Università Campus Bio-Medico di Roma

Corso di dottorato di ricerca in

Scienze Biomediche integrate e Bioetica

Curriculum: Scienze Neurologiche

XXXIV ciclo a.a. 2018-2019

Titolo

Stroke management in the COVID-19 era

Candidato

Matteo Paolucci

Coordinatore

Prof. Raffaele Antonelli Incalzi

Tutori

Prof. Fabrizio Vernieri

Dott. Marco Longoni

Acknowledgments

I wish to thank the whole staff of the Neurology, Neuroradiology and Emergency Department Units of the "M. Bufalini" hospital, Cesena, for their strenuous work, their commitment, and their support, even in a difficult time as during a pandemic outbreak. Particularly, I wish my colleagues of the Neurology unit to thank them for their friendship. Spending the last two years working with them has been a joyful experience.

Many thanks to my mentors, dr. Marco Longoni and prof. Fabrizio Vernieri. From the moment dr. Longoni received me in Cesena, I immediately felt he put his confidence in me. I am grateful for his trust and for all his teachings, not only on acute stroke care but also on the vision about its future. I left Cesena with so many advice from Marco and a sincere friendship between us. Prof. Vernieri has been one of my principal reference as a Neurologist since I attended medical school. I owe him most of my neurological knowledge and my research skills, and I always felt his support during my growth as a student and as a young Neurologist. Most of all, he has always been an example of kindness dedication to the patients. I am honoured of his mentoring.

Eventually, I wish to thank two extraordinary Neurologists that I admire for many reasons and that constantly supported me: my father Stefano and my partner Maria Pia. My deepest love is for them and the rest of my family: I always felt their wholehearted support, and for that I thank them all.

Table of Contents

List of figures

Abstract

Stroke epidemiology and care have been deeply affected by the SARS-CoV-2 pandemic. During the last two years, several brand-new issues emerged, which the medical community has gradually addressed. On the one hand, a paradoxical reduction of stroke cases occurred despite growing evidence of the intimate connections between COVID-19 and hypercoagulability disorders (including stroke). On the other hand, stroke networks were unprepared to face the disruption of regular hospital pathways.

To face the new pandemic-derived challenges, our stroke network of AUSL Romagna, Italy, shifted from a drip-and-ship to a mothership model with direct transport of acute ischemic stroke patients to the Comprehensive Stroke Center ("M. Bufalini" hospital, Cesena, Italy). Moreover, intrahospital routes for stroke management were redesigned, and the Neurology Unit opened a Short-stay Neurological Observation (SSNO) unit. This PhD project aims at evaluating different aspects of the impact of COVID-19 pandemic on stroke epidemiology and acute care by analyzing data from the stroke network of AUSL Romagna. The project includes four studies: (1) an epidemiological study to confirm the decrease in stroke referral during the first pandemic wave, (2) a whole stroke network performance study to evaluate the volume and promptness of reperfusion therapies during the first COVID-19 pandemic wave (3) a SSNO unit performance study to evaluate the usefulness of a Neurologist-managed observations unit and (4) a comparison of the mothership and drip-and-ship models to assess efficiency and efficacy of the MS model during the pandemic outbreak.

Our epidemiological study (1) confirmed a significant 25-28% decrease of confirmed strokes cases managed in the Emergency Department (ED) in March 2020 compared with the same month of the previous two years. (2) Despite the reduction of confirmed stroke cases, the absolute number of treatments performed in the stroke network remained similar to the previous years. (3) The opening of the SSNO was feasible and strategic in managing stroke referrals in

a mothership model. (4) The mothership model proved to be more efficient (promptness of reperfusion therapies) than the drip-and-ship model, with a trend to a better efficacy (functional outcome) despite the pandemic emergency.

The reduction of stroke cases is probably explained by a reduced seek for help and hospitalization of patients with transient or non-debilitating neurological symptoms. The shift to the mothership model during the COVID-19 pandemic was feasible. The COVID-19 pandemic has been a great stress test for stroke networks. The lesson learned is that stroke networks should be ready to adapt organization models and participate in population awareness.

Background and aims

Introduction

Since its outbreak in the first quarter of 2020, the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has deeply affected the health care systems worldwide. It tremendously influenced the management of time-dependent diseases, like stroke, among the many sides. Stroke and Coronavirus Disease 2019 (COVID-19) share a mutual bond. Stroke and stroke-at-risk populations (elders, hypertensives, diabetics) overlap with severe SARS-CoV-2 infection high-risk populations (Aggarwal et al., 2020; Qin, Zhou, Hu, Yang, et al., 2020; Wang et al., 2020). On the other hand, SARS-CoV-2 infection may increase the risk and the severity of cerebrovascular diseases, being associated with systemic hypercoagulability with venous thromboembolic events, arterial thrombosis (including strokes) as well as microvascular thrombotic disorders (Larson et al., 2020; Tsivgoulis et al., 2020; Wool and Miller, 2021; Yaghi et al., 2020). However, during the first phase of the pandemic, there have been worldwide observations of decreased rates of stroke patients' hospital admissions, thrombolysis and thrombectomy (Kerleroux et al., 2020; Montaner et al., 2020; Rudilosso et al., 2020; Zhao et al., 2020). An Italian multicenter study confirmed this trend in Italy (Sacco et al., 2020). One of the main identified reasons relies on the falling rate of patients with milder symptoms presenting to healthcare facilities (Naccarato et al., 2020; Siegler et al., 2020). Increased social isolation, misdiagnosis, or an actual reduction in stroke incidence due to behavioural changes are other possible, although not exhaustive, explanations (Sousa et al., 2020). Apart from the direct and indirect influences on stroke epidemiology, the COVID-19 pandemic forced a complete rearrangement of the territorial and in-hospital healthcare organization, including the neurovascular teams' one. Different solutions have been found depending on each area and hospital characteristics (Baracchini et al., 2020; Naccarato et al., 2020). Intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) are the only reperfusion therapies approved for acute ischemic stroke (AIS) due to large vessel occlusion (LVO) (Powers et al., 2019). Access to IVT and EVT should be granted as soon as possible in patients with AIS. Stroke network organization is, therefore, a critical determinant of prompt revascularization. The choice between the transport of AIS patients to the nearest Primary Stroke Centers (PSC; "Drip-and-Ship" – DS – model) versus the direct transportation to the Comprehensive Stroke Center (CSC; "Mothership" – MS – model) is still a matter of debate (Maas et al., 2020). As literature grows, MS seems to guarantee a better outcome, at least when transportation time to CSC is short (Romoli et al., 2020; Wu et al., 2021). However, results are only partially generalizable and need to be balanced with distinctive regional factors and, notably, they derived from pre-pandemic studies. Other than the overall stroke network model, the intrahospital routes and organization needed to be rethought. Therefore, COVID-19 pandemic can be considered as the paradigm of a perturbing event in front of which healthcare systems need to be prepared.

SARS-CoV-2, COVID-19 and vascular disorders

SARS-CoV-2, an enveloped single-stranded RNA virus, is the causative agent of COVID-19 (figure 1). Transmission of the virus occurs primarily via respiratory droplets from face-to-face contact. The interaction between the virus surface spike (S) protein with human angiotensin-converting enzyme 2 (hACE2) mediates SARS-CoV-2 entry into human cells (Shang et al., 2020).

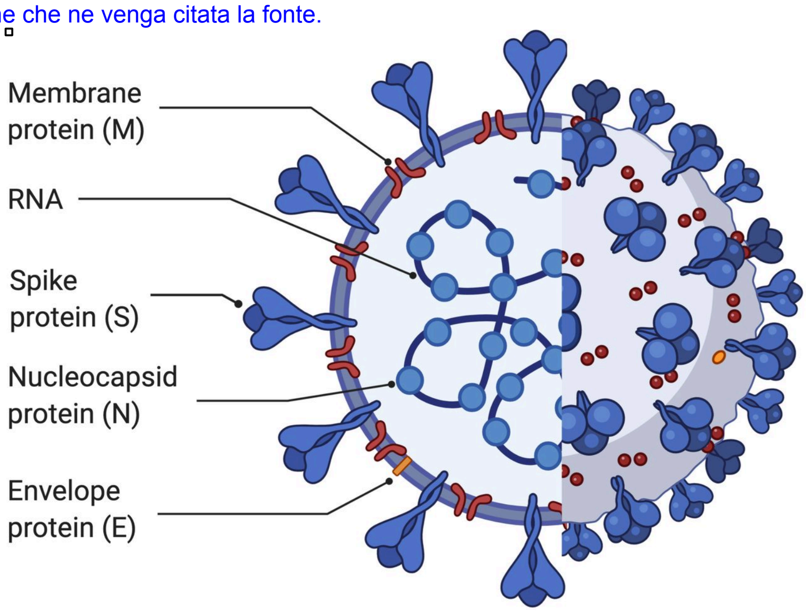


Figure 1. SARS-CoV-2 is a single-stranded RNA virus member of the coronavirus family. The spike protein (S) interacts with ACE2 on host cells. Shared from: Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM (2021) Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. J Neurointerv Surg 13:202–206. Distributed under permission provided by BMJ Publishing Group Ltd. (license number 5224280523782)

hACE2 is a counterregulatory enzyme of the Renin-Angiotensin-Aldosterone System (RAAS): it converts angiotensin I and angiotensin II, generated by renin and ACE, into angiotensin-(1–9) and angiotensin-(1–7), respectively (Donoghue et al., 2000; Keidar et al., 2007). The latter exerts a blood pressure-lowering effect through vasodilatation and performs an immunoregulatory function (Beyerstedt et al., 2021) (figure 2).

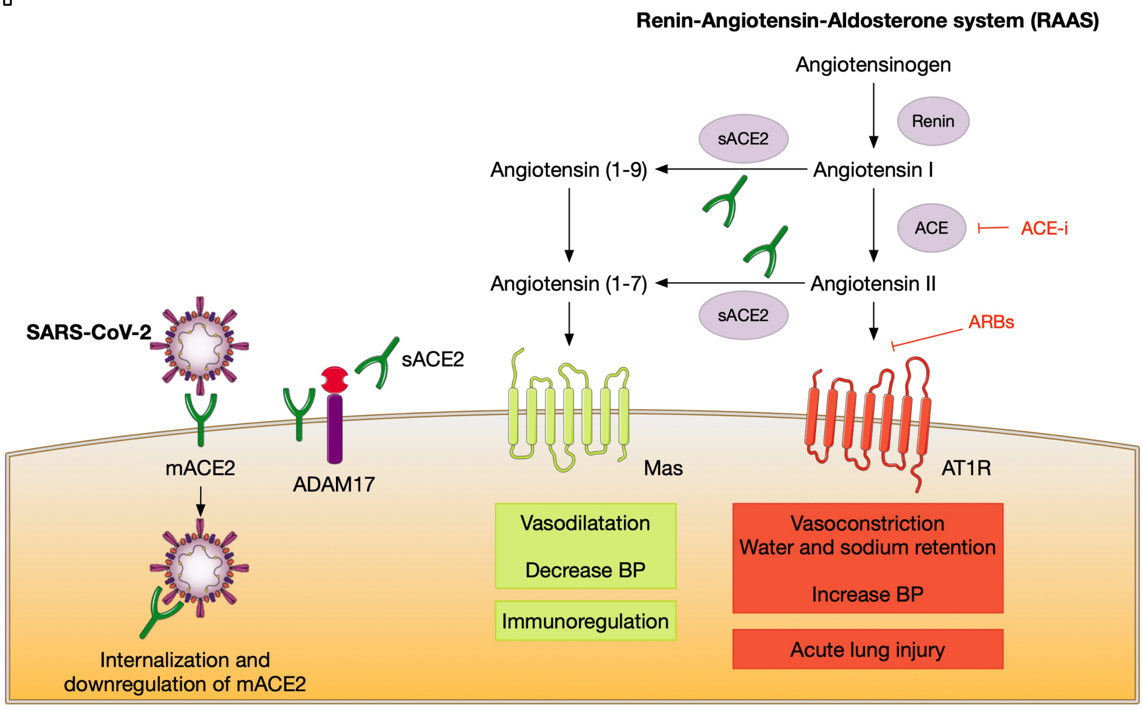


Figure 2. ACE2 is a cell membrane enzyme recognized by SARS-CoV-2 spike protein as its receptor. Membrane ACE2 (mACE2) is converted by ADAM17 into a soluble ACE2 (sACE2) that is involved in the RAAS. ACE-i: ACE-inhibitor. ARBs: angiotensin receptor blockers. Modified from Beyerstedt, 2021.

hACE2 is expressed on cell membranes of nasal epithelium, and its expression gradually decreases through the respiratory tract, reaching the minimum level in the alveoli, where can be found only on type II pneumocytes (Jackson et al., 2022). It is also highly expressed in the small intestine and colon, kidney, heart muscle, vascular endothelial cells, testis, and thyroid gland. This distribution is linked somehow with the SARS-CoV-2 main entry route (upper respiratory tract) and tissues involvement (i.e., cardiac infection, gastrointestinal and renal complications) (Jackson et al., 2022).

At the beginning of the pandemic, concerns were raised about the role COVID-19 risk factors like smoking, hypertension or ACE inhibitors (ACE-i)/angiotensin-receptor blockers (ARBs) therapy, age and diabetes in increasing ACE2 expression level and, hence, facilitating the entry of the virus into cells. To date, none of such factors has been undoubtedly associated with ACE2 levels (Beyerstedt et al., 2021), indicating that they confer the risk of severe infection through other mechanisms. Animal and human studies on ACE-I and ARBs do not suggest that these therapies may increase ACE2 levels (Vaduganathan et al., 2020). Moreover, SARS-CoV-2 cellular infection decreases ACE2 cell membrane expression through internalization, unbalancing the RAAS towards higher Angiotensin II levels, the latter contributing to tissues detrimental effects. Despite the uncertainty in the topic, the international consensus agrees to continue RAAS inhibitors (ACE-I and ARBs) in COVID-19 patients, considering the scarcity of data about facilitation of virus entrance and the well-known risk of abrupt withdrawal of these therapies (Vaduganathan et al., 2020).

Once SARS-CoV-2 penetrates, the first symptoms of COVID-19 may develop after a few days from exposure (2-7 days) (Wiersinga et al., 2020). The most common symptoms are fever, cough, and shortness of breath. Additional symptoms include weakness, fatigue, myalgias, nausea, vomiting, diarrhea, headache, anosmia or ageusia. Common complications among hospitalized patients with COVID-19 include pneumonia (75%); acute respiratory distress syndrome (15%); acute liver injury (19%); cardiac injury, including troponin elevation (7%-17%), acute heart failure, dysrhythmias, and myocarditis; acute kidney injury (9%); neurologic manifestations, including impaired consciousness (8%) and acute cerebrovascular disease (3%); and shock (6%). Prothrombotic coagulopathy resulting in venous and arterial thromboembolic events are present in about 10-25% of hospitalized COVID-19 patients. Approximately 17% to 35% of hospitalized patients with COVID-19 are treated in an Intensive Care Unit (ICU), most commonly due to respiratory failure (Wiersinga et al., 2020). The rate of hospitalization greatly varied during the progression of the pandemic, with a higher hospitalization rate during the first wave and a gradual decrease in the subsequent waves due to vaccination and virus mutations (figure 3).

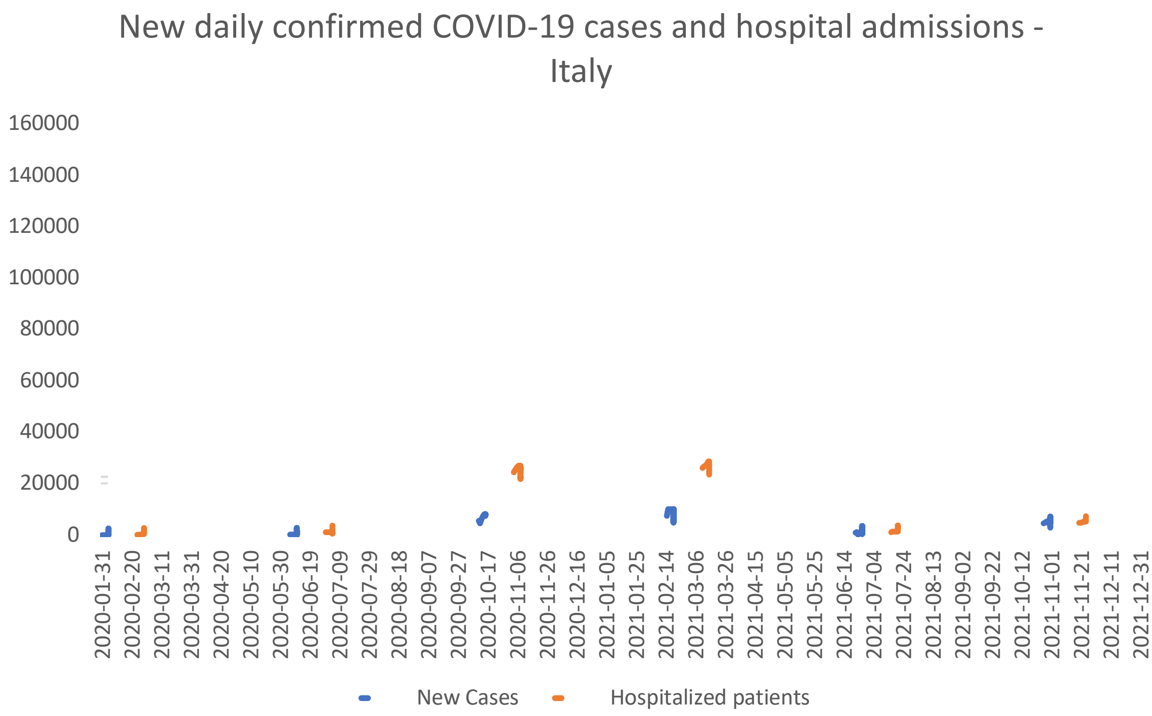


Figure 3. New daily confirmed cases of COVID-19 patients and hospitalized patients in Italy, from the 31st Jan 2020 to the 31st Dec 2022. Data from: Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian and Max Roser (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/coronavirus' [Online Resource].

As noted above, venous and arterial thromboembolic events are possible vascular complications of COVID-19, particularly in moderate-severe hospitalized cases. However, a certain grade of coagulopathy is observed also in patients without overt thromboembolic events. Indeed, a systematic assessment of symptomatic and asymptomatic venous thrombosis in ICU patients using complete duplex ultrasound (CDU) found a rate as high as 69% (100% in patients in prophylactic anticoagulation and 56% in patients with therapeutic anticoagulation) (Llitjos et al., 2020). Like in other coronavirus pneumonia (including severe acute respiratory syndrome - SARS), the procoagulant effect is not directly exerted by the virus itself but is probably the result of the profound inflammatory response and endothelial activation/damage induced by COVID-19 (Connors and Levy, 2020). The most common coagulation abnormalities in patients with COVID-19 pneumonia are a prominent elevation of D-dimer, elevated fibrinogen, and mild thrombocytopenia (Connors and Levy, 2020). A certain degree of thrombin and fibrin generation is part of the systemic host defence to infection ("immunohaemostasis"); however, when the response is uncontrolled or excessive, it leads to sepsis-induced coagulopathy (SIC) or disseminated intravascular coagulation (DIC), a condition characterized by the consumption of thrombin and coagulation factors (figure 4). DIC usually goes through a first thrombotic phase with multiorgan failure, then, with the progressive consumption and hence the decrease of fibrinogen, platelets, and prolongation of PT and aPTT, through a fibrinolytic hemorrhagic phase.

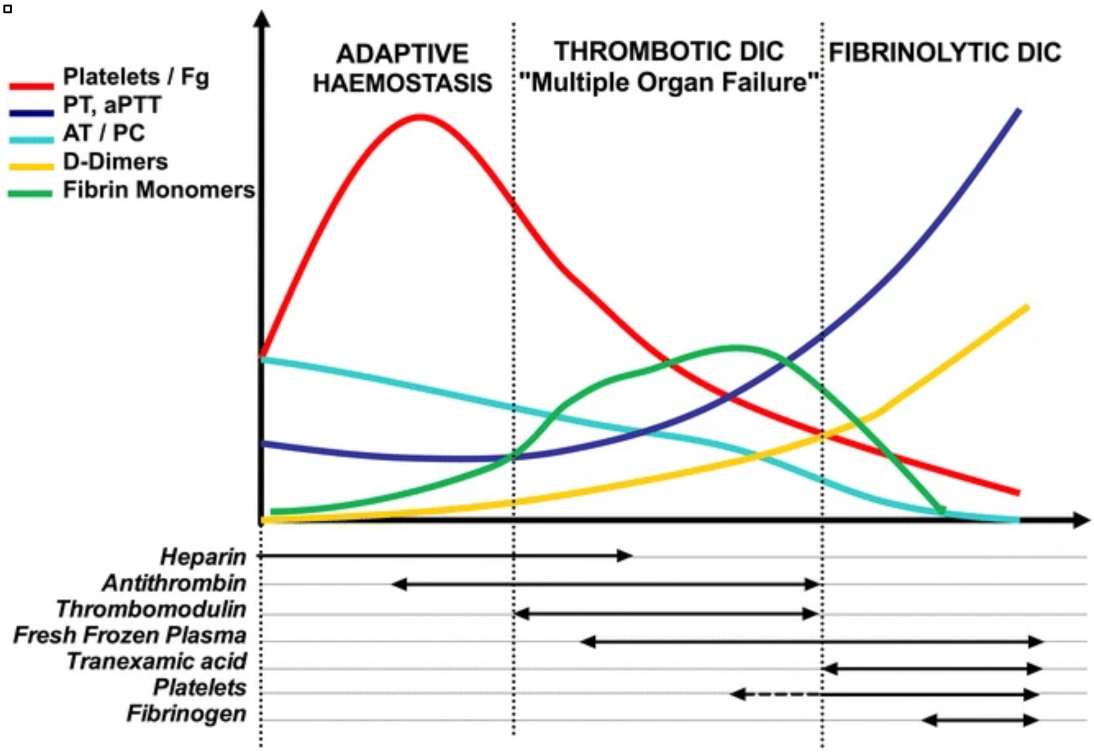


Figure 4. Immunohaemostasis: natural response of coagulation to infections (above) and possible therapeutic options (below). FG: fibrinogen. From Delabranche, X., Helms, J. & Meziani, F. Immunohaemostasis: a new view on haemostasis during sepsis. Ann Intensive Care 7, 117 (2017). DOI: 10.1186/s13613-017-0339-5. Distributed under the terms of the Creative Commons Attribution 4.0 International License.

Analogously, the coagulation abnormalities seen in COVID-19 pneumonia are induced by the inflammatory response. However, some remarkable aspects distinguish COVID-19 pathophysiology. A distinctive COVID-19 feature is that the host response is often dysregulated and uncontrolled, resulting in a "cytokine storm", i.e. the excessive release of many inflammatory cytokines and chemokines as Tumor Necrosis Factor α (TNF-α), Interleukin (IL)-1, IL-6 and IL-8 and in a consumption lymphopenia (Qin, Zhou, Hu, Zhang, et al., 2020). The excessive immune response may be due to the virus-mediated downregulation of ACE2 on type II pneumocytes (Kuba et al., 2005), resulting in an imbalance between the decreased immunoregulatory role of angiotensin-(1-7) and the enhanced detrimental role of angiotensin II in favoring pulmonary vascular permeability and hence leading to pulmonary oedema and acute lung injury (Imai et al., 2005) (figure 1). TNF-α, IL-1 and IL-6 induce a macrophage activation syndrome-like, which triggers tissue factor expression on endothelial cells, macrophages and neutrophils (McGonagle et al., 2020). Furthermore, the resulting endothelial damage and activation (attested by the increase in von Willebrand factor - vWF) with microvascular prothrombotic effects are not limited to lungs, but it may be widespread due to virus tropism for extrapulmonary endothelial ACE2 (Connors and Levy, 2020; Wool and Miller, 2021). Apart from its endotheliopathy-inducing role, IL-6 is a known coagulation activator and favors the production of platelets and fibrinogen (Hadid et al., 2021). In COVID-19 pneumonia, the typical steep increase of IL-6 is significantly positively associated with fibrinogen levels (Ranucci et al., 2020). Meanwhile, up to 40% of SARS-CoV-2 patients develop mild thrombocytopenia secondary to platelet consumption in the lungs and, to some extent, to other mechanisms (Wool and Miller, 2021). A distinguishing element that differentiates the COVID-19-induced coagulopathy (CIC) from the classic infective immunohaemostasis response is the disproportionate increase in D-dimer, reflecting a marked increase in thrombin generation and fibrinolysis, with only a minimal prolongation of PT/aPTT (table 1). This, in part, explains the imbalance towards thrombotic than hemorrhagic complications in COVID-19 (Hadid et al., 2021).

Table 1. Difference in coagulation parameters between COVID-19 and conventional sepsis.

Variable	COVID-19 sepsis	Conventional sepsis
aPTT	N/↑	↑↑/↑↑↑
PT	N/↑	↑↑/↑↑↑
Fibrinogen	↑↑↑/↑↑/↓	↑↑↑/↑↑/↓
Thrombocytopenia	N/↓	↓↓/↓↓↓
FSP	↑/↑↑	↑↑/↑↑↑
D-dimer	↑↑/↑↑↑	↑/↑↑
Schistocytes on peripheral blood smear	Not present	Frequent

Abbreviations: aPTT: activated partial thromboplastin time, PT: prothrombin time, FSP: fibrin split products, N: normal, ↑:mild increase, ↑↑: moderate increase, ↑↑↑, marked increase, ↓:mild decrease, ↓↓: moderate decrease, ↓↓↓: marked decrease. From Hadid, T., Kafri, Z. & Al-Katib, A. Coagulation and anticoagulation in COVID-19. Blood Rev 47, 100761 (2021). Distributed under the terms of the Creative Commons BY-NC-ND license.

An increase in D-dimer ≥0.5 mg/L has been found in 43% of non-severe and 60% of severe hospitalized COVID-19 patients, respectively (Guan et al., 2020). In these patients, an elevated D-dimer positively correlates with one-month mortality (Tang et al., 2020a), particularly when ≥3 mg/L (Tang et al., 2020b). In patients with an elevated D-dimer, therapy with prophylactic low molecular weight heparin significantly reduce mortality, thus indicating the prominence of coagulopathy in the pathophysiology of COVID-19 (Tang et al., 2020a).

The CIC main consequences are microvascular and macrovascular thrombosis. At the microvascular level, autopsy reports on COVID-19 patients described alveolar thickening with fibrin thrombi and patchy haemorrhages, a picture somehow like DIC but confined to small vessels of lungs ("pulmonary intravascular coagulopathy" – PIC) (McGonagle et al., 2020). At the macrovascular level, high rates of deep vein thrombosis and pulmonary embolism have been described, particularly at presentation or short-distance from COVID-19 symptoms onset, implying a direct role of the infection more than the consequence of immobilization or lack of prophylaxis (Hadid et al., 2021). Arterial thrombotic events have also been described, particularly in critically ill patients: acute coronary syndrome (2.1%) and ischemic stroke (6.3%) (Hadid et al., 2021). Ischemic strokes tend to occur in younger patients than non-

COVID-19 patients; while diabetes and obesity represent important risk factors for stroke in COVID-19 patients, hypertension and smoking are less represented (Bass et al., 2021). A stroke usually follows COVID-19 symptoms onset by 7-10 days and are usually more severe with a higher NIHSS (Bass et al., 2021). Up to 60-65% of COVID-19 strokes are classified as cryptogenic, often with multiple-territories large-vessel occlusions (LVO) with fragile fragmenting clots (Bass et al., 2021). Other than the inflammatory-induced hypercoagulable state described above, COVID-19 patients are exposed to embolic events due to pre-existing and new cardiac arrhythmias, systemic hypoxia secondary to cardiopulmonary distress, viral-induced vasculitis (Bass et al., 2021). Comparing patients with similar LVOs, COVID-19 patients present worse clinical pictures (Escalard et al., 2020). A detrimental diffuse brain microvascular and macrovascular damage has been confirmed by neuroradiological (Conklin et al., 2021) and neuropathological studies (Fisicaro et al., 2021). Moreover, the decrease in angiotensin (1–7) secondary to reduced ACE2 function may impair cerebral vascular autoregulation, worsening ischemic brain damage (Zakeri et al., 2021).

COVID-19 pandemic and epidemiology of stroke

Before the COVID-19 pandemic, stroke was the second leading cause of death and the third leading cause of disability worldwide (SPREAD, 2016). In Italy, the general prevalence of cerebral stroke is 6.5%. Ischemic stroke is the main stroke subtype (80% of cases), with a crude annual incidence rate per 100,000 inhabitants between 106 and 313/100,000/year. In Italy, the prevalence of ischemic stroke almost doubled from 1990 to 2010, from 2.7% to 4.9%. The overall (age-standardized) ischemic stroke mortality decreased by 20% over the same period (SPREAD, 2016). In Italy, approximately 196,000 strokes occur every year, of which 20% are relapses (39,000).

In Italy's Emilia-Romagna region, cerebrovascular diseases accounted for 8% of total mortality in 2018, with a standardized mortality rate of 62.5 deaths per 100,000 residents. Mortality at 30 days after ischemic stroke was approximately 20%. In 2019, 6,853 patients with ischemic stroke were hospitalized in Emilia-Romagna, of which 1636 in the AUSL Romagna; 18% of patients with ischemic stroke underwent thrombolysis, and 9% had a thrombectomy (Regione Emilia-Romagna, 2021).

During the first wave of COVID-19 in February-April 2020, an epidemiological paradox occurred: worldwide stroke admissions decreased despite the expected vascular complications related to COVID-19 (Bass et al., 2021). A meta-analysis of 9 observational studies (five from Europe, one from the U.S.A., three from China) found a 36% decrease in stroke alerts in the initial pandemic period (mid-January to mid-April 2020) compared to the previous year, with a concomitant reduction, in a lesser degree, of reperfusion therapies (July and Pranata, 2020). However, concomitant increased proportions of severe stroke among admitted patients have been noted. (Bass et al., 2021). Among the possible reasons proposed for the admission decline are (1) the fear of infection leading patients with milder symptoms to stay home, (2) increased social isolation preventing the identification of stroke symptoms in elderly patients by family members, (3) overwhelmed emergency medical services resulting in reduced activation of stroke codes, (4) COVID-19 illness itself precluding the correct identification of stroke symptoms, (5) and an actual decline in stroke incidence due to environmental or behavioural changes, such as decreased air-pollution secondary to local lockdown (Sousa et al., 2020). However, the latter hypothesis has not been corroborated since the rate of stroke admission returned to steady levels after the initial drop during the very beginning of the pandemic (Bass et al., 2021).

Stroke network response to COVID-19 pandemic

Rapid time to reperfusion is essential to minimize the impact on disability and mortality of ischemic stroke due to LVO. To achieve the goal of the fastest reperfusion possible, adequate pre-hospital and intrahospital pathways are crucial. Hence, the results of each stroke network depend on the type of organizational paradigm chosen. The disparate stroke networks local features such as orographic, facilities and resources limit the application of general paradigms that must be adapted to each situation. Stroke networks are generally composed of different facilities, connected as a wheel's "hub and spokes". The Hub is the Comprehensive Stroke Center (CSC), while Spokes are the Primary Stroke Centers (PSC). The CSC is usually the only centre that performs the EVT, while both the CSC and the PSCs perform IVT. In Italy (DM 70/2015), a CSC is recognized as a stroke hospital unit if it fulfils the following criteria:

- neurological sub-intensive hospitalization unit with dedicated staff 24 hours a day;
- availability of a neurosurgery inpatient unit h24;
- availability of a radiology facility with CT angiography, perfusion CT and brain MRI (diffusion and perfusion) and neurosonological and echocardiographic diagnostics h24;
- availability of Interventional Neuroradiology h24;
- availability of Vascular surgery h24

The PSCs, on the other hand, are hospital units fulfilling the following criteria:

- neurological sub-intensive hospitalization unit with dedicated staff 24 hours a day;
- availability of a radiology facility with Angio-CT and availability of brain MRI (diffusion and perfusion) and diagnostics h24
- availability of neurosonology and echocardiography;
- operational link with the CSC formalized with a procedure.

The two main paradigms for stroke network organization in which CSC and PSCs operate are the "Drip-and-Ship" (DS) model and the "Mothership" (MS) model.

In the DS model, acute ischemic stroke (AIS) patients are transported to the nearest Primary Stroke Centers (PSC). If, after the initial clinical and neuroradiological workout, an AIS is confirmed and there are no contraindications, IVT is performed directly in the PSC. Patients with a demonstrated LVO with indication to thrombectomy are then transferred to the CSC. The hypothetical advantage of the DS model is the shorter interval from stroke onset to the first reperfusion therapy (IVT) since the patient is transported to the nearest centre capable of performing intravenous thrombolysis. However, in the case of confirmed LVO with EVT indication, the patient needs secondary transportation to the CSC, with a potentially longer onset-to-groin time interval. On the contrary, direct transport to the CSCs could ensure a shorter onset-to-groin time at the expense of a possibly delayed thrombolysis. This approach may be theoretically more beneficial in LVOs since these often require mechanical recanalization. Applying a MS model may be wasteful if the entire patient management process is not perfectly designed. The mathematical Queueing theory can help understand the problem. This theory studies the waiting lines, or queues (Sundarapandian, 2009). Three elements define a queue: "customers" that need a service, "servers" that provide the service and the "departures", or customers already served that leave the queue. To avoid the lengthening of the waiting line, a certain balance is needed between the number of customers and servers and an adequate volume of departures. In a MS model, the CSC is the server (EVT being the product served). As seen, CSCs guarantee by definition a h24 interventional Neuroradiologist capable of performing EVT. Both the entrance and the exit from this process must be flawless to avoid a queue. The entrance in the process should be granted only to patients that may be eligible for LVO. An optimal pre-hospital selection should evaluate the pre-stroke disability level and the probability of LVO. Although the modified Rankin scale (mRS) has not been designed to evaluate the pre-stroke disability, simple questions on functional autonomy and need for help in everyday activities may help assign a correct disability mRS category. Most CSCs adopt guideline-derived internal protocols for EVT that exclude from treating patients with a pre-stroke mRS >2 or >3 in particular situations. Regarding the identification of LVOs, multiple scales have been designed for this purpose. A recent meta-analysis evaluated the LVO diagnostic accuracy of 19 pre-hospital scoring systems (Vidale and Agostoni, 2018): the stroke vision, aphasia, neglect assessment (VAN), Los Angeles Motor Scale (LAMS), and classic version of NIH Stroke Scale are the better scoring systems. Particularly, a NIHSS ≥9 has the highest positive predictive value (PPV=0.86). However, it is the most complex scale to be applied in a pre-hospital setting. Current pre-hospital scales fail to identify patients with LVO with low motor impairment or without cortical signs while recognize as LVO patients with hemorrhagic stroke or stroke mimics (Duloquin et al., 2021). Telemedicine may be a helpful tool in the pre-hospital evaluation of suspected LVO patients. A certain rate of futile transportation to the CSC cannot be avoided, but it must be monitored. As for the entrance in the process, "departures" from the queue is fundamental for the correct flow. After EVT and the initial Stroke Unit monitoring, patients transported from a spoke district should be back-transported to their appropriate PSC as soon as possible.

Considering the pros and cons of both DS and MS models and the local peculiarities of different stroke networks, the choice between them is still a matter of debate (Maas et al., 2020).

New insights may come from applying new strategies, such as the "drip-and-drive" paradigm, where the neurointerventionalist reaches the patient and performs the EVT in the PSC. This theoretically could lead to shorter IVT times with a concomitant decrease of the needle-to-groin time (Ernst et al., 2020). However, the application of this model is not widespread but has been applied in limited settings.

Another possible measure to be applied in the CSC is the Direct transfer to angiography suite (DTAS): AIS patients admitted in the CSC with suspected LVO are directly transferred to the angiography suite bypassing the CT imaging, with possible but no definite beneficial effects on the intra-hospital workflow (Bastani et al., 2021; Requena et al., 2021). These advances demonstrate how an adequate organization is fundamental for an optimal administration of reperfusion therapies.

The AUSL Romagna Stroke Network

We operate in a stroke network in the Romagna region, central Italy, covering the provinces of Forlì-Cesena and Rimini. Two major cities constitute the province of Forlì-Cesena (FC), Forlì and Cesena, that numbered a resident population of 394,627 as of the 1st of January 2019 (Statistica, 2020). The province of Rimini (RN) has a resident population of 339,017. Our stroke network historically adopted a DS model. The CSC is the "M. Bufalini" hospital in Cesena, the only EVT-capable centre. The PSCs are the "Infermi" hospital in Rimini (38 km/40 minutes away from the CSC) and the "Morgagni-Pierantoni" hospital in Forlì (29 km/35 minutes away from the CSC) (figure 5).

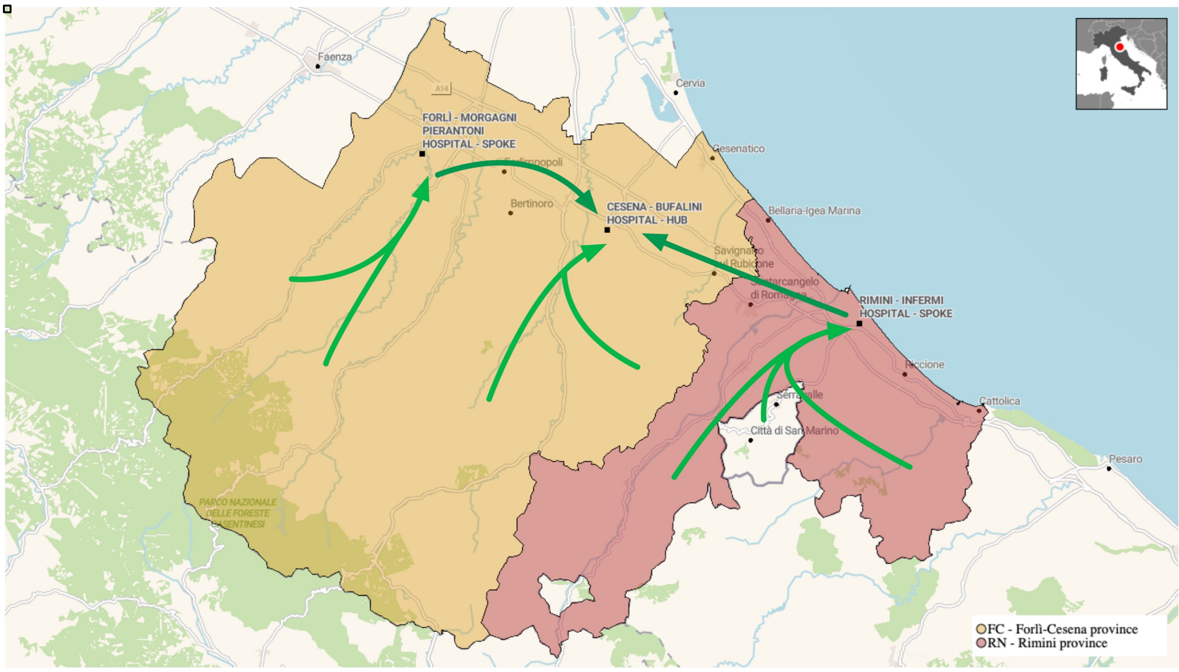


Figure 5. The pre-pandemic organization of AUSL Romagna Stroke Network was based on a drip-and-ship model. The PSCs (spokes) are in Rimini and Forlì, while the CSC (hub) is in Cesena. Light green arrow: primary transportation to the PSC; dark green arrow: secondary transportation to the CSC.

The AUSL Romagna stroke network increased its activity in the last few years, and in 2020 ranked fourth among Italian centres for performed EVT (source: REI, Registro Italiano Endovascolare) (figure 6).

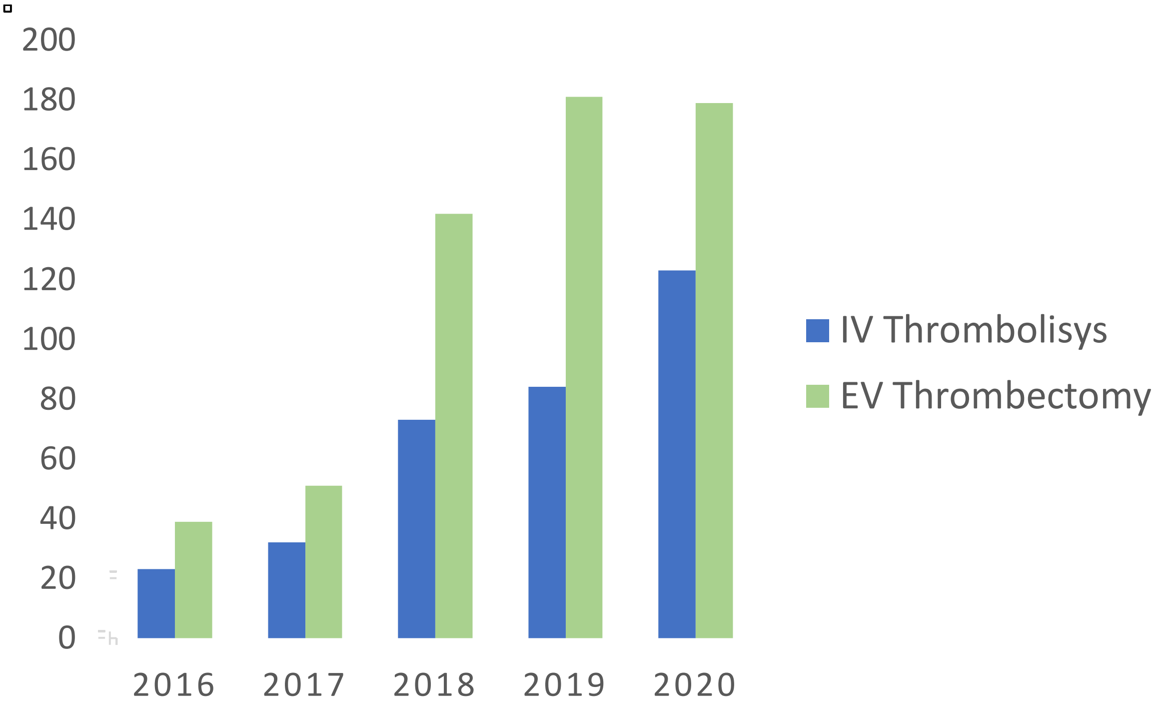


Figure 6. Reperfusion therapies performed in the "M. Bufalini" hospital CSC in Cesena.

During the COVID-19 pandemic in 2020, the PSCs were converted to mainly COVID-hospitals. As far as the COVID-19 pandemic spread out in Italy, Rimini province was one of the most hit. On the 7th of March 2020, it was declared "red zone", two days before the beginning of national lockdown. The Rimini "Infermi" hospital was converted to COVID-19 sole hospital. Hence, on the 15th March 2020, the stroke network shifted towards a MS model 24/7h for Rimini province and overnight for Forlì province until the 15th June 2020. We excluded from direct transportation to the CSC patients with a mRS≥4 or whose symptoms onset was >24h. Since the shift to the MS model aimed to lift the burden of stroke cases on COVID-dedicated PSCs, for all other suspected stroke patients, regardless of the LVO suspicion, the standard of care has been the transportation to the CSC. Hub's and spokes' in-hospitals routes for stroke patients have been rearranged too. At the "M. Bufalini" hospital, the Emergency Department (ED) planned a double separated route, one committed to COVID-19-suspected patients (based on anamnesis of contacts, fever or cough) and one for COVID-19-negative patients. Both routes had a dedicated CT scan. For COVID-19-negative patients, a CT scan outside ED was used, extending the internal transporting time (figure 7).

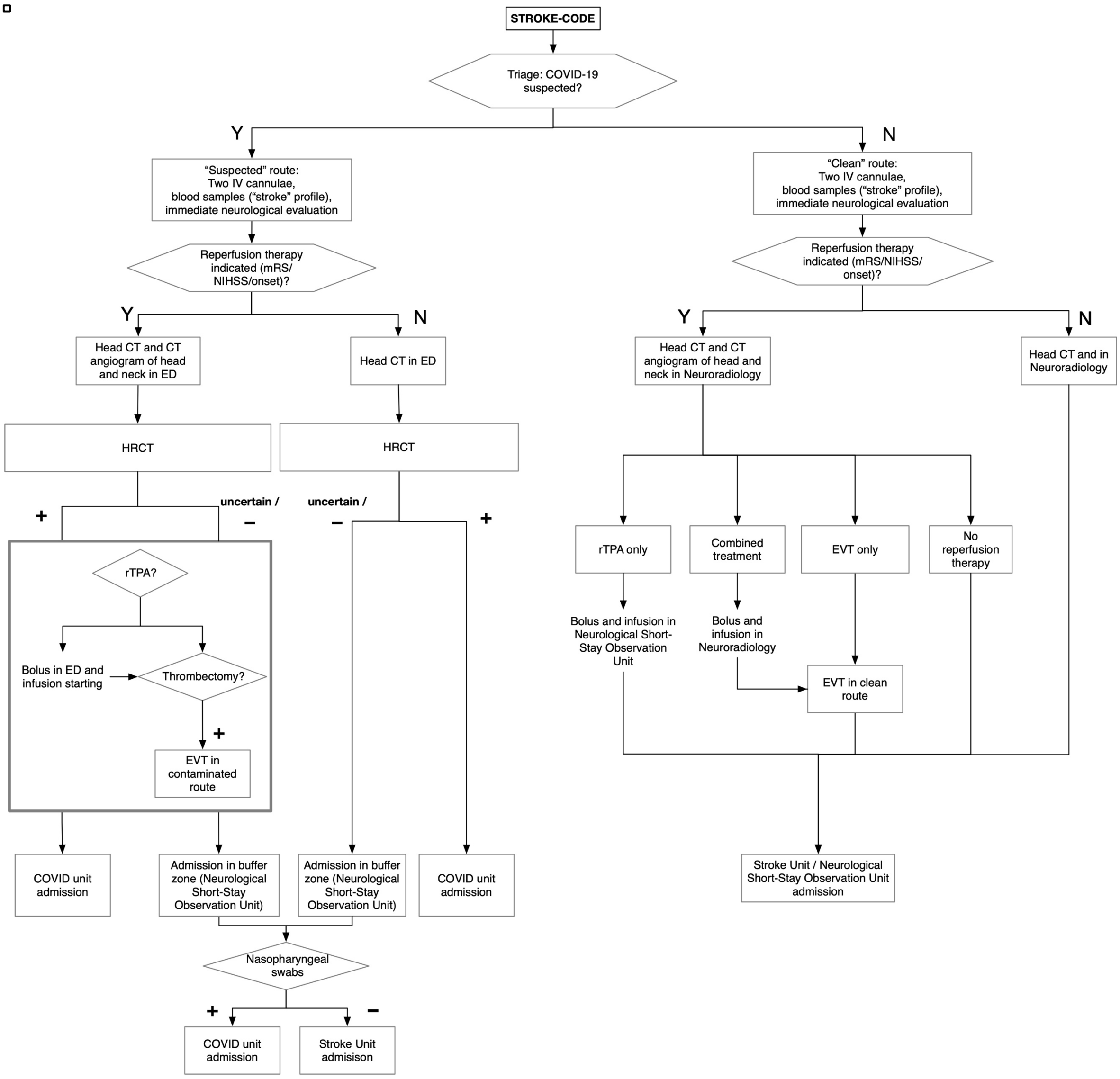


Figure 7. Planned routes for stroke patients with or without suspected COVID-19.

Moreover, to handle the increase in referrals in the CSC due to mothership and guarantee a neurological fast-track in the ED, the Neurology service opened a four-bed Short-Stay Neurological Observation Unit (SSNO or "OBI Neuro").

Aims

This PhD project evaluates different aspects of the impact of COVID-19 pandemic on stroke epidemiology and acute care. Specific aims are:

1. confirming the decrease in stroke referral during the first pandemic wave;
2. evaluate the volume and promptness of reperfusion therapies of the whole stroke network during the first COVID-19 pandemic wave;
3. evaluate the usefulness of the SSNO unit in the CSC;
4. evaluate the efficiency and efficacy of the MS compared to the DS model.

To answer these queries, we designed four studies: (1) an epidemiological study, (2) a whole stroke network performance study, (3) a SSNO unit performance study and (4) a MS vs DS comparison.

Methods

1. Epidemiological study

We designed a retrospective multicenter observational study, addressing two PICO (patient, intervention/exposure, comparator, outcome) questions regarding the influences of COVID-19 pandemic on suspected stroke epidemiology. We compared data from March 2020 with March 2019. Preliminarily, we also compared data from March 2019 with March 2018 to exclude potential bias. Anonymized data have been made publicly available at Harvard Dataverse and can be accessed at https://doi.org/10.7910/DVN/EVHWSB.

Epidemiological study - PICO question 1

Is the number of suspected and confirmed strokes managed in ED decreased in March 2020 compared to March 2019 in the provinces of FC and RN?

- Population: population of FC and RN provinces
- Intervention/Exposure: suspected and confirmed strokes managed in ED in March 2020
- Comparison: suspected and confirmed strokes managed in ED in March 2019
- Outcome: reduction in suspected and confirmed strokes managed in ED

We obtained the number of suspected stroke cases managed in the ED from the database of calls to the Italian emergency number and the database of neurological visits in the ED (fig. 8). The latter criterion was introduced to avoid missing of self-presenting patients to ED. We calculated a self-presentation to the ED of about 28% of total suspected stroke cases from an internal analysis.

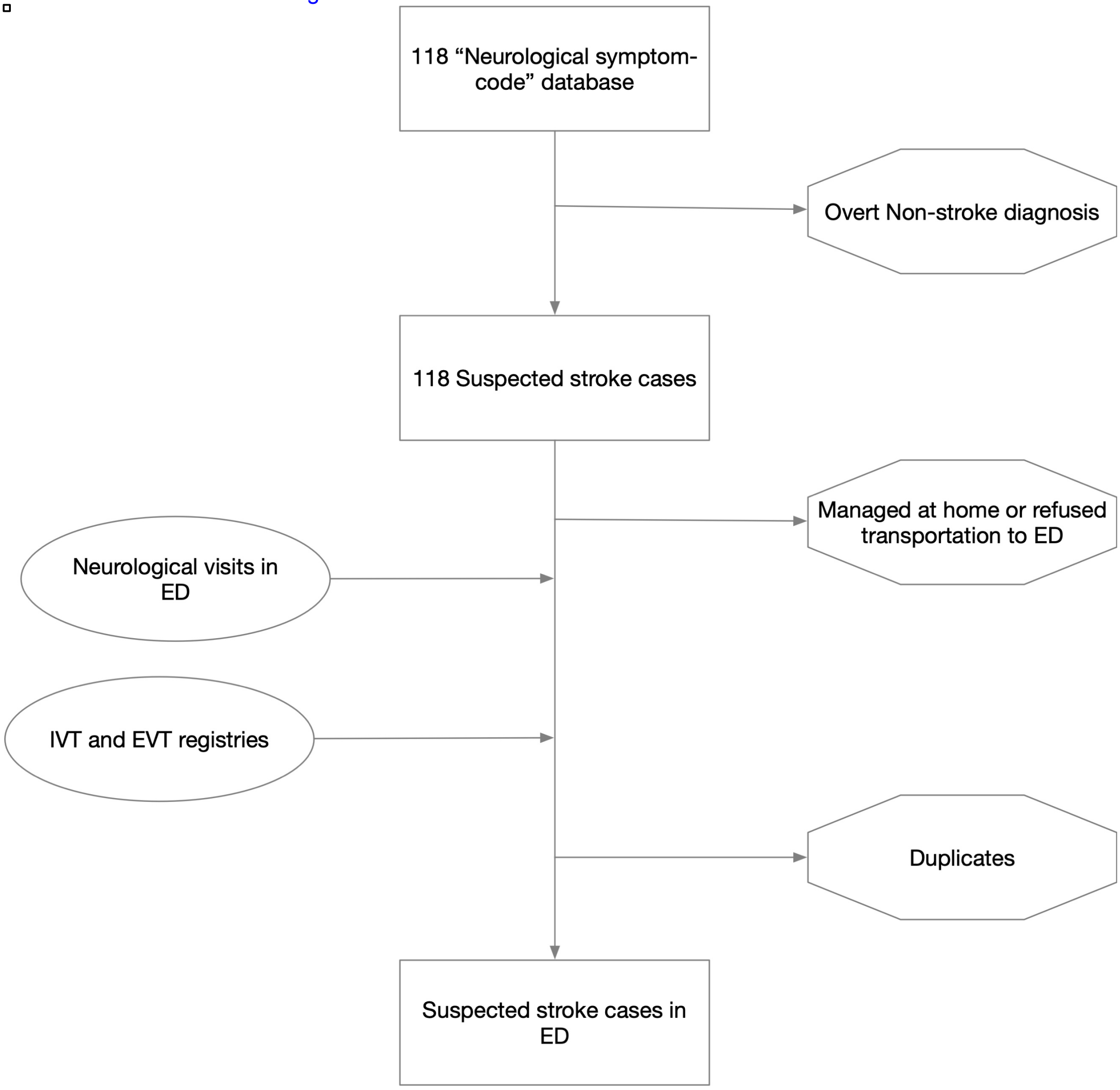


Figure 8. Identification of suspected stroke cases.

A) Identification of suspected stroke cases managed in ED.

To obtain the exact number of suspected stroke cases managed in the provinces' ED, we extracted the "neurological symptom-code" activations from the database of calls to the emergency number (118, the Italian 911). We initially widened the screening to all neurological symptom-code to avoid the risk of underestimation adopting the sole stroke-code. We then narrowed the search, including patients with a defined stroke-code or for whom another overt non-stroke diagnosis was excluded and that were transported to the ED (fig. 8).

To double-check for missing and to include self-presenting patients to the ED, we cross-checked databases of neurological visits in ED and intravenous thrombolysis and endovascular thrombectomy registries for the same period.

B) Identification of confirmed stroke cases managed in ED.

The number of confirmed stroke cases managed in the ED was extracted from the analysis of discharge forms (ICD-9-CM codes 430.x, 431.x, 432.x, 433.x, 434.x, 437.x).

C) Allocation of suspected and confirmed stroke cases managed in ED to provinces.

We allocated suspected stroke patients to one of the provinces based on the place of stroke onset and 118 calls, and not to the hospital of arrival. For patients that self-presented to the ED, we considered the province of the ED itself.

Since ICD-9-CM codes are extracted from the discharge form, we allocated confirmed stroke cases based on the hospital of arrival.

D) Calculation of incidence of suspected and confirmed stroke managed in the ED

We calculated the incidence of suspected and confirmed stroke managed in the ED for March 2019 and March 2020 based on the mean resident population in the two provinces, extracted from the public database of the ISTAT (Italian National Institute of Statistics, 2020). Regarding March 2019, we used the data for that particular month; for March 2020, instead, we adopted the most recent available record of the resident population, that is mean population at November 2019. To evaluate a reduction in the incidence of suspected and confirmed stroke managed in the ED, we calculated the incidence rate ratio (IRR) between observed incidence in the two intervals.

Epidemiological study - PICO question 2

Is there a correlation between COVID-19 pandemic progression and the number of suspected stroke cases managed in the ED in March 2020 in the provinces of FC and RN?

- Population: population of FC and RN provinces
- Intervention/Exposure: COVID-19+ progression in March 2020
- Comparison: progression of suspected stroke cases in ED in March 2020
- Outcome: correlation

We extracted the provincial data of daily new COVID-19 cases recorded by the National Department of Civil Protection (Protezione Civile, 2020) and calculated the cumulative number of cases and incidence of COVID-19. Suspected stroke cases were allocated to the province based on the place of stroke onset. We run a Spearman's rank-order correlation to assess the relationship between daily new COVID-19 cases and daily new suspected stroke cases managed in ED in the two provinces (individually and as a whole) in March 2020.

2. Whole stroke network performance study

Again, we designed a retrospective observational multicenter study, addressing two PICO questions regarding the influences of COVID-19 pandemic on stroke treatments. Similarly, we compared data from March 2020 with March 2019 and March 2018. Anonymized data have been made publicly available at Harvard Dataverse and can be accessed at https://doi.org/10.7910/DVN/EVHWSB.

Whole stroke network performance study – PICO 1

Has a reduction of acute stroke treatment (intravenous thrombolysis, IVT; endovascular thrombectomy, EVT) occurred in the two provinces in March 2020 compared to March 2019?

- Population: patients managed as a suspected stroke in ED in FC and RN provinces

- Intervention/Exposure: IVT, EVT or combined treatments in March 2020
- Comparison: IVT, EVT or combined treatments in March 2019
- Outcome: reduction in stroke treatments
    - Secondary outcome: change in baseline characteristics of stroke patients

This PICO regards the possible negative influence of COVID-19 pandemic on the stroke network organization. We wondered if the rearrangement of the emergency system (both on the territory and in the ED) could affect the volume of performed reperfusion therapies.

We compared the absolute number of IVT, EVT and combined treatments between the two time periods in the two provinces (individually and as a whole). Allocation to the province was based on the managing hospital. To observe differences in clinical characteristics of treated patients (severity on the NIHSS score and age of presentation), we adopted Student T-test and Mann-Whitney U-test.

Whole stroke network performance study – PICO 2

Is the COVID-19 pandemic in March 2020 influencing the call-to-needle (CTN) and door-to-needle (DTN) times of IVT in stroke patients in FC province, compared to March 2019?

- Population: population of FC province presented to ED with a stroke-code
- Intervention/Exposure: IVT (alone or combined) treatments in March 2020
- Comparison: IVT (alone or combined) treatments in March 2019
- Outcome: increase in call-to-needle time (interval from the call to the 118 to the start of IVT) and door-to-needle time (interval from the entrance in the hospital to the start of IVT)

We wanted to address the possibility that COVID-19 could slow stroke patients' out-hospital and in-hospital acute care. We then compared the median call-to-needle and door-to-needle times in March 2020 and 2019 with an independent samples Mann-Whitney U test. We extended the analysis of door-to-needle time comparing March 2018 with a Kruskal-Wallis test. We narrowed the analysis to the sole FC province because a drip-and-ship model remained constant between the years only in this territory. Hence, to permit a direct comparison of the performances of IVT, we excluded from this analysis all the patients of the RN province treated in Cesena during the mothership period.

We chose not to perform an analysis of thrombectomy in this PICO since it would be affected by some bias: an unbalanced number of secondary transports from Forlì to Cesena in 2019 compared to 2020 and the overall small numbers since EVT therapies from RN province would be excluded.

3. SSNO unit performance study

We evaluated one-year (1^{st} April 2020 - 31^{st} March 2021) SSNO patients' admissions, discharge destinations, diagnosis, and mean length of stay.

4. MS vs DS models comparison

We designed a retrospective cohort study comparing stroke network performances on EVT administration in a MS versus a DS model.

Participants and study size. All AIS patients with onset in a PSC-area (spoke-district patients) treated with EVT (with or without concomitant IVT) in 15^{th} March – 15^{th} June 2019-2020 periods were included. We considered as spoke-district patients all EVT patients from Rimini province (24/24h) and Forlì area (on night shift only). EVTs carried out on spoke-district patients from 15^{th} March to 15^{th} June 2020 were included in the MS cohort. EVTs carried out on spoke-district patients on the same time interval of 2019 were included in the DS cohort.

Variables and outcomes. The primary endpoint was to evaluate if the MS model shift during the pandemic wave ensures a shorter onset-to-groin time (OGT) without affecting the onset-to-needle time (ONT).

Secondary endpoints were (1) percentage of IV thrombolysis, (2) treatment timing, including call-to-door time (CDT), door-to-CT time (DCT), door-to-needle time (DNT), door-to-groin time (DGT); (3) functional independence at three months (modified Rankin Scale, mRS). All outcomes were compared between DS and MS paradigms.

We identified several potential factors influencing the out-of-hospital management of acute stroke patients during the COVID-19 pandemic. For instance, the fear of hospitalization may affect the promptness of the request for aid; the use of personal protective equipment and the need for an extended anamnesis may delay the ambulance's departure; the decrease in road traffic during the national lockdown may speed up the transport. To overcome these potential biases, 1) we compared onset-to-call time (OCT), call-to-needle (CNT), and call-to-groin (CGT) between cohorts and 2) we analyzed time logistic of trauma patients (another time-dependent pathology) since a mothership approach has been adopted for trauma since 2019. We compared the duration of on-site intervention and transport (only for "red-code" patients transported by ambulance) of trauma patients from the province of Rimini in the same months (March-June) of 2019 and 2020.

Data were extracted from clinical files of patients, the internal database of treated AIS patients, from 118 (Italian emergency number) database and local SITS (Safe Implementation of Treatments in Stroke) and REI (Registro Endovascolare Italiano) registries.

Statistical analysis. For baseline comparisons (demographic variables, NIHSS and ASPECTS scores and risk factors) and the primary endpoint and secondary endpoints #1 and #2, parametric or non-parametric analyses were adopted based on the normality test. Independent sample Student t-test was used for normally distributed continuous variables. In contrast, the independent sample Mann-Whitney U test was used for non-normally distributed continuous variables or ordinal variables and Pearson Chi-Square or Fisher's exact test for binomial variables.

For secondary endpoint #3, after excluding multicollinearity and confirmation of proportional odds, an ordinal logistic regression was run to determine the effect of stroke network model (MS or DS) adjusted for sex, age, treatment (EVT only or IVT and EVT combined), pre-stroke mRS, ASPECTS score, TICI score, onset-to-door time, NIHSS, on the 3-month mRS category. A dichotomic analysis of mRS 0-1 was also performed with a Mann-Whitney U test. We also applied the inverse probability of treatment weighting (IPTW) using the propensity score to better evaluate the effect of baseline covariates. We calculated the propensity score considering these variables: age, sex, night shift presentation, NIHSS score, ASPECTS score, TICI score, atrial fibrillation, hypertension, diabetes, treatment (EVT alone or combined EVT+IVT).

Anonymized datasets are available at: https://doi.org/10.7910/DVN/BROSVG.

Statistical analyses

Statistical analyses were performed using SPSS version 25, STATA v. 12, GraphPad Prism v.8.

Ethical Committee approval

As we exclusively conducted observational studies, the Institution Review Board has been notified as requested by the Italian law.

Results

1. Epidemiological study

Comparisons between March 2018 and March 2019

The preliminary comparison of stroke referrals incidence of March 2018 and March 2019 showed no significant differences. We found 256 suspected stroke cases managed in the ED in March 2018 and 260 in March 2019 (IRR 0.99, 95% CI 0.83 – 1.18) in the whole stroke network. Confirmed stroke cases discharged from the ED were 184 in March 2018 and 194 in March 2019 (IRR 0.95, 95% CI 0.77 – 1.17).

Epidemiological study - PICO question 1

"Is the number of suspected and confirmed strokes managed in ED decreased in March 2020 compared to March 2019 in the provinces of FC and RN?"

Overall, we found a 15% decrease of suspected strokes managed in ED in March 2020 compared to March 2019 (table 2, fig. 9), in line with a 14% decrease of 118's "neurological symptom-code" activations (details on the volume of 118 calls can be found in Supplementary Results). The IRR of suspected strokes managed in ED presented a non-significant reduction in March 2020 compared to March 2019 in the provinces of FC and RN, considered both individually and as a whole. Nevertheless, there was a statistically significant reduction of confirmed stroke diagnosis in the whole stroke network from March 2019 to March 2020 (28% decrease, IRR 1.40, 95% CI 1.12 – 1.75). The comparison of the incidence confirmed stroke cases between March 2018 and March 2020 validates the 2019-2020 analysis results. The IRR of 2018-2020 is a significant value of 1.33 (95% CI 1.06 – 1.66: -25% of cases). The single-province analysis of confirmed stroke diagnosis of March 2020, due to allocation modality based on discharge forms, needs to be evaluated in the light of the shift to the mothership model so that the considerable decrease in RN province is compensated by FC province.

Interestingly, we observed a considerable difference in the number of patients assisted by ambulances and not transported to hospitals due to refusal or at-home management, since it increased from 15% (113/760) of total "neurological symptom-code" activations in March 2019 to 31% (203/655) in March 2020.

Table 2. Suspected and confirmed stroke cases in ED in March 2019 and March 2020

	FC					RN					Total				
		ED stroke-code[‡]		Final stroke diagnosis[§]			ED stroke-code[‡]		Final stroke diagnosis[§]			ED stroke-code[‡]		Final stroke diagnosis[§]	
	Resident population	Absolute number	Incidence (/100000)	Absolute number	Incidence (/100000)	Resident population	Absolute number	Incidence (/100000)	Absolute number	Incidence (/100000)	Resident population	Absolute number	Incidence (/100000)	Absolute number	Incidence (/100000)
March 2019	394475	145	36.76	116	29.41	339259	115	33.90	78	22.99	733734	260	35.44	194	26.44
March 2020[†]	394609	118	29.90	90	22.81	340125	102	29.99	49	14.41	734734	220	29.94	139	18.92
% variation		-19%		-22%			-11%		-37%			-15%		-28%	
Incidence rate ratio			1.23 (95% CI 0.96 – 1.58)		1.29 (95% CI 0.97 – 1.71)			1.13 (95% CI 0.86 – 1.48)		1.60 (95% CI 1.11 – 2.30)			1.18 (95% CI 0.99 – 1.42)		1.40 (95% CI 1.12 – 1.75)

[†] Resident population based on Nov 2019

[‡] Allocated in each province by place of stroke onset

[§] Allocated in each province by place of hospital admission

Figure 9. Volume of suspected stroke cases managed in ED in the month of March per year

Epidemiological study - PICO question 2

"Is there a correlation between COVID-19 pandemic progression and the number of suspected stroke cases managed in the ED in March 2020 in the provinces of FC and RN?"

To better outline the impact of COVID-19 pandemic progression on stroke epidemiology, we compared cumulative incidences and new daily cases of stroke and COVID-19.

In March 2020, 2120 new cases of COVID-19 had been diagnosticated in the territory of the two provinces. On the 31st March 2020, the total number of cases of COVID-19 were 730 in FC and 1407 in RN. At the same date, the incidence of COVID-19 was 291/100,000 inhabitants in the whole territory, with an important difference between the provinces: 185/100,000 in FC and 414/100,000 in RN.

Figure 10A shows the cumulative incidence of COVID-19 in March 2020 and the cumulative incidence of suspected stroke cases managed in ED in March 2020 and March 2019 in both provinces. Despite the progression of COVID-19 pandemic, the cumulative incidence of suspected stroke cases managed in the ED in March 2020 maintained the same slope, reduced but similar in shape compared to the one of 2019.

As better outlined in figure 10B, the monthly distribution of the number of daily cases of suspected stroke managed in ED in March 2020 was similar to the one on March 2019 in the first part of the month; as the pandemic proceeded, a decrease in suspected stroke cases in ED occurred especially in RN province, where the incidence of COVID-19 increased mostly.

There was a statistically significant negative correlation between COVID-19 progression (cumulative incidence) and daily new cases of suspected stroke managed in ED, $r_s = -.390$, $p = .030$. When considered individually, FC province didn't show the aforementioned correlation (rs = -.220, p = .234), while RN province confirmed the negative correlation (rs = -.434, p= 0.15)

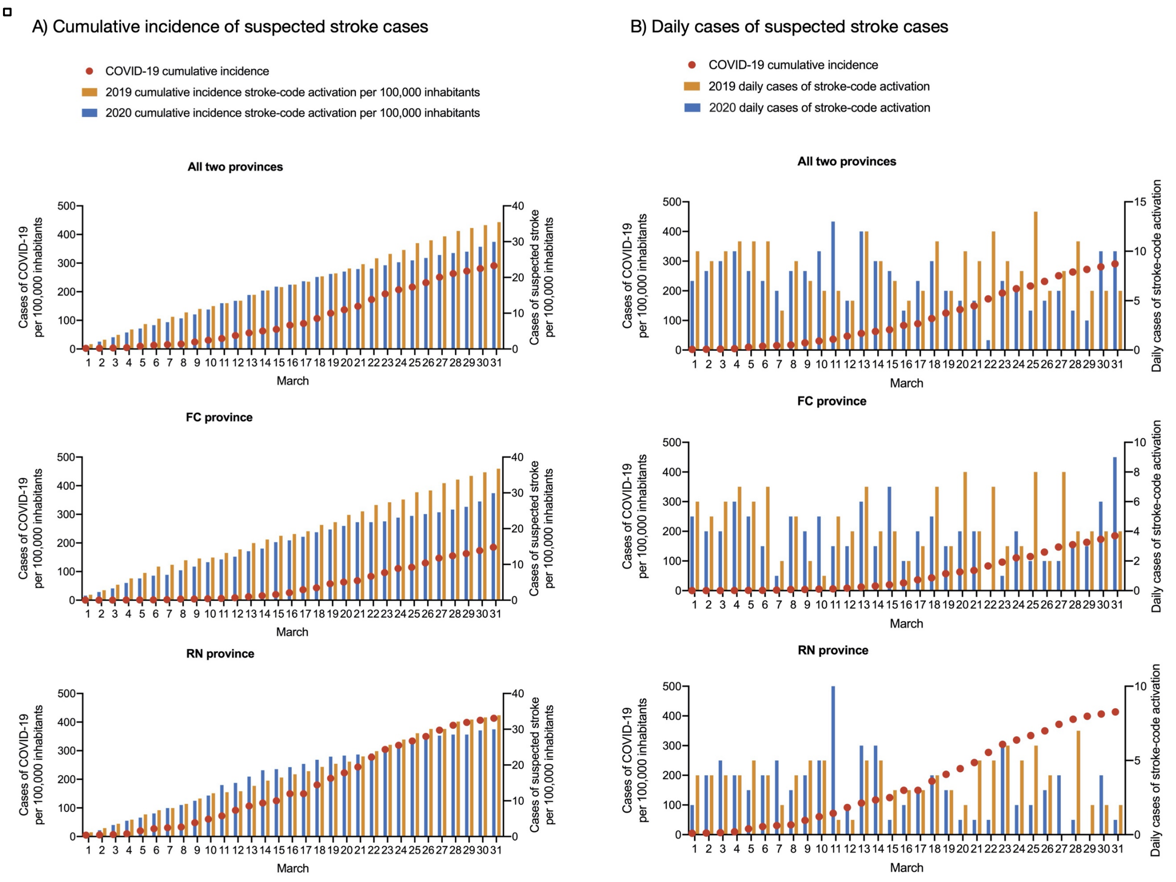


Figure 10. A) Cumulative incidence of suspected stroke cases during March 2020 (blue) and March 2019 (orange) and cumulative incidence of COVID-19 cases in March 2020 (red dots). B) Daily cases of suspected stroke cases during March 2020 (blue) and March 2019 (orange) and cumulative incidence of COVID-19 cases in March 2020 (red dots).

2. Whole stroke network performance study

Comparisons between March 2018 and March 2019

The preliminary comparison of reperfusion therapies of March 2018 and March 2019 showed no significant differences. The volume of reperfusion therapies was similar: 34 patients were treated in March 2018 (22 IVT, 3 EVT, 9 combined treatments), while 32 in March 2019 (22 IVT, 4 EVT, 6 combined treatments) (fig. 11).

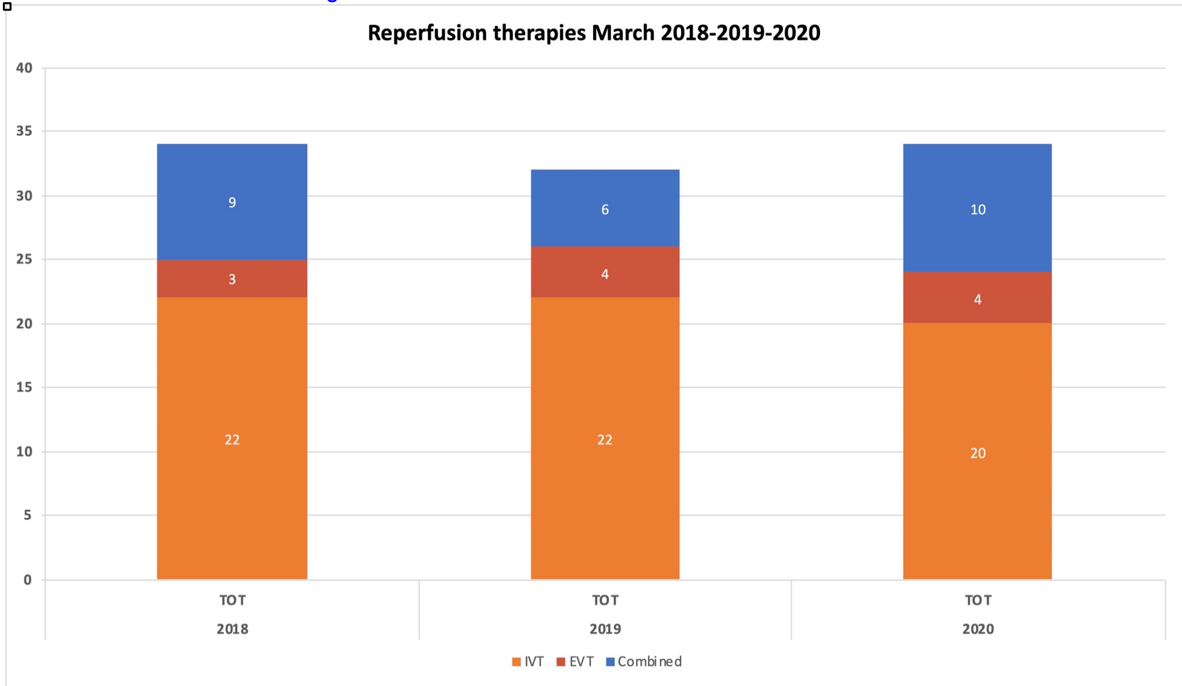


Figure 11. Reperfusion therapies in March 2018, 2019 and 2020 in the AUSL Romagna Stroke Network (Forlì and Rimini PSCs and Cesena CSC),

Whole stroke network performance study – PICO 1

"Has a reduction of acute stroke treatment (intravenous thrombolysis, IVT; endovascular thrombectomy, EVT) occurred in the two provinces in March 2020 compared to March 2019?"

We did not observe a reduction in the absolute number of acute stroke treatments (IVT and EVT) between March 2020 compared to March 2019 or March 2018 in the whole network nor differences in basal NIHSS score or age of treated patients of 2020 compared to 2019 (respectively, 7 vs 6.5, p=.379 and 71 vs 70, p=.852).

In March 2020, the absolute number of treatments remained unchanged (32 in 2019 vs 34 in 2020), despite a reduction of stroke patients. Indeed, 16.5% of confirmed strokes in March 2019 received reperfusion therapy, whereas in March 2020 this percentage increased to 24.5%. From the analysis of the characteristics of treated patients, we could not conclude that treated patients were elderly or had a more severe stroke at baseline.

Whole stroke network performance study – PICO 2

"Is the COVID-19 pandemic in March 2020 influencing the call-to-needle (CTN) and door-to-needle (DTN) times of IVT in stroke patients in FC province, compared to March 2019?"

In FC province, 15/145 (10%) suspected stroke patients managed in ED in March 2019 and 13/118 (11%) in March 2020 received IVT (alone or combined with EVT) (table 3).

We did not find any significant difference in out-hospital (call-to-needle) and in-hospital (door-to-needle) time intervals in acute stroke management in March 2020 compared to March 2019 in treated stroke patients from the province of FC. In March 2018, 16 suspected stroke cases were treated with IVT (alone or combined with EVT) in the same province; the Kruskal-Wallis test comparing median of DTN times of 2018, 2019 and 2020 did not show significant differences (p=.161).

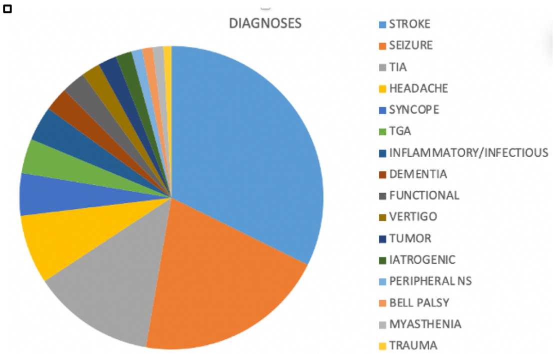
Table 3. Performances of intravenous thrombolysis in FC province in March 2019 and March 2020.

	IVT #	EVT #	Combined treatment #	Median Call-to-Needle time (min)	Median Door-to-Needle time (min)
March 2019	11	2	4	108.5 (IQR 34)	69 (IQR 41)
March 2020†	10	2	3	96 (IQR 23)	49 (IQR 37)
p				.126	.142

† three IVT, one EVT and five combined treatments were carried out in Cesena but were excluded because they were transported from RN province due to the switch to a mothership model

3. SSNO unit performance study

From the 1st of April 2020 to the 31st of March 2021, 556 patients were managed in the SSNO. Of these, 280 (50.4%) were discharged at home, 248 (44.6%) were admitted as in-patients, 20 (3.6%) were transferred to other hospitals, 8 (1.4%) self-discharged. Among patients admitted as in-patients, 91 (36.7%) were admitted in the Neurology ward, 135 (54.4%) were admitted in the Stroke Unit, the remaining (8.9%) in other wards of the hospital. The most common diagnoses were stroke (32.3%), seizure (20.4%), TIA (13%) and headache (7.4%); all other diagnoses individually represented less than 5% of the total (fig. 12). While most stroke patients have been admitted as in-patients (92%), the SSNO permitted to manage and discharge most patients with other diagnoses (>70% of headache, seizures, vertigo, cognitive decline and trauma patients). The mean stay of length was 11.5 h (14.4 h for discharged patients and 7.3 h for admitted as in-patients).



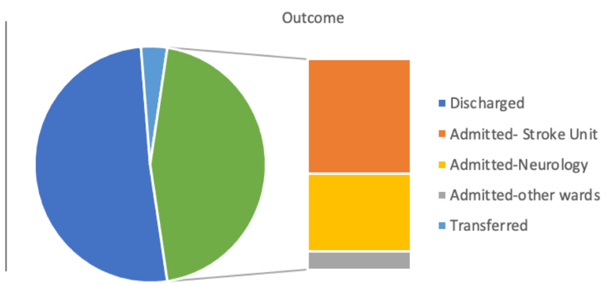


Figure 12. Diagnoses and outcome of patient admitted to the SSNO unit of the Cesena CSC from the 1st of April 2020 to the 31st of March 2021.

4. MS vs DS models comparison

Between 15th March 2020 and 15th June 2020, a similar number of AIS patients from spoke districts was treated with EVT (alone or combined with IVT) compared to the same period of 2019 (table 4). Demographic characteristics, cardiovascular risk factors and stroke severity were similar between groups.

Table 4. Treatments and demographics

	DS (2019)	MS (2020)	p
N of Cases	24	26	
EVT (n, %)	11 (45.8%)	4 (15.4%)	
EVT + IVT (n, %)	13 (54.2%)	22 (84.6%)	.030
Spoke-district			
Forlì (n,%)	3 (12.5%)	3 (11.5%)	
Rimini (n,%)	21 (87.5%)	23 (88.5%)	1
Demographics			
Sex (F, %)	50%	54%	.786
Age, years (mean, SD)	75.9 (11.9)	75.9 (11.1)	.993
mRS pre 0-1 (%)	95.8%	100%	.480
Risk factors			
Previous stroke or TIA (%)	12.5%	11.5%	.627
Hypertension (%)	83.3%	80.8%	.554
Atrial fibrillation (%)	25%	23.1%	.874
Diabetes (%)	8.3%	23.1%	.250
Dyslipidemia (%)	50%	34.6%	.208
Stroke severity and outcome			
NIHSS (median, IQR)	12 (12)	16.5 (14)	.147
ASPECTS (median, IQR)	9 (2)	9 (2)	.944
TICI 2b/3 (%)	87.5%	80.8%	.704
Anterior circulation (%)	91.7%	96.2%	.602
Careggi Collateral Score ≥3 (%)	54.5%	54.6%	.931
mRS 3 month 0-1 (n, %)	8 (33.3%)	10 (38.5%)	.706
mRS 3 month 6 [death] (n, %)	1 (4.2%)	7 (26.9%)	.050
Onset-to-call time, minutes (median, IQR)	163 (376)	29 (101)	.016

All thrombectomy-treated patients of both DS and MS periods have been admitted to the CSC stroke unit, where they remained for a minimum of 48h. After that, they have been back-transported to the PSCs when possible. In all IVT treated patients, the angiography confirmed the cerebral arterial occlusion.

Primary endpoint

Compared to the DS model, the MS model ensured a significant decrease of the median OGT (162.5 minutes [IQR 106] vs 269 minutes [IQR 320], p=.001) without significantly affecting the median ONT (140.5 minutes [IQR 84] vs 136 minutes [IQR 105], p=.853).

Secondary endpoints

1) Compared to the DS model, the MS had higher rates of combined treatment with IVT + EVT (MS: 22/26 [85%]; DS: 13/24 [54%]; p=.030). In most DS model patients (63.7%), IVT was not administered due to wake-up stroke or unknown stroke onset. Details are shown in table 5.

Table 5. Reasons for IVT avoidance

	DS (2019)	MS (2020)
N of Cases	11	4
Unknown onset (n, %)	2 (18.2%)	0
Wake-up stroke (n, %)	5 (45.5%)	1 (25%)
Onset >4.5 h (n, %)	3 (27.3%)	1 (25%)
Anticoagulants/heparin (n, %)	1 (9.1%)	1 (25%)
Low platelet count (n, %)	0	1 (25%)

2) MS model showed a significantly longer transport time from the site intervention to the hospital (median CDT difference: 23 minutes, p<.005). However, the management of AIS patients in the CSC was quicker than in PSCs. Median DCT decreased by 11.5 minutes (p=.017), median CT-to-needle decreased by 20.5 minutes (p=.001), and median CT-to-groin decreased by 78 minutes (p<.005). Altogether, DNT and DGT significantly decreased with the MS model (DNT: DS median 74 min [IQR 27], MS median 43 min [IQR 26], p=.001; DGT: DS median 144.5 min [IQR 55], MS median 62 min [IQR 23], p=<001). Figure 13 shows the detailed median time intervals of every out-of-hospital and in-hospital step in AIS patient management.

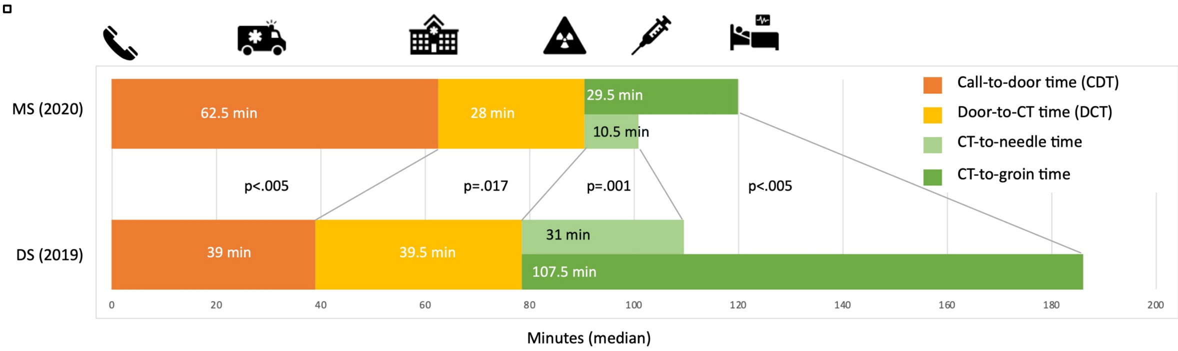


Figure 13. Median diagnostic and intervention times for DS and MS groups.

3) We found no effects of the stroke network model (MS or DS) on the 3-month mRS category (adjusted odds ratio 0.787, 95% C.I. 0.178 – 3.489, p=.753; figure 14). Full details of the logistic regression model can be found in table 6. At 3-month, the proportion of patients in mRS 0-1 categories is 33.3% for spoke-district DS patients and 38.5% for spoke-district MS patients, a non-significant difference (p=.706).

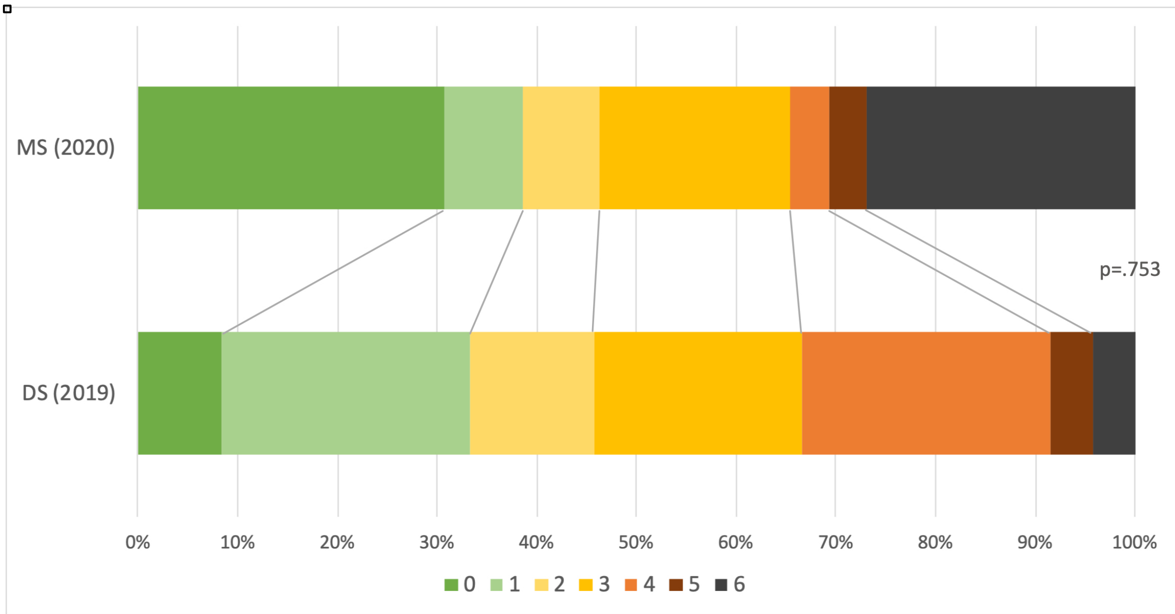


Figure 14. Three-month mRS for DS and MS groups.

Table 6. Logistic regression model.

	Sig.	OR of being in a higher three-month mRS category	95% CI
SEX (F vs M)	.625	1.433	.339 – 6.052
TREATMENT (IVT+EVT vs EVT)	.000	35.797	5.142 – 249.207
DAS VS MS	.753	.787	.178 – 3.489
mRS PRE	.099		
0 vs 2	.160	.055	.001 – 3.146
1 vs 2	.595	.347	.007 – 17.255
TICI	.026		
TICI 2b vs TICI 3	.674	.730	.168 – 3.166
TICI 2a vs TICI 3	.012	17.332	1.861 – 161.372
ASPECTS	.046		
ASPECTS 9 vs ASPECTS 10	.283	2.394	.487 – 11.764
ASPECTS 8 vs ASPECTS 10	.028	0.153	0.029 – 0.819
AGE	.881	.995	.926 – 1.068
ONSET-TO-DOOR	.270	.998	.994 – 1.002
NIHSS	.000	1.259	1.124 – 1.411

Dependent Variable: mRS 3 month

Model: Sex, age, treatment (EVT only or IVT and EVT combined), stroke network model (DS or MS), pre-stroke mRS, ASEPCTS score, TICI score, onset-to-door time, NIHSS.

Multicolinearity: no variable showed multicollinearity.

The assumption of proportional odds was met, as assessed by a full likelihood ratio test comparing the fit of the proportional odds model to a model with varying location parameters, $\chi2(85) = 28.855$, $p = 1.000$. The deviance goodness-of-fit test indicated that the model was a good fit to the observed data, $\chi2(277) = 153.903$, $p = 1.000$.

The final model statistically significantly predicted the dependent variable over and above the intercept-only model, $\chi2(17) = 32.544$, $p = .013$.

Repeated analysis after propensity-score weighting (IPTW) confirmed no difference in the distribution of 3-month mRS (p=.533) nor the rate of 3-month mRS 0-1 category (p=.761).

In 2020, a significantly higher proportion of patients died during the three-month follow-up. Of the seven patients who died in 2020, one died due to COVID-19, three from hemorrhagic transformation, one from cardiac insufficiency, two from other causes. Four out of 7 patients died >30 days after the index stroke, the rest during the first week.

Ascertainment of potential confounders on out-of-hospital management.

Interestingly, median OCT was significantly shorter in 2020 (table 4, p<0.016), refuting the hypothesis of a potential bias due to a delay in request for aid during the pandemic. The considerable difference in OCT may be due to a direct lockdown effect since the domestic confinement could have determined an increase in witnessed stroke onset by family members. However, there were considerable missing data in the 2019 groups (10 patients have missing data for the "Call time" variable, 41.7% of the 2019 groups). To overcome the influence of the difference in the median OCT between groups on the evaluation of ONT and OGT, we compared the difference in CNT and CGT between groups. CNT and CGT may better express the out-of-hospital and in-hospital management efficiency since delays in call for aid do not influence them. Despite missing values for "call time" (up to 75% for CNT and 42% for CGT evaluation), we found a significant decrease in CGT time (median differences: 55.5 minutes, p<.005) without significant differences in CNT (p=.324).

The analysis of the out-of-hospital management of Rimini province trauma patients (for whom the direct transport to Cesena was already active in 2019) showed no differences in on-site intervention time between 2019 and 2020 (p=.182) (table 7). Interestingly, while we expected shorter transport time due to a decrease in road traffic during the lockdown, we found a significantly longer transport time from the intervention site to the emergency department in 2020 than in 2019 (29 min vs 25 min, p=.033).

Table 7. Trauma patients transported from the province of Rimini to the "M. Bufalini" hospital, Cesena. Only "red-code" patients transported by ambulance were included in the analysis.

	Cases	On-site intervention (median)		Transport (median)	
Mar-Jun 2019	17	23 min (IQR 12)	p=.182	25 min (IQR 6)	p=.033
Mar-Jun 2020	47	28 min (IQR 14)		29 min (IQR 14)	

Ascertainment of potential confounders on clinical outcome (mortality and mRS).

As we found a significantly higher mortality rate in 2020 during the mothership period, we conducted a *post hoc* analysis to exclude potential confounders. We compared the mortality rate of the mothership period with that of a three-month drip-and-ship period that equally occurred during the COVID-19 pandemic (second wave). We applied the same selection criteria for spoke-patients treated with EVT from 1st December 2020 to 28th February 2021.

In December 2020 – February 2021 ("DS 2"), we treated 24 spoke patients with EVT, alone or in combination with IVT, a volume similar to that of previous trimesters. These patients did not differ from MS patients for baseline characteristics (table 8).

Table 8. Baseline characteristics.

	MS (2020)	DS (2021)	**p**
N of Cases	26	24	
Sex (F, %)	14 (54%)	13 (54%)	.982
Age, years (mean, SD)	75.9 (11.1)	71.3 (14.2)	.221
mRS pre 0-1 (%)	26 (100%)	22 (92%)	.225
NIHSS (median, IQR)	16.5 (14)	16.5 (10)	.859
ASPECTS (median, IQR)	9 (2)	8 (4)	.098
TICI 2b/3 (%)	80.7%	73.7%	.362

The mortality rate (three-months mRS category=6) was similar between groups (7/26 [26.9%] in MS, 6/24 in DS 2 [25%]; p=.567). However, a significantly lower number of patients was treated with IVT in DS 2 (9/24 [37.5%] vs 22/26 [84.6%], p=.001). The number of IVT in the DS 2 period did not significantly differ from that of the 2019 DS period (9/24 [37.5%] vs 13/24 [54.2%], p=.385). In the DS 2 group, median DNT was 84 min (IQR 42) and median DGT was 166 (IQR 58). Compared to MS, the DS 2 group reached longer DNT (+41 min, p<.001) and DTG (+104 min, p<.001). Detailed time intervals differences between groups are shown in figure 15.

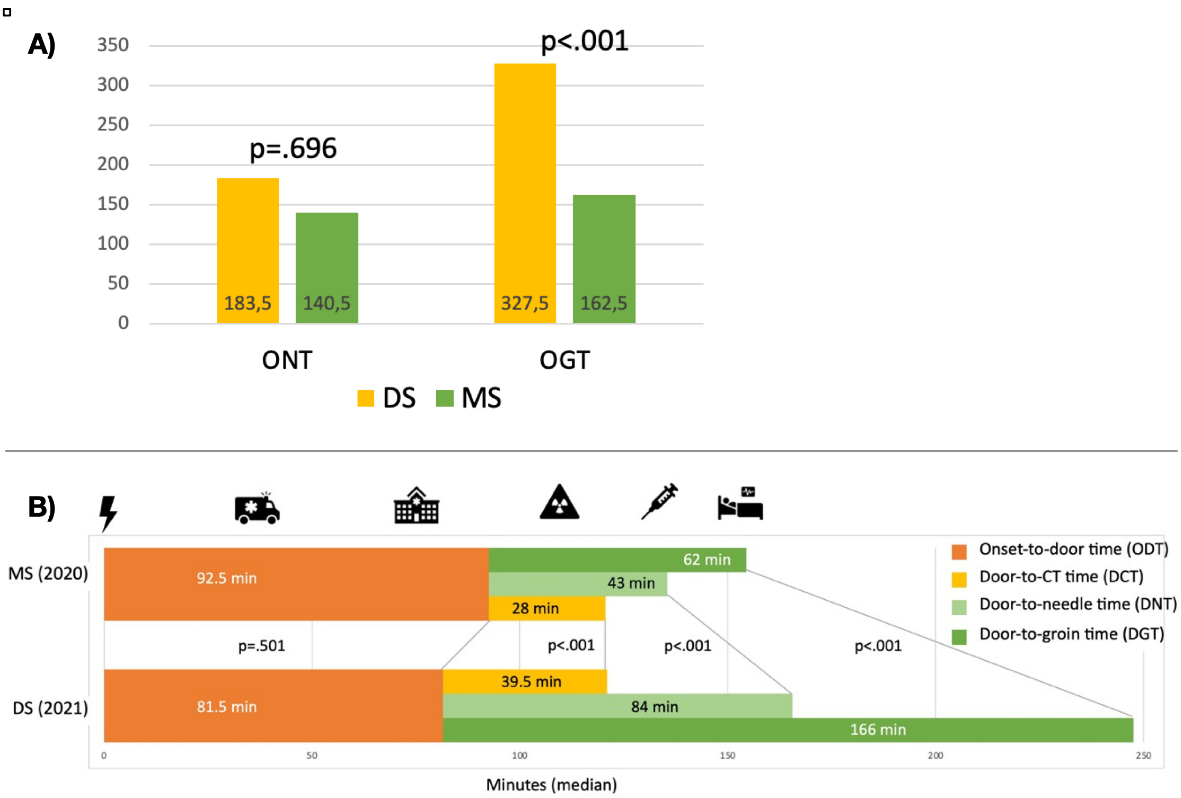


Figure 15. Comparisons of time intervals of reperfusion therapies between MS and DS 2 groups. A) the MS model guaranteed shorter onset-to-groin time (OGT) without affecting onset-to-needle time (ONT. B) the MS model obtained short intra-hospital intervals without lengthening the extra-hospital management.

Again, a multivariate ordinal logistic regression found no effects of the stroke network model (MS or DS 2) on the 3-month mRS category (p=.632; fig. 16). However, although the difference in the proportion of 3-month mRS 0-1 did not reach statistical significance (5/24 [20.8 %] spoke-district DS 2 patients; 10/26 [38.5%] spoke-district MS patients; p=.147), no patients in the DS 2 group reached mRS=0.

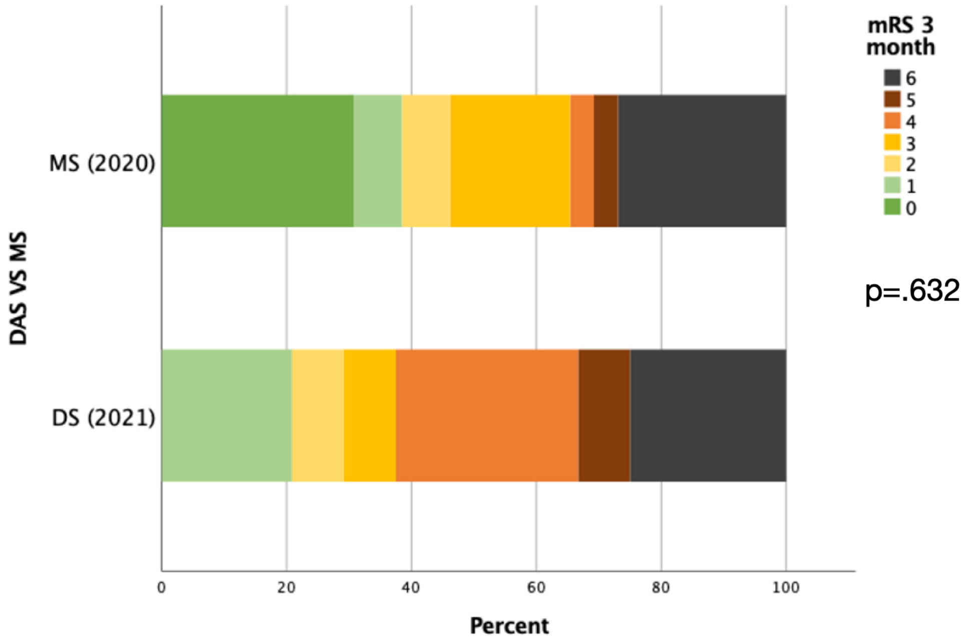


Figure 16. Three-month mRS between MS group and DS 2020-21 group (pandemic).

Discussion

In our epidemiological study, we found a significant 25-28% decrease of confirmed strokes cases managed in ED in March 2020 compared with the same month of the previous two years, confirming the phenomenon observed by other stroke networks. Overall, the total number of calls to the emergency number for neurological symptoms decreased, while it doubled the number of patients managed at home or that refused to be transported to the hospital, probably because of fear of in-hospital SARS-CoV-2 infection. The daily number of suspected strokes in ED in March 2020 negatively correlated with the progression of COVID-19 pandemic, and this was particularly true for the province of RN where the incidence of the infection was more than double. This may confirm that the "hospital avoidance" phenomenon grew as the pandemic spread out. Despite the reduction of confirmed stroke cases, the absolute number of treatments performed in the stroke network remained similar to the previous years. This corroborates the hypothesis of a more refined selection of suspected stroke, with a reduced seek for assistance and hospitalization of patients with transient or non-debilitating neurological symptoms. As a German nationwide retrospective study on AIS hospitalizations noted, during the second pandemic wave (fall/winter 2020) the decline in stroke admission was lower compared to the first pandemic wave (spring 2020), despite a much higher number of COVID-19 patients (Richter et al., 2021). Among the factors explaining this trend, authors indicate a reduction in fear of contracting a SARS-CoV-2 infection and the public awareness campaigns like from the German Society of Neurology that encouraged the public to seek help in hospitals in case of medical emergencies like stroke. Conversely, a Greek study confirmed a similar decline in AIS hospitalization during the second pandemic wave compared to the first wave despite a much higher COVID-19 burden (Katsouras et al., 2021). Authors hypothesized that lockdowns, a common characteristic in both waves, possibly had a negative impact on cerebrovascular diseases regardless of the burden of COVID-19 in the community. Undoubtedly, the "stay-at-home" message has been fundamental to the initial COVID-19 restraint. However, the redundant and often passionate politicians and healthcare professionals or other stakeholders' "stay-at-home" appeals were not counterbalanced by messages regarding the need to regularly seek assistance for non-COVID-19 related emergencies. Public campaigns to increase awareness of stroke risk may be needed, even more than before.

For AIS patients regularly admitted in the ED, screening and triaging COVID-19 suspected patients at the entrance and adopting two parallel intra-hospital routes for suspected or not suspected patients permitted to manage stroke patients in safety without affecting the effectiveness of the neurovascular team. The opening of the SSNO was feasible and strategic in managing stroke referrals in a mothership model and lifting the burden of neurological patients from the ED during the COVID-19 pandemic. Patients with neurological conditions that needed examinations or observation have been managed without weighing on the ED; most conditions have been properly managed with a final discharge after a short staying, avoiding unrequired hospitalization in the Neurology Unit. This was particularly important since, with the adoption of the MS model, a higher number of Stroke Unit beds was required, and available beds in the non-stroke Neurology area granted the turnover of Stroke Unit patients.

Our retrospective analysis on the performances of MS model adopted during the first COVID-19 pandemic wave showed that, in our stroke network, the stroke network paradigm shift was feasible and probably beneficial in such an exceptional setting.

The MS model met the primary endpoint, ensuring a decrease in the OGT without significantly delaying the IVT. Despite longer transportation time to the CSC, the intra-hospital intervals were shorter in the CSC than in the PSCs, contributing to quicker reperfusion therapies. Moreover, the MS guaranteed a higher rate of combined therapies with IVT and EVT. Despite all differences in treatment timing, no significant difference was found in good clinical outcome (3-month mRS).

A shorter interval from onset to call for help (OCT) could have influenced the decrease in OGT interval during the MS period during the pandemic phase; however, the analysis of the intervals from the call to the groin/needle (CGT, CNT) confirmed the superiority of MS. We also evaluated the possible effect of decreased road traffic during the pandemic phase. Still, the analysis of transport time of trauma patients showed an unexpected increase in transport time in 2020.

As literature grows, the most recent and large meta-analysis on organizational paradigm suggested a possible benefit of MS model on 3-month functional independence compared to DS (Romoli et al., 2020). The theoretical advantage of the DS model is the shorter interval of IVT administration from stroke onset (Onset-to-Needle time, ONT) since PSCs are the nearest centres. However, CSCs usually have shorter intrahospital intervals from the entrance to IVT starting (Door-to-Needle time, DNT), leading to shorter ONT in CSCs than PSCs, despite longer transport time (Romoli et al., 2020). A decision-analytic model based on data from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) meta-analysis confirmed that MS is the leading strategy when transportation time to both the PSC and CSC are short (respectively, 30 minutes and 93 minutes) (Wu et al., 2021). Similarly, other mathematical models concluded that MS is generally preferable over DS, except for rural areas (Garcia et al., 2021; Schlemm et al., 2019). Ongoing trials (RACECAT, PRESTO-F, SWIFT DIRECT, TRIAGE) could add some insights in the next future. Meanwhile, each stroke network is constantly involved in adapting its model, balancing the network's peculiarity with the evolving needs of stroke care. The disparate stroke networks local features such as orographic, facilities and resources, along with the limits in out-hospital selection of LVO patients, make it challenging to apply a one-size-fits-all solution. Our stroke network covers an area of 5100 km2 and a population of 1.126.000 inhabitants. Every PSC is less than 40 km away from the CSC. In such a setting, MS proved to be the most efficient. The model shift was feasible and permitted to face the first COVID-19 pandemic wave without affecting the quality of stroke care. Similar results have been inferred by a recent meta-analysis (Romoli et al., 2020) and are in line with the results of the mothership-based Bologna stroke network (Zini et al., 2020). Notably, both stroke networks performed a slightly increased number of reperfusion therapies during the first phase of the pandemic, despite the worldwide epidemiological trend of a decrease in stroke admissions (Paolucci et al., 2020).

Our results pointed out a non-significant difference in three-month functional independence. However, we found a significant increase in three-month mortality during the mothership period. In the study mentioned above, stroke patients treated in Bologna in 2020 (Zini et al., 2020) were more severe than 2019 patients, as was noticed worldwide during the first pandemic (Bass et al., 2021). We did not reach a statistical significance for stroke severity difference between 2019 and 2020, despite a marginal trend in median NIHSS indicating more severe patients admitted during COVID-19 pandemic (DS= 12; MS=16.5; p=.147). This may be due to the small number of patients included. Since non-significant differences in stroke severity and quicker access to reperfusion therapies were borne out, we looked out for potential confounders. Single-patient COVID-19 related clinical complications minimally impacted our cohort since only one death was directly correlated to the infection. However, our post hoc analysis of the second pandemic wave revealed the same higher mortality rate, despite returning to the drip and ship organization model (fig. 16). A possible explanation for the higher mortality rate during the pandemic might be the reduction of subacute and rehabilitation facilities due to the necessity to transform regular wards into COVID units. Indeed, >50% of deaths occurred after the first 30 days post-stroke, during the subacute phase and for other causes than haemorrhagic transformation. In this light, the higher rate of IVT is another strength of the MS model considering that the preliminary data from the SWIFT-DIRECT trial (NCT03192332) presented at the 7th European Stroke Organisation Conference (ESOC 2021; 1–3 September, virtual) demonstrated the lack of non-inferiority of direct EVT compared to the combined IVT-EVT approach. In the DS model, an unknown therapeutic time window (wake-up stroke or unknown onset) was the main reason for IVT avoidance. Spoke-patients with large vessel occlusion documented by CTA and good ASPECTS on non-contrast CT were immediately transported to the CSC for EVT treatment (with or without a preliminary MRI study). This pragmatic approach was preferred to avoid a "time-consuming effect" of performing MRI in the spoke, considering the lack of its prompt availability during the night and weekend. This approach was also supported considering that the indication to EVT was an exclusion criterion to receive rt-PA in the WAKE-UP trial (Thomalla et al., 2018). Comparing the models in the ongoing pandemic waves (MS vs DS 2 periods), the MS model obtained a significantly higher proportion of completely independent patients at three months. Hence, we can conclude that the MS model is not responsible for the higher mortality but instead favours an excellent clinical outcome.

Based on the literature and our experience, we planned to return to the MS model. The model will be implemented with a telemedicine service allowing the selection of patients with probable LVO directly from the intervention site to better manage the risk of Hub over triage and reduce the risk of delaying the IVT access for people with a low probability of LVO stroke.

Our studies have some limitations. For the epidemiological and the whole stroke network performances studies, limiting the analysis to the month of March, this study only considered the first weeks of national lockdown that lasted until mid-May. The mothership model's efficiency has been evaluated on limited data since it was adopted in just one of the provinces. Moreover, we could not obtain data about the onset time of all stroke cases, limiting the evaluation of delays in the onset-to-call interval. Indeed, the call-to-needle/groin time does not account for patient or bystander delay, which is particularly interesting during this pandemic as patients may be more reluctant to contact medical services. The main limitation of the MS vs DS comparison is the study's retrospective design. In addition, we lack data on the "call time" variable, limiting the analysis on the CNT and CGT. Another limitation is that in 2020 there was a lesser volume of patients managed in the ED, possibly speeding up AIS patient management. The small number of patients in each cohort may also have limited the validity of some analyses; particularly, as pointed out above, baseline stroke severity probably suffered from a type II error with a sizeable but non-significant difference in median NIHSS between DS and MS group.

Conclusions

The "hospital avoidance" of stroke patients during the "stay-at-home" appeals need to be considered for future public health campaigns. The shift to the MS model during the COVID-19 pandemic was feasible; in our stroke network, the MS model proved to be more efficient (promptness of reperfusion therapies) than the DS model, with a trend to a better efficacy (functional outcome) despite the pandemic emergency. However, these results cannot be unambiguously generalized due to the study's retrospective nature, the local features of our stroke network, and the exceptional situation of the first COVID-19 pandemic wave.

There are several lessons to be learned from COVID-19 pandemic; as a stroke team, we need to be flexible and prepared for a quick reorganization of our services, not only in the in-hospital settings. We need to know our territory, adapt our models and participate in the awareness of our population.

Bibliography

Aggarwal G, Lippi G and Henry BM (2020) Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): A pooled analysis of published literature. *International journal of stroke : official journal of the International Stroke Society* 15(4): 385–389. DOI: 10.1177/1747493020921664.

Baracchini C, Pieroni A, Viaro F, et al. (2020) Acute stroke management pathway during Coronavirus-19 pandemic. *Neurological Sciences* 41(5): 1003–1005. DOI: 10.1007/s10072-020-04375-9.

Bass DI, Meyer RM, Barros G, et al. (2021) The impact of the COVID-19 pandemic on cerebrovascular disease. *Seminars in Vascular Surgery* 34(2): 20–27. DOI: 10.1053/j.semvascsurg.2021.05.001.

Bastani M, White TG, Martinez G, et al. (2021) Evaluation of direct-to-angiography suite (DTAS) and conventional clinical pathways in stroke care: a simulation study. *Journal of NeuroInterventional Surgery*: neurintsurg-2021-018253. DOI: 10.1136/neurintsurg-2021-018253.

Beyerstedt S, Casaro EB and Rangel ÉB (2021) COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *European Journal of Clinical Microbiology & Infectious Diseases* 40(5): 905–919. DOI: 10.1007/s10096-020-04138-6.

Conklin J, Frosch MP, Mukerji SS, et al. (2021) Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19. *Journal of the Neurological Sciences* 421: 117308. DOI: 10.1016/j.jns.2021.117308.

Connors JM and Levy JH (2020) COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 135(23): 2033–2040. DOI: 10.1182/blood.2020006000.

Donoghue M, Hsieh F, Baronas E, et al. (2000) A Novel Angiotensin-Converting Enzyme–Related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. *Circulation Research* 87(5). DOI: 10.1161/01.res.87.5.e1.

Duloquin G, Graber M, Garnier L, et al. (2021) Assessment of Clinical Scales for Detection of Large Vessel Occlusion in Ischemic Stroke Patients from the Dijon Stroke Registry. *Journal of Clinical Medicine* 10(24): 5893. DOI: 10.3390/jcm10245893.

Ernst M, Schlemm E, Holodinsky JK, et al. (2020) Modeling the Optimal Transportation for Acute Stroke Treatment: The Impact of the Drip-and-Drive Paradigm. *Stroke* 51(1): 275–281. DOI: 10.1161/strokeaha.119.027493.

Escalard S, Chalumeau V, Escalard C, et al. (2020) Early Brain Imaging Shows Increased Severity of Acute Ischemic Strokes With Large Vessel Occlusion in COVID-19 Patients. *Stroke* 51(11): 3366–3370. DOI: 10.1161/strokeaha.120.031011.

Fisicaro F, Napoli MD, Liberto A, et al. (2021) Neurological Sequelae in Patients with COVID-19: A Histopathological Perspective. *International Journal of Environmental Research and Public Health* 18(4): 1415. DOI: 10.3390/ijerph18041415.

Garcia BL, Bekker R, Mei RD van der, et al. (2021) Optimal patient protocols in regional acute stroke care. *Health Care Management Science*: 1–16. DOI: 10.1007/s10729-020-09524-2.

Guan W-J, Ni Z-Y, Hu Y, et al. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine* 382(18): 1708–1720. DOI: 10.1056/nejmoa2002032.

Hadid T, Kafri Z and Al-Katib A (2021) Coagulation and anticoagulation in COVID-19. *Blood Reviews* 47: 100761. DOI: 10.1016/j.blre.2020.100761.

Imai Y, Kuba K, Rao S, et al. (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 436(7047): 112–116. DOI: 10.1038/nature03712.

Italian National Institute of Statistics - ISTAT (2020) Popolazione residente al 1° gennaio - Emilia-Romagna. Available at: http://dati.istat.it/Index.aspx?QueryId=18964 (accessed 1 May 2020).

Jackson CB, Farzan M, Chen B, et al. (2022) Mechanisms of SARS-CoV-2 entry into cells. *Nature Reviews Molecular Cell Biology* 23(1): 3–20. DOI: 10.1038/s41580-021-00418-x.

July J and Pranata R (2020) Impact of the Coronavirus Disease Pandemic on the Number of Strokes and Mechanical Thrombectomies: A Systematic Review and Meta-Analysis. *Journal of Stroke and Cerebrovascular Diseases* 29(11): 105185. DOI: 10.1016/j.jstrokecerebrovasdis.2020.105185.

Katsouras C, Tsivgoulis G, Papafaklis M, et al (2021) Persistent decline of hospitalizations for acute stroke and acute coronary syndrome during the second wave of the COVID-19 pandemic in Greece: collateral damage unaffected. *Therapeutic Advances in Neurological Disorders* 14:17562864211029540. https://doi.org/10.1177/17562864211029540

Keidar S, Kaplan M and Gamliellazarovich A (2007) ACE2 of the heart: From angiotensin I to angiotensin (1–7). *Cardiovascular Research* 73(3): 463–469. DOI: 10.1016/j.cardiores.2006.09.006.

Kerleroux B, Fabacher T, Bricout N, et al. (2020) Mechanical Thrombectomy for Acute Ischemic Stroke Amid the COVID-19 Outbreak: Decreased Activity, and Increased Care Delays. *Stroke* 51(7): 2012–2017. DOI: 10.1161/strokeaha.120.030373.

Kuba K, Imai Y, Rao S, et al. (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nature Medicine* 11(8): 875–879. DOI: 10.1038/nm1267.

Larson AS, Savastano L, Kadirvel R, et al. (2020) Coronavirus Disease 2019 and the Cerebrovascular-Cardiovascular Systems: What Do We Know So Far? *Journal of the American Heart Association* 9(13): e016793. DOI: 10.1161/jaha.120.016793.

Llitjos J, Leclerc M, Chochois C, et al. (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *Journal of Thrombosis and Haemostasis* 18(7): 1743–1746. DOI: 10.1111/jth.14869.

Maas WJ, Lahr MMH, Buskens E, et al. (2020) Pathway Design for Acute Stroke Care in the Era of Endovascular Thrombectomy: A Critical Overview of Optimization Efforts. *Stroke* 51(11): 3452–3460. DOI: 10.1161/strokeaha.120.030392.

McGonagle D, O'Donnell JS, Sharif K, et al. (2020) Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology* 2(7): e437–e445. DOI: 10.1016/s2665-9913(20)30121-1.

Montaner J, Barragán-Prieto A, Pérez-Sánchez S, et al. (2020) Break in the Stroke Chain of Survival due to COVID-19. *Stroke* 51(8): 2307–2314. DOI: 10.1161/strokeaha.120.030106.

Naccarato M, Scali I, Olivo S, et al. (2020) Has COVID-19 played an unexpected "stroke" on the chain of survival? *Journal of the neurological sciences* 414: 116889. DOI: 10.1016/j.jns.2020.116889.

Paolucci M, Biguzzi S, Cordici F, et al. (2020) Impact of COVID-19 pandemic on acute stroke care: facing an epidemiological paradox with a paradigm shift. *Neurological Sciences*: 1–8. DOI: 10.1007/s10072-020-04914-4.

Powers WJ, Rabinstein AA, Ackerson T, et al. (2019) Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 50(12): e344–e418. DOI: 10.1161/str.0000000000000211.

Protezione Civile. National Department Repository home page. Available at: https://github.com/pcm-dpc/COVID-19/tree/master/dati-province. (accessed 3 May 2020).

Qin C, Zhou L, Hu Z, Yang S, et al. (2020) Clinical Characteristics and Outcomes of COVID-19 Patients With a History of Stroke in Wuhan, China. *Stroke* 51(7): 2219–2223. DOI: 10.1161/strokeaha.120.030365.

Qin C, Zhou L, Hu Z, Zhang S, et al. (2020) Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 71(15): 762–768. DOI: 10.1093/cid/ciaa248.

Ranucci M, Ballotta A, Dedda UD, et al. (2020) The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *Journal of Thrombosis and Haemostasis* 18(7): 1747–1751. DOI: 10.1111/jth.14854.

Regione Emilia-Romagna. Giornata mondiale dell'ictus: in Emilia-Romagna aumentate le chiamate al 118 e diminuiti i ricoveri (2021). Available at: https://www.regione.emilia-romagna.it/notizie/2021/ottobre/giornata-mondiale-dell-ictus-in-emilia-romagna-aumentate-le-chiamate-al-118-e-diminuiti-i-ricoveri (accessed 7 January 2022).

Requena M, Olivé-Gadea M, Muchada M, et al. (2021) Direct to Angiography Suite Without Stopping for Computed Tomography Imaging for Patients With Acute Stroke: A Randomized Clinical Trial. *JAMA Neurology* 78(9): 1099. DOI: 10.1001/jamaneurol.2021.2385.

Richter D, Eyding J, Weber R, et al. (2021) A full year of the COVID-19 pandemic with two infection waves and its impact on ischemic stroke patient care in Germany. *European Journal of Neurology* 29:10.1111/ene.15057.

Romoli M, Paciaroni M, Tsivgoulis G, et al. (2020) Mothership versus Drip-and-Ship Model for Mechanical Thrombectomy in Acute Stroke: A Systematic Review and Meta-Analysis for Clinical and Radiological Outcomes. *Journal of Stroke* 22(3): 317–323. DOI: 10.5853/jos.2020.01767.

Rudilosso S, Laredo C, Vera V, et al. (2020) Acute Stroke Care Is at Risk in the Era of COVID-19: Experience at a Comprehensive Stroke Center in Barcelona. *Stroke* 51(7): 1991–1995. DOI: 10.1161/strokeaha.120.030329.

Sacco S, Ricci S, Ornello R, et al (2020) Reduced Admissions for Cerebrovascular Events During COVID-19 Outbreak in Italy. *Stroke* 51:3746–3750. https://doi.org/10.1161/strokeaha.120.031293

Schlemm L, Endres M, Scheitz JF, et al. (2019) Comparative Evaluation of 10 Prehospital Triage Strategy Paradigms for Patients With Suspected Acute Ischemic Stroke. *Journal of the American Heart Association* 8(12): e012665. DOI: 10.1161/jaha.119.012665.

Shang J, Wan Y, Luo C, et al. (2020) Cell entry mechanisms of SARS-CoV-2. *Proceedings of the National Academy of Sciences* 117(21): 11727–11734. DOI: 10.1073/pnas.2003138117.

Siegler JE, Heslin ME, Thau L, et al. (2020) Falling stroke rates during COVID-19 pandemic at a Comprehensive Stroke Center: Cover title: Falling stroke rates during COVID-19. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 29(8): 104953. DOI: 10.1016/j.jstrokecerebrovasdis.2020.104953.

Sousa DA de, Sandset EC and Elkind MSV (2020) The Curious Case of the Missing Strokes During the COVID-19 Pandemic. *Stroke* 51(7): 1921–1923. DOI: 10.1161/strokeaha.120.030792.

SPREAD (2016) *SPREAD Stroke Prevention And Educational Awareness Diffusion VIII Edizione - Ictus Cerebrale: Linee Guida Italiane Di Prevenzione e Trattamento*. VIII Edizione.

Sundarapandian V (2009) *Probability, Statistics and Queuing Theory*. PHI Learning. Available at: https://books.google.it/books?id=ZMq9h2CM5I0C.

Tang N, Bai H, Chen X, et al. (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis* 18(5): 1094–1099. DOI: 10.1111/jth.14817.

Tang, N., Li, D., Wang, X. & Sun, Z. (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 18, 844–847.

Thomalla G, Simonsen CZ, Boutitie F, et al. (2018) MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *The New England Journal of Medicine* 379(7): 611–622. DOI: 10.1056/nejmoa1804355.

Tsivgoulis G, Katsanos AH, Ornello R, et al. (2020) Ischemic Stroke Epidemiology During the COVID-19 Pandemic: Navigating Uncharted Waters With Changing Tides. *Stroke* 51(7): 1924–1926. DOI: 10.1161/strokeaha.120.030791.

Vaduganathan M, Vardeny O, Michel T, et al. (2020) Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. *New England Journal of Medicine* 382(17): 1653–1659. DOI: 10.1056/nejmsr2005760.

Vidale S and Agostoni E (2018) Prehospital stroke scales and large vessel occlusion: A systematic review. *Acta Neurologica Scandinavica* 138(1): 24–31. DOI: 10.1111/ane.12908.

Wang B, Li R, Lu Z, et al. (2020) Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging* 12(7): 6049–6057. DOI: 10.18632/aging.103000.

Wiersinga WJ, Rhodes A, Cheng AC, et al. (2020) Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 324(8): 782. DOI: 10.1001/jama.2020.12839.

Wool GD and Miller JL (2021) The Impact of COVID-19 Disease on Platelets and Coagulation. *Pathobiology* 88(1): 15–27. DOI: 10.1159/000512007.

Wu X, Wira CR, Matouk CC, et al. (2021) Drip-and-ship versus mothership for endovascular treatment of acute stroke: A comparative effectiveness analysis. *International Journal of Stroke*: 174749302110087. DOI: 10.1177/17474930211008701.

Yaghi S, Ishida K, Torres J, et al. (2020) SARS-CoV-2 and Stroke in a New York Healthcare System. *Stroke* 51(7): 2002–2011. DOI: 10.1161/strokeaha.120.030335.

Zakeri A, Jadhav AP, Sullenger BA, et al. (2021) Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. *Journal of NeuroInterventional Surgery* 13(3): 202–206. DOI: 10.1136/neurintsurg-2020-016794.

Zhao J, Li H, Kung D, et al. (2020) Impact of the COVID-19 Epidemic on Stroke Care and Potential Solutions. *Stroke* 51(7): 1996–2001. DOI: 10.1161/strokeaha.120.030225.

Zini A, Romoli M, Gentile M, et al. (2020) The stroke mothership model survived during COVID-19 era: an observational single-center study in Emilia-Romagna, Italy. *Neurological Sciences* 41(12): 3395–3399. DOI: 10.1007/s10072-020-04754-2.