IMPACT OF COVID-19 ON ISCHEMIC STROKE CARE IN HUNGARY

PhD thesis

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1. Introduction

In December of 2019, Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, and with the rapid spreading of the disease, the COVID-19 crisis rapidly evolved into a pandemic by March 2020. 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. 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.

The COVID-19 pandemic has affected healthcare systems and patients around the world. Different countries or even different healthcare systems within a country responded with a varied spectrum of health policy changes trying to balance its healthcare workers' safety and uphold the continued quality of care for the patients presenting with emergencies, including stroke.

Global and international studies showed 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 for COVID-19 and the socio-cultural behaviors, healthcare logistics, and infrastructure encountered across the globe.

Studies from North America, Western Europe, Southern Europe, and Central Europe, and also from China and other low- and middle-income countries suggest that a substantial decline in the volume of IS admissions was a general phenomenon during the first wave of the COVID-19 crisis, which extent varied among countries, regions and health care systems. The acute reperfusion interventions (intravenous thrombolysis (IVT) and endovascular therapy (EVT)) seemed to show a generally lesser extent decrease with greater variations, especially in the case of EVT.

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. Data from Central Europe were limited and controversial.

Studies from Western European countries 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. However, these observations contrast with other studies, as data from China generally suggest that intra-hospital workflow surrounding acute reperfusion treatment was impacted negatively. 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.

The vast majority of studies reflect the first epidemic wave of COVID-19, while data regarding the second epidemic wave are limited and derived from single-center experiences.

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

Methods of the single-center analysis: Patients admitted with acute IS to the Department of Neurology, Semmelweis University, were analyzed retrospectively in the March-April time frame in 2020 and 2019. 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 large vessel occlusion (LVO)) were compared along with early functional outcomes, and time quality parameters of IVT delivery. Stroke severity was rated by the National Institutes of Health Stroke Scale (NIHSS) at admission, and early functional outcome was based on the modified Rankin-scale (mRS) at discharge. 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. 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 re-admissions (discharged IS patients who were readmitted within a short time interval).

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.

In addition, we analyzed the burden of COVID-19 on our center as the rate of acute IS admissions requiring special isolation due to suspicion or confirmation of COVID-19 during the pandemic was examined.

Statistical analysis: 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.

Methods of the national-level analysis: This retrospective observational study was based on the nationwide reimbursement database of the NHIFH that encompasses all IS admissions and all reperfusion interventions, i.e., intravenous thrombolysis (IVT) and endovascular therapy (EVT) from 2 January 2017 to 31 December 2020 in Hungary. The COVID-19 pandemic's effect on the number of IS admissions and reperfusion interventions was analyzed using different statistics.

The 10th version of the International Statistical Classification of Diseases and Related Health (ICD-10) I63, I64, and I66 codes were used to evaluate the number of IS admissions from the database. We computed the number of IS admissions as the number of cases where ICD I63 or I64 or I66 codes presented in any of the five diagnosis positions (i.e., main diagnosis for admission; basic disease; accompanying disorder; complication; cause of death). While with this approach, stroke mimics were not part of the cohort, the following group of patients could be included in the cohort: acute ISs, non-acute ISs, in-hospital ISs, IS chameleons, and incidental asymptomatic cerebral infarcts. Each patient counted only at the time of admission in a given week. However, early re-admissions 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. 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) (205). 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)

Based on the Hungarian COVID-19 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. Wave-1 period: 11th–25th weeks of 2020. Wave-2 period: 36th–52nd weeks of 2020. The 10-week long interval between the Wave-1 and Wave-2 periods designated an epidemic interlude (3rd control period). Data of the COVID-periods were compared to their identical periods of 2019 (1st and 2nd control period). 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. Dates of the most important restrictive and alleviative health emergency operative measures were marked and used during the visual-statistical analyses (Figure 1., 4-5.).

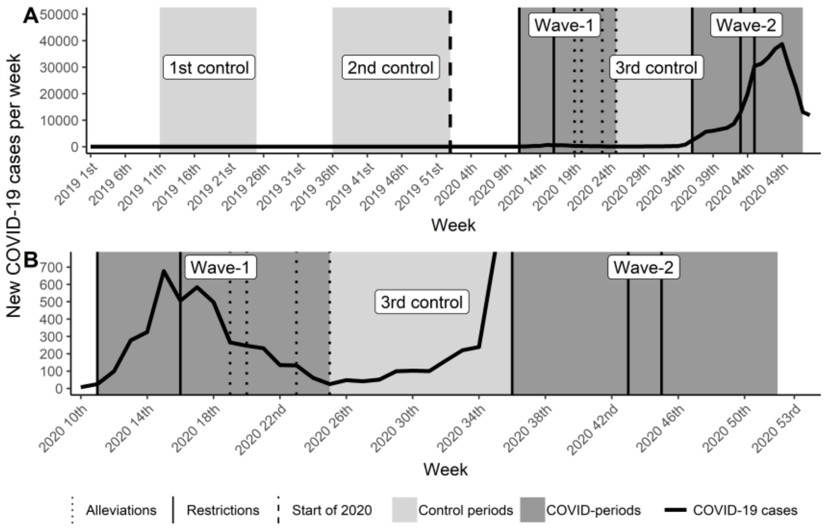

Figure 1. Timeline and summary of the study periods. These graphs summarize the study periods and present them in a timeline, illustrating their temporal relationship to the COVID-19 epidemic waves in Hungary. Dates of the most important restrictive and alleviative health emergency operative measures are also marked in the timelines. (a) illustrates both COVID-19 and control periods, while (b) focuses on the COVID-periods.

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. Since similar findings were apparent using both means and medians, median-based data are presented here.

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. 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. 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 with the same methodology.

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 the 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

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.).

Table 1. Case numbers, demographic and clinical parameters, and functional outcomes during the COVID-19 (2020) and control (2019) intervals. SD: standard deviation.

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 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.

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 (ONT) was prolonged from 190 minutes to 210 minutes (+20 minutes delay), while the mean door-to-needle time (DNT) and door-to-imaging time (DIT) 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 (ONT) mainly came from the delay in the pre-hospital phase as the mean onset-to-door time (ODT) 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. Test: Student paired t test.

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 2.).

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 polymerase chain reaction confirmed SARS-CoV-2 infection in two patients from the 86 acute IS admission (2.3%) during the pandemic period.

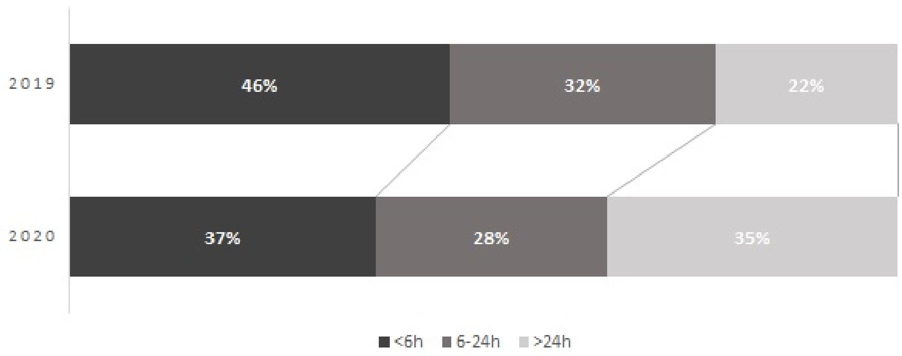

Figure 2. Shift between arrival time categories of acute IS patients. This figure shows how the proportion of acute IS patients changed in the three analyzed time categories (<6h, 6-24h, >24h) between 2019 (control period) and 2020 (COVID-period).

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., Figure 3-4.).

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., Figure 3.). 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., Figure 4.). The trend analysis of the ratio of IVTs or EVTs and IS admissions showed a significant increase during the Wave-1 interval (Table 3., Figure 5.). 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.

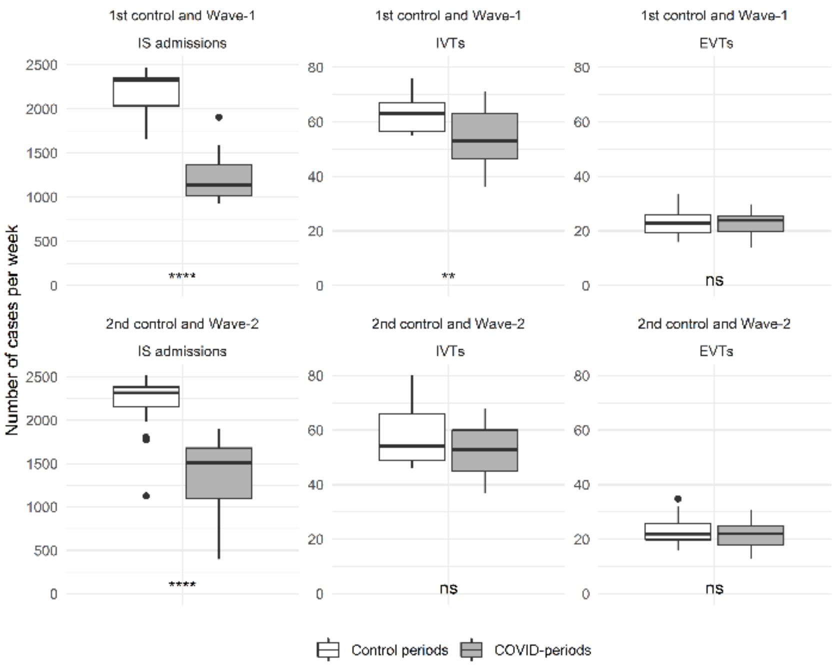

Figure 3. Changes in the raw weekly number of IS admissions and reperfusion interventions during the COVID-periods. full dots: Tukey-defined outliers; p value: ns (not significant) p > 0.05, **p < 0.01, ****p < 0.0001.

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., Figure 4.). 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., Figure 4-5.).

Table 3. Mean-based results of the statistical tests. 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 COVID-periods and the control intervals. Tests are paired where applicable (where the number of weeks equals). SD: standard deviation. Bold font indicates statistical significance.

Variables	1st control period	Wave-1 period	*p* value	3rd control	Wave-1 period	*p* value	2nd control period	Wave-2 period	*p* value	3rd control period	Wave-2 period	*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**	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 (0.86)	−3.42 (1.08)	**< 0.001**	−1.23 (0.64)	−3.42 (1.08)	**< 0.001**	0.21 (1.34)	−3.02 (1.69)	**<0.001**	−1.23 (0.64)	−3.02 (1.69)	**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	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))	0.79 (0.85)	−1.19 (1.26)	**< 0.001**	−0.90 (0.96)	−1.19 (1.26)	0.526	−0.22 (1.25)	−1.73 (1.00)	**0.002**	−0.90 (0.96)	−1.73 (1.00)	**0.045**
EVTs (mean (SD))	22.81 (5.25)	23.02 (4.28)	0.883	26.00 (4.08)	23.02 (4.28)	0.095	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))	0.60 (1.29)	−0.80 (0.98)	**0.001**	−0.41 (1.05)	−0.80 (0.98)	0.358	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))	0.42 (0.86)	2.79 (1.95)	**0.001**	0.25 (1.23)	2.79 (1.95)	**0.001**	−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))	0.39 (1.31)	3.09 (1.84)	**< 0.001**	0.71 (1.49)	3.09 (1.84)	**0.002**	0.04 (1.59)	2.02 (4.23)	**0.045**	0.71 (1.49)	2.02 (4.23)	0.258

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 3., Figure 3.).

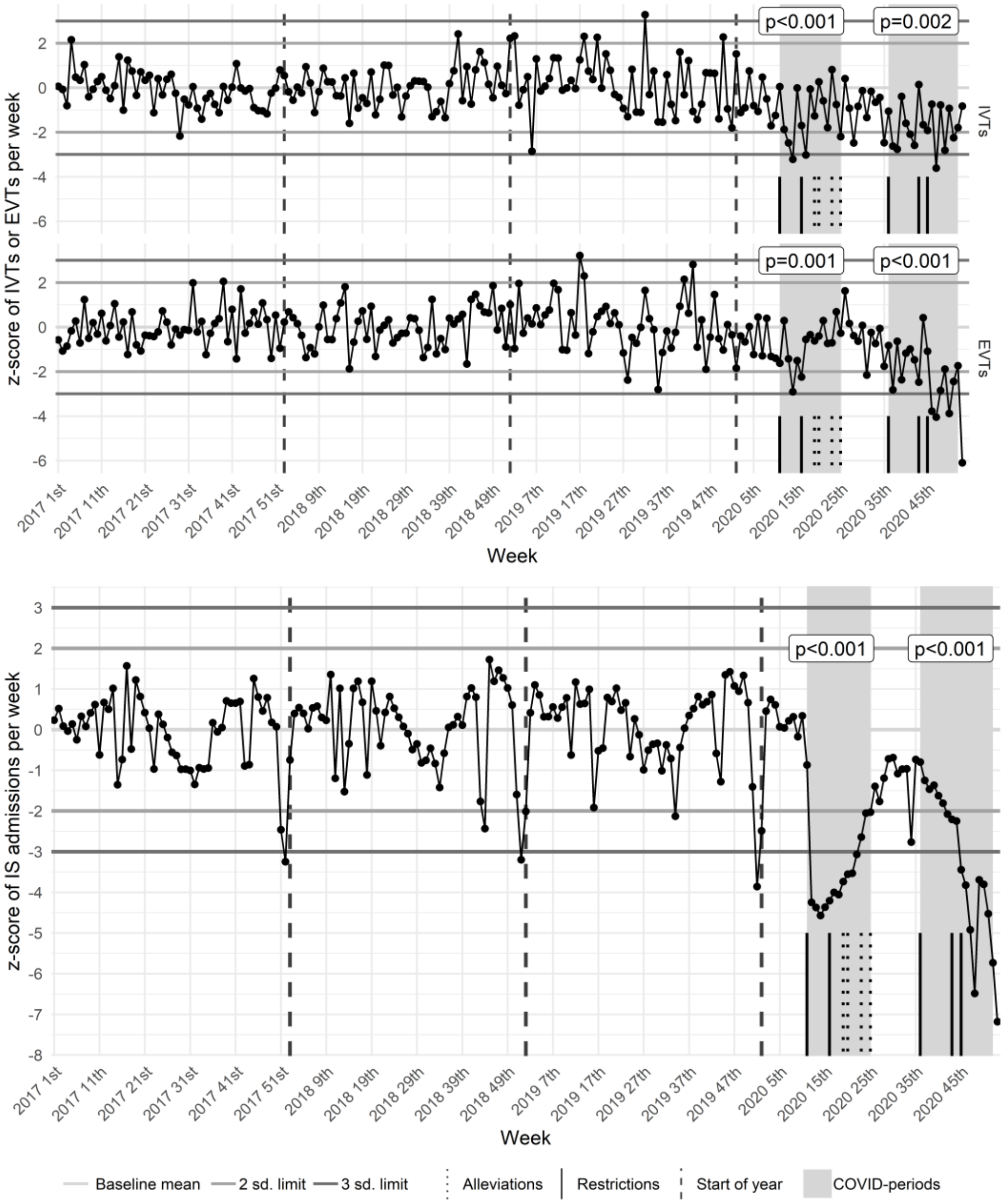

Figure 4. Control chart of IS admissions, IVTs, and EVTs. p values of the paired t tests, which compare the COVID-periods to their respective controls, are also presented. Dates of the most important restrictive and alleviative health emergency operative measures are marked in the timeline.

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 3., Figure 4-5.).

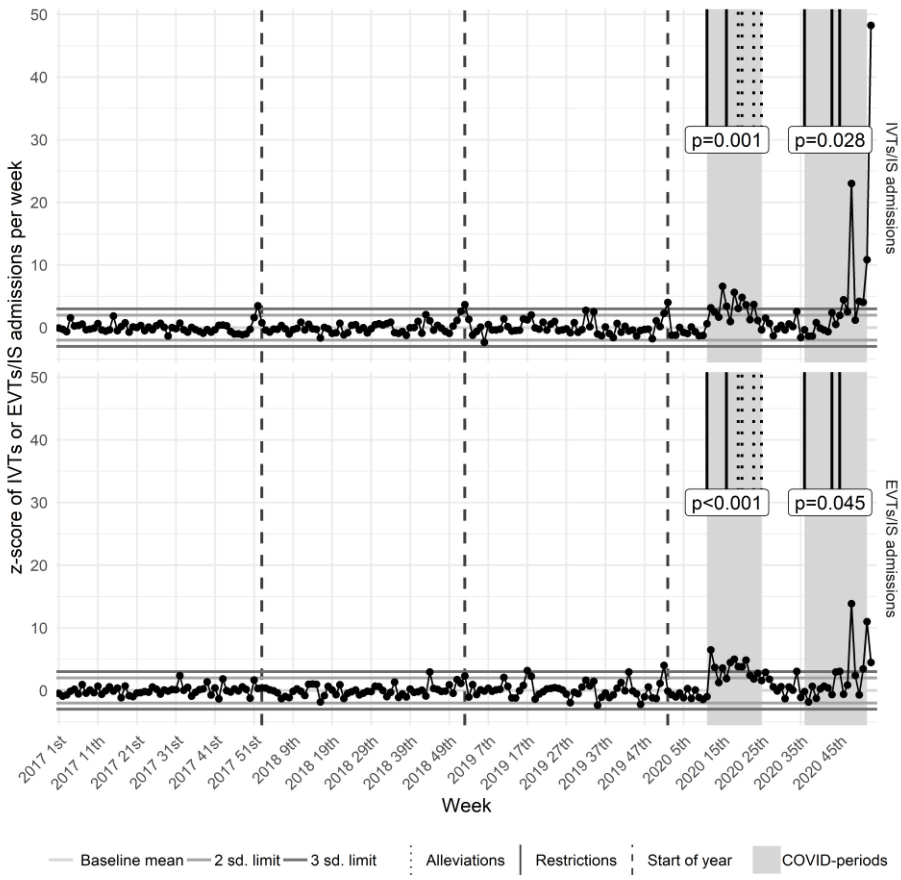

Figure 5. Control chart of the ratio of IVTs or EVTs and IS admissions. p values of the paired t tests, which compare the COVID-periods to their respective controls, are also presented. Dates of the most important restrictive and alleviative health emergency operative measures are marked in the timeline.

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 3., Figure 4-5.).

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 4.). In the control charts of 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 4.).

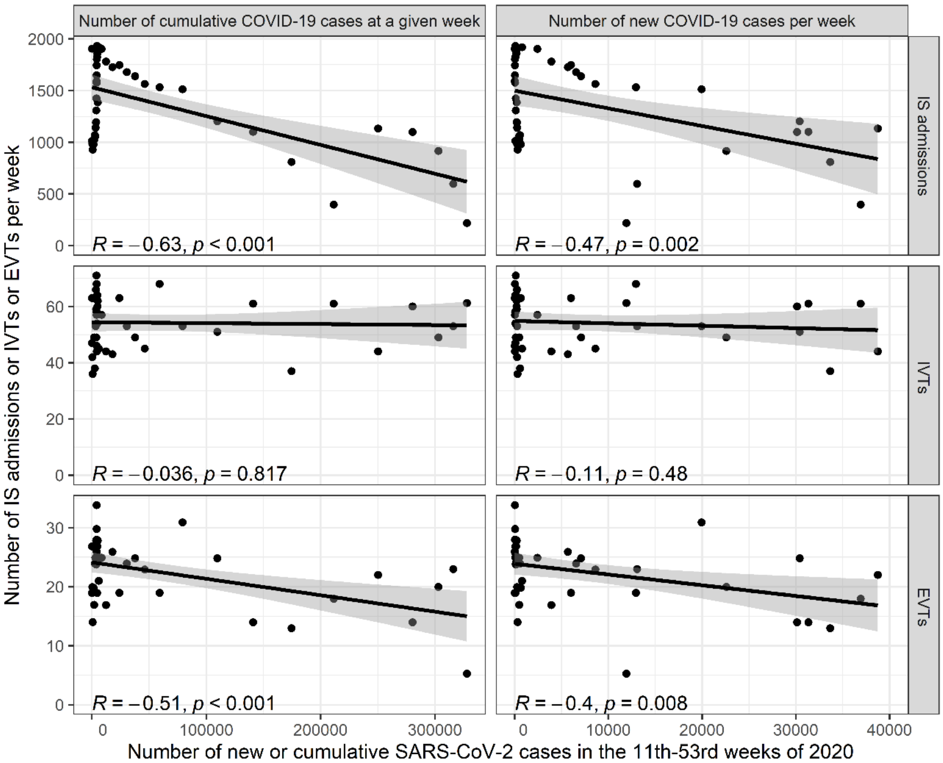

Figure 6. Relationship between the weekly number of IS admissions, IVTs, and EVTs, and the new or cumulative SARS-CoV-2 cases per week in Hungary. R: Pearson's correlation coefficient; p: p value of the correlation (same as the p value of the linear regression); grey area: 95% confidence interval of the slope.

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 4-5.). 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 4-5).

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 6.). 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.

5. Conclusions

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.

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.

6. Bibliography of the candidate's publications

9.1. Publications on the topic of the present thesis

1./ Bereczki D, Stang R, Böjti P, Kovács T. (2020) A SARS-CoV-2 koronavírus által okozott COVID-19-járvány neurológiai vonatkozásai. [Neurological aspects of the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus]. Ideggyogy Sz, 73: 171-175.

2./ Böjti PP, Stang R, Gunda B, Sipos I, Bereczki D. (2020) A járulékos egészségügyi veszteségek retrospektív, egycentrumos felmérése. [Effects of COVID-19 pandemic on acute ischemic stroke care. A single-centre retrospective analysis of medical collateral damage]. Orv Hetil, 161: 1395–1399.

3./ Böjti PP, Bereczki D. (2020) A COVID-19 és az akut stroke kapcsolata. Epidemiológia és patofiziológia. [Relationship between COVID-19 and acute stroke. Epidemiology and pathophysiology]. Metabolizmus, 5: 311-314.

4./ Böjti PP, Szilágyi G, Dobi B, Stang R, Szikora I, Kis B, Kornfeld Á, Óváry C, Erőss L, Banczerowski P, Kuczyński W, Bereczki D. (2021) Impact of COVID-19 on ischemic stroke care in Hungary. Geroscience, 43: 2231-2248.

9.2. Other publications

1./ Böjti PP, Bartha NE, May Zs, Bereczki D Jr, Fülöp Sz, Szakács Z, Szilagyi G. (2018) A foramen ovale apertum és a cryptogen stroke kapcsolata. Retrospektív kórházi vizsgálat. [Relationship between patent foramen ovale and cryptogenic stroke in a retrospective hospital-based study]. Ideggyogy Sz, 71: 169-177.

2./ Kuczynski W, Böjti PP, Stolarz A, Wawrzyniak M, Bialasiewicz P. (2019) Low prevalence of undiagnosed hypothyroidism in obstructive sleep apnea patients. Transylv Rev, 27: 9448-9452.

3./ Gunda B, Sipos I, Stang R, Böjti P, Dobronyi L, Takács T, Berényi T, Futácsi B, Barsi P, Rudas G, Kis B, Szikora I, Bereczki D. (2021) Comparing extended versus standard time window for thrombectomy: caseload, patient characteristics, treatment rates and outcomes-a prospective single-centre study. Neuroradiology, 63: 603-607.

4./ Gunda B, Böjti P, Kozák LR. (2021) Hyperacute hpontaneous intracerebral hemorrhage during computed tomography scanning. JAMA Neurol, 78: 365-366.

5./ Małolepsza A, Kudrycka A, Karwowska U, Hoshino T, Wibowo E, Böjti PP, Białas A, Kuczyński W. (2021) The role of screening questionnaires in the assessment of risk and severity of obstructive sleep apnea - polysomnography versus polygraphy. Adv Respir Med, 89: 188-196.

6./ Gunda B, Neuhaus A, Sipos I, Stang R, Böjti PP, Takács T, Bereczki D, Kis B, Szikora I, Harston G. (2022) Improved stroke care in a primary stroke centre using AI-decision support. Cerebrovasc Dis Extra, 12: 28-32.