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https://orcid.org/0000-0002-8033-9682

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Rytis Masiliūnas

The Effects of a Comprehensive National Policy, Stroke Characteristics, and External Factors on the Reperfusion Therapy of Acute Ischemic Stroke

DOCTORAL DISSERTATION

Medical and Health Sciences,
Medicine (M 001)

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The dissertation was prepared between 2017 and 2022 at the Clinic of Neurology and Neurosurgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University.

Academic supervisor:
Prof. Dr. Dalius Jatužis (Vilnius University, Medical and Health Sciences, Medicine – M 001).
Academic consultant:
Assoc. Prof. Dr. Aleksandras Vilionskis (Vilnius University, Medical and Health Sciences, Medicine – M 001).

Dissertation Defence Panel:
Chairman – **Prof. Dr. Janina Tutkuvienė** (Vilnius University, Medical and Health Sciences, Medicine – M 001).
Members:
Prof. Dr. Vytautas Kasiulevičius (Vilnius University, Medical and Health Sciences, Medicine – M 001),
Prof. Dr. Grzegorz Kozera (Medical University of Gdańsk, Medical and Health Sciences, Medicine – M 001),
Prof. Dr. Juozas Kupčinskas (Lithuanian University of Health Sciences, Medical and Health Sciences, Medicine – M 001),
Prof. Dr. Pranas Šerpytis (Vilnius University, Medical and Health Sciences, Medicine – M 001).

The doctoral dissertation will be defended at a public meeting of the Dissertation Defence Panel at 15:00 on December 6, 2022, in the Red Auditorium of Vilnius University Hospital Santaros Klinikos.
Address: 2 Santariškių Str., Vilnius, Lithuania.
Phone No.: +370 610 25429; email: rytis.masiliunas@mf.vu.lt

The text of this dissertation can be accessed through the library of Vilnius University as well as on the website of Vilnius University:
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https://orcid.org/0000-0002-8033-9682

VILNIAUS UNIVERSITETAS

Rytis Masiliūnas

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Mokslinis vadovas:
prof. dr. Dalius Jatužis (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
Mokslinis konsultantas:
doc. dr. Aleksandras Vilionskis (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Gynimo taryba:
Pirmininkė – prof. dr. Janina Tutkuvienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
Nariai:
prof. dr. Vytautas Kasiulevičius (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001),
prof. dr. Grzegorz Kozera (Gdansko medicinos universitetas, medicinos ir sveikatos mokslai, medicina – M 001),
prof. dr. Juozas Kupčinskas (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, medicina – M 001),
prof. dr. Pranas Šerpytis (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Disertacija ginama viešame Gynimo tarybos posėdyje 2022 m. gruodžio 6 d. 15:00 val. Vilniaus universiteto ligoninės Santaros klinikų Raudonojoje auditorijoje. Adresas: Santariškių g. 2, Vilnius, Lietuva.
Tel. +370 610 25429; el. paštas: rytis.masiliunas@mf.vu.lt

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ABBREVIATIONS

AIS	acute ischemic stroke
ASPECTS	Alberta Stroke Program Early CT Score
CI	confidence interval
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CSC	comprehensive stroke center
CT	computed tomography
CV RF	cardiovascular risk factors
DTN	door-to-needle
ITS	interrupted time series
ED	emergency department
EMS	emergency medical services
EQ-5D-3L	EuroQoL five-dimensional three-level descriptive system
EQ-VAS	EQ-5D-3L with a self-rated visual analog scale
EVT	endovascular therapy
FAST	Face Arm Speech Test
HRQoL	health-related quality of life
IV rtPA	intravenous recombinant tissue plasminogen activator
LVO	large vessel occlusion
MoH	Ministry of Health
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NH	nonspecialized hospital
NIHSS	National Institutes of Health Stroke Scale
OAC	oral anticoagulation
OR	odds ratio
PPV	positive predictive value
PSC	primary stroke center
RT	reperfusion therapy
RT-PCR	real-time polymerase chain reaction
SARS-CoV-2	severe acute respiratory coronavirus 2
SE	standard error
SICMC	Stroke Integrated Care Management Committee
TIA	transient ischemic attack
VUH SK	Vilnius University Hospital Santaros Klinikos
WBC	white blood cells

CONTENTS

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Masiliūnas R**, Vilionskis A, Bornstein NM, Rastenytė D, Jatužis D. *The impact of a comprehensive national policy on improving acute stroke patient care in Lithuania*. Eur Stroke J. 2022 Jun;7(2):134–142. https://doi.org/10.1177/23969873221089158.

II. Sveikata L, Melaika K, Wiśniewski A, Vilionskis A, Petrikonis K, Stankevičius E, Jurjans K, Ekkert A, Jatužis D, **Masiliūnas R**. *Interactive Training of the Emergency Medical Services Improved Prehospital Stroke Recognition and Transport Time*. Front Neurol. 2022 Apr 7;13:765165. https://doi.org/10.3389/fneur.2022.765165.

III. **Masiliūnas R**, Dapkutė A, Grigaitė J, Lapė J, Valančius D, Bacevičius J, Katkus R, Vilionskis A, Klimašauskienė A, Ekkert A, Jatužis D. *High Prevalence of Atrial Fibrillation in a Lithuanian Stroke Patient Cohort*. Medicina. 2022; 58(6):800. https://doi.org/10.3390/medicina58060800.

IV. Melaika K, Sveikata L, Wiśniewski A, Jaxybayeva A, Ekkert A, Jatužis D, **Masiliūnas R**. *Changes in Prehospital Stroke Care and Stroke Mimic Patterns during the COVID-19 Lockdown*. Int J Environ Res Public Health. 2021 Feb 23;18(4):2150. https://doi.org/10.3390/ijerph18042150.

V. Jurkevičienė J, Vaišvilas M, **Masiliūnas R**, Matijošaitis V, Vaitkus A, Geštautaitė D, Taroza S, Puzinas P, Galvanauskaitė E, Jatužis D, Vilionskis A. R*eperfusion Therapies for Acute Ischemic Stroke in COVID-19 Patients: A Nationwide Multi-Center Study*. J Clin Med. 2022 May 26;11(11):3004. https://doi.org/10.3390/jcm11113004.

1. INTRODUCTION

1.1. Research Problem and Relevance of the Study

Stroke is one of the major causes of death and disability-adjusted life years worldwide (1,2). The incidence of acute ischemic stroke (AIS) and stroke mortality in Lithuania is amongst the highest in the world (3), in large part due to a high prevalence and poor control of cardiovascular risk factors (CV RF) (4,5). Moreover, the largest increase in age-adjusted stroke incidence and prevalence rates as well as the lowest average annual percentage decrease in stroke mortality among all European Union countries are expected in Lithuania (6).

Reperfusion therapy (RT) – thrombolysis using intravenous recombinant tissue plasminogen activator (IV rtPA) and endovascular treatment (EVT), is a widely accepted, safe, and cost-effective method to treat AIS with proven clinical efficacy (7,8). However, its broad implementation in daily clinical practice is challenging (9–12). In Lithuania, the first thrombolysis with IV rtPA was performed after its approval for AIS in 2002, whereas EVT was introduced to clinical practice in 2012. Although IV rtPA was recommended as a first-line treatment for AIS according to national guidelines since 2007 (13), the total annual number of IV rtPA remained low across the country.

In 2014, the Ministry of Health (MoH) of the Republic of Lithuania initiated multiple activities in order to promote and implement modern RT for stroke patients on the national level (**Table 1**). The integrated government support included ministerial orders on the establishment of a national network of acute stroke centers, the reorganization of AIS patient flow (all acute stroke patients were obliged to be referred to the nearest acute stroke center directly), a coordinated inventory of the AIS diagnostic and management methods, standard requirements for the accreditation of primary stroke centers (PSCs) and comprehensive stroke centers (CSCs) (14), and the creation of the Stroke Integrated Care Management Committee (SICMC) under the MoH (15). The aim of SICMC was to coordinate new financial incentives, which included a centrally coordinated purchase of rtPA, a retrospective per-case AIS total EVT expense reimbursement to the healthcare providers, and the lift of the budget cap for AIS patients. In addition, it collected and monitored data from emergency medical services (EMS) and stroke treatment sites regarding acute RT, logistics, use of resources and diagnostic investigations, rehabilitation, in-hospital complications, case fatality, and other AIS care performance measures. Quarterly reports were provided to the MoH in order to identify areas that require improvement in the prehospital and in-hospital settings.

Table 1. The elements of the Lithuanian comprehensive national stroke care policy

Non-financial incentives	
	The establishment of a national network of acute stroke centers
	The reorganization of AIS patient flow: all acute stroke patients are obliged to be referred to the nearest acute stroke center directly
	A creation of a coordinated inventory of the AIS diagnostic and management methods
	Standard requirements for the accreditation of PSCs and CSCs
	The creation of the Stroke Integrated Care Management Committee under the Ministry of Health, which aims to:
	Coordinate new financial incentives
	Collect and monitor predefined AIS care performance measures from stroke treatment sites
	Provide quarterly reports to the Ministry of Health in order to identify areas that require improvement
Financial incentives	
	A central coordinated purchase of rtPA
	A retrospective per-case AIS total EVT expense reimbursement to the healthcare providers
	The lift of the budget cap for AIS patients

AIS – acute ischemic stroke, PSC – primary stroke center, CSC – comprehensive stroke center, rtPA – recombinant tissue plasminogen activator, EVT – endovascular treatment.

In prehospital care, a crucial role in identifying acute stroke is played by EMS (16), which are the first healthcare contact for the absolute majority of stroke patients (17,18). Accurate recognition and timely transport of patients with suspected stroke to CSCs are closely correlated with acute stroke care success (18,19), as any delay in administering IV rtPA and EVT negatively impacts patients' functional outcomes (20). Thus, positive predictive value (PPV) for the identification of stroke patients and prehospital timeliness metrics are some of the most important EMS performance indicators.

However, the process of clinically identifying stroke is still the most significant challenge for EMS, as a percentage of stroke mimics reaches up to 50% (21,22). Consequently, stroke mimics utilize the limited resources of acute stroke care pathways that might otherwise be directed towards the actual stroke patients who may benefit from acute time-sensitive revascularization therapies the most (23). This may result in inappropriate usage of stroke care facilities and medical resources and increase the workload on overwhelmed emergency department (ED) personnel (24,25). Of concern, the stroke mimic number in stroke care systems is expected to increase due to demographic changes in the coming decades (26). Therefore, it is crucial to continuously improve EMS performance in early stroke recognition.

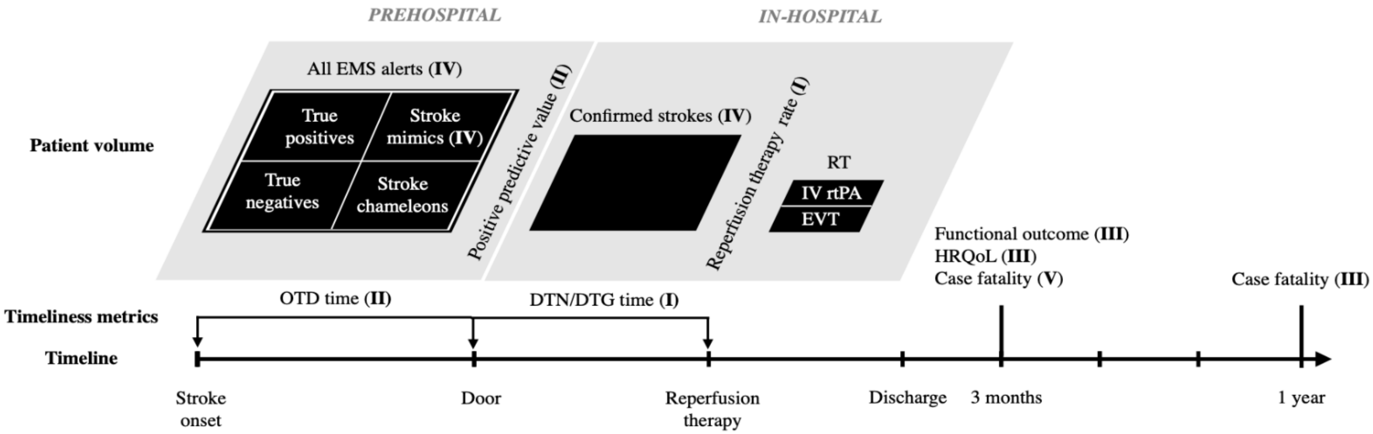
A number of stroke care quality indicators have been identified for in-hospital stroke care as well (27). They offer proxy measures for the implementation of clinical evidence into real-world clinical practice. Among others, they include the rate of admission to specialized stroke units, the rate of RT, the use of oral anticoagulation (OAC), and in-hospital timeliness metrics (28–30). However, the application of the latest stroke care guidelines into routine practice is challenging, and regular monitoring is important (31). In turn, this leads to evidence of better patient outcomes (27,32). In Lithuania, the role of monitoring stroke care performance has been assigned to SICMC, which keeps tabs on all Lithuanian stroke centers quarterly.

Finally, external factors, such as international public health crises, could also profoundly impact the continuum of stroke care measures. During the writing of this doctoral dissertation, a decreasing number of stroke admissions observed during the severe acute respiratory coronavirus 2 (SARS-CoV-2) outbreak causing the coronavirus disease 2019 (COVID-19) pandemic raised the concern of suboptimal prehospital identification and referral of acute illnesses (33–36). The first two state-wide lockdowns have been the subject of this doctoral dissertation.

Soon after identifying the first COVID-19 case in Lithuania, a strict national lockdown was declared on 16 March 2020 (37). Interestingly, in Lithuania, the community spread and death toll due to COVID-19 during the first wave of the pandemic remained exemplarily low (a total of 1,775 infections and 76 deaths by 16 June 2020) (38). However, strict restrictions on public life and reduced access to healthcare services, including primary care and preventive programs (37), as well as public fear of coronavirus, have affected stroke care.

In contrast, during the second national lockdown, extraordinarily many COVID-19 cases were diagnosed throughout the country, including patients with AIS. Despite thousands of daily new confirmed cases and the need for reallocation of specific healthcare resources, stroke services were operating in all major stroke centers across the country throughout the pandemic at full capacity. Both IV rtPA and EVT were used continuously for AIS in COVID-19 patients. However, data on the safety and outcomes of RT in the COVID-19 population have been scarce.

This thesis is based on five published research articles. Its overall aim is to examine the effects of a comprehensive national policy, stroke characteristics, and external factors on multiple stroke care performance measures in Lithuania. **Paper I** analyzes how a comprehensive national policy impacts AIS patients‘ RT rate and its in-hospital timeliness. **Paper II** investigates the effects of interactive EMS training on AIS recognition accuracy and prehospital timeliness metrics. **Paper III** analyzes AIS patients' adjusted case-fatality, functional outcome, and health-related quality of life (HRQoL), depending on if they have received RT. **Paper IV** evaluates the impact of the COVID-19 lockdown on stroke incidence, prehospital stroke triage quality, and distribution of stroke mimics. Finally, **paper V** evaluates the case fatality of COVID-19 patients with AIS treated with RT. The summary of study designs, study populations, and outcomes for the papers included in the doctoral dissertation are shown in **Figure 1** and **Table 2**.



EMS – emergency medical services, Stroke mimics – false positive stroke cases, Stroke chameleons – false negative stroke cases, RT – reperfusion therapy, IV rtPA – intravenous thrombolysis using recombinant tissue plasminogen activator, EVT – endovascular therapy, OTD – onset-to-door, DTN – door-to-needle, DTG – door-to-groin, HRQoL – health-related quality of life.

Figure 1. Summary of the doctoral dissertation. The roman numerals represent the paper of the doctoral dissertation, in which the particular outcome is analyzed.

Table 2. Summary of study designs, study populations, and outcomes for the published papers

	Paper I	**Paper II**	**Paper III**	**Paper IV**	**Paper V**
Study design	Retrospective ITS study	Prospective ITS study	Prospective observational study	Prospective observational study	Retrospective pair-matched case-control study
Scope	Lithuania	Vilnius University Hospital	Vilnius University Hospital	Vilnius University Hospital	Lithuania
Study population	Acute ischemic stroke patients	EMS suspected or hospital confirmed stroke/TIA patients	Acute ischemic stroke patients	All suspected stroke/TIA patients	Acute ischemic stroke patients with COVID-19 undergone RT
Population size	179,520	916	238	719	62
Intervention	Comprehensive national stroke care policy	Interactive EMS training	None	COVID-19 lockdown	None
Observation period	From January 1, 2006 to December 31, 2019	From March 1, 2019 to March 15, 2020	From December 1, 2018 to July 31, 2019 (four non-consecutive months)	From December 1, 2019 to June 16, 2020	From March 15, 2020 to June 30, 2021
RT outcomes	(1) IV rtPA rate; (2) EVT rate; (3) Mean DTN time	(1) PPV for identification of stroke patients; (2) Onset-to-door time ≤90 min	(1) 1-year case fatality; (2) mRS 0–2 at 90 days; (3) HRQoL at 90 days	(1) Stroke alert rate; (2) Stroke admission rate; (3) Stroke mimic pattern	(1) 90-day case fatality

Controls	None	Adjusted for age, sex, and EMS location (urban vs. suburban)	Adjusted for age, gender, cardiovascular risk factors, baseline functional status, and baseline NIHSS score	None	Adjusted for age, hypoxemia, baseline NIHSS score, COVID-19 infection, total WBC count, and CRP concentration
Statistical analysis	Analysis of ITS regresion temporal trends, immediate trend change, and difference between the pre- and post-intervention slopes	Adjusted logistic regression models	Multivariate Cox regression, adjusted logistic regression, and multiple linear regression models	Poisson regression, Mann–Whitney U, Chi-square test	Adjusted logistic regression model

ITS – interrupted time series, EMS – emergency medical services, TIA – transient ischemic attack, COVID-19 – coronavirus disease 2019, RT – reperfusion therapy, IV rtPA – intravenous thrombolysis using recombinant tissue plasminogen activator, EVT – endovascular therapy, DTN – door-to-needle, PPV – positive predictive value, mRS – modified Rankin scale, HRQoL – health-related quality of life, NIHSS – National Institutes of Health Stroke Scale, WBC – white blood cells, CRP – C reactive protein.

1.2. Research Aims

The aim of this thesis was to evaluate the effects of a comprehensive national policy, stroke characteristics, and external factors on multiple stroke care performance measures, reflecting access to and outcomes of RT for AIS patients.

1.3. Research Objectives

1. To evaluate the effects of a comprehensive national policy on AIS patients' RT rate and its in-hospital timeliness across Lithuania (**paper I**);
2. To evaluate the effects of interactive EMS training on AIS recognition accuracy and prehospital timeliness metrics (**paper II**);
3. To evaluate the effects of RT on AIS patients' 1-year case fatality as well as functional outcome and HRQoL at 90 days, adjusted for stroke characteristics (**paper III**);
4. To evaluate the impact of COVID-19 lockdown on stroke alerts and stroke admissions, as well as the distribution of stroke mimics (**paper IV**);
5. To evaluate the case fatality of RT in COVID-19 patients with AIS at 90 days (**paper V**).

1.4. Scientific Novelty

This doctoral research marks the first attempt to demonstrate how integrated efforts of leading stroke specialists, government support, and a balanced stroke care network could be associated with a breakthrough of modern RT for AIS patients in a very high cardiovascular risk region. In addition, previous stroke education interventions in prehospital care have provided mixed results. Following European (19) and North American guidelines (39), it is crucial to systematically assess the effectiveness of specific stroke education interventions and maintain the continuity of EMS education. Our research prospectively evaluates the effect of interactive EMS training on stroke recognition accuracy and the continuum of stroke care metrics. Moreover, it provides novel knowledge on the impact of the state-wide lockdown on prehospital stroke care in low COVID-19 incidence settings and helps guide care delivery strategies during public health emergencies. Lastly, it is one of the few studies on a national scale to investigate long-term outcomes in COVID-19-positive stroke patients who have undergone RT.

1.5. Practical Value of the Study

There is a paucity of studies examining acute stroke care performance in very high cardiovascular risk populations, such as the Baltic states (40). Our nationwide analysis includes all Lithuanian AIS cases, which enables us to elucidate the overall country-wide real-world trends in acute stroke care outcomes. Moreover, it creates a rationale for educational interventions for different stroke care personnel, i.e. nurses, ED personnel, and rehabilitation specialists, in order to improve overall patient outcomes. Finally, understanding the impact of state-wide lockdown measures on acute stroke care is crucial to improving healthcare systems' coordination during public health emergencies. There are currently few studies evaluating stroke care in low COVID-19 incidence settings (41,42) and no studies addressing its impact on prehospital stroke triage. A large representative population of an urban academic center covering one-third of the entire country allows for the generalizability of our findings to similar healthcare systems for future considerations in decision-making during public health emergencies.

1.6. Defended Statements

1. The enactment of a comprehensive national stroke care policy leads to significant trend improvements in RT rates and its timeliness (**paper I**);
2. Interactive EMS training significantly improves the accuracy of stroke patient recognition and their prehospital transport time (**paper II**);
3. RT improves AIS patients' 90-day functional outcome and HRQoL, but not patient survival, when adjusted for different stroke characteristics (**paper III**);
4. The COVID-19 lockdown measures are associated with decreased stroke alerts and admissions, and changes in the pattern of conditions mimicking stroke (**paper IV**);
5. COVID-19 is a significant predictor for poorer 90-day patient survival in AIS patients after RT (**paper V**).

2. LITERATURE REVIEW

2.1. Prehospital Stroke Care

Stroke is a life-threatening condition in which prompt and accurate diagnosis is essential for successfully implementing reperfusion therapies (43). EMS play a crucial role in early recognition, as they are the first-line providers in about two-thirds of stroke patients (44). Although EMS use by stroke patients is associated with earlier ED arrival, quicker evaluation, and more rapid treatment, how healthcare providers respond to stroke remains an essential factor in explaining prehospital delays (43). Fast and correct stroke diagnosis facilitates an early transfer to stroke-ready hospitals, reduces the volume of stroke mimics, and improves outcomes of acute stroke.

Intensive efforts are made to improve the quality of early stroke care. Training programs for EMS staff in simulated neurological environments increase knowledge on awareness of time-sensitive medical emergencies (43,45–50). The hospital prenotification has improved in-hospital timeliness metrics and increased IV rtPA rates (39). In addition, prehospital stroke scales and screening methods for EMS staff have been introduced to allow for a more objective stroke identification (e.g., Face Arm Speech Time test (FAST), Los Angeles Motor Scale, Cincinnati Prehospital Stroke Scale) (51,52). Moreover, specific scales for large vessel occlusion (LVO) stroke were developed to facilitate the identification of candidates for EVT (53). Given the changing landscape of prehospital stroke identification, a continuous educational effort is required to ensure the optimal implementation of prehospital stroke protocols.

Stroke education interventions in prehospital care have provided mixed results. A large multicenter randomized control trial in the United Kingdom did not show any benefit on the IV rtPA rate. Surprisingly, the onsite care duration was prolonged in the EMS group that applied an enhanced stroke assessment protocol (54). On the other hand, several interventions increased the accuracy of stroke identification, the number of patients who underwent RT, and significantly reduced the time from the symptom onset to hospital arrival (45–47,49,55). Furthermore, the duration of the training effects remains unknown (56). Following European (19) and North American guidelines (39), it is crucial to systematically assess the effectiveness of specific stroke education interventions and maintain the continuity of EMS education.

2.2. Comprehensive National Stroke Care Policy

There are worldwide inequalities in acute stroke care, which are also evident within the European region. In many Eastern European countries, the access to and delivery of acute stroke care was more often shown to be insufficient as compared to Northern and Western European countries (57).

Translating evidence-based guidelines into the real-world clinical setting has proven to be a difficult task. To facilitate this process, ample key performance indicators have been proposed to monitor the quality of stroke care (27). Local and international stroke care registries have been widely employed, as they have been shown to increase the provision of evidence-based care (58,59). In Lithuania, stroke-ready hospitals have previously been using different international registries, such as the Kaunas population-based stroke registry (60), the Safe Implementation of Treatments in Stroke International Stroke Treatment Registry (SITS-ISTR) (61), and the Registry of Stroke Care Quality (RES-Q) (62). However, due to being time-consuming and labor-intensive, the data collection process was limited to specific stroke patient populations and short time periods. In contrast, quarterly reporting of key performance indicators to SICMC has been mandatory for all Lithuanian stroke centers continuously ever since its establishment in 2014. However, its data have not been previously published.

There have been several recent attempts to describe national policies of stroke care reorganization that led to improved access to RT in Eastern and Central European countries, although few analyses included pre-intervention trends (63–66). For example, a publication describing policy processes in the Czech Republic has shown positive trends in multiple stroke care quality indicators, i.e. the number of patients treated with intravenous thrombolysis quadrupled in eight years after reorganization, with 26.4% of all AIS patients receiving intravenous rtPA in 2018 (67). However, the impact of the comprehensive national stroke care policy in Lithuania has not been analyzed in the scientific literature to date.

2.3. Stroke and COVID-19

In December 2019, a cluster of patients with pneumonia caused by SARS-CoV-2 was first described in Wuhan, China. Due to the vast spread of the virus across the globe, a pandemic was declared in March 2020. A decreasing number of stroke admissions observed during the COVID-19 pandemic raised the concern of suboptimal prehospital identification and referral of acute illnesses (33–36). The substantial strain imposed by the pandemic on the medical systems worldwide caused significant concern regarding the potential ramifications on acute stroke care (68,69).

Soon after identifying the first COVID-19 case in Lithuania, a strict national lockdown was declared on 16 March 2020 (37). Interestingly, in Lithuania, the community spread and deaths due to COVID-19 during the first wave of the pandemic remained exemplarily low (a total of 1,775 infections and 76 deaths as of 16 June 2020) (38). However, strict restrictions on public life and reduced access to healthcare services, including primary care and preventive programs (37), as well as public fear of the coronavirus, might have affected stroke care. Understanding the impact of state-wide lockdown measures on acute stroke care is crucial to improving healthcare systems' coordination during public health emergencies. There are currently few studies evaluating stroke care in low COVID-19 incidence settings (41,42) and no studies addressing the impact on prehospital stroke triage.

Ever since, a growing number of publications regarding extrapulmonary manifestations of COVID-19 arose. Neurologic manifestations of both the central and the peripheral nervous system described included COVID-19 encephalitis, acute disseminated encephalomyelitis, epileptic seizures, neuromuscular symptoms, acute demyelinating polyneuropathies, and their variants, as well as acute cerebrovascular syndromes (70–76). It has been postulated that COVID-19 patients are at an increased risk for stroke, although the true causality is yet uncertain (77).

Despite thousands of daily new confirmed cases and the need for reallocation of specific healthcare resources, emergency stroke services were operating in all major stroke centers across the country throughout the pandemic at full capacity. Both IV rtPA and EVT were used continuously for AIS in COVID-19 patients. However, data on the safety of RT in the COVID-19 population are scarce.

3. RESEARCH DESIGN AND METHODS

3.1. Ethical Approval

The five papers on which this thesis was based differed in research methodology. Therefore, multiple ethical approvals were sought. All research was conducted in accordance with the Declaration of Helsinki. The main protocol of the study was approved by the Lithuanian Bioethics Committee (protocol code number L-22-08/1-9).

For **paper I** data have been collected as part of routine clinical practice and monitoring from all active Lithuanian CSCs and PSCs by the Institute of Hygiene and the SICMC. Aggregated anonymized publicly available data on all AIS cases treated in Lithuanian hospitals between 2006 and 2019 were obtained retrospectively; therefore, there was no need for specific informed consent, and approval of the Ethics Committee was not required.

For **paper II and IV** the studies were in addition approved by the Vilnius Regional Bioethics Committee (protocol code number 1170), whereas the studies in **paper III** and **paper V** were additionally approved by the Lithuanian Bioethics Committee (protocol code numbers L-14-03/1-6 and L-21-06, respectively).

3.2. Stroke Treatment in Lithuania

In Lithuania, acute stroke care hospitals are categorized into CSCs, PSCs, and NHs, according to available reperfusion treatment. Both EVT and IV rtPA are available in CSCs 24/7 for patients with acute stroke, whereas PSCs offer IV rtPA only. The distribution of the six Lithuanian CSCs and the five PSCs with isochrone distances of time it takes to reach the closest stroke-ready hospital on a Sunday evening by car is shown in **Figure 2**.

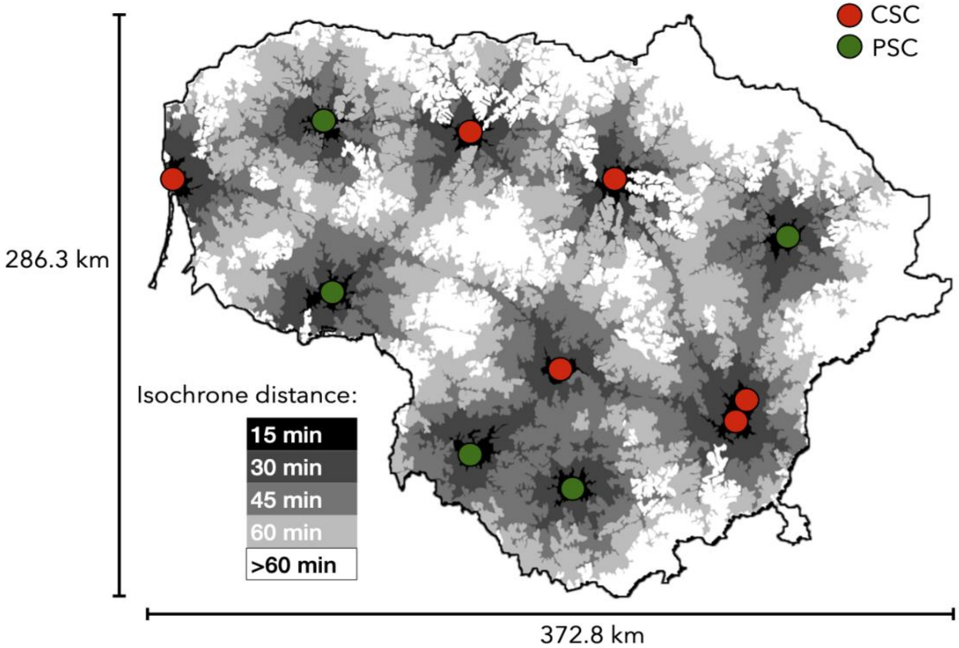


Figure 2. The distribution of Lithuanian primary and comprehensive stroke centers (PSCs and CSCs) and isochrone distances to reach them.

Throughout Lithuania, emergency medical care is provided free of charge to everyone, regardless of health insurance status. EMS staff includes a certified medical specialist – a nurse or a paramedic – who decides whether a patient needs to be taken to a CSC. The FAST scale is uniformly used for the identification of a suspected stroke/transient ischemic attack (TIA) (16). The national stroke triage guidelines require direct transport of all suspected stroke cases to the stroke-ready hospitals with IV rtPA or EVT capability, bypassing regional hospitals irrespective of the time from symptom onset. Alternatively, any primary care or specialist physician can refer a patient directly to the ED, in case of suspected stroke.

Vilnius University Hospital Santaros Klinikos (VUH SK) is one of the two CSCs in Eastern Lithuania with a catchment population of 945,000 (78), served by one EMS agency in urban and seven in suburban municipalities. In 2020, the EMS agencies were staffed by 331 specialists (217 in urban and 114 in suburban locations) and transported ≈20,400 patients (79).

3.3. Study Design and Data Source

The five papers on which this thesis was based differed in study design and data sources: **paper I** had a retrospective interrupted time series (ITS) design, **paper II** was a prospective ITS study, **papers III and IV** were prospective observational studies, whereas **paper V** had a retrospective pair-matched case-control design.

For **paper I** two data sources were used. Firstly, aggregated data on all AIS cases treated in Lithuanian hospitals between 2006 and 2019 were retrospectively obtained from the Institute of Hygiene – an institution that manages public health registers and is responsible for the monitoring of the Lithuanian population's health, health care activities, and resources (80). The dataset included the total number of AIS (corresponding to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Australian Modification, code I63), the number of AIS cases treated in Lithuanian CSCs, PSCs, and nonspecialized hospitals (NHs), their gender, age group, place of residence, days spent in hospital, and in-hospital case fatality. The full description of the statistical research methodology of how the dataset was obtained and how its completeness and patient anonymity were secured is available online (81).

Secondly, the data on the number of RTs performed were collected from the SICMC. Since the establishment of the SICMC in 2014, every quarter all active Lithuanian CSCs and PSCs were obliged to report to it aggregated anonymized data on the predetermined stroke care performance measures, consistent with the information from their hospital information systems. Among others, these include the total number of RT procedures (IV rtPA and EVT) in each hospital and their mean door-to-needle (DTN) time. The full list of performance measures, developed in accordance with the best practice recommendations of the international guidelines (82,83) and adapted to meet the local needs, is shown in **Table 3**.

Table 3. List of performance measures collected by the Lithuanian Integrated Care Management Committee quarterly

Pre-hospital stroke care quality measures
Percentage of patients with acute focal neurological symptoms screened for stroke with FAST test
Percentage of patients with suspected AIS, transported to a stroke center witin 1 hour of EMS notification
Percentage of patients with suspected AIS transported directly to a stroke center
Positive predictive value for all EMS stroke alerts
Emergency Department stroke care quality measures
Percentage of patients with suspected AIS, to whom imaging (CT, MRI) was performed and evaluated within 30 minutes of arrival to ED
Inhospital stroke care quality measures
Number of patients treated with IV rtPA
Percentage of patients, treated with IV rtPA (out of all hospitalized AIS patients)
Number of patients treated with EVT
Percentage of patients, treated with EVT (out of all hospitalized AIS patients)
Number of patients treated with both IV rtPA and EVT (out of all hospitalized AIS patients)
Percentage of patients, treated with both IV rtPA and EVT (out of all hospitalized AIS patients)
Mean DTN time (minutes)

Percentage of patients, treated with IV rtPA within 60 minutes

Percentage of patients, undergone dysphagia screening within 4 hours of hospitalization (out of all hospitalized AIS patients)

Percentage of patients, seen by a Rehabilitation specialist within 24 hours (out of all hospitalized AIS patients)

Percentage of patients, to whom rehabilitation procedurs were initiated within 72 hours (out of all hospitalized AIS patients)

Total number of hospitalized AIS patients

Total number of deaths due to AIS

Percentage of AIS patients, who died in hospital

Percentage of patients with persistent urinary dysfunction, investigated and treated for underlying causes (out of all hospitalized AIS patients)

Percentage of patients, referred for subsequent rehabilitation (out of all hospitalized AIS patients)

Percentage of patients and their realatives, who received written information on stroke diagnosis, stroke treatment plan, and practical stroke patient care recommendations

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FAST – Face Arm Speech Time, AIS – acute ischemic stroke, EMS – emergency medical services, CT – computed tomography, MRI – magnetic resonance imaging, ED – emergency department, IV rtPA – intravenous thrombolysis using recombinant tissue plasminogen activator, EVT – endovascular therapy, DTN – door-to-needle.

For **papers II and IV** the data were derived from a prospectively collected stroke registry of VUH SK. The collected data were compared among two periods – before and after interactive EMS training in **paper II**, and before and during COVID-19 lockdown in the case of **paper IV.**

For **paper III** a prospective observational study was carried out for four full non-consecutive months to account for seasonal differences. All patients with AIS, treated in VUH SK were included. Either AIS patients or their caregivers who could participate in a telephone-based follow-up were surveyed 90 days after stroke onset using the modified Rankin Scale (mRS). In addition, the EuroQoL five-dimensional three-level descriptive system (EQ-5D-3L) with a self-rated visual analog scale (EQ-VAS) was used as a self-reported measure of HRQoL. Information on all-cause patient case fatality, including the date of death, was obtained retrospectively from electronic health records one year after stroke onset. It is mandatory to issue all death certificates electronically in Lithuania (84); therefore, precise information on all patients was available.

Finally, the data for **paper V** were extracted retrospectively from electronic health records of all of the Lithuanian CSCs.

Table 2 summarizes the study designs, statistical methods, and selected outcomes.

3.4. Study population

For **paper I,** the study population included all AIS cases treated in Lithuanian hospitals between 2006 and 2019 depending on their treatment location (CSC, PSC, or NH).

For **papers II and IV** we collected data on suspected stroke or TIA patients referred to the ED of VUH SK. Data on false negatives, i.e. stroke cases that were not identified by the EMS or referring physicians, were also collected. **Paper III** included all AIS patients treated in VUH SK for four full non-consecutive months.

In **paper V** we included AIS patients with diagnosed acute COVID-19 infection prior to or on admission to a CSC, treated with RT (IV rtPA, EVT, or both). COVID-19 status was confirmed by a nasopharyngeal swab SARS-CoV-2 real-time polymerase chain reaction (RT-PCR). Patients who recovered from COVID-19 according to the epidemiological criteria at the time of index AIS were excluded from the analysis despite having a positive SARS-CoV2 RT-PCR test result. Each patient from the subject group was weighted against a control. All control patients were treated in one of the 6 Lithuanian CSCs during the study period and were not concomitant with a COVID-19 infection. In addition, control subjects were matched for age (±5 years), gender, stroke arterial vascular territory, and type of reperfusion therapy (IV rtPA, EVT, or both). To avoid selection bias, cases for this group were collected by independent stroke physicians, who were not part of this study, and were only informed about matching criteria.

3.5. Interventions

Three papers examined the effects of certain interventions on stroke-related outcomes. **Paper I** dealt with the impact of a comprehensive national stroke care policy, **paper II** examined the effects of interactive EMS training, whereas **paper IV** analyzed the impact of a low COVID-19 incidence state-wide lockdown.

3.6. Outcomes

For **paper I**, the impact of the comprehensive national policy, enacted in 2014, on six different stroke-related outcomes was evaluated. The outcome measures relevant for this doctoral thesis included the difference between the pre- and post-intervention slopes in the proportion of patients who received treatment with IV rtPA and EVT, and post-interventional DTN time trend.

Paper II evaluated the impact of interactive EMS training on seven different stroke-related outcomes. The outcome measures relevant for this doctoral thesis included the PPV for the correct identification of stroke patients and the rate of onset-to-door time ≤90 min.

The main outcomes for **paper III** were all-cause 1-year case fatality, a favorable functional outcome at 90 days (mRS ≤2), and self-reported HRQoL at 90 days, measured by the EQ-5D-3L index score and EQ-VAS.

In **paper IV** the main outcomes have been the rates of stroke alerts and stroke admissions, as well as changes in the distribution of stroke mimics.

To investigate the effects of clinical and laboratory factors (evaluated on admission) on the likelihood of 90-day case fatality after stroke and RT, multivariate logistic regression models were built in **paper V**.

The flowchart of the doctoral dissertation with all relevant outcomes is summarized in **Figure 1**.

3.7. Statistical Analysis

In **paper I**, using an ITS analysis we evaluated the yearly time trends of the outcome measures before and after the introduction of a comprehensive national stroke care policy in 2014 (85,86). The analysis was performed using the following regression equation: $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 P_t + \varepsilon_t$, where Y_t is the aggregated outcome at time t (year), T_t is the time (years) since the start of the study period, X_t is the dummy variable representing the period after the introduction of a comprehensive national policy, P_t is a continuous variable indicating time (years) since this intervention (P_t is equal to 0 before intervention), β_0 is the intercept, β_1 is the slope prior to the intervention, β_2 is the change in level in the period immediately following the intervention, and β_3 is the difference between the pre- and post-intervention slopes. The standard errors (SE) were calculated.

In **paper II**, before the EMS training, baseline trends in monthly EMS performance and hospital-based outcomes were assessed using univariate linear regression and the $\chi 2$ test for trend. We performed multivariable logistic regression models to assess the association between the training and EMS performance and in-hospital outcome measures. To account for potential confounding effects of age, sex, EMS location, and stroke subtype where appropriate, we used the hybrid backward/forward stepwise selection using the Akaike information criterion (87), removing variables with a nonsignificant ($P > 0.05$) association. Age was forced into all models as an *a priori* confounder.

Univariate and multivariate Cox regression analyses were performed to determine the prognostic implications of each variable on patient death in **paper III**. "Time 0" for survival analyses was the date of hospitalization for the index stroke event. Variables investigated included AF, age, gender, presence of reperfusion treatment, favorable baseline functional status (mRS ≤2), and baseline NIHSS. Variables with $P < 0.1$ on univariate analysis were entered into the multivariable model. The hazard ratios were presented with their 95% confidence intervals (95% CI). In addition, both unadjusted and adjusted logistic regression analyses were performed with a favorable functional outcome (mRS ≤2) as the dependent variable. The adjusted logistic analyses were performed using stepwise forward selection, based on significant variables in the adjusted models. Finally, multiple linear regression was used to estimate the associations between the independent variables (age, gender, AF, reperfusion treatment, favorable baseline functional status, and baseline National Institutes of Health Stroke Scale (NIHSS)) and HRQoL, represented by EQ-VAS and EQ-5D-3L index scores.

In **paper IV**, individuals were categorized into groups by referral type (EMS and referring physician) and periods (before and during the lockdown). At first, we evaluated the stroke presentation rates during different periods and with different providers. We then used Poisson regression models with the daily counts of stroke alerts and stroke admissions as dependent variables and the study period as an independent variable. Second, we evaluated the distribution of stroke mimics between different healthcare providers and periods.

In **paper V**, the significant predictors in the univariate analysis ($P < 0.1$) were included in the multivariate analysis, and the entered method was applied for the logistic regression model to determine the predictors for a 90-day case fatality after stroke. The odds ratio (OR) and 95% CIs were calculated.

4. RESULTS

4.1. Paper I – Comprehensive National Stroke Care Policy

Altogether, 114,436 cases were treated for AIS in Lithuanian hospitals before the government intervention, and 65,084 during the study period after it. The proportion of AIS patients, treated with IV rtPA, out of all AIS cases increased from 1.5% (or 197 overall cases) in 2013 to 12.6% (or 1,219 overall cases) in 2019 – a sixfold absolute and an eightfold relative increment. Similarly, there was an increase in the number of EVTs performed from 10 cases or 0.1% out of all AIS in 2013 to 518 cases or 5.4% out of all AIS in 2019 (**Table 4, Figure 3**). Only the proportion of patients treated with IV rtPA increased statistically significantly immediately after the implementation of a comprehensive national policy in Lithuania (β_2 = 1.32 ± 0.38, P = 0.006), whereas, a significant change in trend in the period following it was observed for both the proportion of patients treated with IV rtPA (β_3 = 1.42 ± 0.96, P < 0.001) and with EVT (β_3 = 0.85 ± 0.05, P < 0.001).

Table 4. Temporal changes in stroke care quality measures before and after the implementation of a comprehensive national stroke care policy in Lithuania (years 2006 through 2019)

Stroke care quality measure	Regression coefficient, (SE) †	*P* value
Proportion of patients treated with IV rtPA		
Period before intervention, β_1	0.185 (0.052)	0.005
Immediately after intervention, β_2	1.320 (0.382)	0.006
Period after intervention, β_3	1.421 (0.959)	<0.001
Proportion of patients treated with EVT		
Period before intervention, β_1	0.009 (0.026)	0.742
Immediately after intervention, β_2	– 0.134 (0.188)	0.492
Period after intervention, β_3	0.845 (0.047)	<0.001
Mean door-to-needle time ‡		
Period after intervention, β_1	– 5.276 (0.002)	<0.001

SE – standard error, IV rtPA – thrombolysis using intravenous recombinant tissue plasminogen activator, EVT – endovascular treatment.

† β_1, β_2, and β_3 indicate the slope prior to intervention, change in level immediately following the intervention, and difference between the pre- and post-intervention slopes, respectively.

‡ Only post-intervention values available.

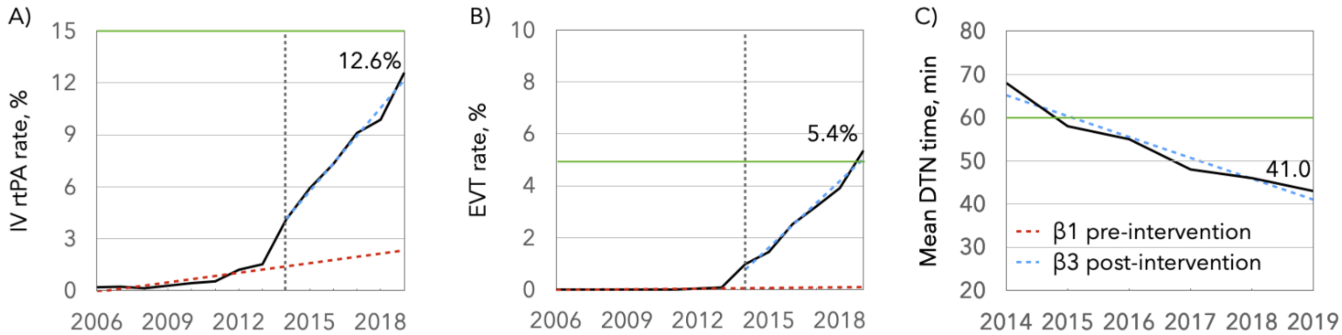

Figure 3. Temporal trends in (A) rate of thrombolysis using intravenous recombinant tissue plasminogen activator (IV rtPA), (B) endovascular treatment (EVT) rate, and (C) post-intervention mean door-to-needle (DTN) time. The dashed lines represent the regression lines. The green lines represent targets, where applicable. The comprehensive national stroke care policy in Lithuania was implemented in 2014 (vertical dashed line).

In addition, there was a statistically significant decreasing trend in mean DTN time within the Lithuanian CSCs and PSCs since 2014, when it was started to be recorded ($\beta_1 = -5.28 \pm 0.002$, $P < 0.001$) (**Figure 3**), by almost 5 minutes on average annually, from 68 minutes in 2014 to 43 minutes in 2019.

4.2. Paper II – Interactive Emergency Medical Services' Training

In total, 677 suspected strokes (73.9%) were admitted to the ED, comprising 509 true positives (55.6%) and 168 false positives (18.3%). In contrast, the EMS did not recognize 239 (26.1%) strokes, labeled false negatives or stroke chameleons. The study groups before and after the training were balanced in terms of demographics, stroke subtype, and baseline NIHSS. Urban EMS providers transported 500 patients (54.6%), whereas suburban EMS transported 416 (45.4%).

We did not identify any trends in EMS performance or prehospital care metrics during the six months before the EMS training; thus, next we assessed the impact of EMS training on these metrics.

In the pairwise comparison, the PPV for the identification of AIS patients was significantly higher in the post-training period (79.8% [75.1–84.4] vs. 71.8% [67.3–76.3], $P = 0.017$). Multivariable logistic regression showed improved odds of stroke identification (PPV) (**Table 5**), which remained significant after adjusting for age, sex, and EMS location (adjusted OR 1.6 [1.1–2.4]). Furthermore, we observed improved odds of patient arrival within 90 minutes of stroke onset (adjusted OR 1.6 [1.1–2.5]), driven by an improvement in OTD ≤90 min time in urban EMS (41.1% [33.5–49.0] pre- vs. 56.8% [46.4–66.7] post-training, $P = 0.019$).

Table 5. Logistic regression models showing the association between emergency medical services (EMS) training and acute stroke care performance measure and hospital-based outcomes, relevant for the doctoral dissertation

Outcome	Unadjusted OR (95% CI)	Adjusted † OR (95% CI)
EMS recognized stroke patients (sensitivity)	1.0 (0.7–1.4)	1.0 (0.7–1.4) ‡
PPV for identification of stroke patients	1.6 (1.1–2.2) *	1.6 (1.1–2.4) *
Onset-to-door time ≤90 min	1.4 (1.0–2.1)	1.6 (1.1–2.5) ‡ *

OR – odds ratio, CI – confidence interval, PPV – positive predictive value.
† Adjusted for age, sex, and EMS location (urban vs. suburban).
‡ Aditionally adjusted for stroke type.
* $P < 0.05$

There was no significant baseline difference in PPV values between urban and suburban EMS (**Figure 4**). However, after the training, the PPV improved in the urban EMS group (84.9% [78.9–90.8] vs. 71.2% [65.1–77.2], $P = 0.003$), but not in the suburban EMS (75.0% [68.0–82.0] vs. 72.6% [66.0–79.2], $P = 0.621$).

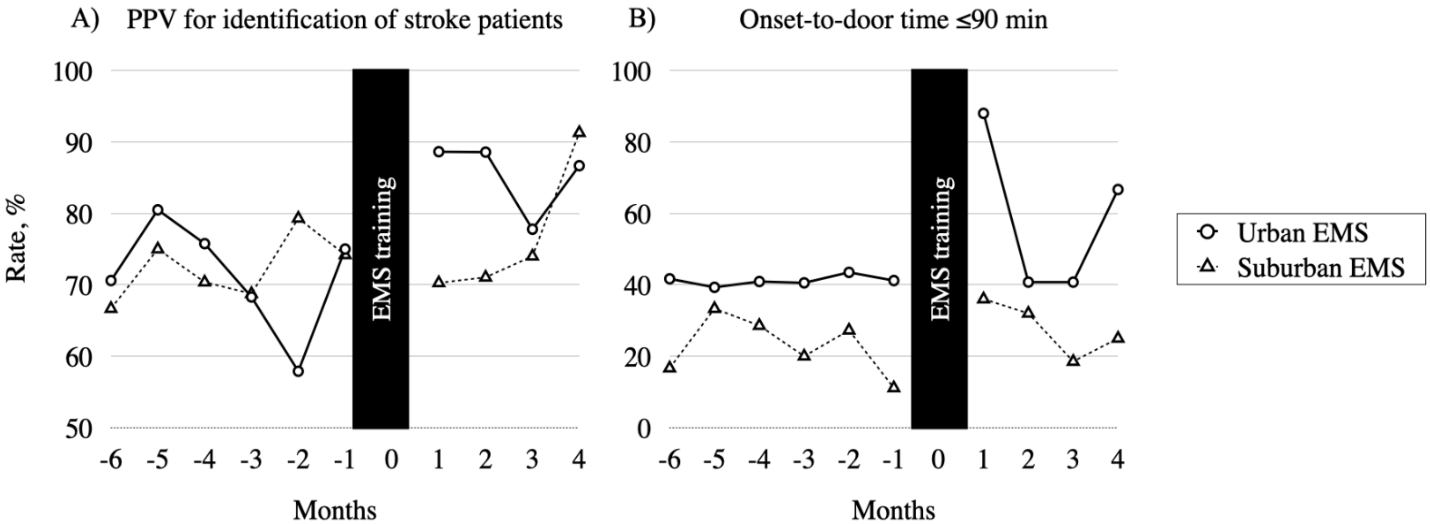

Figure 4. Emergency medical services (EMS) performance before and after EMS training in a) positive predictive value (PPV) for identification of stroke patients, and b) onset-to-door time ≤90 min rate.

Shorter overall median onset-to-door time was observed in patients referred by urban EMS (93 [67–159] min vs. 137 [89–269] min, $P < 0.001$), and more urban patients reached the CSC within 90 min (46.9% [40.6–53.2] 25.3% [19.7–31.8], $P < 0.001$) compared to the suburban EMS. After the training, there was a weak trend for improvement of the absolute onset-to-door time (84.5 min vs. 108.0 min, $P = 0.074$) and a significant improvement in onset-to-door ≤90 min rate in the urban EMS (70.5% [60.2–79.0] vs. 41.1% [33.5–49.0], $P = 0.019$), but not suburban EMS group (28.0% [19.9–37.8] vs. 22.8% [15.7–31.9], $P = 0.406$) (**Figure 4**).

4.3. Paper III – Long-term Outcomes of Reperfusion Therapy

Overall, 238 AIS patients with a mean age of 71.4 ± 11.9 years were included, of which 45.0% were female. In univariate Cox regression analysis, age ($P < 0.001$), presence of AF ($P < 0.001$), baseline favorable functional status ($P < 0.001$), and baseline NIHSS ($P < 0.001$) were found to be significant factors that have influence on overall stroke patient survival (**Table 6**). However, in the multivariable model, only age ($P = 0.007$), and baseline NIHSS ($P < 0.001$) contributed significantly.

Table 6. Univariate and multivariable Cox regression analysis for overall survival of stroke patients

Covariates		**Univariate**		**Multivariable †**	
		HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age		1.05 (1.03–1.07)	**<0.001**	1.03 (1.01–1.06)	**0.007**
Gender	**Female**	1.00 (reference)			
	Male	0.69 (0.43–1.11)	0.125		
Atrial fibrillation	**No**	1.00 (reference)		1.00 (reference)	
	Yes	2.33 (1.44–3.75)	**<0.001**	1.27 (0.74–2.19)	0.385
Reperfusion treatment	**No**	1.00 (reference)			
	Yes	1.18 (0.73–1.90)	0.507		
Baseline mRS ≤ 2	**No**	1.00 (reference)		1.00 (reference)	
	Yes	0.33 (0.19–0.59)	**<0.001**	0.56 (0.30–1.05)	0.072
Baseline NIHSS		1.13 (1.10–1.17)	**<0.001**	1.11 (1.07–1.14)	**<0.001**

HR – hazard ratio, CI – confidence interval, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale.
† Akaike information criterion = 550.9

A total of 133 out of 186 surviving patients or caregivers completed the mRS survey at 90 days; 58.6% of respondents had an mRS score ≤2 and were considered to be able to look after themselves without daily assistance. In a multivariable binary logistic regression analysis the presence of reperfusion treatment (OR 3.91 [95% CI 1.66–10.05], $P = 0.003$) and the baseline NIHSS score (OR 0.82 [95% CI 0.73–0.90], $P < 0.001$) were the only two significant factors that statistically significantly influenced the favorable functional outcome (mRS ≤2) (**Table 7**).

Table 7. Unadjusted and adjusted binary logistic regression analysis for a favorable functional outcome (mRS ≤ 2) as a dependent variable in patients with stroke

Covariates		**Unadjusted**		**Adjusted †**	
		OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age		0.98 (0.95–1.01)	0.125		
Gender	**Female**	1.00 (reference)			
	Male	1.29 (0.64–2.59)	0.475		
Atrial fibrillation	**No**	1.00 (reference)			
	Yes	0.86 (0.42–1.76)	0.673		
Reperfusion treatment	**No**	1.00 (reference)		1.00 (reference)	
	Yes	1.86 (0.91–3.85)	0.091	3.91 (1.66–10.05)	**0.002**
Baseline NIHSS		0.87 (0.79–0.94)	**<0.001**	0.82 (0.73–0.90)	**<0.001**

OR – odds ratio, CI – confidence interval, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale.
† Akaike information criterion = 163.6

A total of 126 patients or caregivers completed the EQ-5D-3L survey, and 111 AIS patients evaluated their EQ-VAS score 90 days after the index AIS event. Multivariate linear regression analyses showed that RT had a significant influence on both EQ-VAS (β ± SE: 9.571 ± 4.583, P = 0.039) and EQ-5D-3L index score (β ± SE: 0.137 ± 0.058, P = 0.021), when adjusted for age, gender, presence of AF, baseline favorable functional status, and baseline NIHSS score (**Table 8**).

Table 8. Multiple linear regression analyses of variables impacting EQ-VAS and EQ-5D-3L index scores

Independent variables		**EQ-VAS score (n = 111)**		**EQ-5D-3L index score (n = 126)**	
		Beta coefficient (SE)	***P* value**	**Beta coefficient (SE)**	***P* value**
Age		–0.055 (0.200)	0.790	0.001 (0.003)	0.955
Gender	**Female**	(reference)		(reference)	
	Male	–5.831 (4.916)	0.238	–0.027 (0.061)	0.658
Atrial fibrillation	**No**	(reference)		(reference)	
	Yes	–11.776 (4.850)	**0.017**	–0.013 (0.060)	0.833
Reperfusion treatment	**No**	(reference)		(reference)	
	Yes	9.571 (4.583)	**0.039**	0.137 (0.058)	**0.021**
Baseline mRS ≤ 2	**No**	(reference)		(reference)	
	Yes	24.733 (10.744)	**0.023**	0.239 (0.131)	0.071
Baseline NIHSS		–1.611 (0.496)	**0.002**	–0.026 (0.006)	**<0.001**

EQ-VAS – EuroQoL visual analog scale, EQ-5D-3L – EuroQoL Five Dimensions Three Levels, SE – standard error, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale.

4.4. Paper IV – Low COVID-19 Incidence Lockdown

In total, 719 patients with suspected stroke were included in the analysis: 493 referred by EMS and 226 by outpatient physicians. None of the patients were diagnosed with COVID-19.

We observed a decrease in the median daily volume of stroke alerts (3 [1–4] vs. 4 [3–6], P < 0.001) and confirmed strokes (2 [1–2] vs. 3 [2–4], P < 0.001) during the lockdown. Strikingly, during the lockdown, there was a threefold decrease in stroke referrals by outpatient physicians. However, the prevalence of confirmed strokes in the ED during the period before and during the state-wide lockdown remained stable (24.6% vs. 24.2%, $P = 0.807$).

Poisson regression revealed that the lockdown period was associated with a reduction in daily stroke alerts with a rate ratio of 0.61 (95% CI 0.52–0.71, $P < 0.001$) and stroke admissions by 0.63 (95% CI 0.52–0.76, $P < 0.001$).

Seizures and infection/sepsis were significantly more common stroke mimics among those referred by EMS compared to the physicians (16.5% vs. 4.5% and 13.9% vs. 4.5%, $P = 0.002$ and $P = 0.010$, respectively), whereas peripheral vestibulopathies were significantly less common (0.9% vs. 18.0%, $P < 0.001$). When comparing the two periods, isolated neurological symptoms associated with normal neurological work-up results were less frequent stroke mimics during the lockdown (2.4% vs. 11.6%, $P = 0.015$), whereas seizures and intracranial tumors were significantly more frequent (16.9% vs. 6.7% and 9.6% vs. 3.0%, $P = 0.012$ and $P = 0.037$, respectively) (**Table 9**).

Table 9. Most common stroke mimics

Stroke mimic, n (%)	All mimics (n = 247)	Referred by EMS (n = 115)	Referred by a physician (n = 132)	*P* value	Admitted before lockdown (n = 164)	Admitted during lockdown (n = 83)	*P* value
Seizure	25 (10.1)	19 (16.5)	6 (4.5)	0.002	11 (6.7)	14 (16.9)	0.012
Peripheral vestibulopathy	25 (10.1)	1 (0.9)	24 (18.0)	<0.001	21 (12.8)	4 (4.8)	0.072
Hypertensive encephalopathy	23 (9.3)	11 (9.6)	12 (9.1)	0.898	17 (10.4)	6 (7.2)	0.423
Infection/Sepsis	22 (8.9)	16 (13.9)	6 (4.5)	0.010	13 (7.9)	9 (10.8)	0.447
Toxic/Metabolic disorder †	18 (7.3)	9 (7.8)	9 (6.8)	0.761	9 (5.5)	9 (10.8)	0.126
Sequels of previous stroke	16 (6.5)	5 (4.3)	11 (8.3)	0.300	11 (6.7)	5 (6.0)	1.000
Intracranial tumor	13 (5.3)	9 (7.8)	4 (3.0)	0.151	5 (3.0)	8 (9.6)	0.037
Psychiatric condition ‡	13 (5.3)	7 (6.1)	6 (4.5)	0.588	11 (6.7)	2 (2.4)	0.153
Migraine and headache	10 (4.0)	4 (3.5)	6 (4.5)	0.755	8 (4.9)	2 (2.4)	0.502
Cardiovascular condition §	10 (4.0)	4 (3.5)	6 (4.5)	0.755	6 (3.7)	4 (4.8)	0.736
Syncope and presyncope	8 (3.2)	2 (1.7)	6 (4.5)	0.291	7 (4.3)	1 (1.2)	0.273

Facial nerve palsy	5 (2.0)	3 (2.6)	2 (1.5)	0.666	2 (1.2)	3 (3.6)	0.338
Musculoskeletal condition	5 (2.0)	2 (1.7)	3 (2.3)	1.000	3 (1.8)	2 (2.4)	1.000
Subdural hematoma	4 (1.6)	3 (2.6)	1 (0.8)	0.341	4 (2.4)	0	0.304
Peripheral neuropathy	4 (1.6)	1 (0.9)	3 (2.3)	0.626	3 (1.8)	1 (1.2)	1.000
Isolated symptoms associated with normal results ¶	21 (8.5)	6 (5.2)	15 (11.4)	0.084	19 (11.6)	2 (2.4)	0.015
Symptoms associated with other neurological diseases ‖	20 (8.1)	10 (8.7)	10 (7.6)	0.748	12 (7.3)	8 (9.6)	0.528
Symptoms associated with other non-neurological diseases #	5 (2.0)	3 (2.6)	2 (1.5)	0.666	2 (1.2)	3 (3.6)	0.338

EMS – Emergency Medical Services, CNS – central nervous system.
† This category includes electrolyte imbalances (n = 14), hypo- and hyperglycaemia (n = 2), hepatic encephalopathy (n = 1), and alcohol intoxication (n = 1).
‡ Organic disorders are ruled out; symptoms may be attributed to a psychiatric condition (panic attacks and anxiety (n = 8), as well as delirium (n = 5)).
§ This category includes cardiac insufficiency (n = 4), cardiac arrhythmia (n = 2), acute myocardial infarction (n = 2), and pulmonary embolism (n = 2).
¶ Neurological symptoms that cannot be classified into any other category since they do not meet any other set of diagnostic criteria or which have no organic explanation but are not clearly associated with a psychiatric disorder.
‖ This category includes multiple sclerosis and other demyelinating diseases (n = 5), dementia (n = 4), transient global amnesia (n = 4), myelopathy (n = 2), CNS infection (n = 2), venous sinus thrombosis (n = 1), Parkinson’s disease (n = 1), and myasthenia (n = 1).
This category includes advanced cancer (n = 2), anemia (n = 2), and herpes zoster (n = 1).

4.5. Paper V – Reperfusion Therapy in Stroke Patients with COVID-19

Thirty-one pairs of subjects and matched controls were included in the study of **paper V**. The mean age was 74.0 years in COVID-19-positive AIS patients and 73.7 years in controls. Forty females (64.5%) comprised the entire cohort. The prevalence of stroke risk factors did not differ statistically significantly between the two groups. Fourteen (22.5%) patients underwent IV rtPA, thirty (48.4%) patients were treated with EVT, and eighteen (29.1%) patients received bridging therapy. Fifty-six (90.3%) patients in the entire cohort were diagnosed with anterior circulation stroke.

Ninety-day case fatality rates were significantly higher in the COVID-19 group compared to controls (54.8% and 12.9% respectively, $P = 0.001$). The significant variables included age ($P = 0.022$), hypoxemia ($P = 0.079$), baseline NIHSS ($P = 0.001$), COVID-19 infection ($P = 0.001$), total white blood cell (WBC) count ($P = 0.079$), and C-reactive protein (CRP) concentration ($P = 0.093$). Increasing age and higher baseline NIHSS on admission were associated with a higher likelihood of 3-month mortality after stroke and RT. COVID-19 infection increased the likelihood of death 3 months after stroke and RT seven times (OR 6.70; 95% CI 1.03–43.58), while hypoxemia, total WBC count, and CRP concentration were not significant predictors (**Table 10**).

Table 10. Logistic regression model on the likelihood of 90-day case fatality after stroke and reperfusion therapy (*n* = 52)

Covariates		**Univariate**		**Multivariable †**	
		OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age		1.07 (1.01–1.13)	**0.022**	1.09 (1.02–1.18)	**0.029**
Hypoxemia (SpO2< 93%)	**No**	1.00 (reference)			
	Yes	4.05 (0.88–22.99)	0.079		
COVID-19 infection	**No**	1.00 (reference)		1.00 (reference)	
	Yes	8.20 (2.49–32.91)	**0.001**	10.04 (2.30–58.73)	**0.004**
Total WBC count		1.17 (1.01–1.44)	0.079		
CRP concentration		1.01 (1.00–1.03)	0.093		
Baseline NIHSS		1.23 (1.10–1.41)	**<0.001**	1.22 (1.07–1.44)	**0.007**

OR – odds ratio, CI – confidence interval, SpO2 – peripheral oxygen saturation, COVID-19 – coronavirus disease 2019, WBC – white blood cells, CRP – C-reactive protein, NIHSS – National Institutes of Health Stroke Scale.
† Akaike information criterion = 55.9

5. DISCUSSION

The investigations of this doctoral thesis are the first to take into account the whole Lithuanian AIS patient population and to evaluate the effects of a comprehensive national policy, stroke characteristics, and external factors on multiple stroke care performance measures. We observed significant trend improvements in RT rates, and a statistically significant decreasing trend in mean DTN time within the Lithuanian CSCs and PSCs since the enactment of a comprehensive national policy 2014, when it was started to be recorded (**paper I**). Second, we found that interactive EMS training significantly improves the accuracy of stroke patient recognition and their prehospital transport time (**paper II**). Third, our data suggest that RT improves AIS patients' 90-day functional outcome and HRQoL, but not patient survival, when adjusted for different stroke characteristics (**paper III**). In addition, we found that the COVID-19 lockdown measures are associated with decreased stroke alerts and admissions, and changes in the pattern of conditions mimicking stroke (**paper IV**). Finally, our data show that COVID-19 is a significant predictor for poorer 90-day patient survival in AIS patients after RT (**paper V**).

The results will be discussed further and compared to previous studies according to the specific papers in question.

5.1. Paper I – Comprehensive National Stroke Care Policy

Ample previous studies have shown a continuous increase in IV rtPA (88–106) and EVT rates for AIS (106–108) in different countries over different study periods. However, our data show that Lithuania experienced a countrywide breakthrough of IV rtPA use only after the introduction of a comprehensive national policy. Similarly, EVT use was in single digits before the government intervention and surged after 2014, although some unmeasured confounders, such as the breakthrough thrombectomy trials in 2015 that increased physicians' confidence in the safety and efficacy of EVT, might have also contributed (107). Nevertheless, we believe that retrospective per-case AIS RT expense reimbursement and budget cap removal might have been a more robust incentive to improve RT numbers countrywide. While there is no agreed benchmark for thrombolysis and thrombectomy rates (these were 12.6% and 5.4% in Lithuania in 2019, respectively) (10), there is still room for improvement, as shown by the remarkable nationwide IV tPA administration rate of 26.4% in the Czech Republic and a 5.6% EVT rate in Malta (57,67,105).

International guidelines recommend developing stroke systems of care so that RT-eligible patients receive treatment in the fastest achievable onset-to-treatment time (109). We found a statistically significant decreasing trend in the mean DTN time within the Lithuanian hospitals from 68 minutes in 2014 to 43 minutes in 2019. We speculate that higher treatment volumes might lead to shorter DTN times – an indicator of experience and confidence (100,110,111). Moreover, quarterly SICMC reports to the MoH, and annual public stroke center progress monitoring may have produced an additional incentive (112). Astonishingly, recent data from the Czech Republic showed that a national median DTN time of 25 minutes or less is feasible (105).

The interrupted time series design in **paper I** is a quasi-experimental approach used to evaluate the impact of a single intervention, and unmeasured confounders (i.e., decreasing CV RF prevalence) may have affected the results. More limitations include the fact that we did not investigate the influence of the COVID-19 pandemic on stroke care outcomes, as we have deliberately chosen to conduct our analysis on the pre-pandemic period. In addition, the breakthrough thrombectomy trials in 2015 might have played a role in the increased thrombectomy rates throughout the country as there was an increase in confidence in the safety and efficacy of EVT among neurologists (107). Fourth, functional and post-discharge long-term outcomes could not be assessed due to limited access to such data. Fifth, our analysis is based on the group of hospitalized AIS cases, not overall AIS incidence, but the actual difference between these rates may not be large, since every patient with AIS requires hospital admission by the current guidelines (112).

The strengths of **paper I** are that our nationwide analysis includes all Lithuanian AIS cases, which enables us to elucidate the overall country-wide real-world trends in acute stroke care outcomes. In addition, this is the first study from a very high CV RF region (40) demonstrating that comprehensive changes in national stroke care policy could be associated with substantial improvements in stroke care outcomes.

5.2. Paper II – Interactive Emergency Medical Services' Training

In our prospective interrupted time-series study evaluating the effect of interactive EMS training on prehospital stroke care we found a sustained improvement of prehospital stroke recognition during at least four consecutive months after the training. Second, we found an improved rate of timely transfers of suspected strokes to the hospital, demonstrating the overall benefit of EMS training on the continuum of prehospital care. Third, the training effect was more pronounced in the urban EMS group.

We found fewer stroke mimics in the post-training period without an increase in the false negative rate. Thus, increasing the PPV did not result in a suboptimal triage of strokes, nor did it deprive stroke patients of time-sensitive revascularization treatment. The improvement of PPV was driven by a reduced rate of stroke mimics in the urban EMS group. One of the reasons for significantly improved PPV in the urban but not the suburban EMS group could be the implementation of a new national regulation of prehospital stroke triage on 1 January 2020 that partially overlapped with the post-training period. According to the new law, suspected stroke patients were transferred directly to stroke-ready hubs bypassing primary evaluation in the regional hospitals irrespective of their last known well time. The new guidelines were designed to improve access to RT for stroke patients in suburban regions. However, the stroke triage pathway change may have increased the false positive rate in the suburban EMS group, as they transported more suspected stroke cases directly to the CSC instead of the regional hospitals. Thus, we speculate that the weak trend of PPV improvement in the suburban EMS group reflects the effect of EMS training offsetting the expected dip of PPV in the suburban EMS group. Another possible explanation could be differences in stroke knowledge between urban and suburban paramedics before the training or other variables, such as differing socioeconomic status, comorbidities, or secular trends, not evaluated in this study.

The increase in PPV after the training is clinically relevant because it can help reduce the false positive cases overflowing the acute stroke care pathways. Optimal utilization of the frontline stroke care and neuroimaging resources is particularly relevant during peak hours of stroke incidence, such as the morning hours (113) or public health emergencies, as was the case during the COVID-19 pandemic. Therefore, continuous efforts are crucial to ensure optimal prehospital stroke identification.

Previous studies have shown that a brief educational EMS intervention could substantially improve EMS knowledge of prehospital stroke scales, prenotification compliance, and field triage protocols (48,114). Moreover, a recent prospective study by Oostema et al. assessed the real-world impact of EMS training on prehospital stroke recognition and found that an online EMS education module coupled with performance feedback was associated with improved stroke recognition sensitivity, increased hospital prenotification, and faster rtPA delivery (47). In addition to these findings, our study demonstrates that in-person interactive EMS training improves prehospital stroke identification and timely transfer to the ED. We also note that the sensitivity in our study did not change after the training, which a relatively high baseline performance might explain. The baseline stroke recognition sensitivity in our study (68.0%) was comparable to the post-training sensitivity in a study by Oostema et al. (69.5%), suggesting a ceiling effect of stroke sensitivity improvement. Consequently, the improvement in PPV did not result in a false negative rate (type II error) increase and thus did not deprive stroke patients of time-sensitive treatment.

A recent attempt to enhance prehospital stroke care was undertaken in the Paramedic Acute Stroke Treatment Assessment (PASTA), a multicenter randomized clinical trial in the UK. Surprisingly, the intervention resulted in 8.5 minutes longer onsite care time and did not show any tPA rate improvement (54). Arguably, sophisticated prehospital assessment protocols did not facilitate IV rtPA decision-making. On the other hand, we find conflicting results from non-randomized intervention studies showing that prehospital intervention improved RT rates (49,56) and in-hospital treatment times (47,49). In addition to the previous studies, our study shows that interactive EMS training can improve stroke recognition and prehospital transfer times and thus improve the overall timeliness of acute stroke care. In contrast, we did not observe changes in hospital-based metrics. However, our study was not designed to evaluate the in-hospital performance since we did not collect data on the hospital prenotification rate, and the EMS staff was not involved in the clinical care after the ED admission. Other in-hospital variables, such as imaging capacity, availability of rapid image interpretation, and ED workload, influence stroke care performance but are not accounted for in our study.

The training effect on timely prehospital transportation was more robust in the urban compared to the suburban EMS group. Since transport time from suburban regions is longer due to greater distances between the patient and the CSC, fewer patients could arrive within 90 minutes of symptom onset. Furthermore, due to the national regulatory changes during the study, all suspected stroke cases were to be transported to stroke-ready hospitals, irrespective of the time of symptom onset. Thus, the number of stroke alerts outside the acute treatment window increased in the suburban but not the urban EMS group. Hence, the actual training effect in the suburban EMS group was confounded by these regulatory changes.

The recent stroke triage changes in Lithuania were aimed to increase EVT access to patients in suburban areas by transporting suspected stroke cases directly to stroke-ready centers. However, the choice between the drip and ship or mothership model is context-specific (115) and poses thorny clinical dilemmas (116). EVT has a remarkable treatment effect with the number needed to treat of 2.6 to reduce disability in the early hours after stroke onset (30). If LVO is suspected, a direct transfer to a CSC with EVT capacity might be privileged, as a shorter time to reperfusion may improve its treatment effect (117). On the other hand, bypassing PSCs with IV rtPA capacity might cause unnecessary delays to IV rtPA and an increase in false positive LVO transfers due to suboptimal triage. To address these questions, the RACECAT study was conceived in Catalonia, Spain – the first randomized clinical trial in the field (ClinicalTrials.gov identifier: NCT02795962). After randomizing 1,401 patients, the preliminary study results showed no difference in ischemic stroke outcomes between drip-and-ship and mothership models in a highly coordinated stroke network (118).

Although direct transfer to the CSC could be most beneficial for LVO patients, the FAST scale used in our study was not explicitly designed to detect LVO. In this context, a prospective study comparing eight prehospital scales for LVO identification showed that an adapted version of Gaze-Face-Arm-Speech-Time (G-FAST) had high LVO recognition accuracy similar or higher to other LVO scores (119). Moreover, improving the PPV of the stroke screening tools can increase the area where the mothership model provides the best stroke treatment outcome (115). More studies will be needed to explore the optimal LVO prediction methods to triage patients for different transfer pathways.

The main strength of **paper II** is its prospective design and relatively large sample size. The blinding of EMS staff to the assessment allowed us to evaluate the training effect and avoid the apprehension bias, also known as the Hawthorne effect, when participants modify their behavior in response to their awareness of being observed (120).

The main limitation of **paper II** was the absence of a control group to fully evaluate the actual effect of the intervention. However, since there were no significant differences in demographic and clinical characteristics of suspected stroke cases before and after the training, the confounding by unmeasured factors was limited. Also, the overlap between the first month before and the last month after the training allowed us to compare similar calendar periods. Second, due to optional attendance, just over half of the EMS staff underwent the training. However, this rather introduces a bias towards the null, and we expect a stronger training effect with higher participation. Third, we found increased daily stroke rates in the post-training period, influenced by the change in the stroke triage regulations in suburban regions. However, the marginal increase in stroke prevalence during the post-training period could not fully explain the PPV improvement. We observed improved PPV with non-overlapping CI in the urban EMS and a weak trend in the suburban group favoring a consistent effect of EMS training across both groups. Fourth, our intervention did not target the dispatcher stroke recognition or hospital prenotification rate; thus, the inclusion of additional actors in the intervention might further improve the prehospital stroke care. Fifth, due to the emerging COVID-19 pandemic, we terminated our analysis before the national lockdown, which significantly limited access to urgent and non-urgent healthcare. Thus, we could not conclude on the long-term effects of the training beyond four months. Lastly, our study was conducted in a very high cardiovascular risk population (40). These findings are generalizable to currently underrepresented populations with similar healthcare systems and EMS staffing patterns, including but not limited to the Baltic states and Eastern European countries. Therefore, this study could inform prehospital clinical care and study design to improve prehospital stroke workflow using publicly available e-learning stroke education resources.

5.3. Paper III – Long-term Outcomes of Reperfusion Therapy

Our single-center prospective observational study showed that RT in AIS patients could be statistically significantly associated with a favorable functional outcome (mRS ≤ 2) and better self-reported HRQoL at 90 days, without a significant difference in patient survival. This is in line with previous research, that in patients with AIS of <4.5 h duration, IV rtPA leads to better functional outcome than no IV rtPA, without an increase in patient mortality (20,121,122). Although there are ongoing discussions about the use of IV rtPA in acute stroke in particular circumstances – before EVT, in patients with lacunar stroke, and in patients with no visible LVO – there is currently no strong evidence that it should be avoided in these instances (121). A similar outcome is attributed to AIS patients having undergone EVT. For adults with LVO-related anterior circulation AIS 6 to 24 h from time last known well and fulfilling the selection criteria of DEFUSE-3 (123) or DAWN (124), EVT plus best medical management improves patients' functional outcome compared with best medical management alone, without increasing patient mortality (125).

In line with our findings, previous studies have shown improvement in HRQoL across multiple dimensions in AIS patients after RT (126), although these findings are not equivocal (127). However, despite the significant improvement in HRQoL after RT, even after 5 years the HRQoL of stroke survivors was shown to exhibit large variability and could remain below the level of the general population (128).

Paper III is the first study on the Lithuanian population that investigates the impact of RT on patients' case fatality, HRQoL, and long-term functional outcomes in a hospital-based AIS patient cohort.

However, this study has several limitations. Foremost, as this was a single-center study with a rather small sample size, our findings could have limited generalizability, and some weak statistical associations could have been missed. In addition, the 90-day follow-up for assessing the functional status and HRQoL was telephone-based, and in many cases, caregivers responded to the survey, which makes it difficult to compare to studies where HRQoL is self-reported using visual aids (129). Third, we used the EQ-5D-3L, which has been validated for stroke patients (130), but as there is no Lithuanian value set available to this date, a European value set was used. Finally, a considerable proportion of the patients were lost to the 90-day follow-up survey due to a short period of time, when the investigators could not conduct the telephone survey because of technical reasons. However, because there was no bias towards a certain group of patients, we believe that this should not have affected our results.

5.4. Paper IV – Low COVID-19 Incidence Lockdown

In this prospective study in an academic stroke center with a large urban catchment population, we found a decreased number of stroke alerts and stroke admissions during the lockdown. In addition, serious neurological conditions, such as seizures and intracranial tumors, were encountered more often as stroke mimics. Our findings provide novel knowledge on the impact of the state-wide lockdown on prehospital stroke care in low COVID-19 incidence settings and help guide care delivery strategies during public health emergencies.

Although Lithuania has not experienced a significant surge of COVID-19 during the lockdown, we observed a significant increase in COVID-19 concern in the public, as indicated by Google Trends data on COVID-19 related searches. All routine medical activities and surgeries during the state-wide lockdown were halted, resulting in a deterioration of preexisting neurological conditions (37). Suboptimal routine care was reflected by a sharp decline in outpatient physician referrals of suspected stroke and an overall increase in the proportion of seizures and intracranial tumors mimicking stroke. Despite a significant decrease in the absolute numbers of daily stroke alerts and confirmed strokes during the lockdown, the prevalence of confirmed strokes in the ED did not differ between the periods.

In line with other reports from China, Europe, Taiwan, and the United States, we also found a significant decrease in stroke alerts and stroke admissions (131,35,36,41,42,132,133). Our findings provide additional knowledge on the effects of lockdown measures on stroke care patterns in a low-incidence low-mortality COVID-19 outbreak setting. Similarly, another study of admission rates at three tertiary university hospitals in Greece, where COVID-19 penetration was also low, showed a remarkable decrease in stroke and acute coronary artery syndrome patients (41). We also found a decreased number of TIAs during the lockdown. Thus, the reduced number of stroke/TIA consultations might be attributable to the reluctance to seek medical attention in the presence of mild or transient neurological symptoms. Even though our study did not find a significant change in presenting stroke severity, we might have been underpowered due to missing NIHSS in patients not considered for reperfusion.

In addition, we found that seizures and intracranial tumors presented more often as stroke mimics during the lockdown. A study from our institution showed that worse seizure control and health status in people with epilepsy were observed during the statewide lockdown (134). Similarly, a study from the United Kingdom reported that delays in cancer diagnosis and care are projected to result in more than 3,200 avoidable cancer deaths in the following five years (135). Altogether, these findings underscore the importance of interventions to optimize specialized care and avoid diagnostic backlog to mitigate the impact of the COVID-19 pandemic. From the public health perspective, our study had a unique opportunity to evaluate the impact of lockdown measures on stroke care independently of the COVID-19 surge. Due to the early and efficient lockdown in Lithuania, the incidence and mortality of COVID-19 during the study period remained one of the lowest in Europe (136). Second, to limit the potential spread of SARS-CoV-2 infection, the Lithuanian government implemented a strict state-wide lockdown, severely restricting social life and access to routine healthcare services (37). Therefore, we could successfully examine the impact of lockdown measures on stroke care not confounded by the COVID-19 surge effect on the healthcare system. Our findings suggest that the state-wide lockdown measures could have had unwanted collateral consequences on prehospital stroke care.

The strengths of **paper IV** include a prospective design and being the first report on the impact of a statewide lockdown on prehospital stroke triage quality and stroke mimics distribution. In addition, a large representative population of an urban academic center covering one-third of the entire country allows for the generalizability of our findings to similar healthcare systems.

Paper IV includes some limitations. Foremost, since this was a single-center study, we cannot account for referral pattern changes in other stroke centers in the country. However, the confounding should not have been significant, as all centers functioned in the same low-incidence, low-mortality COVID-19 setting. Another limitation was the absence of data on medium and long-term functional outcomes. Even though the discharge NIHSS scores did not differ before and during the lockdown, we could not evaluate if longer delays to ED presentation might have resulted in poorer long-term functional outcome. In addition, we did not fully account for the natural seasonal changes in the incidence of stroke. However, in 2018–2019, more strokes were admitted to our CSC during the spring rather than winter months, suggesting an actual decrease of stroke admission in our study rather than a seasonal fluctuation. Finally, our findings have limited generalizability to high-incidence COVID-19 situations, regions with different stroke care protocols, and varying social and healthcare responses to the COVID-19 pandemic.

5.5. Paper V – Reperfusion Therapy in Stroke Patients with COVID-19

This is the first Lithuanian nationwide pair-matched multicenter study evaluating outcomes of COVID-19-positive AIS patients treated with RT. Despite successful reperfusion, the COVID-19 stroke patients had a higher 3-month case fatality rate as compared to control patients. Hypoxia had a major role in our COVID-19 cohort and may have contributed to the high case fatality rate.

Outcomes of COVID-19 patients with AIS seem to be universally unfavorable despite successful reperfusion. Although COVID-19 patients with mild stroke presentations seemed to have more favorable outcomes, in general, COVID-19 patients with AIS were more severely disabled, with a median NIHSS of 15 at discharge as compared to controls. This is in line with other studies reporting in-hospital mortality rates ranging from 31% to 60% (137–139). The European multicenter EVT study provided data on 30-day mortality of 27% (140). In contrast, we report insights on 3-month mortality even higher than previously reported (141).

In our study, the absolute majority of COVID-19 stroke patients had a more severe stroke despite no differences in ASPECTS (Alberta Stroke Program Early CT Score) scores between study groups on admission. These results are comparable to previous reports (141). However, the true size of ischemic territory in COVID-19 patients may be larger than initially anticipated. Significantly lower ASPECTS scores and higher infarct volumes were observed for COVID-19 patients with AIS on magnetic resonance imaging (MRI) despite early imaging in a previous study (142). In contrast, we used computed tomography (CT) as our main screening modality. Although discordances between MRI and CT median ASPECTS scores in non-COVID-19 AIS have been documented, no impact on overall outcomes was observed (143). Therefore, COVID-19-specific endothelial dysfunction may have a role in infarct core size expansion and contribute to poor outcomes.

Hypoxia is a major contributing factor to poor outcomes in AIS patients. In our cohort, 64.5% of COVID-19 stroke patients suffered from respiratory failure. Almost one-third of COVID-19 patients with AIS required prolonged intubation due to severe respiratory system compromise. In a subgroup analysis of the former group (unpublished data), patients in whom respiratory function was severely affected were those who showed no neurologic improvement 24 hours after reperfusion. Most of these patients presented with LVOs and required EVT for reperfusion. Due to a relatively small sample size in our cohort, we could not perform a subgroup analysis with optimal statistical power, but a tendency toward more severe strokes in patients with severe respiratory compromise was observed. This is in line with previous reports. Two meta-analyses showed that severe COVID-19 disease is more often complicated by severe ischemic strokes (139,144). It is proposed that patients with severe respiratory compromise can be deemed as high risk for poor outcomes and in-hospital mortality (138). A stroke center in New York reported good early neurological improvement in COVID-19 stroke patients who underwent EVT. None of the COVID-19 stroke patients who dramatically improved showed signs of respiratory distress (145). Respiratory function, although analyzed in AIS with COVID-19 cohorts, has not been widely addressed in the subpopulation of patients undergoing RT for AIS. In our study, we emphasize the importance of respiratory complications for AIS patients undergoing specialized treatment. Respiratory failure could be an important factor for early neurological deterioration or lack of improvement despite successful reperfusion. Novel strategies involving optimal management of respiratory compromise should be exploited to improve the outcomes for stroke patients undergoing RT.

Risk factors associated with high dependency and mortality in COVID-19 AIS patients include older age, COVID-19 infection, and stroke severity on admission. The logistic regression model in our study showed age, higher baseline NIHSS, and COVID-19 infection to be associated with higher 90-day mortality. COVID-19 infection increased the likelihood of death 3 months after stroke and RT seven times. We acknowledge that the regression analysis model in our study may not reflect the true predictors of poor outcomes in

COVID-19 AIS patients undergoing RT due to the study's retrospective nature, data shortages, and a small sample size. Furthermore, we included in our univariate and multivariate logistic regression only patient history data and clinical and laboratory data evaluated on admission. We argued that hypoxia is an important factor for the expansion of infarcted brain tissue and may be associated with poor outcomes given the high rates of severe respiratory failure in our study. This might explain the higher rates of in-hospital mortality. However, for the survivors, the causes of 3-month mortality rates remain to be validated.

The strength of **paper V** was that the study was conducted across all Lithuanian stroke centers. Second, we have performed one of the few studies reporting COVID-19 patients with AIS mortality at 3 months. As a result, it was possible to compare COVID-19 patients with AIS with controls demonstrating clear differences in case fatality, raising COVID-19 as a potential risk factor predicting poor outcomes in AIS patients.

The major weaknesses of **paper V** are its retrospective nature and a relatively small sample size, restricting subgroup analysis of reperfusion modalities and evaluation of outcomes within. Another weakness is the chosen pair-matched analysis method, which might not accurately represent the control patients' true demographic and stroke-specific data. We could not perform a subgroup analysis of different treatment modalities that would have added additional safety and outcome data. The regression analysis model, albeit significant for some factors, we believe, does not reflect all predictors of poor outcomes in COVID-19 patients. Heterogeneity between different centers concerning treatment management of patients with AIS should be considered. Although we reported 90-day mortality rates, we could not compare functional outcomes of surviving COVID-19 stroke patients to the control group, which would provide additional information on the distant effects of COVID-19 on AIS survivors.

CONCLUDING REMARKS

1. A comprehensive national stroke patient care policy in Lithuania was associated with an increasing trend change in the proportion of AIS patients who received RT: IV rtPA and EVT. In addition, there was a statistically significant decreasing trend in mean DTN time within the Lithuanian stroke centers since 2014, when it was started to be recorded.

2. Interactive EMS training significantly improves the accuracy of prehospital stroke patient recognition for at least four consecutive months. After the training, there was a significant improvement in onset-to-door ≤90 min rate in the urban EMS, but not in the suburban EMS group.

3. RT improves AIS patients' 90-day functional outcome and HRQoL, but not overall patient survival at 1 year, when adjusted for different stroke characteristics.

4. Low-incidence, low-mortality, statewide COVID-19 lockdown measures are associated with decreased stroke alerts and admissions. Furthermore, serious neurological conditions, such as seizures and intracranial tumors, become more frequent stroke mimics. State-wide lockdown measures negatively affect prehospital stroke care independently of the COVID-19 surge.

5. COVID-19 is a significant predictor for poorer 90-day patient survival in AIS patients after RT.

FUTURE PERSPECTIVES/PRACTICAL RECOMMENDATIONS

Although this doctoral dissertation confirms the impact of a comprehensive national policy on multiple stroke-related outcomes, further studies are warranted to elucidate how the use of RT and post-reperfusion functional outcomes change according to time and circumstances in a real-world setting. It emphasizes that the constant monitoring of key performance indicators helps to enforce the latest stroke care guidelines and to identify the areas for possible improvement across the stroke care pathway. As the collection of key performance data is time-consuming and labor-intensive, automatic systems that collect and monitor predefined patient outcome data from electronic health records for audit purposes could be employed and adapted for a particular clinical setting. The usefulness and cost-effectiveness of such automatic monitoring systems are yet to be elucidated.

In addition, future studies should evaluate the long-term effects of interactive EMS training on prehospital stroke care as well as hospital-related outcomes and should aim to determine optimal retraining intervals. Moreover, educational interventions for different stroke care personnel, i.e. nurses, ED personnel, and rehabilitation specialists, should be considered, and further research should investigate their possible impact on the improvement of selected stroke-related outcomes. Lastly, context-tailored training programs should be considered for EMS providers in different locations.

Finally, future studies should evaluate the impact of COVID-19 lockdown measures on a state-wide level, including those concerning stroke patient care. This would help to better understand and adjust specific nationwide restrictions for possible public health emergencies in the future.

SUMMARY IN LITHUANIAN

SANTRUMPOS

ASPECTS	Alberta insulto programos ankstyvos kompiuterinės tomografijos balas (angl. *Alberta Stroke Program Early Computed Tomography Score*)
GSI	galvos smegenų insultas
PI	pasikliautinasis intervalas
COVID-19	koronaviruso liga 2019
CRB	C reaktyvusis baltymas
IGC	insulto gydymo centras
GMP	greitoji medicinos pagalba
EQ-5D-3L	EuroQoL penkių dimensijų trijų lygių aprašomoji sistema
EQ-VAS	EQ-5D-3L su vizualia analogine skale
FAST	*Face Arm Speech Test*
rtPA	rekombinantinis žmogaus audinių plazminogeno aktyvatorius
KT	kompiuterinė tomografija
SAM	Sveikatos apsaugos ministerija
mRS	modifikuota Rankino skalė
MRT	magnetinio rezonanso tomografija
ASPĮ	asmens sveikatos priežiūros įstaiga
NIHSS	Nacionalinių sveikatos institutų insulto skalė
ŠS	šansų santykis
TPR	teigiama prognostinė reikšmė
TPL	tarpinės pagalbos ligoninė
RT	reperfuzinė terapija
RT-PGR	realaus laiko polimerazės grandininė reakcija
SARS-CoV-2	sunkaus ūminio respiracinio sindromo koronovirusas 2
PSIP	praeinantis smegenų išemijos priepuolis
VUL SK	Vilniaus universiteto ligoninė Santaros klinikos

Ši daktaro disertacija parengta mokslinių publikacijų, kurios tolesniame tekste žymimos romėniškais skaitmenimis, rinkinio pagrindu:

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1. ĮVADAS

1.1. Tiriamoji problema ir jos aktualumas

Insultas yra viena iš dažniausių mirties ir negalios koreguotų gyvenimo metų (angl. *disability-adjusted life years*) priežasčių pasaulyje (1, 2). Dėl didelio širdies ir kraujagyslių ligų rizikos veiksnių paplitimo ir prastos jų kontrolės (4, 5) Lietuvos sergamumo ir mirtingumo nuo ūminio išeminio galvos smegenų insulto (GSI) rodikliai yra vieni iš didžiausių pasaulyje (3). Maža to, Lietuvai prognozuojamas didžiausias pagal amžių koreguoto sergamumo insultu ir ligotumo rodiklių augimas tarp visų Europos Sąjungos šalių (6).

Reperfuzinė terapija (RT), kuriai priklauso intraveninė trombolizė rekombinantiniu žmogaus audinių plazminogeno aktyvatoriumi (rtPA) bei mechaninė trombektomija, yra plačiai pripažintas, veiksmingas, saugus ir ekonomiškai efektyvus GSI gydymo metodas (7, 8). Vis dėlto platus RT taikymas kasdienėje klinikinėje praktikoje kelia iššūkių (9–12). Pirmoji intraveninė trombolizė rtPA Lietuvoje buvo atlikta 2002 m., o mechaninė trombektomija klinikinėje praktikoje pradėta taikyti nuo 2012 metų. Nepaisant to, kad jau 2007 m. pagal šalies GSI diagnostikos, gydymo ir profilaktikos metodiką intraveninė trombolizė buvo rekomenduota kaip pirmiausia pasirenkamas gydymo metodas (13), bendras metinis atliktų intraveninės trombolizės atvejų skaičius Lietuvoje išliko mažas.

2014 m., siekdama nacionaliniu lygiu skatinti ir diegti modernią RT pacientams, patyrusiems GSI, Lietuvos Respublikos sveikatos apsaugos ministerija (SAM) inicijavo tam skirtų priemonių paketą. Integruotas priemonių paketas apėmė ūminio insulto gydymo centrų (klasterių) tinklo sukūrimą, GSI pacientų srautų pertvarkymą, asmens sveikatos priežiūros paslaugų, įtariant ar diagnozavus ūminį GSI, teikimo tvarkos aprašo patvirtinimą, reikalavimų insulto gydymo centrų (IGC) ir tarpinės pagalbos ligoninių (TPL) akreditacijai nustatymą (14) bei Insulto integruotos sveikatos priežiūros valdymo komiteto prie SAM įkūrimą (15). Viena iš šio komiteto paskirčių – koordinuoti naujas finansines RT paskatas: centralizuotą rtPA pirkimą bei retrospektyvų išlaidų kompensavimą už atliktas mechaninės trombektomijos procedūras. Be to, nuo jo įkūrimo komitetas renka ir stebi greitosios medicinos pagalbos (GMP) tarnybų ir insulto gydymo įstaigų pateiktus duomenis apie atliktų RT atvejų skaičių, insulto pacientų gydymo savalaikiškumą, išteklių panaudojimą, diagnostinių tyrimų atlikimą, reabilitaciją, stacionarines komplikacijas, hospitalinį mirštamumą nuo insulto ir kt. Siekiant nustatyti tobulintinas sritis, kas ketvirtį teikiamos ataskaitos SAM.

Svarbiausią vaidmenį nustatant ūminį insultą ikihospitaliniame etape atlieka GMP (16). Paramedikai yra pirmieji sveikatos apsaugos specialistai, susiduriantys su dauguma insulto pacientų (17, 18). Tiksliai atpažinti insultą ir laiku pacientą nuvežti į insulto gydymo centrą yra svarbu sėkmingai ūminio insulto priežiūrai (18, 19), nes delsimas skirti intraveninę trombolizę ir atlikti mechaninę trombektomiją gali turėti neigiamą poveikį pacientų gydymo rezultatams (20). Dėl to teisingai atpažintų ūminio insulto pacientų dalis ir pacientų transportavimo į ligoninę laikas yra vieni iš svarbiausių GMP veiklos rodiklių. Į insulto centrą GMP atvežtų insulto imitatorių procentas gali siekti iki 50 proc. (21, 22). Neteisingai surūšiavus insulto pacientus, švaistomi riboti sveikatos apsaugos sistemos ištekliai, skirti pacientams, kuriems būtina skubiai atlikti RT (23), be reikalo eikvojamas priėmimo skubiosios pagalbos skyriaus personalo laikas (24, 25). Deja, dėl demografinių pokyčių artimiausiais dešimtmečiais tikimasi, jog insulto imitatorių skaičius insulto priežiūros sistemose didės (26). Dėl to labai svarbu aktyviai gerinti ankstyvą insulto atpažinimą.

Stacionariniame etape taip pat naudojami tarptautiniu mastu pripažinti insulto priežiūros kokybės rodikliai (27). Jų nuolatinė stebesėna padeda geriausios klinikinės praktikos rekomendacijas įgyvendinti realioje klinikinėje praktikoje. Tarp rekomenduojamų stebėti stacionarinių insulto priežiūros kokybės rodiklių yra hospitalizacijos į specializuotus insulto skyrius dažnis, RT atvejų dalis, dalis insulto pacientų, kuriems išrašant skiriami geriamieji antikoaguliantai, laikas nuo atvykimo į ligoninę iki RT ir kt. (28–30). Naujausių insulto priežiūros gairių diegimas įprastinėje klinikinėje praktikoje yra sudėtingas procesas, todėl svarbu reguliariai vykdyti insulto centrų stebėseną (31). Lietuvoje insulto priežiūros veiklos stebėsenos vaidmuo priskirtas Insulto integruotos sveikatos priežiūros valdymo komitetui, kas ketvirtį analizuojančiam Lietuvos insulto centrų duomenis.

Išorės veiksniai, tokie kaip tarptautinio masto visuomenės sveikatos krizės ar pandemijos, taip pat gali turėti didelį poveikį insulto priežiūrai. Rašant šią daktaro disertaciją per sunkaus ūminio respiracinio sindromo koronoviruso 2 (SARS-CoV-2) protrūkį, sukėlusį koronaviruso ligos 2019 (COVID-19) pandemiją, pastebėtas mažėjantis į priėmimo skubiosios pagalbos skyrių atvežtųjų dėl įtariamo insulto pacientų skaičius. Kilo susirūpinimas dėl neoptimalaus ūminių ligų nustatymo ir siuntimo į ligoninę ikihospitaliniame etape (33–36). Pirmieji du visos šalies mastu skelbti karantino ribojimai buvo šios daktaro disertacijos objektas.

Netrukus po to, kai Lietuvoje buvo nustatytas pirmasis COVID-19 atvejis, 2020 m. kovo 16 d. paskelbtas griežtas visos šalies teritoriją apėmęs karantinas (37). Vis dėlto pirmosios COVID-19 pandemijos bangos metu šios ligos plitimas Lietuvos visuomenėje ir mirčių skaičius nuo COVID-19 išliko išskirtinai mažas (iki 2020 m. birželio 16 d. iš viso nustatyti 1 775 užsikrėtimo SARS-CoV-2 atvejai ir 76 mirtys nuo jo) (38). Tačiau griežti viešojo gyvenimo apribojimai ir sumažėjęs sveikatos priežiūros paslaugų, įskaitant pirminę sveikatos priežiūrą ir prevencines programas, prieinamumas (37), taip pat visuomenės baimė sirgti COVID-19, paveikė insulto priežiūrą.

Antrojo šalies mastu taikyto karantino metu, atvirkščiai, buvo diagnozuota ypač daug COVID-19 atvejų, iš kurių pasitaikė ir GSI sergančių pacientų. Nepaisant tūkstančių kasdien naujų patvirtintų COVID-19 atvejų ir poreikio perskirstyti sveikatos priežiūros sistemos išteklius, insulto pagalbos tarnybos per visą pandemijos laikotarpį visu pajėgumu veikė visuose didžiuosiuose insulto centruose. COVID-19 pacientams, sergantiems GSI, buvo taikoma ir intraveninė trombolizė rtPA bei mechaninė trombektomija. Vis dėlto duomenų apie RT saugumą ir gydymo atokiuosius rezultatus COVID-19 populiacijoje vis dar trūksta.

Ši disertacija grindžiama penkiais moksliniais straipsniais. Pagrindinis jos tikslas – ištirti insulto gydymo reorganizacijos, insulto charakteristikų ir išorinių veiksnių poveikį insulto priežiūros rodikliams. **I publikacijoje** analizuojama insulto gydymo reorganizacijos įtaka GSI pacientų RT dažniui ir savalaikiškumui Lietuvoje. **II straipsnyje** tiriamas GMP mokymų poveikis insulto atpažinimo tikslumui ir savalaikiam pacientų su įtariamu insultu transportavimui į ligoninę. **III publikacijoje** analizuojamas koreguotas insulto pacientų mirtingumas, funkcinė būklė ir su sveikata susijusi gyvenimo kokybė po 90 dienų, atsižvelgiant į tai, ar jiems buvo taikyta RT. **IV straipsnyje** vertinamas visoje šalyje paskelbto COVID-19 karantino ribojimų poveikis įtariamų insulto atvejų ir hospitalizacijų dėl insulto dažniui bei insulto imitatorių pasiskirstymui. Galiausiai **V publikacijoje** vertinamas insulto pacientų, sergančių COVID-19, mirtingumas po RT.

1.2. Tyrimo tikslas

Ūminio išeminio insulto gydymo reorganizacijos, insulto charakteristikų ir išorinių veiksnių poveikio reperfuzinio gydymo rodikliams analizė.

1.3. Tyrimo uždaviniai

1. Ištirti insulto gydymo reorganizacijos Lietuvoje įtaką GSI pacientų RT dažniui ir savalaikiškumui (**I**);

2. Ištirti GMP mokymų poveikį insulto atpažinimo tikslumui ir pacientų, kuriems įtariamas insultas, transportavimo į ligoninę trukmei (**II**);

3. Įvertinti koreguotą insulto pacientų mirtingumą po vienerių metų ir funkcinę būklę bei su sveikata susijusią gyvenimo kokybę po 3 mėnesių, atsižvelgiant į tai, ar jiems buvo taikyta RT (**III**);

4. Įvertinti visoje šalyje paskelbto COVID-19 karantino ribojimų poveikį įtariamų insulto atvejų ir hospitalizacijų dėl insulto dažniui bei insulto imitatorių pasiskirstymui (**IV**);

5. Įvertinti insulto pacientų, sergančių COVID-19, trijų mėnesių mirtingumą po RT (**V**).

1.4. Mokslinis naujumas

Šioje disertacijoje pirmą kartą nagrinėta, kaip insulto gydymo reorganizacijos priemonių paketas gali būti susijęs su RT proveržiu GSI sergantiems pacientams labai didelės širdies ir kraujagyslių ligų rizikos regione. Vadovaujantis Europos (19) ir Šiaurės Amerikos insulto gydymo rekomendacijomis (39), labai svarbu sistemingai vertinti konkrečių insulto mokymo intervencijų veiksmingumą ir palaikyti GMP mokymo tęstinumą. Šioje disertacijoje taip pat perspektyviai vertinamas GMP mokymų poveikis insulto priežiūros rodikliams. Trečia, disertacijoje pateikiami duomenys suteikia naujų žinių apie visos šalies mastu paskelbto karantino poveikį ikihospitalinei insulto priežiūrai mažo COVID-19 sergamumo aplinkoje. Tai svarbu planuojant sveikatos priežiūros strategijas ekstremalių visuomenės sveikatos situacijų metu. Galiausiai tai yra vienas iš nedaugelio nacionalinio masto tyrimų, kuriame tiriamos ilgalaikės COVID-19 sergančių GSI pacientų baigtys po RT.

1.5. Praktinė tyrimo vertė

Tyrimų, nagrinėjančių ūminio insulto priežiūros efektyvumą labai didelės širdies ir kraujagyslių ligų rizikos populiacijose, yra nedaug (40). Mūsų atlikta analizė leidžia daryti patikimas išvadas apie ūminio insulto priežiūros rezultatų tendencijas šalies mastu, nes ji apima visus Lietuvos ūminio išeminio GSI atvejus. Be to, norint pagerinti sveikatos priežiūros sistemų veiklos koordinavimą ekstremalių visuomenės sveikatos situacijų metu, svarbu suprasti visuotinio karantino priemonių poveikį kitų ligų, tokių kaip ūminis insultas, priežiūrai. Tyrimų, kuriuose būtų vertinama insulto priežiūra mažo COVID-19 sergamumo sąlygomis (41, 42), vis dar trūksta. Iki šiol nebūta tyrimų, kuriuose būtų nagrinėjamas poveikis ikihospitaliniam insulto pacientų atpažinimui. Didelė reprezentatyvi vieno akademinio IGC populiacija leidžia apibendrinti mūsų išvadas šalims su panašiomis sveikatos priežiūros sistemomis, ateityje priimant sprendimus dėl karantino ribojimo priemonių ekstremalių visuomenės sveikatos situacijų metu.

1.6. Ginamieji teiginiai

1. Nacionalinė insulto gydymo reorganizacija yra reikšmingai susijusi didesniu RT taikymo dažniu ir savalaikiškumu (**I**);

2. Interaktyvūs GMP mokymai reikšmingai pagerina insulto pacientų atpažinimo tikslumą ir pacientų transportavimo laiką (**II**);

3. Atsižvelgus į insulto charakteristikas, RT pagerina ūminio išeminio GSI pacientų funkcinę būklę ir su sveikata susijusią gyvenimo kokybę po 90 dienų, bet ne pacientų išgyvenamumą (**III**);

4. COVID-19 pandemijos karantino priemonės yra susijusios su mažesniu įtariamų ir hospitalizuotų insulto atvejų skaičiumi bei insultą imituojančių būklių pokyčiais (**IV**);

5. COVID-19 yra reikšmingai susijusi su prastesniu GSI pacientų 90 dienų išgyvenamumu po RT (**V**).

2. METODAI

2.1. Leidimas atlikti mokslinį darbą

Penki moksliniai darbai, kuriais remiantis buvo parengta ši disertacija, skyrėsi tyrimų metodologija. Dėl to buvo gauti keli skirtingi bioetikos leidimai. Visi tyrimai buvo atlikti remiantis Helsinkio deklaracijos nuostatomis. Pagrindinį leidimą moksliniam darbui išdavė Lietuvos bioetikos komitetas (Nr. L-22-08/1-9).

I tyrimui apibendrinti anoniminiai viešai prieinami duomenys apie visus GSI atvejus, kai pacientai buvo gydyti Lietuvos IGC ir TPL 2006–2019 m., buvo gauti retrospektyviai iš Higienos instituto ir Insulto integruotos sveikatos priežiūros valdymo komiteto, todėl atskiras etikos komiteto pritarimas nebuvo reikalingas.

II ir **IV tyrimams** papildomai pritarė Vilniaus regioninis biomedicininių tyrimų etikos komitetas (Nr. 1170), o **III** ir **V tyrimams** – Lietuvos bioetikos komitetas (atitinkamai Nr. L-14-03/1-6 ir L-21-06).

2.2. Insulto gydymas Lietuvoje

Lietuvoje ūminio insulto gydymo ligoninės pagal prieinamą reperfuzinį gydymą skirstomos į IGC, TPL ir kitas asmens sveikatos priežiūros įstaigas (ASPĮ). IGC ūminiu išeminiu insultu sergantiems pacientams visą parą yra prieinama intraveninė trombolizė ir mechaninė trombektomija, o TPL ligoninėse – tik intraveninė trombolizė.

Greitoji medicinos pagalba Lietuvoje teikiama nemokamai 24 valandas per parą 7 dienas per savaitę visiems, nepriklausomai nuo jų turimo sveikatos draudimo. GMP personalą sudaro licencijuotas medikas – slaugytojas, medicinos gydytojas arba paramedikas, sprendžiantis, ar pacientą, kuriam įtariamas insultas, reikia vežti į insulto centrą. Insultui ar praeinančiam išemijos priepuoliui įtarti visoje šalyje privalomai naudojama FAST (angl. *Face Arm Speech Time*) skalė (16). Ūminio GSI diagnostikos ir gydymo tvarkos apraše reikalaujama visais įtariamo insulto atvejais pacientus tiesiogiai transportuoti į IGC ar TPL, neatsižvelgiant į laiką nuo simptomų atsiradimo. Jeigu pacientas į gydytoją kreipiasi ambulatoriškai, šeimos gydytojas ar gydytojas specialistas, įtaręs insultą, taip pat gali siųsti pacientą į priėmimo skubiosios pagalbos skyrių.

Vilniaus universiteto ligoninė Santaros klinikos (VUL SK) yra viena iš dviejų Rytų Lietuvos IGC, kartu aptarnaujančių maždaug 945 000 gyventojų

(78). VUL SK pacientus siunčia viena Vilniaus GMP stotis ir septynios Vilniaus ir Utenos apskričių GMP tarnybos. 2020 m. visose GMP dirbo 331 specialistas (217 Vilniaus miesto ir 114 apskričių GMP), į VUL SK pervežta ≈20 400 pacientų (79).

2.3. Mokslinio darbo struktūra ir duomenų šaltiniai

Penkios publikacijos, kuriomis remiantis parengta ši disertacija, skyrėsi tyrimo pobūdžiu ir duomenų šaltiniais: **I tyrimas** buvo retrospektyvaus pertrauktų laiko intervalų (angl. *interrupted time series*) pobūdžio, **II darbas** – perspektyvaus pertrauktų laiko intervalų pobūdžio, **III** ir **IV darbai** buvo perspektyvūs stebėjimo tyrimai, o **V tyrimas** – retrospektyvus suderintų porų atvejo-kontrolės (angl. *pair-matched case-control*) tyrimas.

I tyrime buvo naudojami du duomenų šaltiniai. Visų pirma iš Higienos instituto buvo retrospektyviai gauti anoniminiai apibendrinti duomenys apie visus 2006–2019 m. Lietuvos ligoninėse gydytus ūminio išeminio GSI atvejus. Higienos institutas – institucija, tvarkanti visuomenės sveikatos registrus ir atsakinga už Lietuvos gyventojų sveikatos, sveikatos priežiūros veiklos ir išteklių stebėseną (80). Duomenų rinkinį sudarė bendras GSI atvejų skaičius (atitinka Tarptautinės statistinės ligų ir sveikatos sutrikimų klasifikacijos dešimtosios redakcijos Australijos modifikacijos kodą I63), GSI atvejų, gydytų Lietuvos IGC, TPL ir kitose ASPĮ, skaičius, pacientų lytis, amžiaus grupė, gyvenamoji vieta, lovadienis ir mirtingumas ligoninėje. Visą statistinio tyrimo metodikos aprašymą, kaip buvo gautas duomenų rinkinys, kaip buvo užtikrintas jo išsamumas ir pacientų anonimiškumas, galima rasti Higienos instituto tinklalapyje (81).

Antra, duomenys apie atliktų RT procedūrų skaičių buvo gauti iš Insulto integruotos sveikatos priežiūros valdymo komiteto. Nuo 2014 m. kas ketvirtį visi Lietuvos IGC ir TPL jam privalo teikti apibendrintus nuasmenintus duomenis apie kai kuriuos insulto priežiūros veiklos rodiklius, atitinkančius ligoninių informacinių sistemų informaciją. Šie rodikliai apima ligoninėje atliktų RT procedūrų (intraveninės trombolizės ir mechaninės trombektomijos) skaičių ir jų vidutinį laiką nuo paciento atvykimo į ligoninę iki intraveninės trombolizės pradžios (angl. *door-to-needle time*).

II ir **IV straipsnių** duomenys buvo gauti iš VUL SK insulto stebėsenos sistemos. Surinkti duomenys buvo lyginami dviejų laikotarpių: prieš interaktyvius GMP mokymus ir po jų **II publikacijoje** bei prieš pirmojo COVID-19 karantino ribojimus ir jų metu **IV publikacijoje**.

III publikacijoje, siekiant atsižvelgti į sezoninius skirtumus, perspektyvus stebėjimo tyrimas buvo atliekamas keturis pilnus ne iš eilės esančius mėnesius. Į tyrimą buvo įtraukti visi GSI sergantys pacientai, gydyti VUL SK. GSI sergantys pacientai arba jų globėjai, galintys dalyvauti stebėjimo tyrime, buvo telefonu apklausti praėjus 90 dienų nuo insulto pradžios, naudojant modifikuotą Rankino skalę (mRS). Be to, su sveikata susijusiai gyvenimo kokybei įvertinti naudota EuroQoL penkių dimensijų trijų lygių aprašomoji sistema (EQ-5D-3L) su savarankiškai vertinama vizualia analogine skale (EQ-VAS). Informacija apie pacientų mirtingumą, įskaitant mirties datą, buvo gauta retrospektyviai iš elektroninių sveikatos įrašų praėjus vieneriems metams nuo insulto pradžios (84).

Galiausiai duomenys **V tyrimui** buvo surinkti retrospektyviai iš IGC elektroninių sveikatos įrašų.

2.4. Tiriamųjų populiacija

I straipsnio tiriamoji populiacija apėmė visus GSI atvejus, gydytus Lietuvos ligoninėse 2006–2019 m., priklausomai nuo jų gydymo vietos (IGC, TPL ar kitos ASPĮ).

II ir **IV tyrimams** duomenys rinkti apie į VUL SK siųstus pacientus, kuriems buvo įtariamas GSI ar praeinantis smegenų išemijos priepuolis, bei apie klaidingai neigiamai diagnozuotus insulto atvejus.

Į **III tyrimą** buvo įtraukti visi GSI sergantys pacientai, gydyti VUL SK keturis pilnus ne iš eilės esančius mėnesius.

Į **V tyrimą** buvo įtraukti GSI pacientai, kuriems prieš patekant į kurį nors iš 6 IGC arba priėmimo skubiosios pagalbos skyriuje buvo diagnozuota ūminė COVID-19 infekcija ir kurie buvo gydomi RT (intravenine trombolize, mechanine trombektomija arba abiem gydymo metodais). COVID-19 statusas buvo patvirtintas SARS-CoV-2 realaus laiko polimerazės grandinine reakcija (RT-PGR) iš nosiaryklės tepinėlio. Pacientai, kurie įvykusio insulto metu pagal epidemiologinius kriterijus jau buvo pasveikę nuo COVID-19, į analizę įtraukti nebuvo, nepaisant teigiamo SARS-CoV2 RT-PGR tyrimo rezultato. Kiekvienam tiriamosios grupės pacientui buvo atrinktas COVID-19 infekcija nesergantis kontrolinės grupės pacientas. Visi kontrolinės grupės pacientai tiriamuoju laikotarpiu buvo gydomi viename iš 6 Lietuvos IGC. Kontrolinės grupės pacientai buvo suderinti su tiriamosios grupės pacientais pagal amžių (±5 metai), lytį, insulto arterinės kraujotakos teritoriją ir RT tipą. Siekiant išvengti atrankos šališkumo, atvejus kontrolinei grupei atrinko nepriklausomi insulto gydytojai, nedalyvavę šiame tyrime ir informuoti tik apie įtraukimo į tyrimą kriterijus.

2.5. Intervencijos

Trijuose disertacijos tyrimuose buvo nagrinėjama įvairių intervencijų įtaka insulto baigtims. **I straipsnyje** buvo nagrinėjamas insulto gydymo reorganizacijos, **II straipsnyje** – interaktyvių GMP mokymų, o **IV straipsnyje** – visuotinio karantino ribojimų, susijusių su nedideliu COVID-19 atvejų skaičiumi, poveikis.

2.6. Tiriamosios baigtys

I tyrime buvo vertinamas 2014 m. Lietuvoje vykusios insulto gydymo reorganizacijos poveikis šešioms su insultu susijusioms baigtims. Šioje disertacijoje nagrinėjami rodikliai apėmė pacientų, kuriems taikytas gydymas intravenine trombolize ir mechanine trombektomija, tiesės krypties koeficiento pokytį prieš intervenciją ir po jos bei laiko nuo atvykimo iki intraveninės trombolizės atlikimo tendenciją po intervencijos.

II tyrime buvo vertinamas interaktyvių GMP mokymų poveikis septynioms skirtingoms su insultu susijusioms baigtims. Šiai daktaro disertacijai svarbios baigtys apėmė teisingo insulto pacientų identifikavimo ir pacientų, nuo insulto pradžios į priėmimo skubiosios pagalbos skyrių transportuotų per 90 minučių, dalį.

Pagrindiniai **III tyrimo** vertinamieji rezultatai buvo GSI pacientų vienerių metų mirtingumas, geros 90 dienų funkcinės baigtys (mRS ≤ 2) ir gera su sveikata susijusi gyvenimo kokybė po 90 dienų pagal EQ-5D-3L.

IV tyrimo vertinamieji rezultatai buvo pacientų, kuriems įtariamas insultas, ir hospitalizacijų dėl insulto atvejų dažnis bei insulto imitatorių pasiskirstymo pokyčiai prieš ir per visoje šalyje paskelbtus COVID-19 karantino ribojimus.

Klinikinių ir laboratorinių veiksnių poveikiui 3 mėnesių mirtingumui po insulto ir RT ištirti **V tyrime** buvo sudaryti daugialypės logistinės regresijos modeliai.

2.7. Statistinė analizė

I tyrime naudotas retrospektyvus pertrauktų laiko intervalų metodas, juo vertintos metinės rodiklių tendencijos prieš ir po to, kai 2014 m. Lietuvoje buvo inicijuota insulto diagnostikos ir gydymo reorganizacija (85, 86). Analizė atlikta taikant šią regresijos lygtį: $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 P_t + \varepsilon_t$, čia Y_t – agreguota baigtis t laiku (metais), T_t – laikas (metais) nuo tiriamojo laikotarpio pradžios, X_t – fiktyvus kintamasis, nusakantis laikotarpį po insulto gydymo reorganizacijos, P_t – tęstinis kintamasis, nurodantis laiką (metais) nuo intervencijos (prieš intervenciją P_t yra lygus 0), β_0 – interceptas, β_1 – tiesės krypties koeficientas iki intervencijos, β_2 – tiesės krypties koeficiento pokytis iš karto po intervencijos, β_3 – skirtumas tarp tiesių krypčių koeficientų prieš ir po intervencijos. Apskaičiuotos standartinės paklaidos.

II tyrime prieš GMP mokymus buvusios mėnesinės GMP ir ligoninės veiklos rodiklių tendencijos įvertintos taikant vienalypę tiesinę regresiją ir χ^2 testą tendencijai nustatyti. Paskui sukurti daugialypės logistinės regresijos modeliai, skirti GMP mokymų ir mėnesinių GMP veiklos ir ligoninės rodiklių pokyčių ryšiui įvertinti. Siekiant atsižvelgti į galimą amžiaus, lyties, GMP lokalizacijos (miesto ar apskrities GMP tarnyba) ir insulto potipio šalutinį poveikį (angl. *confounding*), naudota hibridinė grįžtamoji ir priekinė žingsninė atranka pagal Akaike informacijos kriterijų (87), pašalinant kintamuosius, kurių ryšys buvo nereikšmingas (P > 0,05). Amžius buvo priverstinai įtrauktas į visus modelius kaip *a priori* šalutinis veiksnys.

Siekiant nustatyti kiekvieno kintamojo prognostinę reikšmę pacientų išgyvenamumui, **III tyrime** buvo atliktos vienalypė ir daugialypė Kokso regresijos analizės išgyvenamumo duomenims. Hospitalizavimo dėl insulto data buvo traktuojama kaip pradinis laikas išgyvenamumo analizei. Tirti šie kintamieji: prieširdžių virpėjimas, amžius, lytis, RT taikymas, gera pradinė funkcinė būklė (mRS ≤2) ir pradinis Nacionalinio sveikatos instituto insulto skalės (NIHSS) įvertis balais. Kintamieji, kurie vienalypės analizės metu pasirodė esantys reikšmingi (P < 0,1), buvo įtraukti į daugialypį modelį. Rizikos santykis buvo pateiktas su 95 proc. pasikliautinaisiais intervalais (95 proc. PI). Be to, buvo atlikta tiek nekoreguota, tiek koreguota logistinės regresijos analizė, kai priklausomu kintamuoju laikyta gera funkcinė baigtis (mRS ≤2). Koreguota logistinės regresijos analizė buvo atlikta taikant žingsninę tiesioginę atranką, remiantis reikšmingais kintamaisiais koreguotuose modeliuose. Galiausiai daugialypė tiesinė regresija taikyta įvertinti nepriklausomų kintamųjų (amžiaus, lyties, prieširdžių virpėjimo, RT, geros pradinės funkcinės būklės ir pradinio NIHSS balo) bei su sveikata susijusios gyvenimo kokybės, išreikštos EQ-VAS ir EQ-5D-3L indeksų balais, sąsajas.

IV tyrime asmenys buvo suskirstyti į grupes pagal kreipimosi tipą (GMP ar gydytojo siuntimas) ir laikotarpius (prieš karantino ribojimus ar jų metu). Iš pradžių įvertinome insulto atvejų dažnį skirtingais laikotarpiais ir skirtingiems siuntimo į priėmimo skubiosios pagalbos skyrių būdams. Tada naudojome Puasono regresijos modelius, kuriuose kaip priklausomi kintamieji buvo nurodyti kasdieniai įtariamų insultų ir hospitalizacijų dėl insulto skaičiai, o kaip nepriklausomas kintamasis – tyrimo laikotarpis. Antra, įvertinome insulto imitatorių pasiskirstymą tarp skirtingų sveikatos priežiūros paslaugų teikėjų ir laikotarpių.

V tyrime reikšmingi vienalypės analizės prognostiniai faktoriai ($P < 0{,}1$) buvo įtraukti į daugialypės logistinės regresijos modelį, siekiant nustatyti įtaką 90 dienų mirtingumui po insulto. Apskaičiuotas šansų santykis (ŠS) ir 95 proc. PI.

3. REZULTATAI

3.1. I – Insulto gydymo reorganizacija

Iš viso Lietuvos ligoninėse iki insulto gydymo pertvarkos buvo gydyti 114 436, o po jos – 65 084 pacientai, kuriems buvo diagnozuotas ūminis išeminis GSI. Ūminio išeminio GSI pacientų, gydytų intravenine trombolize rtPA, dalis visų GSI atvejų padidėjo nuo 1,5 proc. (arba 197 atvejų) 2013 m. iki 12,6 proc. (arba 1 219 atvejų) 2019 m. – tai šešiskart absoliutus ir aštuoniskart santykinis padidėjimas. Panašiai padidėjo ir atliktų mechaninių trombektomijų skaičius – nuo 10 atvejų, arba 0,1 proc., visų GSI 2013 m. iki 518 atvejų, arba 5,4 proc., visų GSI 2019 m. Iš karto po insulto gydymo pertvarkos statistiškai reikšmingai padidėjo tik pacientų, kuriems buvo taikyta intraveninė trombolizė, dalis (β_2 = 1,32±0,38, P = 0,006), o reikšmingas tendencijos pokytis ilgalaikiu laikotarpiu po insulto gydymo pertvarkos buvo tiek pacientų, kuriems taikyta intraveninė trombolizė (β_3 = 1,42±0,96, P < 0,001), tiek tų, kuriems taikyta mechaninė trombektomija (β_3 = 0,85±0,05, P < 0,001).

Be to, nuo 2014 m., kai buvo pradėtas registruoti vidutinis laikas nuo insulto pacientų atvykimo į Lietuvos IGC ir TPL iki intraveninės trombolizės pradžios, matoma statistiškai reikšminga jo mažėjimo tendencija (β_1 = –5,28± 0,002, P < 0,001) – vidutiniškai beveik 5 min. per metus nuo 68 min. 2014 m. iki 43 min. 2019 m.

3.2. II – Interaktyvūs greitosios medicinos pagalbos personalo mokymai

Iš viso tyrimo laikotarpiu į VUL SK Priėmimo skubiosios pagalbos skyrių buvo atvežti 677 pacientai, kuriems įtartas insultas (73,9 proc.). Iš jų 509 pacientų diagnozė pasitvirtino (55,6 proc.), o 168 atvejais buvo klaidinga (18,3 proc.). GMP personalas neatpažino 239 (26,1 proc.) insulto atvejų, vadinamų insulto chameleonais. Tiriamosios grupės prieš ir po mokymų nesiskyrė pagal demografinius duomenis, insulto potipį ir pradinį NIHSS balą. Vilniaus miesto GMP stotis į Priėmimo skubiosios pagalbos skyrių pervežė 500 pacientų (54,6 proc.), o rajono ir apskričių GMP – 416 (45,4 proc.).

Per šešis mėnesius iki GMP mokymų nenustatėme jokių reikšmingų GMP veiklos ar ikistacionarinės priežiūros rodiklių tendencijų. Teigiama prognostinė reikšmė (TPR, angl. *positive predictive value*) teisingai nustatant ūminiu insultu sergančius pacientus buvo reikšmingai didesnė laikotarpiu po mokymų (79,8 proc. [75,1–84,4], palyginti su 71,8 proc.

[67,3–76,3], *P* = 0,017). Daugialypė logistinė regresija parodė geresnį TPR ŠS, kuris išliko reikšmingas ir atsižvelgus į amžių, lytį ir GMP lokalizaciją (koreguotas ŠS 1,6 [1,1–2,4]). Be to, nustatyti padidėję paciento atvykimo į ligoninę per 90 min. nuo insulto pradžios šansai (koreguotas ŠS 1,6 [1,1–2,5]), kuriuos lėmė pagerėję Vilniaus miesto GMP stoties rezultatai (41,1 proc. [33,5–49,0], palyginti su 56,8 proc. [46,4–66,7] po mokymų, *P* = 0,019).

Reikšmingo pradinio TPR skirtumo tarp miesto ir apskričių GMP nebuvo. Tačiau po mokymų TPR pagerėjo miesto GMP grupėje (84,9 proc. [78,9–90,8] po ir 71,2 proc. [65,1–77,2] prieš GMP mokymus, *P* = 0,003), bet ne apskričių GMP (75,0 proc. [68,0–82,0] po ir 72,6 proc. [66,0–79,2] prieš GMP mokymus, *P* = 0,621).

Trumpesnė laiko nuo insulto pradžios iki atvykimo į ligoninę mediana buvo rasta tarp miesto GMP siųstų pacientų 93 [67–159] min. palyginti su 137 [89–269] min. apskričių GMP, *P* < 0,001). Taip pat didesnė dalis miesto GMP atvežtų pacientų, palyginti su apskričių GMP, pasiekė IGC per 90 min. (46,9 proc. [40,6–53,2] ir 25,3 proc. [19,7–31,8] atitinkamai, *P* < 0,001). Po mokymų pastebėta silpna absoliutaus laiko nuo insulto pradžios iki atvykimo į ligoninę pagerėjimo tendencija (84,5 min., palyginti su 108,0 min., *P* = 0,074) ir reikšmingai pagerėjęs atvykimo į ligoninę per 90 min. nuo insulto pradžios rodiklis miesto GMP (70,5 proc. [60,2–79,0], palyginti su 41,1 proc. [33,5–49,0], *P* = 0,019), bet ne apskrities GMP grupėje (28,0 proc. [19,9–37,8], palyginti su 22,8 proc. [15,7–31,9], *P* = 0,406).

3.3. III – Ilgalaikiai reperfuzinės terapijos rezultatai

Iš viso mūsų tyrime dalyvavo 238 ūminio išeminio GSI pacientai, kurių vidutinis amžius buvo 71,4±11,9 metų ir iš kurių 45,0 proc. sudarė moterys. Atlikus vienalypę Kokso regresijos analizę išgyvenamumo duomenims, nustatyta, kad amžius (*P* < 0,001), žinomas prieširdžių virpėjimas (*P* < 0,001), pradinė gera funkcinė būklė (*P* < 0,001) ir pradinis NIHSS balas (*P* < 0,001) turėjo reikšmingą įtaką pacientų, patyrusių insultą, išgyvenamumui. Tačiau daugialypiame modelyje reikšmingą įtaką pacientų išgyvenamumui turėjo tik amžius (*P* = 0,007) ir pradinis NIHSS balas (*P* < 0,001).

Iš viso 133 iš 186 išgyvenusių pacientų ar pacientą prižiūrinčių asmenų po 90 dienų užpildė mRS klausimyną: 58,6 proc. respondentų buvo laikomi savarankiškais kasdienėje veikloje (mRS balas ≤2). Daugialypės dvinarės logistinės regresijos analizės metu RT (ŠS 3,91 [95 proc. PI 1,66–10,05], *P* = 0,003) ir pradinis NIHSS balas (ŠS 0,82 [95 proc. PI 0,73–0,90], *P* < 0,001) buvo vieninteliai du veiksniai, statistiškai reikšmingai lėmę gerą funkcinę baigtį (mRS ≤2).

Iš viso 126 pacientai arba pacientų globėjai užpildė EQ-5D-3L klausimyną, o 111 GSI pacientų įvertino savo EQ-VAS balą praėjus 90 dienų insulto. Daugialypė tiesinė regresinė analizė parodė, kad RT turėjo reikšmingą įtaką tiek EQ-VAS (β±SE: 9,571±4,583, P = 0,039), tiek EQ-5D-3L indeksui (β±SE: 0,137±0,058, P = 0,021), atsižvelgus į amžių, lytį, žinomą prieširdžių virpėjimą, pradinę gerą funkcinę būklę ir pradinį NIHSS balą.

3.4. IV – Mažo COVID-19 sergamumo karantino ribojimai

Iš viso į analizę įtraukta 719 pacientų, kuriems buvo įtartas insultas: 493 pacientai nukreipti GMP, o 226 į priėmimo skubiosios pagalvos skyrių atvyko su gydytojo siuntimu. Nė vienam pacientui nebuvo diagnozuotas COVID-19.

Nustatyta, kad karantino ribojimų metu sumažėjo per dieną įtartų insultų skaičiaus (3 [1–4], palyginti su 4 [3–6], P < 0,001) ir patvirtintų insultų skaičiaus (2 [1–2], palyginti su 3 [2–4], P < 0,001) medianos. Karantino ribojimų metu ambulatorinių gydytojų siuntimų dėl insulto sumažėjo tris kartus. Vis dėlto priėmimo skubiosios pagalbos skyriuje patvirtintų insultų prieš karantiną ir karantino laikotarpiu dalis reikšmingai nesiskyrė (24,6 proc., palyginti su 24,2 proc., P = 0,807).

Puasono regresijos modelis atskleidė, kad karantino laikotarpis buvo susijęs su kasdienių įtartų insulto atvejų skaičiaus mažėjimu: santykinė rizika (angl. *rate ratio*) 0,61 (95 proc. PI 0,52–0,71, P < 0,001), o hospitalizacijų dėl insulto – 0,63 (95 proc. PI 0,52–0,76, P < 0,001).

Traukuliai ir infekcija / sepsis buvo reikšmingai dažnesni insulto imitatoriai tarp pacientų, kuriuos atvežė GMP, palyginti su į priėmimo skubiosios pagalbos skyrių atvežtų pacientų su gydytojų siuntimu (16,5 proc., palyginti su 4,5 proc., ir 13,9 proc., palyginti su 4,5 proc., atitinkamai P = 0,002 ir P = 0,010), o periferinės vestibulopatijos nustatytos statistiškai reikšmingai rečiau (0,9 proc., palyginti su 18,0 proc., P < 0,001). Lyginant tiriamuosius laikotarpius, izoliuoti neurologiniai simptomai, susiję su normaliais neurologinio tyrimo rezultatais, buvo retesni insulto imitatoriai karantino metu (2,4 proc., palyginti su 11,6 proc., P = 0,015), o traukuliai ir intrakranijiniai navikai buvo reikšmingai dažnesni (16,9 proc., palyginti su 6,7 proc., bei 9,6 proc., palyginti su 3,0 proc., atitinkamai P = 0,012 ir P = 0,037).

3.5. V – COVID-19 sergančių insulto pacientų reperfuzinis gydymas

Į **V tyrimą** buvo įtraukta 31 tiriamųjų ir kontrolinių GSI pacientų pora. COVID-19 teigiamą rezultatą turintys GSI pacientai vidutiniškai buvo 74,0 metų, o kontroliniai pacientai 73,7 metų amžiaus. Kohortoje buvo 40 moterų

(64,5 proc.). Insulto rizikos veiksnių paplitimas tarp abiejų grupių statistiškai reikšmingai nesiskyrė. Keturiolikai (22,5 proc.) pacientų buvo atlikta intraveninė trombolizė, 30 (48,4 proc.) pacientų taikyta mechaninė trombektomija, o 18 (29,1 proc.) pacientų taikytas kombinuotas gydymas. Penkiasdešimt šešiems (90,3 proc.) pacientams buvo diagnozuotas priekinės kraujotakos insultas.

Devyniasdešimties dienų mirtingumas buvo reikšmingai didesnis COVID-19 grupėje, palyginti su kontroline grupe (54,8 proc., palyginti su 12,9 proc., $P = 0{,}001$). Trijų mėnesių mirtingumui statistiškai reikšmingą įtaką turėję kintamieji buvo amžius ($P = 0{,}022$), hipoksemija ($P = 0{,}079$), pradinis NIHSS balas ($P = 0{,}001$), COVID-19 infekcija ($P = 0{,}001$), bendras leukocitų skaičius bendrame kraujo tyrime ($P = 0{,}079$) ir C reaktyviojo baltymo (CRB) koncentracija ($P = 0{,}093$). Vyresnis amžius ir didesnis pradinis NIHSS buvo susiję su didesniais trijų mėnesių mirtingumo šansais po insulto ir RT. COVID-19 infekcija mirties tikimybę praėjus trims mėnesiams po insulto ir RT padidino septynis kartus (ŠS 6,70; 95 proc. PI 1,03–43,58).

4. DISKUSIJA

Šioje daktaro disertacijoje pirmą kartą analizuota visa Lietuvos ūminio išeminio GSI pacientų populiacija ir įvertintas insulto gydymo reorganizacijos, insulto charakteristikų ir išorinių veiksnių poveikis daugeliui insulto priežiūros rodiklių. Nustatyta reikšminga RT rodiklių gerėjimo tendencija ir vidutinio laiko nuo atvykimo į ligoninę iki intraveninės trombolizės atlikimo mažėjimo tendencija Lietuvos IGC ir TPL nuo 2014 m., kai buvo atliktas insulto gydymo reorganizacija (**I publikacija**). Antra, nustatyta, kad interaktyvūs GMP mokymai reikšmingai pagerina pacientų, patyrusių GSI, atpažinimo tikslumą ir mažina jų transportavimo iki ligoninės laiką (**II publikacija**). Trečia, mūsų duomenys parodė, kad RT pagerina ūminio išeminio GSI pacientų 90 dienų funkcinius rezultatus ir su sveikata susijusią gyvenimo kokybę, bet ne pacientų išgyvenamumą, koreguojant pagal skirtingas insulto charakteristikas (**III publikacija**). Taip pat nustatyta, kad COVID-19 karantino ribojimai yra susiję su sumažėjusiu įtariamų insulto atvejų ir hospitalizacijų dėl insulto skaičiumi bei su insultą imituojančių būklių pokyčiais (**IV publikacija**). Galiausiai mūsų duomenys rodo, kad COVID-19 yra reikšmingas prastesnio ūminio išeminio GSI pacientų 90 dienų išgyvenamumo po RT prognostinis veiksnys (**V publikacija**).

Toliau rezultatai aptariami ir palyginami su ankstesne literatūra, atsižvelgiant į atitinkamą publikaciją.

4.1. I – Insulto gydymo reorganizacija

Daugybė ankstesnių tyrimų parodė, kad skirtingose šalyse įvairiais laikotarpiais nuolat didėjo dalis ūminio išeminio GSI pacientų, kuriems taikyta intraveninė trombolizė (88–106) ir mechaninė trombektomija (106–108). Vis dėlto mūsų duomenys rodo, kad Lietuvoje intraveninės trombolizės atvejų skaičiaus ir dažnio proveržis šalies mastu įvyko tik po insulto gydymo reorganizacijos. Analogiškai bendras mechaninės trombektomijos atvejų skaičius iki nacionalinės politikos pokyčių buvo vienženklis, o po 2014 m. staigiai išaugo. Kita vertus, tam galėjo turėti įtakos ir kai kurie šalutiniai veiksniai, pavyzdžiui, 2015 m. publikuoti teigiami mechaninės trombektomijos tyrimų rezultatai, padidinę gydytojų pasitikėjimą mechaninės trombektomijos saugumu ir veiksmingumu (107). Vis dėlto, mūsų manymu, retrospektyvus RT išlaidų kompensavimas pagal faktą ir kvotų hospitalizacijoms dėl insulto panaikinimas galėjo būti didesnė paskata RT plėtrai šalyje. Nors nėra aiškių intraveninės trombolizės ir mechaninės trombektomijos dalies nuo visų ūminių išeminių GSI etalonų (2019 m. Lietuvoje šie rodikliai buvo atitinkamai 12,6 proc. ir 5,4 proc.) (10), potencialas šalies rodikliams gerėti išlieka. Juolab kad pacientų, kuriems taikyta intraveninė trombolizė nacionaliniu mastu, Čekijoje buvo 23,5 proc., o analogiškas mechaninė trombektomijos rodiklis Maltoje buvo 5,6 proc. (57, 105).

Tarptautinėse gairėse rekomenduojama kurti insulto priežiūros sistemas taip, kad pacientai, kuriems galima taikyti RT, būtų gydomi per trumpiausią įmanomą laiką nuo insulto pradžios (109). Mūsų tyrimo metu nustatyta statistiškai reikšminga vidutinio laiko nuo atvykimo į priėmimo skubiosios pagalbos skyrių iki intraveninės trombolizės taikymo mažėjimo tendencija Lietuvos ligoninėse – nuo 68 min. 2014 m. iki 43 min. 2019 m. Tikėtina, kad didesnės gydymo apimtys gali lemti trumpesnį laiką iki RT – tai gydytojo patirtį ir pasitikėjimą atspindintis rodiklis (100, 110, 111). Be to, ketvirtinės Insulto integruotos sveikatos priežiūros valdymo komiteto ataskaitos ir metinė IGC ir TPL pažangos stebėsena galėjo sukurti papildomą paskatą (112). Vis dėlto naujausi Čekijos duomenys rodo, kad ir nacionalinė laiko nuo susirgimo iki intraveninės trombolizės mediana <25 min. yra įmanoma (105).

I straipsnio retrospektyvus pertrauktų laiko intervalų pobūdis yra kvazieksperimentinis, naudojamas vienos intervencijos poveikiui įvertinti, todėl įmanoma, kad ir neišmatuoti šalutiniai veiksniai (tokie kaip mažėjantis širdies ir kraujagyslių ligų rizikos veiksnių paplitimas) galėjo turėti įtakos rezultatams. Dar vienas tyrimo trūkumas yra tas, kad šiame straipsnyje netyrėme COVID-19 pandemijos įtakos insulto priežiūros rezultatams, nes sąmoningai pasirinkome analizuoti laikotarpį iki pandemijos. Trečia, 2015 m. publikuoti teigiami mechaninės trombektomijos tyrimų rezultatai galėjo turėti įtakos padidėjusiam trombektomijų skaičiui visoje šalyje, didėjant gydytojų neurologų pasitikėjimui mechaninės trombektomijos saugumu ir veiksmingumu (107). Ketvirta, funkcinių ir ilgalaikių rezultatų po išrašymo iš ligoninės nebuvo galima įvertinti dėl ribotos galimybės gauti tokius duomenis iš valstybės institucijų. Penkta, mūsų analizė pagrįsta hospitalizuotų ūminio išeminio GSI pacientų skaičiumi, o ne bendru ūminio išeminio GSI sergamumu. Vis dėlto tikrasis šių rodiklių skirtumas yra nedidelis, nes pagal Lietuvoje taikomą insulto gydymo ir profilaktikos metodiką kiekvienam insultu sergančiam pacientui rekomenduojamas stacionarinis gydymas (112).

I straipsnio stiprybė yra tai, kad analizė apima visus Lietuvos ūminio išeminio GSI atvejus, o tai leidžia išsiaiškinti realias bendras šalies ūminio insulto gydymo rezultatų tendencijas. Be to, tai yra pirmasis tyrimas iš labai didelio širdies ir kraujagyslių ligų rizikos faktorių paplitimo regiono (40), parodantis, kad visapusiškas nacionalinės insulto priežiūros politikos pokyčių paketas gali būti susijęs su geresniais svarbiausių insulto priežiūros rodiklių rezultatais.

4.2. II – Interaktyvūs greitosios medicinos pagalbos personalo mokymai

II tyrimo metu nustatyta, kad geresnis ikihospitalinis insulto atpažinimas išliko mažiausiai keturis mėnesius po interaktyvių GMP mokymų. Antra, po mokymų pagerėjo įtariamo insulto pacientų savalaikis transportavimas į ligoninę. Trečia, mokymų poveikis buvo ryškesnis miesto GMP grupėje.

Po mokymų nustatyta mažiau insulto imitatorių, tačiau neatpažintų insultų dalis nepadidėjo. Taigi TPR padidėjimas neatėmė iš dalies ūminio išeminio GSI pacientų savalaikio RT gydymo galimybės. Viena iš priežasčių, kodėl labai pagerėjo TPR miesto, bet ne rajono ir apskričių GMP grupėje, galėjo būti nuo 2020 m. sausio 1 d. įsigaliojusi nauja Lietuvos Respublikos sveikatos apsaugos ministro įsakymo dėl insulto priežiūros paslaugų teikimo tvarkos aprašo redakcija, kurios įsigaliojimas iš dalies sutapo su tiriamuoju laikotarpiu po GMP mokymų. Pagal naująjį teisės aktą įtariami insulto pacientai turi būti transportuojami tiesiai į kurį nors iš Lietuvos IGC arba TPL, aplenkiant kitas ASPĮ, nepriklausomai nuo laiko, kada pacientas paskutinį kartą buvo matytas sveikas. Šie insulto pacientų transportavimo tvarkos pokyčiai galėjo padidinti insulto imitatorių skaičius rajonų GMP grupėje, nes GMP daugiau pacientų su įtariamu insultu vežė tiesiai į IGC ir TPL, bet ne į kitas ASPĮ. Taigi, silpna TPR pagerėjimo tendencija apskričių GMP grupėje atspindi GMP mokymų poveikį, kompensuojantį tikėtiną TPR sumažėjimą rajono GMP grupėje. Kitas galimas paaiškinimas galėtų būti skirtingos miesto ir rajono paramedikų žinios apie insultą prieš mokymus arba kiti šalutiniai veiksniai, tokie kaip socioekonominės pacientų padėties skirtumai, gretutinės ligos ar kiti kintamieji, nevertinti šiame tyrime.

TPR padidėjimas po mokymų yra kliniškai svarbus, nes rodo, kad GMP mokymai gali padėti reikšmingai sumažinti klaidingai teigiamų insulto atvejų skaičių, be reikalo apkraunančių ūminio insulto priežiūros sistemą. Optimaliai panaudoti ikihospitalinės insulto pagalbos ir radiologinių tyrimų išteklius ypač svarbu didžiausio sergamumo insultu valandomis, pavyzdžiui, rytais (104), arba esant ekstremalioms visuomenės sveikatos situacijoms, tokioms kaip COVID-19 pandemija. Todėl svarbu nuolatos stengtis užtikrinti tikslų insulto identifikavimą ikihospitaliniu periodu.

Iš ankstesnių tyrimų žinoma, kad trumpi GMP mokymai gali pagerinti paramedikų žinias apie insulto atpažinimo skales, ligoninės prenotifikacijos svarbą ir pacientų rūšiavimą (48, 105). Be to, Oostema ir kt. atliktame perspektyviame tyrime buvo įvertintas realus GMP mokymų poveikis ikihospitaliniam insulto atpažinimui ir nustatyta, kad internetinis GMP mokymų modulis kartu su grįžtamuoju ryšiu apie rezultatus buvo susijęs su geresniu insulto atpažinimo jautrumu, dažnesne ligoninės prenotifikacija ir greitesniu intraveninės trombolizės atlikimu (47). Mūsų tyrimas papildo šiuos literatūros duomenis, kad GMP mokymai gali pagerinti ikihospitalinį insulto atpažinimą ir savalaikį transportavimą į priėmimo skubiosios pagalbos skyrių. Taip pat pažymime, kad galimai dėl palyginti aukšto pradinio pacientų atpažinimo po mokymų šis rodiklis reikšmingai nepasikeitė. Insulto atpažinimo jautrumas iki mokymų (68,0 proc.) mūsų tyrime buvo panašus į Oostema ir kt. tyrimo jautrumą po mokymų (69,5 proc.), o tai rodo galimą insulto jautrumo pagerėjimo lubų efektą. Vis dėlto, nepaisant TPR pagerėjimo, nepadidėjo klaidingai neigiamų pacientų dalis, todėl pacientams, patyrusiems insultą, nebuvo atimta galimybė laiku gauti reikalingą gydymą.

Neseniai Jungtinėje Karalystėje atlikto daugiacentrio atsitiktinių imčių klinikinio tyrimo PASTA (angl. *Paramedic Acute Stroke Treatment Assessment*) metu buvo bandoma pagerinti ikihospitalinę insulto priežiūrą. Stebina tai, kad po šios edukacinės intervencijos laikas, paramedikų praleistas insulto įvykio vietoje, pailgėjo 8,5 minutės, o intraveninės trombolizės atlikimo dažnio rodiklis reikšmingai nepasikeitė (54). Tikėtina, kad sudėtingi ikihospitalinio pacientų rūšiavimo protokolai nepalengvino sprendimų dėl intraveninės trombolizės atlikimo priėmimo. Kita vertus, rasta prieštaringų neatsitiktinių imčių intervencinių tyrimų rezultatų, rodančių, kad GMP personalo mokymai gali pagerinti RT rodiklius (49,56) ir laiką nuo insulto pacientų patekimo į ligoninę iki intraveninės trombolizės atlikimo (47, 49). Be ankstesnių tyrimų, mūsų tyrimas rodo, kad interaktyvūs GMP mokymai gali pagerinti insulto atpažinimo ir pacientų transportavimo laiką, taip pagerindami ūminio insulto gydymo savalaikiškumą. Vis dėlto mūsų tyrimas nebuvo skirtas ligoninės veiklos rezultatams vertinti, nes nerinkome duomenų apie ligoninės prenotifikacijos dažnį, o GMP personalo dalyvavimas apsiribojo ikihospitaliniu insulto priežiūros periodu. Kiti ligoninės kintamieji, pavyzdžiui, radiologinių tyrimų prieinamumas, galimybė greitai interpretuoti pacientų radiologinius vaizdus ir priėmimo skubiosios pagalbos skyriaus darbuotojų darbo krūvis, taip pat gali turėti įtakos insulto priežiūros veiksmingumui, tačiau mūsų tyrime į juos nebuvo atsižvelgta.

GMP mokymų poveikis savalaikiam insulto pacientų transportavimui buvo stipresnis miesto GMP grupėje nei tarp rajono GMP. Kadangi transportavimo laikas iš atokių regionų yra ilgesnis dėl didesnio atstumo tarp paciento gyvenamosios vietos ir IGC, mažiau pacientų galėjo spėti atvykti per 90 minučių nuo simptomų pradžios. Be to, dėl tyrimo metu pakeisto insulto priežiūros tvarkos aprašo visais įtariamo insulto atvejais turėjo būti vežama į

IGC ir TPL, neatsižvelgiant į simptomų atsiradimo laiką. Taigi rajono GMP, bet ne miesto GMP grupėje padaugėjo pacientų, dėl įtariamo insulto nepatenkančių į RT langą. Vadinasi, šis ministro įsakymas galėjo iškreipti realų GMP mokymo poveikį rajono GMP grupėje mūsų tyrimo metu.

Pagrindinis **II tyrimo** privalumas – perspektyvus pobūdis ir palyginti didelė imtis. GMP darbuotojai apie konkrečių atokiųjų rezultatų vertinimą iš anksto informuoti nebuvo, norėta išvengti efekto, kai dalyviai keičia savo elgesį, žinodami, kad yra stebimi (111).

Pagrindinis **II tyrimo** trūkumas – nebuvo kontrolinės grupės. Vis dėlto kadangi įtariamo insulto atvejų demografinės ir klinikinės charakteristikos prieš mokymus ir po jų reikšmingai nesiskyrė, šalutinių veiksnių įtaka, tikėtina, buvo ribota. Be to, buvo lyginti panašūs kalendoriniai laikotarpiai. Vykdyti mokymai buvo savanoriški, tad juose dalyvavo šiek tiek daugiau nei pusė GMP darbuotojų. Dėl to sudėtingiau aptikti reikšmingą mokymų efektą, tad tikėtina, jog mokymų efektas būtų stipresnis, jei juose dalyvių būtų daugiau. Trečia, dėl pasikeitusių insulto transportavimo gairių po mokymų padidėjo per dieną diagnozuotų insulto atvejų skaičiaus mediana. Tačiau nežymus insulto paplitimo padidėjimas laikotarpiu po mokymo negali visiškai paaiškinti TPR pagerėjimo. Ketvirta, mūsų mokymuose nedalyvavo dispečeriai, todėl papildomų dalyvių įtraukimas į intervenciją galėtų dar labiau pagerinti ikihospitalinės insulto priežiūros rezultatus. Penkta, dėl prasidėjusios COVID-19 pandemijos tyrimą teko nutraukti prieš paskelbiant karantino ribojimus, kurių metu apribota galimybė gauti planinę sveikatos priežiūrą. Tad negalime daryti išvadų apie ilgalaikį mokymų poveikį, nes turime tik keturių mėnesių rezultatus. Galiausiai, mūsų tyrimas buvo atliktas labai didelės širdies ir kraujagyslių ligų rizikos populiacijoje (40). Šias išvadas galima apibendrinti šiuo metu nepakankamai atstovaujamoms populiacijoms, turinčioms panašias sveikatos priežiūros sistemas ir GMP personalo struktūrą, įskaitant, bet neapsiribojant, Baltijos regiono ir Rytų Europos šalimis. Todėl šis tyrimas gali būti naudingas ikihospitalinei pacientų priežiūrai ir planuojant tyrimus ateityje, kurie siektų pagerinti ikihospitalinio insulto priežiūrą, naudojant viešai prieinamus elektroninius insulto mokymo išteklius.

4.3. III – Ilgalaikiai reperfuzinės terapijos rezultatai

Šis vieno centro perspektyvus stebimasis tyrimas parodė, kad ūminio išeminio GSI pacientams taikoma RT gali būti susijusi su palankia funkcine baigtimi (mRS ≤ 2) ir geresne pacientų su sveikata susijusia gyvenimo kokybe po 90 dienų. Vis dėlto pacientų išgyvenamumas reikšmingai nesiskyrė. Tai atitinka ankstesnius literatūros duomenis, kad nedidėjant pacientų mirtingumui ūminio išeminio GSI pacientams per mažiau nei 4,5 val. nuo susirgimo atlikta intraveninė trombolizė rtPA yra susijusi su geresnėmis funkcinėmis baigtimis nei vien bazinis insulto gydymas (20, 121, 122). Nors vis dar diskutuojama dėl intraveninės trombolizės naudojimo ūminio insulto atveju tam tikrose specifinėse klinikinėse situacijose (pavyzdžiui, prieš mechaninę trombektomiją ar pacientams, patyrusiems lakūninį insultą), šiuo metu nėra tvirtų įrodymų, kad intraveninės trombolizės šiose klinikinėse situacijose reikėtų vengti (121). Panašūs rezultatai nustatyti ir insulto pacientams, kuriems buvo atlikta mechaninė trombektomija. Suaugusiems pacientams, kuriems dėl stambios arterijos okliuzijos priekiniame kraujotakos baseine įvyko GSI, praėjus nuo 6 iki 24 val. nuo tada, kai pacientas paskutinį kartą matytas sveikas, ir atitinkantiems DEFUSE-3 (123) arba DAWN (124) tyrimų atrankos kriterijus, mechaninė trombektomija ir geriausias medicininis gydymas pagerina funkcines baigtis, palyginti su vien tik geriausiu medicininiu gydymu, nedidėjant pacientų mirtingumui (125).

Kaip ir mūsų tyrimo atveju, ankstesni tyrimai parodė, kad mechaninė trombektomija yra susijusi su geresne insulto pacientų gyvenimo kokybe ilguoju laikotarpiu (126), nors šios išvados ir nėra vienareikšmės (127). Tačiau, nepaisant reikšmingo su sveikata susijusios gyvenimo kokybės pagerėjimo po RT, žinoma, kad net ir po 5 metų išgyvenusių insultą asmenų su sveikata susijusi gyvenimo kokybė pasižymi dideliu variabiliškumu ir insulto pacientų gali išlikti žemesnė nei bendrosios populiacijos (128).

III tyrimas yra pirmasis tyrimas Lietuvoje, kuriame tirtas RT poveikis pacientų mirtingumui, su sveikata susijusiai gyvenimo kokybei ir ilgalaikėms funkcinėms baigtims ligoninės ūminio išeminio insulto pacientų grupėje.

Vis dėlto šis tyrimas turi keletą trūkumų. Visų pirma, kadangi tai buvo vieno IGC tyrimas ir gana maža tyrimo imtis, mūsų išvadų apibendrinamumas gali būti ribotas, o kai kurie silpni statistiniai ryšiai galėjo būti nepastebėti. Be to, po 90 dienų funkcinės būklės ir su sveikata susijusios gyvenimo kokybės vertinimas buvo atliekamas telefonu, o kai kuriais atvejais į apklausą atsakinėjo pacientą prižiūrintys asmenys, todėl rezultatus sudėtinga palyginti su tyrimais, kuriuose su sveikata susijusi gyvenimo kokybė vertinama individualiai, naudojant vaizdines priemones (129). Trečia, naudojome EQ-5D-3L indeksą, kuris buvo patvirtintas pacientams, patyrusiems GSI (130), tačiau kadangi iki šiol nėra lietuviško reikšmių rinkinio, naudotas bendras europiečių reikšmių rinkinys. Galiausiai, dalis pacientų buvo prarasta 90 dienų stebėjimo apklausoje dėl trumpo laikotarpio, kai tyrėjai dėl techninių priežasčių negalėjo atlikti apklausos telefonu. Tačiau nebuvo šališkumo jokio pacientų pogrupio atžvilgiu, todėl, manome, kad tai neturėjo įtakos mūsų rezultatams.

4.4. IV – Mažo COVID-19 sergamumo karantino ribojimai

Šio perspektyvaus tyrimo akademiniame IGC, turinčiame didelę gyventojų aprėptį, metu nustatėme, kad visuotinio karantino metu sumažėjo įtariamų insulto pacientų skaičius ir hospitalizacijų dėl insulto dažnis. Be to, kaip insulto imitatoriai dažniau pasitaikė sunkios neurologinės būklės, tokios kaip traukuliai ir intrakranijiniai navikai. Mūsų išvados suteikia naujų žinių apie visuotinio karantino ribojimų poveikį ikihospitalinei insulto priežiūrai mažo COVID-19 sergamumo aplinkoje.

Nors Lietuvoje COVID-19 atvejų antplūdžio karantino metu nenustatyta, vertinant *Google Trends* duomenis apie su COVID-19 susijusias paieškas, visuomenėje gerokai padidėjo susirūpinimas dėl COVID-19. Visos planinės sveikatos priežiūros paslaugos, prevencinės programos ir planinės operacijos šalies mastu paskelbto karantino metu buvo sustabdytos, todėl galėjo pablogėti lėtinių neurologinių ligų kontrolė (37). Neoptimalią įprastinę priežiūrą atspindėjo smarkiai sumažėjęs ambulatorinių gydytojų siuntimų dėl įtariamo insulto skaičius ir padidėjusi traukulių ir intrakranijinių navikų, imituojančių insultą, dalis.

Kaip ir Kinijoje, Europoje, Taivane bei Jungtinėse Amerikos Valstijose atliktuose tyrimuose, mes taip pat nustatėme, kad karantino ribojimų metu gerokai sumažėjo įtariamų insulto atvejų skaičius ir hospitalizacijų dėl insulto (35, 36, 41, 42, 131, 132, 133). Mūsų rezultatai suteikia papildomų žinių apie karantino ribojimų poveikį insulto priežiūros sistemoms COVID-19 protrūkio sąlygomis, kai COVID-19 sergamumas ir mirtingumas nuo šios ligos yra mažas. Dar vienas priėmimo insulto priežiūros rodiklių tyrimas trijose tretinio lygio universitetinėse ligoninėse Graikijoje, kur patvirtintų COVID-19 atvejų skaičius taip pat buvo nedidelis, parodė, kad pastebimai sumažėjo pacientų, patyrusių insultą ir ūminį koronarinį sindromą (41). Mes taip pat nustatėme, kad karantino ribojimų metu sumažėjo praeinančių smegenų išemijos priepuolių (PSIP) atvejų skaičius. Taigi, sumažėjusį insulto ir PSIP konsultacijų skaičių galėjo lemti nenoras kreiptis į gydytoją esant lengviems ar trumpalaikiams neurologiniams simptomams. Tačiau reikia paminėti, kad, nors mūsų tyrime ir nenustatytas reikšmingas insulto sunkumo pokytis, NIHSS balas buvo žinomas tik tų pacientų, kuriems buvo svarstoma galimybė atlikti RT.

Be to, nustatėme, kad traukuliai ir intrakranijiniai navikai karantino metu buvo dažnesni insulto imitatoriai. Neseniai mūsų įstaigoje atliktas tyrimas parodė, kad epilepsija sergančių žmonių priepuolių kontrolė ir sveikatos būklė per visoje šalyje vykdytus karantino ribojimus buvo blogesnė (134). Panašiai ir Jungtinėje Karalystėje atlikto tyrimo duomenimis, prognozuota, kad vėžio diagnostikos ir priežiūros vėlavimas per kitus penkerius metus gali sukelti daugiau kaip 3 200 išvengiamų mirčių nuo vėžio (135). Apskritai šios išvados pabrėžia intervencijų, kuriomis siekiama optimizuoti specializuotą priežiūrą ir išvengti diagnostikos vėlavimo, svarbą siekiant sušvelninti COVID-19 pandemijos poveikį. Visuomenės sveikatos požiūriu mūsų tyrimas turėjo unikalią galimybę įvertinti karantino priemonių poveikį insulto priežiūrai nepriklausomai nuo tiesioginės sergamumo COVID-19 įtakos. Dėl ankstyvų ir veiksmingų karantino ribojimų Lietuvoje sergamumas ir mirtingumas nuo COVID-19 tyrimo laikotarpiu išliko vienas iš mažiausių Europoje (136). Antra, siekdama apriboti galimą SARS-CoV-2 infekcijos plitimą, Lietuvos Respublikos Vyriausybė visoje valstybėje įvedė griežtą karantiną, tai smarkiai apribojo socialinį gyvenimą ir galimybę naudotis įprastinėmis sveikatos priežiūros paslaugomis (37). Todėl galėjome sėkmingai ištirti karantino priemonių poveikį insulto priežiūrai, nesusijusį su sergamumo COVID-19 įtaka sveikatos priežiūros sistemai. Visuotinio karantino priemonės galėjo turėti nepageidaujamų šalutinių padarinių ikihospitalinei insulto pagalbai.

IV tyrimo privalumas yra jo perspektyvus pobūdis ir jog tai buvo pirmasis visuotinio karantino ribojimų įtakos ikihospitalinei insulto rūšiavimo kokybei ir insulto imitatorių paskirstymui tyrimas. Be to, didelė reprezentatyvi tretinio lygio IGC populiacija, apimanti trečdalį visos šalies, leidžia apibendrinti mūsų išvadas panašioms sveikatos priežiūros sistemoms.

IV tyrimas turi tam tikrų trūkumų. Visų pirma, kadangi tai buvo vieno centro tyrimas, negalime atsižvelgti į pokyčius kituose šalies IGC. Tačiau skirtumų neturėtų būti didelių, nes visi IGC ir TPL veikė toje pačioje mažo sergamumo ir mažo mirtingumo COVID-19 aplinkoje. Dar vienas trūkumas – nebuvo duomenų apie atokiąsias insulto pacientų funkcines baigtis. Nors išrašymo iš ligoninės NIHSS balai nesiskyrė iki visuotinio karantino ribojimų ir jų metu, negalėjome įvertinti, ar pacientų delsimas vykti į priėmimo skubiosios pagalbos skyrių galėjo lemti prastesnius ilgalaikius funkcinius rezultatus. Be to, mes pilnai negalėjome atsižvelgti į sezoninius sergamumo insultu pokyčius. Vis dėlto 2018–2019 m. mūsų IGC daugiau insulto atvejų buvo pavasarį, o ne žiemos mėnesiais, tai leidžia manyti, kad hospitalizuotų insulto pacientų sumažėjo ne dėl sezoninių svyravimų. Galiausiai mūsų išvados turi ribotą apibendrinamąjį pobūdį didelio sergamumo COVID-19 atvejais, regionuose, kuriuose taikomi skirtingi insulto priežiūros protokolai ir skiriasi socialinis bei sveikatos priežiūros atsakas į COVID-19 pandemiją.

4.5. V – COVID-19 sergančių insulto pacientų reperfuzinis gydymas

Tai pirmas visos šalies mastu atliktas poromis suderintas daugiacentris atvejo-kontrolės tyrimas, kurio metu vertintas COVID-19 sergančių insulto pacientų, kuriems taikyta RT, mirtingumas. Nepaisant sėkmingos reperfuzijos, COVID-19 sergančių insultą patyrusių pacientų 3 mėnesių mirtingumo rodiklis buvo didesnis, palyginti su kontrolinės grupės insulto pacientais.

COVID-19 sergantys insulto pacientai buvo reikšmingai prastesnės funkcinės būklės, o jų NIHSS mediana išrašymo metu buvo 15 balų. Tai atitinka kitų tyrimų duomenis, kuriuose nurodomas 31–60 proc. COVID-19 sergančių išeminio insulto pacientų hospitalinis mirtingumas (137–139). Europos daugiacentrio mechaninės trombektomijos tyrimo metu buvo nustatytas 27 proc. 30 dienų mirtingumas (140). Tuo tarpu 3 mėnesių mirtingumas, analizuotas mūsų studijoje, buvo dar didesnis nei ankstesnėje literatūroje (141).

Mūsų tyrime absoliuti dauguma COVID-19 sergančių insulto pacientų patyrė sunkesnį insultą, nepaisant to, kad pradiniai tiriamųjų grupių ASPECTS (Alberta insulto programos ankstyvos kompiuterinės tomografijos balas, angl. *Alberta Stroke Program Early Computed Tomography Score*) balai nesiskyrė. Šie rezultatai yra panašūs į ankstesnių tyrimų duomenis (141). Vis dėlto tikrasis išemijos apimtos teritorijos dydis COVID-19 pacientams galėjo būti didesnis. Ankstesniame tyrime COVID-19 sergantiems insulto pacientams, nepaisant anksti atliktos galvos magnetinio rezonanso tomografijos (MRT), buvo nustatyti gerokai mažesni ASPECTS balai ir didesnis infarkto tūris (142). Tuo tarpu mūsų tyrime insultui diagnozuoti naudota kompiuterinė tomografija (KT). Nors ankstesnėje literatūroje buvo duomenų apie galimus nesutapimus tarp MRT ir KT ASPECTS balų medianos COVID-19 nesergančių insulto pacientų radiologiniuose tyrimuose, įtakos insulto gydymo baigtims nebuvo nustatyta (143). Todėl COVID-19 būdinga kraujagyslių endotelio disfunkcija galėjo turėti įtakos infarkto šerdies didėjimui ir prisidėti prie blogų pacientų gydymo baigčių.

Hipoksija yra svarbus veiksnys, susijęs su prastomis insulto gydymo baigtimis. Mūsų tiriamųjų kohortoje 64,5 proc. COVID-19 sergančių insulto pacientų turėjo kvėpavimo nepakankamumą. Beveik trečdaliui COVID-19 pacientų, kuriems buvo ūminis insultas, dėl sunkaus kvėpavimo sistemos sutrikimo prireikė ilgesnės intubacijos. Atlikus tiriamųjų pogrupio analizę (duomenys nepublikuoti), kvėpavimo nepakankamumą turėjusių pacientų neurologinė būklė praėjus 24 val. po RT nepagerėjo. Dauguma šių pacientų turėjo stambios arterijos okliuziją, tad jiems prireikė mechaninės trombektomijos. Dėl santykinai mažos mūsų kohortos imties negalėjome su optimalia statistine galia atlikti pogrupių analizės, tačiau buvo pastebėta tendencija, kad pacientams, kuriems buvo kvėpavimo nepakankamumas, insultas buvo sunkesnis. Tai atitinka ankstesnių tyrimų duomenis. Dviejose ankstesnėse metaanalizėse nustatyta, kad sunki COVID-19 liga dažniau komplikuojasi sunkiu išeminiu insultu (139,144). Pacientai, kuriems yra sunkus kvėpavimo funkcijos sutrikimas, turi didelę prastesnių baigčių riziką ir didesnį hospitalinį mirtingumą (138). Insulto centras Niujorke pranešė apie reikšmingą ankstyvą COVID-19 insultu sergančių pacientų, kuriems buvo taikytas endovaskulinis gydymas, neurologinės būklės pagerėjimą. Nė vienam iš COVID-19 sergančių insulto pacientų, kuriems buvo reikšmingas būklės pagerėjimas, nebuvo nustatyta kvėpavimo funkcijos sutrikimo požymių (145). Kvėpavimo funkcija, nors ir analizuota COVID-19 sergančių insulto pacientų kohortose, nebuvo plačiai nagrinėta tų pacientų, kuriems dėl GSI buvo taikyta RT. Savo tyrime pabrėžiame kvėpavimo komplikacijų svarbą insulto pacientams, kuriems taikomas specializuotas gydymas. Kvėpavimo nepakankamumas gali būti svarbus veiksnys, lemiantis ankstyvą neurologinės būklės pablogėjimą arba pagerėjimo nebuvimą, nepaisant sėkmingos reperfuzijos.

Rizikos veiksniai, susiję su prastesne COVID-19 sergančių insulto pacientų funkcine būkle ir mirtingumu, yra vyresnis amžius, COVID-19 infekcija ir insulto sunkumas atvykus į ligoninę. Mūsų tyrimo logistinės regresijos modelis parodė, kad tik didesnis pradinis NIHSS balas buvo susijęs su blogesnėmis funkcinėmis baigtimis. Trijų mėnesių mirtingumui reikšmingi prognostiniai veiksniai logistinės regresijos modelyje buvo amžius, didesnis pradinis NIHSS ir teigiamas SARS-CoV-2 tyrimo rezultatas. COVID-19 infekcija septynis kartus padidino mirties tikimybę praėjus 3 mėnesiams po insulto ir RT. Pripažįstame, kad mūsų tyrimo regresinės analizės modelis gali neatspindėti tikrųjų COVID-19 sergančių insulto pacientų, kuriems taikoma RT, blogos prognozės dėl retrospektyvaus tyrimo pobūdžio ir mažos imties. Be to, į vienalypę ir daugialypę logistinę regresiją įtraukėme tik paciento anamnezės duomenis ir klinikinius bei laboratorinius duomenis, įvertintus atvykus į ligoninę. Kad hipoksija yra svarbus paveikto smegenų audinio infarkto didėjimo veiksnys ir gali būti susijusi su didesniu hospitaliniu mirtingumu, teigėme, atsižvelgę į didelį kvėpavimo nepakankamumo dažnį mūsų tyrime. Vis dėlto neatmetama, kad didelio 3 mėnesių mirtingumo gali būti ir kitų priežasčių.

V tyrimo stiprybė buvo tai, kad tyrimas apėmė visus Lietuvos IGC. Antra, mes atlikome vieną iš nedaugelio tyrimų, kuriame buvo pateikti duomenys apie COVID-19 sergančių insulto pacientų mirtingumą praėjus

3 mėnesiams. Dėl to buvo galima palyginti COVID-19 sergančius insulto pacientus su kontroline grupe, parodyti aiškius mirtingumo ir funkcinių rezultatų skirtumus, COVID-19 iškeliant kaip potencialų prognostinį blogos insulto baigties veiksnį. Pagrindiniai **V tyrimo** trūkumai yra retrospektyvus tyrimo pobūdis ir palyginti nedidelė imtis, dėl kurių negalėjome patikimai atlikti pogrupių analizės. Kita silpnybė – porų palyginimo analizės metodas, kuris gali netiksliai atspindėti tikruosius kontrolinių pacientų demografinius ir klinikinius duomenis. Nors pateikėme 3 mėnesių mirtingumo rodiklius, negalėjome palyginti išgyvenusių COVID-19 insulto pacientų funkcinių rezultatų su kontroline grupe. Tai būtų suteikę papildomos informacijos apie COVID-19 poveikį išgyvenusiems insulto pacientams.

IŠVADOS

1. Insulto gydymo reorganizacija Lietuvoje buvo susijusi su teigiamu pacientų, gydytų RT (intravenine trombolize ir mechanine trombektomija), dalies tendencijos pokyčiu. Be to, Lietuvos insulto centruose nuo 2014 m., kai buvo pradėtas registruoti vidutinis laikas nuo atvykimo į ligoninę iki intraveninės trombolizės atlikimo, matoma statistiškai reikšminga šio rodiklio mažėjimo tendencija.

2. Interaktyvūs GMP mokymai mažiausiai keturiems mėnesiams reikšmingai pagerino ikihospitalinį insulto atpažinimą. Po mokymų reikšmingai pagerėjo pacientų transportavimo į insulto gydymo centrą per 90 minučių nuo insulto pradžios dalis miesto GMP, bet ne rajono GMP grupėje.

3. Atsižvelgus į insulto charakteristikas, RT pagerina insulto pacientų 90 dienų funkcines baigtis ir su sveikata susijusią gyvenimo kokybę, bet ne bendrą pacientų vienerių metų išgyvenamumą.

4. Kai sergamumas ir mirtingumas nuo COVID-19 yra nedidelis, visuotinio karantino ribojimai yra susiję su mažesniais įtariamų insultų ir hospitalizacijų dėl insulto skaičiais. Karantino metu traukuliai ir intrakranijiniai navikai yra dažnesni insulto imitatoriai. Visuotinio karantino ribojimai neigiamai veikia ikihospitalinę insulto priežiūrą nepriklausomai nuo sergamumo COVID-19.

5. COVID-19 yra reikšmingas prastesnio insulto pacientų 90 dienų išgyvenamumo po RT prognostinis veiksnys.

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ABOUT THE AUTHOR

Rytis Masiliūnas graduated *cum laude* from the Lithuanian University of Health Sciences in 2012, where he obtained a degree of Doctor of Medicine (MD). He finished training in Neurology at Vilnius University Faculty of Medicine in 2016, and continued working in Vilnius University Hospital Santaros Klinikos both as a clinician and a teaching assistant at the Clinic of Neurology and Neurosurgery, Faculty of Medicine, Vilnius University. He has been heading the subdepartment of Emergency Neurology in VUH SK since 2016 and entered the doctoral study program of Vilnius University in 2017.

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The impact of a comprehensive national policy on improving acute stroke patient care in Lithuania

Rytis Masiliūnas[1], Aleksandras Vilionskis[2], Natan M Bornstein[3], Daiva Rastenytė[4] and Dalius Jatužis[1]

Abstract

Introduction: Reperfusion therapy (RT) is a mainstay treatment for acute ischemic stroke (AIS). We aimed to evaluate the impact of a comprehensive national policy (CNP) to improve access to RT for AIS patients across Lithuania.

Patients and methods: Aggregated anonymized data on AIS cases treated in Lithuanian hospitals between 2006 and 2019 were retrospectively obtained from the Institute of Hygiene and the Stroke Integrated Care Management Committee. Through an interrupted time series analysis, we examined the trends in AIS hospital admissions, RT, and in-hospital case fatality rates prior to the enactment of CNP in 2014, changes immediately after the intervention, and differences in trends between the pre- and post-intervention periods. Mean yearly door-to-needle times were calculated post-intervention.

Results: 114,436 cases were treated for AIS in Lithuanian hospitals before, and 65,084 after the government intervention. We observed a significant decreasing post-intervention trend change in AIS hospital admission rate per 100,000 population (regression coefficient ± standard error: $\beta = -16.47 \pm 3.95$, $p = 0.002$) and an increasing trend change in the proportion of AIS patients who received reperfusion treatment: intravenous thrombolysis ($\beta = 1.42 \pm 0.96$, $p < 0.001$) and endovascular therapy ($\beta = 0.85 \pm 0.05$, $p < 0.001$). The proportion of patients treated in stroke centers increased immediately after the intervention ($\beta = 4.95 \pm 1.14$, $p = 0.001$), but the long-term post-intervention trend did not change. In addition, there was a significant decreasing trend in all cause in-hospital case fatality rate within primary and comprehensive stroke centers after the intervention ($\beta = -0.60 \pm 0.18$, $p = 0.008$) despite its prompt initial immediate increase ($\beta = 1.68 \pm 0.73$, $p = 0.043$). The mean countrywide door-to-needle time decreased from 68 min in 2014 to 43 min in 2019.

Conclusion: The comprehensive national stroke patient care policy could be associated with an immediate increase in stroke center treatment rate, increased access to RT, and improved stroke care performance measures.

Keywords

Ischemic stroke, implementation, thrombolysis, thrombectomy, interrupted time series, Lithuania

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Introduction

Stroke is one of the major causes of death and disability-adjusted life years worldwide.[1,2] The incidence of acute ischemic stroke (AIS) and stroke mortality in Lithuania is amongst the highest in the world,[3] in a large part due to a high prevalence and poor control of cardiovascular risk factors (CV RF).[4,5] Moreover, the largest increase in the age-adjusted stroke incidence and prevalence rates, as well as the lowest average annual percentage decrease in stroke mortality among all European Union countries are expected in Lithuania.[6]

[1]Center of Neurology, Vilnius University, Vilnius, Lithuania
[2]Clinic of Neurology and Neurosurgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[3]Neurological Institute, Shaare Zedek Medical Center, Jerusalem, Israel
[4]Department of Neurology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

Corresponding author:
Rytis Masiliūnas, Center of Neurology, Vilnius University, Santariškių g. 2, Vilnius 08661, Lithuania.
Email: rytis.masiliunas@santa.lt

Reperfusion therapy (RT) – thrombolysis using intravenous recombinant tissue plasminogen activator (IV rtPA) and endovascular treatment (EVT), is a widely accepted, safe, and cost-effective method to treat AIS with proven clinical efficacy.[7,8] However, its broad implementation in daily clinical practice is challenging.[9–12] In Lithuania, the first thrombolysis with IV rtPA was performed after its approval for AIS in 2002, whereas EVT was introduced to clinical practice in 2012. Although IV rtPA was recommended as a first-line treatment for AIS according to national guidelines since 2007,[13] the total annual number of IV rtPA remained low across the country until 2013.

Ever since its establishment in 1997, the Lithuanian Stroke Association (LSA) – a national non-governmental organization uniting stroke care specialists – was one of the leading forces seeking improvement in stroke care quality in Lithuania. Many of the LSA's objectives came to fruition in 2014, when the Ministry of Health (MoH) of the Republic of Lithuania initiated multiple activities in order to promote and implement modern RT for stroke patients on the national level (see Supplemental Table 1). The integrated government support included ministerial orders on the establishment of a national network of acute stroke centers, the reorganization of AIS patient flow (all acute stroke patients were obliged to be referred to the nearest acute stroke center directly), a coordinated inventory of the AIS diagnostic and management methods, standard requirements for the accreditation of primary stroke centers (PSCs) and comprehensive stroke centers (CSCs),[14] and the creation of the Stroke Integrated Care Management Committee (SICMC) under the MoH.[15] The aim of SICMC was to coordinate new financial incentives, which included a centrally coordinated purchase of rtPA, a retrospective per-case AIS total EVT expense reimbursement to the healthcare providers, and the lift of the budget cap for AIS patients. In addition, it collected and monitored data from stroke treatment sites regarding acute RT, logistics, use of resources and diagnostic investigations, rehabilitation, in-hospital complications, case fatality, and other AIS care performance measures. Quarterly reports were provided to the MoH in order to identify areas that require improvement.

Our study aimed to evaluate the impact of the comprehensive national policy on multiple stroke care performance measures, reflecting access to RT for AIS patients across Lithuania. We analyzed data on cases, treated in acute care hospitals for AIS between 2006 and 2019, using a nationwide public health register and reports supplied to SICMC by all individual stroke-ready hospitals.

Patients and methods

Study design and data collection

Two data sources were used for this study. Firstly, aggregated data on all AIS cases treated in Lithuanian hospitals between 2006 and 2019 were retrospectively obtained from the Institute of Hygiene – an institution, which manages public health registers and is responsible for the monitoring of the Lithuanian population health, health care activities, and resources.[16] The dataset included the total number of AIS (corresponding to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Australian Modification, code I63), the number of AIS cases treated in Lithuanian CSCs, PSCs, and nonspecialized hospitals (NHs), their gender, age group, place of residence, days spent in hospital, and in-hospital case fatality. The full description of the statistical research methodology of how the dataset was obtained, and how its completeness and patient anonymity were secured is available online.[17]

Secondly, the data on the number of RTs performed were collected from the SICMC. Since the establishment of the SICMC in 2014, every quarter all active Lithuanian CSCs and PSCs (see Supplemental Table 2) were obliged to report to it aggregated anonymized data on the predetermined stroke care performance measures, consistent with the information from their hospital information systems. Among others, these include the total number of RT procedures (IV rtPA and EVT) in each hospital and their mean door-to-needle (DTN) time. It should be noted that there are no data on patients who received bridging therapy (IV rtPA in combination with EVT), therefore, a proportion of cases could have received both modes of treatment. The full list of performance measures, developed in accordance with the best practice recommendations of the international guidelines[18,19] and adapted to meet the local needs, is shown in Supplemental Table 3.

Our research project was proposed to the MoH and had been designed in accordance with the Declaration of Helsinki. A government advisory committee reviewed our proposal and recommended that the MoH grant us permission to use the required data and perform the study. Data have been collected as part of routine clinical practice, therefore, there was no need for specific informed consent, and approval of the Ethics Committee was not required.

Setting

In Lithuania, acute stroke care hospitals are categorized into CSCs, PSCs, and NHs, according to available reperfusion treatment. The distribution of the six Lithuanian CSCs and the five PSCs with isochrone distances of time it takes to reach the closest stroke-ready hospital on a Sunday evening by car is shown in Figure 1. The map was created using publicly available data from Google Maps.

As noted above, different actions were taken on a national level in order to encourage the implementation of modern RTs for stroke patients in 2014, marking the introduction of the comprehensive national policy in Lithuania. Thus, we defined the period before 2014 as the pre-intervention period

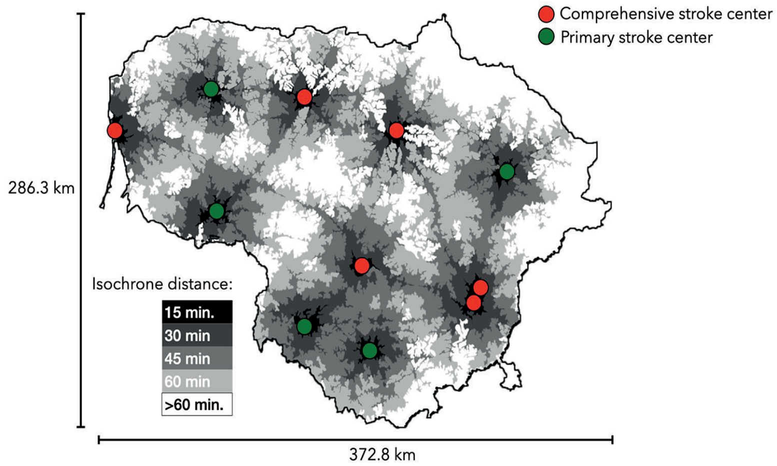


Figure 1. The distribution of Lithuanian primary and comprehensive stroke centers and isochrone distances to reach them.

(eight calendar years) and the period from 2014 to 2019 as the post-intervention period (six calendar years).

Outcome measures

The impact of the comprehensive national policy on six different stroke-related outcomes was evaluated. They included the AIS hospital admission rate per 100,000 population, the proportion of patients who received RT, the proportion of cases treated within CSCs and PSCs, and in-hospital case fatality. The in-hospital case fatality was defined as a proportion of all-cause in-hospital AIS patient deaths out of all admitted AIS cases. Since DTN time data were available just for the post-intervention period, only the post-interventional DTN time trend was analyzed. These outcome measures were selected by the authors as they were judged to be most influenced by the changes in the comprehensive national policy.

Statistical analysis

We compared categorical variables using the χ^2 test. Based on their Gaussian distribution, the quantitative variables were compared using the Student's *t*-test. Available sociodemographic characteristics were compared before and after the introduction of a comprehensive national policy in Lithuania. The 95% confidence intervals (CI) were calculated, where applicable.

We analyzed the yearly trends of the outcome measures – AIS hospital admission rate, the proportion of patients who received RT, the proportion of cases treated within CSCs and PSCs, and all-cause in-hospital case fatality (overall and within CSCs and PSCs). To calculate the AIS hospital admission rate per 100,000 population, the patient numbers were standardized to the population of Lithuania on the first day of each calendar year.[20] Using an interrupted time series analysis, we evaluated the time trends of the outcome measures before and after the introduction of a comprehensive national policy in 2014.[21,22]

The analysis was performed using the following regression equation: $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 P_t + \varepsilon_t$, where Y_t is the aggregated outcome at time t (year), T_t is the time (years) since the start of the study period, X_t is the dummy variable representing the period after the introduction of a comprehensive national policy, P_t is a continuous variable indicating time (years) since this intervention (P_t is equal to 0 before intervention), β_0 is the intercept, β_1 is the slope prior to the intervention, β_2 is the change in level in the period immediately following the intervention, and β_3 is the difference between the pre- and post-intervention slopes. The standard errors (SE) were calculated. $p < 0.05$ (two-sided) was considered statistically significant. R version 3.6.2 was used for statistical analysis.

Results

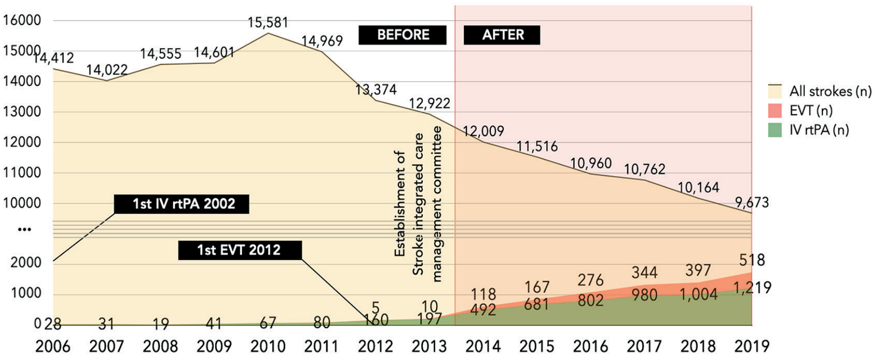
Demographic characteristics

Altogether, 114,436 cases were treated for AIS in Lithuanian hospitals before the government intervention, and 65,084 during the study period after it (Table 1). The absolute number of AIS admissions decreased by a striking 25.1% between 2013 and 2019 (Figure 2). As compared with the pre-intervention period, after the introduction of the comprehensive national policy, significantly fewer female patients were diagnosed with AIS (57.2% (95% CI 56.8–57.6) vs 59.0% (58.7–59.3), $p < 0.001$), there were proportionally fewer individuals under 45 years of age (1.4%

Table 1. Demographic characteristics for stroke patients in Lithuania.

	Stroke patients 2006–2013 (n = 114,436)	Stroke patients 2014–2019 (n = 65,084)	*p*-Value
Female, *n* (%)	67,510 (59.0)	37,234 (57.2)	<0.001
Age range in years, *n* (%)			
0–17	27 (0.02)	34 (0.05)	0.002
18–44	2001 (1.7)	866 (1.3)	<0.001
45–64	26,212 (22.9)	12,958 (19.9)	<0.001
⩾65	86,168 (75.3)	51,226 (78.7)	<0.001
No data	28 (0.02)	0	
Place of residence, *n* (%)			
Urban	76,083 (66.5)	42,089 (64.7)	<0.001
Rural	37,869 (33.1)	22,900 (35.2)	<0.001
No data	484 (0.4)	95 (0.1)	
Treatment place, *n* (%)			
CSC	35,584 (31.1)	27,625 (42.4)	<0.001
PCS	10,486 (9.2)	7784 (12.0)	<0.001
Nonspecialized hospital	68,366 (59.7)	29,675 (45.6)	<0.001
Days in hospital, mean (SD)	13.0 (1.7)	10.2 (0.2)	<0.001

CSC: comprehensive stroke center; PSC: primary stroke center; SD: standard deviation.



IAT - intraarterial thrombolysis, IV rtPA - thrombolysis using intravenous recombinant tissue plasminogen activator, EVT - endovascular treatment.

Figure 2. The absolute number of ischemic stroke cases and those who received any kind of reperfusion therapy in Lithuania.

(1.3–1.5) vs 1.8% (1.7–1.9), $p < 0.001$), and significantly fewer patients came from urban areas (64.7% (64.3–65.0) vs 66.5% (66.2–66.8), $p < 0.001$). In addition, significantly more cases were treated in CSCs and PSCs after the government intervention (54.4% (54.0–54.8) vs 40.3% (40.0–40.5), $p < 0.001$), and the mean hospital stay decreased significantly (mean ± standard deviation: 10.2 ± 1.7 vs 13.0 ± 0.2 days, $p < 0.001$).

Temporal trends in AIS hospital admission rates

There was no significant AIS hospital admission rate trend during the pre-intervention period (see Supplemental Table 4). In contrast, it decreased significantly immediately after the intervention (regression coefficient ± standard error: $\beta_2 = -35.93 \pm 15.72$, $p = 0.045$), and continued to consistently decrease throughout the post-intervention period ($\beta_3 = -16.47 \pm 3.95$, $p = 0.002$) (Figure 3).

The proportion of cases in hospitals, designated as CSCs and PSCs in 2014, had a positive trend for an increase before the intervention ($\beta_1 = 1.31 \pm 0.002$, $p < 0.001$). Although there was a significant increase in the proportion of CSC and PSC cases immediately after the intervention ($\beta_2 = 4.95 \pm 1.14$, $p = 0.001$), we observed no significant trend change in the post-intervention period, as the proportion continued to increase to 58.1% in 2019.

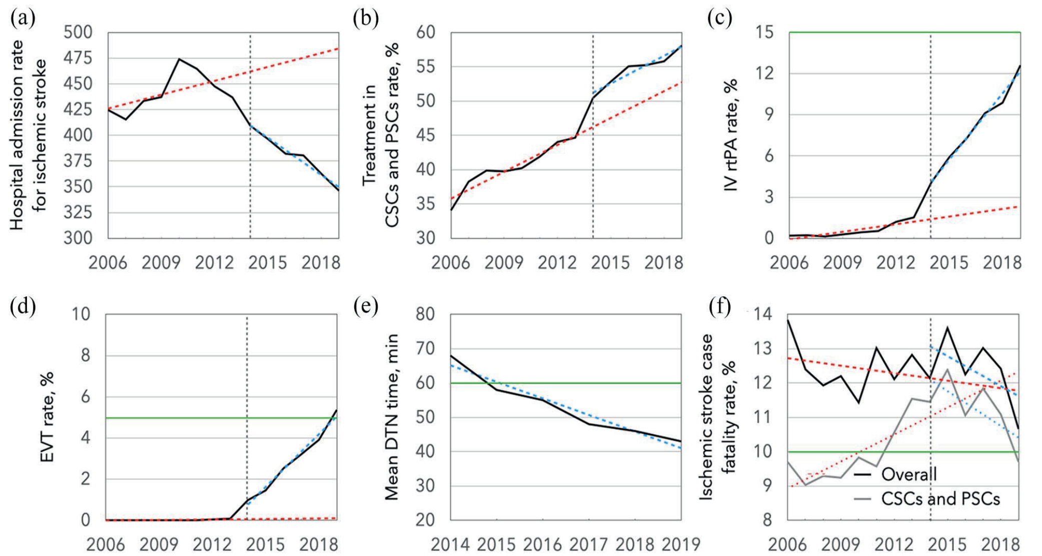


Figure 3. Temporal trends in (a) ischemic stroke hospital admission rate per 100,000 population, (b) rate of patient treatment in comprehensive and primary stroke centers (CSCs and PSCs), (c) rate of thrombolysis using intravenous recombinant tissue plasminogen activator (IV rtPA), (d) endovascular treatment (EVT) rate, (e) post-intervention mean door-to-needle (DTN) time, and (f) case fatality from ischemic stroke. The dashed lines represent the regression lines. The green lines represent targets, where applicable. The comprehensive national stroke care policy in Lithuania was implemented in 2014 (vertical dashed line).

Temporal trends in the proportion of AIS patients receiving RT

The proportion of AIS patients, treated with IV rtPA, out of all AIS cases increased from 1.5% (or 197 overall cases) in 2013 to 12.6% (or 1219 overall cases) in 2019 – a sixfold absolute and an eightfold relative increment. Similarly, there was an increase in the number of EVT performed from 10 cases or 0.1% out of all AIS in 2013 to 518 cases or 5.4% out of all AIS in 2019 (Figure 2). Only the proportion of patients treated with IV rtPA increased statistically significantly immediately after the implementation of a comprehensive national policy in Lithuania ($\beta_2 = 1.32 \pm 0.38$, $p = 0.006$), whereas, a significant change in trend in the period following it was observed for both the proportion of patients treated with IV rtPA ($\beta_3 = 1.42 \pm 0.96$, $p < 0.001$) and with EVT ($\beta_3 = 0.85 \pm 0.05$, $p < 0.001$).

In addition, there was a statistically significant decreasing trend in mean DTN time within the Lithuanian CSCs and PSCs since 2014, when it was started to be recorded ($\beta_1 = -5.28 \pm 0.002$, $p < 0.001$) (Figure 3), by almost 5 min on average annually from 68 min in 2014 to 43 min in 2019.

Temporal trends in case fatality rates for AIS patients

There were no significant changes in the overall all-cause in-hospital AIS case fatality rates during the pre- and post-intervention periods as well as immediately after the intervention. Nevertheless, the in-hospital AIS case fatality rates in CSCs and PSCs increased during the pre-intervention period ($\beta_1 = 0.26 \pm 0.10$, $p = 0.024$) and immediately following the intervention ($\beta_2 = 1.68 \pm 0.73$, $p = 0.043$), and decreased significantly during the post-intervention period ($\beta_3 = -0.60 \pm 0.18$, $p = 0.008$).

Discussion

In our interrupted time series design study on the impact of a comprehensive national policy on improving acute stroke patient care in Lithuania, we observed a significantly decreased AIS hospital admission rate, significant trend improvements in RT rates, and an immediate increase in the proportion of AIS cases treated in CSCs or PSCs after the policy change. In addition, there was a sustained significant decreasing trend of all-cause in-hospital case fatality rates within CSCs and PSCs despite a prompt initial immediate increase. To our knowledge, this is the first study from a very high CV RF region[23] demonstrating that comprehensive changes in national stroke care policy could be associated with substantial improvements in stroke care outcomes.

Lithuania has one of the highest AIS incidences in the world.[2] However, we suspect that a considerable part of the AIS diagnosed in the NHs could have been misdiagnosed cases of peripheral vertigo,[24] sequelae of previous strokes, and other diseases.[25] We speculate that as an increasing proportion of AIS cases have been treated in CSCs and PSCs, more patients received a correct AIS diagnosis. The gradual and significant decrease in the prevalence of CV RFs could have also played a role.[5] Although we assessed AIS hospital admission rather than AIS incidence rate, the actual difference between them may not be large as sudden death from stroke is very uncommon in the pre-hospital setting,[26] and every patient with AIS requires hospital admission by the current guidelines.[27] However, hospital admission rates for AIS in Lithuania in 2019 were still high despite an obvious downward trend from the highest stroke incidence worldwide in 2010.[2,28]

Ample previous studies have shown a continuous increase in IV rtPA[26,29–46] and EVT rates for AIS[46–48] in different countries over different study periods. However, our data show that Lithuania experienced a countrywide breakthrough of IV rtPA use only after the introduction of a comprehensive national policy. Similarly, EVT use was in single digits before the government intervention and surged after 2014, although some unmeasured confounders, such as the breakthrough thrombectomy trials in 2015 that increased physicians' confidence in the safety and efficacy of EVT, might have also contributed.[48] Nevertheless, we believe that retrospective per-case AIS RT expense reimbursement and budget cap removal might have been a more robust incentive to improve RT numbers countrywide. While there is no agreed benchmark for thrombolysis and thrombectomy rates (these were respectively 12.6% and 5.4% in Lithuania in 2019),[10] there is still room for improvement as shown by remarkable nationwide IV tPA administration rates of 23.5% in the Czech Republic and a 5.6% EVT rate in Malta.[45,49]

Previous research has shown that the development of stroke centers could improve patient outcomes and result in a substantial increase in the proportion of AIS patients receiving IV rtPA.[26,50,51] International guidelines recommend the certification of stroke centers by an independent external body,[52] and suggest that 90% or more of stroke patients should be treated in a stroke unit as the first level of care.[53] In our study despite the significant immediate level change, a non-significant slope change for the proportion of cases treated in CSCs or PSCs suggests a lack of effect of this government intervention over time. We contemplate that other types of interventions, such as centralization of AIS care requiring to bypass the NHs, or increase in stroke unit density within the country could have a higher impact on CSC/PSC treatment rate.

We found declining overall all-cause in-hospital stroke case fatality rates from 13.8% in 2006 to 10.7% in 2019 – comparable to those found in a similar study from neighboring Poland, where in-hospital case fatality rates declined from 13.6% in 2009 to 12.9% in 2013.[26] It was significantly lower in CSCs and PSCs with a sustained significant decreasing trend after the change of government policy. Still, AIS mortality was three times higher in Lithuania than the Organisation for Economic Co-operation and Development (OECD) average (145.08 vs 47.28 per 100,000 population, respectively).[2,54]

International guidelines recommend developing stroke systems of care so that RT-eligible patients receive treatment in the fastest achievable onset-to-treatment time.[52] We found a statistically significant decreasing trend in the mean DTN time within the Lithuanian hospitals from 68 min in 2014 to 43 min in 2019. We speculate that higher treatment volumes might lead to shorter DTN times – an indicator of experience and confidence.[40,55,56] Moreover, quarterly SICMC reports to the MoH, and annual public stroke center progress monitoring may have produced an additional incentive.[27] Astonishingly, recent data from the Czech Republic showed that a national median DTN time of 25 min or less is feasible.[45]

Our study has several limitations. First, the interrupted time series design is a quasi-experimental approach used to evaluate the impact of a single intervention, and unmeasured confounders (i.e. decreasing CV RF prevalence) may have affected the results. In addition, we did not investigate the influence of the coronavirus disease 2019 (COVID-19) pandemic on stroke care outcomes, as we have deliberately chosen to conduct our analysis on the pre-pandemic period. Moreover, the breakthrough thrombectomy trials in 2015 might have played a role in the increased thrombectomy rates throughout the country as there was an increase in confidence in the safety and efficacy of EVT among neurologists.[48] Fourth, functional and post-discharge long-term outcomes could not be assessed, due to limited access to such data. Fifth, our analysis is based on the group of hospitalized AIS cases, not overall AIS incidence, but the actual difference between these rates may not be large, since every patient with AIS requires hospital admission by the current guidelines.[27]

The strengths of our study are that our nationwide analysis includes all Lithuanian AIS cases, which enables us to elucidate the overall country-wide real-world trends in acute stroke care outcomes. In addition, this is the first study from a very high cardiovascular risk region demonstrating that comprehensive changes in national stroke care policy could be associated with substantial improvements in stroke care outcomes.

Conclusion

We found that a comprehensive national stroke patient care policy in Lithuania was associated with an improvement in a wide array of quality measures both immediately after the intervention and in the period following it. This is the first study from a very high cardiovascular risk region demonstrating how integrated efforts of leading stroke specialists, government support, and a balanced stroke care network could be associated with a breakthrough of modern RTs for AIS patients. Further studies are warranted to elucidate how the use of RT and post-reperfusion functional outcomes change according to time and circumstances in real-world settings.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RM, AV, and DJ have previously received honoraria payments and travel support from Boehringer-Ingelheim; RM, AV, DJ, and DR are members of Lithuanian Stroke Association. AV, DJ, and DR have been personally involved in the activities of SICMC.

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Informed consent

Data have been obtained from an anonymized national public health register and official reports to the MoH from individual stroke-ready hospitals, therefore, there was no need for specific informed consent.

Ethical approval

Because the data have been collected from an anonymized national public health register and official aggregated reports from individual stroke-ready hospitals, approval of Ethics Committees for data collection was not required.

Guarantor

RM.

Author contributions

AV, DJ and DR researched literature and conceived the study. RM, AV and DJ were involved in protocol development and data collection. RM did the data analysis, visualized the data, and wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

ORCID iDs

Rytis Masiliūnas https://orcid.org/0000-0002-8033-9682

Aleksandras Vilionskis https://orcid.org/0000-0002-8055-3558

Supplemental material

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Supplementary Table 1. The elements of the Lithuanian comprehensive national stroke care policy

Non-financial incentives	
	The establishment of a national network of acute stroke centers
	The reorganization of AIS patient flow: all acute stroke patients are obliged to be referred to the nearest acute stroke center directly
	A creation of a coordinated inventory of the AIS diagnostic and management methods
	Standard requirements for the accreditation of PSCs and CSCs
	The creation of the Stroke Integrated Care Management Committee under the Ministry of Health, which aims to:
	Coordinate new financial incentives
	Collect and monitor predefined AIS care performance measures from stroke treatment sites
	Provide quarterly reports to the Ministry of Health in order to identify areas that require improvement
Financial incentives	
	A central coordinated purchase of rtPA
	A retrospective per-case AIS total EVT expense reimbursement to the healthcare providers
	The lift of the budget cap for AIS patients

AIS – acute ischemic stroke, PSC – primary stroke center, CSC – comprehensive stroke center, rtPA – recombinant tissue plasminogen activator, EVT – endovascular treatment.

Supplementary Table 2. List of Lithuanian primary and comprehensive stroke centers

Comprehensive stroke centers	
	Vilnius University Hospital Santaros Clinics
	Republican Vilnius University Hospital
	Lithuanian University of Health Sciences Hospital Kaunas Clinics
	Klaipėda Seamen's Hospital
	Republican Šiauliai Hospital
	Republican Panevėžys Hospital
Primary stroke centers	
	Alytus County Stasys Kudirka Hospital
	Marijampolė Hospital
	Regional Telšiai Hospital
	Tauragė Hospital
	Utena Hospital

Supplementary Table 3. List of performance measures collected by the Lithuanian Stroke Integrated Care Management Committee quarterly

Pre-hospital stroke care quality measures
Percentage of patients with acute focal neurological symptoms screened for stroke with FAST test
Percentage of patients with suspected AIS, transported to a stroke center witin 1 hour of EMS notification
Percentage of patients with suspected AIS transported directly to a stroke center
Positive predictive value for all EMS stroke alerts
Emergency Department stroke care quality measures
Percentage of patients with suspected AIS, to whom imaging (CT, MRI) was performed and evaluated within 30 minutes of arrival to ED
Inhospital stroke care quality measures
Number of patients treated with IVT
Percentage of patients, treated with IVT (out of all hospitalized AIS patients)
Number of patients treated with EVT
Percentage of patients, treated with EVT (out of all hospitalized AIS patients)
Number of patients treated with both IVT and EVT (out of all hospitalized AIS patients)
Percentage of patients, treated with both IVT and EVT (out of all hospitalized AIS patients)
Mean DTN time (minutes)
Percentage of patients, treated with IVT within 60 minutes
Percentage of patients, undergone dysphagia screening within 4 hours of hospitalization (out of all hospitalized AIS patients)
Percentage of patients, seen by a rehabilitation specialist within 24 hours (out of all hospitalized AIS patients)

Percentage of patients, to whom rehabilitation procedures were initiated within 72 hours (out of all hospitalized AIS patients)
Total number of hospitalized AIS patients
Total number of deaths due to AIS
Percentage of AIS patients, who died in hospital
Percentage of patients with persistent urinary dysfunction, investigated and treated for underlying causes (out of all hospitalized AIS patients)
Percentage of patients, referred for subsequent rehabilitation (out of all hospitalized AIS patients)
Percentage of patients and their relatives, who received written information on stroke diagnosis, stroke treatment plan, and practical stroke patient care recommendations

FAST – Face Arm Speech Time, AIS – acute ischemic stroke, EMS – emergency medical services, CT – computed tomography, MRI – magnetic resonance imaging, ED – emergency department, IVT – intravenous thrombolysis, EVT – endovascular treatment, DTN time – door-to-needle time.

Supplementary Table 4. Temporal changes in stroke care quality measures before and after the implementation of a comprehensive national stroke care policy in Lithuania (years 2006 through 2019)

Stroke care quality measure	Regression coefficient, (SE) †	*P* value
Acute ischemic stroke hospital admission rate		
Period before intervention, β_1	4.49 (2.14)	0.062
Immediately after intervention, β_2	– 35.93 (15.72)	0.045
Period after intervention, β_3	– 16.47 (3.95)	0.002
Proportion of patients treated in CSCs or PSCs		
Period before intervention, β_1	1.31 (0.002)	<0.001
Immediately after intervention, β_2	4.95 (1.14)	0.001
Period after intervention, β_3	0.04 (0.29)	0.885
Proportion of patients treated with IV rtPA		
Period before intervention, β_1	0.19 (0.05)	0.005
Immediately after intervention, β_2	1.32 (0.38)	0.006
Period after intervention, β_3	1.42 (0.96)	<0.001
Proportion of patients treated with EVT		
Period before intervention, β_1	0.01 (0.03)	0.742
Immediately after intervention, β_2	– 0.13 (0.19)	0.492
Period after intervention, β_3	0.85 (0.05)	<0.001
Mean door-to-needle time ‡		
Period after intervention, β_1	– 5.28 (0.002)	<0.001
Overall in-hospital AIS case fatality		
Period before intervention, β_1	– 0.07 (0.13)	0.587
Immediately after intervention, β_2	1.15 (0.96)	0.255
Period after intervention, β_3	– 0.22 (0.24)	0.384

In-hospital AIS case fatality in CSCs and PSCs		
Period before intervention, β_1	0.26 (0.10)	0.024
Immediately after intervention, β_2	1.68 (0.73)	0.043
Period after intervention, β_3	– 0.60 (0.18)	0.008

SE – standard error, IV rtPA – thrombolysis using intravenous recombinant tissue plasminogen activator, EVT – endovascular treatment, CSC – comprehensive stroke center, PSC – primary stroke center.

† β_1, β_2, and β_3 indicate the slope prior to intervention, change in level immediately following the intervention, and difference between the pre- and post-intervention slopes, respectively.

‡ Only post-intervention values available.

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Interactive Training of the Emergency Medical Services Improved Prehospital Stroke Recognition and Transport Time

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Interactive Training of the Emergency Medical Services Improved Prehospital Stroke Recognition and Transport Time

Lukas Sveikata[1,2†‡], Kazimieras Melaika[3†‡], Adam Wiśniewski[4†], Aleksandras Vilionskis[5,6†], Kęstutis Petrikonis[7†], Edgaras Stankevičius[2], Kristaps Jurjans[8,9†], Aleksandra Ekkert[10†], Dalius Jatužis[10†] and Rytis Masiliūnas[10*†]

[1] J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2] Institute of Cardiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania, [3] Faculty of Medicine, Vilnius University, Vilnius, Lithuania, [4] Department of Neurology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland, [5] Clinic of Neurology and Neurosurgery, Institute of Clinical Medicine, Vilnius University, Vilnius, Lithuania, [6] Stroke Center, Republican Vilnius University Hospital, Vilnius, Lithuania, [7] Department of Neurology, Lithuanian University of Health Sciences, Kaunas, Lithuania, [8] Department of Neurology and Neurosurgery, Riga Stradins University, Riga, Latvia, [9] Department of Neurology, Pauls Stradins Clinical University Hospital, Riga, Latvia, [10] Center of Neurology, Vilnius University, Vilnius, Lithuania

Background and Purpose: Acute stroke treatment outcomes are predicated on reperfusion timeliness which can be improved by better prehospital stroke identification. We aimed to assess the effect of interactive emergency medical services (EMS) training on stroke recognition and prehospital care performance in a very high-risk cardiovascular risk population in Lithuania.

Methods: We conducted a single-center interrupted time-series study between March 1, 2019 and March 15, 2020. Two-hour small-group interactive stroke training sessions were organized for 166 paramedics serving our stroke network. We evaluated positive predictive value (PPV) and sensitivity for stroke including transient ischemic attack identification, onset-to-door time, and hospital-based outcomes during 6-months prior and 3.5 months after the training. The study outcomes were compared between EMS providers in urban and suburban areas.

Results: In total, 677 suspected stroke cases and 239 stroke chameleons (median age 75 years, 54.8% women) were transported by EMS. After the training, we observed improved PPV for stroke recognition (79.8% *vs*. 71.8%, $p = 0.017$) and a trend of decreased in-hospital mortality (7.8% *vs*. 12.3, $p = 0.070$). Multivariable logistic regression models adjusted for age, gender, EMS location, and stroke subtype showed an association between EMS stroke training and improved odds of stroke identification (adjusted odds ratio [aOR] 1.6 [1.1–2.3]) and onset-to-door $\leq$ 90 min (aOR 1.6 [1.1–2.5]). The improvement of PPV was observed in urban EMS (84.9% *vs*. 71.2%, $p = 0.003$), but not in the suburban group (75.0% *vs*. 72.6%, $p = 0.621$).

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Richard Zweifler,
Ochsner Health System, United States

***Correspondence:**
Rytis Masiliūnas
rytis.masiliunas@santa.lt

†ORCID:
Lukas Sveikata
orcid.org/0000-0001-8015-7929
Kazimieras Melaika
orcid.org/0000-0003-4413-0635
Adam Wiśniewski
orcid.org/0000-0001-5839-0126
Aleksandras Vilionskis
orcid.org/0000-0002-8055-3558
Kęstutis Petrikonis
orcid.org/0000-0002-6258-5767
Kristaps Jurjans
orcid.org/0000-0003-1730-8354
Aleksandra Ekkert
orcid.org/0000-0003-2069-8744
Dalius Jatužis
orcid.org/0000-0001-6159-4795
Rytis Masiliūnas
orcid.org/0000-0002-8033-9682

‡These authors have contributed equally to this work and share first co-authorship

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Conclusions: The interactive EMS training was associated with a robust improvement of stroke recognition, onset to hospital transport time, and a trend of decreased in-hospital mortality. Adapted training strategies may be needed for EMS providers in suburban areas. Future studies should evaluate the long-term effects of the EMS training and identify optimal retraining intervals.

Keywords: training, triage, emergency medical services (EMS), transient ischemic attack (TIA), prehospital/EMS, stroke

INTRODUCTION

Stroke is a life-threatening condition in which prompt and accurate diagnosis is essential for successfully implementing reperfusion therapies (1). Emergency medical services (EMS) play a crucial role in early recognition of stroke, as they are the first-line providers in about two-thirds of cases (2). Although EMS use by stroke patients is associated with earlier emergency department (ED) arrival, quicker evaluation, and more rapid treatment, how healthcare providers respond to stroke remains an essential factor in explaining prehospital delays (1). The process of clinically identifying a stroke is still the most significant challenge for EMS, as a percentage of stroke mimics reaches up to 50% (3, 4). Consequently, stroke mimics utilize the limited resources of acute stroke care pathways that might otherwise be directed toward the actual stroke patients who may benefit from acute time-sensitive revascularization therapies the most (5). Of concern, stroke mimic number in stroke care systems is expected to rise due to demographic changes in the coming decades (6). Therefore, it is crucial to improve the EMS performance in early stroke recognition. Fast and correct stroke diagnosis facilitates an early transfer to stroke-ready hospitals, reduces the volume of stroke mimics, and improves outcomes of acute stroke.

Intensive efforts are made to improve the quality of early stroke care. Training programs for EMS staff in simulated neurological environments increase knowledge on stroke recognition and awareness of time-sensitive medical emergencies (1, 7–12). The hospital prenotification has improved in-hospital timeliness metrics and increased intravenous thrombolysis (IVT) rates (13). In addition, prehospital stroke scales and screening methods for EMS staff have been introduced to allow for a more objective stroke identification (e.g., Face Arm Speech Time test, Los Angeles Motor Scale, Cincinnati Prehospital Stroke Scale) (14, 15). Moreover, specific scales for large vessel occlusion stroke were developed to facilitate the identification of candidates for endovascular therapy (EVT) (16). Given the changing landscape of prehospital stroke identification, a continuous educational effort is required to ensure optimal implementation of prehospital stroke protocols.

Stroke education interventions in prehospital care provided mixed results. A large multicenter randomized control trial in the United Kingdom did not show any benefit on the IVT rate. Surprisingly, the onsite care duration was prolonged in the EMS group that applied an enhanced stroke assessment protocol (17). On the other hand, several interventions increased the accuracy of stroke identification, the number of patients who underwent reperfusion therapy, and significantly reduced the time from the symptom onset to hospital arrival (7–9, 11, 18). Furthermore, the duration of the training effects remains unknown (19). Finally, the paucity of studies in very high cardiovascular risk populations, such as the Baltic countries, urged us to investigate prehospital stroke care intervention in Lithuania (20). Following the European (21) and North American guidelines (13), it is crucial to systematically assess the effectiveness of specific stroke education interventions and maintain the continuity of EMS education.

This study aimed to prospectively evaluate the effect of interactive EMS training on stroke recognition accuracy and the continuum of stroke care metrics. Second, we hypothesize that the EMS training effect might differ in the communities served and compare the training effect in urban and suburban locations.

METHODS

Study Design

We used an interrupted time-series design (22) to examine the impact of interactive EMS stroke training on EMS and hospital-based performance measures. We evaluated the positive predictive value (PPV) and sensitivity for identifying stroke patients, onset-to-door (OTD) $\leq$90 min rate, and hospital-based outcomes, including door-to-CT $\leq$30 min rate, reperfusion therapy, door-to-needle $\leq$30 min rate, and in-hospital mortality. We compared these variables between two periods−6 months before and 3.5 months after the interactive EMS training. The EMS personnel were blinded to the assessment.

The study was approved by the Vilnius Regional Biomedical Research Ethics Committee and conducted following the Declaration of Helsinki. The manuscript complies with STROBE guidelines for observational research.

Setting

This single-center study was conducted in Vilnius University Hospital (VUH) from 1 March 2019 to 16 March 2020, terminated earlier due to an unanticipated state-wide COVID-19 lockdown (23). VUH is one of the two comprehensive stroke centers (CSC) in Eastern Lithuania with a catchment population of 945,000[1], served by one EMS agency in urban and seven in suburban municipalities (24). The EMS response team consisted of a two-person team—paramedic and driver-paramedic. The

[1]Lithuanian Department of Statistics. (2020). Statistics Lithuania. Available at: https://www.stat.gov.lt/home [Accessed December 12, 2020].

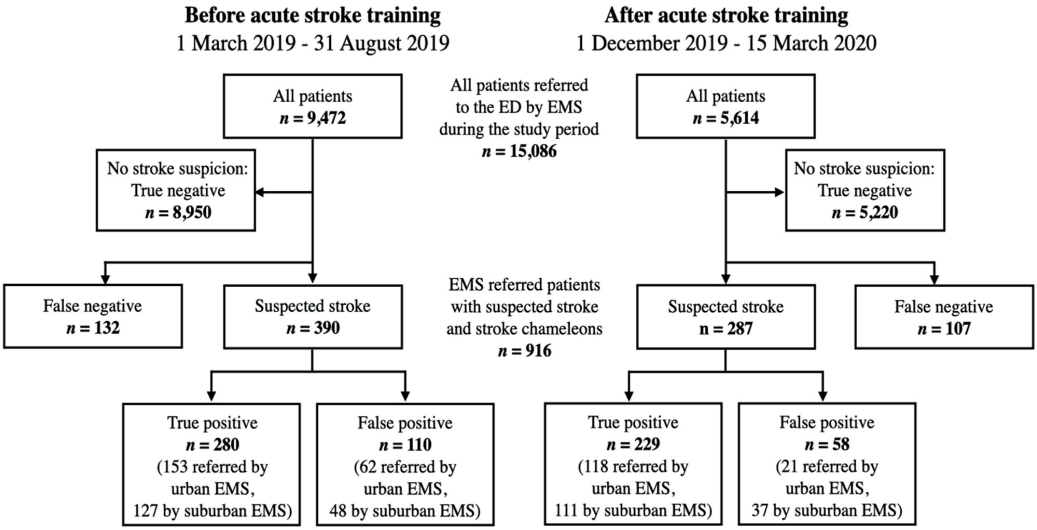

FIGURE 1 | Flowchart of the study population. Patients were referred to the emergency department (ED) of Vilnius University Hospital by emergency medical services (EMS) between March 1, 2019 and March 15, 2020.

EMS agencies were staffed by 331 specialists (217 in urban and 114 in suburban locations) and transported ≈20,400 patients.[2] The paramedics had prior training in nursing (307, 92.7%) or medicine (24, 7.3%).

The post-training period coincided with the change in national stroke triage guidelines, implemented on January 1, 2020. The new regulations affected the workflow of suburban EMS as it required direct transport of all suspected stroke cases to the stroke-ready hospitals with IVT or EVT capability, bypassing regional hospitals irrespective of the time from symptom onset.[3]

Study Population

We collected data of suspected stroke or transient ischemic attack (TIA) patients referred by the EMS to the VUH ED. Secondary transfers from other hospitals and in-hospital strokes were not included. We also collected data on false negatives, that is, stroke cases that were not identified by the EMS. EMS used the Face Arm Speech Time test (FAST) for the identification of suspected strokes (25). Overall, 15,086 patients were referred to the ED by the EMS, of whom 916 patients with EMS suspected or hospital confirmed strokes were included in the analysis (**Figure 1**). Stroke case ascertainment was done after arrival at the hospital by an attending neurologist after a complete stroke work-up. We did not include cases admitted during the 3-month training period.

Interactive EMS Training

Twelve 2-h interactive prehospital stroke recognition training sessions were held in the Neurology Department of VUH over 3 months (from September to November 2019). Interactive training sessions were given by stroke neurologists from the Lithuanian Stroke Association. Each training session was limited to 20 EMS staff members. In total, 166 out of 331 (50.2%) paramedics working in our stroke network participated in the training. The training curriculum was based on the publicly available ANGELS initiative's e-learning course for stroke education for emergency medical teams[4] adapted for local needs and in-person delivery (available online[5]). The EMS stroke training covered stroke epidemiology, pathophysiology, acute stroke treatment, and outcomes, emphasizing the time-sensitive aspects of acute stroke care. The EMS staff was trained to recognize stroke with the FAST test and identify the major stroke syndromes and stroke mimics. Additionally, participants received an update on prehospital acute stroke management. The presentation emphasized the importance of last known well (LKW) documentation, glucose check, minimizing the on-scene time, and hospital prenotification, followed by an interactive discussion.

[2]Institute of Hygiene, Ministry of Health of The Republic of Lithuania. (2019). Health and Healthcare Institutions in Lithuania. *https://hi.lt/uploads/pdf/leidiniai/Statistikos/LT_gyv_sveikata/leid2019.pdf* [Accessed June 21, 2021].

[3]Ministry of Health of The Republic of Lithuania. (2019). The Statement on Acute Stroke Work-up and Management Guideline Change. https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/24591240ff0411e993cb8c8daaf8ff8a [Accessed June 21, 2021].

[4]Angels Initiative. (2020). The Advanced Stroke Life Support e-Learning. *https://www.angels-initiative.com/academy/emergency-services/advanced-stroke-life-support* [Accessed June 21, 2021].

[5]Lietuvos insulto asociacija. (2020). Informacija gydytojams. Available at: http://www.insultoasociacija.lt/index.php/profesionalams/gydytojams [Accessed June 15, 2021].

TABLE 1 | Baseline characteristics and outcomes of emergency medical services suspected stroke admissions.

	All patients ($n = 916$)	Admitted before training ($n = 522$)	Admitted after training ($n = 394$)	*P*-value	Referred by urban EMS ($n = 500$)	Referred by suburban EMS ($n = 416$)	*P*-value
Median age, years (IQR)	75 (66–82)	74 (65–82)	75 (66–82)	0.596	75 (66–82)	75 (65–82)	0.340
Female sex, *n* (%)	502 (54.8)	276 (52.9)	226 (57.4)	0.177	272 (54.4)	230 (55.3)	0.788
Confirmed strokes, *n* (%)	748 (81.7)	412 (78.9)	336 (85.3)		417 (83.4)	331 (79.6)	
Ischemic stroke	606 (66.2)	339 (64.9)	267 (67.8)	0.371	335 (67.0)	271 (65.1)	0.555
Hemorrhagic stroke	86 (9.4)	46 (8.8)	40 (10.2)	0.491	48 (9.6)	38 (9.1)	0.810
ICH	68 (7.4)	37 (7.1)	31 (7.9)	0.656	38 (7.6)	30 (7.2)	0.823
SAH	18 (2.0)	9 (1.7)	9 (2.3)	0.545	10 (2.0)	8 (1.9)	0.933
Transient ischemic attack	56 (6.1)	27 (5.2)	29 (7.4)	0.171	34 (6.8)	22 (5.3)	0.342
Stroke mimics, *n* (%)	168 (24.8)	110 (28.2)	58 (20.2)	0.017	83 (23.4)	85 (26.3)	0.388
Stroke chameleons, *n* (%)	239 (32.0)	132 (32.0)	107 (31.8)	0.955	146 (35.0)	93 (28.1)	0.044
Daily volume, median (IQR)							
Stroke alerts	2 (1-3)	2 (1-3)	3 (2-4)	0.002	1 (0-2)	1 (0-2)	0.275
Confirmed strokes	2 (1-4)	2 (1-3)	3 (2-4)	<0.001	1 (1-2)	1 (1-2)	0.005
Reperfusion of ischemic strokes, *n* (%)	203 (33.5)	126 (37.2)	77 (28.8)		110 (32.8)	93 (34.3)	
Not eligible	403 (66.5)	213 (62.8)	190 (71.2)	0.031	225 (67.2)	178 (65.7)	0.701
IVT	97 (16.0)	54 (15.9)	43 (16.1)	0.953	59 (17.6)	38 (14.0)	0.231
EVT	86 (14.2)	62 (18.3)	24 (9.0)	0.001	41 (12.2)	45 (16.6)	0.126
Combined treatment	20 (3.3)	10 (2.9)	10 (3.7)	0.586	10 (3.0)	10 (3.7)	0.629
Median timeliness metrics, min (IQR)							
Onset-to-door[†]	114 (75-198)	119 (78-205)	110 (74-196)	0.606	93 (67-159)	137 (89-269)	<0.001
Door-to-needle	41 (29-59)	41.5 (31-58)	41 (29-60)	0.850	46 (31-63)	37.5 (28-51)	0.078
Door-to-groin	81.5 (61-102)	73.5 (61-100)	90 (65-110)	0.206	88 (60-107)	78 (61-98)	0.517
Baseline NIHSS, median (IQR)[‡]	8 (4–15)	9 (5–15)	7 (4–15)	0.072	8 (4–15)	8 (5–15)	0.643
Discharge NIHSS, median (IQR)[‡]	3 (1–5)	3 (1–5)	3 (1–5)	0.962	3 (1–4)	3 (1–5)	0.360

IQR, interquartile range; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; IVT, intravenous thrombolysis; EVT, endovascular treatment; NIHSS, National Institutes of Health Stroke Scale.

[†]Only patients with established onset of symptoms are included ($n = 433$).

[‡]Baseline ($n = 343$) and discharge NIHSS ($n = 172$) are reported only for ischemic stroke patients who were considered for reperfusion therapy.

Data Collection

Demographic and clinical characteristics such as age, gender, stroke type, daily stroke volume, type of reperfusion therapy, acute stroke care timeliness metrics (onset-to-door, door-to-needle, door-to-groin), and the National Institutes of Health Stroke Scale (NIHSS) scores at admission and discharge were collected for all confirmed strokes and stroke alerts referred by EMS. True positives were defined as EMS-suspected strokes followed by in-hospital confirmation of stroke (ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage) or TIA after a complete neurologic evaluation, including neuroimaging by CT or MRI. False positives, or stroke mimics, were defined as stroke alerts given an alternative diagnosis after a full assessment. Furthermore, we collected information on false negative cases, termed stroke chameleons. The NIHSS score was documented only for patients who were considered for reperfusion therapy.

Statistical Analysis

We compared categorical variables using the χ^2 test and Fisher's exact test, as appropriate. Based on their Gaussian distribution, the quantitative variables were compared using the Student's *t*-test or Mann–Whitney *U* test. Baseline characteristics and outcome measures were compared before and after the training and based on EMS location strata (urban *vs*. suburban). The 95% confidence intervals (CI) were calculated, where applicable.

Before the training, baseline trends in monthly EMS performance and hospital-based outcomes were assessed using univariate linear regression and the χ^2 test for trend. We performed multivariable logistic regression models to assess the association between the training and EMS performance and in-hospital outcome measures. To account for potential confounding effects of age, gender, EMS location, and stroke subtype where appropriate, we used the hybrid backward/forward stepwise selection using the Akaike information criterion (26), removing variables with a nonsignificant ($p > 0.05$) association. Age was forced into all models as an *a priori* confounder. $P < 0.05$ (two-sided) was considered statistically significant. IBM SPSS Statistics 23.0 software (IBM Corp., Armonk, NY, United States) and R version 3.6.2 were used for statistical analyses.

RESULTS

We enrolled 916 patients with a median age of 75 (interquartile range: 66–82) years, of which 502 (54.8%) were female. In total, 677 suspected strokes (73.9%) were admitted to the ED, comprising 509 true positives (55.6%) and 168 false positives (18.3%). In contrast, EMS did not recognize 239 (26.1%) strokes, labeled false negatives or stroke chameleons. The study groups before and after the training were balanced in terms of demographics, stroke subtype, and baseline NIHSS (**Table 1**). Urban EMS providers transported 500 patients (54.6%), whereas suburban EMS transported 416 (45.4%).

Demographic and Clinical Characteristics Before and After the Training

More daily stroke alerts (3 [2–4] *vs.* 2 [1–3], $p = 0.002$) and confirmed strokes (3 [2–4] *vs.* 2 [1–3], $p < 0.001$) were observed in the post-training period. However, proportionally fewer patients were eligible for reperfusion therapy (28.8% post-training *vs.* 37.2% pre-training, $p = 0.031$) due to a decreased rate of endovascular therapy compared to the pre-training period (9.0% *vs.* 18.3%, $p = 0.001$). No significant differences in IVT and combined treatment groups were observed.

The median onset-to-door time (110 [74–196] min *vs.* 119 [78–205] min, $p = 0.606$) improved numerically after the training but did not reach statistical significance. The door-to-needle, door-to-groin times, and discharge NIHSS did not differ significantly before and after the stroke training.

We did not identify any trends in EMS performance or prehospital care metrics during the 6 months before the EMS training (**Table 2**); thus, next, we assessed the impact of EMS training on these metrics.

EMS Training Effect

In the pairwise comparison, the PPV for the identification of acute stroke patients was significantly higher in the post-training period (79.8% [75.1–84.4] *vs.* 71.8% [67.3–76.3], $p = 0.017$). Notably, however, the proportion of false negatives and the EMS recognized stroke patients (sensitivity) did not differ before and after the intervention (**Table 3**). Although there was a weak trend for improvement in door-to-needle times and in-hospital mortality, there was no statistically significant difference in other hospital-based outcomes before and after the EMS training.

Multivariable logistic regression showed improved odds of stroke identification (PPV) (**Table 4**), which remained significant after adjusting for age, gender, and EMS location (adjusted odds ratio (aOR) 1.6 [1.1–2.4]). Furthermore, we observed improved odds of patient arrival within 90 min of stroke onset (aOR 1.6 [1.1–2.5]), driven by an improvement in OTD $\leq$ 90 min time in urban EMS (56.8% [46.4–66.7] post-training *vs.* 41.1% [33.5–49.0] pre-, $p = 0.019$).

Urban vs. Suburban EMS

EMS-referred patients from urban and suburban areas did not differ in demographic characteristics, acute stroke types, baseline and discharge stroke severity, and eligibility for reperfusion therapy (**Table 1**). Although there were more overall daily confirmed strokes referred by urban EMS (1 [1–2] *vs.* 1 [0–2], $p = 0.005$), there was no difference in the proportion of suspected strokes *vs.* total patients transported by urban and suburban EMS; thus, indicating similar suspected stroke prevalence in both groups.

There was no significant baseline difference in PPV values between urban and suburban EMS (**Figure 2**). However, after the training, the PPV improved in the urban EMS group (84.9% [78.9–90.8] *vs.* 71.2% [65.1–77.2], $p = 0.003$), but not in the suburban EMS (75.0% [68.0–82.0] *vs.* 72.6% [66.0–79.2], $p = 0.621$). Marginally more stroke chameleons were referred by urban than suburban EMS (35.0% [30.6–39.7] *vs.* 28.1% [23.5–33.2], $p = 0.044$), indicating lower sensitivity in the urban EMS group. However, there was no significant difference in sensitivity before and after the training within each EMS group.

Shorter overall median onset-to-door time was observed in patients referred by urban EMS (93 [67–159] min *vs.* 137 [89–269] min, $p < 0.001$), and more urban patients reached the CSC within 90 min (46.9% [40.6–53.2] 25.3% [19.7–31.8], $p < 0.001$) compared to the suburban EMS. After the training, there was a weak trend for improvement of the absolute onset-to-door time (84.5 min *vs.* 108.0 min, $p = 0.074$) and a significant improvement in onset-to-door $\leq$ 90 min rate in the urban EMS (70.5% [60.2–79.0] *vs.* 41.1% [33.5–49.0], $p = 0.019$), but not in the suburban EMS group (28.0% [19.9–37.8] *vs.* 22.8% [15.7–31.9], $p = 0.406$) (**Figure 2**).

DISCUSSION

We have several main findings from this prospective interrupted time-series study evaluating the effect of interactive EMS training on prehospital stroke care. First, we found a sustained improvement of prehospital stroke recognition during at least four consecutive months after the training. Second, we found an improved rate of timely transfers of suspected strokes to the hospital, demonstrating the overall benefit of EMS training on the continuum of prehospital care. Third, we

TABLE 2 | Trends in emergency medical services performance and hospital-based outcomes during the 6 months before the training.

Performance	Regression coefficient†	*P*-value‡
EMS recognized stroke patients (sensitivity)	−0.0173	0.527
PPV for identification of stroke patients	−0.0027	0.692
Onset-to-door ≤90 min	−0.0131	0.924
Door-to-CT ≤30 min	−0.0035	0.848
IVT rate	−0.0054	0.425
Door-to-needle time ≤30 min	−0.0169	0.415
In-hospital mortality	0.0028	0.606

PPV, positive predictive value; CT, computed tomography; IVT, intravenous thrombolysis.
†Linear regression coefficient for the proportion of cases with each outcome during 1-month intervals.
‡χ2 or Fisher's Exact Test for trend, as appropriate.

found a trend of decreased in-hospital mortality that could be related to more timely stroke patient transport to the hospital. Finally, the training effect was more pronounced in the urban EMS group and, thus, we discuss the possible reasons and implications.

We found fewer stroke mimics in the post-training period without an increase in the false negative rate. Thus, increasing the PPV did not result in suboptimal triage of strokes, nor did it deprive stroke patients of time-sensitive revascularization treatment. The improvement of PPV was driven by a reduced rate of stroke mimics in the urban EMS group. One of the reasons for significantly improved PPV in the urban but not the suburban EMS group could be the implementation of new national regulation of prehospital stroke triage on January 1, 2020, that partially overlapped with the post-training period. According to the new law, suspected stroke patients were transferred directly to stroke-ready hubs bypassing primary evaluation in the regional hospitals irrespective of their LKW time. The new guidelines were designed to improve access to reperfusion therapy for stroke patients in the suburban regions. However, the stroke triage pathway change may have increased the false positive rate in the suburban EMS group as they transported more suspected stroke cases directly to the CSC instead of the regional hospitals. Thus, we speculate that the weak trend of PPV improvement in the suburban EMS group reflects the effect of EMS training offsetting the expected dip of PPV in the suburban EMS group. Another possible explanation could be differences in stroke knowledge between urban and suburban paramedics before the training or other variables, such as differing socioeconomic status, comorbidities, or secular trends, not evaluated in this study.

The increase in PPV after the training is clinically relevant because it can help reduce the false positive cases overflowing the acute stroke care pathways. Optimal utilization of the frontline stroke care and neuroimaging resources is particularly relevant during peak hours of stroke incidence, such as the morning hours (27) or public health emergencies, as was the case during the COVID-19 pandemic (23). Therefore, continuous efforts are crucial to ensure optimal prehospital stroke identification.

Previous studies have shown that a brief educational EMS intervention could substantially improve EMS knowledge of prehospital stroke scales, prenotification compliance, and field triage protocols (10, 28). Moreover, a recent prospective study by Oostema et al. assessed the real-world impact of EMS training on prehospital stroke recognition and found that an online EMS education module coupled with performance feedback was associated with improved stroke recognition sensitivity, increased hospital prenotification, and faster tPA delivery (9). In addition to these findings, our study demonstrates that in-person interactive EMS training improves prehospital stroke identification and timely transfer to the ED. We also note that the sensitivity in our study did not change after the training, which might be explained by a relatively high baseline performance. The baseline stroke recognition sensitivity in our study (68.0%) was comparable to the post-training sensitivity in the Oostema et al. study (69.5%), suggesting a ceiling effect of stroke sensitivity improvement. Consequently, the improvement in PPV did not

TABLE 4 | Logistic regression models showing the association between emergency medical services training and acute stroke care performance measure and hospital-based outcomes.

Outcome	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
EMS recognized stroke patients (sensitivity)	1.0 (0.7–1.4)	1.0 (0.7–1.4)‡
PPV for identification of stroke patients	1.6 (1.1–2.2) *	1.6 (1.1–2.4) *
Onset-to-door time ≤90 min	1.4 (1.0–2.1)	1.6 (1.1–2.5)‡*
Door-to-CT time ≤30 min	1.0 (0.4–2.9)	0.8 (0.3–2.4)
IVT rate	1.1 (0.7–1.6)	1.1 (0.7–1.6)
Door-to-needle time ≤30 min	1.5 (0.7–3.5)	1.5 (0.6–3.5)
In-hospital mortality	0.6 (0.3–1.0)	0.6 (0.4–1.1)‡

OR, odds ratio; CI, confidence interval; PPV, positive predictive value; CT, computed tomography; IVT, intravenous thrombolysis.
†Adjusted for age, gender, and EMS location (urban vs. suburban).
‡Adjusted for age, gender, EMS location, and stroke type.
**P < 0.05.*

TABLE 3 | Emergency medical services performance and hospital-based outcomes among 916 suspected or confirmed strokes before and after the training.

Performance	All patients (95% CI)	Before training (95% CI)	After training (95% CI)	*P*-value
EMS recognized stroke patients (sensitivity)	68.0% (64.6–71.3)	68.0% (63.3–72.3)	68.2% (63.0–72.9)	0.955
PPV for identification of stroke patients	75.2% (71.9–78.4)	71.8% (67.3–76.3)	79.8% (75.1–84.4)	0.017
Onset-to-door ≤90 min	37.2% (32.8–41.8)	33.7% (28.2–39.8)	42.0% (35.0–49.3)	0.079
Door-to-CT ≤30 min†	84.2% (78.6–88.6)	84.1% (76.8–89.5)	84.4% (74.7–90.9)	0.956
IVT rate‡	19.3% (16.4–22.6)	18.9% (15.1–23.4)	19.9% (15.5–25.1)	0.764
Door-to-needle time ≤30 min	27.4% (20.1–36.1)	23.4% (14.8–35.1)	32.1% (21.1–45.5)	0.297
In-hospital mortality§	10.5% (8.4–13.2)	12.3% (9.4–16.0)	7.8% (5.1–11.8)	0.070

CI, confidence interval; PPV, positive predictive value; CT, computed tomography; IVT, intravenous thrombolysis.
†Included stroke patients, who underwent reperfusion treatment (n = 203).
‡Only ischemic stroke patients (n = 606).
§Only hospitalized stroke patients (n = 636).

result in a false negative rate (type II error) increase and, thus, did not deprive stroke patients of time-sensitive treatment. Similarly, our intervention did not affect the reperfusion therapy rate. Nevertheless, our baseline IVT rate was at least two times higher (15.9%) than in 10 out of 13 studies reported in a recent meta-analysis (19). Therefore, this suggests interventions had less effect in populations with high baseline performance.

A recent attempt to enhance prehospital stroke care was undertaken in the Paramedic Acute Stroke Treatment Assessment (PASTA), a multicenter randomized clinical trial in the UK. Surprisingly, the intervention resulted in 8.5 min longer onsite care time and did not show any tPA rate improvement (17). Arguably, sophisticated prehospital assessment protocols did not facilitate IVT decision-making. On the other hand, we find conflicting results from non-randomized intervention studies showing that prehospital intervention improved reperfusion therapy rates (11, 19) and in-hospital treatment times (9, 11). In addition to the previous studies, our study shows that interactive EMS training can improve stroke recognition and prehospital transfer times and, thus, improve the overall timeliness of acute stroke care. In contrast, we did not observe changes in hospital-based metrics. However, our study was not designed to evaluate the in-hospital performance since we did not collect data on hospital prenotification rate, and the EMS staff was not involved in the clinical care after the ED admission. Other in-hospital variables, such as imaging capacity, availability of rapid image interpretation, and ED workload influence the stroke care but are not accounted for in our study.

The training effect on timely prehospital transportation was more robust in the urban compared to the suburban EMS group. Since transport time from suburban regions is longer due to greater distances between the patient and the CSC, fewer patients could arrive within 90 min of symptom onset. Furthermore, due to the national regulatory changes during the study, all suspected stroke cases were to be transported to stroke-ready hospitals, irrespective of the time of symptom onset. Thus, the number of stroke alerts outside the acute treatment window increased in the suburban but not the urban EMS group. Hence, the actual training effect in the suburban EMS group was confounded by these regulatory changes.

The recent stroke triage changes in Lithuania were aimed to increase EVT access to patients in suburban areas by transporting suspected stroke cases directly to stroke-ready centers. However, the choice between drip and ship or mothership model is context-specific (29) and poses thorny clinical dilemmas (30). EVT has a remarkable treatment effect with the number needed to treat of 2.6 to reduce disability in the early hours after stroke onset (31). If large vessel occlusion (LVO) is suspected, direct transfer to a CSC with EVT capacity might be privileged, as a shorter time to reperfusion would improve the treatment effect (32). On the other hand, bypassing primary stroke centers with IVT capacity might cause unnecessary delays to IVT and an increase in false positive large vessel occlusion transfers due to suboptimal triage. To address these questions, the RACECAT study was conceived in Catalonia, Spain, a first randomized clinical trial in the field (ClinicalTrials.gov, identifier: NCT02795962). After randomizing 1,401 patients, the preliminary study results showed no difference in ischemic stroke outcomes between drip-and-ship and mothership models in a highly coordinated stroke network (33). Similarly, in our study, we did not observe any change in IVT rate, whereas surprisingly there was a decrease in EVT rate. However, the comparison of IVT and EVT rates before and after the training should be made with caution. The post-training period coincides with the increased transfer rate of suspected suburban stroke cases with elongated LKW, resulting in a higher number of strokes arriving at the CSC beyond the EVT window. Another explanation could be a cyclical variation in EVT eligible cases. Nevertheless, since all stroke alerts were analyzed, the regulation change was not expected to confound the comparison of EMS stroke recognition. Future studies should evaluate the impact of the triage regulation change on reperfusion therapy accessibility and stroke outcomes that was out of scope of the current study.

Although the direct transfer to the CSC could be most beneficial for LVO patients, the FAST scale used in our study

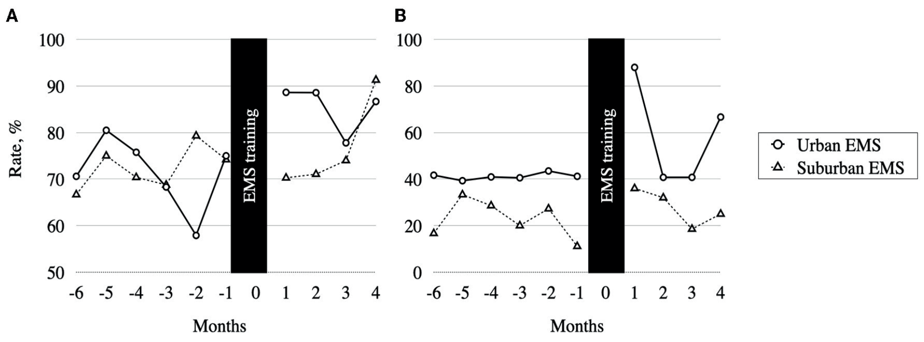

FIGURE 2 | Emergency medical services (EMS) performance before and after the EMS training. **(A)** Positive predictive value (PPV) for identification of stroke patients. **(B)** Onset-to-door time ≤90 min rate stratified by EMS location.

was not explicitly designed to detect LVO. In this context, a prospective study comparing eight prehospital scales for LVO identification showed that an adapted version of Gaze-Face-Arm-Speech-Time (G-FAST) had high LVO recognition accuracy similar or higher to other LVO scores (34). Moreover, improving the PPV of the stroke screening tools can increase the area where the mothership model provides the best stroke treatment outcome (29). More studies will be needed to explore the optimal LVO prediction methods to triage patients for different transfer pathways.

The main strength of our study is a prospective design and relatively large sample size. The blinding of EMS staff to the assessment allowed us to evaluate the training effect and avoid the apprehension bias, also known as the Hawthorne effect, when participants modify their behavior in response to their awareness of being observed (35). The main limitation of our study was the absence of a control group to fully evaluate the actual effect of the intervention. However, since there were no significant differences in demographic and clinical characteristics of suspected stroke cases before and after the training, the confounding by unmeasured factors was limited. Also, the overlap between the first month before and the last month after the training allowed us to compare similar calendar periods. Second, due to optional attendance, just over half of the EMS staff underwent the training. However, this rather introduces a bias toward the null, and we expect a stronger training effect with higher participation. Third, we found increased daily stroke rates in the post-training period, influenced by the change in the stroke triage regulations in suburban regions. However, the marginal increase in stroke prevalence during the post-training period could not fully explain the PPV improvement. We observed improved PPV with non-overlapping CI in the urban EMS and a weak trend in the suburban group favoring a consistent effect of EMS training across both groups. Fourth, our intervention did not target the dispatcher stroke recognition or hospital prenotification rate; thus, the inclusion of additional actors in the intervention might further improve the prehospital stroke care. Fifth, due to the emerging COVID-19 pandemic, we terminated our analysis before the national lockdown which significantly limited access to urgent and non-urgent healthcare (23). Had the study been continued and more cases were included in the post-training period, we could have expected a more significant effect on the in-hospital mortality. Also, we could not conclude on the long-term effects of the training beyond four months. Finally, our study was conducted in a very high cardiovascular risk population (20). These findings are generalizable to currently underrepresented populations with similar healthcare systems and EMS staffing patterns, including but not limited to Baltic states and Eastern European countries. Therefore, this study could inform prehospital clinical care and study design to improve prehospital stroke workflow using publicly available e-learning stroke education resources.

CONCLUSIONS

Interactive EMS training improved the prehospital stroke recognition that was maintained during at least four consecutive months. Consequently, we found a measurable improvement in prehospital stroke transfer metrics and a trend toward decreased in-hospital mortality providing evidence for EMS training's positive effect on overall acute stroke care. The EMS training effect was more robust in the urban than the suburban EMS group. Thus, context-tailored training programs should be considered for EMS providers in different locations. Future studies should evaluate the long-term effects of the EMS training on prehospital stroke care, hospital-related outcomes, and aim to determine optimal retraining intervals.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Vilnius Regional Bioethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LS, KM, DJ, AV, and RM: conception and design of the research. KM and RM: acquisition of the data. LS, KM, and RM: analysis and interpretation of the data and drafting the manuscript. LS, KM, AW, AV, KP, ES, KJ, AE, DJ, and RM: critical revision of the manuscript. All authors approved the final version to be published.

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Article

High Prevalence of Atrial Fibrillation in a Lithuanian Stroke Patient Cohort

Rytis Masiliūnas [1,*], Austėja Dapkutė [1], Julija Grigaitė [1], Jokūbas Lapė [2], Domantas Valančius [1], Justinas Bacevičius [3], Rimgaudas Katkus [3], Aleksandras Vilionskis [4], Aušra Klimašauskienė [1], Aleksandra Ekkert [1] and Dalius Jatužis [1]

[1] Center of Neurology, Vilnius University, 08661 Vilnius, Lithuania; austeja.dapkute@santa.lt (A.D.); julija.grigaite@santa.lt (J.G.); domantas.valancius@santa.lt (D.V.); ausra.klimasauskiene@santa.lt (A.K.); aleksandra.ekkert@santa.lt (A.E.); dalius.jatuzis@santa.lt (D.J.)
[2] Faculty of Medicine, Vilnius University, 03101 Vilnius, Lithuania; jokubaslape@gmail.com
[3] Center of Cardiology and Angiology, Vilnius University, 08661 Vilnius, Lithuania; justinas.bacevicius@santa.lt (J.B.); rimgaudas.katkus@santa.lt (R.K.)
[4] Clinic of Neurology and Neurosurgery, Vilnius University, 03101 Vilnius, Lithuania; aleksandras.vilionskis@rvul.lt
* Correspondence: rytis.masiliunas@santa.lt; Tel.: +370-688-62356

Abstract: *Background and Objectives*: Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a five-fold increased risk for acute ischemic stroke (AIS). We aimed to estimate the prevalence of AF in a Lithuanian cohort of stroke patients, and its impact on patients regarding case fatality, functional outcome, and health-related quality of life (HRQoL) at 90 days. *Materials and Methods*: A single-center prospective study was carried out for four non-consecutive months between December 2018 and July 2019 in one of the two comprehensive stroke centers in Eastern Lithuania. A telephone-based follow-up was conveyed at 90 days using the modified Rankin Scale (mRS) and EuroQoL five-dimensional three-level descriptive system (EQ-5D-3L) with a self-rated visual analog scale (EQ-VAS). One-year case fatality was investigated. *Results*: We included 238 AIS patients with a mean age of 71.4 ± 11.9 years of whom 45.0% were female. A striking 97 (40.8%) AIS patients had a concomitant AF, in 68 (70.1%) of whom the AF was pre-existing. The AIS patients with AF were at a significantly higher risk for a large vessel occlusion (LVO; odds ratio 2.72 [95% CI 1.38–5.49], $p = 0.004$), and had a more severe neurological impairment at presentation (median NIHSS score (interquartile range): 9 (6–16) vs. 6 (3–9), $p < 0.001$). The LVO status was only detected in those who had received computed tomography angiography. Fifty-five (80.9%) patients with pre-existing AF received insufficient anticoagulation at stroke onset. All patients received a 12-lead ECG, however, in-hospital 24-h Holter monitoring was only performed in 3.4% of AIS patients without pre-existing AF. Although multivariate analyses found no statistically significant difference in one-year stroke patient survival and favorable functional status (mRS 0–2) at 90 days, when adjusted for age, gender, reperfusion treatment, baseline functional status, and baseline NIHSS, stroke patients with AF had a significantly poorer self-perceived HRQoL, indicated by a lower EQ-VAS score (regression coefficient ± standard error: $\beta = -11.776 \pm 4.850$, $p = 0.017$). *Conclusions*: In our single-center prospective observational study in Lithuania, we found that 40.8% of AIS patients had a concomitant AF, were at a higher risk for an LVO, and had a significantly poorer self-perceived HRQoL at 90 days. Despite the high AF prevalence, diagnostic tools for subclinical AF were greatly underutilized.

Keywords: ischemic stroke; atrial fibrillation; antithrombotic treatment; Lithuania; survival

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 33.5 million people globally, and is a well-established independent risk factor for acute ischemic stroke (AIS) [1,2]. Cardioembolic stroke is known to be more severe [3] and associated with greater morbidity, mortality, and disability [4,5]. In addition, stroke patients with AF exhibit a high risk of recurrent ischemic events [6,7]. Therefore, detecting AF is crucial both for primary and secondary stroke prevention. The earlier and the longer cardiac monitoring occurs after a stroke, the higher the chance to detect AF and consequently prescribe the right antithrombotic treatment for secondary prevention of stroke [8,9].

Oral anticoagulation (OAC) reduces the risk of stroke and all-cause mortality compared with control or placebo in patients with non-valvular AF [10,11]. In addition, there is no evidence of better stroke outcomes in patients with AF taking antiplatelet agents versus not taking any antithrombotic medication [12,13]. However, OAC is frequently under-prescribed, especially in the elderly [14], and of those treated, the proportion of adherent patients could be as low as 41% one year later [15–17].

The incidence of AIS and stroke mortality in Lithuania is amongst the highest in the world [18,19], in large part due to a high prevalence and poor control of cardiovascular risk factors [18,20]. Moreover, in Lithuania the expected increase in age-adjusted stroke incidence and prevalence rates is the highest, and the expected decrease in stroke mortality is the lowest among all European Union countries [21]. However, data regarding the proportion of AIS cases associated with AF is lacking, although studies from the other two Baltic States indicate some of the highest AF prevalence among AIS patients globally, reaching up to a striking 48.6% [22–24].

The aim of our study was (1) to estimate the prevalence of AF in a Lithuanian cohort of stroke patients, and its (2) impact on patients' case fatality, functional outcome, and health-related quality of life (HRQoL) at 90 days.

2. Materials and Methods

2.1. Study Design and Population

A single-center prospective study was carried out for four full non-consecutive months to account for seasonal differences—between December 2018 and July 2019. All patients with AIS, treated in Vilnius University Hospital—one of the two comprehensive stroke centers in Eastern Lithuania—were included.

The study was approved by the Lithuanian Bioethics Committee and complied with STROBE guidelines for observational research.

2.2. Baseline Characteristics

Demographic and clinical characteristics such as age, sex, presence of AF, National Institutes of Health Stroke Scale (NIHSS) score on admission, presence of a large vessel occlusion (LVO), reperfusion therapy, antithrombotic treatment used, and AF screening status were collected. The AF screening included 24-h Holter monitoring only, as Stroke Unit telemetry was not routinely performed during the study period. Pre-existing AF was defined as AF known prior to a stroke onset. Atrial fibrillation detected after a stroke (AFDAS) was defined as a newly detected AF after a stroke in patients without pre-existing AF [25].

2.3. Follow-Up and Outcomes

The main outcomes for this analysis were: (1) all-cause in patient, 90-day, and 1-year case fatality, (2) favorable functional outcome at 90 days (modified Rankin Scale (mRS) 0–2), and (3) self-reported HRQoL at 90 days, measured by the EuroQoL five-dimensional three-level descriptive system (EQ-5D-3L).

Either AIS patients or their caregivers who could participate in a telephone-based follow-up were surveyed 90 days after stroke onset using the mRS. In addition, the EQ-5D-3L with a self-rated visual analog scale (EQ-VAS) was used as a self-reported measure of

HRQoL. The EQ-5D-3L is a widely used instrument, describing the respondent's health state in terms of three severity levels in each of the five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [26,27]. Individual values were transformed into an index value ranging from −0.074 to 1 using a European value set with 1 being the best health possible, 0 being dead, and a score < 0 representing a health condition worse than death [28]. The EQ-VAS provided information about the participants' subjective health perception: the AIS patients were asked to score their health state on that specific day of the survey on a scale from 0 to 100, with 0 being "the worst health you can imagine" and 100 being "the best health you can imagine".

Information on all-cause patient case fatality, including the date of death, was obtained retrospectively from electronic health records one year after stroke onset. It is mandatory to issue all death certificates electronically in Lithuania [29], therefore, precise information on all patients was available.

2.4. Statistical Analysis

The qualitative variables were presented as count and percentage. The quantitative variables, based on their Gaussian distribution, were presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Individuals were categorized into groups by the presence of AF. The AF group was further divided depending on whether the AF was known prior to admission or was detected after the stroke during the hospital stay. Student's *t*-test or Mann–Whitney U test was used to compare quantitative variables, as appropriate. For categorical variables, Chi-square test or Fisher's exact test was used, and 95% confidence intervals (CI) were calculated, as appropriate. We used a binary multiple logistic regression model to calculate the odds ratio (OR) of having an LVO in patients with pre-existing or newly diagnosed AF, adjusted by age and sex. Our definition of an LVO included the occlusion sites accessible for thrombectomy: middle cerebral artery 1st and 2nd segments (M1, M2), anterior cerebral artery (A1 segment), posterior cerebral artery 1st and 2nd segments (P1, P2), basilar artery, vertebral artery, and internal carotid artery [30].

"Time 0" for survival analyses was the date of hospitalization for the index stroke event. A comparison of the probability of freedom from the prognostic binary endpoints between groups with and without AF was performed by Kaplan–Meier survival analysis. Differences in the Kaplan–Meier curves were evaluated with the log-rank test. Univariate and multivariate Cox regression analyses were also performed to determine the prognostic implications of each variable on patient death. Variables investigated included AF, age, gender, presence of reperfusion treatment, good baseline functional status (mRS 0–2), and baseline NIHSS. Variables with $p < 0.1$ on univariate analysis were entered into the multivariable model. The hazard ratios (HR) were presented with their 95% confidence intervals.

In addition, both unadjusted and adjusted logistic regression analyses were performed with a good functional outcome (mRS 0–2) as the dependent variable. The adjusted logistic analyses were performed using stepwise forward selection, based on significant variables in the adjusted models.

Finally, multiple linear regression was used to estimate the associations between the independent variables (age, gender, AF, reperfusion treatment, good baseline functional status, and baseline NIHSS) and HRQoL, represented by EQ-VAS and EQ-5D-3L index scores. A value of $p < 0.05$ (two-sided) was considered to be statistically significant. The software R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

3. Results

3.1. Demographic and Clinical Characteristics

Overall, 238 AIS patients with a mean age of 71.4 ± 11.9 years were included in our study of which 45.0% were female (Table 1). Ninety-seven (40.8%) AIS patients were found to have concomitant atrial fibrillation: 68 (28.6%) were diagnosed with AF prior to hospital arrival, and 29 (12.2%) had AFDAS (Table 2, Figure 1, Table S1). While comparing the groups with and without AF, stroke patients with AF were significantly older (75.7 vs. 68.4 years, $p < 0.001$), and had a more severe neurological impairment at presentation (a median NIHSS score of 9 [IQR 6–16] vs. 6 [3–9], $p < 0.001$). However, the baseline level of functional independence (mRS 0–2) did not differ between groups and reached an overall 89.5%. In addition, the proportion of female patients was significantly larger in the AF group (58.8% vs. 35.5%, $p < 0.001$).

A total of 160 (67.2%) AIS patients underwent computed tomography angiography (CTA), in 51.3% of whom an LVO was found. Patients with AF were at a significantly higher risk for an LVO compared to patients without AF with an odds ratio of 2.72 (95% CI 1.38–5.49, $p = 0.004$), when adjusted by age and gender. Sixty-one (38.1%) patients had an LVO in the anterior circulation, 17 (10.6%) in the posterior circulation, and 4 (2.5%) patients had an LVO in both. Anterior circulation stroke was significantly more common in patients with a known LVO and AF (55.2% vs. 25.8%, $p < 0.001$).

Table 1. Demographic and clinical characteristics for stroke patients with and without atrial fibrillation. Significant *p*-values are shown in bold.

	All Stroke Patients (*n* = 238)		Stroke Patients with AF (*n* = 97)		Stroke Patients without AF (*n* = 141)		*p*-Value
Female, *n* (%)	107	(45.0)	57	(58.8)	50	(35.5)	<0.001
Mean age, years (SD)	71.4	(11.9)	75.7	(11.0)	68.4	(11.5)	<0.001
Baseline median mRS ≤ 2, *n* (%)	213	(89.5)	88	(90.7)	125	(88.7)	0.609
Baseline NIHSS, median (IQR)	6	(4–12)	9	(6–16)	6	(3–9)	<0.001
Risk factors, *n* (%)							
Hypertension	217	(91.2)	93	(95.9)	124	(87.9)	0.034
Diabetes mellitus	50	(21.0)	26	(26.8)	24	(17.0)	0.069
Dyslipidemia	185	(77.7)	65	(67.0)	120	(84.1)	<0.001
History of stroke/TIA	51	(21.4)	25	(25.8)	26	(18.4)	0.175
Congestive heart failure	91	(38.2)	58	(59.8)	33	(23.4)	<0.001
Coronary artery disease	82	(34.5)	51	(52.6)	31	(22.0)	<0.001
Peripheral artery disease	12	(5.0)	5	(5.2)	7	(5.0)	0.947
Underlying malignancy	15	(6.3)	4	(4.1)	11	(7.8)	0.251
CTA performed, *n* (%)	160	(67.2)	67	(69.1)	93	(66.0)	0.615
Reperfusion, *n* (%)	91	(38.2)	38	(39.2)	53	(37.6)	
Not eligible	147	(61.8)	59	(60.8)	88	(62.4)	0.805
IVT	41	(17.2)	13	(13.4)	28	(19.9)	0.195
EVT	41	(17.2)	20	(20.6)	21	(14.9)	0.250
Combined treatment	9	(3.8)	5	(5.2)	4	(2.8)	0.357
Large vessel occlusion, *n* (%) †	82	(51.3)	44	(65.7)	38	(40.9)	0.002
Anterior	61	(38.1)	37	(55.2)	24	(25.8)	<0.001
Posterior	17	(10.6)	5	(7.5)	12	(12.9)	0.271
Both	4	(2.5)	2	(3.2)	2	(2.0)	0.739
None	78	(48.8)	23	(34.3)	55	(59.1)	0.002
24-h Holter monitoring, *n* (%) ‡							
Performed					5	(3.5)	
Not performed					136	(96.5)	

AF—atrial fibrillation, SD—standard deviation, mRS—modified Rankin Scale, NIHSS—National Institutes of Health Stroke Scale, IQR—interquartile range, TIA—transient ischemic attack, CTA—computed tomography angiography, IVT—intravenous thrombolysis, EVT—endovascular treatment. † Out of those in whom CTA was performed. ‡ Only stroke patients without known AF.

Table 2. Antithrombotic treatment status for stroke patients with pre-existing atrial fibrillation (AF) on admission and for all AF patients on discharge.

	Pre-Existing AF before Stroke Onset (*n* = 68)		All AF on Discharge ¶ (*n* = 84)	
Antithrombotic treatment status, *n* (%)				
No treatment	23	(33.8)	0	(0)
Antiplatelets	8	(11.8)	10	(11.9)
LMWH †	0	(0)	10	(11.9)
Warfarin †	26	(36.8)	23	(27.4)
NOACs †	11	(16.2)	41	(48.8)
INR, median (IQR) ‡	1.28	(1.20–1.79)		
INR within therapeutic range, *n* (%) ‡	5	(19.2)		
Insufficient anticoagulation, *n* (%) §	55	(80.9)		

AF—atrial fibrillation, LMWH—low molecular weight heparin, NOACs—non-vitamin K antagonist oral anticoagulants, INR—international normalized ratio, IQR—interquartile range. † With or without antiplatelets. ‡ Only for patients using warfarin (*n* = 26). § Includes AF patients with no treatment, treated with antiplatelets, INR < 2, and inadequate NOAC dosing. ¶ Excluding diseased patients.

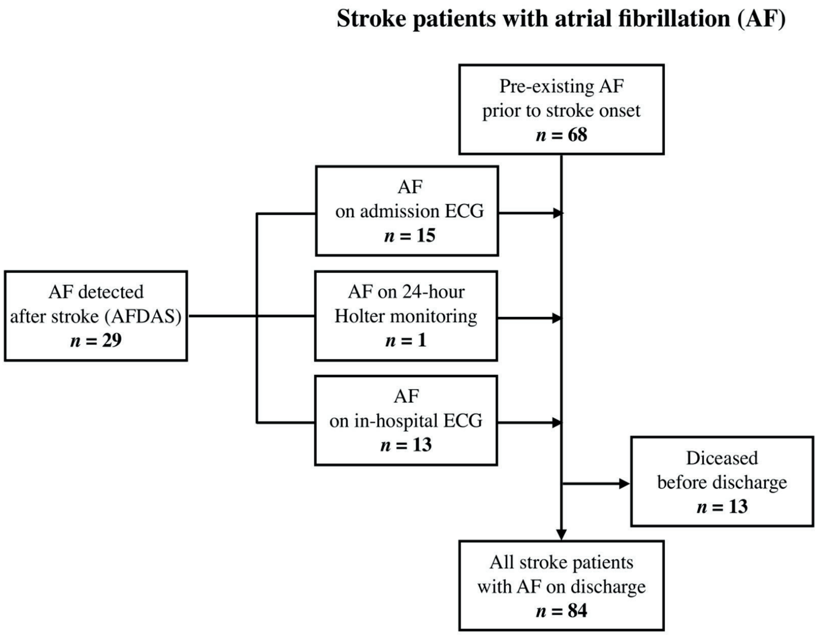

Figure 1. Flowchart of acute ischemic stroke patients with atrial fibrillation.

3.2. Antithrombotic Treatment

Out of 68 patients with pre-existing AF, 11 (16.2%) took non-vitamin K antagonist oral anticoagulants (NOACs), 26 (36.8%) vitamin K antagonists, 8 (11.8%) antiplatelets, and 23 (33.8%) did not take any antithrombotic treatment at index stroke event (Table 2).

Out of 26 (36.8%) patients on vitamin K antagonists, only five (19.2%) had an International Normalized Ratio (INR) within the therapeutic range on admission. Strikingly, 55 (80.9%) stroke patients with pre-existing AF at stroke onset were receiving insufficient anticoagulation (received no antithrombotic treatment, took antiplatelets, warfarin with INR < 2, or had inadequate NOAC dosing). The therapeutic range for INR was considered to be 2.0–3.0.

At discharge, 64 (76.2%) patients were prescribed oral anticoagulants—23 (27.4%) warfarin and 41 (48.8%) NOACs. Out of the 20 remaining patients, 10 (11.9%) were given low-molecular-weight heparins and 10 (11.9%) were prescribed treatment with antiplatelets. In the antiplatelets group, oral anticoagulants were contraindicated for four patients due to a high risk of bleeding, for one patient due to high stroke severity, and five (6.0%) patients with AF had no documented contraindications (unexplained reasons).

3.3. Screening for AF

All patients received at least one 12-lead ECG, however, only five (3.4%) patients without pre-existing AF had 24-Holter monitoring performed during the hospitalization for the index event.

3.4. Patient Survival, Functional Outcome, and HRQoL

The Kaplan–Meier survival curve displays the 1-year probability of survival of AIS patients with and without AF (Figure 2). The overall all-cause case fatality was greatest in the first 90 days after stroke (21.8%; 95% CI: 16.8–27.6%), and the 1-year cumulative risk of death was 29.0% (95% CI: 23.3–35.2%) (Table 3). A log-rank test for a difference in time to death among stroke patients with and without AF was significant ($p < 0.001$), in favor of patients without AF. In univariate Cox regression analysis, age ($p < 0.001$), presence of AF ($p < 0.001$), baseline good functional status ($p < 0.001$), and baseline NIHSS ($p < 0.001$) were found to be significant factors that have influence on overall stroke patient survival (Table 4). However, in the multivariable model, only age ($p = 0.007$), and baseline NIHSS ($p < 0.001$) contributed significantly.

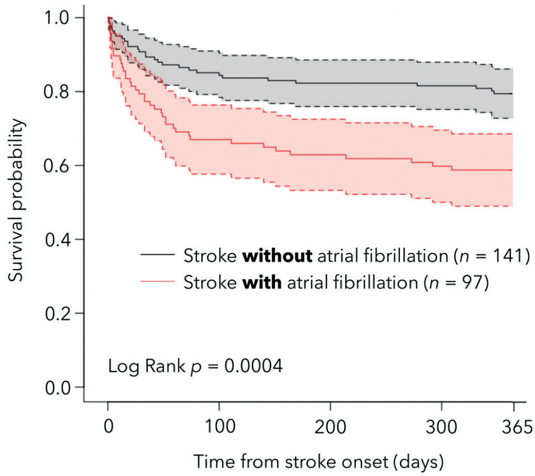

Figure 2. Kaplan–Meier survival plots and 95% confidence intervals for ischemic stroke patients with and without atrial fibrillation.

A total of 133 out of 186 surviving patients or caregivers completed the mRS survey at 90 days; 58.6% of respondents had an mRS score ≤ 2 (56.3% in stroke with AF group, 60.0% in stroke without AF group, $p = 0.673$), and were considered to be able to look after themselves without daily assistance (Table 3). However, AF did not have a statistically significant influence on the favorable functional outcome (mRS 0–2) in a multivariable binary logistic regression analysis, where the presence of reperfusion treatment (OR 3.91

[95% CI 1.66–10.05], $p = 0.003$) and the baseline NIHSS score (OR 0.82 [95% CI 0.73–0.90], $p < 0.001$) were the only two significant factors (Table S2).

Table 3. Case fatality, functional outcome, and health-related quality of life of stroke patients with and without atrial fibrillation at 90 days.

	All Stroke Patients (n = 238)		Stroke Patients with AF (n = 97)		Stroke Patients without AF (n = 141)		p-Value
Case fatality, n (%)							
In-hospital case fatality	19	(8.0)	13	(13.4)	6	4.3)	0.011
90-day case fatality	52	(21.8)	31	(32.0)	21	(14.9)	0.002
1-year case fatality	69	(29.0)	40	(41.2)	29	(20.6)	<0.001
Median mRS ≤ 2 at 90 days, n (%) †	78	(58.6)	27	(56.3)	51	(60.0)	0.673
Missing mRS, n (%)	53	(28.5)	18	(27.3)	35	(29.2)	0.784
EQ-5D domain, n (%)							
Decreased mobility	48	(36.6)	17	(36.2)	31	(36.9)	0.933
Difficulty with self-care	54	(41.2)	26	(48.9)	31	(36.9)	0.041
Problems performing usual activities	88	(67.7)	31	(67.4)	55	(65.5)	0.825
Pain or discomfort	56	(43.8)	21	(45.7)	35	(42.7)	0.745
Anxious or depressed	51	(40.5)	18	(39.1)	33	(40.7)	0.935
EQ-5D score index, mean (SD)	0.61	(0.32)	0.62	(0.32)	0.58	(0.33)	0.549
Missing EQ-5D, n (%)	60	(32.3)	21	(31.8)	39	(32.5)	0.924
EQ-VAS, median (IQR)	50	(40–70)	50	(30–70)	60	(40–76.25)	0.022
Missing EQ-VAS, n (%)	75	(40.3)	27	(40.9)	48	(40.0)	0.904

AF—atrial fibrillation, mRS—modified Rankin Scale, EQ-5D—EuroQoL Five Dimensions, SD—standard deviation, EQ-VAS—EuroQoL visual analog scale, IQR—interquartile range. † Out of those alive at 90 days, not lost to follow-up (n = 133).

Table 4. Univariate and multivariable Cox regression analysis for overall survival of stroke patients.

Covariates		Univariate			Multivariable †		
		HR (95% CI)		p-Value	HR (95% CI)		p-Value
Age		1.05	(1.03–1.07)	**<0.001**	1.03	(1.01–1.06)	**0.007**
Gender	**Female**	1.00	(reference)				
	Male	0.69	(0.43–1.11)	0.125			
Atrial fibrillation	**No**	1.00	(reference)		1.00	(reference)	
	Yes	2.33	(1.44–3.75)	**<0.001**	1.27	(0.74–2.19)	0.385
Reperfusion treatment	**No**	1.00	(reference)				
	Yes	1.18	(0.73–1.90)	0.507			
Baseline mRS ≤ 2	**No**	1.00	(reference)		1.00	(reference)	
	Yes	0.33	(0.19–0.59)	**<0.001**	0.56	(0.30–1.05)	0.072
Baseline NIHSS		1.13	(1.10–1.17)	**<0.001**	1.11	(1.07–1.14)	**<0.001**

HR—hazard ratio, CI—confidence interval, mRS—modified Rankin Scale, NIHSS—National Institutes of Health Stroke Scale. † Akaike information criterion = 550.9.

A total of 126 patients or caregivers completed the EQ-5D-3L survey and 111 AIS patients evaluated their EQ-VAS score 90 days after the index AIS event. Stroke patients with AF evaluated their EQ-VAS score significantly worse in comparison to those without AF (50 [IQR: 30–70] vs. 60 [40–76.25], $p = 0.022$), suggesting a lower perception of the HRQoL (Table 3). However, the EQ-5D-3L index scores did not differ significantly between groups. Although multivariate linear regression analyses showed that AF had a significant influence on EQ-VAS (β ± SE: −11.776 ± 4.850, $p = 0.017$), no such influence was demonstrated for the EQ-5D-3L index score (β ± SE: −0.013 ± 0.060, $p = 0.833$), when adjusted for age, gender, presence of reperfusion treatment, baseline good functional status, and baseline

NIHSS score (Table S3). In addition, the only statistically significant difference between the five EQ-5D-3L domains' values was found for difficulty with self-care, which was more common in patients with AF (48.9% vs. 36.9, $p = 0.041$) (Table 3).

3.5. Stroke Patients with AFDAS

A history of stroke/TIA and congestive heart failure were significantly less common in AIS patients with AFDAS as compared to AIS patients with pre-existing AF (10.3% vs. 32.4, $p = 0.024$, and 44.8% vs. 66.2, $p = 0.050$, respectively). In addition, stroke patients with AFDAS evaluated their EQ-VAS score as significantly better in comparison to those with pre-existing AF, even when adjusted for age, gender, cardiovascular risk factors, reperfusion treatment, baseline functional status, and baseline NIHSS (42.5 [IQR: 22.5–57.5] vs. 70 [50–75], $p = 0.022$) (Table S1).

4. Discussion

In our single-center prospective observational study, we found that 40.8% of AIS patients had a concomitant AF—one of the largest figures in the available literature. In addition, 80.9% of stroke patients with pre-existing AF received insufficient anticoagulation at stroke onset. Finally, although multivariate analyses found no statistically significant difference in one-year stroke patient survival and functional status at 90 days, when adjusted for age, gender, reperfusion treatment, baseline functional status, and baseline NIHSS, stroke patients with AF had a significantly worse self-perceived HRQoL, indicated by a lower EQ-VAS score.

The prevalence of AF among AIS patients varies between countries and was found to be as high as 31–38% in a population-based registry in Greece [31,32], and up to 48.6% in two separate hospital-based registries in neighboring Latvia [22,24]. The high prevalence of AF found in our investigated AIS patient population could indicate a regional trend, as other cardiovascular risk factors are largely similar within the Baltic States [32]. This contrasts with the fact that the regional prevalence of AF in the Eastern European general population is lower than in Western Europe and North America [2]. Herein, a small penetration of NOACs due to the poor reimbursement conditions could play a role, as NOACs are reimbursed only following the warfarin failure or contraindications, and cannot be initially prescribed by a general practitioner or a neurologist—a policy previously common in the Central and Eastern European states [33]. This reasoning is supported in our patient cohort by the low rate of OAC in patients with pre-existing AF before stroke onset. Although a patient's personal decision to deliberately discontinue OAC in asymptomatic AF or currently normal rhythm could also play a role.

Our sample confirmed the association between AF in AIS patients and an LVO—a fact long identified in previous literature [34]. While LVOs are present in less than one-third of stroke cases, they contribute to around three-fifths of post-stroke dependence and death, and more than 90% of post-stroke mortality [35]. Therefore, it is crucial to ensure adequate AF screening in AIS patients, as prompt administration of OAC could contribute to an 8.4% annual absolute risk reduction of stroke recurrence compared with antiplatelet therapy [36].

The 2018 American Heart Association/American Stroke Association guidelines state that cardiac monitoring for potential arrhythmia should be performed for at least the first 24 h after a stroke [37]. Whereas the 2020 European Society of Cardiology guidelines recommend extending cardiac monitoring to at least 72 h in patients after AIS without pre-existing AF [38]. Finally, in patients with ischemic stroke of undetermined origin, the use of implantable devices for long-term cardiac monitoring instead of non-implantable devices is recommended by the recent European Stroke Organization guidelines [38,39]. However, we found that a mere 3.4% of the AIS patients without pre-existing AF underwent 24-h Holter monitoring while in hospital, suggesting that AF prevalence could be even higher. This may be due to the poor availability of 24-h Holter devices in addition to the lack of strict standard operational procedures, as the current national Lithuanian stroke care guidelines do not mention extensive cardiac monitoring [40].

There is a growing trend in utilizing new wearable devices for screening for AF or even mitigating the risks of patients with known AF, guided by the newest consensus document of the European Heart Rhythm Association [41]. This is especially so as previous randomized controlled trials have demonstrated that a composite outcome of 'ischemic stroke/systemic thromboembolism, death, and rehospitalization' could be lower with mobile AF application interventions compared with usual care [42]. However, more randomized controlled trials are needed to prove the concept in a hospital-based AIS setting.

Although multivariate analysis found no statistically significant difference in one-year stroke patient survival and functional status at 90 days, multiple previous studies have shown that AF could be associated with an increased risk of death and severe disability after AIS [4,5,43]. As the magnitude of the association is shown to be substantially diminished after multivariable adjustment, much of the association can be explained by other factors. Our findings are in line with other studies, showing that the most important determinants underlying the association between AF and mortality after ischemic stroke are age and baseline stroke severity [43]. We speculate that the small sample size precluded us from finding a significant association, and further studies with a larger study population should give more robust conclusions.

In our study population, patients with previously diagnosed AF were found to have a significantly lower perception of their HRQoL—a finding reiterated from previous studies [44]. However, a significant difference was observed only in EQ-VAS, but not in EQ-5D-3L index scores—a pattern that had been observed previously [45]. Furthermore, stroke patients with pre-existing AF evaluated their EQ-VAS score as significantly worse in comparison to those with AFDAS, indicating that a subgroup of patients with known AF had the worst self-perceived quality of life at three months. This is consistent with previous literature in which pre-existing AF has been shown to be associated with a higher disease burden and worse clinical outcomes [25]. Nevertheless, these patterns must be interpreted cautiously due to a small patient sample.

Our study is the first on the Lithuanian population that estimates the prevalence of AF among a hospital-based AIS patient cohort, and investigates its impact on patients' case fatality, HRQoL, and long-term functional outcomes. In addition, it raises awareness about the potential need for more stringent national guidelines for cardiac monitoring in stroke patients, as suggested by the exceptionally low in-hospital 24-h Holter monitoring rates in the studied population. Finally, we explore the profile of antithrombotic treatment received by AIS patients with AF, discussing the possibility of insufficient anticoagulation, as it may be one of the overlooked causes of stroke in this group of patients.

Our study has several limitations. Foremost, as this was a single-center study with a rather small sample size, our findings could have limited generalizability, and some weak statistical associations could have been missed. Furthermore, due to the small rate of in-hospital 24-h Holter monitoring, some patients could have been misclassified as not having AF, which could have impacted the overall differences in case fatality and functional outcome. In addition, the use of antithrombotic medication was determined from documentation only, and anti-factor Xa activity was not measured, amounting to some error in OAC adherence. Fourth, the 90-day follow-up for assessing the functional status and HRQoL was telephone-based, and in many cases, caregivers responded to the survey, which makes it difficult to compare to studies where HRQoL is self-reported using visual aids. Fifth, we used the EQ-5D-3L which has been validated for stroke patients [46], but as there is no Lithuanian value set available to this date, a European value set was used. Finally, a considerable proportion of the patients were lost to the 90-day follow-up survey due to a short period of time when the investigators could not conduct the telephone survey because of technical reasons. However, because there was no bias towards a certain group of patients, we believe that this should not have affected our results.

5. Conclusions

In our single-center prospective observational study in Lithuania, we found that 40.8% of AIS patients had a concomitant AF, were at a higher risk for an LVO, and had a significantly poorer self-perceived HRQoL at 90 days. Despite the high AF prevalence, only a small proportion of subjects received proper anticoagulation at stroke onset, whereas in-hospital diagnostic tools for subclinical AF were greatly underutilized.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/medicina58060800/s1. Table S1: Demographic, clinical characteristics, and outcomes for stroke patients with pre-existing atrial fibrillation, and atrial fibrillation detected after stroke (AFDAS); Table S2: Unadjusted and adjusted binary logistic regression analysis for good functional outcome (mRS $\leq$ 2) as dependent variable in patients with stroke; Table S3: Multiple linear regression analyses of variables impacting EQ-VAS and EQ-5D-3L index scores.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Lithuanian Bioethics Committee (protocol code number 1-14-03/1-6).

Informed Consent Statement: The data analyzed in this study were derived from a prospectively collected institutional stroke registry. Written informed consent was obtained from the patients to publish this paper.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviations

AF	Atrial fibrillation
AFDAS	Atrial fibrillation detected after stroke
AIS	Acute ischemic stroke
CI	Confidence intervals
CTA	Computed tomography angiography
EQ-5D-3L	EuroQoL five-dimensional three-level descriptive system
EQ-VAS	EQ-5D-3L with a self-rated visual analog scale
HR	Hazard ratio
HRQoL	Health-related quality of life
INR	International Normalized Ratio
IQR	Interquartile range
LVO	Large vessel occlusion
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NOACs	non-vitamin K antagonist oral anticoagulants
OAC	Oral anticoagulation
OR	Odds ratio
SD	Standard deviation

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Table S1. Demographic, clinical characteristics, and outcomes for stroke patients with pre-existing atrial fibrillation, and atrial fibrillation detected after stroke (AFDAS)

	Pre-existing AF before stroke onset (n = 68)	**AFDAS (n = 29)**	***P* value**
Female, n (%)	39 (57.4)	18 (62.1)	0.666
Mean age, years (SD)	74.6 (11.1)	78.3 (10.5)	0.122
Baseline median mRS ≤ 2, n (%)	63 (92.6)	25 (86.2)	0.444
Baseline NIHSS, median (IQR)	8.5 (5.75–16.25)	10 (6–16)	0.959
Risk factors, n (%)			
Hypertension	67 (98.5)	27 (93.1)	0.212
Diabetes mellitus	23 (33.8)	6 (20.7)	0.196
Dyslipidemia	50 (73.5)	24 (82.8)	0.514
History of stroke/TIA	22 (32.4)	3 (10.3)	**0.024**
Congestive heart failure	45 (66.2)	13 (44.8)	**0.050**
Coronary artery disease	38 (55.9)	14 (48.3)	0.492
Peripheral artery disease	5 (7.4)	0 (0.0)	0.317
Underlying malignancy	3 (4.4)	1 (3.4)	1
CTA performed, n (%)	50 (73.5)	17 (58.6)	0.146
Reperfusion, n (%)	27 (39.7)	11 (37.9)	
Not eligible	41 (60.3)	18 (62.1)	0.870
IVT	7 (10.3)	6 (20.7)	0.169
EVT	16 (23.5)	4 (13.8)	0.412
Combined treatment	4 (5.9)	1 (3.4)	1

Large vessel occlusion, n (%) †	34 (68.0)	10 (58.8)	0.491
Anterior	27 (39.7)	10 (34.5)	0.230
Posterior	5 (7.4)	0 (0.0)	0.319
Both	2 (2.9)	0 (0.0)	1
None	16 (50.0)	7 (65.5)	0.160
Case fatality, n (%)			
In-hospital case fatality	9 (13.2)	4 (13.8)	1
90-day case fatality	19 (27.9)	12 (41.4)	0.194
1-year case fatality	28 (41.2)	12 (41.4)	0.985
Median mRS ≤ 2 at 90 days, n (%) ‡	17 (50.0)	10 (71.4)	0.174
Missing mRS, n (%)	15 (30.6)	3 (17.6)	0.361
EQ-5D domain, n (%) ‡			
Decreased mobility	16 (48.5)	1 (7.1)	**0.008**
Difficulty with self-care	19 (57.6)	4 (28.6)	0.111
Problems performing usual activities	22 (68.8)	11 (78.6)	0.496
Pain or discomfort	16 (50.0)	5 (35.7)	0.371
Anxious or depressed	14 (45.2)	4 (28.6)	0.343
EQ-5D score index, median (IQR) ‡	0.57 (0.22–0.81)	0.75 (0.59–0.85)	0.127
Missing EQ-5D, n (%)	18 (36.7)	3 (17.6)	0.227
EQ-VAS, median (IQR) ‡	42.5 (22.5–57.5)	70 (50–75)	**0.004**
Missing EQ-VAS, n (%)	19 (38.8)	8 (47.0)	0.141

AF – atrial fibrillation, AFDAS – atrial fibrillation detected after stroke, SD – standard deviation, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale, IQR – interquartile range, TIA – transient ischemic attack, CTA – computed tomography angiography, IVT – intravenous thrombolysis, EVT – endovascular treatment, EQ-5D – EuroQoL Five Dimensions, EQ-VAS – EuroQoL visual analog scale.
† Out of those in whom CTA was performed.
‡ Out of those alive at 90 days, not lost to follow-up.

Table S2. Unadjusted and adjusted binary logistic regression analysis for good functional outcome (mRS ≤ 2) as dependent variable in patients with stroke

Covariates		**Unadjusted**		**Adjusted †**	
		OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age		0.98 (0.95–1.01)	0.125		
Gender	**Female**	1.00 (reference)			
	Male	1.29 (0.64–2.59)	0.475		
Atrial fibrillation	**No**	1.00 (reference)			
	Yes	0.86 (0.42–1.76)	0.673		
Reperfusion treatment	**No**	1.00 (reference)		1.00 (reference)	
	Yes	1.86 (0.91–3.85)	0.091	3.91 (1.66–10.05)	**0.002**
Baseline NIHSS		0.87 (0.79–0.94)	**<0.001**	0.82 (0.73–0.90)	**<0.001**

OR – odds ratio, CI – confidence interval, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale.
† Akaike information criterion = 163.6

Table S3. Multiple linear regression analyses of variables impacting EQ-VAS and EQ-5D-3L index scores

Independent variables		**EQ-VAS score (n = 111)**		**EQ-5D-3L index score (n = 126)**	
		Beta coefficient (SE)	***P* value**	**Beta coefficient (SE)**	***P* value**
Age		–0.055 (0.200)	0.790	0.001 (0.003)	0.955
Gender	**Female**	(reference)		(reference)	
	Male	–5.831 (4.916)	0.238	–0.027 (0.061)	0.658
Atrial fibrillation	**No**	(reference)		(reference)	
	Yes	–11.776 (4.850)	**0.017**	–0.013 (0.060)	0.833
Reperfusion treatment	**No**	(reference)		(reference)	
	Yes	9.571 (4.583)	**0.039**	0.137 (0.058)	**0.021**
Baseline mRS ≤ 2	**No**	(reference)		(reference)	
	Yes	24.733 (10.744)	**0.023**	0.239 (0.131)	0.071
Baseline NIHSS		–1.611 (0.496)	**0.002**	–0.026 (0.006)	**<0.001**

EQ-VAS – EuroQoL visual analog scale, EQ-5D-3L – EuroQoL Five Dimensions Three Levels, SE – standard error, mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale.

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Changes in Prehospital Stroke Care and Stroke Mimic Patterns during the COVID-19 Lockdown

Kazimieras Melaika [1,†], Lukas Sveikata [2,3,†], Adam Wiśniewski [4], Altynshash Jaxybayeva [5], Aleksandra Ekkert [6], Dalius Jatužis [6] and Rytis Masiliūnas [6,*]

1 Faculty of Medicine, Vilnius University, 03101 Vilnius, Lithuania; k.melaika@gmail.com
2 J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02109, USA; lsveikata@mgh.harvard.edu
3 Institute of Cardiology, Medical Academy, Lithuanian University of Health Sciences, 50161 Kaunas, Lithuania
4 Department of Neurology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, 85-094 Bydgoszcz, Poland; adam.lek@wp.pl
5 Department of Neurology, Astana Medical University, Nur-Sultan 010000, Kazakhstan; altynshash@gmail.com
6 Center of Neurology, Vilnius University, 08661 Vilnius, Lithuania; aleksandra.ekkert@mf.vu.lt (A.E.); dalius.jatuzis@mf.vu.lt (D.J.)
* Correspondence: rytis.masiliunas@santa.lt; Tel.: +370-688-62744; Fax: +370-688-62728
† Co-first authorship.

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Abstract: The impact of COVID-19 lockdown on prehospital stroke care is largely unknown. We aimed to compare stroke care patterns before and during a state-wide lockdown. Thus, we analysed prospective data of stroke alerts referred to our stroke centre between 1 December 2019 and 16 June 2020, and compared them between two periods—15 weeks before and 13 weeks during the state-wide lockdown declared in Lithuania on 16 March 2020. Among 719 referrals for suspected stroke, there was a decrease in stroke alerts (rate ratio 0.61, 95% CI (0.52–0.71)), stroke admissions (0.63, 95% CI (0.52–0.76)), and decrease in prehospital stroke triage quality (positive predictive value 72.1% vs. 79.9%, $p = 0.042$) during the lockdown. The onset-to-door time was longer (153.0 vs. 120.5 min, $p = 0.049$) and seizures and intracranial tumours were more common among stroke mimics (16.9% vs. 6.7%, $p = 0.012$ and 9.6% vs. 3.0%, $p = 0.037$, respectively). We conclude that there was a decline in prehospital stroke triage quality during the lockdown despite low COVID-19 incidence in the country. Moreover, we observed an increase in hospital arrival delays and severe conditions presenting as stroke mimics. Our findings suggest that improved strategies are required to maintain optimal neurological care during public health emergencies.

Keywords: COVID-19; emergency medical services; stroke; misdiagnosis; stroke mimic; triage

1. Introduction

Emergency medical services (EMS) are the first healthcare contact for most stroke patients [1,2] and play a crucial role in identifying acute stroke [3]. Accurate recognition and timely transport of patients with suspected stroke to comprehensive stroke centres (CSCs) are closely correlated with acute stroke care success [2,4]. Any delay in administering intravenous thrombolysis (IVT) and endovascular treatment (EVT) negatively impacts patients' functional outcomes [5].

The typical presentation of stroke consists of a sudden onset of a focal neurological deficit. However, other disorders may also have similar clinical presentations. These false positives, called stroke mimics, comprise from 15% to 37% of suspected stroke patients at the Emergency Department (ED) [6,7]. The consequences of stroke mimics may result in inappropriate usage of stroke care facilities and medical resources and increased workload on overwhelmed ED personnel [6,8]. A decreasing number of stroke admissions observed during the ongoing severe acute respiratory coronavirus 2 (SARS-CoV-2) outbreak causing the coronavirus disease 2019 (COVID-19) pandemic raised the concern of suboptimal prehospital identification and referral of acute illnesses [9–12].

The substantial strain imposed by the pandemic on the medical systems worldwide caused significant concern regarding the potential ramifications on acute stroke care [13,14]. Soon after identifying the first COVID-19 case in Lithuania, a strict national lockdown was declared on 16 March 2020 [15]. Interestingly, in Lithuania, the community spread and deaths due to COVID-19 during the first wave of the pandemic remained exemplarily low (a total of 1775 infections and 76 deaths as of 16 June 2020) [16]. However, strict restrictions on public life and reduced access to healthcare services, including primary care and preventive programs [15], as well as public fear of coronavirus, might have affected stroke care. Understanding the impact of state-wide lockdown measures on acute stroke care is crucial to improving healthcare systems' coordination during public health emergencies. There are currently few studies evaluating stroke care in low COVID-19 incidence settings [17,18] and no studies addressing the impact on prehospital stroke triage.

To assess the impact of COVID-19 lockdown on prehospital stroke care and referral patterns, we analysed data from our stroke care network. The aim of our study was (1) to compare the accuracy of the prehospital identification of acute stroke among different healthcare providers, (2) to assess stroke incidence and acute care timeliness metrics, and (3) to evaluate the distribution of stroke mimics before and during the state-wide COVID-19 lockdown. We hypothesised that lockdown measures would be associated with decreased stroke triage quality, increased delays in stroke care, and changes in the pattern of conditions mimicking stroke.

2. Methods

2.1. Study Design

A single-centre prospective observational study was carried out on prehospital stroke triage quality between 1 December 2019 and 16 June 2020, at Vilnius University Hospital (VUH)—one of the two comprehensive stroke centres in Eastern Lithuania with a catchment population of 945,000 inhabitants. The collected data were compared among two equal periods—15 weeks before and 13 weeks during a state-wide lockdown declared on 16 March 2020 (Figure 1) [15].

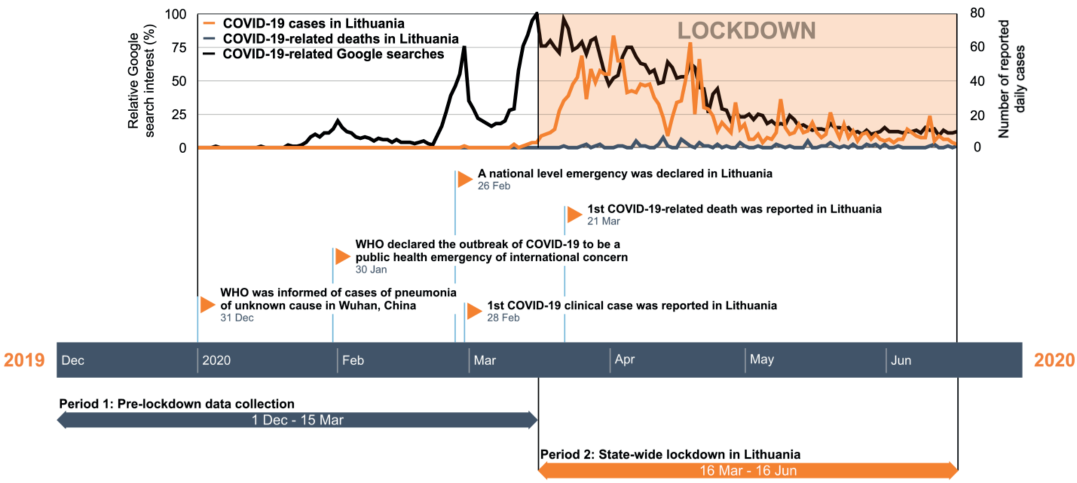

Figure 1. COVID-19 public concern and study timeline. Timeline of data collection periods overlapped with normalised data from COVID-19 related Google searches in Lithuania (100—high interest; 0—no or insufficient interest data) and COVID-19 daily incidence as reported by the Lithuanian National Public Health Center. COVID-19, coronavirus disease 2019; WHO, World Health Organization.

The study was approved by a regional bioethics committee and complies with STROBE guidelines for observational research [19].

2.2. Study Population

All patients referred to the VUH Emergency Department either by EMS or an outpatient physician with a prehospital diagnosis of suspected stroke or transient ischaemic attack (TIA) were included. A specialist neurologist in the ED ascertained stroke cases. Study flowchart of patients included in the study can be seen in Figure 2.

Throughout Lithuania, emergency medical care is provided free of charge 24/7 to everyone, regardless of health insurance status. EMS staff includes a certified medical specialist—a nurse or a paramedic—who decides whether a patient needs to be taken to a CSC. Face Arm Speech Test (FAST) is uniformly used for the identification of a suspected stroke/TIA [3]. Alternatively, any primary care or specialist physician can refer a patient directly to the ED, in case of suspected stroke.

2.3. Data Collection

Demographic and clinical characteristics such as age, sex, stroke type, National Institutes of Health Stroke Scale (NIHSS) scores at admission and discharge, number and type of stroke mimics, reperfusion therapy, and acute stroke care timeliness metrics were collected for all stroke alerts. The NIHSS score was documented only for patients who were considered for reperfusion therapy. We compared the variables and positive predictive value (PPV) for the correct stroke identification among the EMS and referring physicians before and during the state-wide lockdown.

Public concern for COVID-19 was evaluated based on the relative Lithuanian Google search interest of the five most common COVID-19-related terms—"corona", "korona", "koronavirusas", "coronavirus", and "COVID", publicly available through Google Trends [20]. Google Trends has emerged as a useful tool to measure public concern of SARS-CoV-2 infection in the population [21]. Search query data was collected from Google Trends and was normalised to reflect the interest, expressed by 100 as high interest and lack of interest or insufficient data as 0. Lithuanian National Public Health Center data on daily COVID-19 cases and patient mortality were used to illustrate the magnitude of the COVID-19 pandemic in Lithuania [16].

2.4. Statistical Analysis

A Student's *t*-test and Mann–Whitney U test was used to compare quantitative variables, as appropriate. For categorical variables, the Chi-square test and Fisher's exact test were used, as appropriate. Individuals were further categorised into groups by referral type (EMS and referring physician) and periods (before and during the lockdown). At first, we evaluated the stroke presentation rates during different periods and different providers. We then used Poisson regression models with the daily counts of stroke alerts and stroke admissions as dependent variables and the study period as an independent variable. Second, we evaluated the stroke care metrics and the distribution of stroke mimics between different healthcare providers and periods. To assess the stroke triage quality, we calculated the positive predictive value (PPV) of acute stroke identification for each group with 95% confidence intervals (CI) and compared them before and during the lockdown. $p < 0.05$ (two-sided) was considered to be statistically significant. IBM SPSS Statistics 23.0 software (Armonk, NY, USA: IBM Corp) was used for statistical analyses.

3. Results

3.1. Demographic and Clinical Characteristics

In total, 719 patients with suspected stroke were included in our analysis: 493 referred by EMS and 226 by outpatient physicians (Figure 2). Patients did not differ significantly in sex and age, regardless of being referred by EMS or a physician (Table 1). None of the patients were diagnosed with COVID-19.

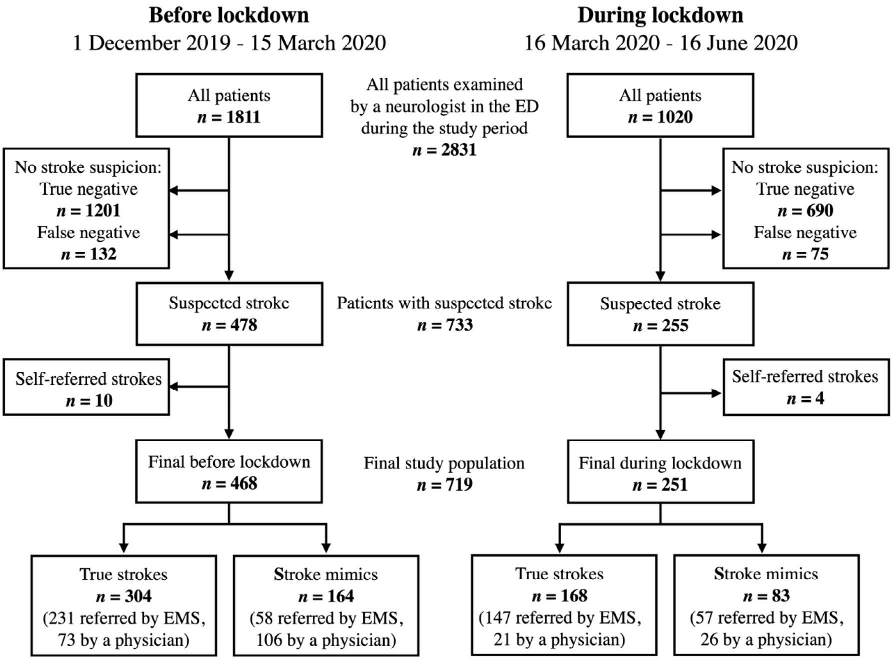

Figure 2. Flowchart of study population: patients examined by a neurologist in the Emergency Department (ED) of Vilnius University Hospital between 1 December 2019 and 16 June 2020. ED, emergency department; EMS, emergency medical services.

We observed significantly more daily stroke alerts and confirmed strokes in the EMS group compared to the outpatient physicians' group (2 [1–4] and 2 [1–2] vs. 1 [0–2] and 0 [0–1], respectively, $p < 0.001$). There were significantly fewer stroke mimics in the EMS group (23.3% vs. 58.4%, $p < 0.001$).

The median onset-to-door (OTD) time was twice as short in patients referred by EMS (116 min vs. 245, $p < 0.001$), however, the door-to-needle (DTN) time and the door-to-groin (DTG) time did not differ significantly between the groups. The baseline and discharge NIHSS scores also did not differ significantly, but there was a tendency for lower baseline NIHSS in the physicians' group (8 (4–15) vs. 6.5 (3–12), $p = 0.175$).

There were more patients with ischaemic stroke eligible for reperfusion therapy in the group referred by EMS (31.5% vs. 9.2%, $p < 0.001$). This significance was driven by a higher proportion of patients eligible for IVT (15.3% vs. 1.3%, $p < 0.001$). However, the eligibility for EVT (10.9% vs. 6.6%, $p = 0.395$) or combined treatment (5.3% vs. 1.3%, $p = 0.217$) did not differ significantly between the groups.

Table 1. Demographic and clinical characteristics of all stroke alerts.

	All Patients (n = 719)		Referred by EMS (n = 493)		Referred by A Physician (n = 226)		p-Value	Before Lockdown (n = 468)		During Lockdown (n = 251)		p-Value
Female, n (%)	431	59.9	286	58	145	64.2	0.118	280	59.8	151	60.2	0.931
Mean age, years (SD)	72.3	13.3	73	12.4	70.7	14.9	0.139	72.2	13.5	72.4	12.9	0.894
All strokes, n (%)	472	65.6	378	76.7	94	41.6		304	65.0	168	66.9	
Ischaemic stroke	397	55.2	321	65.1	76	33.6	<0.001	246	52.6	151	60.2	0.051
Haemorrhagic stroke	42	5.8	36	7.3	6	2.7	0.014	31	6.6	11	4.4	0.222
ICH	36	5	31	6.3	5	2.2	0.026	26	5.6	10	4.0	0.357
SAH	6	0.8	5	1.0	1	0.4	0.671	5	1.1	1	0.4	0.671
Transient ischaemic attack	33	4.6	21	4.3	12	5.3	0.532	27	5.8	6	2.4	0.039
Stroke mimics, n (%)	247	34.4	115	23.3	132	58.4	<0.001	164	35	83	33.1	0.595
Daily volume, median (IQR)												
Stroke alerts	3	(2–5)	2	(1–4)	1	(0–2)	<0.001	4	(3–6)	3	(1–4)	<0.001
Confirmed strokes	2	(1–3)	2	(1–2)	0	(0–1)	<0.001	3	(2–4)	2	(1–2)	<0.001
Reperfusion, n (%) †	108	27.2	101	31.5	7	9.2		66	26.8	42	27.8	
Not eligible	289	72.8	220	68.5	69	90.8	<0.001	180	73.2	109	72.2	0.830
IVT	50	12.6	49	15.3	1	1.3	<0.001	33	13.4	17	11.3	0.530
EVT	40	10.1	35	10.9	5	6.6	0.395	24	9.8	16	10.6	0.787
Combined treatment	18	4.5	17	5.3	1	1.3	0.217	9	3.7	9	6.0	0.285
Median timeliness metrics, min (IQR)												
Onset−to−door ‡	138.5	(82–274)	116	(76–245)	245	(145–378)	<0.001	120.5	(79–247)	153	(89–329)	0.049
Door−to−needle	37	(25–51)	37	(26–50)	35.5	(-)	0.790	39.5	(25–51)	35	(27–46)	0.557
Door−to−groin	86	(65–103)	86	(66–103)	83.5	(60–112)	0.918	85	(60–107)	87	(68–103)	0.946
Baseline NIHSS, median (IQR) §	7	(4–15)	8	(4–15)	6.5	(3–12)	0.175	8	(4–16)	7	(4–14)	0.415
Missing NIHSS, n (%)	167	42.1	113	35.2	54	71.1		110	44.7	57	37.7	
Discharge NIHSS, median (IQR) §	3	(1–6)	3	(1–6)	2.5	(0–5)	0.501	3	(1–6)	3	(1–5)	0.914
Missing NIHSS, n (%)	267	67.3	203	63.2	64	84.2		168	68.3	99	65.6	

EMS, emergency medical services; SD, standard deviation; ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; EVT, endovascular treatment; NIHSS, National Institutes of Health Stroke Scale. † Percentage of all ischaemic strokes. ‡ Only patients with established onset of symptoms are included (n = 282). § NIHSS is reported only for ischaemic stroke patients who were considered for reperfusion therapy.

3.2. Lockdown Data

There were no significant differences in age, sex, the proportion of stroke mimics, percentage of patients eligible for reperfusion therapy, median baseline and discharge NIHSS scores, median DTN or DTG time between patients admitted in the period before and during the lockdown. However, we found fewer patients with TIA (2.4% vs. 5.8%, $p = 0.039$), and longer median OTD time in patients admitted during the lockdown (153.0 vs. 120.5 min, $p = 0.049$). We also observed a decrease in the median daily volume of stroke alerts (3 [1–4] vs. 4 [3–6], $p < 0.001$) and confirmed strokes (2 [1–2] vs. 3 [2–4], $p < 0.001$) during the lockdown. Strikingly, during the lockdown, there was a threefold decrease in stroke referrals by outpatient physicians. However, the prevalence of confirmed strokes in the ED during the period before and during the state-wide lockdown remained stable (24.6% vs. 24.2%, $p = 0.807$) (Figure 2).

Poisson regression revealed that the lockdown period was associated with a reduction in daily stroke alerts with a rate ratio of 0.61 (95% CI 0.52–0.71, $p < 0.001$) and stroke admissions by 0.63 (95% CI 0.52–0.76, $p < 0.001$).

3.3. Prehospital Stroke Triage Quality

The positive predictive value (PPV) for identifying patients with acute stroke or TIA by EMS was significantly lower during the lockdown than the period before (72.1% vs. 79.9%, $p = 0.042$). However, the PPV did not change in the outpatient physicians' group (44.7% vs. 40.8%, $p = 0.629$). The overall PPV for acute strokes was significantly higher in the EMS group than the outpatient physicians' group (76.7% vs. 41.6%, $p < 0.001$) (Table 2).

Table 2. Positive predictive values (PPV) for the identification of patients with acute stroke by the Emergency Medical Services (EMS) and referring physicians.

	Total PPV (95% CI)	PPV before Lockdown (95% CI)	PPV during Lockdown (95% CI)	*p*-Value
Referred by				
EMS	76.7% (72.9–80.4) (*n* = 493)	79.9% (75.3–84.5) (*n* = 289)	72.1% (65.9–78.2) (*n* = 204)	0.042
Physician	41.6% (35.2–48.0) (*n* = 226)	40.8% (33.6–48.0) (*n* = 179)	44.7% (30.5–58.9) (*n* = 47)	0.629
p-value	<0.001	<0.001	<0.001	

CI, confidence interval.

3.4. Public Concern for COVID-19

As reflected by the relative Lithuanian Google search interest of the COVID-19-related terms, the coronavirus concern increased just before the national-level emergency was declared in Lithuania on 26 February 2020 and peaked at the start of the state-wide lockdown on 16 March 2020 (Figure 1). At that point, only 12 patients were diagnosed with COVID-19 overall in the country, and none had died from the disease [16]. In general, throughout the study period, the incidence and mortality of COVID-19 in Lithuania remained one of the lowest in Europe: 63.8 vs. 264.7/100,000 cumulative cases and 2.7 vs. 29.7/100,000 cumulative deaths by 16 June 2020 in Lithuania vs. the European Union, respectively [22].

3.5. Stroke Mimics

Seizures and infection/sepsis were significantly more common stroke mimics among those referred by EMS compared to the physicians (16.5% vs. 4.5% and 13.9% vs. 4.5%, $p = 0.002$ and $p = 0.010$, respectively), whereas peripheral vestibulopathies were significantly less common (0.9% vs. 18.0%, $p < 0.001$).

When comparing the two periods, isolated neurological symptoms associated with normal neurological work-up results were less frequent stroke mimics during the lockdown (2.4% vs. 11.6%, $p = 0.015$), whereas seizures and intracranial tumours were significantly more frequent (16.9% vs. 6.7% and 9.6% vs. 3.0%, p = 0.012 and p = 0.037, respectively) (Table 3).

Table 3. Most common stroke mimics.

Stroke Mimic, n (%)	All Mimics (n = 247)		Referred by EMS (n = 115)		Referred by A Physician (n = 132)		p-Value	before Lockdown (n = 164)		during Lockdown (n = 83)		p-Value
Seizure	25	(10.1)	19	(16.5)	6	(4.5)	0.002	11	(6.7)	14	(16.9)	0.012
Peripheral vestibulopathy	25	(10.1)	1	(0.9)	24	(18.0)	<0.001	21	(12.8)	4	(4.8)	0.072
Hypertensive encephalopathy	23	(9.3)	11	(9.6)	12	(9.1)	0.898	17	(10.4)	6	(7.2)	0.423
Infection/Sepsis	22	(8.9)	16	(13.9)	6	(4.5)	0.010	13	(7.9)	9	(10.8)	0.447
Toxic/Metabolic disorder †	18	(7.3)	9	(7.8)	9	(6.8)	0.761	9	(5.5)	9	(10.8)	0.126
Sequels of previous stroke	16	(6.5)	5	(4.3)	11	(8.3)	0.300	11	(6.7)	5	(6.0)	1.000
Intracranial tumour	13	(5.3)	9	(7.8)	4	(3.0)	0.151	5	(3.0)	8	(9.6)	0.037
Psychiatric condition ‡	13	(5.3)	7	(6.1)	6	(4.5)	0.588	11	(6.7)	2	(2.4)	0.153
Migraine and headache	10	(4.0)	4	(3.5)	6	(4.5)	0.755	8	(4.9)	2	(2.4)	0.502
Cardiovascular condition §	10	(4.0)	4	(3.5)	6	(4.5)	0.755	6	(3.7)	4	(4.8)	0.736
Syncope and presyncope	8	(3.2)	2	(1.7)	6	(4.5)	0.291	7	(4.3)	1	(1.2)	0.273
Facial nerve palsy	5	(2.0)	3	(2.6)	2	(1.5)	0.666	2	(1.2)	3	(3.6)	0.338
Musculoskeletal condition	5	(2.0)	2	(1.7)	3	(2.3)	1.000	3	(1.8)	2	(2.4)	1.000
Subdural haematoma	4	(1.6)	3	(2.6)	1	(0.8)	0.341	4	(2.4)	0		0.304
Peripheral neuropathy	4	(1.6)	1	(0.9)	3	(2.3)	0.626	3	(1.8)	1	(1.2)	1.000
Isolated symptoms associated with normal results ¶	21	(8.5)	6	(5.2)	15	(11.4)	0.084	19	(11.6)	2	(2.4)	0.015
Other neurological disease ❘❘	20	(8.1)	10	(8.7)	10	(7.6)	0.748	12	(7.3)	8	(9.6)	0.528
Other non−neurological disease #	5	(2.0)	3	(2.6)	2	(1.5)	0.666	2	(1.2)	3	(3.6)	0.338

EMS, Emergency Medical Services; CNS, central nervous system. † Includes electrolyte imbalances (n = 14), hypo- and hyperglycaemia (n = 2), hepatic encephalopathy (n = 1), and alcohol intoxication (n = 1). ‡ Panic attacks and anxiety (n = 8), as well as delirium (n = 5)). § Cardiac insufficiency (n = 4), cardiac arrhythmia (n = 2), acute myocardial infarction (n = 2), and pulmonary embolism (n = 2). ¶ Neurological symptoms that could not be classified into any other category since they did not meet any other set of diagnostic criteria or which have no organic explanation but are not clearly associated with a psychiatric disorder. ❘❘ Includes multiple sclerosis and other demyelinating diseases (n = 5), dementia (n = 4), transient global amnesia (n = 4), myelopathy (n = 2), CNS infection (n = 2), venous sinus thrombosis (n = 1), Parkinson's disease (n = 1), and myasthenia (n = 1). # Includes advanced cancer (n = 2), anemia (n = 2), and herpes zoster (n = 1).

4. Discussion

In this prospective study in an academic stroke centre with a large urban catchment population, we found a significant decrease in prehospital stroke triage quality and longer delays from symptom onset to hospital arrival during a state-wide COVID-19 lockdown. We also found a decreased number of stroke alerts and stroke admissions during the lockdown. In addition, serious neurological conditions, such as seizures and intracranial tumours, were encountered more often as stroke mimics. Our findings provide novel knowledge on the impact of the state-wide lockdown on prehospital stroke care in low COVID-19 incidence settings and help guide care delivery strategies during public health emergencies.

Although in our study, the overall 76.7% stroke identification accuracy by EMS was on the higher end compared to 64–78% reported in previous studies [3,23,24], we found that the PPV for acute stroke decreased during the lockdown in the EMS group. Although Lithuania has not experienced a significant surge of COVID-19 during the lockdown, we observed a significant increase in COVID-19 concern in the public, as indicated by Google Trends data on COVID-19 related searches. We speculate that the latter might have influenced prehospital stroke care and the decreased stroke triage quality could have in part resulted from the fear of COVID-19 exposure and EMS staff's hesitation to perform a thorough neurological evaluation rather than relocation of healthcare resources. Besides, the PPV could have decreased due to the barriers from personal protective equipment, such as performing language evaluation with a surgical mask or a respirator [25]. On the other hand, all routine medical activities and surgeries during the state-wide lockdown were halted, resulting in a deterioration of preexisting neurological conditions [15]. Suboptimal routine care was reflected by a sharp decline in outpatient physician referrals of suspected stroke and an overall increase in the proportion of seizures and intracranial tumours mimicking stroke. Despite a significant decrease in the absolute numbers of daily stroke alerts and confirmed strokes during the lockdown, the prevalence of confirmed strokes in the ED did not differ between the periods, suggesting an effective reduction in PPV.

Decreased stroke triage quality has clinical implications during a public health crisis. More patients without the need for urgent time-sensitive care are delivered to the ED as stroke alerts, thus, increasing the workload on the ED personnel. Secondly, patients and personnel may be increasingly exposed to the risk of SARS-CoV-2 infection. Finally, continuous medical education is crucial even during a pandemic. Remote stroke care training and electronic learning modules can help ensure maintenance and adaptability of prehospital stroke care during public health emergencies [26].

In addition, the PPV for confirmed stroke was significantly higher among patients referred by the EMS rather than those referred by physicians. In contrast, a meta-analysis composed of 23 studies and 8839 patients found that the proportion of confirmed strokes was higher among the primary care (72%, 95% CI 58–86) than the ambulance referrals (55%, 95% CI 1–108) [27]. Nonetheless, the wide confidence intervals suggest that the proportion of correctly identified stroke cases vary greatly between different healthcare systems. For example, two studies in neighbouring Poland, a country with a similar primary care system, showed a resembling PPV and stroke mimic pattern [7,28]. One reason behind the difference in PPV between EMS and outpatient physicians could be a striking number of peripheral vestibulopathies being referred to the ED as stroke mimics by the outpatient physicians (18.0% vs. 0.9% of all stroke mimics, $p < 0.001$). In line with our findings, a previous study confirmed that peripheral vertigo is largely misdiagnosed in the primary care setting [29]. On the other hand, the lower diagnostic accuracy of stroke could pinpoint the lack of neurology training in the primary care and the ED serving as a pathway for a patient to receive an urgent neurology consultation. Finally, FAST screening is mandatory for EMS personnel to evaluate stroke alerts in Lithuania [3,30]. In contrast, outpatient physicians refer patients based on clinical suspicion of stroke, which carries a greater risk of false positives.

Second, we found a significantly increased delay from stroke symptom onset to hospital arrival during the lockdown. In contrast, ED stroke care delivery timeliness, such as DTN and DTG times, did not differ before and during the lockdown. Studies in Spain, one of the most heavily stricken countries by COVID-19, found a delay in prehospital and DTN times [10,31]. These findings partially differ from the analyses of major stroke care networks in the United States. Two studies found decreased stroke/TIA admission rates but no change in prehospital and ED stroke care delivery timeliness [12,32]. Similar to our study, a survey of stroke centres in China showed a 45% reduction in TIA and 32% in stroke admissions in mild epidemic regions, as well as overall increased delays to acute stroke care [33]. Although the reasons for increased onset-to-door delays are unclear, fear of virus exposure in the ambulance or at the hospital and absence of bystanders to initiate the stroke alarm during social distancing mandate might have delayed initiation of the EMS call [34]. Also, the need to perform additional respiratory screening and use of personal protective equipment could increase prehospital delays. Another possibility could be the saturation of ambulance services or stroke alerts referred to other hospitals before being transferred to a stroke centre [10].

In line with other reports from China, Europe, Taiwan, and the United States, we also found a significant decrease in stroke alerts and stroke admissions [9,11,12,17,18,31,32]. Our findings provide additional knowledge on the effects of lockdown measures on stroke care patterns in a low-incidence low-mortality COVID-19 outbreak setting. Similarly, another study of admission rates at three tertiary university hospitals in Greece, where COVID-19 penetration was also low, showed a remarkable decrease in stroke and acute coronary artery syndrome patients [17]. We also found a decreased number of TIAs during the lockdown. Thus, the reduced number of stroke/TIA consultations might be attributable to the reluctance to seek medical attention in the presence of mild or transient neurological symptoms. Even though our study did not find a significant change in presenting stroke severity, we might have been underpowered due to missing NIHSS in patients not considered for reperfusion.

Thirdly, we found that seizures and intracranial tumours presented more often as stroke mimics during the lockdown. A recent study from our institution showed that worse seizure control and health status in people with epilepsy were observed during the state-wide lockdown [35]. Similarly, a study from the United Kingdom reported that delays in cancer diagnosis and care are projected to result in more than 3200 avoidable cancer deaths in the following five years [36]. Altogether, these findings underscore the importance of interventions to optimise specialised care and avoid diagnostic backlog to mitigate the impact of the COVID-19 pandemic.

From the public health perspective, our study had a unique opportunity to evaluate the impact of lockdown measures on stroke care independently of the COVID-19 surge. Due to early and efficient lockdown in Lithuania, the incidence and mortality of COVID-19 during the study period remained one of the lowest in Europe [22]. Second, to limit the potential spread of SARS-CoV-2 infection, the Lithuanian government implemented a strict state-wide lockdown, severely restricting social life and access to routine healthcare services [15]. Therefore, we could successfully examine the impact of lockdown measures on stroke care not confounded by the COVID-19 surge effect on the healthcare system. Our findings suggest that the state-wide lockdown measures could have had unwanted collateral consequences on prehospital stroke care.

Our study's strengths include a prospective design and being the first report on the impact of state-wide lockdown on prehospital stroke triage quality and stroke mimics distribution. In addition, a large representative population of an urban academic centre covering one-third of the entire country allows for the generalisability of our findings to similar healthcare systems.

Our study includes some limitations. Foremost, since this was a single-centre study, we cannot account for referral pattern changes in other stroke centres in the country. However, the confounding should not have been significant as all centres functioned in the same low-incidence, low-mortality COVID-19 setting. Another limitation was the absence of data on medium and long-term functional outcomes. Even though the discharge NIHSS scores did not differ before and during the lockdown, we could not evaluate if longer delays to ED presentation might have resulted in poorer long term functional outcome. In addition, we did not fully account for the natural seasonal changes in the incidence of stroke. However, in 2018–2019 more strokes were admitted to our CSC during the spring rather than winter months, suggesting an actual decrease of stroke admission in our study rather than a seasonal fluctuation. Finally, our findings have limited generalisability to high-incidence COVID-19 situations, regions with different stroke care protocols, and varying social and healthcare responses to the COVID-19 pandemic.

5. Conclusions

In this prospective analysis of prehospital stroke care in a large academic stroke centre, we found a decreased incidence of stroke alerts and stroke/TIA admissions, as well as a drop in prehospital stroke triage quality during the state-wide COVID-19 lockdown. Furthermore, we observed an increase in hospital arrival delays and the proportion of severe conditions presenting as stroke mimics. Our findings suggest that public concern for SARS-CoV-2 infection and the state-wide lockdown negatively affected prehospital stroke care independently of the COVID-19 surge. These data are essential for policymakers to drive change in stay-at-home messaging, emphasising the importance of rapid transport to the hospital for acute conditions and improving access to neurological care during public health emergencies. Future studies should evaluate the impact of COVID-19 lockdown on functional stroke outcomes and stroke referral patterns at a national level.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Vilnius Regional Bioethics Committee (protocol code number 1170).

Informed Consent Statement: The data analysed in this study is derived from a prospectively collected institutional stroke registry. All of the stroke alerts are included in the stroke registry, and the participant consent is waived as per national guidelines.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Reperfusion Therapies for Acute Ischemic Stroke in COVID-19 Patients: A Nationwide Multi-Center Study

Jurkevičienė J, Vaišvilas M, **Masiliūnas R**, Matijošaitis V, Vaitkus A, Geštautaitė D, Taroza S, Puzinas P, Galvanauskaitė E, Jatužis D, Vilionskis A.

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Reperfusion Therapies for Acute Ischemic Stroke in COVID-19 Patients: A Nationwide Multi-Center Study

Justina Jurkevičienė [1,*], Mantas Vaišvilas [1], Rytis Masiliūnas [2], Vaidas Matijošaitis [3], Antanas Vaitkus [3], Dovilė Geštautaitė [3], Saulius Taroza [4], Paulius Puzinas [5], Erika Galvanauskaitė [6], Dalius Jatužis [2] and Aleksandras Vilionskis [7]

1 Stroke Centre, Republican Vilnius University Hospital, 04130 Vilnius, Lithuania; mantas.vaisvilas@rvul.lt
2 Center of Neurology, Vilnius University, 08661 Vilnius, Lithuania; rytis.masiliunas@santa.lt (R.M.); dalius.jatuzis@santa.lt (D.J.)
3 Department of Neurology, Lithuanian University of Health Sciences, 50009 Kaunas, Lithuania; vaidas.matijosaitis@kaunoklinikos.lt (V.M.); antanas.vaitkus@kaunoklinikos.lt (A.V.); dovile.gestautaite@kaunoklinikos.lt (D.G.)
4 Laboratory of Behavioral Medicine (Palanga), Neuroscience Institute, Lithuanian University of Health Sciences, 00135 Palanga, Lithuania; saulius.taroza@lsmuni.lt
5 Department of Neurology, Republican Panevėžys Hospital, 35144 Panevėžys, Lithuania; pauliuspuzinas@gmail.com
6 Department of Neurology, Republican Šiauliai Hospital, 76231 Šiauliai, Lithuania; erika.galvanauskaite@siauliuligonine.lt
7 Clinic of Neurology and Neurosurgery, Vilnius University, 03101 Vilnius, Lithuania; aleksandras.vilionskis@rvul.lt
* Correspondence: justina.jurkeviciene@rvul.lt

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Abstract: (1) Background: Acute ischemic stroke (AIS) is a possible complication of the coronavirus disease 2019 (COVID-19). Safety and efficacy data on reperfusion therapies (RT)—intravenous thrombolysis and endovascular treatment (EVT)—in stroke patients with COVID-19 is lacking. (2) Methods: We performed a retrospective nationwide multi-center pair-matched analysis of COVID-19 patients with AIS who underwent RT. We included adult COVID-19 patients with AIS who were treated with RT between 16 March 2020 and 30 June 2021. All subjects were paired with non-infected controls, matched for age, sex, stroke arterial vascular territory, and RT modality. The primary outcome measure was a favorable functional outcome defined by the modified Rankin scale (mRS 0–2). (3) Results: Thirty-one subjects and thirty-one matched controls were included. The median baseline National Institutes of Health Stroke Scale (NIHSS) score was higher in the COVID-19 group (16 vs. 12, $p = 0.028$). Rates of ischemic changes and symptomatic intracerebral hemorrhages did not differ significantly between the two groups at 24 h after RT. The median NIHSS 24 h after reperfusion remained significantly higher in the COVID-19 group (16 vs. 5, $p = 0.003$). MRS 0–2 at discharge was significantly less common in COVID-19 patients (22.6% vs. 51.8%, $p = 0.018$). Three-month mortality was 54.8% in the COVID-19 group versus 12.9% in controls ($p = 0.001$). (4) Conclusion: Reperfusion therapies on AIS in COVID-19 patients appear to be safe; however, functional outcomes are significantly worse, and 3-month mortality is higher.

Keywords: COVID-19; ischemic stroke; thrombolysis; thrombectomy; Lithuania; reperfusion therapies; outcomes; safety

1. Introduction

In December 2019, a cluster of patients with pneumonia caused by a novel severe acute respiratory coronavirus 2 (SARS-CoV-2) was first described in Wuhan, China [1]. Due to the vast spread of the virus across the globe, a pandemic was declared in March 2020. Ever since, a growing number of publications regarding extrapulmonary manifestations of coronavirus disease (COVID-19) arose. Neurologic manifestations of both the central and the peripheral nervous system described included COVID-19 encephalitis, acute disseminated encephalomyelitis, epileptic seizures, neuromuscular symptoms, acute demyelinating polyneuropathies, and their variants, as well as acute cerebrovascular syndromes [2–8]. It has been postulated that COVID-19 patients are at an increased risk for stroke, although the true causality is yet uncertain [9].

The first COVID-19 case in Lithuania was confirmed in late February 2020, followed shortly by the introduction of a strict nationwide lockdown. Despite thousands of daily new confirmed cases and the need for allocation of specific healthcare resources, emergency stroke services were operating in all major stroke centers across the country throughout the pandemic at full capacity [10,11]. Both intravenous thrombolysis (IVT) and endovascular treatment (EVT) were used continuously for acute ischemic stroke (AIS) in COVID-19 patients. However, data on the safety of reperfusion therapies (RT) in the COVID-19 population is scarce, and potential adverse effects of RTs could be life-threatening. Therefore, we sought to evaluate the safety and outcomes of reperfusion therapies in COVID-19 patients with AIS in a nationwide pair-matched retrospective study.

2. Materials and Methods

We conducted a multi-center retrospective pair-matched analysis of reperfusion therapy in COVID-19 patients with AIS across all six comprehensive stroke centers (CSCs) in Lithuania [12].

Data collection. The data were extracted retrospectively from electronic health records. We collected demographic data (age, gender), cardiovascular risk factors (hypertension, dyslipidemia, smoking, diabetes, atrial fibrillation, presence of symptomatic internal carotid artery (ICA) >70% or intracranial artery stenosis > 70% on computed tomography angiography), clinical (hypoxemia, body temperature, blood pressure on admission) and laboratory test data (white blood cell (WBC) and lymphocyte count, C reactive protein (CRP) and D-dimer levels on admission), head computed tomography (CT) findings (Alberta Stroke Programme Early CT Score (ASPECTS) on admission, ischemic changes on CT scan 24 h after RT), median timeliness metrics (onset-to-door (OTD), door-to-needle (DTN) and door-to-puncture (DTP) times), National Institute of Health Stroke Scale (NIHSS) on admission, at 24 h after reperfusion therapy, and on day 7 after stroke or at discharge (whichever occurred first) and reperfusion therapy data (treatment modality, Thrombolysis in Cerebral Infarction (TICI) score). Neurologic (symptomatic intracerebral hemorrhage (sICH), cerebral edema), COVID-19-related, and other complications (urinary tract infection, pulmonary embolism, myocardial infarction, acute heart failure, pulmonary edema, other organ dysfunction, or major bleeding) were collected. Patient functional outcomes corresponding to modified Rankin Scale (mRS) score at discharge, as well as in-hospital and 3-month mortality rates, were retrieved.

Patient selection. We included adult (18 years old or older) AIS patients with diagnosed acute COVID-19 infection prior to or on admission to a CSC, treated with reperfusion therapy (IVT, EVT, or both) between 16 March 2020 and 30 June 2021. Our patients had not received full vaccination doses. COVID-19 status was confirmed by a nasopharyngeal swab SARS-CoV-2 real-time polymerase chain reaction (RT-PCR). Patients who recovered from COVID-19 according to the epidemiological criteria at the time of index AIS were excluded from the analysis despite having a positive SARS-CoV2 RT-PCR test result.

Control group. Each patient from the subject group was weighted against a control. All control patients were treated in one of the 6 Lithuanian CSCs during the study period and were not concomitant with a COVID-19 infection. In addition, control subjects were matched for age (±5 years), gender, stroke arterial vascular territory, and type of reperfusion therapy (IVT, EVT, or both). To avoid selection bias, cases for this group were collected by independent stroke physicians, who were not part of this study, and were only informed about matching criteria.

Outcomes. The primary outcome measure was a favorable functional outcome, defined as the mRS score of 0–2 on the day of discharge.

Secondary outcome measures included: early neurological improvement, defined as reduction of NIHSS score by 4 points or more or score 0–1 at 24 h after reperfusion therapy; change in NIHSS score 24 h after reperfusion therapy; change in NIHSS score 7 days after stroke onset or on discharge (whichever occurred first); neurological complications of reperfusion therapy: sICH was classified using the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) classification (parenchymal hemorrhage type 2, 22–36 h after treatment leading to neurologic deterioration 4 points or more on NIHSS from baseline or lowest NIHSS or leading to death as previously reported) [13], and cerebral edema; in-hospital mortality rate; mortality rate 3 months after stroke.

To investigate the effects of clinical and laboratory factors (evaluated on admission) on the likelihood of favorable functional outcome (mRS 0–2) on the day of discharge and of 3-month mortality after stroke and reperfusion therapies, multivariate logistic regression models were built.

Statistical analysis. Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 26 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to verify the normality of the distribution of continuous variables. The qualitative variables were expressed as absolute frequencies and percentages. For continuous data, the mean and standard deviation (SD) or median and interquartile range (IQR) were reported, as appropriate. The Student's *t* test (for normally distributed data) or the Mann–Whitney U test (for not normally distributed data) was used for the continuous variables and the Chi-square test for the categorical variables. $p < 0.05$ was considered to be statistically significant. The significant predictors (using a significance level of <0.1) in the univariate analysis were included in the multivariate analysis, and the entered method was applied for the logistic regression model to determine the predictors for a favorable functional outcome (mRS 0–2) on discharge and 3-month mortality after stroke. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated.

3. Results

3.1. Demographic, Clinical, and Stroke-Related Data

Thirty-one pairs of subjects and matched controls were included in the study. The mean age was 74.0 years in COVID-19-positive AIS patients and 73.7 years in controls. Forty females (64.5%) comprised the entire cohort. Prevalence of stroke risk factors did not differ statistically significantly between the two groups. Fourteen (22.5%) patients underwent IVT, thirty (48.4%) patients were treated with EVT, and eighteen (29.1%) patients received bridging therapy. Fifty-six (90.3%) patients in the entire cohort were diagnosed with anterior circulation stroke. The detailed demographic data and stroke risk factors are displayed in Table 1.

The median NIHSS score on admission was significantly higher in the COVID-19 patient group compared to controls (16 [10–19] vs. 12.5 (5–15), $p = 0.028$). The timeliness metrics (OTD, DTN, and DTP times) did not differ significantly between the two groups. Albeit not significant, the OTD time was longer for COVID-19 patients as compared to controls (126 (83–218) vs. 95 (66–205) minutes, respectively). The ASPECTS score on admission also did not differ significantly.

As expected, the baseline body temperature was statistically significantly higher in COVID-19 patients compared to controls ($p = 0.025$), while the rate of hypoxemia and arterial blood pressure on admission did not differ significantly (Table 2). A significantly lower lymphocyte count ($p = 0.013$) and higher CRP values ($p < 0.001$) were observed in the COVID-19 group compared to controls, while total WBC count and D-dimer concentration on admission did not differ.

Table 1. Patient demographic data and stroke characteristics.

	Stroke Patients with COVID-19 (n = 31)	Control Group without COVID-19 (n = 31)	p Value
Female, n (%)	20 (64.5)	20 (64.5)	1.000
Mean Age, Years (SD)	74.0 (12.9)	73.7 (12.3)	0.912
Cardiovascular Risk Factors, n (%)			
Hypertension	29 (93.5)	26 (83.9)	0.425
Dyslipidemia	15 (48.4)	23 (74.2)	0.067
Smoking	5 (16.1)	2 (6.5)	0.229
Diabetes	6 (19.4)	2 (6.5)	0.255
Atrial Fibrillation	12 (38.7)	19 (61.3)	0.075
Symptomatic ICA Stenosis	6 (19.4)	2 (6.5)	0.255
Intracranial Artery Stenosis	3 (9.7)	5 (16.1)	0.707
Circulation of Stroke, n (%)			
Anterior Circulation	28 (90.3)	28 (90.3)	1.000
Posterior Circulation	3 (9.7)	3 (9.7)	1.000
Reperfusion Treatment, n (%)			
IVT	7 (22.5)	7 (22.5)	1.000
EVT	15 (48.4)	15 (48.4)	1.000
Bridging Therapy	9 (29.1)	9 (29.1)	1.000
Median Timeliness Metrics, min (IQR)			
Onset-To-Door Time	126 (83–218)	95 (66–205)	0.294
IVT	94 (81–137)	80 (55–105)	
EVT	245 (121–720)	154.5 (67.75–198.75)	
Bridging Therapy	101 (65–130.5)	84 (67.75–220)	
Door-To-Needle Time	40.5 (26–72.5)	36 (27–46)	0.626
Door-To-Puncture Time	101 (80.75–162.5)	116.5 (75.5–138.75)	1
Baseline NIHSS, Median (IQR)	16 (10–19)	12.5 (5–15)	**0.028**
ASPECTS, Median (IQR) §	9 (7.75–10)	10 (8–10)	0.229

SD—standard deviation, ICA—internal carotid artery, IV—Intravenous thrombolysis, EVT—endovascular treatment, mRS—modified Rankin Scale, IQR—interquartile range, NIHSS—National Institutes of Health Stroke Scale, ASPECTS—Alberta Stroke Programme Early CT Score. § Sample size differs for both subjects (n = 30), and control group (n = 27) due to missing data. Bold values denote statistical significance at the $p < 0.05$ level.

Table 2. Baseline clinical and laboratory data.

	Stroke Patients with COVID-19 (n = 31)	Control Group without COVID-19 (n = 31)	p Value
Clinical Data			
Hypoxemia, n (%) †	5(16.1)	3 (9.7)	0.712
Median Body Temperature, °C (IQR)	36.6 (36.4–36.8)	36.5 (36.1–36.6)	**0.025**
Mean Systolic Blood Pressure, mmHg (SD)	159 (28.6)	168 (28.6)	0.214
Mean Diastolic Blood Pressure, mmHg (SD)	86 (21.8)	90 (14.9)	0.350
Laboratory Data			
Mean Total WBC Count, $\times 10^9$/L (SD)	8.8 (5.4)	8.7 (2.6)	0.473
Mean Lymphocyte Count, $\times 10^9$/L (SD)	1.5 (0.7)	2.1 (1.4)	**0.013**
Mean CRP, mg/L (SD)	44.3 (63.8)	5.3 (6.4)	**<0.001**
CRP > 5 mg/L, n (%)	23 (74.2)	8 (25.8)	**<0.001**
Median D-Dimer, µg/L (IQR)	675 (78–4898)	1048 (479–2065)	0.979

IQR—interquartile range, SD—standard deviation, WBC—white blood cells, CRP—C-reactive protein. † Defined as SpO2 < 93%. Bold values denote statistical significance at the $p < 0.05$ level.

3.2. Primary and Secondary Outcomes

Only 22.6% of COVID-19 patients with AIS in the subject cohort achieved favorable functional outcomes (mRS 0–2) on discharge as compared to 51.6% in the control group ($p = 0.018$) (Table 3).

Table 3. Patient treatment outcomes and complications.

	Stroke Patients with COVID-19 (n = 31)	Control Group without COVID-19 (n = 31)	p Value
TICI Score, n (%) †			0.190
2b/3	19 (79.2)	21 (95.5)	
0/1/2a	5 (20.8)	1 (4.5)	
Ischemic Changes on CT Scan 24 h After RT, n (%)	24 (77.4)	21 (67.7)	0.393
Stroke Severity, NIHSS, Median (IQR)			
24 h After Reperfusion Therapy	16 (5–24)	5 (2–13)	**0.003**
24 h Change From Baseline	0 (−3–3)	−2 (−7.25–0)	**0.029**
Day 7 or Discharge ‡	15 (5–21)	4 (1–10)	**<0.001**
Overall Change From Baseline	−1 (−6–2)	−4 (−9–1)	**0.022**
Early Neurological Improvement, n (%) §	6 (19.4)	12 (38.7)	0.077
Functional Outcome at Discharge ǀǀ			
Median mRS (IQR)	4 (3–6)	2 (1–4)	**0.004**
mRS $\leq$ 2, n (%)	7 (22.6)	16 (51.6)	**0.018**
Complications, n (%)			
Symptomatic ICH	0 (0)	0 (0)	1.000
Cerebral Edema	7 (22.6)	6 (19.4)	0.755
Pneumonia ¥	21 (67.7)	2 (8.0)	**<0.001**
Respiratory Failure ¥¥	20 (64.5)	4 (22.2)	**0.007**
Other ¶	8 (25.8)	9 (29.0)	0.776
Prolonged Stay in ICU (>1 day), n (%)	12 (38.7)	6 (19.4)	0.093
Mortality, n (%)			
In-Hospital	9 (29.0)	2 (6.5)	**0.043**
Day 90	17 (54.8)	4 (12.9)	**0.001**

TICI—thrombolysis in cerebral infarction, NIHSS—National Institutes of Health Stroke Scale, IQR—interquartile range, mRS—modified Rankin Scale, ICH—intracerebral hemorrhage, ICU—intensive care unit. † Only patients who had undergone mechanical thrombectomy (n = 46, data of 2 patients was missing). ‡ Whichever occurred first. § Defined as reduction of NIHSS score by 4 points or more or score 0–1 at 24 h after reperfusion therapy. ǀǀ Sample size differs for both subjects (n = 26) and control group (n = 29) due to missing data. ¥ Sample size differs for both subjects (n = 31) and control group (n = 25) due to missing data. ¥¥ Sample size differs for both subjects (n = 31) and control group (n = 18) due to missing data. ¶ Including urinary tract infection, pulmonary embolism, myocardial infarction, acute heart failure, pulmonary oedema, other organ dysfunction, major bleeding (excluding pneumonia and respiratory failure). Bold values denote statistical significance at the $p < 0.05$ level.

Significantly higher NIHSS scores 24 h after reperfusion therapy (16 (5–24) vs. 5 (2–13), p = 0.003) and on day 7 or discharge (15 (5–21) vs. 4 (1–10), $p < 0.001$) were evident in the COVID-19 group as compared to matched controls. The detail outcome data are shown in Table 3. Rate of cerebral edema after the reperfusion treatment did not differ between the two groups, and no sICHs were observed. Both in-hospital and 3 month mortality rates were significantly higher in the COVID-19 group compared to controls (29% and 54.8% vs. 6.5% and 12.9%, p = 0.043 and p = 0.001, respectively).

The analysis of in-hospital mortality patients in both groups showed severe stroke from onset (baseline NIHSS > 15). COVID-19-positive stroke patients who died in hospital: 5/9 (55.6%) underwent MTE and 4/9 (44.4%) underwent bridging therapy, 2/9 (22.2%) had unsuccessful MTE (TICI 1 and 2a), 7/9 (77.8%) had acute ischemic changes on CT scan 24 h after RT, 2/9 (22.2%) experienced reperfusion complications (small scattered petechiae and subarachnoid hemorrhage, confluent petechiae), 5/9 (55.6%) had various degree cerebral edema, 8/9 (88.9%) had pneumonia and respiratory failure, 2/9 (22.2%) had other somatic complications (sepsis, acute kidney failure and urinary tract infection), 2/2 (100%) control group stroke patients who died in hospital underwent MTE, and reperfusion therapy was successful (TICI 3) in both cases, Both patients had acute ischemic changes on CT scan 24 h after RT, both experienced reperfusion complications (hematoma within infarcted tissue, occupying <30%, intraventricular hemorrhage), both had cerebral edema, and both had pneumonia and respiratory failure and no other somatic complications.

3.3. COVID-19 Associated Complications

Severe respiratory failure was observed in 64.5% of COVID-19 patients during any time point of inpatient treatment, and it was significantly more common compared to controls, where only 22% of patients were in respiratory compromise ($p = 0.007$). Importantly, on admission, rates of respiratory failure did not differ between the two groups (hypoxemia rate 5 (16.1%) in COVID-19 group vs. 3 (9.7%) in controls, $p = 0.712$). Pneumonia complicated the disease course of 67.7% of COVID-19 patients as compared to 8% of controls ($p < 0.001$). Prolonged stay in ICU was observed in 38.7% of COVID-19 patients compared to 19.4% in control group ($p = 0.093$).

3.4. Multivariate Analysis

The accuracy of a favorable functional outcome prediction was 83.6%. The significant variables in the univariate analysis included age ($p = 0.028$), baseline NIHSS ($p < 0.001$), and COVID-19 infection ($p = 0.011$). In the multivariable model, only baseline NIHSS retained significance (OR 0.790; 95% CI 0.691–0.902) (Table 4).

Table 4. Logistic regression model on the likelihood of favorable functional outcome (mRS 0–2) on discharge ($n = 61$).

Covariates	Univariate Analysis	Multivariate Analysis	
	***p* Value**	**OR (95% CI)**	***p* Value**
Age	0.028	0.959 (0.899–1.022)	0.199
Baseline NIHSS	<0.001	0.790 (0.691–0.902)	**0.000**
COVID-19 Infection	0.011	0.312 (0.077–1.260)	0.102

OR—odds ratio, CI—confidence interval, NIHSS—National Institutes of Health Stroke Scale. Bold values denote statistical significance at the $p < 0.05$ level in multivariate analysis.

The accuracy of 3-month mortality after stroke and reperfusion therapy was 78.8%. The significant variables included age ($p = 0.022$), hypoxemia ($p = 0.079$), baseline NIHSS ($p = 0.001$), COVID-19 infection ($p = 0.001$), total WBC count ($p = 0.079$), and CRP concentration ($p = 0.093$). Increasing age and higher baseline NIHSS on admission were associated with a higher likelihood of 3-month mortality after stroke and reperfusion therapy. COVID-19 infection increased the likelihood of death 3 months after stroke and reperfusion therapy seven times (OR 6.696; 95% CI 1.029–43.584), while hypoxemia, total WBC count, and CRP concentration were not significant predictors (Table 5).

Table 5. Logistic regression model on the likelihood of 3-month mortality after stroke and reperfusion therapy ($n = 52$).

Covariates	Univariate Analysis	Multivariate Analysis	
	***p* Value**	**OR (95% CI)**	***p* Value**
Age	0.022	1.086 (1.002–1.178)	**0.045**
Hypoxemia (SpO2 < 93%)	0.079	1.861 (0.225–15.406)	0.565
Baseline NIHSS	0.001	1.184 (1.013–1.383)	**0.034**
COVID-19 infection	0.001	6.696 (1.029–43.584)	**0.047**
Total WBC count	0.079	1.126 (0.829–1.530)	0.447
CRP concentration	0.093	1.004 (0.990–1.018)	0.586

OR—odds ratio, CI—confidence interval, NIHSS—National Institutes of Health Stroke Scale, WBC—white blood cells, CRP—C-reactive protein. Bold values denote statistical significance at the $p < 0.05$ level in multivariate analysis.

4. Discussion

This is the first Lithuanian nationwide pair-matched multicenter study evaluating outcomes of COVID-19-positive AIS patients treated with reperfusion therapies. We demonstrated that COVID-19 stroke patients present with a significantly higher neurologic burden than non-infected controls. We also found that reperfusion therapies appear safe for COVID-19 stroke patients in relation to reperfusion-associated complications (symptomatic ICH and cerebral edema). Despite successful reperfusion, the COVID-19 stroke patients had significantly worse outcomes and a high 3-month mortality rate as compared to control patients. We additionally report 3-month mortality of COVID-19-positive patients with AIS representing distant sequalae of AIS. Hypoxia had a major role in our COVID-19 cohort and may have contributed to the high in-hospital and 3-month mortality rate.

Outcomes of COVID-19 patients with AIS seem to be universally unfavorable despite successful reperfusion. Although COVID-19 patients with mild stroke presentations seemed to have more favorable outcomes, in general, COVID-19 patients with AIS were more severely disabled, with a median NIHSS of 15 at discharge as compared to controls. This is in line with other studies reporting in-hospital mortality rates ranging from 31% to 60% [14–16]. The European multicenter EVT study provided data on 30-day mortality of 27% [17]. In contrast, we report insights on 3-month mortality even higher than previously reported [18].

In our study, the absolute majority of COVID-19 stroke patients had a more severe stroke despite no differences in ASPECTS scores between study groups on admission. These results are comparable to previous reports [18]. However, the true size of ischemic territory in COVID-19 patients may be larger than initially anticipated. Significantly lower ASPECTS scores and higher infarct volumes were observed for COVID-19 patients with AIS on MRI despite early imaging in a previous study [19]. In contrast, we used CT as our main screening modality. Although discordances between MRI and CT median ASPECTS scores in non-COVID-19 AIS have been documented, no impact to overall outcomes was observed [20]. Therefore, COVID-19-specific endothelial dysfunction may have a role in infarct core size expansion and contribute to poor outcomes.

Moreover, in our study, we demonstrated that COVID-19 stroke patients eligible for reperfusion therapies had prolonged onset-to-door times. Prolonged ODT in COVID-19 patients might be explained by human factors: first, the lack of available paramedical teams on-call could have delayed arrival to the hospital. Second, both stroke admission rates and prolonged ODT were previously reported owing to the reluctance of stroke patients to seek medical care, especially during the start of the pandemic when vaccination was not yet available [21]. However, the impact of prolonged ODT on stroke severity is debatable. Prolonged ODT might also be explained in part by the expanded intervention window for EVT according to the DAWN trial, demonstrating the undeniable benefits of EVT beyond 6 h for rigorously selected patients [22]. However, this approach was not validated for COVID-19 patients, but despite the lack of evidence, the DAWN criteria were applied according to best clinical practice and consensus statements valid at the time of therapy [23,24]. Second, data regarding the efficacy of EVT beyond 6 h in COVID-19 stroke patients are conflicting, since there are no studies specifically addressing this issue in the COVID-19 population. Studies specifically addressing reperfusion beyond 6 h are required to assess their safety and efficacy profile and more importantly, assess the impact of COVID-19 in these patients, especially in cases with respiratory compromise.

In our study, DTN and DTP times did not differ significantly between patients infected with COVID-19 and controls. Every stroke center was pre-notified about COVID-19 positivity in cases when information was available to the paramedical team and when stroke teams made safety preparations in advance. However, in most cases, COVID-19 status was unknown. Treatment of stroke and reperfusion therapy was considered a priority and did not cause delays in logistics in the emergency departments in either of the stroke centers.

Another aspect to consider is early neurological improvement after reperfusion therapy. In our cohort, successful reperfusion (TICI 2b or TICI 3) was observed in 79.2% of COVID-19 patients with AIS who underwent EVT, and in all but one patient (95.5%) in the control group. In addition, the rate of ischemic changes on CT scan 24 h after RT did not differ between COVID-19 and control groups. Despite successful and timely reperfusion, COVID-19 stroke patients did not improve neurologically 24 h after reperfusion. We acknowledge the possibility that some patients may have exhibited a higher neurological burden due to their severe general state and the need for intensive care due to COVID-19.

We did not calculate the ICU severity scores to represent the general state of these patients. However, NIHSS scores were evaluated either at 7 days or on discharge for every patient. At these time points, the absolute majority of patients were discharged from the ICU. Therefore, we believe that evaluation of NIHSS later in the disease course more accurately reflects the true neurologic burden. Moreover, a lack of early neurological improvement was observed in other studies owing to several factors. Early consecutive ischemic strokes or re-occlusions of the same vessel after successful or complete recanalization were observed at a higher than expected rate of 8% in a systematic study [25]. In our cohort, we have no data regarding early re-occlusions in COVID-19 stroke patients, since this was a retrospective study and we do not routinely perform CTA after successful reperfusion according to national guidelines, unless there is a high clinical suspicion of re-occlusion.

Another proposed explanation for no neurological improvement is the difference in clot composition in COVID-19 and non-COVID-19 patients. Wang et al. described several patients with excessive clot fragmentation and distal migration during thrombectomy. Moreover, once evaluated with thromboelastography, the thrombi showed features of high clot consolidation and reduced time of clot formation consistent with a severe procoagulant state [26]. Several other studies reported a hypercoagulable state in COVID-19 patients as compared to controls, which may attribute to both the devastating multivessel occlusions, clot fragmentation, consecutive ischemic strokes, or early re-occlusions of blood vessels that might contribute to poor outcomes [27]. Although we cannot confirm the different clot features for COVID-19 stroke patients in our study, other aspects of these patients are worth considering.

Hypoxia is a major contributing factor to poor outcomes in AIS patients. In our cohort, 64.5% of COVID-19 stroke patients suffered from respiratory failure. Almost one-third of COVID-19 patients with AIS required prolonged intubation due to severe respiratory system compromise. In a subgroup analysis of the former group (unpublished data), patients in whom the respiratory function was severely affected were those who showed no neurologic improvement 24 h after reperfusion. Most of these patients presented with LVOs and required EVT for reperfusion. Due to a relatively small sample size in our cohort, we could not perform a subgroup analysis with optimal statistical power, but a tendency toward more severe strokes in patients with severe respiratory compromise was observed. This is in line with previous reports. Two meta-analyses showed that severe COVID-19 disease is more often complicated by severe ischemic strokes [16,28]. It is proposed that patients with severe respiratory compromise can be deemed as high risk for poor outcomes and in-hospital mortality [15]. A stroke center in New York reported good early neurological improvement in COVID-19 stroke patients who underwent endovascular treatment. None of the COVID-19 stroke patients who dramatically improved showed signs of respiratory distress [29]. Respiratory function, although analyzed in AIS with COVID-19 cohorts, has not been widely addressed in the subpopulation of patients undergoing reperfusion therapies for AIS. In our study, we emphasize the importance of respiratory complications for AIS patients undergoing specialized treatment. Respiratory failure could be an important factor for early neurological deterioration or lack of improvement despite successful reperfusion. Novel strategies involving optimal management of respiratory compromise should be exploited to improve the outcomes for stroke patients undergoing reperfusion therapy.

Although available safety evidence is scarce, reperfusion in cases of AIS was recommended by an international panel of experts [23,24]. For IVT, various studies report sICH rates from 2.8% to 10% in COVID-19 stroke patients [30–33]. As for EVT, a European multicenter retrospective study of 93 COVID-19 stroke patients reported a rate of sICH of 5.4% [17]. In contrast, results from the largest to date EVT trial MR CLEAN reports sICH rates of 7.7%, although differences between the two studies' sample sizes have to be taken into account [34]. Results from our study are comparable to the aforementioned studies and provide additional insights into the safety of reperfusion therapies for COVID-19 stroke patients. All ICHs were asymptomatic in the COVID-19 group and did not differ statistically from controls. As given the information provided, reperfusion therapies appear to be safe and beneficial for some patients, but large prospective trials evaluating both the safety and efficacy of these treatments are warranted.

Risk factors associated with high dependency and mortality in COVID-19 AIS patients include older age, COVID-19 infection, and stroke severity on admission. The logistic regression model in our study showed only higher baseline NIHSS to be associated with worse functional outcomes. As for 3-month mortality, age, higher baseline NIHSS and COVID-19 infection were significant predictors in the logistic regression model. COVID-19 infection increased the likelihood of death 3 months after stroke and reperfusion therapy seven times. We acknowledge that the regression analysis model in our study may not reflect the true predictors of poor outcomes in COVID-19 AIS patients undergoing RT due to the retrospective nature of the study, data shortages, and a small sample size. Furthermore, we included to our univariate and multivariate logistic regression only patient history data and clinical and laboratory data evaluated on admission. Earlier, we argued that hypoxia is an important factor for the expansion of infarcted brain tissue and may be associated with poor outcomes given the high rates of severe respiratory failure in our study. This might explain the higher rates of in-hospital mortality. However, for the survivors, the causes of 3-month mortality rates remain to be validated.

Strengths. The strength of our study lies within a couple of points. First, the study was conducted across all Lithuanian stroke centers. Second, we added valuable insights to the available safety data of reperfusion therapies in AIS with COVID-19 demonstrating relative safety of all treatment modalities. We have performed one of the few studies reporting COVID-19 patients with AIS mortality at 3 months. As a result, it was possible to compare COVID-19 patients with AIS with controls demonstrating clear differences in mortality and functional outcomes, raising COVID-19 as a potential risk factor predicting poor outcomes in AIS patients.

Limitations. The major weaknesses of our study are the retrospective nature and a relatively small sample size, restricting subgroup analysis of reperfusion modalities and evaluation of outcomes within. Another weakness is the chosen pair-matched analysis method, which might not accurately represent the true demographic and stroke-specific data of the control patients. We could not perform a subgroup analysis of different treatment modalities that would have added additional safety and outcome data. The regression analysis model, albeit significant for some factors, we believe, does not reflect all predictors of poor outcomes in COVID-19 patients. Heterogeneity between different centers concerning treatment management of patients with AIS should be considered. Although we reported 3-month mortality rates, we could not compare functional outcomes of surviving COVID-19 stroke patients to the control group, which would provide additional information on distant effects of COVID-19 on AIS survivors.

5. Conclusions

In conclusion, reperfusion therapies on AIS in COVID-19 patients appear to be safe and should be used. COVID-19-positive AIS patients seem to have more debilitating strokes from onset. Despite successful and timely reperfusion, they tend to have poor functional outcomes with high in-hospital and 3-month mortality rates. For the surviving patients, studies to compare functional outcomes in the post-acute COVID phase between COVID-19 patients with AIS and non-infected stroke survivors are needed.

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1. Melaika K, Sveikata L, Vilionskis A, Wiśniewski A, Jurjans K, Klimašauskas A, Jatužis D, **Masiliūnas R**. *Prehospital Stroke Care, Paramedic Training Needs, and Hospital-Directed Feedback in Lithuania*. Healthcare. 2022; 10(10):1958.
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LIST OF PRESENTATIONS

1. Melaika K, Sveikata L, Wiśniewski A, Vilionskis A, Ekkert A, Jatužis D, **Masiliūnas R**. *Emergency Medical Service Training Improves Prehospital Stroke Recognition*. Poster presentation. 21st Nordic Congress on Cerebrovascular Diseases. Rīga, Latvia. August 26-27, 2021.
2. **Masiliūnas R**, Melaika K, Sveikata L, Wiśniewski A, Jaxybayeva, A, Ekkert A, Jatužis D. *Changes in Prehospital Stroke Care and Stroke Mimic Patterns during the COVID-19 Lockdown*. Oral presentation. 21st Nordic Congress on Cerebrovascular Diseases. Rīga, Latvia. August 26-27, 2021.
3. Melaika K, Vilionskis A, Sveikata L, Jatužis D, **Masiliūnas R**. *A paramedic survey on prehospital stroke care, training needs, and current attitude toward Lithuanian stroke network*. Poster presentation. 7th Congress of the European Academy of Neurology. June 19-22, 2021.
4. **Masiliūnas R**, Dapkutė A, Grigaitė J, Valančius D, Lapė J, Jatužis D. *Functional Outcome and Health Related Quality of Life at Three Months After Acute Ischemic Stroke Onset for Patients Treated in Vilnius University Hospital*. Poster presentation. Joint European Stroke Organization and World Stroke Organization Conference (ESO-WSO 2020). November 7-9, 2020.
5. Vilionskis A, **Masiliūnas R**, Jatužis D, Rastenytė D. *The Impact of a Comprehensive National Policy on Improving Acute Stroke Patient Care*. Oral presentation. Joint European Stroke Organization and World Stroke Organization Conference (ESO-WSO 2020). November 7-9, 2020.
6. Lapė J, **Masiliūnas R**, Grigaitė J, Valančius D, Jatužis D. *Inadequate In-hospital Screening and Insufficient Oral Anticoagulation on Admission in Acute Ischemic Stroke Patients with Atrial Fibrillation*. Oral presentation. International Congress on Brain, Heart & Kidney 2020. Vilnius, Lithuania. October 22-24, 2020.
7. **Masiliūnas R**. *Emergency Procedures in Stroke – Lithuanian experience*. Oral presentation. 16th Interdisciplinary Forum of the Polish Stroke Association. Toruń, Poland. September 26-27, 2019.

NOTES

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Vilniaus universiteto leidykla
Saulėtekio al. 9, III rūmai, LT-10222 Vilnius
El. p. info@leidykla.vu.lt, www.leidykla.vu.lt
bookshop.vu.lt, journals.vu.lt
Tiražas 25 egz.