stroke severity assessment and LVO detection, however it may be too complex for routine prehospital or ED use. We should emphasize that these scales would still misdiagnose a significant proportion of patients (around 25%), therefore a compromise must be made between high SN and high SP when selecting a cut-off value.

Scales and cut-off values with at least 80% SN and 50% SP (NIHSS 6, mNIHSS 5, sNIHSS-EMS 5, sNIHSS-8 4, sNIHSS-5 3 and 3I-SS 2) are good to detect a very high proportion of AIS patients with actual LVO (true positives) at the cost of misdiagnosing almost a half of non LVO patients as LVO suspicious (false positives). By comparison, scales with thresholds resulting at least 70% SN and 75% SP (NIHSS 9, mNIHSS 7, sNIHSS-8 6, sNIHSS-5 4 and RACE 4) can reduce the proportion of false positive diagnoses, on the expense of missing higher number of true positive LVO patients. Cut-off values should be selected according to local circumstances considering the capacity of EMS and stroke centres[7, 11].

In conclusion NIHSS, mNIHSS, sNIHSS-EMS, sNIHSS-8, sNIHSS-5, RACE and 3I-SS may be good tools to detect LVO in AIS. Further studies are needed to prospectively validate these scales also in prehospital settings and to assess inter-rater agreement and intra-rater reproducibility. Optimal patient transportation pathways should also be determined in case of high probability of LVO in AIS, according to local circumstances.

LIMITATIONS

The main limitation of our study is its single-centre, observational nature. Besides, we only included patients with AIS, and we did not have data on patients with haemorrhagic strokes and stroke-mimics. Around 18% of screened patients did not undergo CTA assessment (mainly due to minor symptoms or contraindication), that might lead to selection bias. This may also be the reason for slightly higher LVO prevalence rate in our study compared to previous studies (54% vs. 20-40%)[2].

DISCLOSURES
Authors report no conflict of interest.

FUNDING
In this study we used data from the STAY ALIVE Acute Stroke Registry, which is a part of GINOP 2.3.2-15-2016-00048 Stay Alive.

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RESEARCH ARTICLE Open Access

Detailed severity assessment of Cincinnati Prehospital Stroke Scale to detect large vessel occlusion in acute ischemic stroke

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Abstract

Background: Selecting stroke patients with large vessel occlusion (LVO) based on prehospital stroke scales could provide a faster triage and transportation to a comprehensive stroke centre resulting a favourable outcome. We aimed here to explore the detailed severity assessment of Cincinnati Prehospital Stroke Scale (CPSS) to improve its ability to detect LVO in acute ischemic stroke (AIS) patients.

Methods: A cross-sectional analysis was performed in a prospectively collected registry of consecutive patients with first ever AIS admitted within 6 h after symptom onset. On admission stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and the presence of LVO was confirmed by computed tomography angiography (CTA) as an endpoint. A detailed version of CPSS (d-CPSS) was designed based on the severity assessment of CPSS items derived from NIHSS. The ability of this scale to confirm an LVO was compared to CPSS and NIHSS respectively.

Results: Using a ROC analysis, the AUC value of d-CPSS was significantly higher compared to the AUC value of CPSS itself (0.788 vs. 0.633, $p < 0.001$) and very similar to the AUC of NIHSS (0.795, $p = 0.510$). An optimal cut-off score was found as d-CPSS≥5 to discriminate the presence of LVO (sensitivity: 69.9%, specificity: 75.2%).

Conclusion: A detailed severity assessment of CPSS items (upper extremity weakness, facial palsy and speech disturbance) could significantly increase the ability of CPSS to discriminate the presence of LVO in AIS patients.

Keywords: Acute stroke, Large vessel occlusion, Stroke scales, Prehospital, Emergency medicine, Neurology

Background

Endovascular thrombectomy (EVT) is effective to treat patients with acute ischemic stroke (AIS) caused by large vessel occlusion (LVO), which occurs in 20–40% of cases [1, 2]. There is a growing need for simple diagnostic methods that can detect these patients early on. A reliable LVO detection tool could be useful for emergency medical services (EMS) to select patients with a high likelihood of LVO, as these patients may benefit from a direct transportation to an EVT capable comprehensive stroke centre (CSC) [3].

Cincinnati Prehospital Stroke Scale (CPSS) is a simple, three item scale, widely used by EMS. It is easy and quick to learn or perform and has good ability to identify potential stroke patients. Nonetheless, it only has moderate ability to detect AIS patients with LVO, however, important aspect is that CPSS only tests for the presence of three symptoms (facial palsy, upper extremity weakness and speech disturbance), but do not assess the severity of them [4–6]. The aim of our study was to

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examine whether the detailed severity assessment of these items can improve the overall ability of CPSS to detect LVO in AIS patients.

Methods

Study population

We have performed a cross-sectional analysis based on a prospectively collected registry of consecutive patients with first ever AIS, who were admitted up to 6 h after symptom onset to the CSC of three university hospitals between November 2017 and July 2019 (more information on this registry is presented in the Supplementary material). Demographic data, vascular risk factors, baseline clinical variables and time from onset to first assessment in the emergency room were recorded on admission, along with detailed evaluation of the National Institutes of Health Stroke Scale (NIHSS). Our outcome of interest was the presence of LVO on the on admission computed tomography angiography (CTA) scan, evaluated by trained neuroradiologists as a standard of care. The results were subsequently checked by one of the authors (PC or LS) who were blinded to the clinical parameters and stroke severity. In case of disagreement final decision was made after personal communication. NIHSS was routinely assessed before CTA was performed. According to *Rennert* et al. [7] unilateral occlusion of the internal carotid artery (ICA), occlusion in the M1, M2 or M3 segment of the middle cerebral artery (MCA), occlusion of the anterior cerebral artery (ACA), vertebral artery (VA), basilar artery (BA) and posterior cerebral artery (PCA) occlusions were considered. Based on the 2019 update of the 2018 guidelines for the early management of AIS by the American Heart Association and the American Stroke Association we have created three groups of LVO patients. In the first group we have included patients with ICA or M1 occlusions as there is a strong (class Ia) recommendation to consider EVT in these patients. In the second group patients with LVO in the more distal segments of the anterior vascular territory (M2, M3 segments of MCA, ACA) were included. The third group included those with LVO in the posterior circulation (VA, BA or PCA). In these cases, the benefit of EVT is uncertain, however it should be considered on a case-by-case basis (recommendation class IIb and IIc respectively) [8, 9]. Patients who did not have CTA scan on admission were excluded.

Scale design

We derived CPSS from four items of NIHSS (item 4: facial palsy, item 5: unilateral upper extremity weakness, item 9: language and item 10: dysarthria), according to *Kothari* et al. [4] we have combined NIHSS items 9 and 10 to get the speech item of CPSS. We designed a detailed version of CPSS (d-CPSS) derived from the same NIHSS items, but without being converted to bivariate as in CPSS. Detailed scoring criteria are shown in Table 1. The ability of d-CPSS to discriminate an LVO was compared to the ability of CPSS and NIHSS.

Table 1 Detailed scoring of CPSS and d-CPSS compared to NIHSS scores

Severity of symptoms	CPSS score	d-CPSS score	NIHSS source item and score	
ARM			Item 5: arm motor drift	
No drift for 10 s	0	0	0	
Drift, but does not hit bed	1	1	1	
Some effort against gravity	1	2	2	
No effort against gravity	1	3	3	
No movement	1	4	4	
FACIAL PALSY			Item 4: facial palsy	
Normal symmetry	0	0	0	
Minor paralysis	1	1	1	
Partial paralysis	1	2	2	
Complete paralysis	1	3	3	
SPEECH			Item 9: aphasia	Item 10: dysarthria
Normal	0	0	0	0
Mild/moderate aphasia or dysarthria	1	1	1	1
Severe aphasia or dysarthria	1	2	2	2
Global aphasia or anarthic or mute	1	3	3	2
TOTAL	0–3	0–10		

Abbreviation: *CPSS* Cincinnati Prehospital Stroke Scale; *d-CPSS* Detailed CPSS; *NIHSS* National Institutes of Health Stroke Scale

Statistical analysis

Data analysis was performed using SPSS (version 26.0, IBM, New York). Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range (IQR) where appropriate. Categorical variables were presented as counts and percentages. Comparison of continuous variables were performed using *t* test or *Mann-Whitney U* test. Normality was assessed using the *Shapiro-Wilk* test and visually, based on Q-Q plots and histograms. *Kruskal-Wallis* test was used to compare stroke scale scores between multiple groups. Categorical data were compared using the *Pearson* X^2 test. Binary logistic regression with enter method was used to assess associations between baseline clinical variables and the presence of LVO. Adjustment was made for potential confounders, variables with $P < 0.1$ in the univariable analysis were entered to the multivariable logistic regression model. Stroke scales and symptoms were entered in separate models because of multicollinearity. The ability of scales to detect the presence of LVO and optimal cut-off points was assessed using the receiver operating characteristic (ROC) analysis. Area under the curve (AUC) was calculated for each scale and *z* test was used for comparison. Sensitivity (SN), specificity (SP), positive and negative predictive values and accuracy were calculated for different cut-off values. Where appropriate 95% confidence intervals (CI) were presented. A *P* value < 0.05 was considered statistically significant.

Results

During the study period 528 patients were screened, 421 (79.7%) of whom underwent CTA imaging. The mean age of the study cohort was 67.2 ± 13.2 years (48.7% female), 183 patients had LVO (43.5%). Baseline demographics and clinical factors of the two studied groups (according to the presence of LVO) are shown in Table 2. On admission CPSS, d-CPSS and NIHSS scores were significantly higher in those with LVO. The frequency of upper extremity weakness (92.3% vs. 71.8%, $p < 0.001$) and facial palsy (85.8% vs. 69.8%, $p < 0.001$) were higher among LVO patients, but there was no significant difference in the presence of speech disturbance between the groups (77.0% vs. 74.5%, $p = 0.408$). After adjustment for potential confounders (onset-to-assessment time, systolic and diastolic blood pressure, the presence of atrial fibrillation, coronary artery disease and chronic heart failure), significant associations were observed between LVO and: (i) known atrial fibrillation (AF) (OR: 2.564, $p < 0.001$); (ii) systolic blood pressure (SBP) on admission (OR: 0.904 per 10 mmHg increase, $p = 0.046$); (iii) the presence of upper extremity weakness (OR: 5.370, $p < 0.001$); and (iv) the presence of facial palsy (OR: 3.107, $p < 0.001$). Increasing severity of all three symptoms examined in d-CPSS were independently associated with higher odds of LVO presence. Higher CPSS, d-CPSS and NIHSS scores were also associated with increased odds of LVO (detailed results are presented in **Table S1** in the Supplementary material).

Using a ROC analysis, the AUC value of d-CPSS was significantly higher compared to the AUC value of CPSS itself (0.788, 95% CI: 0.743 to 0.832 vs. 0.633, 95% CI: 0.580 to 0.686; $p < 0.001$). The AUC for NIHSS was 0.795 (95% CI: 0.751 to 0.839), which was not

Table 2 Demography and clinical characteristics of the cohort according to the presence of LVO

	LVO present (*N* = 183)	LVO absent (*N* = 238)	*P* value
Age, years, median (IQR)	67 (60–78)	69 (58.75–76.25)	0.652
Gender, female, % (n)	52.5 (96)	45.8 (109)	0.175
NIHSS score, median (IQR)	11 (6–16)	6 (4–9)	**< 0.001**
CPSS score, median (IQR)	3 (2–3)	2 (2–3)	**< 0.001**
d-CPSS score, median (IQR)	5 (3–7)	3 (2–4.25)	**< 0.001**
Onset to ER assessment time, min, median (IQR)	80 (58–121.25)	92 (58.75–137.25)	0.053
On admission SBP, mmHg, mean (SD)	159.0 (30.3)	167.8 (29.9)	**0.003**
On admission DBP, mmHg, mean (SD)	88.2 (16.0)	91.2 (17.1)	0.066
Smoking, % (n), 51 missing	37.0 (57)	31.5 (68)	0.267
Hypertension, % (n), 15 missing	79.5 (140)	79.6 (183)	0.996
Diabetes mellitus, % (n), 19 missing	19.4 (34)	26.0 (59)	0.122
Hyperlipidaemia, % (n), 37 missing	55.7 (93)	55.3 (120)	0.939
Atrial fibrillation, % (n), 23 missing	35.8 (62)	16.9 (38)	**< 0.001**
Coronary artery disease, % (n), 29 missing	25.9 (45)	17.4 (38)	**0.042**
Chronic heart failure, % (n), 25 missing	14.4 (25)	8.1 (18)	**0.047**

Abbreviation: *LVO* Large vessel occlusion; *NIHSS* National Institutes of Health Stroke Scale; *IQR* Interquartile range; *CPSS* Cincinnati Prehospital Stroke Scale; *d-CPSS* Detailed CPSS; *ER* Emergency room; *SBP* Systolic blood pressure; *DBP* Diastolic blood pressure; *SD* Standard deviation

significantly different from the AUC for d-CPSS (p = 0.510). ROC curves are presented in Fig. 1. The optimal cut-off scores to discriminate an LVO were CPSS = 3 (SN: 64.5%, SP: 58.4%), d-CPSS≥5 (SN: 69.9%, SP: 75.2%) and NIHSS≥11 (SN: 64,5%, SP: 87.0%) respectively (**Table S2** in the Supplementary material).

Median NIHSS and d-CPSS scores tended to be higher in patients with LVO in the ICA or M1 segment of MCA compared to those with LVO in the more distal segments of the anterior vascular territory (M2, M3, ACA) (NIHSS: 15 vs. 10, $p < 0.001$; d-CPSS: 7 vs. 5, p = 0.001). Patients with ICA or M1 occlusions had higher median NIHSS and d-CPSS scores than patients with posterior circulation LVO (VA, BA, PCA) (NIHSS: 15 vs. 9, $p < 0.047$; d-CPSS: 7 vs. 4, $p = 0.001$). No significant difference in NIHSS and d-CPSS scores were found between the distal anterior territory LVO and posterior LVO groups ($p = 0.697$ and 0.274 respectively). No differences were recorded in CPSS scores between these groups (median score: 3 respectively; $p = 0.783$) (see Fig. 2).

Discussion

The main finding of our study is that detailed severity assessment of CPSS items (upper extremity weakness, facial palsy and speech disturbance) could significantly increase the ability of CPSS to discriminate the presence of LVO in AIS patients.

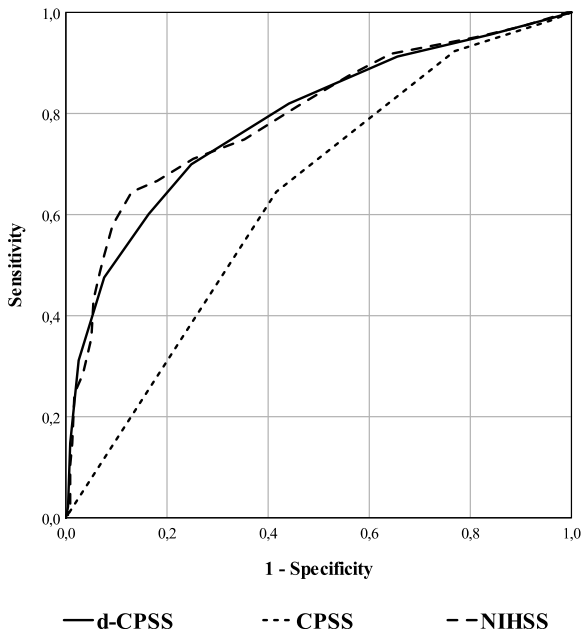

Fig. 1 Receiver operating characteristic curves describing the capability of investigated scales to confirm a large vessel occlusion in acute ischemic stroke: Cincinnati Prehospital Stroke Scale (CPSS), detailed CPSS (d-CPSS) and National Institutes of Health Stroke Scale (NIHSS)

Currently NIHSS is the gold-standard of stroke severity assessment and it has good ability to detect LVO [10]. However, its complexity, time-consuming nature and the need for a special training can make its application in emergency situations or prehospital environment challenging [11]. Our results suggest that a detailed evaluation of CPSS may have similar capabilities as NIHSS to predict the presence of LVO, nonetheless, both NIHSS and d-CPSS still misdiagnose a significant proportion of stroke patients.

The definition of LVO is heterogenous among studies according to different diagnostic and therapeutic approaches [7]. Endovascular thrombectomy is primarily recommended within 6 h from symptom onset in cases of ICA or M1 occlusions, however more distal and posterior occlusions might also be treatable using EVT on a case-by-case basis [8]. Perhaps the main aim of prehospital LVO detection is to identify patients who should undergo adequate EVT eligibility screening early on, therefore the identification of every type of LVO may be useful in this regard.

Our findings are highlighting that stroke severity may related to the location of LVO as NIHSS and d-CPSS scores tended to be the higher in cases of proximal occlusions (ICA or M1) than in those with more distal or posterior occlusions. This result suggests that it may be worth considering proximal LVO in patients with high NIHSS or d-CPSS scores, but it should be noted that posterior LVO may also cause severe strokes, which is also shown by our results (Fig. 2). However, this tendency is not noticeable for CPSS, which points out the benefit of detailed severity analysis in d-CPSS.

Over the past few years, attempts have been made to develop new, shorter and modified LVO detection scales in order to fit them for prehospital use, but only few have been examined extensively yet and only a minority of them have been implemented into the practice of EMS [12]. Since CPSS is one of the most widely used and well-established scales in the field of stroke assessment, it would be obvious to optimize this scale for early LVO detection.

Our results are consistent with previous studies suggesting that certain baseline variables (e.g. known AF, SBP on admission) and the presence of certain symptoms (especially aphasia, neglect and hemiparesis) are related to the presence of LVO [13, 14]. The presence of speech disturbance is not, but its severity was associated with LVO in our study, which highlights how severity assessment may improve stroke scales. Weighting of scale items or adding anamnestic data (such as history of AF) to stroke scales could improve their ability to predict LVO in AIS [14, 15].

Based on previous result and the findings of our study, we think that future studies should focus on optimizing

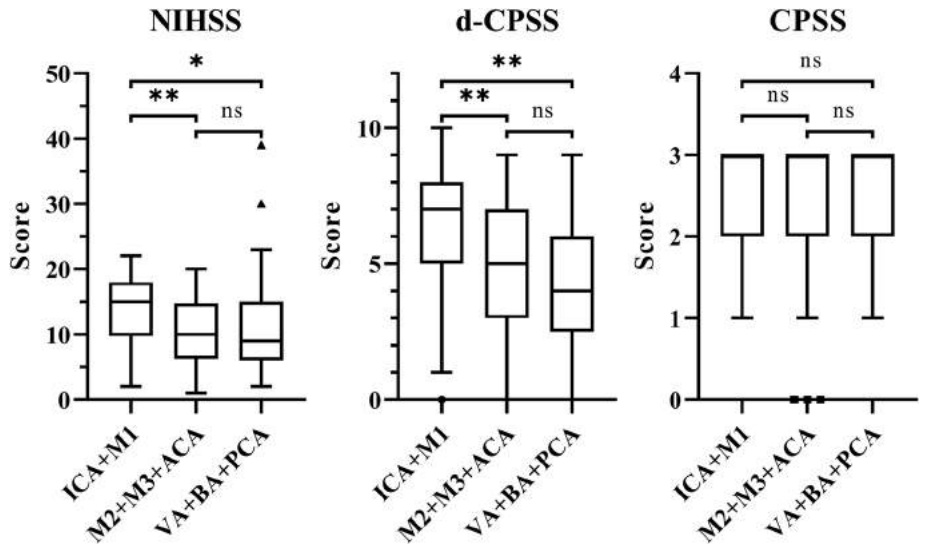

Fig. 2 Differences in National Institutes of Health Stroke Scale (NIHSS), detailed CPSS (d-CPSS) and Cincinnati Prehospital Stroke Scale (CPSS) scores between groups according to the location of large vessel occlusion (LVO): proximal LVO in the anterior vascular territory (internal carotid artery [ICA] and M1 segment of the middle cerebral artery [MCA]; $n = 118$), distal LVO in the anterior circulation (M2 or M3 segments of MCA and anterior cerebral artery [ACA]; $n = 48$) and posterior circulation LVO (vertebral artery [VA], basilar artery [BA] and posterior cerebral artery [PCA]; $n = 17$). Boxes, 25 to 75% interquartile range; central horizontal bars, median; outer horizontal bars, minimum and maximum values excluding outliers (triangle, dot or square icons). Abbreviation: ns, not significant; *, $p \leq 0.05$; **, $p \leq 0.001$

existing stroke scales to LVO detection, instead of developing new ones. More detailed severity assessment or proper weighting of symptoms could be a good perspective and adding items to scales that are strongly associated with LVO could also be beneficial and should be considered. Prehospital prospective validation of these scales and comparison of their predictive power should also be the scope of further studies. Furthermore, the impact of such scales on prehospital pathways in cases of different likelihoods of LVO should also be clarified. Another interesting scope of future stroke scale studies could be not only the detection of LVO but the early recognition of patients potentially eligible for thrombectomy taking other indication criteria (Alberta stroke program early CT score, age, pre-stroke modified Rankin Scale score etc.) into consideration.

The retrospective analysis of prospectively collected data is the main limitation of our study. Besides, we only examined patients with AIS, and we did not have data on patients with haemorrhagic stroke and stroke-mimics. A significant proportion of screened AIS patients did not have CTA imaging, mainly due to minor symptoms (**Table S3** in the Supplementary material), which may have caused selection bias. The assessment of CTA scans was performed by neuroradiologists as a standard of care, however no inter-rater reliability test was performed which might have led to diagnostic bias. It is important to highlight that we did not prospectively validate d-CPSS in this study, however we intend to do so in the future, with the abovementioned considerations in mind.

Conclusions

In conclusion, we can say that detailed severity assessment of symptoms can improve the ability of CPSS to detect LVO in AIS, while remaining simple to perform. Despite the remarkable number of stroke scales developed, future studies should focus on optimizing existing well-established scales, aiming to provide a faster triage and therapeutic intervention for AIS patients with LVO.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12873-020-00360-9.

Additional file 1: Table S1. Associations between baseline characteristics and LVO. **Table S2.** Diagnostic performance of investigated scales according to different cut-off values. **Table S3.** Baseline characteristics of the included and excluded patients.

Abbreviations

EVT: Endovascular thrombectomy; LVO: Large vessel occlusion; AIS: Acute ischemic stroke; EMS: Emergency medical service; CSC: Comprehensive stroke centre; CPSS: Cincinnati prehospital stroke scale; NIHSS: National institutes of health stroke scale; CTA: Computed tomography angiography; ICA: Internal carotid artery; MCA: Middle cerebral artery; ACA: Anterior cerebral artery; VA: Vertebral artery; BA: Basilar artery; PCA: Posterior cerebral artery; d-CPSS: Detailed cincinnati prehospital stroke scale; SD: Standard deviation; IQR: Interquartile range; ROC: Receiver operating characteristic; AUC: Area under the curve; SN: Sensitivity; SP: Specificity; CI: Confidence interval; OR: Odds ratio; AF: Atrial fibrillation; SBP: Systolic blood pressure

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Authors' contributions

GT designed the study, performed literature search, data acquisition and analysis, statistical analysis and wrote the manuscript. PC performed data acquisition, data analysis and reviewed the manuscript. IS performed data collection, data analysis and reviewed the manuscript. EF performed data acquisition and reviewed the manuscript. AA performed data collection, data analysis and literature research. TM performed literature research, statistical analysis, reviewed and approved the manuscript. LS is the guarantor and designed the concepts of the study, interpreted the data, reviewed and approved the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Hungarian Medical Research Council (35403–2/2017/EKU). Written informed consent was obtained from each patient according to the Good Clinical Practice (GCP) guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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RESEARCH ARTICLE Open Access

Relationship between leukocyte counts and large vessel occlusion in acute ischemic stroke

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Abstract

Background: Neuroinflammation plays an important role in the pathogenesis of acute ischemic stroke (AIS) and peripheral leukocyte counts have proved to be independent predictors of stroke severity and outcomes. Clinical significance of large vessel occlusion (LVO) in AIS is increasing, as these patients are potential candidates for endovascular thrombectomy and likely to have worse outcomes if not treated urgently. The aim of our study was to assess the relationship between on admission leukocyte counts and the presence of LVO in the early phase of AIS.

Methods: We have conducted a cross-sectional, observational study based on a registry of consecutive AIS patients admitted up to 4.5 h after stroke onset. Blood samples were taken at admission and leukocyte counts were measured immediately. The presence of LVO was verified based on the computed tomography angiography scan on admission.

Results: Total white blood cell (WBC) and neutrophil counts were significantly higher in patients with LVO than those without LVO ($P < 0.001$ respectively). After adjustment for potential confounders total WBC counts (adjusted OR: 1.405 per 1×10^9/L increase, 95% CI: 1.209 to 1.632) and neutrophil counts (adjusted OR: 1.344 per 1×10^9/L increase, 95% CI: 1.155 to 1.564) were found to have the strongest associations with the presence of LVO. Total WBC and neutrophil counts had moderate ability to discriminate an LVO in AIS (AUC: 0.667 and 0.655 respectively). No differences were recorded in leukocyte counts according to the size of the occluded vessel and the status of collateral circulation in the anterior vascular territory. However, total WBC and neutrophil counts tended to be higher in patients with LVO in the posterior circulation ($p = 0.005$ and 0.010 respectively).

Conclusion: Higher admission total WBC and neutrophil counts are strongly associated with the presence of LVO and has moderate ability to discriminate an LVO in AIS. Detailed evaluation of stroke-evoked inflammatory mechanisms and changes according to the presence of LVO demands further investigation.

Keywords: Ischemic stroke, Large vessel occlusion, Leukocytes, Neutrophils, Neuroinflammation

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Background

Secondary neuroinflammation plays an important role in the pathogenesis of acute ischemic stroke (AIS). Ischemic brain damage elicits systematic inflammatory response and cause a time-dependent activation of peripheral immune cells [1]. Leukocyte counts and ratios (such as neutrophil-to-lymphocyte ratio) in peripheral blood proved to have good prognostic value to predict outcomes and post-stroke complications [2, 3]. Higher leukocyte counts, especially neutrophil elevation is also associated with increasing severity and larger infarct volumes in AIS [4, 5].

Approximately 20 to 40% of AIS cases are caused by large vessel occlusion (LVO), early detection of which is crucial because these patients are potential candidates for endovascular thrombectomy (EVT) and have worse outcomes if not treated urgently [6, 7]. Large vessel occlusion tends to cause more severe strokes and place large cerebral territories at ischemic risk [8]. Therefore, the magnitude of peripheral inflammatory response may be related to the presence of LVO, however previous studies did not investigate this context. The aim of our study was to examine the relationship between on admission total and differential leukocyte counts and the presence of LVO in the early phase of AIS.

Methods

Study population

We have conducted a cross-sectional, observational study based on a prospectively collected registry of consecutive AIS patients admitted up to 4.5 h after symptom onset to the comprehensive stroke centres (CSC) of two university hospitals between October 2017 and October 2019. Blood samples were collected on admission. Total and differential leukocyte counts were measured immediately with an automated hemocytometer (Sysmex XN-1000; Sysmex, Kobe, Japan). We have recorded demographic data, vascular risk factors, baseline clinical variables, baseline laboratory values, medications at stroke onset and times from onset to sample collection for each patient. On admission stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).

Our outcome of interest was the presence of LVO on the admission computed tomography angiography (CTA) scan. According to *Rennert* et al. [9] unilateral, acute occlusion of the internal carotid artery (ICA), M1, M2 and M3 segments of the middle cerebral artery (MCA), A1 and A2 segments of the anterior cerebral artery (ACA), vertebral artery (VA), basilar artery (BA), P1 and P2 segments of the posterior cerebral artery (PCA) and tandem occlusions were considered. Collateral circulation in the anterior vascular territory was evaluated using the multiphase CTA (mCTA) collateral score. Patients were dichotomized into two groups according to good (mCTA 4–5 points) and poor (mCTA 0–3 points) collateral circulation [10]. Evaluation of CTA scan and mCTA collateral score was done by trained neuroradiologist as a standard of care who were blinded to clinical data. Data on early post-stroke infections (PSI) were recorded considering any type of infection occurred within 72 h from stroke onset and were at least Grade 2 in severity according to Common Terminology Criteria for Adverse Events [11].

Patients without CTA assessment or whose laboratory results were missing due to sampling or measurement errors were excluded. We have also excluded patients who had infection or surgery within 2 weeks prior to the stroke, those who had relevant neurological events (transient ischemic attack [TIA] before or seizures after stroke onset), those who take immunomodulatory medications and those with haematological malignancies, as these conditions could influence peripheral leukocyte counts.

Statistical analysis

Data analysis was performed using SPSS (version 26.0, IBM, New York). Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range (IQR) where appropriate. Categorical variables were presented as counts and percentages. In the univariate analysis the comparison of continuous variables was performed using *t* test or *Mann-Whitney U* test. Normality was assessed using the *Shapiro-Wilk* test and visually, based on Q-Q plots and histograms. Categorical data were compared using the *Pearson* X^2 test or the *Fischer* exact test when expected value in any cell was below 5. Univariable and multivariable binary logistic regression analysis was performed to assess the associations between leukocyte counts and the presence of LVO, variables with P value ≤0.1 in the univariable analysis were included in the multivariable model. Total white blood cell (WBC) count, each leukocyte subtype counts and neutrophil-to-lymphocyte ratio (NLR) were entered in a separate model because of multicollinearity. The ability of leukocyte counts to discriminate the presence of LVO was assessed using the receiver operating characteristic analysis, area under the curve (AUC) was calculated for each variable. Optimal cut-off values were calculated using *Youden J* statistics. Odds ratios (OR) and 95% confidence intervals (CI) were presented where appropriate, $P < 0.05$ was considered as statistical significance.

Results

During the study period 514 patients were screened, after exclusions the data of 419 patients were analysed (Fig. 1). The main age of the study cohort was 67.7 ± 12.2 years (43.9% female), 167 patients had LVO (39.9%). Demography and baseline characteristics of the cohort are presented in Table 1. Univariable associations between baseline variables and the presence of LVO are presented in Table S1 of the Supplementary material.

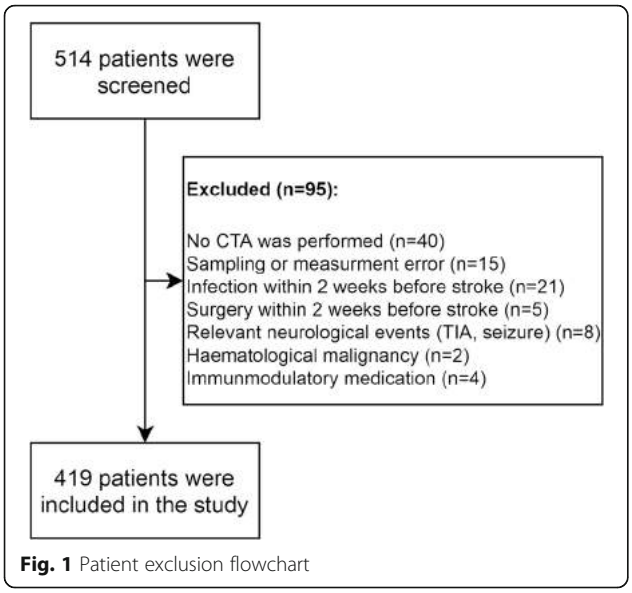

Fig. 1 Patient exclusion flowchart

Higher total WBC counts were recorded in LVO patients than those without LVO (9.27×10^9/L vs. 7.61×10^9/L; $P < 0.001$). Regarding major leukocyte subtypes, median neutrophil counts were significantly higher in the LVO group (6.05×10^9/L vs. 4.69×10^9/L; $P < 0.001$). In contrast, no significant difference was recorded between the groups for the other subtypes (Fig. 2). Neutrophil-to-lymphocyte ratio values was slightly higher in patients with LVO (2.83 versus 2.56; $P = 0.034$). Increasing onset to sample times correlated with higher neutrophil counts (Spearman r, 0.175; $P < 0.001$), lower lymphocyte counts (Spearman r, − 0.229; $P < 0.001$) and increasing NLR values (Spearman r, 0.275; $P < 0.001$).

Univariable binary logistic regression analysis showed associations between on admission total WBC, neutrophil, lymphocyte, monocyte and basophil counts and the presence of LVO. After adjustment for potential confounders independent associations were only found between total WBC, neutrophil, lymphocyte and basophil counts and the presence of LVO (Table 2). There was a trend between increasing NLR values and the presence of LVO in the univariable analysis (OR: 1.079 per 1-point increase, 95% CI: 1.001 to 1.164; $P = 0.048$), but this trend was not present after adjustment for confounders (OR: 1.022 per 1-point increase, 95% CI: 0.924 to 1.131; $P = 0.672$).

Receiver operating characteristic analyses demonstrated moderate ability of total WBC (AUC: 0.667, 95% CI: 0.613 to 0.721; $P < 0.001$) and neutrophil counts (AUC: 0.655, 95% CI: 0.600 to 0.710; $P < 0.001$) to discriminate the presence of LVO. Marginally significant ability was detected for NLR values (AUC: 0.563, 95% CI: 0.505 to 0.621; $P = 0.030$), and the abilities of other leukocyte subtypes to discriminate an LVO were not significant (Figure S1 and Table S2 in the Supplementary material).

Out of 167 LVO patients 147 (88.0%) had occlusion in the anterior circulation (ICA, M1, M2 and M3 segments of MCA, A1 and A2 segments of ACA). Proximal occlusions (defined as occlusion of ICA or M1 segment of MCA) were found at 105 patients (71.4%). These patients had more severe strokes (median NIHSS score 15 vs. 8; $P < 0.001$) compared to those with more distal occlusions (M2 and M3 segment of MCA, A1 and A2 segments of ACA), but no significant differences were recorded in leukocyte counts (Table S3 in the Supplementary material). Data on collateral status was available for 145 patients (98.6%). Good collateral circulation was found in 86 patients (59.3%). Patients with poor collateral circulation had higher NIHSS median scores on admission than those with good collaterals (16 vs. 11; $P < 0.001$), but no significant differences in leukocyte counts were found between the two groups (Table S4 in the Supplementary material).

Twenty patients (12.0%) had LVO in the posterior circulation (VA, BA, P1 and P2 segments of PCA). These patients tended to be younger and had lower median NIHSS scores than patients with LVO in the anterior circulation. Median admission total WBC and neutrophil counts were significantly higher in patients with posterior LVO ($p = 0.005$ and 0.010 respectively). Lymphocyte and monocyte counts were slightly higher in posterior LVO patients; however, differences did not reach the significance level (Table S5 in the Supplementary material).

A total of 100 patients (23.9%) have suffered early post-stroke infections, the majority of which was pneumonia (37%) and urinary tract infections (51%). In the group of non LVO patients on admission neutrophil counts were higher and lymphocyte counts were lower in those with early PSI ($p = 0.003$ and 0.037). However, no differences were found in leukocyte counts according to the development of PSI among patients with LVO (Table S6 in the Supplementary material). No significant differences were recorded in leukocyte counts between the groups of patients with and without hypertension or diabetes. In contrast, lymphocyte, eosinophil and basophil counts were slightly higher in patients with hyperlipidaemia (Table S7 of the Supplementary material).

Discussion

The main finding of our study is that leukocyte counts (especially total WBC and neutrophil) are associated with the presence of LVO in the acute phase of ischemic stroke. Higher total WBC and neutrophil counts could be detected in LVO patients compared to those without LVO, already in the first hours after stroke onset. This highlights the rapid response of systematic inflammatory mechanisms after ischemic brain injury, the extent of which may differ among leukocyte subtypes according to the presence of LVO.

Table 1 Demography and clinical characteristics of the cohort according to the presence of LVO

	LVO present (*N* = 167)	LVO absent (*N* = 252)	*P* value
Demographic characteristics			
Age, years, median (IQR)	68 (61–79)	69 (59–77)	0.258
Gender, female, % (n)	52.1 (87)	38.5 (97)	**0.006**
Elapsed times			
Onset-to-sample time, min, median (IQR)	83 (55–124)	88 (59–139)	0.313
Sample-to-CTA time, min, median (IQR)	16 (6–25)	12 (5–28)	0.684
Parameters on admission			
NIHSS score on admission, median (IQR)	12 (7–17)	6 (4–8)	**< 0.001**
On admission SBP, mmHg, median (IQR)	158 (140–177)	167 (145–180)	**0.004**
On admission DBP, mmHg, median (IQR)	85 (78–96)	90 (80–100)	**0.004**
Body temperature, °C, median (IQR)	36.4 (36.1–36.5)	36.4 (36.2–36.6)	0.069
Blood glucose, mmol/L, median (IQR)	6.89 (5.90–8.10)	6.43 (5.61–8.35)	0.120
INR, ratio, median (IQR)	1.02 (0.95–1.08)	0.99 (0.94–1.04)	**0.003**
Vascular risk factors			
Smoking, % (n), 60 missing	39.1 (52)	31.4 (71)	0.139
Hypertension, % (n), 13 missing	81.6 (133)	77.8 (189)	0.352
Diabetes mellitus, % (n), 19 missing	21.4 (34)	30.3 (73)	**0.049**
Hyperlipidaemia, % (n), 36 missing	50.7 (76)	53.6 (125)	0.568
Atrial fibrillation, % (n), 23 missing	32.9 (52)	17.2 (41)	**< 0.001**
Coronary artery disease, % (n), 33 missing	27.7 (43)	23.4 (54)	0.332
Chronic heart failure, % (n), 23 missing	15.0 (24)	7.6 (18)	**0.019**
Previous stroke/TIA, % (n), 22 missing	17.6 (28)	25.2 (60)	0.074
Malignancy, % (n), 31 missing	16.4 (25)	9.3 (22)	0.036
Therapy at stroke onset			
Antiplatelet, % (n), 23 missing	40.3 (62)	36.0 (87)	0.388
Anticoagulant, % (n), 28 missing	17.6 (27)	9.7 (23)	**0.021**
Lipid lowering, % (n), 23 missing	27.7 (43)	22.4 (54)	0.228
Antihypertensive, % (n), 24 missing	72.9 (113)	66.7 (160)	0.190
Antidiabetic, % (n), 24 missing	16.4 (25)	24.0 (58)	0.070

Abbreviation: *LVO* large vessel occlusion; *NIHSS* National Institutes of Health Stroke Scale; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *IQR* interquartile range; *INR* International Normalized Ratio; *TIA* transient ischemic attack

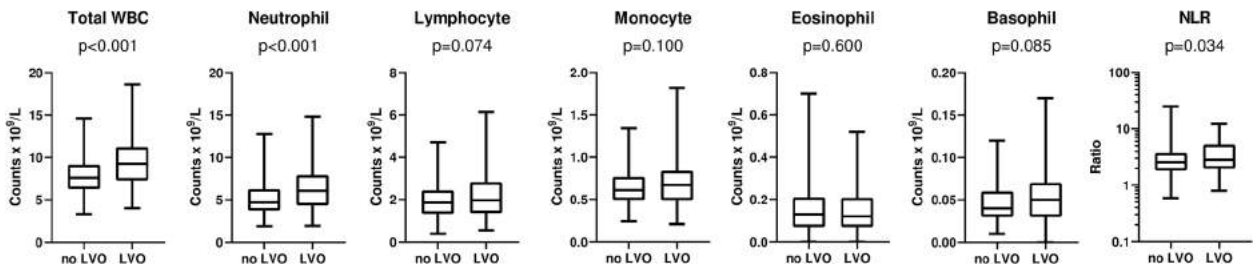

Fig. 2 Comparison of admission total white blood cell (WBC) counts, leukocyte subtype counts and neutrophil-to-lymphocyte ratio (NLR) values in acute ischemic stroke according to the presence of large vessel occlusion (LVO). Boxes, 25 to 75% interquartile range; central horizontal bars, median; outer horizontal bars, minimum and maximum values. Statistics: Mann-Whitney *U* test

Table 2 Associations between leukocyte counts and the presence of large vessel occlusion in acute ischemic stroke

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)[a]	*P* value
Total WBC (1×10^9/L increase)	1.292 (1.187 to 1.405)	**< 0.001**	1.405 (1.209 to 1.632)	**< 0.001**
Neutrophil (1×10^9/L increase)	1.296 (1.181 to 1.421)	**< 0.001**	1.344 (1.155 to 1.564)	**< 0.001**
Lymphocyte (1×10^9/L increase)	1.321 (1.064 to 1.641)	**0.012**	1.631 (1.106 to 2.407)	**0.014**
Monocyte (0.1×10^9/L increase)	1.112 (1.018 to 1.214)	**0.018**	1.048 (0.903 to 1.217)	0.535
Eosinophil (0.1×10^9/L increase)	0.955 (0.807 to 1.131)	0.596	1.043 (0.799 to 1.363)	0.755
Basophil (0.01×10^9/L increase)	1.106 (1.024 to 1.194)	**0.010**	1.296 (1.119 to 1.501)	**< 0.001**

Abbreviation: *OR* odds ratio; *CI* confidence interval; *WBC* white blood cell; *L* litre

[a] Adjusted to sex, on admission NIHSS score, systolic blood pressure, diastolic blood pressure, body temperature, INR value, the presence of diabetes mellitus, atrial fibrillation, chronic heart failure, previous stroke/TIA, malignancy in patient history and anticoagulant or antidiabetic therapy at stroke onset

Proinflammatory factors and pathways are activated within minutes after ischemic onset [12]. Neutrophils are the first leukocyte subtype to be upregulated and subsequently infiltrate the ischemic brain tissue [13]. A previous study has reported that neutrophilia is associated with the volume of ischemic tissue in AIS [5]. The presence of LVO can cause blood supply disturbances in large vascular territories and places substantial cerebral areas under ischemic risk, thereby probably increase the magnitude of proinflammatory response. This may explain why higher total WBC counts (mainly due to the increase in neutrophil counts) can be detected in LVO patients compared to those without LVO in AIS.

Our results are consistent with previous studies highlighting the longitudinal changes in leukocyte activation: elevation of neutrophil and decrease in lymphocyte counts over time [14, 15]. It should be noted that lymphocytes are recruited in the later stages of ischemic brain injury [16]. In our study no differences were found in baseline lymphocyte counts between LVO and non LVO patients, which may be because lymphocytes have not yet been extensively activated at this early stage of AIS. This may also be the reason why NLR, which is well established in stroke prognosis prediction [3, 14, 15], hardly differed between the two groups.

Independent associations between increasing counts of neutrophils, lymphocytes and basophils and higher odds of LVO may represent a broad, bi-directional crosstalk between the ischemic brain and the peripheral immune system, which likely affects almost all participants of the immune response quite early after stroke onset. Interestingly in addition to the strong association between neutrophil counts and LVO, association was also found for basophil counts. Basophil leukocytes have unique role in allergic reactions, parasite infections and autoimmune diseases, however, little data are available on their role in acute stroke. Several years ago, a study has raised the role of basophils in stroke, while another study has confirmed the role of mast cells in regulating the blood-brain barrier following cerebral ischemia [17, 18]. However, it should be noted that automated analysis of leukocyte subtypes with very low number of cells (eosinophil and basophil counts) might be slightly inaccurate. In addition, routine hemogram results (which we also used in this study), despite low concentrations, usually only present two decimal places in the numerical values of absolute basophil counts, hence statistical analysis might be somewhat biased.

Raising the suspicion of LVO in AIS early on is crucial to ensure appropriate imaging methods and early transportation of patients to an EVT capable CSC. Hence reliable blood-based biomarkers would be valuable to detect patients with LVO early on. Our results demonstrated that the ability of leukocyte counts to discriminate the presence of LVO are limited on their own. This may be because changes in peripheral leukocyte counts are not specific for brain damage and can be influenced by many other confounding factors.

Interestingly leukocytes did not associate with the size of the occluded vessel and with the status of collateral circulation in the anterior vascular territory. These findings are partly consistent with the result of a previous study by *Semerano* et al., reporting no significant differences in admission leukocyte counts according to the status of collateral circulation [14]. The interplay between the size of occluded vascular territory and the quality of collateral circulation supplemented by other metabolic and genetic factors are highly related to the size of the core and penumbra within ischemic brain lesions [19, 20]. A study by *Buck* et al. suggests that early changes in peripheral counts are related to the size of bioenergetically compromised brain tissue [5]. Based on our results the magnitude of early peripheral inflammatory response after LVO may not related to the collateral circulation or the size of occluded artery separately. However, the interaction between these factors may affect the size of ischemic core and penumbra, and thus probably the extent of neuroinflammation as well.

A previous study has reported no differences in leukocyte counts between anterior circulation (AC) and posterior circulation (PC) strokes and revealed that NLR values are only correlating with infarct volumes in the

AC territory, but not in the PC. However, this study also assessed AIS patients without LVO [21]. The etiology of LVO in the PC and the composition of such thrombi (including the proportion of leukocytes) are different from those of the anterior circulation LVO [22, 23]. It should also be noted that the distribution of neuronal and non-neuronal cells is different in the various areas of the human brain [24, 25], including the proportion of microglia and astrocytes, which may also influence the extent of neuroinflammation. In our study higher median neutrophil and slightly higher lymphocyte and monocyte counts in the posterior LVO group may be related to these conditions. Further studies are needed to assess the relationship between the location of ischemia and the extent of neuroinflammation.

The rapidly evolving, new options in the treatment of AIS due to LVO facilitate the need for better understanding the nature of this type of stroke. Reliable blood based LVO biomarkers would be valuable to detect patients with high likelihood of LVO early on. Such a biomarker could be useful for emergency medical services and emergency department personnel to organize optimal patient pathways and to allocate necessary diagnostic and therapeutic resources as soon as possible. Based on our results leukocyte counts are not sufficiently suitable for this purpose, due to low sensitivity and specificity. However, these findings may warrant further investigation to explore the relationship between LVO and neuroinflammation in details. The scope of further studies could be the interplay between LVO and well-established inflammatory markers such as acute phase proteins, cytokines, cell adhesion molecules, matrix metalloproteinases, damage-associated molecular patterns, markers of oxidative stress, markers of the complement pathway and annexins [1, 26–29]. Inflammatory markers may also be good candidates to find suitable blood-based biomarkers for early LVO detection [30]. Further, larger scale studies are also needed to examine alterations in neuroinflammation according to the location and the volume of cerebral infarction and ischemic penumbra. A recent study has found that NLR values can be useful biomarkers to predict the occurrence of PSI in AIS patients [31]. Although our result only showed differences in NLR values among non LVO patients and no differences were observed in the group of LVO patients. This highlights that the presence of LVO may affect the prognostic ability of NLR to predict PSI, further investigations may be required to clarify this.

As previously discussed, the changes in peripheral leukocyte counts may be epiphenomenal to brain damage. However, previous studies have revealed that higher leukocyte counts in healthy patients are also associated with the increased risk of ischemic stroke events [2, 32]. Further investigation may clarify how peripheral leukocyte counts are related to the risk of suffering an LVO is AIS, or how it may affect the composition of the thrombi.

The main strength of our study is the thorough investigation of multiple leukocyte subtypes in a reasonable number of patients from two university centres. However, our study also has some limitations. The observational, cross-sectional design did not allow to assess cause-effect relationship. No assessment of ischemic lesion volume or of the size of ischemic core and penumbra was made on admission. Although we attempted to exclude patients whose leukocyte counts may be affected by other conditions, we cannot be sure that all such patients have been excluded. There is a chance of other, unknown confounding factors that were not considered in this study. No CTA was performed in almost 8% of screened cases (mainly due to minor symptoms or contraindications), which might lead to selection bias. The small number of patients with posterior LVO resulted a probably underpowered subanalysis. Finally, it is important to emphasize that NIHSS may not appropriately assess the spectrum and severity of PC related neurologic deficits. Therefore, NIHSS scores are usually lower in patients with PC territory strokes than patients with stroke in anterior circulation [33, 34].

Conclusion

Our study demonstrates that higher on admission total WBC and neutrophil counts are strongly associated with the presence of LVO and has moderate ability to discriminate an LVO in AIS. Further studies are needed to ensure these findings in larger cohorts and to explore the detailed mechanisms of changes in inflammatory pathways after AIS according to the presence of LVO.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-020-02017-3.

Additional file 1: Table S1. Univariable associations between baseline characteristics and the presence of LVO in acute ischemic stroke. **Figure S1.** Receiver operating characteristic curves demonstrating the ability of total and differential leukocyte counts to discriminate the presence of LVO in AIS. Area under the curve (AUC) values and 95% confidence intervals are presented. **Table S2.** Capability of leukocyte counts to detect large vessel occlusion in acute ischemic stroke. **Table S3.** Baseline characteristics of patients according to the site of occlusion in the anterior circulation. **Table S4.** Baseline characteristics of patients according to collateral status in the anterior circulation. **Table S5.** Demography and clinical characteristics of LVO patients according to the location of LVO. **Table S6.** Differences in leukocyte counts according to the development of early post-stroke infections (PSI). **Table S7.** Differences in leukocyte counts according to the presence of cardiovascular risk factors.

Abbreviations

AIS: Acute ischemic stroke; LVO: Large vessel occlusion; EVT: Endovascular thrombectomy; CSC: Comprehensive stroke centre; NIHSS: National Institutes of Health Stroke Scale; CTA: Computed tomography angiography; ICA: Internal carotid artery; MCA: Middle cerebral artery; ACA: Anterior

cerebral artery; VA: Vertebral artery; BA: Basilar artery; PCA: Posterior cerebral artery; mCTA: multiphase computed tomography angiography; PSI: Post-stroke infection; TIA: Transient ischemic attack; SD: Standard deviation; IQR: Interquartile range; WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio; AUC: Area under the curve; OR: Odds ratio; CI: Confidence interval; AC: Anterior circulation; PC: Posterior circulation

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None.

Authors' contributions
GT designed the study, performed literature search, data acquisition and analysis, statistical analysis and wrote the manuscript. ZNK performed data acquisition, data analysis and reviewed the manuscript. ZS performed data acquisition, data analysis and reviewed the manuscript. IS performed literature search, data acquisition and reviewed the manuscript. LC designed the concepts of the study, interpreted the data, reviewed and approved the manuscript. LS is the guarantor and designed the concepts of the study, interpreted the data, reviewed and approved the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study protocol was approved by the Hungarian Medical Research Council (35403–2/2017/EKU). Written informed consent was obtained from each patient according to the Good Clinical Practice (GCP) guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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Optimization of Large Vessel Occlusion Detection in Acute Ischemic Stroke Using Machine Learning Methods

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Abstract: The early detection of large-vessel occlusion (LVO) strokes is increasingly important as these patients are potential candidates for endovascular therapy, the availability of which is limited. Prehospital LVO detection scales mainly contain symptom variables only; however, recent studies revealed that other types of variables could be useful as well. Our aim was to comprehensively assess the predictive ability of several clinical variables for LVO prediction and to develop an optimal combination of them using machine learning tools. We have retrospectively analysed data from a prospectively collected multi-centre stroke registry. Data on 41 variables were collected and divided into four groups (baseline vital parameters/demographic data, medical history, laboratory values, and symptoms). Following the univariate analysis, the LASSO method was used for feature selection to select an optimal combination of variables, and various machine learning methods (random forest (RF), logistic regression (LR), elastic net method (ENM), and simple neural network (SNN)) were applied to optimize the performance of the model. A total of 526 patients were included. Several neurological symptoms were more common and more severe in the group of LVO patients. Atrial fibrillation (AF) was more common, and serum white blood cell (WBC) counts were higher in the LVO group, while systolic blood pressure (SBP) was lower among LVO patients. Using the LASSO method, nine variables were selected for modelling (six symptom variables, AF, chronic heart failure, and WBC count). When applying machine learning methods and 10-fold cross validation using the selected variables, all models proved to have an AUC between 0.736 (RF) and 0.775 (LR), similar to the performance of National Institutes of Health Stroke Scale (AUC: 0.790). Our study highlights that, although certain neurological symptoms have the best ability to predict an LVO, other variables (such as AF and CHF in medical history and white blood cell counts) should also be included in multivariate models to optimize their efficiency.

Keywords: acute ischemic stroke; large-vessel occlusion; prehospital care; stroke scales; machine learning

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1. Introduction

Large-vessel occlusion (LVO) is present in 20–40% of acute ischemic stroke (AIS) cases, resulting in more severe symptoms and worse outcomes if not treated urgently [1]. In addition to well-established intravenous thrombolysis (IVT), experience using endovascular thrombectomy (EVT) to treat AIS patients with LVO is increasing [2]. However, the number of EVT-capable institutions, so-called comprehensive stroke centres (CSC), is limited [3]. The reliable detection of an LVO is currently only possible using radiological methods, primarily computed tomography angiography (CTA), which is mostly available in hospitals only [4].

Regarding patient pathways, two approaches have emerged. According to the first approach, AIS patients should first be transported to the nearest IVT-capable primary stroke center (PSC). If the presence of an LVO is confirmed, the patient is referred and

transported to a CSC for EVT (drip-and-ship approach). In these cases, IVT could be started as soon as possible; however, the time spent in the PSC and the time of transportation may significantly delay the administration of EVT [5]. It should also be considered that IVT is only moderately effective if an LVO is present [6]. The second approach is to transport patients with a high likelihood of LVO directly to a CSC (mothership approach). This may slightly delay the start of the IVT due to the longer transportation time; however, it could significantly reduce the time to EVT administration [5].

One of the current major limitations of applying the mothership approach routinely is the deficit of easy-to-perform and sufficiently reliable prehospital methods to identify LVO [7]. Current stroke scales primarily focus on the assessment of clinical symptoms; however, other factors such atrial fibrillation (AF) in medical history or systolic blood pressure (SBP) may also have good predictive value [8,9]. The aim of our study was to comprehensively assess the associations between clinical symptoms, medical history variables, vital parameters, laboratory values and the presence of LVO in AIS, and to develop an optimal combination of them using machine learning tools and methods.

2. Methods

2.1. Study Cohort

A cross-sectional, observational study was performed based on a prospective registry of consecutive AIS patients presenting up to 4.5 h after symptom onset at the CSC of three university hospitals in Hungary (Figure S1 of the Supplementary Materials) between November 2017 and July 2019. Data on medical history were collected from past medical documentation and based on personal interview with the patient and relatives upon arrival to the emergency department (ED) when possible. Baseline vital parameters and laboratory values were measured as a part of standard care. On admission, stroke symptoms and severity were assessed using the National Institutes of Health Stroke Scale (NIHSS). Detailed information on the registry is available in the Supplementary Materials.

2.2. Outcome

Our outcome of interest was the presence of LVO on the on-admission CTA scan. Acute occlusions of the internal carotid artery (ICA), M1, M2 and M3 segments of the middle cerebral artery (MCA), A1 and A2 segments of the anterior cerebral artery (ACA), P1 and P2 segments of the posterior cerebral artery (PCA), basilar artery (BA), vertebral artery (VA) and tandem occlusions were considered according to Rennert et al. [10]. Scans were evaluated by trained neuroradiologist (who were blinded to clinical parameters) as a part of standard care. Patients who did not undergo CTA were excluded.

2.3. Statistical Analysis

Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range (IQR). Normality was assessed using the Shapiro–Wilk test and visually, based on Q–Q plots and histograms. Categorical variables were presented as counts and percentages. In the univariate analysis, a comparison of continuous variables was performed using a *t*-test or Mann–Whitney U test. Categorical data were compared using the Pearson X^2 test or the Fischer exact test where appropriate. Receiver operating curve (ROC) analysis was used to assess the ability of variables and models to discriminate the presence of an LVO. The optimal cut-off score was calculated using the Youden J index.

2.4. Data Analysis

Data on 41 variables were collected and used for the modelling task. During preprocessing, variables were excluded from the analysis based on (i) having more than 20% missing values (Body temperature, SpO_2), (ii) larger than 0.9 correlation with another variable (Hgb), and/or (iii) near zero variance (Extinction). Rows with missing values were omitted from the analysis. Variables were further processed with Yeo Johnson transformation to reduce skewness in lab variables and variables were centered and scaled to obtain

statistical uniformity for machine learning (ML) modeling. Smote resampling was used to balance the sample difference in LVO and non-LVO groups. Grid search was used to select optimal hyperparameter for the models. For final model validation, a randomly selected hold-out test cohort was used consisting of 20% of the patient population. To assess the generalizability of the models a 10-fold cross validation was used.

Four covariate groups were created based on the nature of variables including 6 baseline and demographic variables, 9 medical history variables with yes/no values, 10 laboratory variables with numeric values and 14 symptom-related variables with values on an ordinal scale. The predictive ability of these groups of variables was measured using binary logistic regression analysis and ROC analysis was performed based on probability values.

Feature selection was carried out using least absolute shrinkage and selection operator (LASSO) regression to determine the optimal combination of variables to predict LVO [11]. For further ML modeling, the selected variables were used only as covariates. The performance of three ML models—namely, logistic regression, random forest, and neural network—and elastic net method was compared with each other and with a logistic regression model with NIHSS as the only covariate using area under the ROC curve (AUC) statistic (see Figure S2 in the Supplementary Materials). For neural network modeling, a multi-layer perceptron was used with one hidden layer of four neurons. Analysis was carried out in SPSS (version 26, IBM, New York, NY, USA) and R using the Caret ML library [12,13].

3. Results

A total of 646 patients were screened during the study period, 526 (81.4%) of whom underwent CTA imaging and were finally included in the analysis (46.2% female). The mean age of the study cohort was 68 ± 13 years; 227 patients had LVO (43.2%). The baseline characteristics of the study cohort and the ability of the variables to distinguish an LVO are presented in Table 1. NIHSS had the best discriminative ability with an AUC of 0.783 (95% CI: 0.742–0.824); the optimal cut-off value of NIHSS to detect an LVO was ≥9 points (sensitivity: 70.9%; specificity: 72.6%). The prevalence of several symptoms and the severity of symptoms were higher among LVO patients (Table 2.) The distribution of LVO location was as follows: 54 (23.8%) ICA, 74 (32.6%) MCA M1, 52 (22.9%) MCA M2, 4 (1.8%) MCA M3, 2 (0.9%) ACA, 1 (0.4%) PCA, 12 (5.3%) BA, 11 (4.8%) VA, and 17 (7.5%) tandem occlusions. The etiology of LVO strokes was more commonly cardioembolism and less commonly small-vessel disease, as compared to non-LVO cases (Table 1).

Table 1. Baseline characteristics of the cohort according to the presence of LVO.

	LVO Present (*n* = 227)	LVO Absent (*n* = 299)	*p* Value	AUC (95% CI)
Demographic characteristics				
Age, years, median (IQR)	68 (61–79)	69 (59–77)	0.231	0.524 (0.467–0.582)
Gender, female, % (n)	49.8 (113)	43.5 (130)	0.151	0.530 (0.474–0.587)
Elapsed times				
Onset-to-ER assessment time, min, median (IQR)	83 (58–124)	88 (59–135)	0.110	-
ER assessment-to-CTA time, min, median (IQR)	14 (6–23)	17 (6–32)	0.043	-
Parameters on admission				
NIHSS score on admission, median (IQR)	12 (8–16)	6 (4–9)	<0.001	0.783 (0.742–0.824)
On admission SBP, mmHg, median (IQR)	160 (140–178)	169.5 (145–185)	0.005	0.420 (0.365–0.474)
On admission DBP, mmHg, median (IQR)	86 (78–99)	90 (80–100)	0.034	0.456 (0.401–0.511)
Heart rate, 1/min, median (IQR)	82 (72–93)	80 (71–92)	0.251	0.533 (0.477–0.589)
SpO_2, %, median (IQR)	97 (96–98)	97 (96–99)	0.025	0.447 (0.345–0.550)
Body temperature, °C, median (IQR)	36.4 (36.0–36.5)	36.5 (36.2–36.6)	0.008	0.372 (0.270–0.474)
BMI, kg/m^2, median (IQR)	25.78 (23.34–30.12)	26.72 (23.46–31.21)	0.125	0.447 (0.392–0.502)

Table 1. *Cont.*

	LVO Present (*n* = 227)	LVO Absent (*n* = 299)	*p* Value	AUC (95% CI)
Laboratory parameters				
Blood glucose, mmol/L, median (IQR)	6.90 (5.91–8.28)	6.50 (5.60–8.30)	0.084	0.548 (0.495–0.602)
INR, ratio, median (IQR)	1.03 (0.96–1.10)	1.00 (0.95–1.05)	<0.001	0.587 (0.534–0.640)
CRP, mg/L, median (IQR)	3.30 (1.50–7.20)	2.98 (1.55–5.80)	0.262	0.540 (0.486–0.595)
WBC, 10^9/L, median (IQR)	8.62 (6.88–10.62)	7.94 (6.55–9.61)	0.005	0.583 (0.530–0.636)
Platelet, 10^9/L, median (IQR)	233.5 (195–271)	224 (186–267)	0.078	0.532 (0.479–0.586)
Haematocrit, %, median (IQR)	40.0 (37.6–42.8)	41.1 (38.0–44.0)	0.034	0.449 (0.396–0.503)
Haemoglobin, g/dL, median (IQR)	138 (126–146)	141 (130–152)	0.005	0.433 (0.380–0.486)
Creatinine, µmol/L, median (IQR)	82 (69–99)	83 (69–101)	0.561	0.485 (0.431–0.539)
BUN, mmol/L, median (IQR)	6.26 (4.80–8.19)	6.10 (4.68–7.63)	0.173	0.527 (0.473–0.581)
AST, U/L, median (IQR)	20 (16–24)	20 (16–25)	0.480	0.476 (0.422–0.530)
ALT, U/L, median (IQR)	15 (11–22)	16 (12–22.5)	0.381	0.466 (0.412–0.520)
Presence of vascular risk factors				
Smoking, % (n)	34.9 (66)	31.4 (85)	0.424	0.517 (0.460–0.574)
Hypertension, % (n)	81.4 (180)	80.4 (234)	0.768	0.496 (0.439–0.553)
Diabetes mellitus, % (n)	21.5 (47)	28.6 (82)	0.069	0.475 (0.418–0.531)
Hyperlipidaemia, % (n)	59.2 (125)	58.3 (161)	0.840	0.495 (0.438–0.552)
Atrial fibrillation, % (n)	35.8 (78)	17.5 (50)	<0.001	0.590 (0.533–0.647)
Coronary artery disease, % (n)	29.6 (64)	21.9 (61)	0.051	0.535 (0.478–0.592)
Chronic heart failure, % (n)	17.9 (39)	8.9 (25)	0.002	0.549 (0.492–0.606)
Previous stroke/TIA, % (n)	21.0 (46)	23.2 (66)	0.564	0.494 (0.438–0.551)
Malignancy, % (n)	15.6 (33)	11.7 (33)	0.217	0.520 (0.462–0.577)
Etiology (TOAST), % (n)			<0.001	
Large-artery atherosclerosis	26.4 (60)	27.8 (83)		
Cardioembolism	51.1 (116)	20.7 (62)		
Small vessel disease	0 (0)	21.7 (65)		
Other determined origin	0.4 (1)	5.0 (15)		
Undetermined etiology	22.0 (50)	24.7 (74)		

Abbreviation: LVO, large-vessel occlusion; AUC, area under the curve; CI, confidence interval; IQR, interquartile range; ER, emergency room; CTA, CT angiography; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; INR, International Normalized Ratio; CRP, C-reactive protein; WBC, white blood cell; BUN, blood urea nitrogen; AST, aspartate-aminotransferase; ALT, alanine-aminotransferase, TIA, transient ischemic attack.

Table 2. Distribution of symptom severity and prevalence as a function of LVO.

Symptoms (NIHSS Items)	Points			Presence			AUC (95% CI)
	LVO Present	LVO Absent	*p* Value	LVO Present	LVO Absent	*p* Value	
1A. Level of consciousness (LOC)	0 (0–0)	0 (0–0)	0.003	12.8%	5.4%	0.003	0.537 (0.487–0.587)
1B. LOC questions	1 (0–2)	0 (0–1)	<0.001	56.4%	33.1%	<0.001	0.638 (0.589–0.686)
1C. LOC commands	0 (0–2)	0 (0–0)	<0.001	47.1%	24.7%	<0.001	0.618 (0.569–0.667)
2. Gaze	0 (0–2)	0 (0–0)	<0.001	46.3%	15.1%	<0.001	0.666 (0.617–0.714)
3. Visual fields	0 (0–2)	0 (0–0)	<0.001	47.6%	21.4%	<0.001	0.632 (0.583–0.681)
4. Facial palsy	2 (1–2)	1 (0–2)	<0.001	85.9%	70.9%	<0.001	0.644 (0.597–0.692)
5. Arm weakness	3 (1–4)	1 (0–2)	<0.001	91.2%	72.6%	<0.001	0.738 (0.695–0.782)
6. Leg weakness	3 (1–3)	1 (0–2)	<0.001	83.3%	64.9%	<0.001	0.717 (0.671–0.762)
7. Limb ataxia	0 (0–0)	0 (0–0)	0.001	7.0%	17.4%	<0.001	0.450 (0.401–0.499)
8. Sensory deficit	0 (0–1)	0 (0–1)	0.688	26.9%	30.1%	0.418	0.492 (0.442–0.542)
9. Language/aphasia	1 (0–2)	0 (0–1)	<0.001	56.8%	37.1%	<0.001	0.634 (0.586–0.683)
10. Dysarthria	0 (0–1)	0 (0–1)	0.893	37.0%	38.1%	0.792	0.497 (0.447–0.547)
11. Extinction/inattention	0 (0–0)	0 (0–0)	0.001	9.7%	2.7%	0.001	0.535 (0.485–0.585)

Abbreviation: LVO, large-vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; AUC, area under the curve; CI, confidence interval.

Regarding predefined covariate groups, the combination of symptoms had the best ability to discriminate an LVO (AUC: 0.779 on hold-out set and 0.785 after 10-fold cross validation; $p < 0.001$, respectively), followed by medical history (AUC: 0.602 and 0.686; $p < 0.001$), laboratory values (AUC: 0.637 and 0.641; $p < 0.001$) and baseline and demographic parameters (0.599 and 0.567; $p < 0.001$). NIHSS had an AUC of 0.783 and 0.790 after cross validation ($p < 0.001$).

Data Driven Analysis

The results of the covariate group analysis showed that, over a combination of symptoms (NIHSS items), further variables could have potential discriminative power for LVO, especially among the anamnestic and laboratory related variables. Thus, we explored the potential of a mixed-covariate model for discriminate LVO patients using data-driven analysis and a variable selection process (see Supplementary Figure S2).

In the initial dataset, there was a relatively high amount of missing data (4% of the dataset), mainly at random properties (see Supplementary Table S1 and related comments) and was mainly concentrated in a few variables. Our analysis showed that imputing missing values would negatively affect the performance of the final models (see Supplementary Materials); thus, patients with missing values were omitted from the analysis and a two-step approach was followed to maximize sample size for modelling. After preprocessing the dataset, all samples with missing values were omitted ($n = 293$) and lasso regression was used to select the most predictive variables to LVO. Then, the final data-driven analysis was carried out using the original dataset, filtering only to these selected variables, and omitting patients with missing values ($n = 483$). During feature selection, a total of nine variables were selected for subsequent ML modelling (six symptom variables: language, facial palsy, LOC questions, visual field disturbance, gaze palsy and upper limb weakness; two medical history variables: atrial fibrillation (AF) and chronic heart failure (CHF); and one laboratory value: white blood cell (WBC) count).

Including the selected variables, four ML tools were applied: random forest (RF), logistic regression (LR), elastic net method (ENM), and simple neural network (SNN). The calculated AUC values on the hold-out set and after 10-fold cross-validation were 0.986 and 0.736 for the RF model, 0.816 and 0.775 for the LR, 0.813 and 0.773 for ENM and 0.808 and 0.772 for SNN.

4. Discussion

Our study has highlighted that the severity of certain neurological symptoms may have the best ability to predict an LVO, but our results also pointed out that other variables (notably, AF or CHF in medical history and on-admission WBC values) also have good predictive ability.

The clinical presentation of LVO in AIS is highly dependent on the site of occlusion [10]. Currently, NIHSS is the "gold-standard" for stroke severity assessment and has the best ability to detect LVOs—the previously reported AUC values were similar to our findings [7]. Despite the wide spectrum of symptoms assessed in NIHSS, it still occasionally fails to detect and assess posterior territory strokes appropriately. For short stroke scales, the challenge is to examine the full spectrum of symptoms corresponding to different vascular territory strokes without the process becoming too complicated. The results of a retrospective study suggested that cortical symptoms are better predictors of LVO than motor symptoms, but their combination has the highest accuracy [14]. Our findings showed that upper and lower extremity weakness had the best discriminative abilities, followed by gaze disturbance and facial palsy. However, it should be noted that the majority of the LVO cases in our study involved anterior circulation; therefore, the findings should be interpreted accordingly.

The use of ML methods to optimize prediction models is emerging in the field of stroke research to maximize the predictive performance of variable combinations [15]. Based on the previously mentioned findings, it is not surprising that feature selection using

the LASSO method in our study mainly selected symptom variables (motor and cortical symptoms as well) for modeling. The selected symptoms represent a wide spectrum of LVOs in various vascular regions, as they mostly occur in anterior and posterior territory strokes as well. In addition, variables that had a strong association with the presence of LVO in the univariate analysis were selected—notably, AF, CHF, and WBC count. In a recent article by Wang et al. using a similar approach, a set of variables were initially selected based on research in the literature and clinical relevance for subsequent feature selection [15]. In contrast, in our study, we included all variables that were available in adequate quality from a multi-center registry. However, after feature selection, it appeared in both studies that, although symptoms provide the backbone of the models, other types of variables may be important factors and should be included as well.

Including these variables, all applied ML tools performed well on the full set of data (AUC > 0.800); however, after 10-fold cross validation, the performance of each markedly decreased and the AUC values of three models (RF, LR and ENM) ranged from 0.775 to 0.772; the SNN lagged slightly with an AUC of 0.736. The study by Wang et al. has applied a similar approach to optimize LVO prediction, and their results regarding the performance of ML tools were quite similar. The abilities of stroke scales for LVO detection has also been reported generally around this range in previous retro- and prospective studies [7,8,15].

Over recent years, a plethora of LVO detection methods have been developed and examined. For a tool to be applicable for prehospital use, several criteria must be met, such as high diagnostic accuracy, easy and fast application, user-friendliness, and cost-effectiveness [16]. The NIHSS may be too complex for routine prehospital use; therefore, the use of shorter scales is warranted at the cost of some reduction in accuracy. It should also be noted that some symptoms are not easily examinable by non-neurologists, such as gaze disturbance and visual field loss, two symptoms that were also selected for modelling in our study and, therefore, may limit prehospital applicability [17]. However, the inclusion of non-symptom variables is not common in LVO scales yet.

Regarding patient history and clinical parameters, a study has found that the history of AF and SBP $\leq$ 170 mm Hgmm are independent predictors of LVO in AIS, and these correlations were also confirmed by our results [9]. There have been some attempts to attach AF to various scales with heterogeneous results. A retrospective analysis has shown no improvement in the accuracy of four broadly used short stroke scales when AF was added as an element [18]. In contrast, another study found that the adding of AF to the Los Angeles Motor Scale (LAMS) could significantly improve its ability to detect LVOs [19]. In addition, several recently created LVO scales include AF as a variable [20,21]. The utility of including SBP in stroke scales is much less studied. A prospective observational study demonstrated that SBP may help to identify patients potentially eligible for EVT [22]. Chronic heart failure is an independent risk factor of stroke, and other diseases should be considered (such as AF, CAD and valvular disease) that are predisposing factors for CHF and AIS [23]. The association between CHF and the presence of LVO probably represents a wide spectrum of confounding and additive conditions. Therefore, CHF might be interchangeable or be combinable with the aforementioned cardiac diseases. Future studies may use a combined variable containing all predisposing cardiac diseases at once.

Despite the amount of biomarker research in the field of AIS, so far, only a few markers that are potentially suitable for LVO detection have been identified. Our group has previously found an association between WBC counts and the presence of LVO which is also confirmed by the current investigation; however, the studied population was partially overlapping [24]. Other studies have revealed independent associations between protein markers (such as serum troponin and D-dimer) [25,26]. However, to date, they are not routinely used for screening in the prehospital setting.

Univariate analyses in our study revealed that the strength of associations between most variables and LVO is mild to moderate, the reason for which is probably that associations are affected by many known and unknown confounding factors (e.g., LVO location regarding symptoms). It is also clear that a combination of variables with such specificity

cannot exceed a certain accuracy. The study highlighted that machine learning tools are extremely useful to reduce the dimensions of large datasets, and to assess and optimize predictive ability. However, the result should also be approached and interpreted from clinical and practical aspects as well, since the heterogeneity of clinical presentations may limit the clinical utility of these methods.

Molecular biomarkers supporting the clinical care of stroke, especially its classification and objective monitoring, are yet to be available. A better understanding of the biochemical and pathophysiological pathways and processes associated with LVO is needed to identify more specific biomarkers. Screening for a large number of potential biomarkers, i.e., the "omics" approach, and the combined analysis of multi-omic data, including proteomic, more recently glycomic, and metabolomic data, is a particularly promising solution for identifying new biomarkers. Extended stroke registers and multi-omic databases combining clinical and biomedical data are needed together with data analysis platforms that can facilitate to organize and analyze large amounts of data with modern machine learning methods, to identify new, complex biomarkers that support stroke typing and therapy monitoring [27,28].

It should also be noted that the definition of LVO is quite heterogenous, and previous studies and clinical trials have used various criteria for LVO classification [10]. Mechanical thrombectomy cannot be performed in some cases that are radiologically considered as cases of LVO. However, from a clinical aspect, the 2019 AHA/ASA stroke guidelines recommend considering MT in a wide spectrum of LVO cases. In the case of distal occlusions (e.g., MCA M2 and M3) and occlusions in the posterior circulation, the decision to indicate MT should be made on a case-by-case basis, weighing the potential costs and benefits [29]. Consequently, the scope of future studies should not only be the detection of LVO, but to detect the eligibility to MT early on.

Anterior and posterior circulation territory occlusions and strokes may show quite different clinical appearances and have different predisposing factors [30,31]. The NIHSS also investigates more anterior territory stroke symptoms and, thus, occasionally fails to correctly assess the severity of posterior strokes [32]. Although we aimed to create a universal LVO detection model in our study, we considered all types of LVO. However, for future studies, it may be worthwhile to optimize the prediction of anterior and posterior circulation LVOs separately in a similar way using ML methods, due to the aforementioned differences. Another possible direction is that, after performing a method optimized for anterior circulation LVOs, a method optimized for a posterior circulation LVOs should follow.

The main strength of our study is the comprehensive assessment of real-life, prospectively collected data from multiple centers using novel statistical methods that are not extensively used in medical research yet. However, our study also has some limitations. Firstly, the cross-sectional design only allows to assess associations but not causality. It is important to emphasize that potentially important variables may not have been included to the analyses due to multiple reasons (e.g., a large amount of missing data, or variables were not available in the stroke registry) which could have caused bias. In this study, we used 10-fold cross validation to estimate the generalizability and the true accuracy of the models; however, validation using an external dataset is needed to clinically validate our findings. Finally, ML tools function the best when applied to large datasets ("big-data"), which our dataset did not necessarily match.

5. Conclusions

The need for accurate LVO detection scales is emerging. A novel approach for this could be the machine-learning-based development of prediction models. Our study confirmed this, highlighting that neurological symptoms are the most useful to increase the accuracy of prediction models, but other types of variables (certain medical history data, and laboratory values) should also be included to maximize efficiency.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/life12020230/s1, Figure S1: Location of participating centres and distribution of patient enrolment; Table S1: Proportions of missing values; Figure S2: Chart of analysis workflow; Figure S3: Comparison of the distribution of variables between samples with- and without missing values; Table S2: Comparison of variables distributions of samples of the original dataset vs dataset used for variable selection; Table S3: Comparison of variables distributions of samples of the original dataset vs dataset used for model comparison after feature selection; Figure S4: Effect of missing value imputation methods (predictive mean matching (PMM), midas touch, random forest, CART, random sampling, omitting missing values) on the performance of predicting LVO (measured by AUC) of the different imputation methodologies

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Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient privacy considerations (HIPPA).

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