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IMPACT OF COVID-19 ON ISCHEMIC STROKE CARE IN HUNGARY

PhD thesis

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List of Abbreviations

ABI: absolute benefit increase;

ACE1: angiotensin-converting enzyme 1

ACE2: angiotensin-converting enzyme 2

BBB: blood-brain barrier

BOSC: Big Data Observatory Platform for Stroke of China

CC: Spearman rank correlation coefficient

CI: confidence interval

CNS: central nervous system

CSSG: COVID-19 Stroke Study Group

CT: computed tomography

COVID, COVID-19: Coronavirus disease 2019

DIT: door-to-imaging time

DNT: door-to-needle time

ESO: European Stroke Organization

EVT: endovascular treatment/therapy for ischemic stroke; mechanical thrombectomy

GNI: gross national income

HBCs: Homogén Betegségcsoportok; Hungarian adaptation of Diagnosis Related Groups

ICD-10: 10th version of the International Statistical Classification of Diseases and Related Health

ICU: intensive care unit

IQR: interquartile range

IS: ischemic stroke

IRR: incidence rate ratio

IVT: intravenous thrombolysis

IV-tPA: intravenous tissue-type plasminogen activator

LKW: last-known-well

LMICs: low- and middle-income countries

LVO: large vessel occlusion

MRI: magnetic resonance imaging

mRS: modified Rankin-scale

MT: mechanical thrombectomy

NIHSS: National Institutes of Health Stroke Scale

NHIFH: National Health Insurance Fund of Hungary

NHSC: National Healthcare Service Center of Hungary

ODT: onset-to-door time

OENO: Orvosi Eljárások Nemzetközi Osztályozása; Hungarian adaptation of International Classification of Procedures in Medicine codes

ONT: onset-to-needle time

PCR: polymerase chain reaction

PNS: peripheral nervous system

PPE: personal protective equipment

R: Pearson's correlation coefficient

RAS: renin angiotensin system

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

RNA: ribonucleic acid

SD/sd: standard deviation

S protein: spike protein

SNIS: Society of Neurointerventional Surgery

SVIN: Society of Vascular and Interventional Neurology

TIA: transient ischemic attack

TRISP: Thrombolysis in Ischemic Stroke Patients

UK: United Kingdom

U.S.: United States

USA: United States of America

USD: United States Dollar

VTE: venous thromboembolism

WSO: World Stroke Organization

1. Introduction

1.1. Importance of cerebrovascular diseases and acute ischemic stroke treatments

Cerebrovascular diseases are the second leading cause of death worldwide and one of the leading causes of disability. Up to 50% of stroke survivors are chronically disabled, which causes a tremendous public health burden with severe economic and social consequences (1-3). Over the past decade, the treatment of acute ischemic stroke (IS) has undergone fundamental changes due to the high-quality evidence that shows reperfusion interventions (intravenous thrombolysis, mechanical thrombectomy) within the 4.5 or 6 hours of stroke onset can reduce the risk of death or disability and improve the functional outcome. In recent years, the range of acute IS patients eligible for reperfusion interventions has further expanded as studies showed that these treatments could be used effectively up to 24 hours after symptom onset in certain cases (3-12). Although during the public health emergency caused by the COVID-19 pandemic, the focus and resources were rechanneled, cerebrovascular diseases continue to be a cause of neurologically devastating injury and remain a significant cause of morbidity and mortality worldwide (1, 13).

1.2. General overview of the COVID-19 pandemic

In December of 2019, Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, and with the rapid spreading of the disease on 24 January 2020, the first European case was recorded in France. By March 2020, the COVID-19 crisis rapidly evolved into a pandemic (14-19).

COVID-19 pandemic reached Hungary on 4 March 2020, and by the end of May 2021, with the 83 thousand cumulative COVID-19 cases per million people, Hungary was one of the most severely affected countries in Europe and the European Union. Considering the COVID-19 outbreak’s extent in neighboring countries, Hungary is in the middle of the range in the Central European region. The impact of the ongoing epidemic on the Hungarian population is further emphasized by the particularly high number of COVID-19 deaths (3000 deaths per million people by the end of May 2021). It is important to note that testing capacities and case definitions influence the number of COVID-19 cases and COVID-19-related deaths. Therefore further adjustment might be needed for an accurate comparison between countries (12, 18-22).

More details about the COVID-19 pandemic in Hungary and in different countries are presented in later chapters (Chapter 1.3.2. and Chapter 3.2.).

1.3. Associations between COVID-19 and ischemic stroke

Associations between COVID-19 and ischemic stroke could be analyzed from two perspectives (22). First, direct associations of COVID-19 and IS: can COVID-19 be associated with IS, and can it modify the course of IS? Second, COVID-19's indirect, collateral effect on IS: does the COVID-19 pandemic impact stroke care, especially acute stroke interventions?

1.3.1. Direct associations of COVID-19 and ischemic stroke

COVID-19, the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a multisystemic disease whose associations with IS have been known since the very beginning of the epidemic, but its details are still unclear in many respects (15, 16, 23-25).

1.3.1.1. Epidemiological correlations between acute stroke and COVID-19

The incidence of acute stroke among patients with COVID-19 s is not known precisely. Since the clinical presentation of SARS-CoV-2 infection is varied considerably, ranging from often asymptomatic infection to severe pneumonia that may lead to respiratory failure and death. Besides, critically ill patients may not be diagnosed with stroke due to dominating respiratory symptoms, impaired consciousness, or confounding systemic illness (16, 23, 26-32).

In two initial Chinese studies, acute stroke occurred in 3-5% of symptomatic COVID-19 patients. The incidence of acute IS was 2.3% and 4.6%, while intracerebral hemorrhage occurred in 0.5–1% of cases (26, 33). However, a later study from New York found a lower occurrence rate: 0.9% of 3556 patients hospitalized with COVID-19 had acute IS (23). This result is supported by a more extensive study from the United States of America (USA) in which 103 (1.3%) individuals developed acute IS among 8163 patients hospitalized with COVID-19 (34). The low incidence of stroke among COVID-19 patients is further emphasized by the analysis of the COVID-19 global registry of the Society of Vascular and Interventional Neurology (SVIN) which showed a 1.5% stroke rate across 54366 COVID-19 hospitalizations (35). Based on these data, acute IS seems to be an infrequent complication in patients with COVID-19 (16, 28, 34, 36). Nevertheless, acute cerebrovascular diseases could be more frequent in severe COVID patients. A study from Wuhan showed that the proportion of acute cerebrovascular diseases was seventeen times higher (17% versus 1%) in patients with COVID-19 who required intensive care than those who received a standard level of care (15, 16).

The median time from first COVID-19 symptoms to the onset of stroke is 10-12 days (16, 23, 26, 28). Although early observations from small case series suggested that COVID-19 patients who developed acute IS stroke were younger and without preexisting cardiovascular risk factors, other and more extensive studies showed that COVID-19 patients who developed acute stroke were older with a higher rate of cardiovascular risk factors and more likely to have increased inflammatory response and hypercoagulable state (16, 23, 25, 26, 34, 36). These results suggest that even if COVID-19 is a predisposing factor of acute IS, the risk is mainly seen in those who are already at risk for acute IS due to other cardiovascular risk factors (34, 36).

There is growing evidence that the course and prognosis of COVID-19 are more severe in patients who also develop acute IS, and conversely that COVID-19 is a negative prognostic factor in acute IS patients (15, 16, 23, 26, 33, 34, 37-40). The study mentioned above from the USA reported that in-hospital mortality (19.4% versus 6.2%; $p<0.0001$) and discharge to a destination other than home (62.1% versus 29.1%; $p<0.0001$) were significantly higher in COVID-19 patients with acute IS compared with those without stroke. Besides, in the multivariate analysis, COVID-19 was associated (relative risk 1.2; $p=0.03$) with discharge to a destination other than home or death in patients with acute IS (34). Furthermore, it is worth mentioning that in the nationwide analysis of Chen and colleagues, cerebrovascular disease in the past medical history was identified as an independent risk factor associated with fatal outcomes (hazard ratio 3.1) in patients hospitalized with COVID-19 (16, 37).

1.3.1.2. Pathogenesis of ischemic stroke in COVID-19

The pathogenesis of IS in patients with COVID-19 is not known precisely (28, 31, 41). Considering that COVID-19 is a multisystemic disease with highly complex pathogenesis, several interrelated possible pathomechanisms can be assumed in the development of IS as a complication: thromboinflammation or COVID-19-associated coagulopathy, viral invasion of cerebral vessels, cardiogenic embolization, atherothrombosis and thromboembolism, paradoxical cerebral embolism, and autonomic dysfunction (16, 24, 28, 31, 32, 37, 41-51). Instead of well-defined pathomechanisms, these pathophysiological processes should be considered hallmarks in the web of causes, which interact with each other, and further unknown contributing factors ultimately could result in IS (16).

The principal mode by which people are infected with SARS-CoV-2 is exposure to respiratory fluids carrying the infectious virus. Exposure principally occurs as inhalation of the virus, deposition on exposed mucous membranes, and touching mucous membranes with soiled hands contaminated with the virus (52). SARS-CoV-2 enters into host cells via angiotensin-converting enzyme 2 (ACE 2) as a specific viral receptor on the membrane of the host cells. The virus's S (spike) protein binds to the ACE2, which activates the membrane fusion of the virus and the host cell. Subsequently, the viral ribonucleic acid (RNA) is released into the cytoplasm, establishing infection. After replication, the virus spreads through the body from the host cell by a hematogenous route. Besides, some data suggest that SARS-CoV-2 could also enter the central nervous system in a retrograde neuronal pathway (16, 24, 28, 31, 32, 37, 38, 41, 48, 53-58).

ACE2 is not only expressed in the respiratory system (mainly in the lungs on type II alveolar epithelial cells, but also on the surface of the oral and nasal mucosa epithelial cells), but it is widely expressed in other organs and tissues like in the heart (cardiac myocytes, fibroblasts, vascular endothelial and smooth muscle cells), in the brain (predominantly on neurons, but also on glial cells), in the small intestine (epithelial cells of the intestinal mucosa), or in the kidney (proximal tubular epithelial cells). Furthermore, ACE2 is also highly expressed on the vascular endothelial and smooth muscle cells of small and large blood vessels. This extensive expression of ACE2 is the molecular basis for the multisystemic nature of COVID-19 (16, 24, 28, 31, 41, 57, 59-62).

SARS-CoV-2 can cause tissue and organ injury directly and perhaps mainly via infection-induced systemic inflammatory and immune responses (16, 24, 28, 37, 42). In tissue and organ injury, ACE2 dysfunction through receptor internalization and downregulation is considered to play a central role. In this process, the balance from the ACE2 axis (summary of ACE2/angiotensin (1-7)/Mas receptor and ACE2/angiotensin (1-

9)/angiotensin type 2 receptor axes), which mediates vasodilatative, antifibrotic, antiproliferative, anti-inflammatory, and antithrombotic effect, tilts towards the RAS axis (ACE1/angiotensin II/angiotensin type 1 receptor axis) resulting in vasoconstrictive, fibrotic, proliferative, proinflammatory and prothrombic effects (16, 24, 31, 38, 59-61).

1.3.1.2.1. Thromboinflammation or COVID-19-associated coagulopathy

The interplay between inflammation and coagulation (so-called thromboinflammation) is a well-known phylogenetically conserved defense mechanism in which endothelial cell dysfunction plays a central role, which could result in proinflammatory and procoagulant changes, and ultimately in thrombosis. Ranucci et al. demonstrated this association also in patients with COVID-19 (16, 42, 44, 63). There is growing evidence that patients with COVID-19 (especially in severe cases) are in a clinically significant prothrombotic state. Elevated D-dimer level was the first laboratory finding which called attention to altered hemostasis in COVID-19. Later, a high D-dimer level was identified as a marker of the severity of the disease and an independent predictor of mortality. Zhou et al. found that a D-dimer level greater than 1μg/l was associated with higher odds of in-hospital mortality (odds ratio 20.04), while in a more extensive study, Zhang et al. found that a 2μg/ml cutoff value could effectively predict in-hospital mortality (15, 16, 27, 37, 41, 44, 46, 62, 64-68).

The procoagulant profile of COVID-19 patients can be characterized by enhanced clot strength, high D-dimer and fibrinogen levels, elevated prothrombin time, increased C-reactive protein, procalcitonin and ferritin levels, elevated white blood cell and decreased lymphocyte and platelet counts. Besides, it has emerged that in some cases, antiphospholipid antibodies might take part in procoagulant changes. It is noteworthy that there are reasonable data that well-chosen anticoagulant therapy may improve prothrombotic changes and COVID-19 outcomes. Although some of the changes might resemble disseminated intravascular coagulation, thrombotic microangiopathy, or hemophagocytic syndrome, distinct differences outline COVID-19-associated coagulopathy as a new entity (16, 27, 28, 31, 33, 37, 41, 42, 44-46, 62, 64-66, 69).

Endothelial dysfunction seems to be a key contributor to COVID-19-associated coagulopathy. SARS-CoV-2 directly and perhaps mainly via the infection-induced systemic inflammatory and immunological responses could cause activation and damage of the vascular endothelium (endotheliitis), which could lead to activation of platelets, neutrophil cells, complement system and coagulation cascade, downregulation of natural anticoagulant pathways and dysregulation of fibrinolysis. Overall, these processes could result in micro- and macrothrombosis and organ damage. In these changes, ACE2 dysfunction, shifting the balance between ACE2 and RAS axes toward the RAS axis, is considered a central role (16, 24, 38, 65, 70).

1.3.1.2.2. Viral invasion of cerebral vessels

In April 2020, using electron microscopy and polymerase chain reaction (PCR), a pathology laboratory in New York reported the presence of SARS-CoV-2 in neuronal and vascular endothelial cells of the frontal lobe of a patient who died in a typical COVID-19 disease (16, 53).

The molecular basis of cerebral vascular viral invasion is the high expression of ACE2 on cerebral smooth muscle and vascular endothelial cells, which serves as a specific viral receptor for SARS-CoV-2. It is hypothesized that SARS-CoV-2 directly and through local inflammatory responses and by causing an imbalance between ACE2 and RAS axes may result in local inflammation and thrombosis, and subsequent cerebral infarction. Atherosclerotic lesions of intracranial arteries could be responsible for triggering local intracranial atherothrombosis since they are more susceptible to inflammatory stimuli. Atherothrombosis could be augmented considerably by COVID-19-associated prothrombotic and systemic inflammatory and immunological changes. Others hypothesize a mechanism similar to the vasculopathy caused by the varicella zoster virus (16, 24, 28, 31, 41, 60-62, 70-73).

1.3.1.2.3. Cardiogenic embolization

Heart diseases are well-known and significant risk factors for acute IS (16, 74). The relevance of acute - particularly respiratory - infections in triggering acute coronary syndromes (ACS) is a well-recognized and studied association (16, 75, 76). The role of coronaviruses in the development of ACS and acute myocardial injury has been described in the epidemic of SARS-CoV. Since SARS-CoV-2 shares a close resemblance with SARS-CoV (genetically identical in 79.5%), the acute myocardial injury could also be presumed in COVID-19 (15, 16, 28, 46, 77-80). Later, this presumption was verified, and now the myocardial injury is considered one of the important pathogenic features of

COVID-19. As a surrogate for myocardial injury, multiple studies have shown increased cardiac biomarkers, mainly cardiac troponins I and T, in patients with COVID-19, especially those with severe disease. Furthermore, it appears that SARS-CoV-2 has an increased propensity for developing cardiac involvement. A review of 26 studies that included at least 100 patients with COVID-19 reported a 20% overall weighted pooled prevalence of acute myocardial injury in COVID-19. Autopsy studies also showed that cardiomyocyte damage is a frequent complication of COVID-19. Acute myocardial injury is typically seen in the advanced stages of the disease and is associated with a worse prognosis (15, 16, 24, 28, 37, 46, 62, 71, 79, 80). Via cardiomyopathy, arrhythmias, myocardial infarction, decreased left ventricular ejection fraction, left ventricular dyskinesia or akinesia, the acute myocardial injury may result in cerebral cardioembolism and acute IS (16, 28, 41, 62, 71, 80).

The pathophysiology of acute myocardial injury is not well known. However, several mechanisms could be hypothesized, such as direct damage of cardiac myocytes, vascular endothelial and smooth muscle cells of the coronary arteries, myocardial interstitial fibrosis, infection-induced inflammatory and immunological responses, hypercoagulation related coronary micro-and macrovascular thrombosis, respiratory failure and hypoxia, supply-demand mismatch caused by inflammation and/or stress. Besides, thrombosis due to destabilization and rupture of coronary plaques may be an important way of myocardial damage (16, 28, 62, 71, 75-77, 79, 80). This pathophysiological process is mainly identical to the mechanism of the thromboembolic ischemic stroke caused by atherosclerotic plaque rupture, so it is detailed there. In the changes above, the pivotal role of ACE2 and its dysfunction (tilting the balance between ACE2 and RAS axes toward the RAS axis) is delineated. Thus, extensive expression of ACE2 on the surface of cardiac myocytes, fibroblasts, and vascular endothelial and smooth muscle cells of coronary arteries seems to be the molecular pathological basis of acute myocardial injury (16, 24, 59, 60, 71).

1.3.1.2.4. Atherothrombosis and thromboembolism

Inconvertible evidence supports the importance of immune and inflammatory pathways in the pathogenesis of atherosclerosis. Nowadays, some authors define atherosclerosis as an inflammatory process occurring as a response to the accumulation of lipids within the arterial wall. Furthermore, there is considerable evidence that acute and chronic, especially respiratory, infections directly and mainly through systemic inflammatory and immunological responses can provoke remote cellular and humoral local arterial inflammation, thus promoting atherosclerotic lesions' progression. Together with the infection-induced procoagulant changes (thromboinflammation), these local inflammatory changes may precipitate atherosclerotic plaque destabilization and rupture, leading to an augmented risk of vascular thrombotic events. The local arterial inflammatory response to systemic inflammatory stimuli is greater in atherosclerotic arteries than in normal arteries. Furthermore, atherosclerotic lesions responsible for triggering a vascular event (culprit lesions) are characterized by more advanced infiltration of inflammatory cells than any other plaques (16, 71, 72, 75, 76).

Atherosclerotic plaque rupture with a superimposed thrombus formation (atherothrombosis) and thromboembolism are major causes of ACS and IS (16, 73, 74, 76, 81). Since vascular endothelial and smooth muscle cells of coronary, cervical, and cerebral small and large arteries highly express ACE2, SARS-CoV-2 directly and through ACE2 dysregulation may cause local inflammation, endothelium damage, and atherosclerotic plaque destabilization, which lead to atherothrombosis and thromboembolism, and subsequently ACS or IS. COVID-19-associated coagulopathy and infection-induced systemic inflammatory and immunological changes additionally and synergically could contribute to this process (16, 24, 28, 31, 41, 46, 59, 60, 71, 79, 80).

This pathomechanism has already emerged for SARS-CoV. In May 2020, Esenwa et al. reported a radiology-pathology case series of patients with COVID-19 with acute IS due to atherothrombosis overlying mild atherosclerotic carotid plaque, supporting this pathomechanism also is the case of SARS-CoV-2 (16, 28, 73, 77).

1.3.1.2.5. Paradoxical cerebral embolism

Clinicopathological and epidemiological studies show evidence that the rate of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is remarkably high in patients with COVID-19. The risk for VTE is particularly high in severe and critically ill patients, and VTE events could occur in a considerable number despite thromboprophylaxis. A meta-analysis by Di Minno et al., which examined mainly COVID-19 patients treated in the intensive care unit, found that the prevalence of VTE is approximately 30% in COVID-19 patients, with deep vein thrombosis being reported at around 20% and with pulmonary embolism being reported for around 18% of patients. VTE risk is further emphasized by the fact that most of the included studies reported ongoing thromboprophylaxis at the time of VTE by using standard or even therapeutic doses of heparin. Besides, it is noteworthy that autopsy studies suggest that the actual VTE burden could be even higher and clinically underestimated in patients with COVID-19 (27, 42, 62, 65, 68, 69, 82, 83).

Paradoxical cerebral embolism is a clinically significant and distinct cause of acute IS. This stroke etiology is rare but considered more prevalent in young patients, which gives its particular significance. Paradoxical cerebral embolism is a severe complication among patients with VTE in the presence of a right-to-left shunt. The most common right-to-left shunt associated with paradoxical cerebral embolism is the patent foramen ovale, which can be detected in 25% of the general population. Considering the high prevalence of right-to-left shunt in the general population and the exceptionally high rate of VTE in patients with COVID-19, paradoxical cerebral embolism could be presumed in a particular portion of acute IS events associated with COVID-19. Since the diagnosis of paradoxical cerebral embolism is clinically challenging and often remains presumptive, the frequency of this entity is unknown in the current literature. However, case reports of paradoxical cerebral embolism in patients with COVID-19 support this etiology's hypothesized role in acute IS in patients with COVID-19 (49-51, 83-86).

In the multifactorial pathophysiology of VTE in COVID-19, among and besides the conventional risk factors for VTE, vascular endothelium damage (endotheliitis) caused by SARS-CoV-2 directly and via systemic inflammatory and immunological responses, COVID-19-associated coagulopathy, ACE2 dysfunction, hypoxia triggered increased blood viscosity and hypoxia-inducible transcription factor-dependent signaling, immobilization, and therapeutic factors (e.g., central venous catheters, mechanical ventilation, medications) could be highlighted. Enhancing persistent or transient right-to-left shunt, cough, severe lung involvement, central venous catheters, and mechanical ventilation may trigger paradoxical embolism among COVID-19 patients with VTE (49-51, 65, 68, 69, 82, 83).

1.3.1.2.6. Autonomic dysfunction

Compelling data show that the autonomic nervous system and its dysfunction considerably impact the risk, progression, and prognosis of acute IS by altering cerebral hemodynamics, cardiovascular and metabolic risk factors, and the effect of different therapies. Therefore, therapeutic alteration of the autonomic nervous system (especially neuromodulation) is currently a topic of high interest (87-90).

Autonomic dysfunction characterized by increased sympathetic activity and decreased parasympathetic activity is a common pathophysiological hallmark in cardiovascular and metabolic diseases. In patients with COVID-19, both enhanced sympathetic tone and parasympathetic withdrawal may play a pivotal role in increasing the risk of cardiovascular events, like acute IS COVID-19 might aggravate pre-existing autonomic dysfunction in patients with chronic cardiovascular and metabolic diseases, which may be an important factor that contributes to higher morbidity and mortality of COVID-19 patients with pre-existing conditions (55, 56).

Based on clinical, pathological, and experimental data, it is hypothesized that SARS-CoV-2 could affect either the central or the peripheral nervous system (CNS, PNS), resulting in autonomic dysfunction. The pathophysiology of nervous system damage is not entirely explored yet, but direct and indirect mechanisms are postulated with the pivotal role of ACE2. Based on the high rate of anosmia and dysgeusia in patients with COVID-19, one of the most plausible pathways of CNS involvement is the olfactory route. ACE2 expressing olfactory neuroepithelial cells in this pathway could be the entry sites, from SARS-CoV-2 could reach the olfactory-piriformis cortex by retrograde axonal and transsynaptic neuronal transport. Subsequently, by axonal and transsynaptic neuronal transport, the coronavirus could spread further and cause damage to the limbic system and the cardiovascular and cardiorespiratory centers of the brainstem. ACE2 is highly expressed in neuronal and glial cells, especially in these autonomic centers. Furthermore, Fenrich et. postulated that from the autonomic centers and the cranial ganglia nuclei (especially vagal nuclei) of the brainstem, SARS-CoV-2 could reach and alter basically every organ through cranial and peripheral nerves by neuronal transport. Besides, others suggest that SARS-CoV-2 could damage peripheral nerve endings and autonomic postganglionic cells directly in the periphery. There is also compelling data that SARS-CoV-2 could reach the CNS by hematogenous route, either directly via ACE2, which acts as a specific viral receptor on the blood-brain barrier's (BBB) endothelial cells, or by infected leukocytes that pass the BBB. Among the indirect mechanisms of nervous system damage, acute and post-infectious, systemic and local inflammatory and immunological responses, RAS axis upregulation and ACE2 axis downregulation, and the effect of hypoxia and COVID-associated coagulopathy emerged as contributing factors (16, 22, 24, 32, 33, 38, 39, 47, 48, 53, 56-58, 61, 91).

1.3.2. Indirect associations of COVID-19 and ischemic stroke

The COVID-19 pandemic has affected healthcare systems and patients around the world. In many countries, healthcare systems have become overburdened as the efforts to treat patients with COVID-19 have placed a tremendous strain on personnel and resources. Although the control of COVID-19 is crucial, at the same time, the management of acute health conditions, like stroke, must not be neglected. It cannot be right that treatment for one potentially curable disease is euthanized at the expense of another. Accordingly, there is a consensus amongst the international medical communities that the presence of COVID-19 as a public health emergency should not alter the inclusion or exclusion criteria for acute reperfusion interventions. Thus, emergency interventions such as intravenous thrombolysis (IVT) and endovascular therapy (EVT) for acute IS should be performed without any delay, even during the pandemic, to rescue important functions and save lives. Nevertheless, the extent of the COVID-19 epidemic has been so large and widespread that no previous experience can be used to develop plans for the emergency management of acute stroke treatment under such extreme situations. Thus, different countries or even different healthcare systems within a country responded with a varied spectrum of policy changes trying to balance the safety of its healthcare workers and uphold the continued quality of care for the patients presenting with emergencies, including stroke (92-96).

In this chapter, we will present the currently available data about the impact of COVID-19 on stroke care systems globally and in different geographical regions such as North America, Southern Europe, Western Europe, and Central Europe. In addition, we will detail in separate the collateral damages of COVID-19 on stroke care systems of the low- and middle-income countries (LMICs) and especially in China. Besides, we will present data about how COVID-19 impacted different acute stroke care models/logistic paradigms.

1.3.2.1. Collateral damages of COVID-19 on stroke care from a global and international aspect

In April 2020, the World Stroke Organization (WSO) reported significant stroke service reorganizations in most countries, and just a tiny minority of countries could maintain a full range of acute stroke services. WSO members reported reallocation of neurology and stroke beds, including intensive care units (ICUs) to COVID-19 patients necessitating a move of stroke units to less optimal accommodation and redeployment of stroke physicians, nurses, and other stroke healthcare-related workers to look after COVID-19 patients. Offering EVT for acute IS has been reduced or stopped in many units. Even IVT is under threat with, at best, service pressures and delays imposed by managing potentially infected patients, resulting in increased door-to-needle times. At worst, stroke patients are missing the therapeutic window altogether due to delays in hospital admissions or referrals, or patients prefer not to enter the hospital at all. Correspondingly, the World Stroke Organization (WSO) membership survey in spring 2020, including over 100 responses from countries worldwide, revealed that only slightly over 10% of the respondents had not observed a reduction in stroke admissions. In the other centers, admissions decreased from 10-90% as compared to a comparable period in 2019 (median decrease was 50-70%) (95, 97).

In 2020 spring, the international survey by the European Stroke Organization (ESO), which included 426 stroke care providers from 55 European countries, reported similar data to WSO. In this survey, 77% reported that not all stroke patients were receiving the usual care in their centers, and 38% estimated that this was happening in more than one-quarter of patients. Besides, 25% of the participants experienced that stroke code pathways were affected at their centers, 21% reported that their center avoided admitting patients whenever possible, 12% described a lack of beds for stroke patients, and 4% had to redirect stroke patients to other hospitals. In addition, a shortage of personal protective equipment (PPE) was reported by more than half of the respondents (54%). Thus, more than 70% estimated that stroke patients' functional outcomes and recurrence rates would be affected by the changes in stroke care related to the COVID-19 outbreak (98).

A global cross-sectional study by Nogueira et al. conducted across six continents, 70 countries, and 457 stroke centers reported that the COVID-19 pandemic was associated with a global decline in stroke hospitalizations and IVTs. Notably, there were 80,894 stroke hospitalizations during the first four months of the COVID-19 pandemic (March-June 2020) compared to 91,373 stroke hospitalizations in the preceding four months (November 2019 to February 2020), representing an overall 11.5% decrease ($p<0.0001$). The magnitude of decline in stroke hospitalizations varied geographically: Asia, −6.5% ($p<0.0001$); North America, −18.8% ($p<0.0001$); Europe, −10.9% ($p<0.0001$); South America, −17.4% ($p<0.0001$); Africa, −30.2% ($p<0.0001$); whereas Oceania −1.9% ($p=0.3$) did not demonstrate significant alteration. Similarly, the volume of intravenous tissue-type plasminogen activator (IV-tPA) delivery declined remarkably by 13.2% during the COVID-crisis compared to the pre-pandemic epoch (11,570 versus 13,334; $p<0.0001$). Decline in IVT delivery was seen in most regions: Asia, −9.9% ($p<0.0001$); North America, −14.4% ($p<0.0001$); Europe, −13.5% ($p<0.0001$); South America, −24.2% ($p<0.0001$); Africa −23.5% ($p<0.01$). While there was no appreciable difference in Oceania −1.9% ($p=0.7$) (99).

Besides, the study of Nogueira et al. noted a significant decrease in stroke hospitalizations and IVTs across centers with low, intermediate, and high COVID-19 hospitalization burden (≤6.2 versus >6.2 to 61.9 versus >61.9 COVID-19 admissions/month), and the magnitude of decreases was significantly greater in centers with higher COVID-19 inpatient volume. During the four-month COVID-period, the reduction in stroke admissions in low, intermediate, and high COVID-19 hospitalization burden centers was 3.2% ($p<0.0001$), 12.0% ($p<0.0001$), and 17.5% ($p<0.0001$), respectively, compared to the pre-pandemic period. Similarly, the volume of IV-tPA delivery declined during the COVID-epoch in low, intermediate, and high COVID-19 hospitalization burden centers with -9.2% ($p<0.0001$), −12.6% ($p<0.0001$), and −19.1% ($p<0.0001$), respectively, compared to the pre-pandemic period (99).

A comparable global large-scale analysis conducted by the SVIN, which included six continents, 40 countries, and 187 comprehensive stroke centers, revealed that the COVID-19 pandemic was associated not only with a global decline in the volume of overall stroke hospitalizations and IS admissions but also in EVT volume (Figure 1.). During the first three months of the COVID-19 pandemic (March-May 2020), the overall stroke hospitalizations were dropped by 19.2% (21,576 versus 26,699, $p<0.0001$, respectively), the admissions for IS or TIA reduced by 15.1% (16,884 versus 19,882, $p<0.0001$, respectively) and the EVT volume decreased by 12.7% globally (4533 versus

5191, p<0.0001, respectively), compared the to a three months pre-pandemic period (December 2019–29 February 2020) (Figure 1.) (35).

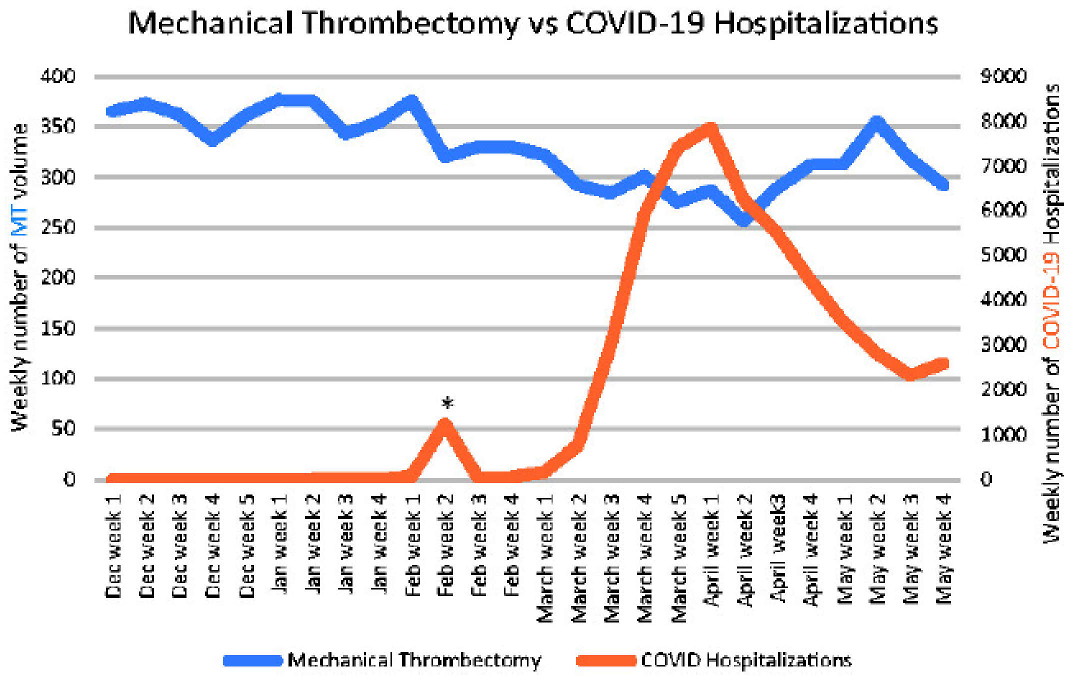

Figure 1. Weekly volume of EVTs and COVID-19 hospitalizations. This figure shows the temporal correlation between weekly hospitalizations for COVID-19 and EVTs per week in the analyzed cohort. *Peak of 1235 COVID hospitalizations in the second week of February, predominantly from one hospital in Wuhan, China. MT: mechanical thrombectomy. Figure of Nogueira et al. 2021. Original publisher: SAGE. CC-BY (35)

Congruently to the study of Nogueira et al. above, broad geographic variations were noted in the magnitude of declines in stroke care (stroke admissions, EVTs). Besides, the authors noted a significant decrease in stroke hospitalizations and EVT delivery across centers with low, mid, and high COVID-19 hospitalization burden (10.6 versus >10.6–103.6 versus >103.6 COVID-19 admissions/month), with a significantly greater decline in centers with higher COVID-19 inpatient volume, which in line again with the observations made by the above study of Nogueira et al. In addition, as a novelty, the reduction in stroke hospitalizations and EVT volumes were demonstrated across low-, mid-, and high-volume thrombectomy centers (4.8 versus >4.8 to 11.4 versus >11.4 procedures/month), with a largest 17.6% (p<0.0001) and 15.6% (p=0.0002) drop in mid-volume thrombectomy centers, respectively (35). At this point, it is important to note that the reduction in IVT and EVT volumes can only be interpreted in countries and regions where IVT and EVT delivery for acute IS has existed before the SARS-CoV-2 epidemic. In countries and areas where IVT and EVT were not available, the COVID-19 crisis could not cause a decline in the procedure numbers.

Similarly to the study of the SVIN, the survey of the Global Executive Committee of the Mission Thrombectomy 2020+ alliance distributed in North America, South America, Europe, India, and Asia in 25 countries and 103 centers noted a median 33% decrease in stroke admissions and a median 25% decrease in EVT procedures globally, with board variations among different geographical regions and centers with the different workload, during the first surge of COVID-19 outbreak, compared to pre-pandemic months (96).

The meta-analysis by July et al., which included 59,233 subjects from 9 studies, showed that the number of stroke alerts (stroke code activations), acute reperfusion therapies (IVT and/or EVT), and EVTs during the COVID-19 pandemic were 64% (56-71%), 69% (61-77%) and 78% (75-80%) of that during the pre-pandemic period, respectively (100). Although the large-scale analysis of the SVIN reported that, despite the absolute decrease in EVT volumes, the rate of EVT relative to stroke admissions remained stable during the COVID-19 outbreak, July et al. found that the number of EVTs per stroke patient was higher during the COVID-crisis (OR 1.23 [1.12-1.36], $p<0.001$) (35, 100).

In a large international analysis of 17 neurovascular centers (11 from the USA, two from Poland, and one-one from Egypt, China, Turkey, South Korea, and France) in the first four months of 2020, the number of EVTs for acute IS was decreased by 8% (635 versus 690, respectively), compared to the same epoch in 2019. Moreover, in March-April 2020, the EVT volume dropped by 15.3% (322 versus 380, respectively) compared to March-April 2019 (101). These observations seem in line with the international multi-center study of Hajdu et al., in which 17 stroke centers participated from 8 countries (Switzerland, Italy, France, Spain, Portugal, Germany, Canada, and the USA) and showed a 32% reduction in EVT procedures and an estimated 54-minute increase in symptom onset-to-groin puncture time after confinement measures for the COVID-19 pandemic were implemented in 2020 spring (102).

Although delay in EVT delivery was further confirmed by the systematic review of Kurnianto et al., the analysis of the Thrombolysis in Ischemic Stroke Patients (TRISP) registry showed conflicting data (103, 104). This multicenter cohort study (20 well-established European stroke centers) showed that the COVID-19 pandemic lockdown resulted in a mild (7%) decline in the number of acute IS patients treated with acute reperfusion therapies (IVT and/or EVT). However, the time-based performance indicators of stroke care service (onset-to-door, door-to-imaging, door-to-needle, and door-to-groin times) did not change considerably between the 2020 and 2019 periods in these well-established European stroke centers (104).

In summary, global and international data clearly point to a significant reduction in the quantity of stroke care provided during the COVID-19 pandemic, while data regarding quality indicators of stroke care are limited and conflicting. Available data also depicts variations within and across the different regions reflecting the diversity in the epidemiology of COVID-19 and the socio-cultural behaviors, healthcare logistics, and infrastructure encountered across the globe (35).

1.3.2.2. Impact of COVID-19 on stroke care systems in different geographical regions

1.3.2.2.1. North America

Less data could be found regarding changes in stroke care systems during the SARS-CoV-2 pandemic in Canada (105, 106). However, these data seem in line with the observation in the USA. Therefore Canadian data are not detailed in this chapter.

The first case of SARS-CoV-2 infection in the USA was confirmed on 20 January 2020 (107). Then, in early March 2020, COVID-19 became recognized as a major public health threat in the USA, causing unprecedented demand and burden on emergency health care services (108, 109).

An early analysis of 11 comprehensive stroke centers and one primary stroke center in southeast Michigan (USA) showed that the rate of IS admissions was significantly lower for March 2020 as compared to February 2020 (17.8% reduction; incidence rate ratio (IRR):0.85, 95% confidence interval (CI): 0.76-0.95; p=0.006) and March 2019 (IRR: 0.82, 95% CI: 0.73-0.92, p=0.001). The rate of EVT for acute IS was even lower for March 2020 as compared to February 2020 (75.6% reduction; IRR: 0.57, 95% CI: 0.40-

0.81, p=0.002) and March 2019 (IRR: 0.61, 95% CI: 0.43-0.88, p=0.007), while there was no significant difference in the administration of IV-tPA between the study and control periods. No significant changes could be observed in time metrics of stroke care between the periods (110). Another study from Michigan reported an even greater reduction in the number of acute cerebrovascular patients presented at the emergency department or admitted to the stroke unit (-54.2% and -50.7%; p<0.001, respectively) during the first wave of the SARS-CoV-2 epidemic. However, there were no differences in the rate of acute reperfusion interventions (IVT, EVT) between 2020 and 2019. In addition, no significant differences were seen in stroke-to-door, door-to-needle, and door-to-groin times between the periods (111).

On 1 March 2020, New York City reported its first case of COVID-19 and became the global epicenter within a month. The first epidemic wave peaked in April 2020, and the velocity of the increased demand for emergency health care services, disruptions in supply chains, and the highly infectious nature of SARS-CoV-2 placed unprecedented demands on emergency health care services, including ambulances, emergency departments, and inpatient units (108, 112). The New York Langone Health comprehensive stroke center observed a lower volume of AIS admissions and performed less thrombolysis and MT during the COVID19 pandemic. They analyzed a quality parameter called defect-free care score, defined as compliance with five care measures: door-to-CT time<25 minutes, door-to-needle time<60 min, discharge on an anti-platelet, anticoagulation for patients with atrial fibrillation, and statin medication at discharge. Patients were classified as having had defect-free care if they received all elements for which they were eligible. Agarwal et al. found that despite the longer median door-to-CT times (16 versus 12 minutes, p=0.05), which could reflect the epidemic precaution measures, the rate of defect-free care (95.2% versus 94.7%; p=0.84, respectively) and median door-to-needle (36 versus 35 minutes, p=0.83, respectively) were similar in the pandemic and pre-pandemic groups. The median door-to-groin groin times showed a tendency to increase, while the door-to-reperfusion times were similar between the COVID-19 and control periods (80 versus 71 minutes, p=0.06; 103 versus 97 min, p=0.18, respectively) (108). These data suggest that although there was a decline in the volume of acute stroke care, they could preserve the quality of care, similarly to the above-cited studies from Michigan. Another study from New York City compared the first eight weeks of 2020 (pre-pandemic period) and 9-16 weeks of 2020 (pandemic period), at which time New York City had one of the highest COVID-19 attack rates in the world. During the COVID-period, the number of acute stroke admissions decreased by an average of 4.4 per week (p=0.005), with a 44% reduction from the baseline. However, it was not associated with a decrease in the rate of IVTs or EVTs (109).

Using the Vizient Clinical Data Base platform, a large-scale analysis included data from 65 hospitals (of which 55 were academic medical centers) across all four United States (U.S.) Census Bureau statistical regions compared March 2020 to the average of March 2018 and 2019. They found a 17.9% decrease in the acute IS hospitalization numbers and a 3.3% decline in IVT numbers, while an 18.8% increase in EVT volume. There were regional differences, but the overall trend was a decrease in stroke hospitalizations throughout the USA. Compared to the previous two years' average, stroke hospitalization volume decreased in March 2020 by 21.4% in the Midwest, 17.6% in the Northeast, 10.4% in the South, and 22.7% in the West. It is noteworthy that the 18.8% increase in EVT volume was interpreted as a relative decrease because, in February 2020, the increase was 36.8% (113).

In the analysis of acute reperfusion interventions for acute IS, the University of Cincinnati Stroke Team not only compared a COVID-19 period with an identical or immediately preceding pre-pandemic period but performed a trend analysis using segmented regression analysis. During a five weeks pandemic period (11-15 weeks of 2020) in the Cincinnati Tri-State Region, capturing around 2 million inhabitants, the mean of the composite acute reperfusion treatment numbers reduced by 31% (p=0.03) compared to the first ten weeks of 2020. Among acute reperfusion treatment types, the mean of IVT reduced significantly to a greater extent (-33%, p=0.03), while the EVT volume decreased to a lower degree and non-significantly (-20%, p=0.45). The trend analysis of IVTs and EVTs of the first 15 weeks of 2019 and 2020 showed that the trends were flat in 2019, with an increasing trend in 2020 before week 11 (6% increase [95% CI, 1%–11%]). Immediately following the announcements of restrictive measures in week 11 of 2020, acute stroke reperfusion treatments per week appeared to decline by 62% (95% CI, 35%–78%; p<0.01) with and 31% without accounting for time trends (114).

The Endovascular Research Group, by analyzing a prospectively maintained database of 12 comprehensive stroke centers across the USA, found that during March 2020, the mean time interval between last-known-well (LKW) and presentation to the stroke center was increased by a 161 minutes average (442±435 minutes versus 603±1035 minutes, $p<0.03$, respectively) compared to a pre-pandemic control period (February-March 2019) (115). These results were confirmed by White et al., who reported that acute IS patients were more likely to present after 24 hours from LKW (p=0.03) during the COVID-19 crisis (March-April 2020) compared to a pre-pandemic period (January-February 2020). They found a higher proportion of acute IS patients presented in the late time window (>24 hours from LKW), while a smaller percentage of patients presented during the eligible treatment windows for IV-tPA (0–4.5 hours) and EVT (0–24 hours) during the COVID-19 crisis, compared to the pre-pandemic period (0-4.5 hours: 12.2% (22/180) versus 25.1% (50/199), 0-24 hours: 30.0% (54/180) versus 53.3% (106/199), >24 hours: 54.4% (98/180) versus 26.6% (53/199), unknown: 15.6% (28/180) versus 20.1% (40/199); respectively) (116). The SVIN analyzed the pooled clinical data of consecutive acute IS patients from 14 comprehensive stroke centers across nine states of the USA. Noteworthy that at the time of the study, these nine states accounted for 47% of all COVID-19 cases in the USA and 37% of all COVID-19-associated deaths. Siegler et al. found that acute IS patients treated during the COVID-19 crisis (Marcs-July 2020) had 45% lower odds of receiving IV-tPA within 60 minutes of arrival (adjusted odds ratio, 0.55 [95% CI, 0.35–0.858]; $p<0.01$). Furthermore, they found the median door-to-needle time increased significantly (46 versus 42 minutes, p=0.03, respectively), while the median door-to-CT times decreased (29 versus 37 minutes, $p<0.01$, respectively) and the median CT-to-needle time increased (29 versus 22 minutes, p=0.02, respectively) during the COVID-period compared to the identical pre-pandemic period of 2019. It means that the observed slight but persistent delay in time from patient arrival to IVT at least partly due to delays from imaging to treatment initiation rather than arrival to imaging. There was no significant delay in door-to-groin puncture times (median 83 versus 90 minutes, p=0.30, respectively) (117).

Two studies with the use of surrogate markers enable the analysis of national-level changes in acute stroke care in the USA during the COVID-19 crisis. Adapa et al. analyzed a real-time thrombectomy device sales registry from the Decision Resources

Group covering 945 hospitals across the USA. The authors reported a significant decline (−3.7%) in thrombectomy device sales from 2019 to 2020 (January through June), which is in contrast to a 30.0% increase in thrombectomy device sales from 2018 to 2019. The reduction in sales of thrombectomy devices from 2019 to 2020 could be observed across all the four U.S. Census Bureau regions, with the highest magnitude in the Midwest (South: -1.8%, Midwest: -12.2%, West: -2-0%, Northeast: -2.6%).

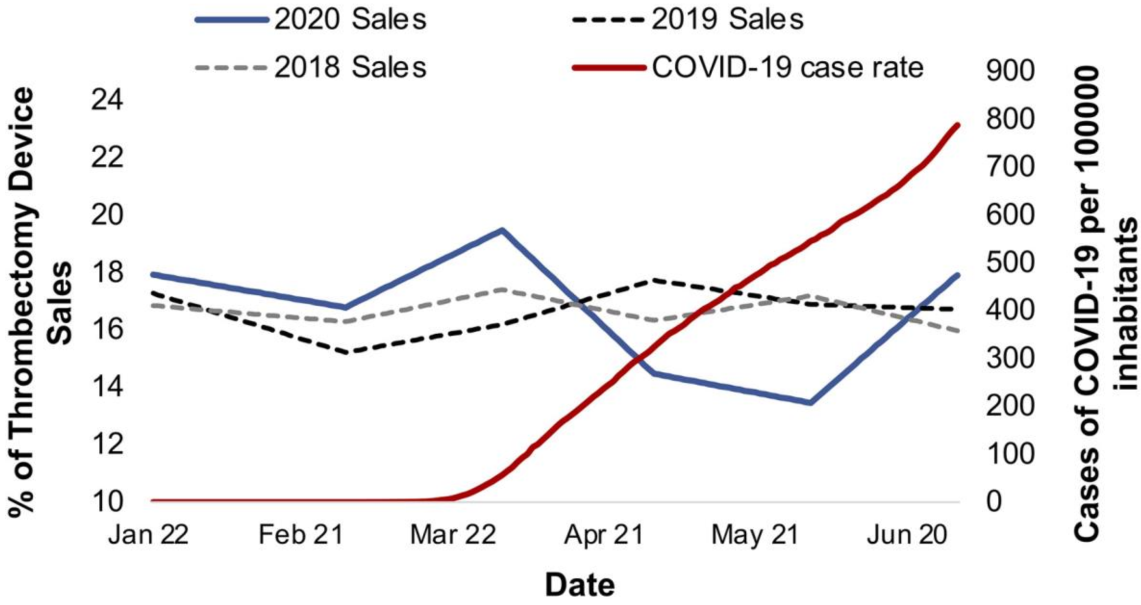

Figure 2. Cumulative incidence of COVID-19 and thrombectomy device sales in the U.S. The red line shows the cumulative number of cases of COVID-19 per 100,000 inhabitants in 2020 from January through June. The blue line represents the rate of thrombectomy device sales in 2020. The dashed black line represents the rate of thrombectomy device sales in 2019, and the dashed gray line represents the rate of thrombectomy device sales in 2018. Figure of Adapa et al. 2021, used with permission. (118)

Interestingly the proportion of thrombectomy device sales by month in 2020 was strongly and negatively associated with the cumulative incidence of COVID-19 in the USA overall (Spearman rank correlation coefficient (CC) -0.56, p<0.0001), with an even stronger correlation during April 2020 (CC -0.97, p<0.0001) (Figure 2.). This significant negative association between thrombectomy device sales and the cumulative incidence of COVID-19 was also seen in all geographical regions (South: CC -0.59, p<0.001), Midwest: CC -0.19, p=0.04, West: CC -0.66, p<0.0001), Northeast: CC -0.75, p<0.0001), with the strongest association being in the Northeast. For all regions, the greatest decline in the rate of thrombectomy device sales in 2020 was seen in April (118).

In another study, Kansagra et al. used the numbers of patients in a commercial neuroimaging database associated with the RAPID software platform (iSchemaView) as a surrogate for the quantity of care that hospitals provided to acute IS patients. This software system is typically used to support the selection of patients who may benefit from IVT or EVT by identifying large vessel occlusions and visualizing and quantifying the volume of brain infarct core and penumbra. RAPID imaging is performed in 856 hospitals distributed across 49 of 50 states in the USA. This neuroimaging database provides nearly real-time insight because this software is generally used at the time of the patient's presentation. In the analysis, the authors found that the number of patients who underwent imaging decreased by 39.1% (95% CI: -36.4%, -41.9%), from 1.18 patients per day per hospital in the pre-pandemic epoch (1-29 February 2020) to 0.72 patients per day per hospital in the pandemic epoch (26 March – 8 April 2020). The decrease in the use of stroke imaging was seen across all age, sex, and stroke severity subgroup. In addition, this decline could be observed in most states and across a range of hospital volumes, with the highest magnitude of decrease in high volume centers [low volume (0-1 patients/day): - 23.7%, medium volume (1-5 patients/day): -36.6%, high volume (>5 patients/day): -47.2%] (119).

In the survey conducted by three neurointerventional societies [the Society of Neurointerventional Surgery (SNIS), the SVIN, and the American Association of Neurological Surgeons/Congress of Neurological Surgeons Combined Cerebrovascular Section] across the USA, the majority of respondents (68%) indicated a greater than 25% reduction in EVT volumes during the COVID-19 pandemic compared with pre-pandemic levels (32% reported >50%, and 36% reported 25-50% decrease). In contrast, only 9% of respondents indicated a higher rate of EVTs. Among respondents, 21% indicated no change in door-to-groin times, while 14% reported an average of 30 min or longer delay, 35% indicated an average of 10–30 min delays, and 29% reported mild average delay in door-to-groin times of 10 minutes or less (120).

The above-presented data suggest that a substantial decline in the volume of IS admissions was a general phenomenon during the COVID-19 crisis, to which extent varied among regions and health care systems. The acute reperfusion intervention numbers seemed to show a generally lesser extent decrease with greater variations, especially in the case of EVT. It seems that there was a tendency for acute IS patients to be presented in the hospital in a delay. However, the data about the time metrics of intra-hospital acute IS care was inconsistent and conflicting. This phenomenon could reflect the uniqueness of every stroke care system. As every stroke center operates differently, their reaction to the COVID-19 crisis might be at least as different.

1.3.2.2.2. Southern Europe

1.3.2.2.2.1. General remarks

The first SARS-CoV-2 infection (an imported case) in Spain was detected in La Gomera, in the Canary Islands, on 31 January 2020, while the first case of locally acquired COVID-19 was confirmed on 26 February 2020 (121, 122). The first COVID-19 case was confirmed in Italy on 20 February 2020 at the Codogno Hospital in Lodi, Lombardia (123). Although the majority of cases were first reported in China, soon after that, Europe became the core center of the disease (124). As of the end of April 2020, 2,878,196 confirmed COVID-19 cases were notified globally, including 198,668 deaths, of which 1,359,380 cases and 124,525 deaths occurred in Europe (121). During the first surge of the COVID-19 crisis, Spain and Italy were the epicenters of the pandemic in Europe, followed by France and Germany. Spain experienced the highest number of SARS-CoV-2 cases, while Italy observed the highest number of COVID-19-associated deaths (121, 124). Since the beginning of the COVID-19 outbreak, European countries have adopted unprecedented measures such as large-scale social isolation, closing borders, and nationwide lockdowns. In addition, some radical healthcare reorganizations have been implemented in several countries to fight against COVID-19, with different time lags and approaches, also in relation to national healthcare system organization and resources (124).

1.3.2.2.2.2. Italy

A study from North-Eastern Italy (three regions with 12 comprehensive stroke and ten primary stroke centers) which counts around seven million inhabitants, examined the temporal trend of acute IS stroke care in the first five months of 2020. They found a marked decrease in IS admissions and EVTs, with a maximum reduction in April 2020 and a recovery in May 2020. However, the absolute and relative number of IVT was almost unvaried in this period. The oscillation in the volume of IS admission and EVTs followed the peak and the descending slope of the SARS-CoV-2 epidemic in Italy (125). An analysis from Campania, Southern Italy (a region where COVID-19 numbers were less burdensome) did not observe a significant difference in the number of patients admitted for acute IS (estimate of effect 3.5; 95% CI, -29.3 to 36.4; p=0.817), while reported a significant reduction in the number of acute reperfusion treatments (-27%, p=0.001) during lockdown (9 March - 12 April 2020) compared to the pre-lockdown period (2 February - 8 March 2020). During this COVID-period, Candelaresi et al. observed a remarkable delay in the pre-hospital phase [mean LKW-to-door: 230 (120-397) versus 155 (90-347) minutes, p=0.016, respectively] and also to some extent in the hospital phase of acute stroke care. Although the median door-to-groin times were unchanged [82 (65-118) versus 80 (64-110), p=0.89, respectively], the median door-to-imaging times were significantly prolonged [40 (30-60) versus 30 (20-44) minutes, p=0.0005, respectively], and the median door-to-needle times showed a tendency to increase during the lockdown, compared to the pre-lockdown period [90 (67-112) versus 75 (55-110) minutes, p=0.23, respectively] (126).

The Italian Stroke Organization performed a large-scale, multicenter study involving 93 (43 in Northern, 34 in Central, and 16 in South Italy) stroke units covering the entire national territory of Italy. The number of admission for IS decreased from 2399 to 1810, with a corresponding hospitalization rate ratio of 0.75 (95% CI: 0.71–0.80, p<0.001) during March 2020 (COVID-period) compared to the identical pre-pandemic period of the previous years. A decline in the volume of IS hospitalizations could be observed in all three regions of Italy (North, Central, and South), with a 36% maximal reduction in South Italy. IV-tPA administrations decreased across Italy, reducing the overall numbers from 531 in 2019 to 345 in 2020 (rate ratio: 0.86 [95% CI, 0.75–0.99]; p=0.032). Although during the COVID-period, the absolute number of EVTs decreased by 8.06% (171 versus 186, respectively), the rate ratio of EVTs did not show a significant change (rate ratio: 1.22 [95% CI, 0.98–01.51]; p=0.069). Analysis by regions showed that the rate of EVT increased remarkably in Northern Italy (RR: 1.61 [95% CI, 1.13–2.32]; p=0.008), driven mainly by Lombardia (rate ratio: 1.74 [95% CI, 1.00–3.12]; p=0.045) (127). This phenomenon could be linked to the centralization measures adopted in Northern Italy at the time and to the different logistic paradigms of acute stroke care (mothership versus drip-and-ship). These possible correlations are discussed in Chapter 1.3.2.3.

1.3.2.2.2.3. Spain

Rudilosso et al. analyzed the number of emergency calls to the Emergency Medical System (EMS) of Catalonia (7.5 million inhabitants) and the number of stroke codes activations by EMS during March 2020 (COVID-period) compared to March 2019 (control period). While the EMS of Catalonia received 158.005 emergency calls in March 2019 and 679.569 in March 2020, representing an overall 330% increment (p<0.0001), the number of stroke codes activations decreased by 18% (517 in 2019 and 426 in 2020, p<0.01). In agreement with the decline of stroke code activations, they found a trend of decline in the volume of stroke admissions, IVTs, and EVTs in the Hospital Clinic of Barcelona during the COVID-period compared to the control period (83 versus 108, p=0.07; 3 versus 9, p=0.57; 16 versus 21, p=0.8, respectively). The reduction of stroke admissions was most noticeable during the higher peaks of emergency calls. Notably, there was not a single stroke admission at the Hospital Clinic of Barcelona between March 15 and 17, although there was an average of 30 to 40 thousand emergency calls during these three days in Catalonia (14).

A study analyzed data from sixteen tertiary hospitals of the NORDICTUS network in North-West Spain (11.5 million inhabitants), which belongs to eight Spanish autonomous regions. The analysis showed a substantial decline in the weakly median IS admission (124 [115-134] versus 173 [171-179], p<0.001) during the first surge of the COVID-19 crisis compared to the antecedent, pre-pandemic period of 2020. The decline could be observed in all the eight autonomous regions of North-West Spain (Aragón, Asturias, Cantabria, Castilla y León, Euskadi, Galicia, La Rioja, and Navarra). The IS admissions' decline maximum coincided with the peak of the cumulative SARS-CoV-2 cases in Spain. Although during the COVID-period, the absolute number of IVTs and EVTs decreased remarkably (-48.5% and -41.9%, respectively), there were no differences in the proportion of IVT (16.1% versus 17.3%, p=0.405, respectively) or EVT (23% versus 22%, p=0.504, respectively), compared to the pre-pandemic period (128). Another large-scale study analyzed the impact of COVID-19 on acute reperfusion treatment numbers and treatment time parameters in North Spain, which reported a significant reduction in the volume of acute revascularization interventions (IVT, EVT) during March 2020, compared to a pre-pandemic period [weekly median 39 (30.8-45.8) versus 46.5 (39.8-60.0), p=0.043] (129).

During the first wave of the COVID-19 epidemic, Tejada Meza et al. observed a remarkable pre-hospital delay, especially in those acute IS patients who were transferred from another hospital (mean symptoms-to-door time: 110 [63-217] versus 95 [58-180] minutes, p=0.043; mean interhospital transfer time: 251 [205-345] versus 223 [162-296] minutes, p=0.013, respectively). Regarding the time metrics representing the intra-hospital workflow, although the mean door-to-needle time increased (55 [43-74] versus 51 [36-70] minutes, p=0.038), the mean door-to-groin and door-to-reperfusion times remained unchanged (129). These results are in line with the observations of Candelaresi et al. from South Italy (126). Although during the COVID-19 outbreak, Brunetti et al. also reported a remarkable pre-hospital delay (median onset-to-door increased by 138.5 minutes, p<0.001), they found the opposite in the intra-hospital time metrics: the door-to-groin times (+24.5 minutes increase in medians, p=0.034) increased, but there were no significant differences in median door-to-needle times (2020: 58.5 minutes versus 2019: 59.5 minutes, p=0.560, respectively) (130). A study from Madrid reported that in March-May 2020, acute stroke patients arrived at a significantly lower rate within 4.5 hours from symptoms onset (43% versus 58%, p=0.043), while there was no considerable change in the intra-hospital time course, including door-to-CT, door-to-needle and door-to-groin times, compared to the respective period of 2019 (131).

The observations and data from Southern Europe seem in accordance with the North American experiences during the first attack of the COVID-19 pandemic. Notably, data suggest that a considerable decline in the volume of IS admissions was a general phenomenon during the COVID-19 crisis, to which extent varied among regions and health care systems. The acute reperfusion treatment numbers seemed to show a generally lesser decline with greater variations, especially in the case of EVT. Current data convey the impression that there was a tendency for the pre-hospital delay in the presentation of acute IS patients. However, the data about the time metrics of intra-hospital acute IS care was inconsistent and conflicting. Data (especially from Italy) suggests that during the COVID-19 crisis, the performance of acute stroke care systems might differ based on different logistic paradigms (presented and discussed in Chapter 1.3.2.3.)

1.3.2.2.3. Western Europe

1.3.2.2.3.1. France

Three cases of SARS-CoV-2 infection were confirmed on 24 January 20, as the first cases in France and also in Europe. The first COVID-19-related death in Europe also occurred in France on 15 February 2020 (132-136). The COVID-19 epidemic rapidly spread afterward, causing unprecedented demand and burden on health care services in France (133). Response measures were triggered in France on 1 March 2020 and gradually developed until 17 March 2020, when a nationwide lockdown was enforced, with strict home confinement of the entire population (134). On 6 March 2020, the French government launched the emergency plan called “plan blanc” for hospitals. As a result, many hospital beds and staff were reallocated to patients with SARS-CoV-2 infection or suspected infection. Due to reorganizations, at the beginning of the COVID-19 crisis, acute stroke patients were managed in non-dedicated beds intermingled with non-stroke patients, with daily visits from stroke neurologists and nurses, and staff who were not stroke specialists. However, after a few weeks, in many stroke centers, stroke units were restored and divided into two separate areas (COVID-19 suspected or positive, and COVID-19 negative) (124).

Alsace (1.9 million inhabitants, North-East France) was the first French region affected by the COVID-19 epidemic. An early study that analyzed the acute stroke care network in Alsace reported a 39.6% decline in stroke alerts (174 versus 288, respectively), yet there was no marked variation observed in the number of stroke admissions (159 vs. 160, respectively) in March 2020, compared to March 2019. During the COVID-crisis, both the absolute number and proportion of acute revascularization treatments reduced substantially (– 33.3%: 34 versus 51; 34/159 (21.3%) versus 51/160 (31.8%) p=0.034, respectively), compared to the control period. Between these two periods, the number of IVTs decreased by 40.9% (13 versus 22, respectively), and the number of EVTs reduced by 27.6% (21 versus 29, respectively). However, there were no significant changes in pre- and intra-hospital time metrics of acute stroke care, including onset-to-door, door-to-imaging, door-to-needle, and door-to-groin times (134).

The national-level study of Kerleroux et al., which included 32 thrombectomy centers across all French administrative regions, reported a 21% significant decrease (668 versus 844; rate ratio: 0.79; [95%CI, 0.76–0.82]; p<0.001, respectively) in EVT case volume and a lower rate of IV-tPA use before EVT (43% versus 51%, p=0.029, respectively) during the first 45 days of the COVID-epidemic, compared to the identical period of the previous year. Although over the entire 2020 period, the authors found a weak negative correlation between the total number of hospitalizations for COVID-19 and the number of EVT cases in France (Pearson's correlation coefficient (R): −0.27, p=0.07 for the comparison with 0), yet after the statement of strict epidemic mitigation measures with the steep progression in COVID-19 hospitalizations, the correlation strengthened and became significant (R: −0.51, p=0.04 for the comparison with 0). Regarding the time parameters of EVT care, while during the COVID-19 outbreak, the mean onset-to-imaging time was unchanged (143.3±96.7 versus 147.5±89.8 minutes, p=0.524), there was a significant increase in the mean imaging-to-groin time, overall (144.9±86.8 versus 126.2±70.9 minutes, p<0.001, respectively) and in patients requiring interhospital transfer (182.6±82.0 versus 153.25±67, p<0.001, respectively) (137).

1.3.2.2.3.2. United Kingdom

The index patient with COVID-19 entered the United Kingdom (UK) on 23 January 2020 from Hubei province in China. SARS-CoV-2 RNA was detected at the Public Health England Respiratory Virus Unit, Colindale, London, and reported on 30 January 2020 (138, 139). Subsequently, public health measures such as large-scale social isolation, closing borders, and nationwide lockdown were adopted in the UK from 23 March 2020 throughout June 2020 to fight against COVID-19 (138). Concern that the COVID-19 epidemic might overwhelm health services in the UK led to rapid decisions to create additional hospital capacity for infected or suspected COVID-19 patients primarily by reducing elective hospital treatments, early discharge of patients who could be managed in other settings, and advising the public only to present to hospital in case of real need. The COVID-19 pandemic has presented new and varied challenges to the UK's acute stroke care services. Practices have had to be significantly modified to protect both staff and patients. Dedicated COVID-19 suspected or positive, and COVID-19 negative pathways were implemented (138, 140, 141).

An early small-scale single-center study from the tertiary stroke center of Stoke-on-Trent (population of half a million people) in England reported a statistically non-significant 36.5% reduction in stroke admissions (92 versus 145, p=0.39, respectively), a 50% decline in the number of IVTs (11 versus 22, p=0.72, respectively) and a 25% decrease in the EVT volume (4 versus 8, p=0.90, respectively) during the first surge of COVID-19 (15 March - 14 April 2020), compared the corresponding period of 2019. In addition, during the COVID-period the analysis of Padmanabhan et al. showed a trend for a delay in the pre-hospital workflow but a trend for shortening in the intra-hospital time metrics of acute stroke care: a 158 minutes increase in the median time from onset to arrival (734 [246-1091] versus 576 [128-1197] minutes, p=0.34, respectively), a 10 minutes decrease in the mean time from arrival to IV-tPA (54±30 versus 64±47 minutes, p=0.43, respectively), and a 264 minutes reduction in the mean time from arrival to thrombectomy (181±62 versus 445±566 minutes, p=0.72, respectively) (142).

Later, the leading comprehensive tertiary stroke center of North West London (population of over 6.4 million people) reported a significant 31.33% fall in acute stroke admission (353 versus 514, p<0.05, respectively) with a remarkable 80 minutes delay in the median onset-to-door time (240 [20-10] versus 160 [27-23] minutes, p=0.020) during the first surge of COVID-19 (23 March – 30 June 2020), compared to the same period of 2019. At the same time, the number and proportion of patients treated with IV-tPA decreased significantly (27/235 (11.49%) versus 46/283 (16.25%), while the EVT volume did not show a remarkable alteration. While during the COVID-19 outbreak, D'Anna et al. observed a significant delay in the pre-hospital phase of acute stroke care, the time metrics for the intra-hospital workflow were unchanged, including door-to-CT, door-to-needle, and door-to-groin times (median 19 [2-50] minutes versus 17 [6-53] minutes, p=0.643; median 39 [34-45] minutes versus 40 [34-45] minutes, p=0.878; median 58 [20-325] minutes versus 55 [21-289] minutes, p=0.982, respectively) (138).

The national-level analysis of four (2017-2020) consecutive years' data from the national quality register of the UK for stroke care (Sentinel Stroke National Audit Programme) includes all hospitals that admit patients with acute stroke in England, Wales, and Northern Ireland (covering 92% of the 67.8 million population of the United Kingdom) showed that the number of acute stroke admissions remained stable (estimated weekly percentage change of −0.05% [95% CI, −0.42 to 0.33]) up until the second week of February 2020 when there was a steep decline in the number of acute stroke admissions (−3.10% [95% CI, −4.14 to −2.03]; p<0.001 for change in slope) (141, 143). During the lockdown period (23 March - 30 April 2020), there was a trend for reduction in the overall number of stroke admissions compared with the mean of historical control periods (-

12.4%, 6923 versus 7902, p>0.05, respectively), but this decline was statistically significant only for IS (-70.98%, 5975 versus 20591, p<0.05), and not for primary intracerebral hemorrhage or undetermined stroke (Figure 3.) (141).

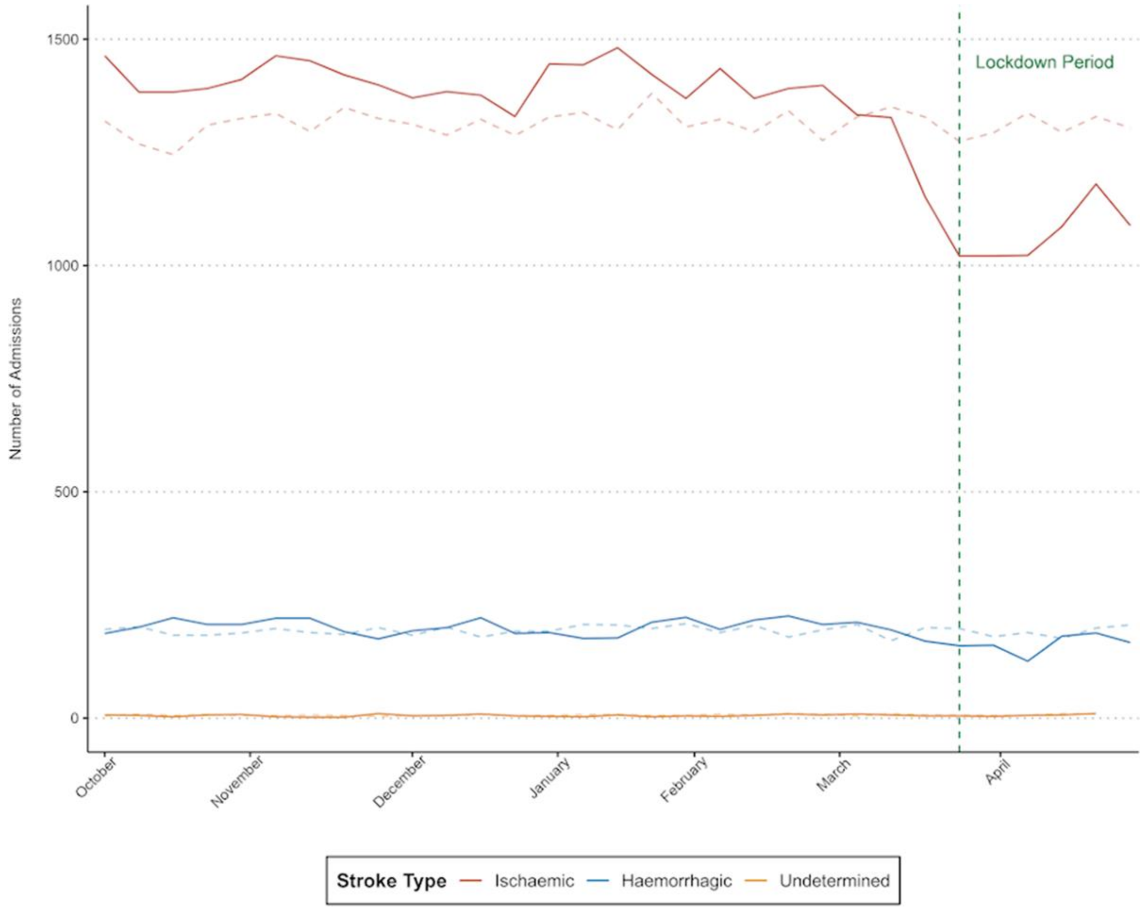

Figure 3. Weekly number of admissions for IS, primary intracerebral hemorrhage, and undetermined stroke from 1 October 2019 to 30 April 30 2020, compared with the three previous years (dashed lines). Figure of Douri et al. 2021. Original publisher: Stroke on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. (141)

However, the absolute volume of IVT decreased considerably by 69.67%, and the rate of IVT remained unchanged during the lockdown period compared with the mean of historical control periods (13.99% (836/5975) versus 13.38% (2756/20591), p=0.235, respectively). Regarding the absolute number and rate of EVT, no remarkable changes could be observed during the lockdown period compared to the identical period of 2019 (2.03% (121/5974) versus 1.76% (128/7269), p=0.293, respectively) (141). Interestingly

Douiri et al. reported that the quality of acute stroke care was preserved for all measures and in some domains improved during the lockdown: there was a 9.1% ($p<0.001$) absolute benefit increase (ABI) for direct admission to a stroke unit within 4 hours of hospital arrival, a 5.0% ($p<0.001$) ABI for receiving a brain scan within 1 hour of hospital arrival, a 5.6% ($p<0.001$) ABI for stroke specialist physician assessment within 24 hours, a 2.2% ($p<0.001$) ABI in stroke nurse assessment within 24 hours ($p<0.001$) and a 3.3% ($p<0.001$) ABI for swallow screen within 4 hours of hospital arrival (141). Nonetheless, it is important to note that all these quality parameters describe only the intra-hospital workflow but not the pre-hospital phase of acute stroke care. Notably, the pre-hospital delay was not accessed in this study.

The nationwide survey conducted by the U.K. Neurointerventional Group and the British Society of Neuroradiologists, in which all but one thrombectomy-capable center (27/28) participated, showed a significant 27.7% decline in EVT volume in April 2020 compared to the first three months of the year. Half of the active centers (three of the 27 thrombectomy-capable centers did not provide thrombectomy service at the time of the study) reported delays to the patient pathway, especially related to the pre-hospital phase of acute stroke care. Two-thirds of the responders stated that the reason for the delay was delayed presentation from stroke onset (longer onset-to-door time). Additional reasons were delayed referral and delayed inter-facility transfer to the thrombectomy center, and delayed investigation of thrombectomy candidates. Furthermore, 16/24 centers reported limited resources, including scarcity of appropriate beds, lack of anesthetic availability, angiography room occupancy for patient recovery, and delays from additional COVID-19-related angiography room cleaning (140).

1.3.2.2.3.3. The Netherlands

On 15 March 2020, the Dutch government implemented a nationwide lockdown, maintained for nearly two months until May 11th, when several restrictions were abated. At the peak of the first COVID-19 epidemic wave, there were 65 daily new confirmed SARS-CoV-2 cases per day per million inhabitants and 189 weekly COVID-19 hospital admissions per million inhabitants; compared to 71 daily cases and 317 hospital admissions per million in the UK and 96 daily cases per million in the USA (144).

An early study from Amsterdam, which analyzed data from the three hospitals (two primary and one comprehensive stroke center) that provide acute stroke care for the Amsterdam region (approximately 1.1 million inhabitants), reported a 24% fall in the stroke code activations (309 versus 407, IRR 0.76, 95% CI: 0.65–0.88, respectively; p value is not reported) and a 15% decrease in the number of admissions for transient ischemic attack (TIA) or IS (212 versus 248, IRR 0.85, 95%CI: 0.71–1.02, respectively) during the peak of the COVID-19 outbreak in The Netherlands (16 March – 31 May 2020), compared an antecedent seven-weeks control period. While the absolute numbers of IVT and EVT decreased by 15% and 13% (IVT: 50 versus 59; EVT: 20 versus 23, respectively), the rate of IVT and EVT delivery among patients admitted for IS did not change remarkably (IVT: 28% (50/180) versus 30% (59/194), p=0.58; EVT: 11% (20/180) versus 12% (23/194), p=0.82, respectively) during the COVID-period, compared to the control period. While Rinkel et al. presented a 37 minutes delay in the pre-hospital phase of acute stroke care (median onset-to-door time: 187 [71-606] versus 150 [75-544] minutes, p=0.39), the time metrics of intra-hospital workflow (median door-to-CT time: 13 [8-22] versus 12 [8-21] minutes, p=0.42; median door-to-needle time: 31 [21-51] versus 28 [21-40] minutes, p=0.39; median door-to-groin time: 112 [70-155] versus 96 [61-128] minutes, p=0.24, respectively) were comparable during the peak of the first COVID-19 wave, compared to the control period (145).

Later, Benali et al. performed a comprehensive nationwide analysis in The Netherlands, including all consecutive acute IS patients who received one or both acute reperfusion treatments in one of the 17 Dutch comprehensive stroke centers from 11 May 2017 to 11 May 2020. Noteworthy that in The Netherlands, EVT is not performed outside these centers, but IVT could be given in other primary stroke centers. Compared to the identical period of 2019, the lockdown period (15 March - 11 May 2020) resulted in a decline of 14% in patients with acute IS treated with reperfusion treatments in the comprehensive stroke centers of The Netherlands. As for the IV-tPA treatments, a decline of 11% was observed (317 versus 355, p=0.153, respectively), while EVT volume declined by 4% (293 versus 305, p=0.653, respectively) (144).

Withal, the authors not only compared data of a COVID-19 period with the identical period of the previous year, but they performed a trend analysis using linear regression analysis of previous years' data up to May 2017. During this analysis, while the monthly

EVT numbers showed an increase since 2017, there was a profound decline from April to May 2020 (152 and 159 cases were observed compared to the expected 200 and 202, respectively). These numbers even declined below 95% (April 173–226 cases; May 176–229 cases) and 99% CI (April 164–236 cases; May 166–239 cases) (Figure 4.) (144).

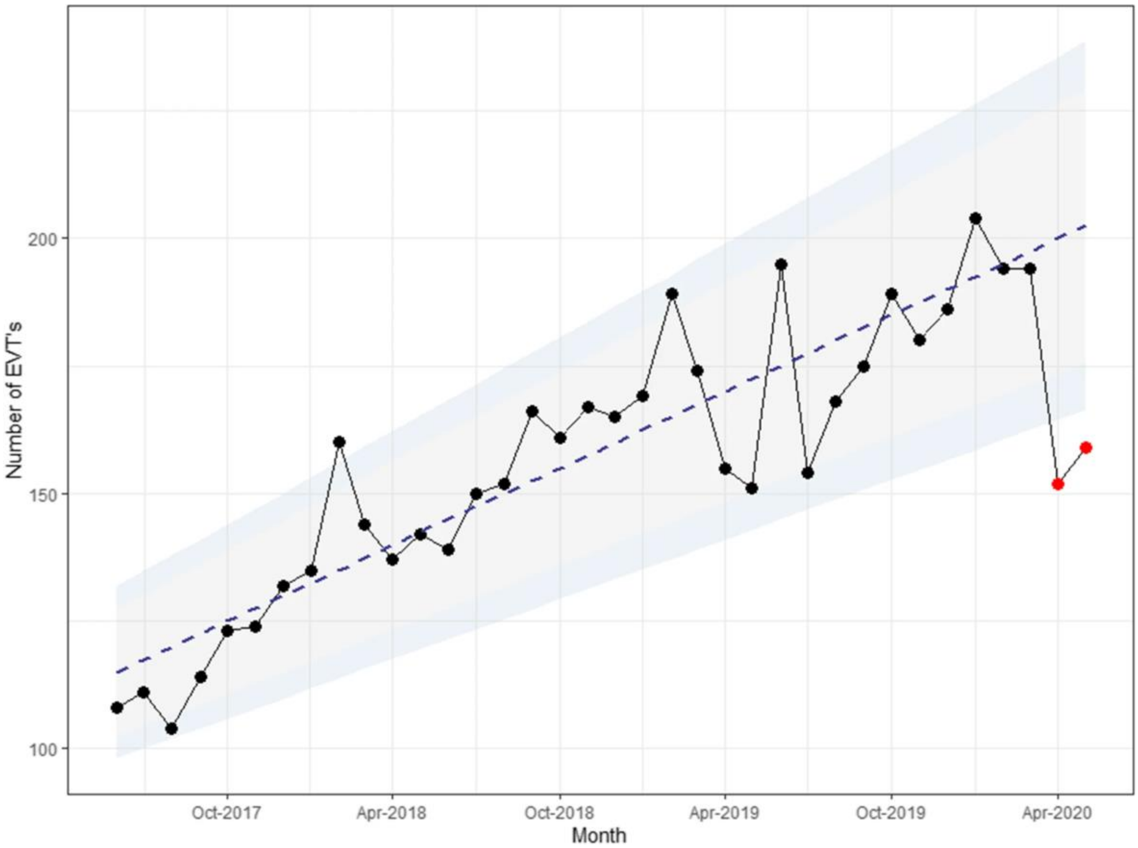

Figure 4. Number of EVTs per month of all Dutch comprehensive stroke centers from 12 May 2017 until 11 May 2020. The red dots represent the lockdown months. The grey and blue area represent the regression line's 95 and 99% confidence intervals (based on the non-COVID months). The monthly numbers are based on the period ranging from the 12th of the previous month to the 11th of the mentioned month; i.e., October 2018 includes data from 12 September 2018 until 11 October 2018. Figure of Benali et al. 2022. Original publisher: Springer Nature. CC-BY. (144)

While the onset-to-door times for patients receiving reperfusion therapy did not show a remarkable change, the median door-to-needle time was slightly prolonged (30 [20-42] and 27 [20-40] minutes, $p=0.052$, respectively), and the door-to-groin time showed a significant increase of 12 minutes (62 [40-86] versus 50 [27-73] minutes, $p<0.001$) during the lockdown period compared to the reference period of 2019 (144). In addition, lengthening door-to-groin time was observed in those patients who received only EVT (median 46 to 58 minutes, p=0.001) and also in the subgroup of patients who received both treatments (median 66 to 70 min, p= 0.651). These results suggest that the pre-hospital phase of acute IS care and the intra-hospital workflow surrounding IVT were largely unaffected, while the intra-hospital workflow of EVT was prolonged during the lockdown period. Interestingly, the time metrics of acute reperfusion treatments were similar for the COVID-19 positive or suspected cohort and the COVID-19 negative or not-suspected cohort, which suggest that the same quality of care could be provided for both cohorts (144).

1.3.2.2.3.4. Belgium

Belgium was one of the first European countries affected by the COVID-19 pandemic after Italy and France. On 4 February 2020, the first Belgian tested positive for SARS-CoV-2, and on 4 March 2020, the first death associated with COVID-19 in Belgium was reported. On 18 March, the Belgian government declared a lockdown for the entire country to close schools, shops, bars, and restaurants. At the same time, the Belgian Public Federal Health service recommended performing only emergency and oncological surgeries and postponing elective cases to increase the availability of ICU beds and hospital beds on regular wards for patients with COVID-19 to overcome potential scarce medical resources (146).

Raymaekers et al. evaluated the impact of the first wave of the COVID-19 epidemic on the volume and quality parameters of acute stroke care in Belgium by analyzing data from the seven main comprehensive stroke centers and one primary stroke center. They compared a COVID-period (March-May 2020) with the three months directly preceding the first wave (December 2019 - February 2020) and the corresponding time epoch in the prior year (March-May 2019). During the first wave of the COVID-pandemic, the volume of hospitalizations for acute stroke was reduced by 15.9% and 14.5%, compared to the pre-pandemic and the corresponding prior-year epoch, respectively (860 versus 1023, p=0.030; 860 versus 1006, p=0.045, respectively). Similarly, in March-May 2020, the mean monthly stroke hospitalizations decreased by 15.8% (35.8±4.0 versus 42.5±1.1, p=0.025) and 14.6% (35.8±4.0 versus 41.9±1.9, p=0.002) compared to the pre-COVID epoch and the prior-year periods. In addition, in 2020 spring, the COVID-19 hospitalizations peaked in April, coinciding with the maximum decline in stroke hospitalizations. Although the absolute volume of acute revascularization treatments did not alter statistically significantly between the examined periods, there was a clear trend for a decline in IVT volume during the COVID-19 outbreak compared to the prep-pandemic (-14.5%, 177 versus 207, p=0.055, respectively) and the prior-year periods (-10.6%, 177 versus 198, p=0.200, respectively). During the COVID-19 crisis, a similar reduction could be shown in the EVT numbers compared to the pre-pandemic epoch (-12.7%, 145 versus 166, p=0.240) but not compared to the prior-year period (+7.4%, 145 versus 135, p=0.280, respectively). The relative rate of IV-tPA delivery was comparable between the COVID-period (20.6%), the pre-pandemic epoch (20.2%), and the prior-year control period (19.7%). Similarly, the proportion of EVT treatments was similar in the COVID-19 pandemic epoch (16.9%) and the pre-pandemic period (16.2%) but was significantly higher with 3.5% compared to the prior-year period (13.4%, p=0.022). Time metrics reflecting intra-hospital workflow of acute revascularization treatments were unchanged between the different time epochs, including door-to-needle and door-to-groin times. Data regarding pre-hospital delay was not presented. Raymaekers et al. found no difference in stroke outcome after 90 days between patients treated during the first COVID-19 wave (median mRS 2) and the prior year (median mRS 2, p 0.440) or the pre-pandemic period (median mRS 2, p=0.455) (147).

1.3.2.2.3.5. Germany

On 27 January, the first SARS-CoV-2 infection in Germany was detected in the Bavaria region near Munich (135, 148, 149). After the first two COVID-19-related deaths were reported on 9 March 2020 in North Rhine-Westphalia, on 16 March 2020, The German Ministry of Health recommended postponing all elective treatments to increase hospital capacities for patients with COVID-19. Shortly afterward, during 12. week of 2020, the German government introduced strict hygiene and lockdown measures in all German federal states for strong social distancing to control the spread of the COVID-19 epidemic (3, 150, 151). However, there was no major reorganization in the stroke care system in Germany, including 332 certified stroke units. Most stroke units were not closed or transformed into ICUs for patients with COVID-19, except for a few hospitals with stroke units that were temporarily unable to admit new patients due to a clustered SARS-CoV-2 infection among patients and medical staff (124). On 21 May, Germany reported 178,545 cumulative SARS-CoV-2 infections and 8,172 COVID-19-related deaths (124).

An early single-center study from the Bavarian Comprehensive Stroke Center reported that the number of stroke codes activations by EMS and IS admissions did not change during the Bavarian lockdown period (21 March - 19 April 2020) compared to the pre-lockdown period of 2020. Similarly, the portion of patients receiving invasive stroke treatment (IV-tPA or EVT) between both periods did not change. These data suggest that the COVID-19 outbreak and strict containment measures do not necessarily disrupt acute stroke care systems (149). In contrast, a single-center study from the University Hospital Düsseldorf, the only tertiary stroke center in Düsseldorf providing EVT for around one million inhabitants, experienced a 37.4% drop in the mean number of patients admitted to the emergency department per day (73.8 versus 117.8, $p<0.0001$) along with an 18.8% decline in the mean daily number of stroke diagnosis in the emergency department (2.6 versus 3.2, $p>0.05$) and an 8.0% reduction in the mean daily stroke hospitalizations at the stroke unite (2.5 versus 2.3, $p>0.05$) during the lockdown period (16 March - 12 April 2020), compared to the identical period of 2019. While the volume of IV-tPA delivery was comparable (23.8% (15/63) versus 24.3% (17/70), $p>0.05$, respectively), the rate of EVT decreased significantly by 58% (12.7% (8/63) versus 30% (21/70) $p<0.05$, respectively) during the lockdown period, compared to the control period. Compared to the identical control period of 2019, Jansen et al. observed a marked 21.5 minutes pre-hospital delay (median onset-to-door time 120.5 [55.5-300.5] versus 99.0 [57.0-445.25] minutes, $p>0.05$, respectively), while the median door-to-needle time shortened with 5 minutes (42 [20.0-62.5] versus 47 [37.3-57.3] minutes, $p>0.05$, respectively) and the median door-to-groin time lengthened with 8 minutes (85 [36-85] versus 77 [32-116] minutes, $p>0.05$, respectively) during the lockdown period (151).

Accordingly to the previous two studies, a report from four German academic comprehensive stroke centers showed that centers were affected differently, partly might be attributable to the COVID-19 burden. While in two centers (University Hospital Dresden and University Medical Center Mannheim), stroke admission rates decreased significantly by 38 % (IRR 0.62, $p=0.046$) and 46% (IRR 0.54, $p=0.005$) during the 12-15. weeks of 2020, compared to the 1-11. weeks of 2020, the stroke hospitalization volume did not alter considerably at the other two centers (Medical Center University of Freiburg, University Medical Center Mannheim). Regarding the volume of acute reperfusion therapies, only the University Hospital Dresden reported a significant drop in the IV-tPA (-60%, IRR 0.40, p=0.003) and EVT delivery rate (-61%, IRR 0.39, p=0.022) during the COVID-period, while the other centers did not observe a significant alteration. As a unique approach, the authors correlated the hospitalization volumes for stroke or TIA and the public mobility generated through the registration of mobile phones with cell towers. A pronounced decrease in public mobility was noted in all four cities, reflecting the confinement measures. Besides, in three of four stroke centers, Hoyer et al. found a significant positive correlation between the cumulative admission rates for stroke or TIA and the public mobility (kilometers traveled) during the COVID-19 pandemic (University Hospital Dresden: correlation coefficient=0.54, p=0.047; Medical Center University of Freiburg: correlation coefficient=0.54, p=0.045; University Medical Center Mannheim: correlation coefficient=0.61, p=0.020). In summary, COVID-19 had a significant impact on most of the analyzed academic stroke centers, especially on those affected early and more severely by the COVID-19 pandemic (81.38-237.90 SARS-CoV-2 infections/100 000 inhabitants during 12-15 weeks of 2020). In contrast, at the Medical Center University of Freiburg, no significant impact of the COVID-19 pandemic was noted, which might be partly attributable to its location in a state with lower numbers of COVID-19 cases (56.39 COVID-19 cases/100 000 inhabitants during 12–15 weeks of 2020) (3).

An analysis of a large German cohort of 12 centers (seven university hospitals, five municipal hospitals) with highly standardized pre-hospital and intra-hospital algorithms distributed across Germany evaluated the trend of IS, TIA, and EVT volumes. The study showed that while the numbers of patients with IS and TIA were slightly reduced during the first surge of COVID-19 (March-May 2020), the trend of EVT numbers did not show relevant alteration during the whole study period (January 2019-May 2020). Besides, they analyzed the workflow time intervals in patients treated with EVT during the COVID-19 outbreak (March-May 2020) compared to the same time interval in 2019. Direct-to-center patients treated with EVT in 2020 showed similar pre- and intra-hospital workflow time intervals compared to patients admitted in 2019. EVT patients admitted through inter-hospital transfer in 2020 also showed similar workflow time intervals compared to patients in 2019, except for a longer door-to-groin puncture time in 2020 (47 min versus 38 min, p=0.005, respectively). Noteworthy that the rate of patients admitted through inter-hospital transfer was not significantly different between 2019 and 2020 (152).

A nationwide analysis of acute stroke care during the COVID-19 pandemic with almost 100% coverage of all hospitalized patients in Germany (1463 hospitals) showed that during the pandemic period (16 March - 15 May 2020), admissions for acute IS sharply dropped by 17.4% (31 165 versus 37 748, respectively) compared with the pre-pandemic period (16 January - 15 March 2020) and fell by 18.5% compared to the corresponding period in 2019 (31 165 versus 38 247), respectively. Concerning acute reperfusion treatment in patients with acute IS, differences between absolute numbers and relative rates, and between IVT and EVT were noted. While the absolute numbers of IVT markedly decreased by 16.4% (51750 versus 6186), parallel to the decline in IS hospitalizations' volume, the IV-tPA delivery rate remained unchanged during the COVID-period compared to the pre-pandemic (16.6% versus 16.4%, p=0.478, respectively) or historical control period (16.6%, versus 16.2%, p=0.190, respectively). The absolute EVT numbers also decreased during the COVID-19 outbreak, compared to the pre-pandemic control, but to a lesser degree with 13.0% (2514 versus 2888, respectively). However, the relative rate of EVT delivery slightly but significantly increased during the COVID-crisis compared to the pre-pandemic and historical control periods (8.1% versus 7.7%, p=0.044; 8.1% versus 6.8%,p<0.001, respectively) (150). As a strength of the study, they reported EVT efficacy and functional outcome measures in a large German cohort. ET efficacy measures, such as the number of retrieval attempts and the rate of successful reperfusion, did not differ between patients in 2020 and 2019. Functional outcome at discharge (modified Rankin-scale, mRS) was not different between 2020 and 2019 (adjusted odds ratio, 1.00 [95% CI, 0.77–1.31]) after adjustment for potential baseline confounders (sex, age, National Institutes of Health Stroke Scale (NIHSS)) (150).

In summary, regarding the volume of stroke care, the observations and data from Western Europe seem in line with the Southern European and Northern American experiences. Data suggest that a considerable decline in the volume of IS admissions was a general phenomenon during the COVID-19 crisis, to which extent varied among regions and health care systems. The acute reperfusion treatment numbers seemed to show a generally lesser decline with greater variations, especially in the case of EVT. However, in contrast to Southern Europe, pre-hospital delay in the presentation of acute IS patients was not a general phenomenon in Western Europe, except in the UK. Data about the time metrics of intra-hospital acute IS care were less consistent but generally suggested that intra-hospital workflow surrounding acute reperfusion treatment was largely unaffected in Western Europe. The time and other quality parameters suggest that those patients with acute IS who did seek acute hospital care during the COVID-19 crisis were treated with the same high quality as before the COVID-19 pandemic. Differences between countries, regions, and centers might be attributable to the extent of the COVID-19 burden, the system of stroke care, the level of organization and standardization of workflows, and the diversity of health care reorganizations due to COVID-19.

1.3.2.2.4. Central Europe

1.3.2.2.4.1. Poland

The first case of COVID-19 in Poland was diagnosed on 4 March (10. calendar week) 2020. By 30 April 2020, 12,877 laboratory-confirmed COVID-19 cases and 644 COVID-related deaths were reported in Poland. According to data from the European Centre for Disease Prevention and Control, the number of reported cases per 100 000 population in Poland was one of the lowest in the European Union during the spring of 2020 (136, 153). Within two weeks of the first laboratory-confirmed COVID-19 case, Poland had implemented numerous public health interventions to mitigate the early spread of SARS-CoV-2, including encouraging social distancing, cancellation of scheduled hospital admissions, banning mass events, closing borders, limiting trade, closing educational institutions, introducing childcare allowances (136). On 20 March 2020, Poland was placed on lockdown by the government (136, 154). The four-step lifting of these restrictions began on 20 April 2020 (153).

A small-scale study from a rural stroke center in Sandomierz, southeastern Poland, during the first epidemic wave of COVID-19 (15 March - 31 May 2020) noted about one-fifth fewer patients admitted with stroke (74 versus 88, respectively) and three times lower rate of IVT delivery (9,86 versus 29,3%, respectively) with a 14 minutes delay in the median door-to-needle time (54 minutes versus 40 minutes, respectively), compared to the same epoch in 2019. Furthermore, in 2020 there were no EVT procedures in this timeframe, but no proper comparison with the pre-pandemic year was possible, as EVT was not available in 2019 because the thrombectomy center was under set up at that time (155).

The stroke network of Małopolska Voivodeship, a region in southeastern Poland with a population of 3.36 million inhabitants, encompasses 15 primary stroke centers and one comprehensive stroke center (University Hospital in Krakow). Słowik et al. reported a 15.5% fall in stroke admissions (891 versus 1042, respectively) during March-April 2020, compared to the first two months of the year. Similarly, the absolute number and the relative rate of IV-tPA delivery decreased remarkably by 26.5% and 13.9% during this first wave of the COVID-epidemic (16.1% (143/891) versus 18.7% (195/1042), respectively). The number of patients treated with EVT was 25% lower between January and May 2020 (n=74) than in 2019 (n=99). Interestingly, in May 2020, when COVID-19 restrictions began to be lifted, the authors noted an increase in the volume of stroke admissions and IVT (no data provided regarding EVT): the number of stroke admissions in March, April, and May 2020 was 472, 419, and 451; the number of IVTs in March, April, and May 2020 was 77, 66, 76, respectively (153).

Dębiec et al. analyzed the case volumes and logistics time metrics of acute stroke care, during the first surge of COVID-19, in the two major comprehensive stroke centers of Masovian Voivodeship in east-central Poland that serve as referral bases for 15 primary stroke centers in this region (population of 800,000 inhabitants). They noted a 20.2% significant reduction in the overall stroke admissions (186 versus 233, p<0.05, respectively) and a 10.0% marked decrease in the number of IS admissions (153 versus 170, p=0.2, respectively), along with a remarkable fall in the volume of hospitalizations for TIA (-55.6%, 20 versus 45, p=0.01, respectively) during 10-18. weeks of 2020 compared to the same period in 2019. Although the absolute numbers of IVT and EVT reduced by 20.6% and 12.8%, the relative rate of IV-tPA and EVT were comparable between 2020 and 2019 (29.0% (54/186) versus 29.2% (68/233), p=0.09; 18.3% (34/186) versus 16.7% (39/233), p=0.60, respectively). Besides, the study reported a remarkable pre-hospital and intra-hospital delay in the delivery of acute reperfusion treatments during the first wave of the COVID-19 epidemic compared to the control period: the mean onset-to-groin time lengthened by 36 minutes (259±80 versus 223±71 minutes, p<0.01, respectively), the mean door-to-CT-time prolonged with 12-14 minutes (IVT cohort: 38±25 versus 26±10 minutes, p<0.01; EVT cohort: 41±27 versus 27±10 minutes, p=0.04, respectively), the mean door-to-needle time lengthened with 18 minutes (48±24 versus 30±21 minutes, p<0.01, respectively) and the door-to-groin time delayed with 38-48 minutes (inter-facility transfer cohort: 73±76 versus 35±41 minutes, p=0.04; no inter-facility transfer cohort: 124±75 versus 76±56 minutes, p=0.03 respectively) (154).

1.3.2.2.4.2. Czech Republic

In the Czech Republic, the first three cases of infection with SARS-CoV-2 were confirmed on 1 March 2020. By the end of 2020, the Czech Republic accounted for 718,661 cumulative SARS-CoV-2 infections and more than 11 thousand confirmed COVID-19 deaths (18, 156). A nationwide analysis that included all the 13 tertiary and two secondary neurovascular centers in the Czech Republic showed that EVT volume increased from 440 procedures in 2013 to 1468 procedures in 2019 (+233.64%). The number of EVTs increased in every year from 2013 until 2019: 2014: +40.68% (179) , 2015: +35.54% (220), 2016: +23.24% (195), 2017: +12.77% (132), 2018: +13.21% (154), 2019: +11.21% (148). However, the increasing trend in the number of EVTs was disrupted in 2020, with a 1.29% (19) decrease in the procedure volume, compared to 2019, which could be highly attributable to the COVID-19 pandemic (157).

1.3.2.2.4.3. Slovakia

The first SARS-CoV-2 patient in Slovakia was registered on 6 March 2020. By the end of April 2020, Slovakia (population: 5.458 million) registered 1396 COVID-19 patients, and 23 had confirmed deaths related to SARS-CoV-2. The national lockdown was ordered on 13 March, but due to the low incidence of COVID-19-positive patients in Slovakia, there was only a small reorganization of hospitals and, unlike in Italy, the number of comprehensive or primary stroke centers was not reduced (18, 158). Gdovinová et al. conducted a nationwide study in Slovakia using the stroke register of the National Health Information Centre, which includes data from all the 43 hospitals that participate in the network for acute stroke treatment in Slovakia. The authors reported that the volume of overall stroke hospitalizations declined by 28.1% and 22.4% in March-April 2020, compared to the identical period in 2019 and January-February 2020 (1673 versus 2328; 1673 versus 2155, respectively). Similarly, a marked reduction was found in the number of IS admission in March-April 2020, compared to March-April 2019 and January-February 2020 (-25.7%, 1332 versus 1792; -31.8%, 1332 versus 1954, respectively). Although the absolute number of IVTs decreased remarkably to 20.2% and 29.8% during the COVID-crisis, compared to March-April 2019 and January-February 2020 (274 versus 346; 276 versus 393, respectively), the proportion of patients treated with IV-tPA was comparable (22.4% in March-April 2020 versus 20.1% in March-April 2019, p=0.43; 22.4% in March-April 2020 versus 21.1% in January-February 2020, p>0.05). Similarly, there was a remarkable fall in EVT volume in March-April 2020, compared to the identical period in 2019 and January-February 2020 (-29.2%, 109 versus 154; -36.6%, 109 versus 172, respectively). However, no significant difference was found in the rate of EVT delivery between the COVID-19 period (10.2%) and the same period in 2019 (10.7%) and January to February 2020 (13.1%). Besides, during the first surge of COVID, no significant pre-hospital or intra-hospital delay was noted in the onset-to-door and onset-to-needle times, compared to the control periods: median door-to-needle time: 30 [16–45] versus 35 [20–50] minutes, p=0.06 (March-April 2020 versus March-April 2019); 30 [16–45] versus 30 [20–50] minutes, p=0.27 (March-April 2020 versus January-February 2020); median onset-to needle time: 130 [100–195] versus 130 [95–180] minutes, p=0.13 (March-April 2020 versus March-April 2019); 130 [100–195] versus 140 [106–188] minutes, p=0.86 (March-April 2020 versus January-February 2020). As a strength of this national scale study, Gdovinová et al. reported early functional outcomes of acute stroke patients, which were not significantly different during the COVID-19 epidemic, compared to the identical period in 2019 (median mRS 3 [1-5] versus 2 [1-4], p =0.32, respectively) and January-February 2020 (median mRS 3 [1-5]) versus 3 [1-5], p=0.41, respectively) (158).

In summary, data regarding changes in stroke care systems during the SARS-CoV-2 pandemic in Central European countries are more limited than in Western or Southern Europe. However, available data suggest that a considerable drop in the volume of IS admissions could be considered a general phenomenon during the COVID-19 crisis, the extent of which varied among counties, regions, and health care systems. A decline in acute reperfusion treatment numbers could also be detected in every Central European country (with available data), the extent of which varied widely. Data about the time metrics of pre-hospital and intra-hospital acute IS care were more limited and conflicting (no date from the Czech Republic). While Dębiec et al. from Poland reported a remarkable pre-hospital and intra-hospital delay in delivering acute reperfusion treatments, Gdovinová et al. from Slovakia did not find a considerable delay in the workflow during the first epidemic wave of COVID-19. The impact of COVID-19 on countries and regions might differ based on different stroke care systems, the level of development of the acute reperfusion interventions, the amplitude of the SARS-CoV-2 epidemic, and the diversity of health care reorganizations due to COVID-19.

1.3.2.2.5. Impact of COVID-19 on low- and middle-income countries

1.3.2.2.5.1. World Bank classification of country economies by gross national income

Every year World Bank classifies every country by its economy's performance through the gross national income (GNI) per capita parameter, calculated using the World Bank Atlas method. For the current 2022 fiscal year, high-income countries are defined as those with a GNI per capita of 12,696 USD (United States Dollar) or more, middle-income countries are those with a GNI per capita between 1,046 USD and 12,695 USD, and low-income economies are characterized by a GNI per capita of 1,045 USD or less (159). The high-income countries comprise the Northern American countries, Australia, and almost every European country like France, the United Kingdom, Italy, Germany, The Netherland, Hungary, Poland, or the Czech Republic, but includes many other countries like Japan, Chile, Singapore, Israel, Saud Arabia, the United Arab Emirates, and Taiwan. The group of LMICs contains many countries worldwide, through Asia (i.e., India, Iran, Thailand, Syria, Afghanistan, China, Vietnam), Africa (i.e., Tunisia, Malawi, Ghana, South Africa, Central-African Republic, Nigeria), South America (i.e., Brazil, Bolivia, Guinea, Guatemala, Ecuador), and Europe (i.e., Romania, Bulgaria, Georgia) (159).

1.3.2.2.5.2. Stroke burden in low- and middle-income countries

Stroke is a global health problem of great importance, with the second leading cause of death worldwide and one of the leading causes of disability. Up to 50% of stroke survivors are chronically disabled, which causes a tremendous public health burden with severe economic and social consequences (1-3, 160, 161). Stroke-associated deaths have risen globally from 5.3 million to 6.2 million between 2007-2017. The PURE study showed that clinical outcomes after stroke were substantially poorer in LMICs than in high-income countries. In 2013, 75% of stroke-associated deaths and 81% of disabilities due to stroke occurred in LMICs. Based on the high prevalence of stroke in LMICs, some authors predict that any further increase in stroke prevalence will most likely be driven by LMICs (2, 160, 162).

The INTERSTROKE study, which included 32 countries at different economic levels, showed that the people in LMICS more often had severe strokes and intracranial hemorrhages than people in high-income countries. Besides, evidence-based treatments, diagnostics, and stroke units were less commonly available or used in LMICs than in high-income countries (2). In several LMICs, a large percentage of specialized health services, such as advanced stroke care, are provided by private hospitals, limiting access to specialized stroke care for individuals from poorer sections of society (161, 163-165). Although over the past decade, improvements in stroke care (especially with IVT and EVT) have led to a substantial reduction in the risk of death or disability and improvement in functional outcomes, this is most likely driven by high-income countries (2, 4-12). In Johnson et al.'s systematic analysis of the global stroke burden, the decline in the age-standardized stroke death rate between 1996-2016 was considerably lower in LMICs (21-23%) than in high-income countries (35-52%) (160, 166).

These data suggest that the global burden of stroke is uneven and disproportionately higher in LMICs than in high-income countries (2, 160-162, 167). Guidelines for stroke care are based on evidence from studies in high-resource settings and might have lower relevance to settings where resources are more bounded. Many challenges with stroke care in LMICs are fairly different from those in high-income countries. A high number of patients and a shortage of special expertise are the major barriers to implementing evidence-based stroke management (including IVT and EVT), especially in remote and rural areas. Additionally, restricted funding limits resources such as medications and devices in the public health system (160, 161).

1.3.2.2.5.3. Stroke care during the COVID-19 pandemic in low- and middle-income countries

The COVID-19 pandemic has affected healthcare systems and patients around the world. In many countries, healthcare systems have become overburdened as the efforts to treat patients with COVID-19 have placed a tremendous strain on personnel and resources. Stroke care has been significantly impacted, as evidenced by the widespread observation of a reduction in patient numbers presenting for acute evaluation and treatment (95). Most countries have reorganized infrastructure to optimize human resources and critical services. While high-income countries have many diagnostic and therapeutic resources available for the treatment of acute IS, and recommendations have been published related to maintaining stroke systems of care during the pandemic, LMICs have strained medical resources at baseline and often face challenges in the delivery of optimal stroke care (168). In the following, we will describe how the elements of acute stroke care were impacted in LMICs during the SARS-CoV-2 pandemic.

Public awareness about warning signs and symptoms of stroke is generally low in LMICs. Even when stroke symptoms are recognized, medical help is often not sought because people commonly prefer to consult traditional healers. Lower educational levels and traditional cultural beliefs contribute to a poor understanding of the need for quarantine and distancing measures. These factors may eventually lead to a rise in COVID-19–related as well as stroke-related mortality and morbidity. The pre-hospital component of the chain of stroke care is not well developed in LMICs. Ambulance services are frequently unavailable or have a shortage of trained personnel and proper equipment. In addition, stroke patients are not prioritized many times. As a result, personal conveyance was often used to reach hospitals, and just a very few patients with stroke arrive by ambulance in many LMICs (i.e., 12% in northwest India, 26% in south India, 17% in Tunisia, and none in Ghana and Nigeria). Studies from India showed that from 1.5% to less than 10% of patients reach hospitals by ambulance medical services. During the COVID-19 crisis, the lack of PPE and work overload by the high number of COVID-19 patients adversely affected and further overwhelmed the strained pre-hospital stroke care. Given the high rate of personal conveyance, restrictions in public transport during the lockdown might further restrict the availability of stroke care, especially for patients from remote areas (160, 164, 165, 168-170).

Medical services in LMICs are often ill-equipped to diagnose and treat acute strokes. Recommendations of protected code stroke protocols, when the emergency department and stroke team respond with the most appropriate PPE and reduce exposure risk until COVID-19 status become known, formulated early. However, the implications of protected stroke code protocols in LMICs were often challenging since PPE was in limited supply. A survey from stroke centers in India during the first COVID-19 wave reported that PPE was available for all hospital workers in the triage area only in five of 13 centers, and only 58.3% of centers used full PPE during endovascular procedures (160, 164, 165, 168). Managing the scarcity of SARS-CoV-2 testing capacities was also troublesome in many LMICs. In LMICs, laboratories are often located in the capital cities, so it is not easy to achieve an early diagnosis, and infrastructures for the screening and treatment of COVID-19 are not separate from those devoted to non-COVID-19 healthcare, facilitating the spread of the infection. Munharo et al. reported that during the COVID-19 crisis, Malawi struggled with testing due to inadequate capacity, untrained laboratory personnel, inadequate funding, and lack of policies (160, 168, 171, 172). The absence of timely accessible neuroimaging aggravates the difficulties of diagnosing stroke in LMICs. A systematic review of stroke services in Africa showed that only 13–36% of patients underwent CT or magnetic resonance imaging (MRI) scans, even in areas with operational CT or MRI machines. An early consensus emerged that preserving the standard acute stroke imaging is essential. In order to do this, it was recommended that hospitals design dedicated imaging pathways for COVID-19 suspected or positive patients. However, in many places, separate COVID-19 corridors from the emergency department to imaging units and dedicated CT or MRI scans for COVID-19 suspected or positive patients with acute IS were unavailable (160, 164, 168). These factors might further worsen acute stroke care quality in the already ill-equipped and overburdened emergency departments during the COVID-19 pandemic. This may also be indicated by data reported by the COVID-19 Stroke Study Group (CSSG) India: significantly lower rate of vascular imaging and a significantly higher rate of in-hospital and three months mortality during the first COVID-19 wave (COVID-period versus prior-year control period: 83.19% versus 91.64%, p=0.00001; 6.9% versus 4.12%, p=0.03; 11.96% versus 8.3%, p=0.04) (170).

In the LMICs, the number of hospital beds and health workers is generally lower compared in high-income countries. WHO reports only 0.8-2.3 hospital beds per 1000 people in LMICs, while high-income countries have 5.3 hospital beds per 1000 people. According to the WHO, 90% of low-income countries have fewer than ten medical doctors per 10,000 people, compared to only 5% of high-income countries (172). Care of patients in dedicated stroke units is one of the most cost-effective evidence-based interventions which have shown benefit in improving outcomes. However, in LMICs, the availability of neurologists, neurosurgeons, physiotherapists, occupational therapists, speech and language pathologists, and nurses is poor; therefore, internists or family physicians are the ones who usually treat patients with stroke (160, 164, 168). Very few centers have stroke units in some Latin American countries, such as Guatemala and

Ecuador. Despite 90–100% population coverage by the health care system in Uruguay and Bolivia, acute stroke care services are available to only 37% and 65% of the population, respectively. In a systematic review of stroke systems of care in Africa, stroke unit was found only in three (South Africa, Central-African Republic, and Ghana) of 14 countries (160, 164, 168). In most LMICs, the overwhelming need for care for patients with COVID-19 forced the conversion of stroke unit beds into COVID-19 designated beds and the reallocation of staff of stroke units to COVID-19 wards (168). These processes further diminished the already limited number of beds and health care professionals dedicated to stroke care. Although during the COVID-19 pandemic, reduction in stroke hospitalizations was a general phenomenon globally, significant geographic variations could be observed mainly to the detriment of LMICs. In a large-scale cross-sectional study, while the monthly median stroke hospitalization volume dropped by 11.5% globally and 10.9% in Europe, Africa presented a 30.2% decline (99). In a study from Iran, the normalized hospitalization rates for stroke decreased from 68.09 per 100,000 people to 44.50 per 100,000 people during the COVID-19 epidemic (173). The analysis of the CSSG India included 18 stroke centers across the country and showed a marked reduction in the number of stroke admissions in April 2020 compared to the previous year, which correlated well with the surge of COVID-19 cases during the lockdown period (170). The study by Diegoli et al. showed a 36.5% decrease in stroke admissions during the first surge of COVID-19 in Joinville, Brazil (174). The national survey of the Chinese Stroke Association reported a significant reduction of admission patients with stroke, with a lower chance of receiving acute reperfusion treatments during the COVID-19 crisis. In addition, stroke care service in severe COVID-19 epidemic areas was much more severely impacted than in other regions in China (175).

The greatest burden of stroke is in LMICs, and even though the strong evidence for the effectiveness of IVT and EVT in acute IS patients, their use in LMICS is shallow (160, 163, 164, 167). The meta-analysis of Berkowitz et al. from 2014 showed that only 3% of low-income countries and 19% of LMICs reported use of IVT, compared to 50% of high-income countries. In addition, they found that reported use of IV-tPA is strongly associated with total health care expenditure per capita in a country. Of the ten countries with the highest healthcare expenditure per capita, only one country did not report IVT use (Monaco). In contrast, none of the ten countries with the lowest healthcare expenditure per capita reported IVT use for acute IS (160, 163). Even in LMIC, where IVT is available for acute IS treatment, IVT accessibility and affordability are limited. The most critical barriers to IVT use are delayed presentation, lack of emergency transport facilities, and drug cost. Only 30% of acute IS patients could afford IV-tPA in one study from Iran. In Vietnam, a lowered dose of IV-tPA is offered to patients who cannot afford the full dose of the drug (161, 163, 164). With the burden of the COVID-19 crisis, LMICs faced further challenges in delivering IVT, which was already limited in availability at baseline. The cross-sectional study of Nogueira et al. conducted across six continents and 70 countries reported that while in the March-June time frame, the IVT volumes declined by 13.2% globally and 14.4% in North America, the number of IVTs decreased by 24.2% in South America and 23.5% in Africa in 2020 compared to the pre-pandemic year (99). It is noteworthy that the reduction in IVT volumes can only be interpreted in countries and regions where IV-tPA delivery for acute IS has existed before the COVID-19 epidemic. In countries and areas where IV-tPA was not available, the COVID-19 crisis could not cause a decline in the treatment numbers. A study from Iran reported that besides a notable drop in stroke hospitalization numbers, the rate of the already limitedly available IVT was reduced by 10% during the COVID-pandemic (173). Besides the decline in stroke hospitalizations, CSSG India reported a marked reduction in the rate of IV-tPA delivery in April 2020 compared to the previous year, which correlated well with the surge of COVID-19 cases and the lockdown period (170). Similarly, a survey conducted in 13 high-volume stroke centers in India reported a remarkable 61.22% drop in weekly stroke hospitalizations and a dramatic 64.76% fall in IV-tPA delivery in 2020 spring (165). Analysis data from the Big Data Observatory Platform for Stroke of China (BOSC) registry showed that during the first month of the COVID-19 epidemic, the capacity for stroke care was reduced in the majority of the hospitals, and the volume of IVT decreased by 26.7% in China, compared to the previous year (176).

There are substantial socioeconomic disparities in EVT utilization for acute IS, especially in LMICs. In Brazil, for 75% of the population, health care is provided by the public national health system, while private providers cover the remaining 25%. EVT in private practice shares the same profile as developed countries. However, EVT is not reimbursed by the public national health system, thus precluding its use for the majority of the population. In addition, although 64 stroke centers are capable of EVT, only three perform EVT 24/7. In Uruguay, EVT is vastly underused and performed only by a private facility in Montevideo. Similarly, the bulk of EVT delivery is provided by corporate hospitals in India. Literature about the African continent is very limited, and it is unclear which countries have access to EVT. Among the most common limitations are lack of devices, irregular supply of catheters and materials (either due to shortage of funding or inadequate stock logistics), limited access to angiography machines, and shortage of trained neurointerventionalists. Because of the limited access to reperfusion catheters in LMICs, in challenging cases, experienced operators often try unconventional techniques, maneuvers, and accesses (radial or direct carotid accesses) to overcome this limitation. Furthermore, the lack of consistently (24/7) available anesthesia coverage further restricts the number of EVTs. The number of ICU beds is insufficient concerning the population of LMICs. For example, Africa has fewer than 5000 ICU beds, corresponding to five beds per one million people, while in Europe, there are 4000 beds per one million people (161, 172). With the burden of the COVID-19 crisis, LMICs faced further challenges in delivering EVT, which was already limited in availability at baseline. During the SARS-CoV-2 pandemic in most LMICs, some of the stroke unit beds were designated for COVID-19 care, further restricting the already limited number of beds. Socioeconomic disparities in EVT utilization could be worsened during the COVID-19 crisis. For example, in India, individuals suspected of having COVID-19 are supposed to go to designated public hospitals, whereas EVT is mainly accessible in private hospitals, excluding these patients from endovascular treatment. In addition, as the COVID-19 waves evolved, the increasing need for intensive care could shrink further the number of available ICU beds for EVT (165, 168, 172).

The analysis conducted by the SVIN, which included six continents, 40 countries, and 187 comprehensive stroke centers, revealed that the COVID-19 pandemic was associated not only with a global decline in the volume of overall stroke hospitalizations but also in EVT volume. During the first three months of the COVID-19 crisis, while EVT volume dropped by 19.2% globally and 14.4% in Europe, Africa presented a 21.2% decline compared to the data of three months immediately preceding the COVID-19 pandemic (35). The BOSC registry data analysis demonstrated a significant 23.5% drop in the number of EVTs during the first month of the COVID-19 epidemic across China (176).

A survey conducted among 13 high-volume stroke centers across India in 2020 reported a notable fall in the volume of stroke hospitalizations and IVTs (-64.76% and -61.22%, respectively). The EVT numbers also decreased remarkably by 67.21% during the first COVID-19 wave. Moreover, it is noteworthy that EVT for acute IS patients was utterly halted in five of the 13 stroke centers (165). Similarly, CSSG India reported a dramatic 26.5% fall in the rate of EVT delivery during the first six months of the COVID-19 epidemic, compared to the identical epoch in 2019 (36.75% versus 63.25%, p=0.00007) (170). It is important to note that the reduction in EVT volumes can only be interpreted in countries and regions where EVT delivery for acute IS has existed before the SARS-CoV-2 epidemic. In countries and areas where EVT was not available, the COVID-19 crisis could not cause a decline in the procedure numbers.

The COVID-19 pandemic has overwhelmed health care systems, including stroke care, even in high-income countries, experiencing shortages of health personnel, ventilators, PPE, and testing capacity. Based on the above presented data, it seems reasonable to think that in LMICs, where medical resources are scarce at baseline, the impact of the COVID-19 pandemic on the stroke system of care in LMICs could be substantially worse compared to most high-income countries, which is deeply troubling concerning the high prevalence of stroke in LMICs.

1.3.2.2.5.4. China

The first national health care system faced with COVID-19 was China’s, as the SARS-CoV-2 pandemic started in December 2019 in Wuhan, China (14-16, 18, 177). Considering this fact and China's large population and territory (over 9000 new stroke cases occur each day in China), it seems essential to discuss the impact of COVID-19 on stroke care in China in a separate chapter (94).

As the COVID-19 crisis emerged, comprehensive measures were mandated in China to contain the spread of the disease, including converting general medical wards to quarantine wards, locking down the communities, suspending routine outpatient clinics, stopping all elective procedures, and providing treatment only for very highly selective cases in many areas across China. Thus, standard medical care across China has been seriously impaired, with stroke being at the forefront, given that it is the top cause of death and disability in the country (94). During the COVID-19 crisis, thousands of designated

COVID-19 hospitals have been established in China to centralize and treat patients with SARS-CoV-2 infection. These COVID-19 designated hospitals were often large regional tertiary care centers. While designated COVID-19 hospitals have played an essential role in fighting the SARS-CoV-2 pandemic, their stroke centers have suffered an unprecedented strain. Besides, over 40 000 medical professionals from all over China have been sent to the disease's epicenter. These clinicians included all subspecialties, such as neurologists and anesthesiologists, draining resources for other disease conditions. Thus, many stroke centers across China have greatly reduced functioning because lack of experienced stroke care experts and the fear of in-hospital cross-infection. To help the COVID-19-related measures and maintain the safety and efficacy of stroke emergency management, several expert recommendations (e.i, protected stroke code) were issued by the China National Health Commission and Chinese Medical Association, which were then implemented locally (94, 175, 177-179).

Chinese Stroke Association reported data (results of a cross-sectional survey) about Wuhan, the first city that had to face the COVID-19 epidemic and maintain acute stroke care simultaneously. Wang et al., in this survey, reported that 84.2% of the responders from Wuhan noted very severe (almost no patients) or severe reduction (>50%) in acute IS admissions during February-March 2020, compared to the same period in 2019. At the same time, 89.5% reported that IVT volume was severely (>50%) or moderately (20%–50%) decreased, and 73.7% experienced that thrombectomy was severely (>50%) or moderately (20%–50%) impacted. The most common reason for IVT and EVT delay was missing the 4.5 hours therapeutic time window on hospital arrival and staff reallocation, respectively (175).

A small-scale study from a comprehensive stroke center in Sichuan Province, covering a four million population, reported a marked 60% fall in acute IS admissions (235 versus 588, p<0.001) in January-March 2020, compared to the identical period of 2019 (comparative numbers regarding IVT and EVT were not reported). Besides, they noted a significant delay in IV-tPA but not in EVT delivery (door-to-needle time: 62±12 versus 47±8 minutes, p=0.019; door-to-groin time: 124±58 versus 135±23 minutes, p=0.682) (180). Another study from a comprehensive stroke center in Hong Kong showed an 18% drop in the number of admissions (stroke, TIA) via the acute stroke pathway during the first 60 days of the COVID-19 epidemic (23 January - 24 March 2020), compared to the same period of 2019. There were no significant differences in the absolute number and rate of IVT (7 [14.9%] versus 8 [15.4%], p=0.95, respectively) and EVT (4 [8.5%] versus 7 [13.4%], p=0.43, respectively) between the two periods. Compared with the same period in 2019, during the COVID-19 crisis, the median symptom onset-to-door time was about 60 minutes longer (154 [60-618] versus 95 [58-291], p=0.12, respectively), and the proportion of patients arriving within the therapeutic time window of IV-tPA was significantly lower (40/73 [54.8%] versus 64/89 [71.9%], p=0.024, respectively), while the metrics of intra-hospital workflow were preserved, including door-to-needle, door-to-groin and groin-to-recanalization times (181).

In contrast, three single-center studies reported a significant disruption in EVT delivery (92, 182, 183). The Xuanwu Hospital, a comprehensive stroke center, reported a 38% drop (21 versus 34, respectively) in the number of acute IS patients treated with EVT during the lockdown period (23 January - 7 March 2020) compared to the same epoch in 2019. Compared to the prior-year epoch, the median door-to-groin time (174 [139-204] versus 126 [113-153] minutes, p=0.002) and median door-to-recanalization time (213 [177-256] versus 172 [148-219] minutes, p=0.047) in the pandemic group was prolonged significantly (92). A single-center study from Beijing noted a 50% decrease in the EVT volume (21 versus 42, respectively) and 132 minutes longer median onset-to-recanalization time (672 [516-1796] versus 540 [450-734] minutes, p=0.049, respectively) with a trend to delay in pre-hospital and intra-hospital time metrics (median onset-to-door time: +50 minutes, p>0.05; median door-to-groin time +24 minutes, p>0.05; median groin-to-recanalization: +14 minutes, p>0.05; respectively) during the first surge of the COVID-19 epidemic (23 January - 8 April 2020) compared with a similar period in the previous year (182). Similarly, another single-center study from the Beijing Tiantan Hospital (the largest comprehensive stroke center in China) observed a gradual increase in the number of EVTs from 2017 to 2019 (36, 62, and 70 patients in the period from 1 January to 30 April, respectively). However, in 2020 (1 January - 30 April, COVID-period), this continuous growth of EVT volume was disrupted and reduced by almost half (36 patients). Regarding intra-hospital workflow time metrics, during the COVID-period, the median door-to-groin time and median groin-to-recanalization time increased remarkably by 110 and 30 minutes, respectively, compared to the identical epoch of 2019 (225 [140-299] versus 115 [92-18] minutes, p<0.0001; 100 [61-146] versus

70 [58-122] minutes, p=0.044, respectively). Despite the delay in the workflow, the safety, efficacy, and functional outcome parameters of EVT were unaffected (183).

The analysis of the data of all (77) stroke centers in Beijing reported a 45.6% reduction (1281 versus 2354, respectively) in all stroke admissions and a 42.9% drop (1132 versus 1984, respectively) in IS admissions during 24 January - 29 April 2020, compared to the same period in 2019. Besides, a negative correlation was shown between newly diagnosed COVID-19 cases and stroke admissions with marginal statistical significance (CC = −0.176, p=0.084). While the absolute number of IVTs and EVTs decreased markedly by 34% (791 versus 1199, respectively) and 26% (185 versus 250, respectively) during the COVID-19 epoch, the rate of IV-tPA and EVT delivery significantly increased (69.9% versus 60.4%, p<0.001; 16.3% versus 12.6%, p<0.001, respectively), compared to the identical period of 2019, which suggest that the number of IS admissions decreased to a disproportionally larger extent than the volume of acute reperfusion therapies. Regarding time metrics, there was no significant difference in the pre-hospital stage, as indicated by the unchanged median onset-to-door time in the two periods (90 [60-148] versus 90 [58-137] minutes, p=0.306, respectively). However, there was small, but statistically significant delay in the intra-hospital workflow (door-to-CT time: + 1 minutes, p=0.012; door-to-needle time: + 4 minutes, p<0.001; door-to-groin time: +29 minutes, p=0.046, respectively) during the COVID-period, compared to the control epoch (93).

The survey of Zhao et al., which was distributed to the leaders of stroke centers in 280 Chinese hospitals (227 answered, which covers 29 of 31 provinces and municipalities across China), showed that during the peak of the COVID-19 epidemic in China (February 2020), the volume of stroke admissions reduced by 37.9% (21,581 versus 34,725, respectively) with 25.5% drop in the number of IVTs (2031 versus 2726, respectively) and a 22.7% decrease in the EVT volume (727 versus 941, respectively), compared to February 2019. Consistently with the study of Wu et al. above, the significant and remarkable reduction in the absolute number of IVTs and EVTs is accompanied by a slight but significant increase in the rate of IV-tPA and EVT delivery (IVT rate: 9.4% (2031/21,581) versus 7.8% (2726/34 725), p<0.0001; EVT rate: 3.4% (727/21 581) versus 2.7% (941/34 725), p<0.0001, respectively), which suggests that the number of stroke admissions decreased to a considerably larger extent than the volume of acute reperfusion therapies (176). Correspondingly to the survey of Zhao et al., the analysis of these 280 Chinese hospitals' data in the registry of BOSC showed a 26.7% reduction ($p<0.0001$) in the IVT and a 25.3% decrease in the EVT volume ($p<0.0001$) in February 2020, compared to the same period in 2019. Similarly, the number of IVT cases dropped significantly from 3638 cases in January 2020 to 2508 in February 2020 (31.1% decrease, $p<0.0001$), and the number of EVT cases reduced from 1378 cases in January 2020 to 970 in February 2020 (29.6% decrease, $p<0.0001$) (176).

In the national cross-sectional survey of the Chinese Stroke Association, 73.7% of the participant reported that the number of acute IS admissions reduced by 20% or more (32.0% noted a 50% or more decrease) in February-March 2020, compared to the same period in 2019, while just 7.7% experienced no impact of COVID-19. Regarding acute reperfusion treatments, 54.4% of the responders noted a 20% or more fall in the number of IV-tPA delivery, and 39.3% experienced a 20% or more reduction in the EVT volume. The most common reason was missing the therapeutic window on hospital arrival (pre-hospital delay) or too many tests for ruling out COVID-19. Besides, 11.8% and 20.1% reported more than one hour delay in the door-to-needle and door-to-groin times (intra-hospital delay), respectively (175).

While the survey of Zhao et al. did not find differences in the pattern of changes of acute stroke care (IS admissions, IVT, EVT) between hospitals designated for COVID-19 and non-designated hospitals, the survey of the Chinese Stroke Association reported that the volume of IS admissions and acute reperfusion treatments were more severely impacted in COVID-19 designated hospitals compared with non-designated hospitals and also in the severely impacted provinces compared with other regions (175, 176). This phenomenon was also confirmed by the multi-center (77 stroke centers) analysis of Wu et al., in which they reported that the reduction of stroke admissions was significantly greater ($p<0.05$) in COVID-19 designated hospitals (52.6%) than in non-designated hospitals (41.8%) during 24 January - 29 April 2020, compared to the same period in 2019 (93).

China was the first country that had to face the unprecedented epidemic of COVID-19. The health authorities had to take measures to contain the spread of the disease and find the best way to maintain acute stroke care at the same time. The above-presented data convey the impression that a substantial decline in the volume of IS admissions was a general phenomenon during the COVID-19 crisis, to which extent varied among regions and health care systems. The acute reperfusion intervention numbers seemed to show a generally lesser extent decrease with greater variations, and IV-tPA delivery generally looked more severely impacted than EVT volume. Besides, current data suggest that stroke emergency management was more severely impacted in COVID-19-designated hospitals than non-designated hospitals and in the severely COVID-19-impacted regions compared with other areas. Results of the available studies propose there was a tendency to delay acute stroke treatment both in the pre-hospital and in the intra-hospital phase.

1.3.2.3. Impact of COVID-19 on different acute stroke care networks/logistic paradigms

1.3.2.3.1. Mothership and drip-and-ship logistic paradigms overview

The optimal acute stroke network to deliver acute reperfusion treatments is still under scientific debate, and data are conflicting. Complex algorithms combining probabilistic information on vessel status and transport time are available, but there are two main paradigms, the mothership and the drip-and-ship model. In the mothership model, the suspected acute IS patients are directly delivered to a comprehensive stroke center, where both acute reperfusion strategies are available. However, in the drip-and-ship model, patients are carried first to the nearest primary stroke center (spoke), where intravenous thrombolysis (IVT) is available, and then transferred to a comprehensive stroke center (hub) in case of eligibility for mechanical thrombectomy (EVT) (130, 184-186).

A recent, unpublished randomized controlled trial (RACECAT) presented at ESO-WSO and the SVIN annual conferences in 2020 showed a non-superiority or -inferiority of the concept that all patients with suspected large vessel occlusion (LVO) should be redirected to a comprehensive stroke center and bypass the nearby primary stroke center (187). However, a systematic review and meta-analysis from 2020, which encompassed 18 studies (one randomized controlled trial) and 7170 patients, showed that the patients treated in the mothership model had a higher rate of functional independence at 90 days than in the drip-and-ship model while safety parameters (symptomatic intracerebral hemorrhage, mortality at three months) were comparable (184). Similarly, a recent systematic review and meta-analysis of 7824 patients from 13 studies (3 randomized control trials) showed that while the onset-to-needle time did not differ (117.0±19.95

versus 128.25±26.05 minutes, $p=0.205$, respectively) between the mothership and the drip-and-ship paradigm, the onset-to-groin and onset-to-successful recanalization times were significantly shorter with 64.2 minutes ($p \leq 0.001$) and 79.78 minutes ($p \leq 0.001$) in the mothership model, respectively. Besides, Mohamed et al. noted a significantly lower likelihood of good functional outcome (mRS 0–2) at 90 days (odds ratio: 0.74, 95% CI: 0.68–0.84, $p<0.00001$) and a higher likelihood of symptomatic intracerebral hemorrhage (odds ratio: 1.49, 95% CI: 1.22–1.81, $p<0.0001$) among patients in the drip-and-ship model compared to the MS model (186). These results suggest that the mothership paradigm might be superior to the drip-and-ship model

1.3.2.3.1. Impact of COVID-19 on the mothership and drip-and-ship models

The impact of COVID-19 on acute stroke networks based on different logistic paradigms might be different. Romoli et al. conducted a meta-analysis to analyze the effect of different stroke network models on the variations in acute stroke care service performance through the COVID-19 pandemic. This meta-analysis included 29 studies from the first epidemic wave of COVID-19 and data regarding 212,960 patients from three continents (Europe, Asia, and America). During the first surge of the COVID-crisis, a substantial decrease was found in the overall normalized IS admission rates, with a slight trend of reduction for the mothership model and a significant 34% decrease for the drip-and-ship paradigm. Regarding IVT variations, the mothership paradigm preserved the rates of treatment during the COVID-period, while the drip-and-ship model faced a 30% reduction in the weekly normalized IVT rates. Besides, the weekly normalized rates of EVT were unchanged during the COVID-period compared to the control period, independently from the stroke network model. Furthermore, while the most crucial intra-hospital time metrics of acute IS care (door-to-needle, door-to-groin, and door-to-recanalization times) were similar across time frames in either paradigm, the onset-to-door time was considerably longer (+32 minutes, 95% CI: 0–64) in the drip-and-ship model and non-significantly shorter (–12 minutes, 95% CI: -30 - +7) in the mothership paradigm. Besides, the meta-regression analysis showed that the mothership model had a significant impact on shortening onset-to-door time (188). These results suggest that although none of the acute stroke networks were intact by the COVID-19 pandemic, the mothership paradigm seems more able to resist and adapt to the challenges of the COVID-19 epidemic. Further data and phenomenons might further support this hypothesis.

During the COVID-19 outbreak, many acute stroke care systems experienced a trend toward the mothership logistic paradigm through centralization measures due to the pandemic. Patients from large areas started to be primarily directed toward a limited number of centers where they could get comprehensive care without additional interhospital transfer (124).

Italy was one of the most impacted countries in 2020. The overwhelming need for care for patients with COVID-19 induced a substantial reorganization of the Italian health care system, especially in severely hit regions like the Lombardia region. New acute stroke networks have been established in Northern Italy and other Italian parts to centralize care in a limited number of centers. During the centralization, stroke units were closed, hospitals exclusively for COVID-19 were created, healthcare professionals were reallocated, dedicated COVID-19 suspected or positive, and COVID-19 negative pathways were implemented (123, 124, 127, 189, 190). In Lombardy, which was hit by COVID-19 most intensely, as centralization of stroke care, the number of stroke units (hub and spoke) has been reduced from 28 to 10. All stroke patients were transferred by ambulance to these ten hub stroke centers (123). In the region of Veneto, similar centralization measures were implemented, which resulted in a 50% reduction in the number of transfers from the spokes to the comprehensive stroke center during the first surge of COVID-19, as observed by Baracchine et al. (123, 191).

Similarly, in a cross-sectional survey targeting practitioners involved in acute stroke care during the first surge of the COVID-19 crisis in the USA, approximately half of the responders stated (82.5% from a comprehensive stroke center) some change in hospital transport practices, with 17% reporting transferring only some or a limited number of patients (11). A large tertiary health system in southeast Michigan in the USA reported that during the first wave of the SARS-CoV-2 epidemic, the method of arrival was significantly different with more direct transports (51% versus 28%, $p<0.001$) and fewer transfers from other spokes (28% versus 42%, $p =0.015$) (111). Similarly, the multicenter analysis of the TRISP registry depicts a significantly lower rate of IVT and/or EVT patients transferred from other hospitals (29.1% versus 34.9%, $p=0.040$) during the first 6-weeks lockdown period in 20 well-established European stroke centers, compared to an identical period in 2019 (104). Correspondingly, China's largest comprehensive stroke center noted that the proportion of EVT patients who arrived with the inter-hospital transfer was significantly reduced from 37.1% to 13.9% (p=0.014) during the first surge of COVID-19 comparing the identical epoch of 2019 (183).

The rapid spreading of COVID-19 forced a rearrangement of the stroke network also in the Romagna region, central Italy (123, 192). Before the COVID-19 pandemic, this network encompassed two spokes ("Morgagni-Pierantoni" and "Infermi" hospitals) and one hub ("M. Bufalini" hospital). However, in March 2020, the evolving COVID-19 crisis made it necessary to convert the spoke of Rimini province ("Infermi" hospital) into a COVID-19-only hospital. Thus, the acute stroke care in Rimini province was shifted from the drip-and-ship model to the mothership paradigm. Interestingly, the adoption of the mothership model did not cause a delay in IVT but led to a significant reduction in the median call-to-groin (from 192 to 137 minutes, p=0.018) and door-to-groin (from 145 to 79 minutes, p=0.010) times (192).

The Bologna Metropolitan Stroke Network, which has been functioning in the mothership paradigm since 2018, reported that in the March-April time frame, the number of IS admissions did not reduce but slightly increased in 2020 compared to the previous year (118 versus 97, p<0.05, respectively). In addition, the number of EVTs increased significantly (42 versus 21, p=0.025, respectively), and the number of IVTs showed a tendency to increase (51 versus 37, p>0.05, respectively) in 2020. Besides, although the stroke-to-call and door-to-scan times increased (65.5±104.3 versus 33.7±40.2 minutes, p=0.06; 36.7±14.6 versus 28.4±12.6 minutes, p=0.03, respectively), the overall timing from stroke to treatment was preserved during the COVID-19 epidemic (193). Conversely, the acute stroke network of the northern area of Lazio in Italy, which works in the drip-and-ship model, reported considerably greater damages during the first epidemic wave of COVID-19. This network, which was unchanged in its structure during the COVID-crisis, observed a 9% decrease in the number of IS admissions (p=0.061) and a 51% reduction in the number of IVTs (p=0.023), while the number of EVTs did not change remarkably. Regarding time metrics of acute IS care, they reported a significant increase in onset-to-door (+138.5 minutes increase in medians, p<0.001) and door-to-groin times (+24.5 minutes increase in medians, p=0.034), but no significant differences in door-to-needle time (123, 130).

In Northern Italy, where the mothership paradigm is predominant, despite a 24% decline in IS admission (857 versus 1133, p<0.001), the absolute number and the rate ratio of EVTs were not reduced but increased [72 (8.4) versus 59 (5.2), rate ratio: 1.61 (1.13-2.32), p=0.008, respectively] in March 2020 compared to the respective period of 2019. In contrast, in South Italy, where the drip-and-ship model is predominant (as in Italy generally), the volume of IS hospitalizations was reduced (hospitalization rate ratio: 0.61 (0.52-0.71), p<0.001) along with a decrease in the absolute number and rate ratio of EVTs [20 (7.5) versus 46 (10.5, rate ratio: 0.72 (0.40-1.24), p= 0.253, respectively] in that period (123, 125, 127).

In the national-level analysis of Kerleroux et al., which included 32 thrombectomy centers across all French administrative regions, besides a 21% significant decrease (p<0.001) in EVT case volume, they reported a significant increase in the mean imaging-to-groin time for the whole cohort (145±87 versus 126±71 minutes, p<0.001, respectively) during the COVID-crisis (15 February - 30 March 2020), compared to the identical period in the previous year. However, by dissecting the EVT cohort, it could be found that the increase in the overall mean imaging-to-groin time is mainly driven by a subgroup where patients required inter-hospital transport for the thrombectomy (drip-and-ship subgroup). Notably, while the mean imaging-to-groin time in the mothership subgroup did not increase significantly (mean 138±96 minutes versus 145±91, p=0.5519, respectively), it was prolonged remarkably with 30 minutes in the drip-and-ship subgroup (183±82 versus 153±67, p<0.001, respectively) during the COVID-period, compared to control period (137). Similarly, a smaller study from Poland, which analyzed the impact of COVID-19 on acute stroke care in Masovian Voivodeship (a region in east-central Poland with a population of 800,000 inhabitants), besides a marked 20.6% and 12.8% (p=0.09 and p=0.60, respectively) drop in the volume of IVT and EVT, reported a considerable 36 minutes increase in the overall mean onset-to-groin time (259±80 versus 223±71 minutes, p<0.01, respectively) during 10-18. weeks of 2020 compared to the same period in 2019. During the COVID-19 outbreak, the mean onset-to-groin time for patients treated in the mothership model was prolonged by 29 minutes, while for patients treated in the drip-and-ship paradigm was lengthened by 53 minutes (mothership: 232±104 versus 203±74 minutes, p=0.04; drip-and-ship: 293±51 versus 240±69 minutes, p=0.01, respectively). These data show that during the first wave of the COVID-19 epidemic, the onset-to-groin time was prolonged by 24 minutes more in the drip-and-ship model, and the mothership model provided remarkably shorter (-61 minutes) onset-to-groin delays (293 versus 232 minutes, p=0.03) than the drip-and-ship model (154).

In summary, a trend toward the mothership logistic paradigm through centralization measures could be observed in many acute stroke care systems during the COVID-19 pandemic. The above-presented data might support the theory that the different acute stroke network models might have consistently affected the acute stroke care service performance through the COVID-19 pandemic. Furthermore, these data might advocate the hypothesis that the mothership model would be more advantageous in preserving the acute stroke care standards during the COVID-19 pandemic.

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2. Objectives

The impact of the COVID-19 pandemic on stroke care in Hungary is unknown in the current literature. Besides, data about the effect of the second epidemic wave of COVID-19 on stroke care is very limited in general since the vast majority of the data are related to the first epidemic wave. In Hungary, the second wave of the COVID-19 outbreak was different from the first wave: the number of SARS-CoV-2 related infections and deaths was substantially higher, and pressure on the healthcare system was more intense, while the confinement measures were considerably milder. Thus, it can be hypothesized that the effect of COVID-19 on the stroke care systems in Hungary could differ between the epidemic waves, if there were any.

To elucidate these questions, first, we sought to analyze the volume and the quality of acute IS care in our academic stroke center during the first two months of the COVID-19 crisis in Hungary compared to the identical period of the previous year. Then, to find out whether our single-center results can be generalized to Hungary, we performed a national-level study using the reimbursement database of the National Health Insurance Fund of Hungary (NHIFH). In this study, we sought to evaluate and quantify the dynamics of IS care by analyzing the number of IS admissions and reperfusion interventions during the first two waves of the COVID-19 pandemic in Hungary by comparison to baseline and control periods.

3. Methods

3.1. Methods of the single-center analysis

We retrospectively analyzed the electronic medical records of patients admitted with acute IS to the Department of Neurology, Semmelweis University, in the 1 March - 30 April timeframe in 2020 and 2019. The time period from 1 March 2020 to 30 April 2020 was defined as a pandemic period, and the 1 March - 30 April 2019 epoch was considered as a control, pre-pandemic period.

Besides the overall case volumes, absolute numbers and rates of acute reperfusion treatments (IVT, EVT), demographic and clinical parameters (sex ratio, age, stroke severity, rate of LVO) were analyzed, along with the early functional outcomes and time quality parameters. Stroke severity was rated by the NIHSS at admission, and early functional outcome was based on mRS at discharge. LVO was defined (based on the board definition of previous thrombectomy studies (194)) as occlusion of any of the following arteries: internal carotid artery, M1 and M2 segments of the middle cerebral artery, A1 portion of the anterior cerebral artery, vertebral artery, basilar artery, P1 and P2 segments of the posterior cerebral artery. The rate of LVO was determined only among acute IS patients examined with CT- or MR-angiography, IS admissions without vessel imaging were not included in this analysis.

The arrival time of IS patients from stroke onset or from the last known well time point was categorized into three categories based on the potential eligibility for acute reperfusion therapies. Standard time window (arrival ≤6 hours), when acute revascularization treatments (IVT and/or EVT) could be performed based on regular criteria. Late time window (arrival between 6 to 24 hours), when IVT and/or EVT could be indicated based on particular, extended time-window criteria. Out-of-therapy time window (arrival after 24 hours), when acute reperfusion treatments were no longer possible. The distribution of acute IS patients' arrival time between these three time categories (<6h, 6-24h, >24h) was calculated and compared between the pandemic and pre-pandemic epochs. Furthermore, in case of a shift between time categories, we evaluated which factors could be associated with this phenomenon.

The quality of IV-tPA delivery was characterized by the following time metrics: onset-to-needle time, onset-to-door time, door-to-needle time, and door-to-imaging time.

Definitions of the time parameters: onset-to-needle time: time from stroke onset or from the last known well time point to start of IVT; onset-to-door time: time from stroke onset or from the last known well time point to hospital arrival; door-to-needle time: time from hospital arrival to start of IVT; door-to-imaging time: time from hospital arrival to brain imaging. In the analysis of the time metrics, we included only those cases where no time-related data were missing.

We were unable to analyze the time quality parameters of EVT delivery for acute IS patients since our academic stroke center was not capable of mechanical thrombectomy. Thus, eligible patients for EVT were transferred for the procedure to an external partner institution (National Institute of Clinical Neurosciences, the predecessor institution of the current National Mental, Neurological and Neurosurgical Institute) and after the intervention and the postoperative observation period (24-48 hours) patients were readmitted. To avoid double-counting and overestimation, each EVT patient was counted only at the first time of admission, similarly to the early readmissions (discharged IS patients who were readmitted within a short time interval).

It is important to note that our institutional guideline for acute IS treatment during the COVID-19 crisis was the same as in the previous control period. Personal, material, and legal conditions of stroke care were provided, and at the same time, safe COVID-19 designated (protected stroke code) and non-designated pathways were established. These were in line with the recommendations by the Divisions of Neurology and Neurosurgery of the Medical College of Health Care of the Ministry of Human Capacities, which recommended the use of COVID-19 designated and non-designated pathways, and clearly stated that acute reperfusion interventions are urgent and should be carried out regardless of the epidemic situation (195, 196). All patients were screened for COVID-19 at presentation, and SARS-CoV-2 PCR nasopharyngeal swab tests were made in case of suspicion of COVID-19. Patients suspected or confirmed for COVID-19 were treated under special isolation in a designated COVID-19 area. The rate of acute IS admissions requiring special isolation due to suspicion or confirmation of COVID-19 during the pandemic was examined. The definition of a suspected and confirmed COVID-19 case was determined according to the current case definitions of the National Public Health Center and the Semmelweis University at that time; no retrospective revaluation was made (197, 198).

Data regarding lifestyle, nutrition, and environment were not collected, and thus, their potential changes and influence on IS hospitalizations during the COVID-19 outbreak could not be evaluated.

All statistical analyses were performed with the software TIBCO Statistica version 13.4.0. Mean, standard deviation, and percentage were calculated by descriptive statistical methods. Continuous numerical variables were compared with Student t test, and Mann-Whitney U test was used for discrete numerical variables. A contingency table and Pearson's $\chi 2$ test were used to compare categorical variables. The effect of the different parameters on the shift between arrival time categories was analyzed by univariable and multivariable ordinal logistic regression. Results were evaluated with a 95% confidence interval, and a p value of <0.05 was considered statistically significant.

3.2. Methods of the national-level analysis

3.2.1. Source of data

This retrospective observational study was based on the reimbursement database of the National Health Insurance Fund of Hungary (NHIFH). The NHIFH database prospectively registers all healthcare activities performed by healthcare providers supervised by the National Healthcare Service Center of Hungary (NHSC). Hungary has a single-payer healthcare financing system, and NHSC is the largest supplier and supporter of healthcare services in Hungary, serving 9.8 million people (199, 200). In summary, our database encompasses all admissions for IS and all reperfusion interventions - IVT and EVT - performed by healthcare providers supervised by NHSC from 2 January 2017 to 31 December 2020. All patient data were obtained in an anonymized form from the NHIFH.

We used the ICD-10 (10th version of the International Statistical Classification of Diseases and Related Health) I63, I64, and I66 codes to evaluate the number of IS admissions from the reimbursement database of NHIFH. A recent study showed that the cerebrovascular ICD-10 codes submitted for reimbursement purposes in Hungary could be used reliably for stroke epidemiological studies (201). Since some institutes use the ICD-10 I66 code instead of the I63 code, we used this code in addition to I63 and I64 codes to evaluate the number of IS admissions. However, this method could result in an overestimation of IS incidence with an 8% maximal value based on NHSC calculation

(202). Some authors suggest using not only the main discharge diagnosis but diagnoses in all five positions (i.e., main diagnosis for admission; basic disease; accompanying disorder; complication; cause of death) to select IS patients in an administrative database with maximal sensitivity (201, 203). We computed the number of IS admissions as the number of cases where ICD I63 or I64 or I66 codes presented in any of these five discharge diagnosis positions. While with this approach, stroke mimics (conditions not resulting from cerebral ischemia that present with neurological symptoms indistinguishable from a stroke) were not part of the cohort, the following group of patients could be included in the cohort: acute ISs (patients admitted with acute onset neurological symptoms caused by cerebral ischemia), non-acute ISs (patients formerly treated with acute IS admitted for follow-up investigations), in-hospital ISs (patients admitted for non-stroke reasons but had an IS while hospitalized), IS chameleons (patients presented with clinical symptoms suggestive of another condition, which represents IS), and incidental asymptomatic cerebral infarcts (patients who were hospitalized for a condition other than stroke and had a brain imaging that showed an incidental asymptomatic brain infarct). Each patient counted only at the time of admission in a given week. However, early readmissions (discharged IS patients who were readmitted within a short time interval) were captured from the NHIFH database as separate IS cases, which could result in an overestimation of IS incidence.

To compute the number of IVTs and EVTs, we used the Orvosi Eljárások Nemzetközi Osztályozása (OENO) and the Homogén Betegségcsoportok (HBCs) codes, which are the Hungarian adaptations of International Classification of Procedures in Medicine codes, and Diagnosis Related Groups (204, 205).

IVT has clinical indications other than neurological ones, but acute IS is the only condition where IVT is performed in neurology. Thus, using the OENO code of IVT (OENO 06042), we first identified all IVT cases, irrespective of the clinical indication. Then, we excluded the non-neurological cases by excluding cases where the HBCs showed other than a neurological indication. IVT cases where HBCs code was missing were included in the analysis, which could overestimate the number of IVTs, but do not alter our goal to detect changes in a process. With this approach, IVT performed in stroke mimics and in-hospital ISs might be included in the cohort.

For EVT coding, most Hungarian neurointerventional facilities use (Type I coding) the OENO 33933 code (intracranial transarterial revascularization therapy). However, two neurointerventional institutions use the OENO 53958 code (intracranial percutaneous transluminal angioplasty) in part or in full instead of the 33933 code (Type II coding) (206). Therefore we used both codes to obtain the best estimate of EVT numbers.

Our analysis of the Hungarian SARS-CoV-2 data was based on the Our World in Data GitHub database (sourced from the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University) (18).

3.2.1. Study periods

The first SARS-CoV-2 infection occurred in Hungary on 4 March 2020 (10th week of 2020). On 11 March 2020 (11th week of 2020), the Hungarian government declared a state of emergency, which lasted until 18 June 2020 (25th week of 2020). With a repeated surge of COVID-19 cases, on 1 September 2020 (36th week of 2020), a COVID-19 entry control scheme was instituted, and on 4 November 2020 (45th week of 2020), a state of emergency went into effect again. To date, some sort of containment measures are still in place (18-20, 207).

The study periods are summarized in Figure 5. Based on the epidemic's dynamic, we defined two COVID periods (Wave-1 and Wave-2) as representative of the first and the second waves of the COVID-19 epidemic in Hungary. The Wave-1 period was defined as a 15-week long interval between the 11th and 25th weeks of 2020. The Wave-2 period was defined as a 17-week long period between the 36th and 52nd weeks of 2020. The 10-week long interval between the Wave-1 and Wave-2 periods designated an epidemic interlude (3rd control period, 26th–35th weeks of 2020). Data of the COVID-periods were compared to their respective periods of 2019 (1st control period: 11th–25th weeks of 2019; 2nd control period: 36th–52nd week of 2019) and with the epidemic interlude. The comprehensive interval of the 11th–53rd weeks of 2020, which extends from the start of the Wave-1 period to the end of 2020, was used in the analyses to study the relationship between the number of COVID-19 cases and the investigated variables. Data from the 1st week of 2017 to the 10th week of 2020 were defined as a baseline period for trend analysis.

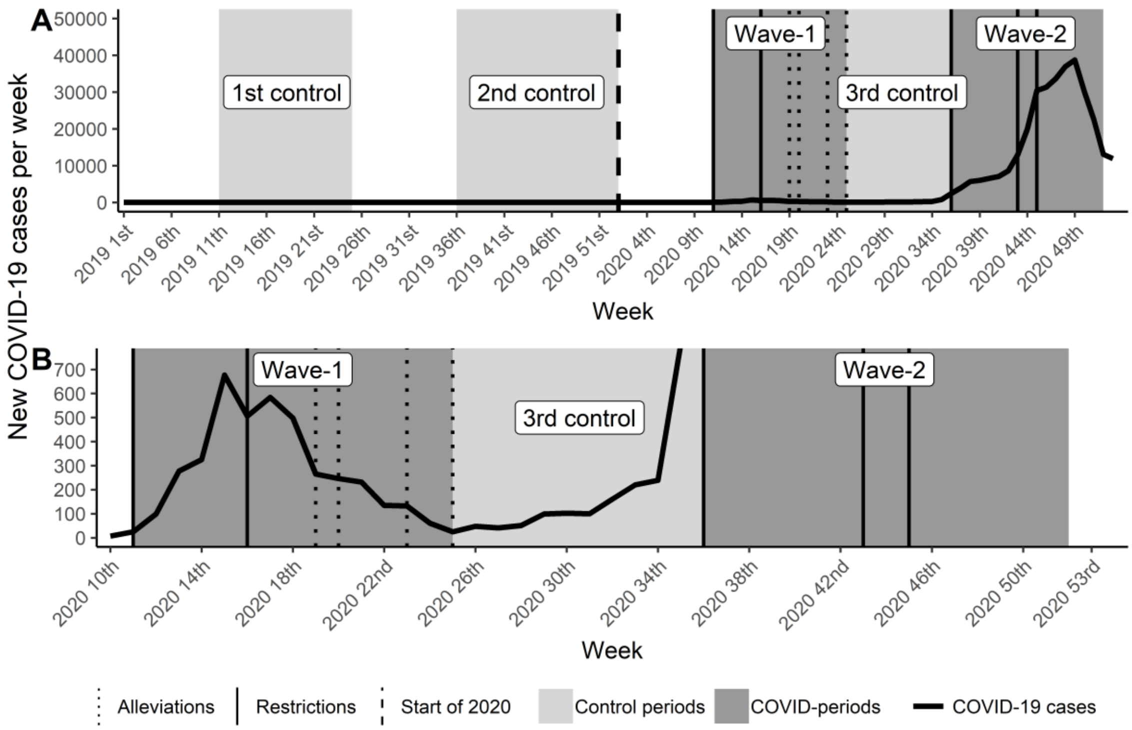

Figure 5. Timeline and summary of the study periods. These graphs summarize the study periods and present them in a timeline, illustrating their temporal relationship to the COVID-19 epidemic waves in Hungary. Dates of the most important restrictive and alleviative health emergency operative measures are also marked in the timelines. (a) illustrates both COVID-19 and control periods, while (b) focuses on the COVID-periods. Wave-1 period: 11th–25th weeks of 2020. Wave-2 period: 36th–52nd weeks of 2020. 1st control period: 11th–25th weeks of 2019. 2nd control period: 36th–52nd week of 2019. 3rd control period: 26th–35th weeks of 2020. (12)

Dates of the most important restrictive and alleviative health emergency operative measures were marked and used during the visual-statistical analyses (Figure 5, 8-10.): 11th week of 2020, order of complete restriction of elective health care; 16th week of 2020, order to make 50–60% of beds free to COVID-care; 19th, 20th, 23rd, 25th weeks of 2020, four-step alleviation of restrictive health measures; 36th week, order to make 20% of beds free to COVID-care; 43rd week of 2020, orders to significantly expand the COVID-19 designated hospitals' number and make 20–30% of beds free to COVID-care; 45th week of 2020, orders to make 40% of beds free to COVID-care, to designate almost every hospital for COVID-care, and to partially restrict elective health care (18, 208-216).

3.2.2. Statistical analysis

Statistical analysis was conducted on all characteristics (IS admissions, IVTs, EVTs) both separately and together. The smallest timeframe considered was weekly patient numbers due to the nature of the data.

We analyzed the COVID-19 epidemic waves' effect on the patient numbers with different tools: means, medians, trends, relative rates, and linear regression. The mean and median differences were tested with t test and Wilcoxon-Mann–Whitney test, respectively. Differences between the COVID-periods and their respective controls were compared with the paired version of the tests. However, the COVID-periods and the epidemic interlude were compared with non-paired tests due to differing lengths.

Trends and unexpected changes in patient numbers were analyzed using control charts, which are simple visual-statistical tools for detecting changes in a process and are widely used in outbreak analysis (217-220). The basic idea was to analyze a baseline timeframe (1st week of 2017–10th week of 2020) where it can be assumed that everything is in order and set up definitions for normal behavior. All data were linearly de-trended and standardized; thus we obtained z-scores. The potential effect of heteroscedasticity and seasonality was considered. However, we ultimately decided not to transform the data further due to two reasons: one was not to "over standardize" the data (i.e., categorize possibly extreme behavior during baseline as normal). The second was that these effects could be easily detected and taken into account visually. The z-cores were put on control charts, and the 2 and 3 standard deviation (SD) control limits were set. Changes in z-scores were then determined using Western Electric rules (218). We also conducted statistical testing on the z-scores because compared to the raw numbers' means and medians; z-scores consider the trends based on the whole study period.

The rate of IVTs or EVTs relative to the number of IS admissions was also analyzed using control charts. These control charts used the same methodology as described above, but the de-trended and standardized IVT or EVT numbers were first divided by the number of IS admissions to get the relative number of patients.

Linear regression was used to analyze the relationship between the new or cumulative COVID-19 cases per week in Hungary and the weekly number of IS admissions, IVTs, or EVTs. The linear regression took the number of COVID-19 cases per week as the explanatory variable, and the weekly IS admission, IVT, or EVT numbers as the outcome one.

While statistical tests did not use the incomplete last week of 2020 (data only for the first four days of the week were available), it was included in linear regression analysis and control charts to make the analysis and visual assessment as complete as possible. In this regard, when the characteristics were analyzed by themselves, the last patient number was multiplied by 7/4 to boost it to a whole week level, but when the IVT and EVT numbers were divided by the number of IS admissions, the ratio was left because both data were equally incomplete; thus their ratio is valid.

Due to the different OENO coding practices for EVT, a correction had to be implemented to obtain the best estimate of patient numbers. This correction was based on Type I coding centers by dividing the number of 53958 codes by the sum of the number of 33933 and 53958 codes, taking into account the whole study period. This gave an estimate of the true ratio of the 53958 codes, which was used to adjust the number of procedures in the Type II coding centers by multiplication. In the end, we added these adjusted 53958 numbers to the 33933 numbers.

R version 4.0.3 was used for data analysis with packages forecast, rgdal, ggplot2, ggpubr, gridExtra, flextable, and tableone.

4. Results

4.1. Results of the single-center analysis

In March-April 2020, 86 patients with acute IS were admitted to our academic stroke center, while in the same time frame in 2019, there were 97 acute IS admissions, representing an 11% fall in the pandemic period (Table 1.). The demographic and clinical parameters and early functional outcomes were balanced between the pandemic and the pre-pandemic cohort, and no significant differences could be detected (Table 1.). The sex (female/male) ratio was similarly well balanced between the cohorts. Patients were similarly elderly with a moderate severity acute IS stroke in general. There was no difference in the rate of LVO in acute IS patients examined with CT- or MR-angiography. The early functional outcome of acute IS patients was unchanged during the COVID-crisis; on average, patients were discharged with the same good (mRS 2) functional status.

Table 1. Case numbers, demographic and clinical parameters, and functional outcomes during the COVID-19 and control intervals. This table shows the results of the different statistical tests, which correspondingly compared the absolute and mean values of the analyzed variables in the COVID-19 (2020) and the control (2019) periods. SD: standard deviation. (221)

Variables	2019	2020	p value
IS admissions	97	86	-
Sex (female/male)	52/45	43/43	0.63
Age (mean (SD))	71 (12) years	69 (13) years	0.26
NIHSS (mean (SD))	7 (6) points	6 (5) points	0.29
LVO (%, n/n)	38 (29/76)	39 (23/59)	0.92
mRS (mean (SD))	2 (2) points	2 (2) points	0.48
IVT (%, n/n)	26 (25/97)	16 (14/86)	0.12
EVT (%, n/n)	8 (8/97)	8 (7/86)	0.98

The absolute number of EVT procedures was similar (7 versus 8, respectively), and the relative rate of EVT delivery was unchanged (8% versus 8%, p=0.98) in the pandemic epoch compared to the pre-pandemic period (Table 1.). In contrast, the IVT procedure numbers declined by 44%, and the relative rate of IV-tPA delivery reduced by 10% during the first two months of the COVID-crisis, compared to the prior-year epoch (14/86 (16%) versus 25/97 (26%), p=0.12, respectively). The changes in the volume of IVTs approached but did not reach statistical significance (Table 1.).

Compared to the pre-pandemic epoch, during the COVID-19 pandemic, the mean onset-to-needle time was prolonged from 190 minutes to 210 minutes (+20 minutes delay), while the mean door-to-needle time and door-to-imaging time were delayed by 5 minutes (from 54 minutes to 59 minutes) and 4 minutes (from 19 minutes to 23 minutes), respectively. This means that the marked 20 minutes delay in the onset-to-needle time mainly came from the delay in the pre-hospital phase as the mean onset-to-door time increased from 135 minutes to 152 minutes (+17 minutes). The delay in IV-tPA delivery did not reach the margin of statistical significance (Table 2.).

Table 2. Time metrics of IVT delivery during the COVID-19 and control intervals. This table shows the results of the Student paired t tests, which compared the mean values of the analyzed time parameters (ONT: onset-to-needle time, ODT: onset-to-door time, DNT: door-to-needle time, DIT: door-to-imaging time) in the COVID-19 (2020) and the control (2019) periods. SD: standard deviation. (221)

Variables	2019	2020	p value
ONT (mean (SD))	190 (44) minutes	210 (54) minutes	0.26
ODT (mean (SD))	135 (47) minutes	152 (60) minutes	0.20
DNT (mean (SD))	54 (23) minutes	59 (19) minutes	0.56
DIT (mean (SD))	19 (13) minutes	23 (13) minutes	0.35

Compared to the control period, during the COVID-19 outbreak, 9% fewer acute IS patients arrived in the early time window, and there were 4% fewer cases in the late time window, while 13% more acute IS patients arrived in the out-of-therapy time category (p=0.046) (Figure 6.). In the univariate logistic regression analysis, we found that the effect of the study year (2019 or 2020; COVID-19), stroke severity (NIHSS), and patient age on the shift between arrival time categories approached the margin of statistical significance (p=0.073, p=0.06, p=0.119, respectively). In the multivariable ordinal logistic regression analysis, the study year (COVID-19) appeared to have the strongest association with the shift between arrival time categories (p=0.096), followed by stroke severity (p=0.17) and patient age (p=0.34). These associations were not statistically significant.

In March-April 2020, 20% of admission for acute IS (17/86) were treated under special isolation requirements due to suspicion or confirmation of COVID-19. Besides, the PCR test confirmed SARS-CoV-2 infection in two patients from the 86 acute IS admission (2.3%) during the pandemic period.

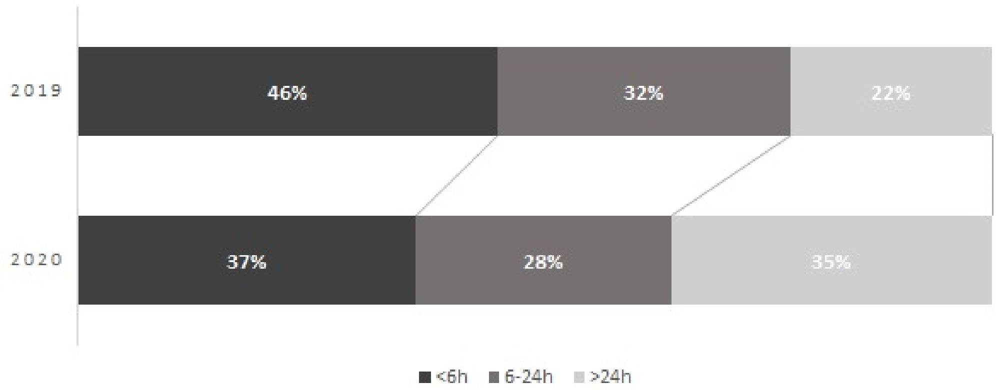

Figure 6. Shift between arrival time categories of acute IS patients. This figure shows how the proportion of acute IS patients changed in the three analyzed time categories (<6h, 6-24h, >24h) between 2019 (control period) and 2020 (COVID-period). <6h: patients' arrival in 0-6 hours from stroke onset or from the last known well time point. 6-24h: patients' arrival from stroke onset or from the last known well time point between 6 and 24 hours. >24h: patients' arrival after 24 hours from stroke onset or from the last known well time point. (221)

4.2. Results of the national-level analysis

In the Wave-1 period, compared to the 1st control interval, we observed a significant decrease in the weekly IS admissions' mean and median. In the control chart, during the Wave-1 period, a marked negative deviation from the trend could be observed: values below the -2 SD control limit indicate alterations, and even if we consider the effect of multiple testing and use the -3 SD control limit, the disruption in the trend is clearly visible. Paired t tests on IS admission z-scores also demonstrated a significant decline (Table 3-4., Figure 7-8.).

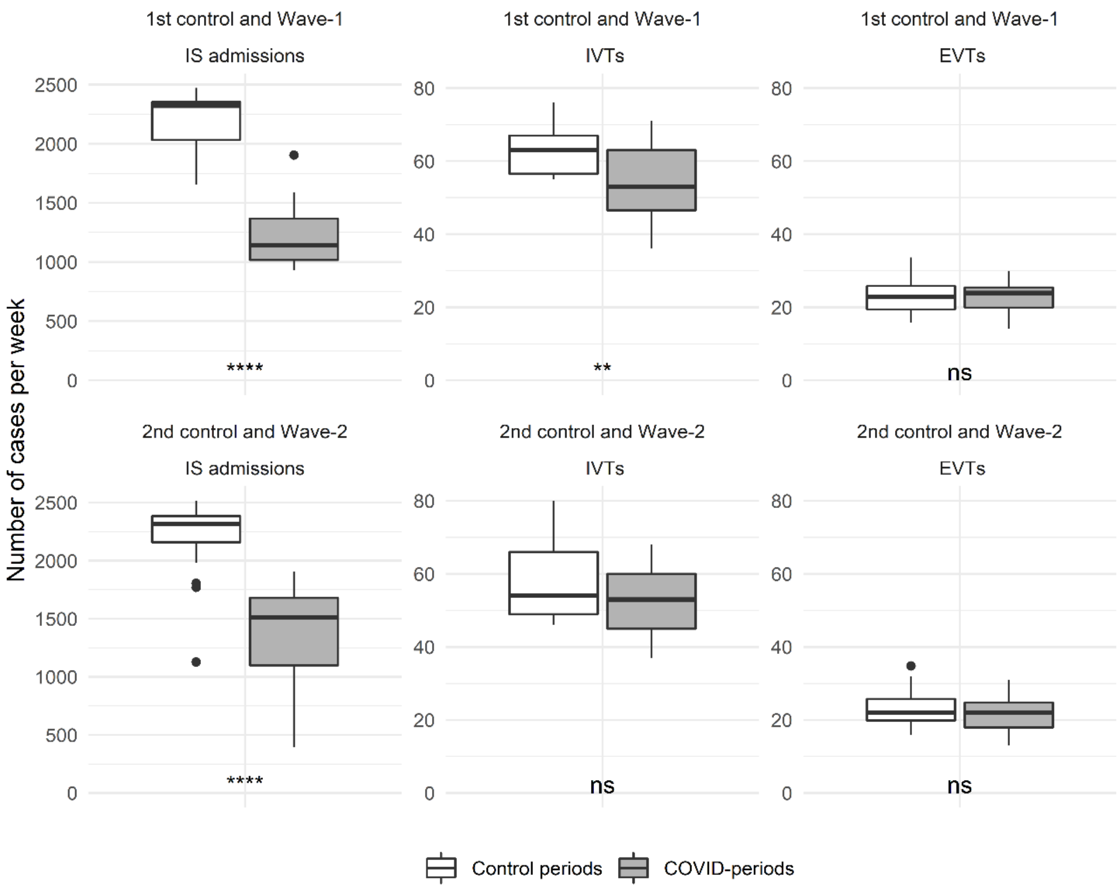

Figure 7. Changes in the raw weekly number of IS admissions and reperfusion interventions during the COVID-periods. This figure shows the raw weekly number of IS admissions, IVTs, and EVTs in the COVID-periods and their respective controls using standard box plots. p values of the paired Wilcoxon-Mann-Whitney tests, which compare the COVID-periods to their respective controls, are also presented. full dots: Tukey-defined outliers; p value: ns (not significant) $p > 0.05$, **$p < 0.01$, ****$p < 0.0001$. (12)

While the Wave-1 period did not alter the mean and median of weekly EVT numbers considerably, the weekly IVT numbers' mean and median values reduced significantly in the Wave-1 period, compared to the 1st control interval (Table 3-4., Figure 7.). Nevertheless, the de-trended and standardized weekly number of IVTs and EVTs showed a significant decrease in the Wave-1 period, representing a remarkable decline from the trend. In the control charts, the Wave-1 period's effect on the weekly EVT numbers was milder but detectable and significant: several consecutive observations were below the centerline, there was a case of 2-out-of-3 consecutive weeks below the -2 SD control limit, and the results of the difference tests on z-scores were also significant (Table 3-4., Figure 9.). The trend analysis of the ratio of IVTs or EVTs and IS admissions showed a significant increase during the Wave-1 interval (Table 3-4., Figure 10.). It implies that even though both the de-trended and standardized weekly number of IVTs, EVTs, and IS admissions reduced in the Wave-1 period, the decrease of IS admissions was disproportionally greater.

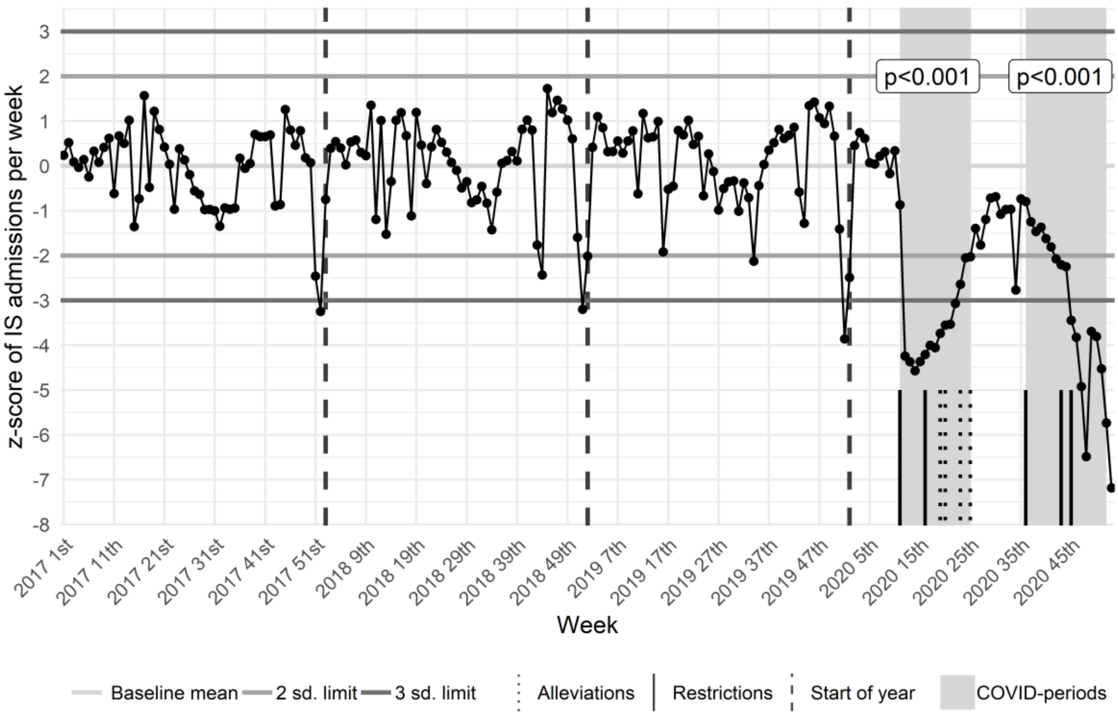

Figure 8. Control chart of IS admissions. This graph visualizes the trend and changes using the de-trended and standardized weekly number of IS admissions during the whole study period. p values of the paired t tests, which compare the COVID-periods to their respective controls, are also presented. Dates of the most important restrictive and alleviative health emergency operative measures are marked in the timeline. sd: standard deviation. (12)

Compared to the Wave-1 period, in the 3rd control period, the weekly number of IS admissions showed a clearly detectable increase in the raw numbers and the de-trended and standardized data (Table 3-4., Figure 8.). In contrast, compared to the Wave-1 period, the weekly number of IVTs and EVTs did not change significantly in the epidemic interlude, neither in the raw data nor in the de-trended and standardized data. Simultaneously, the ratio of IVTs or EVTs and IS admissions returned to the baseline levels (Table 3-4., Figure 9-10.).

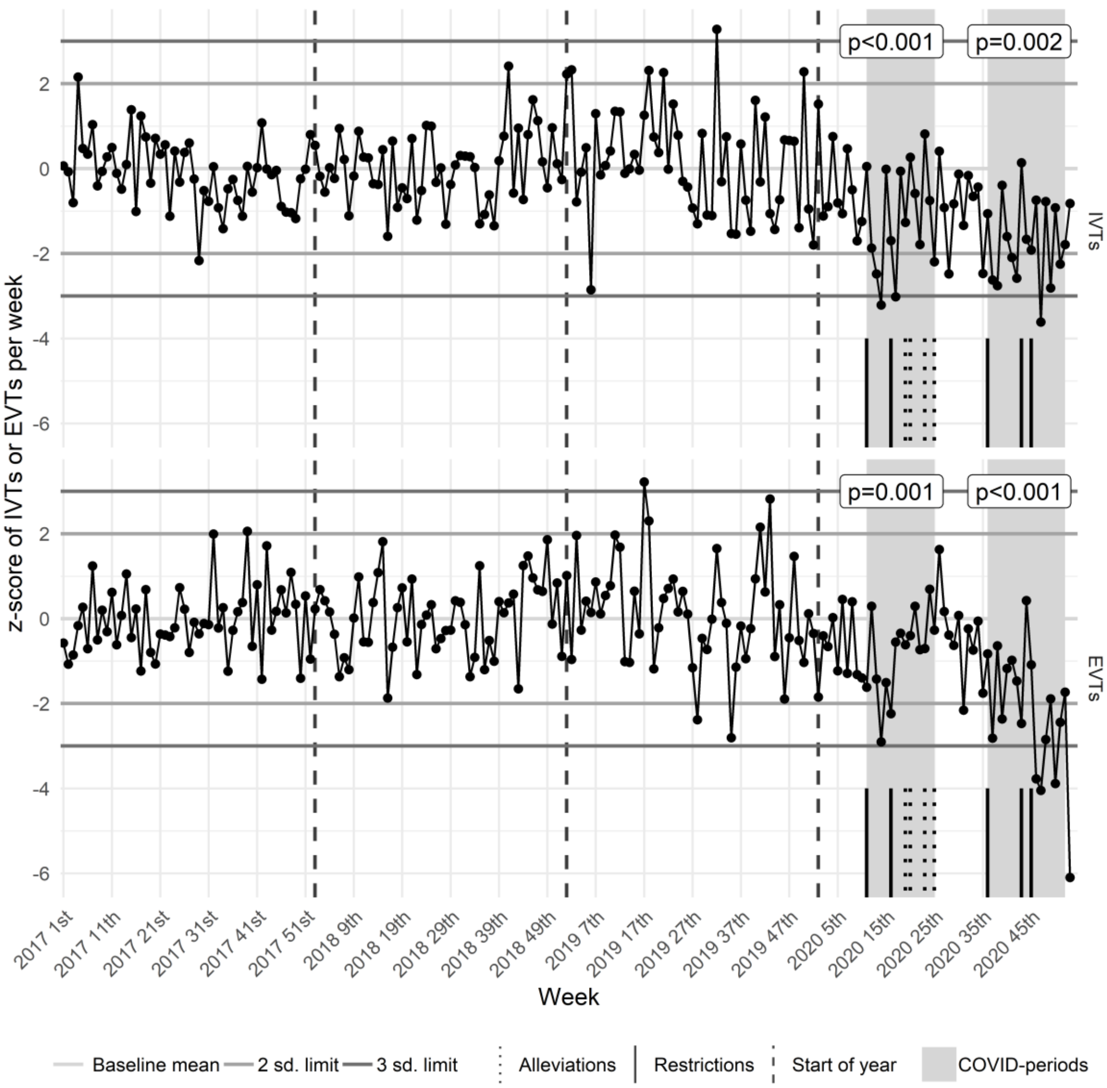

Figure 9. Control chart of IVTs and EVTs. These charts visualize the trend and changes using the de-trended and standardized weekly number of IVTs and EVTs during the whole study period. p values of the paired t tests, which compare the COVID-periods to their respective controls, are also presented. Dates of the most important restrictive and alleviative health emergency operative measures are marked in the timeline. sd: standard deviation. (12)

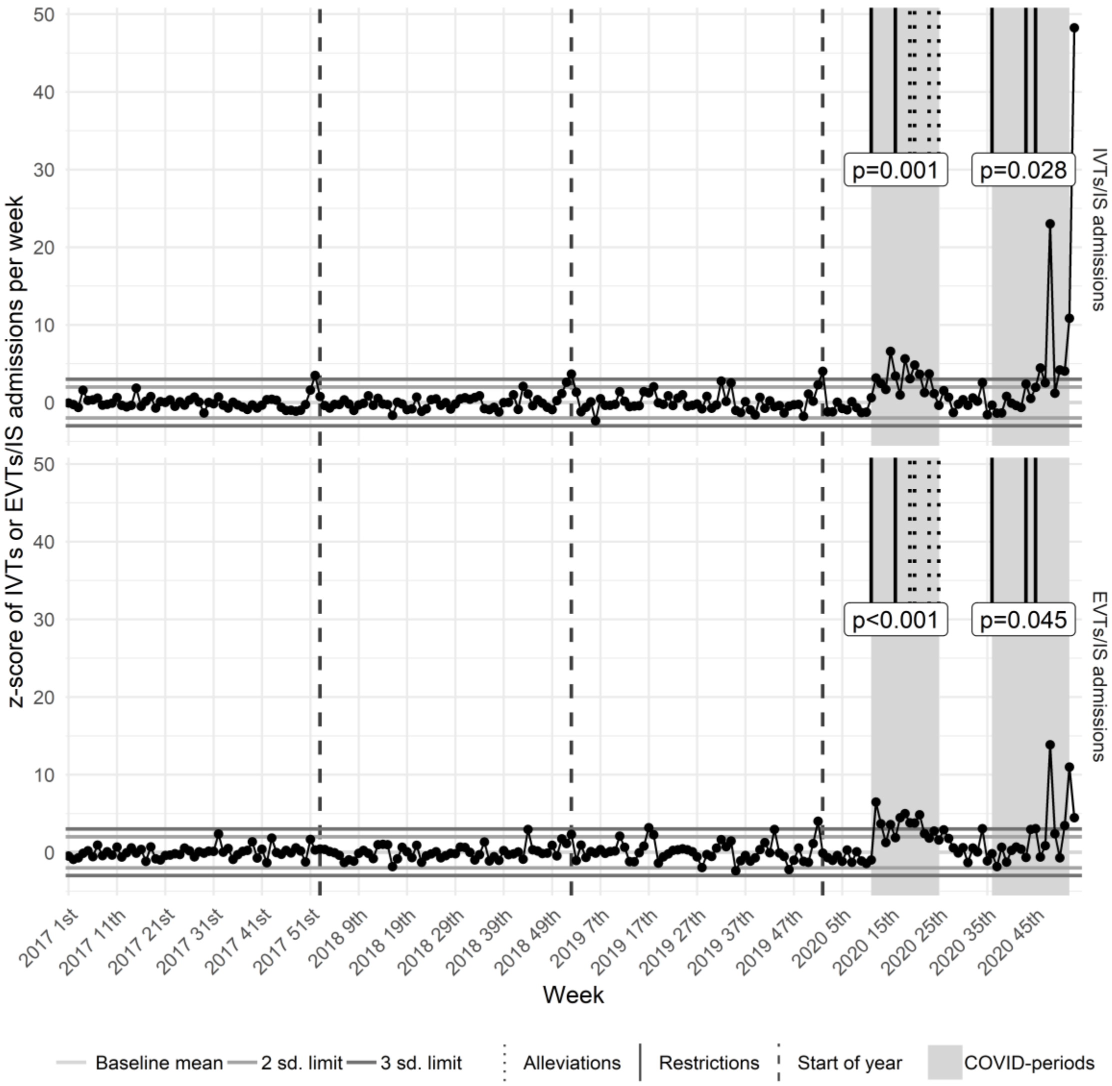

Figure 10. Control chart of the ratio of IVTs or EVTs and IS admissions. These charts visualize the trend and changes using the de-trended and standardized weekly number of IVTs or EVTs relative to IS admissions during the whole study period. p values of the paired t tests, which compare the COVID-periods to their respective controls, are also presented. Dates of the most important restrictive and alleviative health emergency operative measures are marked in the timeline. sd: standard deviation. (12)

In the Wave-2 period, compared to the 2nd control interval, the weekly IS admissions' mean and median values significantly decreased, but the mean and median of weekly IVTs and EVTs did not show a remarkable change (Table 5-6., Figure 7.). However, the de-trended and standardized data analysis demonstrated a significant drop from the trend of IS admissions, IVTs, and EVTs. In the control charts, during the Wave-2 period, the ratio of IVTs or EVTs and IS admissions significantly increased, reaching even more extreme values (values beyond the 10 SD limit) than in the Wave-1 interval (Table 5-6., Figure 8-10.).

Comparing the raw numbers and z-scores of IS admissions and reperfusion interventions from the Wave-2 period with the 3rd control period, we found similar results as compared with the 2nd control period, with two exceptions: compared to the epidemic interlude, not only the z-scores of EVT reduced significantly in the Wave-2 period, but also the mean and median of raw numbers. Although the ratio of IVTs or EVTs and IS admissions showed an extreme increase in the control charts, the mean and median z-scores did not significantly alter. The cause of this apparent contradiction is that the mean and median of z-scores use the whole length of the Wave-2 period, but the analyzed ratios' z-scores started to increase significantly only in the 43rd week of 2020 (Table 5-6., Figure 8-10.).

General analysis of the control charts:

In the IS admissions' control chart, the weekly number of IS admissions shows mild seasonality, guided mainly by vacations and national holidays. These changes may have inflated the variance in the baseline period (Figure 8.). In the control charts of acute reperfusion interventions, the baseline periods do not show any striking artifacts, only a mild increase in the variance can be seen. Occasional random extremes ("false alarms") occurred as expected (Figure 9.).

The winter holiday season (generally the 51st–1st weeks of a calendar year) tends to bring the weekly number of IS admissions extremely low (below a distance of -3 SD), while the weekly IVT and EVT numbers do not alter remarkably. Thus concurrently, the ratio of IVTs or EVTs and IS admissions shows a significant (above a distance of 2 or 3 SD) increase (Figure 8-10.). The summer holiday season (generally the 24th–35th weeks of a calendar year) has a similar but longer-lasting and less potent effect on the weekly number of IS admissions, IVTs, and EVTs (Figure 8-10.).

Linear regression analysis:

The weekly number of IS admissions, IVTs, and EVTs was compared with the new or cumulative SARS-CoV-2 infections' weekly number in Hungary during the comprehensive interval of the 11th–53rd weeks of 2020. The weekly number of IS admissions and EVTs significantly decreased with the increase of the new or cumulative COVID-19 cases per week (negative linear correlation), while the number of IVTs did not show a significant linear correlation with the number of SARS-CoV-2 infections (Figure 11.). The relationship between variables may not be linear in several cases, but we did not investigate this angle any further as this sub-analysis was mainly exploratory and just a complementary tool.

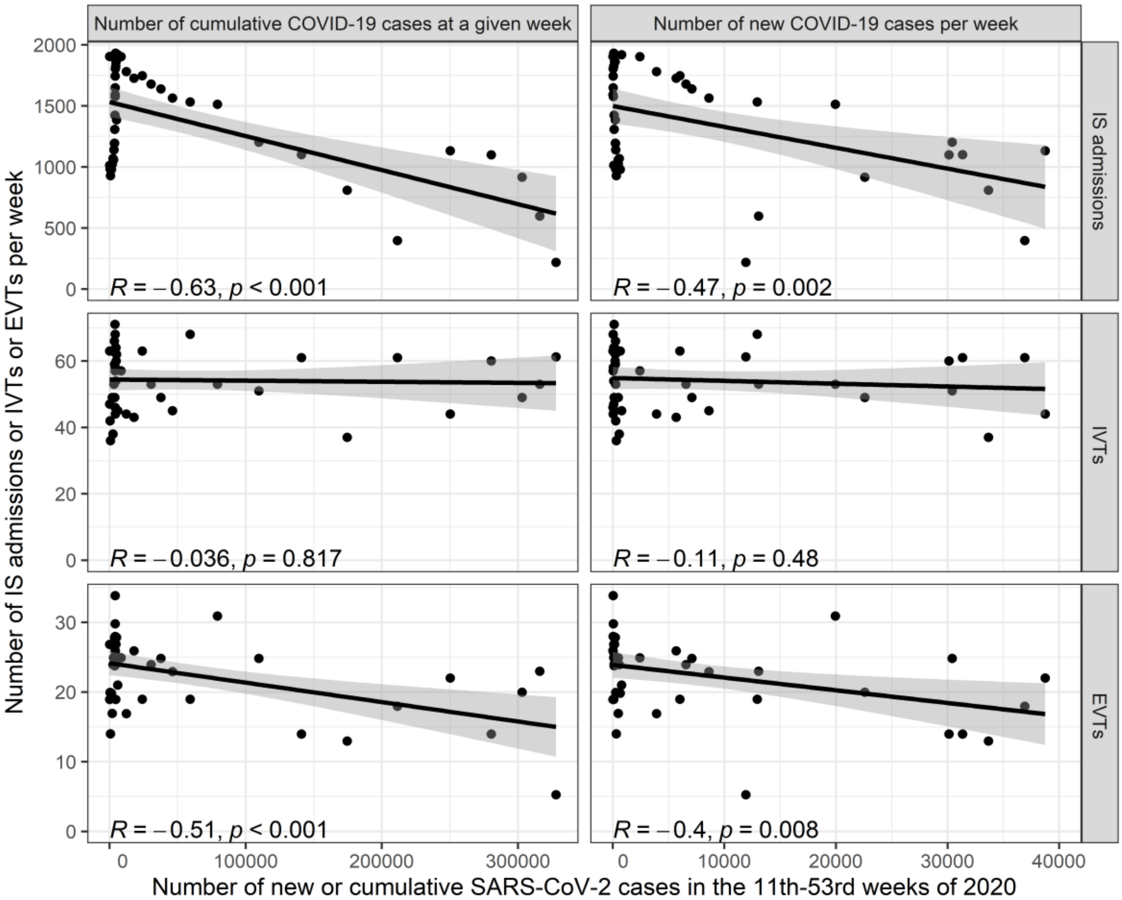

Figure 11. Relationship between the weekly number of IS admissions, IVTs, and EVTs, and the new or cumulative SARS-CoV-2 cases per week in Hungary. This figure visualizes the linear regression analysis results, which compared the weekly number of IS admissions, IVTs, and EVTs with the new or cumulative SARS-CoV-2 infections' weekly number in Hungary during the comprehensive interval of the 11th–53rd weeks of 2020. R: Pearson's correlation coefficient; p: p value of the correlation (same as the p value of the linear regression); grey area: 95% confidence interval of the slope. (12)

Table 3. Mean-based results of the statistical tests that compare the Wave-1 period with the 1st and 3rd control intervals. This table shows the results of the t tests, which compared the mean values of the analyzed variables (raw number and z-score of IS admissions, IVTs, and EVTs per week, and z-score of the ratio of de-trended weekly number of IVTs or EVTs and IS admissions) in the Wave-1 and the 1st and 3rd control intervals. Tests are paired where applicable (where the number of weeks equals). SD: standard deviation. Bold font indicates statistical significance. (12)

Variables	1st control	Wave-1	p value	3rd control	Wave-1	p value
IS admissions (mean (SD))	2214.73 (225.85)	1225.67 (282.78)	**<0.001**	1790.50 (167.27)	1225.67 (282.78)	**<0.001**
z-score of IS admissions (mean (SD))	0.21 (0.86)	-3.42 (1.08)	**<0.001**	-1.23 (0.64)	-3.42 (1.08)	**<0.001**
IVTs (mean (SD))	63.20 (7.18)	53.53 (10.70)	**0.001**	57.60 (7.97)	53.53 (10.70)	0.288
z-score of IVTs (mean (SD))	0.79 (0.85)	-1.19 (1.26)	**<0.001**	-0.90 (0.96)	-1.19 (1.26)	0.526
EVTs (mean (SD))	22.81 (5.25)	23.02 (4.28)	0.883	26.00 (4.08)	23.02 (4.28)	0.095
z-score of EVTs (mean (SD))	0.60 (1.29)	-0.80 (0.98)	**0.001**	-0.41 (1.05)	-0.80 (0.98)	0.358
z-score of IVTs/IS admissions (mean (SD))	0.42 (0.86)	2.79 (1.95)	**0.001**	0.25 (1.23)	2.79 (1.95)	**0.001**
z-score of EVTs/IS admissions (mean (SD))	0.39 (1.31)	3.09 (1.84)	**<0.001**	0.71 (1.49)	3.09 (1.84)	**0.002**

Table 4. Median-based results of the statistical tests that compare the Wave-1 period with the 1st and 3rd control intervals. This table shows the results of the Wilcoxon–Mann–Whitney tests, which compared the median values of the analyzed variables (raw number and z-score of IS admissions, IVTs, and EVTs per week, and z-score of the ratio of de-trended weekly number of IVTs or EVTs and IS admissions) in the Wave-2 and the 2nd and 3rd control intervals. Tests are paired where applicable (where the number of weeks equals). IQR: interquartile range. Bold font indicates statistical significance. (12)

Variables	1 control	Wave-1	p value	3rd control	Wave-1	p value
IS admissions (median [IQR]))	2320.00 [2033.50, 2354.50]	1141.00 [1017.50, 1365.50]	**<0.001**	1842.50 [1758.25, 1904.75]	1141.00 [1017.50, 1365.50]	**<0.001**
z-score of IS admissions (median [IQR])	0.63 [-0.49, 0.74]	-3.73 [-4.23, -2.86]	**<0.001**	-1.03 [-1.34, -0.79]	-3.73 [-4.23, -2.86]	**<0.001**
IVTs (median [IQR])	63.00 [56.50, 67.00]	53.00 [46.50, 63.00]	**0.003**	59.00 [54.75, 63.50]	53.00 [46.50, 63.00]	0.405
z-score of IVTs (median [IQR])	0.75 [-0.01, 1.35]	-1.27 [-2.03, -0.03]	**<0.001**	-0.74 [-1.23, -0.23]	-1.27 [-2.03, -0.03]	0.723
EVTs (median [IQR])	22.86 [19.41, 25.86]	23.93 [19.87, 25.43]	1.000	26.34 [24.93, 27.90]	23.93 [19.87, 25.43]	0.055
z-score of EVTs (median [IQR])	0.64 [-0.29, 1.31]	-0.61 [-1.46, -0.31]	**0.002**	-0.31 [-0.71, 0.04]	-0.61 [-1.46, -0.31]	0.461
z-score of IVTs/IS admissions (median [IQR])	0.17 [-0.39, 1.13]	3.08 [1.21, 3.66]	**0.001**	0.26 [-0.31, 0.65]	3.08 [1.21, 3.66]	**0.001**
z-score of EVTs/IS admissions (median [IQR])	0.32 [-0.39, 0.74]	3.58 [1.87, 4.13]	**0.002**	0.57 [-0.03, 1.49]	3.58 [1.87, 4.13]	**0.002**

Table 5. Mean-based results of the statistical tests that compare the Wave-2 period with the 2nd and 3rd control intervals. This table shows the results of the t tests, which compared the mean values of the analyzed variables (raw number and z-score of IS admissions, IVTs, and EVTs per week, and z-score of the ratio of de-trended weekly number of IVTs or EVTs and IS admissions) in the Wave-2 and the 2nd and 3rd control intervals. Tests are paired where applicable (where the number of weeks equals). SD: standard deviation. Bold font indicates statistical significance. (12)

Variables	2nd control	Wave-2	p value	3rd control	Wave-2	p value
IS admissions (mean (SD))	2194.47 (352.19)	1314.00 (448.19)	**<0.001**	1790.50 (167.27)	1314.00 (448.19)	**0.001**
z-score of IS admissions (mean (SD))	0.21 (1.34)	-3.02 (1.69)	**<0.001**	-1.23 (0.64)	-3.02 (1.69)	**0.001**
IVTs (mean (SD))	58.18 (10.57)	52.41 (8.40)	0.107	57.60 (7.97)	52.41 (8.40)	0.125
z-score of IVTs (mean (SD))	-0.22 (1.25)	-1.73 (1.00)	**0.002**	-0.90 (0.96)	-1.73 (1.00)	**0.045**
EVTs (mean (SD))	23.63 (5.03)	20.99 (4.89)	0.127	26.00 (4.08)	20.99 (4.89)	**0.009**
z-score of EVTs (mean (SD))	0.05 (1.23)	-2.00 (1.25)	**<0.001**	-0.41 (1.05)	-2.00 (1.25)	**0.002**
z-score of IVTs/IS admissions (mean (SD))	-0.29 (1.03)	3.06 (5.94)	**0.028**	0.25 (1.23)	3.06 (5.94)	0.076
z-score of EVTs/IS admissions (mean (SD))	0.04 (1.59)	2.02 (4.23)	**0.045**	0.71 (1.49)	2.02 (4.23)	0.258

Table 6. Median-based results of the statistical tests that compare the Wave-2 period with the 2nd and 3rd control intervals. This table shows the results of the Wilcoxon–Mann–Whitney tests, which compared the median values of the analyzed variables (raw number and z-score of IS admissions, IVTs, and EVTs per week, and z-score of the ratio of de-trended weekly number of IVTs or EVTs and IS admissions) in the COVID-periods and the control intervals. Tests are paired where applicable (where the number of weeks equals). IQR: interquartile range. Bold font indicates statistical significance. (12)

Variables	2nd control	Wave-2	p value	3rd control	Wave-2	p value
IS admissions (median [IQR]))	2314.00 [2159.00, 2383.00]	1513.00 [1099.00, 1679.00]	**<0.001**	1842.50 [1758.25, 1904.75]	1513.00 [1099.00, 1679.00]	**0.001**
z-score of IS admissions (median [IQR])	0.67 [0.03, 0.95]	-2.25 [-3.82, -1.62]	**<0.001**	-1.03 [-1.34, -0.79]	-2.25 [-3.82, -1.62]	**0.001**
IVTs (median [IQR])	54.00 [49.00, 66.00]	53.00 [45.00, 60.00]	0.135	59.00 [54.75, 63.50]	53.00 [45.00, 60.00]	0.102
z-score of IVTs (median [IQR])	-0.73 [-1.39, 0.66]	-1.79 [-2.58, -0.92]	**0.003**	-0.74 [-1.23, -0.23]	-1.79 [-2.58, -0.92]	**0.040**
EVTs (median [IQR])	21.96 [19.89, 25.78]	22.00 [17.96, 24.82]	0.113	26.34 [24.93, 27.90]	22.00 [17.96, 24.82]	**0.007**
z-score of EVTs (median [IQR])	-0.23 [-0.89, 0.63]	-1.89 [-2.81, -1.09]	**<0.001**	-0.31 [-0.71, 0.04]	-1.89 [-2.81, -1.09]	**0.002**
z-score of IVTs/IS admissions (median [IQR])	-0.38 [-0.94, 0.19]	1.21 [-0.32, 4.06]	**0.003**	0.26 [-0.31, 0.65]	1.21 [-0.32, 4.06]	0.187
z-score of EVTs/IS admissions (median [IQR])	-0.41 [-1.07, 0.55]	0.66 [-0.60, 2.96]	**0.027**	0.57 [-0.03, 1.49]	0.66 [-0.60, 2.96]	0.639

5. Discussion

5.1. Discussion of the single-center analysis

5.1.1. General remarks

In the first two months of the COVID-19 pandemic, the demographic and clinical parameters (sex ratio, age, stroke severity, rate of LVO) of acute IS patients admitted to our academic stroke center were comparable to the identical pre-pandemic period, and the early functional outcomes did not differ between periods. However, admissions for acute IS decreased markedly by 11% during the pandemic epoch. Besides, the proportion of acute IS patients who arrived beyond 24 hours, when there were no options for acute reperfusion treatment, increased significantly by 13%. Accordingly, the absolute number of IVTs reduced remarkably by 44%, and the rate of IV-tPA delivery fell from 26% to 16% during the COVID outbreak. Although these reductions in the volume of hospitalizations and IVTs for acute IS stroke did not reach statistical significance - which might be due to a low number of cases - but still could be considered clinically relevant. No changes could be observed in the volume of EVT delivery, but due to the low number of cases, no hard conclusions can be drawn from this.

The analysis of time quality metrics of IVT delivery showed a remarkable delay in the start of IVT (mean onset-to-needle time increased by 20 minutes), which was mainly attributable to the delay in the pre-hospital phase rather than in the intra-hospital phase, as the mean onset-to-door time prolonged with 17 minutes, while the door-to-needle time increased only with 5 minutes on average. Although the delay in IV-tPA delivery did not reach the margin of statistical significance, it still can be considered a clinically notable tendency.

5.1.2. Comparison with international data

Our results revealed that the first wave of the COVID-19 pandemic was associated with a decline in the volume of acute stroke care in our academic stroke center, which is in line with the global and international data, as it was a general experience in studies from across Europe, North America, and also China and in other LMICs (3, 14, 35, 92-106, 108-111, 113-117, 120, 123-131, 134, 137, 138, 140-142, 144, 145, 147, 149-155, 157, 158, 165, 169, 170, 173-176, 178, 182, 183, 190-193, 222-231). The 11% fall in the number of IS admissions and the 10% reduction in the rate of IV-tPA delivery mirrors the results of the global cross-sectional study of Nogueira et al., which noted an 11.5% global decrease in stroke admissions and a 13.2% drop in the IVT volume, similarly to Europe where stroke hospitalizations decreased with 10.9% and the number of IVTs reduced by 13.5% in general (99).

Contrary to Nogueira et al., we did not find differences in the volume of EVT delivery, which might be due to the low number of EVT cases (35). However, data from China, North America, Western, Southern Europe, and Central Europe suggest that acute reperfusion treatment numbers declined to a lesser extent and with board variations among counties, regions, and health care systems, especially in the case of EVT (3, 14, 92-94, 105, 106, 108-111, 113-120, 123-131, 134, 137, 138, 140-142, 144, 145, 147, 149-155, 157, 158, 175, 176, 178, 182, 183, 190-193, 222, 226, 228-234). Based on this, beyond the resilience of EVT delivery in our stroke care system or region, it can be hypothesized that the decline in EVT volume was such a small extent that it could not be reflected in our small-scale study.

Our stroke center's COVID-19 burden was low as only 2.3% of acute IS cases were COVID-19 positive, and 20% of patients needed special isolation due to suspicion or confirmation of the SARS-CoV-2 infection. This suggests that the negative impact of COVID-19 on stroke care volume might also be determined by factors other than the COVID-19 burden. This was also suggested by the results of Nogueira et al., who noted a significant decrease in stroke hospitalizations and IVTs across centers with low, intermediate, and high COVID-19 hospitalization burden (≤6.2 versus >6.2 to 61.9 versus >61.9 COVID-19 admissions/month) (99).

5.1.3. Comparison with Central European data

The results of our single-center study seem in line with the experiences of studies from other Central European countries. The decline in IS hospitalization volume and acute reperfusion treatment numbers appeared to be a general phenomenon during the first surge of the COVID-19 crisis in Central Europe, the extent of which varied among countries, regions, and health care systems. The larger-scale studies from Poland reported a similar size decrease in stroke or IS hospitalizations (15.5% and 10%, respectively), while the single-center analysis of Sobolewski et al., along with data from Slovakia, showed a greater extent of decline (19,31% and 25.7%, respectively) during the first wave of the COVID-19 pandemic (153-155, 158). While similar to our study, Dębiec et al. from Poland reported a remarkable pre-hospital delay, they also noted a significant delay in the intra-hospital workflow, similarly to Sobolewski et al., which contrasts with our data (154, 155). On the other hand, Gdovinová et al. from Slovakia did not find a considerable delay in the workflow during the first epidemic wave of COVID-19, while our results show a marked pre-hospital delay in acute stroke care (158). The impact of COVID-19 on Central Europe stroke centers might differ based on different stroke care systems, the level of development of the acute reperfusion interventions, the amplitude of the SARS-CoV-2 epidemic, and the diversity of health care reorganizations due to COVID-19.

5.1.4. Discussion of time quality data

The slight 5 minutes increase on average in the intra-hospital workflow might reflect the screening procedures and precautionary measures implanted because of COVID-19. Nonetheless, the relative steadiness of the intra-hospital workflow and patients' unchanged early functional outcome suggests that although there was a decline in the volume of acute stroke care, our stroke center could efficiently adapt to the pandemic situation and preserve the quality of care. In concordance with our results, data from Western Europe generally suggested that those patients with acute IS who did seek acute hospital care during the COVID-19 crisis were treated with the same high quality as before the COVID-19 pandemic (3, 134, 137, 138, 140-142, 144, 145, 147, 149-152). However, these observations contrast with other studies, as data from China generally suggest that intra-hospital workflow surrounding acute reperfusion treatment was impacted negatively (92-94, 175, 176, 178, 182, 183). Moreover, data regarding time-based intra-hospital performance indicators were inconsistent and conflicting in North America, Southern Europe and Central Europe, similarly to global and international scale studies (14, 97, 103-105, 108, 110, 111, 117, 120, 124, 126, 129-131, 134, 137, 138, 140-142, 144, 145, 147, 151, 152, 154, 155, 158, 190-193, 222, 223, 226, 231, 234, 235). These controversial data could reflect the uniqueness of every stroke care system. Differences between countries, regions, and centers might be attributable to the infrastructure and logistics paradigm of stroke care, the level of organization and standardization of workflows, the extent of the COVID-19 burden, and the diversity of health care reorganizations due to COVID-19.

Delay in the presentation of acute IS patients was mirrored in multiple other studies, as delay in the pre-hospital phase of acute stroke care was a general tendency during the first wave of the COVID-19 pandemic in China, North America, Southern Europe, and also in Western European countries, except the UK (14, 92-94, 105, 108, 110, 111, 115, 116, 123, 124, 126, 129-131, 134, 137, 138, 140-142, 144, 145, 147, 151, 152, 175, 176, 178, 182, 183, 190-193, 223, 226, 230, 231, 234). Data from Central Europe were limited and controversial (154, 158).

The shift between arrival time categories during the pandemic period means a significant reduction (-13%) in the number of potentially treatable acute IS patients, as was also reflected by the marked 10% decline in the rate of IVT delivery. Similar to our results, the study of White et al. from the New York City metropolitan area showed that during the COVID-19 outbreak in March-April 2020, a higher proportion of acute IS patients presented beyond 24 hours after symptom onset, while a smaller percentage of patients presented in the eligible treatment windows for IV-tPA and EVT (p=0.03) (116). Correspondingly, a tertiary stroke center from Madrid reported that a significantly lower proportion of stroke patients arrived within 4.5 hours from symptoms onset (43 versus 58%, p=0.043) during the first surge of COVID-19 as in the same period of the previous year (131). This was further confirmed by Teo et al., who observed a significantly lower proportion of patients with TIA or stroke within 4.5 hours from symptoms onset in the Queen Mary Hospital in Hong Kong, China, during the first 60 days of the COVID-19 outbreak (181). Delay in stroke care and missing acute reperfusion treatments may potentially devastate patient outcomes as it may result in death or permanent disability. Our study is unable to define the causes, although the ordinal logistic regression analysis supports the assumption that the COVID-19 pandemic itself might play a major role in these changes, as the study year (COVID-19) appeared to have the strongest association with the shift between arrival time categories.

5.1.5. Potential causes of collateral damage

In light of the considerable pre-hospital delay of IVT delivery and the relative steadiness of the intra-hospital workflow, the impact of the COVID-19 pandemic on our stroke care system might be explained mainly by reasons outside of the hospital. Similarly to many authors, we hypothesize that changes in patients' social behavior might be one of the leading causes (35, 93, 94, 97, 99, 100, 104, 106, 127, 128, 131, 138, 141, 145, 149, 150, 154, 174, 176, 181, 223, 229, 231, 234, 236, 237). Acute IS patients (especially non-disabling cases) might be reluctant to present with their symptoms because of the fear of acquiring the SARS-CoV-2 infection in the hospital. This mental state was reflected in the national survey of the American College of Emergency Physicians, as four in five adults reported they are concerned about contracting COVID-19 from another patient or visitor if they need to go to the emergency room. Furthermore, three-quarters of the surveyed adults were first and foremost concerned about contracting another illness while being at a medical facility during the COVID-19 outbreak (150, 238).

Besides the fear of getting infected with SARS-CoV-2, stay-at-home campaigns and restrictive measures might impel patients to consider seeing a doctor with their complaints. The emphasis on social distancing might have inappropriately persuaded patients with acute stroke to avoid in-person medical care. Beyond anecdotal reports, it was mirrored in a Portuguese study that reported a significant increase in the time from symptom onset to emergency call during the COVID-19 crisis, with an outstandingly high number of patients waiting for more than four hours (March 2020: 20.8% versus March 2019: 6.8%, p=0.034; April 2020: 23.8% versus April 2019: 6%, p=0.01) (25, 94, 106, 127, 237).

Furthermore, stroke patients often do not recognize neurological symptoms themselves, therefore, the initiative to seek medical help frequently comes from bystanders. Thus, increased social isolation due to social distancing and restrictive measures may have decreased the chance of friends, co-workers, and family members to timely recognize that a patient was having a stroke. This phenomenon could affect elderly patients disproportionately greater as they live more socially isolated in North American and European countries at baseline (35, 99, 131, 138, 141, 145, 154, 174, 176, 223, 231, 234, 237).

As LVOs cause severe neurological symptoms that can not be neglected, it can be hypothesized that the majority of missing stroke cases are mild, non-disabling strokes. While acute reperfusion interventions (especially EVT) might not have been indicated in mild, non-disabling cases, acute IS patients with LVO are potential candidates for EVT and IVT, which might explain why the number of acute IS admissions and IVTs decreased in our study, while the volume of EVT delivery was unchanged. Howbeit, the similar rate of LVOs and stroke severity between the pandemic and control cohorts might not support this hypothesis.

As a hospital-based study, we were also not able to determine whether ambulance response times have changed during COVID-19. Nevertheless, pre-hospital emergency services and transportation might be surpassed by the vast amount of respiratory patients attended during the COVID-19 epidemic peak and having to apply enhanced disinfection and security protocols that may have slowed down the chain of acute stroke care (14, 126, 129, 131, 181). Arguably, the EMS of Catalonia noticed an overall 330% increment in emergency calls (with peaks of >41,000 emergency calls on a single day) in association with a marked fall in the number of stroke codes activations and stroke hospitalizations, IVTs, and EVTs in March 2020. An overload of emergency calls could have led to saturation of the EMS patient transport system, which could contribute to the decline of acute stroke care volume (14). Nonetheless, Ikenberg et al. from Munich, Germany, showed that COVID-19 containment measures do not necessarily disrupt the interplay of stroke units and EMS (149).

Considering that different acute stroke network models might have consistently affected the acute stroke care service performance through the COVID-19 pandemic and a trend toward the mothership logistic paradigm through centralization measures could be observed in many acute stroke care systems during the COVID-19 crisis (as presented in the Chapter 1.3.2.3.), changes can also be hypothesized in the acute stroke network in which our stroke center is embedded (104, 111, 123, 125, 127, 130, 137, 154, 183, 188-193). Howbeit, we were unable to analyze this aspect as it was a hospital-based study (154).

Although a decrease in stroke incidence was raised, the ESO and most authors agree that there is still no well-grounded reason to assume that stroke incidence has declined since the onset of the COVID-19 crisis (3, 35, 99, 129, 239). Nevertheless, lifestyle, nutritional and environmental changes during a COVID-19 pandemic might also affect stroke epidemiology, but our study did not evaluate their effect.

Epidemiological studies have demonstrated a strong association between air pollution and stroke. The Global Burden of Disease Study estimated that the population-attributable risk factor of ambient air pollution for stroke is around 18%. There is also evidence that short-term increases in an airborne particular matter and nitrogen dioxide levels are correlated with more hospital admissions for stroke. Therefore, the reduction in air pollution during the COVID-19 crisis may have contributed to reducing stroke incidence, as a striking reduction in air pollution has been reported in multiple countries during the COVID-19 pandemic secondary to confinement measures (35, 97, 99, 100, 174, 240, 241).

Besides, one might assume that there were changes in the lifestyle during the COVID-19 pandemic which might lower the incidence of cardiovascular diseases, like stroke: decreased access to fast food, unhealthy salt-rich and fatty foods with restaurant closures along with the home cooking and baking fads, a decrease in alcohol consumption due to reduction of social drinking, lower level of work stress due to home office, more time for recreational sports activities, and improved medication compliance (35, 99, 100, 241, 242). However, there are data regarding changes in the opposite direction, making an actual decrease in stroke incidence unlikely. During the COVID-19 pandemic, it was more challenging than usual to continue regular physical activity patterns because of public health orders, recommendations to stay at home, school and park closures, and self-isolation by high-risk groups. Accordingly, Hemphill et al. reported markedly lower step counts in children with congenital heart disease (243). Likewise, the international study by Tison et al. reported that during the COVID-19 pandemic, individuals became more sedentary worldwide (244). Besides, existential uncertainty due to the economic and financial difficulties and the increased anxiety induced by the COVID-19 pandemic resulted in stress eating and increased alcohol consumption in many individuals, particularly parents, essential workers, young people, and people of color (242, 245, 246). Accordingly, in the survey by the American Psychological Association, the majority of adults (61%) reported experiencing undesired weight changes since the start of the COVID-19 pandemic, with more than two in five saying they gained more weight than they intended (29 pounds [13.2 kilograms] on average) (242). Similarly, the longitudinal study by Li et al. found a significant increase in weight after implementing confinement measures at a rate of roughly a pound and a half [0,68 kilograms] weight gain per month (247).

During the COVID-19 pandemic, the adherence of patients with chronic non-communicable diseases, like stroke, to pharmacotherapy might not be improved but deteriorated. Martsevich et al. reported a substantial decline in stable coronary artery disease patients' adherence to pharmacotherapy. Although the adherence to beta-blockers, renin-angiotensin-aldosterone system inhibitors, and dihydropyridine calcium antagonists remained unchanged, as a particularly negative trend, the adherence to antiplatelet drugs ($p=0.047$) and statins ($p=0.055$) significantly decreased (248). Correspondingly, Bandyopadhyay et al. noted that diabetic patients' compliance with medications and healthy lifestyle habits were significantly reduced during the lockdown period in India (249). This unfortunate trend was further confirmed also in other countries (250, 251).

The widespread implementation of community mitigation measures due to the COVID-19 pandemic, including stay-at-home orders, school closures, bans on mass gatherings, social distancing, and mask-wearing, dramatically reduced the exposure to other common viruses, like influenza (35, 99, 252, 253). The Centers for Disease Control and Prevention in 2020 reported a decline in influenza virus circulation in the USA and other Northern Hemisphere countries and the tropics, while the Southern Hemisphere had virtually no influenza circulation (252). It was further confirmed by the large-scale global analysis of Spantideas et al., who reported that in 2020 and 2021, all directly transmitted respiratory infections almost disappeared (253). Although the marked reduction in exposure to other common viruses that might trigger vascular events may have pointed to lower stroke incidence, this might not be the case in the context of the COVID-19 pandemic. If anything, stroke incidence might have risen given the disease-associated predisposition for thromboembolic events, like stroke (acute IS incidence among symptomatic COVID-19 patients is 0.9-5% as presented in Chapter 1.3.1.1.) (3, 23, 26, 33-35).

5.1.6. Strengths and limitations

The strength of our study is that beyond the volume of acute IS care, it also provides data about the quality of stroke care during the COVID-19 outbreak. Our study's main limitations are the small sample size and the inherent limitations of a single-center and retrospective nature.

5.2. Discussion of the national-level analysis

5.2.1. General remarks

Our study revealed that the mean and median values of weekly IS admissions and acute reperfusion interventions showed a decrease only in some measure during the two epidemic waves of COVID-19 in Hungary. However, the control charts demonstrated that these values reflect a significant disruption in the trends and decline in the number of IS admissions, IVTs, and EVTs. It is also notable that results regarding IS admissions were similar if we computed the number of IS admissions as the number of cases where ICD I63 or I64 or I66 codes were presented only as primary discharge diagnosis (i.e., main diagnosis for admission) in the reimbursement database of NHIFH (data presented in the Supplementary; Chapter 11. Fig. S1-2.).

Notwithstanding that a negative deviation from the trend could be observed both in IS admission numbers and IVT and EVT numbers, the decline's dynamic and amplitude have differed for each variable. During the COVID-periods, the number of IS admissions showed a high amplitude negative steep wave of decrease with a significant restoration in the epidemic interlude. Similarly, the EVT numbers decline also presented with a negative wave dynamic but with a smaller amplitude and without significant rearrangement in the epidemic interlude. In contrast, the IVT's decline from the trend was rather stepwise (larger amplitude but less dynamic) during the first wave of the COVID-19 outbreak, and the extent of the deviation from the trend persisted through the epidemic interlude and the second epidemic wave. Additionally, our study demonstrated a significant negative correlation between the number of SARS-CoV-2 cases in Hungary and the number of IS admissions and EVTs. However, the number of IVTs changed regardless of the amplitude of the COVID-19 epidemic waves.

5.2.2. Comparison with international data

The results of our study are in line with the global and international data, as the decline in the quantity of acute stroke care (IS admissions, IVTs, EVTs) was a broad experience during the COVID-19 pandemic in studies from across Europe, North America, and also China and other LMICs (3, 14, 35, 92-106, 108-111, 113-117, 120, 123-131, 134, 137, 138, 140-142, 144, 145, 147, 149-155, 157, 158, 165, 169, 170, 173-176, 178, 182, 183, 190-193, 222-231). Our national-level data also confirms the general phenomenon that acute reperfusion treatments decreased to a lesser extent than the number of IS hospitalizations; at the same time, IV-tPA delivery was more severely impacted than EVT delivery. The disproportionally greater reduction in IS admissions was further confirmed by the significant, and at some time points extreme, increase in the ratio of IVTs or EVTs and IS admissions during the first and second epidemic wave of COVID-19. Similar results were found by Zhao et al., who noted in their large-scale national analysis that although the number of IVTs and EVTs significantly dropped by around 25% among all hospitals, the rate IVTs and EVTs significantly increased during the COVID-19 crisis (176). It was also reflected in the metanalysis of July et al., which showed that whereas the absolute number of EVTs was reduced during the COVID-19 pandemic, the number of patients receiving EVT per patient with a stroke increased (100).

The second epidemic wave of COVID-19: The vast majority of studies reflect the first epidemic wave of COVID-19, while data regarding the second epidemic wave are limited. Contrary to our data, a tertiary stroke center in North Rhine-Westphalia, Germany - where similarly to Hungary, the restrictive COVID-19 measures were less severe during the second epidemic wave than in the first wave – reported that the reduction in the volume of acute stroke care was comparable between the first and second epidemic waves but less pronounced in fall 2020 (151). Similar results were reported by a rural stroke center located in south-eastern Poland, as they observed a lower reduction in the volume of stroke hospitalizations and acute reperfusion treatments during the second COVID-19 wave than in the first epidemic wave. Besides, despite the greater number of COVID-19 infections during the second epidemic wave, more patients underwent IVT (26.4% versus 9.9%, $p<0.008$) and EVT (5.3% versus 0.0%, $p<0.001$) during the second than the first wave (155). Furthermore, a single-center (thrombectomy center) study from Milan, Italy, which has a study setting that does not make it possible to compare the volume of stroke care, noted a significant delay in EVT delivery during the COVID-19 pandemic in 2020. However, better management was done during the second epidemic wave, where time metrics were improved relative to the first wave, despite a much higher incidence of SARS-CoV-2 cases (254). Our study was not able to analyze the quality metrics of stroke care. However, similar trends might also be assumed in Hungary based on different characteristics in the control charts: the z-scores of IS admissions and EVTs started to decrease less abruptly at the beginning of the Wave-2 period than in the Wave-1 epoch;

furthermore, the ratio of reperfusion interventions and IS admissions increased with later onset during the Wave-2 period.

5.2.3. Comparison with results of the single-center study

In the light of our national-level study, the reduction in the number of IS admissions and IVTs in our academic stroke center mirrored well the general situation in Hungary during the spring of 2020. However, while our single-center study did not find differences in the number of EVTs, we noted a marked reduction in the EVT delivery in the nation-level analysis, which is most likely due to the low sample size. Nevertheless, based on the board variations in the data regarding EVT delivery among counties, regions, and health care systems, one might still hypothesize that the EVT delivery in our stroke care system or region was resilient during the COVID-crisis. Further studies are needed to elucidate this question.

5.2.4. Potential causes of collateral damage

Our most robust result is that the decline of IS admissions, IVTs, and EVTs showed a different timely pattern and correlated differently with the amplitude of the COVID-19 epidemic wave. These results suggest that multiple different factors might play a role in disrupting the trends of the analyzed characteristics. Our study is unable to evaluate the causes, but several factors can be hypothesized. The hypothesized causes of the collateral damage of COVID-19 were presented in detail in the previous chapter (Chapter 5.1.5.). Thus, hereby we present additional data.

We speculate that besides changes in the social behavior, the impact of COVID-19 on the Hungarian acute stroke care might be first and foremost explained by the impact of the health emergency operative measures, as there was a 20–60% reduction in the number of available hospital beds to ensure the care of COVID-19 patients accompanied with a complete or partial restriction of elective health care (20, 197, 208, 209, 211-215).

During the two epidemic waves, the number of IS admissions decreased to a disproportionally larger extent than the number of reperfusion interventions. We hypothesize that the health emergency operative measures could be one of the causes because the dynamic of the disproportionally greater decrease of IS admissions seems to be mostly concurrent with the health emergency operative measures. During the Wave-1 period, the peak of the disproportionally greater reduction of IS admissions overlaps when

50–60% of beds had to be reserved for COVID-19 patients, and the gradual termination of this phenomenon co-occurs with the four-step alleviation of restrictive measures. During the Wave-2 period, the IS admission numbers started to decrease to a disproportionally larger extent when the number of COVID-designated hospitals was expanded, and 20–40% of beds had to be reserved for COVID-19 patients.

It could also be presumed that COVID-19 itself or the lifestyle altered by confinement measures could change the proportion of IS patients eligible for reperfusion therapies.

Changes in patients' social behavior (namely, non-disabling IS cases, where reperfusion interventions would not have been indicated, could stay at home because of the fear of getting infected with SARS-CoV-2) could also contribute, as suggested by several authors (113, 127, 129, 141, 144, 153, 174, 183, 193, 223, 229, 234). The large-scale study by Diegoli et al. showed that the onset of the COVID-19 pandemic correlated with a reduction in admissions for TIA, mild and moderate strokes (NIHSS≤8), while there was no difference in admissions for severe stroke cases (NIHSS>8) (174). Similarly, the analysis of 114 hospitals in the UK showed that admissions fell more for patients with less severe stroke (NIHSS≤4) (141). Correspondingly, an analysis of 7969 acute IS patients in the USA reported that besides the marked reduction in the volume of admissions and IVTs, acute IS patients presenting during the COVID-19 period were at significantly greater odds of having a severe stroke (NIHSS>14, odd ratio: 1.22, 95 % CI: 1.03–1.46, p=0.025) (229). This was further confirmed by a similar scale study from the USA, as it noted that during the COVID-19 pandemic, besides the reduction in stroke hospitalizations, IVTs, and EVTs, patients were less likely to present with milder stroke symptoms (NIHSS≤5; odds ratio=1.01, 95% CI = 1.00-1.02, p=0.04) (234). In addition, Hou et al. from the largest stroke center in China reported that the ratio of acute IS patients with mild stroke symptoms among EVT cases significantly declined during the COVID-19 pandemic (183). Besides, since stroke mimics are usually characterized by mild neurological symptoms, similarly to non-disabled IS cases, their reduced presentation, led by the fear of getting infected with SARS-CoV-2, might also be presumed in the COVID-periods (255). However, while it could contribute to the decrease of IVTs, it cannot explain the decline in IS admissions because stroke mimics are not included in our cohort of IS admissions.

In addition, as the numbers of SARS-CoV-2 infections increased in each epidemic wave, the burden on health care increased, and patients with infective symptoms were at the center of attention. This might have resulted in missing (under-diagnosing) stroke cases, especially in less severe, non-disabling cases, which might have increased the ratio of reperfusion interventions and IS admissions during the epidemic waves (129, 145, 236).

In the COVID-periods, a numerical pattern very similar to the winter and summer holiday seasons could be observed (an increase in the ratio of IVTs or EVTs and IS admissions), which might indirectly support both the behavioral and the healthy policy hypothesis. One might hypothesize that patients may not seek medical attention for acute neurological symptoms during winter and summer holidays unless they perceive that the symptoms are so severe (potentially IVT and EVT candidate cases) that it allows them no other choice. This theory could explain the increase in the ratio of reperfusion interventions and IS admissions during the winter and summer holiday seasons. During the epidemic waves, patients might have a very similar attitude, which might be motivated by the fear of getting infected with SARS-CoV-2 rather than not wanting to miss festivities. In the Wave-1 period, when patients might have little idea of what to expect from the COVID-19 epidemic, the fear might be high, which could cause an abrupt increase in the ratio of reperfusion interventions and IS admissions. While in the Wave-2 interval, when patients already had experiences of the epidemic's dangers, the fear might not reach Wave-1 level, despite SARS-CoV-2 cases being higher, until the COVID-19 case numbers and deaths reached an exceptionally high value. This theory could explain the later onset increase in the ratio of reperfusion interventions and IS admissions in the Wave-2 period.

Furthermore, it is also presumable that non-acute IS admissions for follow-up investigations are less likely in the winter and summer holiday seasons, which might also explain the increase in the ratio of reperfusion interventions and IS admissions in these periods. In the Wave-1 interval, when governments and healthcare authorities might have little knowledge about the COVID-19 epidemic, strict restrictive measures were abruptly implemented. These restrictive measures rapidly made it impossible to admit elective, non-acute IS cases, which might also increase the ratio of reperfusion interventions and IS admissions in the Wave-1 interval. Presumably, based on the experiences from the Wave-1, despite the higher COVID-19 case numbers, strict confinement measures and restriction of elective health care took place later in the Wave-2 period, which might also contribute to the later onset increase in the ratio of reperfusion interventions and IS admissions. Moreover, it can also be presumed that during the COVID-19 epidemic, patients were less likely to accept elective hospital admissions because of the fear of getting infected with SARS-CoV-2, even if it was allowed.

Behind the decline of EVT numbers, the deceleration of the continuous growth of EVT numbers could also be hypothesized, which overlaps the time of the COVID-19 epidemic. However, it seems less likely since, in our database, annually maximum of 3% of patients with ICD-10 I63/I64/I66 primary discharge diagnosis codes were treated with EVT, while population-based studies from 2016 to 2017 estimated that 7–16% of all IS admissions are potentially eligible for EVT (256, 257). Moreover, evidence from recent years might increase further the proportion of acute IS patients eligible for EVT, making the theory of EVT's deceleration less probable (4-11, 145). Additionally, the inclusion of the first ten weeks of 2020 in the baseline period also makes such a steep and prominent deviation from the EVT's baseline less like solely due to the deceleration of EVT's growth.

As data from China and the UK showed that some thrombectomy centers used stricter selection criteria for EVT during the COVID-19 pandemic, this may have also occurred in Hungary and might have played a role in the decline of EVTs (140, 183). The national survey of the UK Neurointerventional Group and the British Society of Neuroradiologists showed that during the COVID-19 outbreak, half of the active thrombectomy centers in the UK had changed their case selection towards stricter adherence to national guidelines, and some had introduced an age threshold (140). Similarly, China's largest comprehensive stroke center reported that during the COVID-19 crisis, acute IS patients with older age, more underlying diseases, and a higher risk of complications were preferred to take conservative treatment (183). In addition, although our study was unable to elucidate, EVT procedures might have been further restricted during the COVID-19 pandemic by the scarcity of ICU or other appropriate beds, respirators, and anaesthesiologists (140, 168, 172, 258).

During the two epidemic waves of COVID-19, the number of IVTs decreased more than the number of EVTs. The discrepancy between the observed decline in the volume of IVTs and EVTs could hypothetically be explained by the fact that IVT is a more time-sensitive treatment than EVT. Notably, the therapeutic time window for IVT is much narrower than for EVT. Thus, assuming that the delay in the patients' presentation, as our single-center study reported, was a general phenomenon, it could have led to missing therapy to a greater extent in the case of IVT than EVT (4-6, 8, 9, 11). Moreover, suppose it is true that the missing stroke cases are mainly attributable to less severe cases also in our cohort. In that case, it might also explain, at least partially, why the volume of IVTs decreased more than the EVT volume, as acute IS patients without LVO could have disabling symptoms yet lower NIHSS scores (i.e., aphasia), which makes them a candidate for IVT (144, 223).

5.2.5. Strengths and limitations of the study

The most important strength of our study is the large nationwide dataset covering all IS admissions, IVTs, and EVTs from 2017 to 2020 in Hungary. In addition to absolute comparisons of raw case numbers, this gave us the ability to perform trend analysis and measure the impact of COVID-19 on de-trended and standardized case numbers in a timeline. The other strength of the study is that we analyzed not only the first but also the second COVID-19 epidemic wave and epidemic interlude, which gives our analysis a broader scope. The main limitations of this study are the reimbursement purpose of the database, the retrospective and observational nature of our research, and the different coding practices that had to be addressed. The incidence of COVID-19 in the IS population was unknown, so we could not assess the direct effects of SARS-CoV-2 infections. In the lack of qualitative parameters of IS cases and care, we could not elucidate the emerged causes of IS care disruption during the COVID-19 outbreak in Hungary. Furthermore, our study does not cover the entire second wave of the COVID-19 epidemic in Hungary, and data from the last calendar week were incomplete and therefore artificially boosted by 7/4.

6. Conclusion

Our work demonstrated that the COVID-19 pandemic had a negative impact on IS stroke care in Hungary. During the first wave of the COVID-19 pandemic, we observed a significant decline in the volume of IS admissions and acute reperfusion interventions in a hospital and at a national level, which was in line with the international, North American, and European data.

During the second epidemic wave of COVID-19, we found a similar pattern of changes in the volume of IS stroke care with an even greater decrease in the volume of IS admissions, IVTs and EVTs. These national-level results contrast with the limited international single-center data about the impact of the second epidemic wave of COVID-19 on stroke care. However, given the national scope of our data, we believe that our results will have generalizability to other settings beyond Hungary.

Since we showed a significant, and at some time points extreme, increase in the ratio of acute reperfusion treatments and IS admissions during the first and second epidemic wave of COVID-19, we could statistically confirm those international observations from North America, Europe, and China that acute reperfusion treatments decreased to a lesser extent than the number of IS hospitalizations. We demonstrated that this phenomenon could partially be explained by the effect of health emergency operative measures and changes in patients' social behavior. In addition, our data propose that the impact of these factors is not constant over time.

In addition, we provided data that support the association between COVID-19 and the observed changes in the IS care during the pandemic, as the first year of the COVID-19 pandemic appeared to have the strongest association with the significant delay in the presentation of acute IS patients in our stroke center, and mainly as we demonstrated a significant negative correlation between the number of SARS-CoV-2 cases in Hungary and the number of IS admissions and EVTs.

The use of z-scores and the visual-statistical tool of the control chart gave us the opportunity to compare different time points and perform a time-series analysis of IS admissions, IVTs, and EVTs across the COVID-19 epidemic waves and control periods. Hence, one of our most robust results is that the decline of IS admissions, IVTs, and EVTs showed a different timely pattern and correlated differently with the amplitude of the COVID-19 epidemic wave. These results suggest that multiple factors might have disrupted IS care, which could have affected IS admissions, IVTs, and EVTs differently.

Beyond the reduction in acute IS stroke care volume, our most robust findings are the marked delay in IVT delivery resulting from increased onset-to-door time and the significant delay in presentation of acute IS patients during the first wave of the COVID-19 pandemic, which resulted in a significant reduction in the number of acute IS patients who are potentially treatable with acute reperfusion therapies. However, further national-level analysis is needed to validate these results' generalizability; they mirror the general tendency during the first wave of the COVID-19 pandemic in China, North America, Southern Europe, and Western European countries, except the UK. Delay in stroke care and missing acute reperfusion treatments is of paramount importance as they may result in death or permanent disability.

The relative steadiness of the intra-hospital workflow and patients' unchanged early functional outcome in our academic stroke centers suggests that although there was a decline in the volume of acute stroke care, our stroke center could efficiently adapt to the pandemic situation and preserve the quality of care. The results suggest that those patients with acute IS who did seek acute hospital care during the COVID-19 crisis were treated with the same high quality as before the COVID-19 pandemic, at least in our stroke center. Although these results are consistent with data from Western European countries, further studies are needed to elucidate whether they can be generalized to a national level.

Our work provides supportive data that changes in patients’ social behavior, and health emergency operative measures could be among the leading causes that might contribute to the negative impact of COVID-19 on IS care in Hungary. In addition, our time-series analysis data propose that the impact of contributing factors is not constant over time. Further studies are needed to reveal all the contributing factors and clarify their role in the collateral damages of COVID-19.

As the COVID-19 pandemic continues, every effort should be made to mitigate collateral damages. Although the control of COVID-19 is very important, at the same time, the management of stroke must not be neglected. Public information campaigns are of paramount importance. During informational campaigns, it should be emphasized that effective treatment of stroke is only possible within a few hours from symptoms onset, and missing acute reperfusion treatments because of fear of getting infected with SARS-CoV-2 may result in death or permanent disability. Patients should be encouraged to seek timely medical care and be reassured that hospitals make every possible precaution against infectious diseases.

Our study highlights the importance of the continuous effort to mitigate collateral damages of COVID-19, including public information campaigns and surveillance of health policy measures and IS care systems. What we learned from these two COVID-19 waves we can use to preserve IS care in subsequent waves or future epidemics.

7. Summary

Previous studies reported remarkable collateral damages in stroke care during the COVID-19 pandemic, which varied among countries, regions, and health care systems. However, the impact of the COVID-19 pandemic on stroke care in Hungary is unknown in the current literature. Moreover, data about the effect of the second wave on stroke care is very limited. Hence, first, we analyzed the volume and the quality of acute IS care in our academic stroke center during the first two months of the COVID-19 crisis. Then, to determine whether our single-center results can be generalized to Hungary, we performed a national-level study using a national reimbursement database and analyzed both the first and the second waves. Our retrospective works demonstrated that the COVID-19 pandemic had a negative impact on IS care in Hungary. During the first wave, we observed a significant decline in the volume of IS admissions and acute reperfusion interventions in a hospital and at a national level. During the second wave, similar changes were found with even greater reductions. We verified that the decline in IS care is associated with COVID-19, and we found that the decline of IS admissions, IVTs, and EVTs had a different timely pattern and correlation with the amplitude of the epidemic waves. Our work statistically confirmed those international observations that acute reperfusion treatments decreased to a lesser extent than IS hospitalizations, which could partially be explained by health emergency operative measures and changes in patients' social behavior. In addition, we propose that the impact of these factors is not constant over time. We noted a marked delay in IVT delivery resulting from increased onset-to-door time and a significant delay in the presentation of acute IS patients in our stroke center during the first wave, which significantly reduced the number of acute IS patients who are potentially treatable with acute reperfusion therapies. Delay in stroke care and missing acute reperfusion treatments is of paramount importance as they may result in death or permanent disability. Nevertheless, the relative steadiness of the intra-hospital workflow and patients' unchanged early functional outcome in our center suggests that those stroke patients who did seek acute hospital care during the COVID-19 crisis were treated with the same quality as before the COVID-19 pandemic, at least in our stroke center. Our study highlights the importance of the continuous effort to mitigate collateral damages of COVID-19, including public information campaigns and surveillance of health policy measures and IS care systems.

Összefoglalás

A korábbi nemzetközi tanulmányok a stroke ellátás COVID-19-pandémia alatti jelentős kollaterális károsodását mutatták, melynek mértéke országonként, régiónként és egészségügyi rendszerenként jelentősen eltért. A COVID-19-nek a magyar stroke ellátásra kifejtett hatása jelenleg nem ismert. Ráadásul, a második hullámról szóló nemzetközi adatok is korlátozottak. Így, először megvizsgáltuk, hogy az egyetemi stroke centrumunkban a járvány első két hónapja során miként változott az iszkémiás stroke (IS) ellátás volumene és minősége, majd hogy ez tükrözi-e az országos helyzetet egy további kvantitatív elemzést végeztünk az országos finanszírozási adatbázis segítségével. Retrospektív vizsgálataink kimutatták, hogy a COVID-19 negatív hatással volt a magyar IS ellátásra. Az első hullám során az IS miatti felvételek és akut reperfúziós kezelések száma jelentősen visszaesett, mind kórházi, mind országos szinten. A második hullám során hasonló, de még súlyosabb visszaesést találtunk. Emellett igazoltuk az IS ellátás visszaesése és a COVID-19 közötti kapcsolatot, illetve rámutattunk arra, hogy az IS felvételek, az intravénás trombolízisek (IVT) és az endovaszkuláris kezelések (EVT) csökkenésének mintázata eltért és a járványhullámokkal való összefüggése különbözött. Munkánk statisztikailag alátámasztotta azokat a nemzetközi megfigyeléseket, miszerint az akut reperfúziós kezelések kisebb mértékben estek vissza, mint az IS felvételek. Adataink arra utalnak, hogy ezt a jelenséget részben az egészségügyi operatív intézkedések és a betegek szociális magatartásváltozása magyarázhatja, illetve felvetik, hogy ezeknek a hatása időben változó lehet. Az első járványhullám során centrumunkban az IVT megkezdésének, a prehospitális szak megnyúlásából adódó, jelentős késedelmét, illetve az akut IS betegek kórházba érkezésének jelentős késését mutattuk ki, ami az akut reperfúziós kezelésekkel potenciálisan kezelhető beteg számának jelentős csökkenését jelentette, mely azért is különös jelenetőségű, mert ennek maradandó rokkantság vagy halál lehet a következménye. Mindazonáltal, a kórházon belüli munkafolyamatok relatív állandósága és a betegek változatlan funkcionális kimenetele arra utal, hogy azok az IS betegek, akik a COVID-járvány alatt akut kórházi kezelést vettek igénybe változatlan színvonalú ellátásban részesülhettek, legalábbis a mi centrumunkban. Tanulmányunk kiemeli a COVID-19 járulékos veszteségeinek mérséklésére irányuló folyamatos erőfeszítések fontosságát, ideértve a lakossági tájékoztató kampányokat, valamint az egészségpolitikai intézkedések és az IS ellátó rendszerek felügyeletét.

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9. Bibliography of the candidate's publications

9.1. Publications on the topic of the present thesis

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11. Supplementary

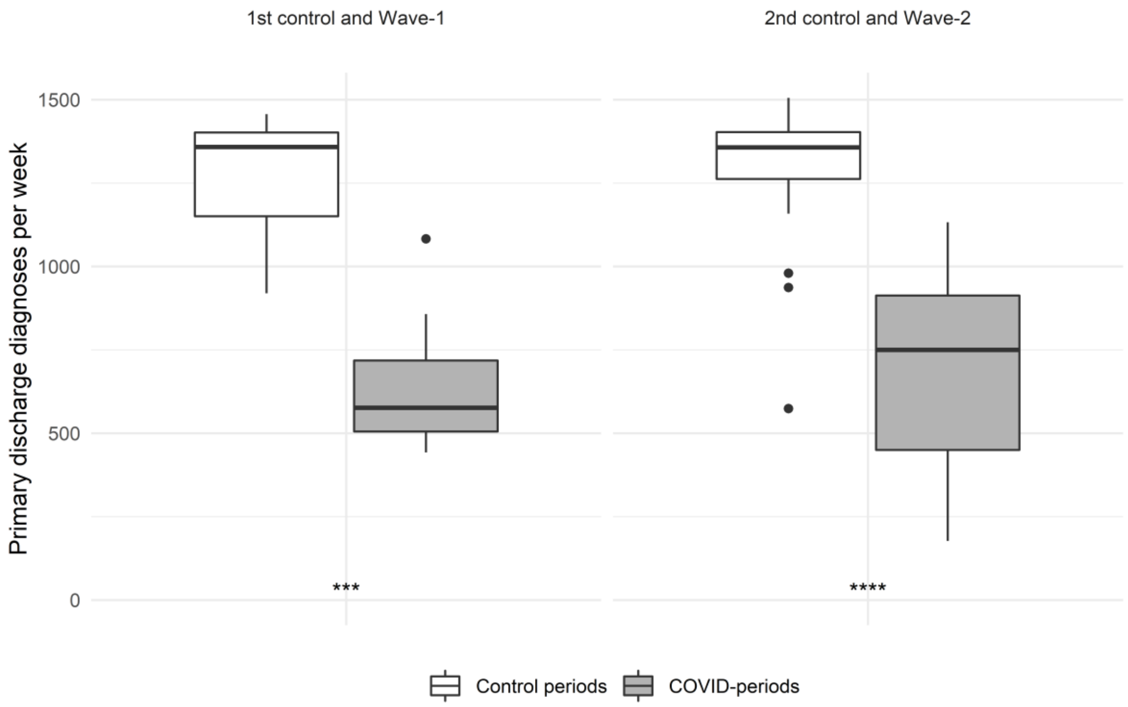

Figure S1. Changes in the raw weekly number of primary discharge diagnoses during the COVID-periods. This figure shows the raw weekly number of primary discharge diagnoses with ICD-10 I63/64/66 codes in the COVID-periods and their respective controls using standard box plots. p values of the paired Wilcoxon-Man-Whitney tests, which compare the COVID-periods to their respective controls, are also presented. full dots: Tukey-defined outliers; p value: *** p<0.001, **** p<0.0001. (12)

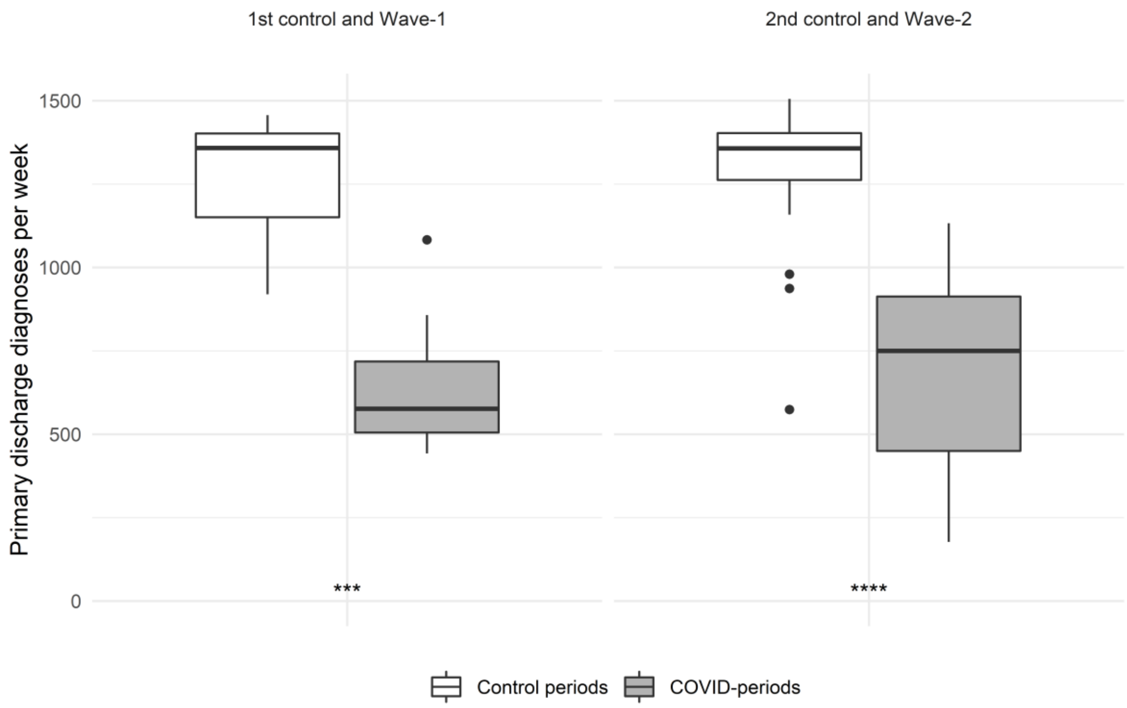

Figure S2. Control chart of primary discharge diagnoses. This graph visualizes the trend and changes using the de-trended and standardized weekly number of primary discharge diagnoses with ICD I63/64/66 codes during the whole study period. p values of the paired t tests, which compare the COVID-periods to their respective controls, are also presented. Dates of the most important restrictive and alleviative health emergency operative measures are marked in the timeline. sd: standard deviation. (12)