



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Impact of the COVID-19 pandemic on pre-hospital and in-hospital time-dependent performance measures of treatment of patients with acute ischemic stroke – experience of a tertiary healthcare center

Lana Macura¹, Rea Mikulan¹, Višnja Pađen^{1,2}¹University of Belgrade, Faculty of Medicine, Belgrade, Serbia;²University Clinical Centre of Serbia, Neurology Clinic, Belgrade, Serbia**SUMMARY**

Introduction/Objective The outbreak of the COVID-19 pandemic has posed major challenges to the process of urgent care of patients with acute ischemic stroke (AIS) that requires optimal and well-coordinated pre- and in-hospital chains in order to enable recanalization therapy commencement at the earliest possible opportunity. The objective of the study was to compare time-dependent performance measures and treatment results of patients with AIS hospitalized at a tertiary healthcare center before and during the COVID-19 pandemic.

Methods A retrospective analysis was performed on AIS patients treated with recanalization therapy at the Emergency Neurology Department of the University Clinical Centre of Serbia, during the March–June period of 2019, 2020, and 2021. Besides demographic and clinical characteristics, the following were calculated for each patient: time elapsed from stroke onset to hospital arrival (“onset-to-door”), time elapsed from hospitalization to the beginning of recanalization therapy (“door-to-needle”), and total time elapsed from symptoms’ onset to treatment initiation (“onset-to-needle”). The patients’ functional outcome was assessed after three months by using modified Rankin Scale score.

Results A total of 84 patients were included [25/2019, 30/2020, and 29/2021; ($p = 0.512$)]. No statistical significance was detected regarding the age, sex, severity of stroke symptoms at hospital admission, or the type of received recanalization therapy. Our study showed no statistical difference regarding time needed to reach the hospital ($p = 0.441$), “door-to-needle” time ($p = 0.549$), nor overall times elapsed from symptoms’ onset to therapy ($p = 0.481$) among three groups of patients. Furthermore, comparison of the patients’ three-month functional outcomes did not show statistical significance ($p = 0.922$).

Conclusion The experience of this tertiary healthcare system has shown notable resilience to the side-effects of the COVID-19 pandemic.

Keywords: acute ischemic stroke; recanalization therapy; pandemic; impact

INTRODUCTION

Acute ischemic stroke (AIS) is a clinical term that refers to the sudden onset of an infarcted area in the brain due to thrombotic or embolic occlusion of a blood vessel [1]. The infarcted zone implies irreversible necrotic changes of parenchyma and it is the most severely affected brain area by stroke. It is surrounded by the penumbra zone, in which the neuronal tissue is functionally altered, due to reduced perfusion, but still structurally preserved [2]. Neurons from the penumbra zone have the ability to restore their function if the circulation is re-established in a short period of time, otherwise, their necrosis and expansion of the infarct area will occur. Recovery of penumbra tissue is the main focus of recanalization therapy, and time is the most important factor of treatment success [3, 4]. It has been shown that administration of intravenous thrombolytic therapy (IVT), performed with alteplase, within the first 4.5 hours of symptoms reduces mortality and disability by 10–30% in the first six months after the stroke [3]. Furthermore, several recent

studies showed a clear benefit of endovascular mechanical thrombectomy (EVT) in patients with large vessel occlusion [4]. As a result, the use of EVT (in the first six hours, or in clearly defined cases even 24 hours after the stroke onset), along with drug therapy, has become a standard method of treatment for patients with AIS and large vessel occlusion [4]. Patients with AIS require urgent treatment, optimal and well-coordinated pre- and in-hospital chains in order to receive recanalization therapy at the earliest possible opportunity.

Cases of pneumonia of unclear etiology were reported in Wuhan, China at the end of 2019 [5]. Soon after, viral causative agent was identified and named *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) [6]. Since then, interhuman transmission of this newly discovered type of virus reached global proportions within a few months, and the World Health Organization declared a pandemic in March of 2020 [7]. The pandemic has seriously challenged healthcare systems due to the large number of COVID-positive patients and has disrupted the normal functioning of the

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remaining healthcare centers that treat acute and chronic conditions of non-COVID patients. This study focused on assessing the quality of treatment patients with AIS by recanalization therapy in a non-COVID tertiary institution under pandemic circumstances.

METHODS

A retrospective data analysis was conducted on AIS patients treated with recanalization therapy at the Department of Emergency Neurology, Neurology Clinic of the University Clinical Center of Serbia. The analysis was performed for the March–June of 2020 period (immediately after the pandemic proclamation and during the declared state of emergency in Serbia) compared to the same period in 2019 (when pandemic and consequential measures did not exist) and 2021 (when the healthcare system already adapted to functioning in pandemic circumstances).

Inclusion criteria for the study were as follows: implementation of recanalization therapy in acute stroke treatment, as well as known time of symptoms onset, arrival to the hospital, and commencement of reperfusion therapy. At admission, all patients were examined by a senior neurologist. The stroke diagnosis was made based on clinical criteria and stroke severity was assessed by using the National Institutes of Health Stroke Scale (NIHSS) score [8]. The clinical stroke diagnosis was confirmed by CT examination, analyzed by a neuroradiologist. The patient's arterial blood pressure was measured, electrocardiogram and complete laboratory analyses were done on admission. All the patients included in the study were treated with recanalization therapy, whose type (IVT, EVT, or both) was determined after consideration of clinical and neuroimaging parameters by a multidisciplinary team (neurologist, neuroradiologist), and according to current European and North American guidelines of stroke treatment [9]. Patients who did not meet the criteria for recanalization therapy administration were not included in the study. During hospitalization, patients underwent additional CT examinations 12–72 hours after admission, or earlier in case of clinical deterioration. The neurologist assessed the patient's clinical status seven days after, on discharge, and three months after the stroke. For all the patients, basic clinical and demographical characteristics were analyzed. Furthermore, the assessment of pre-hospital

and in-hospital time-dependent performance measures were performed. We considered time of symptoms' onset, time of admission to the hospital, and time when the reperfusion therapy started. Therefore, for each patient we calculated and expressed in minutes time they needed to reach the hospital after the stroke onset ("onset-to-door"), time that elapsed from hospitalization to the beginning of recanalization therapy ("door-to-needle"), and overall time-period that elapsed from the onset of symptoms to the onset of treatment ("onset-to-needle"). The final outcome of stroke was assessed after three months by using modified Rankin Scale (mRS) score.

For statistical data analysis, IBM SPSS Statistics, Version 28.0 (IBM Corp, Armonk, NY, USA) was used. Patients' demographic and clinical characteristics were analyzed by descriptive methods and represented by average values or frequencies. Time intervals are represented by median and interquartile range. Patient group sizes and age variables were compared using the ANOVA test. The category variables were compared using the χ^2 or Fisher test. The numerical variables presented by medians were compared using the Mann–Whitney test, or in case of looking for a difference among data from all three years at the same time, the Kruskal–Wallis test.

This research was approved by the Ethics Board of the University Clinical Centre of Serbia.

RESULTS

The study included a total of 84 AIS patients treated with recanalization therapy [25 patients treated in 2019, 30 patients treated in 2020, and 29 patients treated in 2021; ($p = 0.512$)]. There were no statistically significant differences regarding age, sex, severity of clinical presentation of stroke (assessed by using NIHSS score on admission), nor the type of recanalization therapy applied. The patients' demographic and clinical characteristics are presented in Table 1.

Among patients from 2019, 52% were male (13 patients); comparing to 60% (18 male patients) from 2020 and 44.8% (13 male patients) from 2021 ($p = 0.506$). The mean age of patients in all three groups was 64 ± 15 years. From other hospitals, we admitted two patients with AIS (8% of admissions) in 2019, four patients (13.3%) in 2020, and nine patients (31%) in 2021 ($p = 0.064$). The median (IQR) NIHSS score was 13 (7–18) for patients treated in

Table 1. Demographic and clinical characteristics of the study population

| Characteristics | 2019 n = 25 | 2020 n = 30 | 2021 n = 29 | 2019/2020/2021 p-value |
|---|-------------------|-------------------|----------------|---------------------------|
| Age, mean ($x \pm sd$) | 64.28 \pm 15.38 | 64.13 \pm 14.25 | 64.72 \pm 15 | 0.988 |
| Sex: male (%) | 13 (52%) | 18 (60%) | 13 (44.8%) | 0.506 |
| Severity of stroke presentation – NIHSS, median (IQR) | 13 (7–18) | 11 (5–16.25) | 11 (8–14) | 0.728 |
| Patients transferred from other hospital, n (%) | 2 (8%) | 4 (13.3%) | 9 (31%) | 0.064 |
| Type of reperfusion (%) | | | | |
| IVT | 13 (52%) | 15 (50%) | 11 (37.9%) | 0.52 |
| EVT | 11 (44%) | 11 (36.7%) | 14 (48.3%) | 0.66 |
| IVT + EVT | 1 (4%) | 4 (13.3%) | 4 (13.8%) | 0.455 |

IQR – interquartile range; NIHSS – National Institutes of Health Stroke Scale; EVT – endovascular treatment; IVT – intravenous thrombolysis

Table 2. Time-dependent treatment performance measures (prehospital and intrahospital)

| Performance measures | 2019 | 2020 | 2021 | 2019/2020/2021 p-value |
|---|-----------------|-------------------|--------------------|------------------------|
| Stroke onset – hospital arrival, minutes, median (IQR) | 120 (75–162.5) | 95 (61.5–177.3) | 135.5 (68.3–193.8) | 0.441 |
| Stroke onset – treatment commencement minutes, median (IQR) | 180 (162.5–285) | 175.5 (158.3–277) | 235 (168.5–296.3) | 0.481 |
| Door-to-needle minutes, median (IQR) | 75 (55–117.5) | 83 (69.3–123.5) | 99.5 (65.8–131.8) | 0.549 |

IQR – interquartile range

2019; 11 (5–16) in 2020, and 11 (8–14) among those treated in 2021 ($p = 0.728$). Intravenous thrombolysis, as the only method of reperfusion, was conducted in 13 patients (52%) from 2019, in 15 patients (50%) from 2020, and in 11 patients (37.9%) from 2021 ($p = 0.52$). Endovascular thrombectomy, without previous IVT, was conducted in 11 patients (44%) in 2019, also 11 patients (36.7%) in 2020, and 14 patients (48.3%) in 2021 ($p = 0.66$). Both types of recanalization therapy (IVT + EVT) were performed in one patient in 2019 (4%), compared to four patients in 2020 (13.3%) and also four in 2021 (13.8%) ($p = 0.455$).

The analysis of time-dependent performance measures was conducted in two steps: the first step was comparison of data from all three years at the same time in order to detect possible statistical difference; then we separately compared results from each year (2019/2020, 2019/2021, 2020/2021). These results are shown in Table 2.

There were no statistically significant differences among the analyzed data. After the symptoms' onset, the patients needed 120 minutes (75–162.5) to arrive to the hospital in 2019; 95 minutes (61.5–177.25) in 2020, and 135.5 minutes (68.25–193.75) in 2021 ($p = 0.441$). From the patients' arrival to the hospital to the beginning of therapy ("door-to-needle" time), 75 minutes (55–117.5) passed in 2019; 83 minutes (69.25–123.5) in 2020; and 99.5 minutes (65.75–131.75) in 2021 ($p = 0.549$). The overall time period elapsed from symptoms onset to the beginning of recanalization amounted to 180 minutes (162.5–285) in 2019; 175.5 minutes (158.25–277) in 2020, and 235 minutes (168.5–296.25) in 2021. Although the average time needed to start therapy is obviously longer in 2021, statistical significance has not been reached ($p = 0.481$).

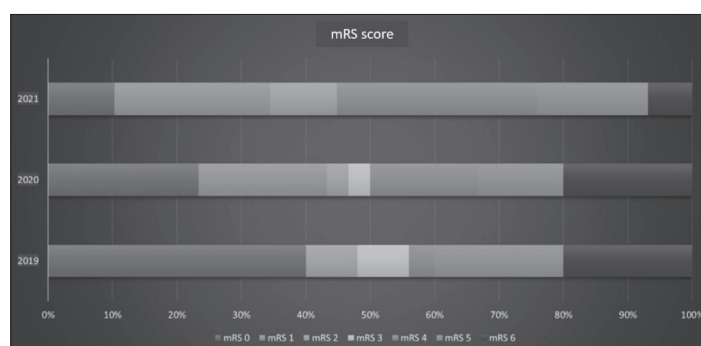
Stroke outcome was assessed three months later by using mRS: median (IQR) in 2019 was 3 (0–5), in 2020 it was 4 (0.75–5), and also 4 (1–4.5) in 2021 [$p = 0.922$]. Detailed results are presented in Figure 1.

DISCUSSION

Stroke, as a thromboembolic event, has been recognized as one of the possible complications of coronavirus infection [10, 11, 12]. Elderly patients with pre-existing comorbidities are at greater risk of developing this rare but severe complication [13]. Therefore, the incidence of AIS is expected to be higher during a pandemic. However,

Table 2a. The resulting p-values obtained by comparing the data listed above (results from every year versus other two years)

| Compared data | 2019/2020 | 2019/2021 | 2020/2021 |
|--|-----------|-----------|-----------|
| Onset of symptoms – hospital arrival | 0.548 | 0.301 | 0.286 |
| Onset of symptoms – onset of treatment | 0.787 | 0.345 | 0.272 |
| Door-to-needle | 0.253 | 0.417 | 0.840 |

**Figure 1.** Three-month functional outcomes of patients with acute ischemic stroke treated with recanalization therapy [presented by modified Rankin (mRS) score]

the conclusion of numerous studies [14–18] as well as the World Stroke Organization [19] is a paradoxical decline in the number of stroke hospitalizations and administered recanalization therapies during the pandemic, at the expense of fewer diagnosed transient ischemic attacks and minor strokes. The probable reason for this apparent drop in incidence is the patient's neglect of milder stroke symptoms in fear of COVID-infection in hospitals [20].

Regarding timely-dependent performance measures worldwide, results of studies published thus far are somewhat discrepant. Studies conducted in Canada and the USA showed a prolongation of admission and diagnosis of patients with AIS during the pandemic, which affected the delayed initiation of recanalization therapy [21, 22]. In a USA multicenter study, faster access to CT scanners was registered upon admission to the hospital, during the pandemic: median (IQR) times in 2019 and 2020 were 37 (15–101) and 29 (14–77) minutes, respectively ($p < 0.01$); the time required to start recanalization therapy after CT diagnosis was significantly extended: the median (IQR) in 2019 was 22 (13–37) vs. 29 (18–47) minutes in 2020 ($p = 0.02$) [21]. Overall, this led to a statistically significant delay in recanalization therapy in 2020 compared to 2019: the 2019/2020 median is 42/46 minutes ($p = 0.03$). A Canadian study found a delay in starting IVT upon arrival at the hospital (medians from 2019 and 2020 were 35 and 61 minutes, respectively, $p = 0.005$), which was caused by delayed CT diagnostics [from hospital arrival to CT usually 7.5 minutes elapsed in 2019, and 19 minutes in 2020 ($p = 0.004$)] [22].

In Hong Kong, at the very beginning of the pandemic (January–March of 2020), an average delay of 60 minutes was noted in the inception of recanalization therapy compared to the period immediately before the pandemic [23]. Also, lower percentage of patients arrived to hospital within the “golden hour” (4.5 hours from the onset of the symptoms) for intravenous thrombolysis.

Although we did not find statistical significance when comparing “door-to-needle” time in our study ($p = 0.549$), the observed delay in recanalization upon arrival at the hospital during the pandemic cannot be ignored (2019/2020/2021 medians were 75/83/99.5 minutes), which, as in the case of the Canadian study, could be explained by implementation of “covid-screening” protocols in emergency rooms – each patient is evaluated for possible symptoms of respiratory infection or tested with a rapid antigen test prior to hospitalization [22]. These necessary procedures certainly postpone diagnostics and therapy actions. Patients from our study reached the hospital faster in 2020 (median of 95 minutes) than in 2019 or 2021 (medians of 120 and 135.5 minutes, respectively), probably due to the lockdown and curfew proclaimed in Serbia from March to May of 2020.

On the other hand, a recent European multicenter study that involved 20 centers, including the UCCS Emergency Neurology Service, noticed that the number of recanalization therapies was 7% lower in the first wave of the pandemic than in the reference period (March–June) of 2019, but the quality of treatment remained the same – prehospital and intrahospital time-dependent performance measures of treatment did not differ [2019/2020 in the minutes elapsed from the onset of symptoms to hospital admission: 145/133, ($p = 0.777$), and the minutes elapsed from admission to hospital to the beginning of therapy: 48/51, ($p = 0.653$)] [24]. Equal success of treatment before and during the pandemic was proven by comparing the values of NIHSS 24 hours after hospital admission: medians (IQR) in 2019 and 2020 were, respectively, 5 (2–13) and 6 (2–14), ($p = 0.674$) [24]. These results are in line with the conclusions of our study. Our center, as well as other European centers participating in this multicenter study, are experienced centers with many years of practice in caring for patients with AIS, which may be an explanation for such results [24].

A small number of studies have analyzed the performance of emergency neurological services in 2021 and their long-term adaptations to pandemic operating conditions. The state of emergency in Serbia lasted from March to June of 2020, during which an occasional ban on movement and strict anti-epidemic measures were proclaimed. At that time, the health service was able to respond well to the new situation due to the small number of COVID-positive hospitalized patients. After that period, anti-epidemic measures were periodically introduced and abolished, and, as a result, the number of those infected increased. During most of 2021, the burden on the health system in Serbia was incomparably higher than at the pandemic’s beginning, due to the large number of COVID-positive cases, overcrowding of hospital capacities,

fewer non-COVID institutions, and the overall lack of staff (because of redistribution to COVID-hospitals or easy possibility of infection and consequent absence from work) [25]. Chinese studies published recently showed a significant delay in door-to-needle time during the pandemic period, compared to prepandemic 2019 [26, 27]. A study from Chongqing also found that patients had higher NIHSS score, and that hospital mortality was higher during the pandemic period [26]. A Beijing study, besides lower quality of stroke care service during the pandemic, noticed a drop in admissions of AIS patients in that period [27]. In the future, we will probably have many studies that analyze the newly created way of functioning of all health institutions, including performance measures for the pandemic ending period, which could be a future target for our study project as well.

Possible limitations of this study are reflected in the relatively small sample of patients and the retrospective nature of the study. Additional interpreting of the results of this study is necessary because this center is the largest in the country and has many years of experience in dealing with severe cases of stroke, so it is very possible that it is not a representative sample for the country’s smaller centers, since they have been more severely affected by pandemic due to the lack of staff and capacity to care for urgent patients.

CONCLUSION

The study showed that the new pandemic conditions in 2020 and the necessary adaptation of the health system to a new way of functioning, which was still taking place in 2021, did not significantly affect the effective implementation of recanalization therapy for AIS and that time-dependent parameters and treatment results of AIS were similar to those from the prepandemic year of 2019. The results are important and encouraging and prove that the emergency neurology service of this tertiary center successfully resists the challenges of the current global situation. Still, the main focus is to further reduce time needed for patients to receive therapy and thus get a chance for fuller recovery and less disability, now with maximum respect for all recommended preventive epidemic measures during the admission and diagnosis of patients in the emergency rooms.

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Утицај пандемије ковида 19 на мере прехоспиталног и интрахоспиталног лечења акутног исхемијског можданог удара – искуство терцијарног центра

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САЖЕТАК

Увод/Циљ Појава пандемије ковида 19 поставила је велике изазове при процесу збрињавања болесника са акутним исхемијским можданим ударом (АИМУ), који захтева оптимално функционисање свих служби у ланцу ургентног збрињавања како би се омогућило започињање спровођења реканализационе терапије што је пре могуће. Циљ рада је анализа учинка временски зависних мера прехоспиталног и интрахоспиталног збрињавања болесника са АИМУ лечених реканализационом терапијом у терцијарном здравственом центру у периоду пре и током пандемије ковида 19.

Методe Спроведена је ретроспективна анализа података о болесницима са АИМУ леченим реканализационом терапијом на Одељењу ургентне неурологије Универзитетског клиничког центра Србије, у периоду март–јун током 2019, 2020. и 2021. године. Уз демографске и клиничке карактеристике, за сваког болесника је процењено време протекло од појаве симптома до доласка у болницу, период од доласка у болницу до почетка примене реканализационе терапије и укупно време од јављања симптома до започињања лечења.

Процена функционалног исхода је вршена после три месеца применом модификоване Ранкинове скале.

Резултати У студију су укључена 84 болесника [25/2019, 30/2020. и 29/2021; ($p = 0,512$)]. Није утврђено постојање статистички значајне разлике према старости, полу, тежини клиничке презентације АИМУ, као ни типу примењене реканализације. Није утврђена статистички значајна разлика када је реч о периоду потребном да се дође до болнице ($p = 0,441$), нити је идентификовано значајно кашњење у спровођењу терапије ($p = 0,549$). Није доказана статистички значајна разлика у поређењу тромесечних функционалних исхода болесника ($p = 0,922$).

Закључак Упркос великим изазовима у функционисању здравственог система, лечење болесника са АИМУ реканализационом терапијом у систему терцијарне здравствене заштите је показало релативну отпорност на ефекте актуелне пандемије ковида 19.

Кључне речи: акутни исхемијски мождани удар; реканализациона терапија; утицај; пандемија