



# Drip-and-ship toward mothership model for mechanical thrombectomy during COVID-19 pandemic: a retrospective analysis

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## Abstract

**Introduction** During the first wave of the COVID-19 pandemic in spring 2020, our stroke network shifted from a drip-and-ship strategy (transport of acute ischemic stroke patients to the nearest primary stroke centers) toward a mothership model (direct transportation to the Comprehensive Stroke Center). We retrospectively analyzed stroke network performances comparing the two models.

**Patients and methods** All spoke-district patients treated with endovascular thrombectomy (EVT) between 15th March–15th June 2019 (drip-and-ship) and 2020 (mothership) were considered. We compared onset-to-groin time (OGT) and onset-to-needle time (ONT) between the two periods. Secondly, we investigated other performances parameters (percentage of IV thrombolysis, timing of diagnostic and treatment) and clinical outcome (3-month modified Rankin Scale).

**Results** Twenty-four spoke-district patients in 2019 (drip-and-ship) and 26 in 2020 (mothership) underwent EVT. The groups did not differ for age, sex, risk factors, pre-stroke mRS 0–1, NIHSS, and ASPECTS distribution. The MS model showed a significant decrease of the OGT (162.5 min vs 269 min,  $p=0.001$ ) without significantly affecting the ONT (140.5 min vs 136 min,  $p=0.853$ ), ensuring a higher number of IV thrombolysis in combination with EVT ( $p=0.030$ ). The mothership model showed longer call-to-door time (median + 23 min,  $p < 0.005$ ), but shorter door-to-needle (median – 31 min,  $p=0.001$ ), and door-to-groin time (– 82.5 min,  $p < 0.001$ ). We found no effects of the stroke network model on the 3-month mRS (ordinal shift analysis,  $p=0.753$ ).

**Conclusions** The shift to the mothership model during the COVID-19 pandemic guaranteed quicker EVT without significantly delaying IVT.

**Keywords** Thrombectomy · Thrombolysis · Fibrinolytic therapy · Stroke network model

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## Introduction

Intravenous thrombolysis (IVT) and EVT are the only reperfusion therapies approved for acute ischemic stroke (AIS) due to large vessel occlusion (LVO) [1]. 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) vs the direct transportation to the Comprehensive Stroke Center (CSC; “mothership” (MS) model) is still a matter of debate [2]. Recent studies suggest MS might result in better functional outcomes, at least when transportation time to CSC is short [3, 4]. However, results are only partially generalizable and must be put in context to the local logistic.

The first wave of coronavirus disease 2019 (COVID-19) pandemic in spring 2020 required a profound rearrangement of hospitals organization. In our stroke network, PSCs were converted to COVID-hospital. From March to June 2020, we shifted from a DS model toward a MS model to reduce the load on PSCs. We retrospectively compared onset-to-needle and onset-to-groin times obtained during the pandemic period with a MS model with those of the DS model period to evaluate if a MS model could ensure an adequate organizational response during such an exceptional event as a pandemic outbreak. We also compared other stroke network parameters (percentage of IV thrombolysis, timing of diagnostic and treatment) and clinical outcome (3-month modified Rankin Scale) between the two models.

## Methods

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

### Setting

Our stroke network usually adopts a DS model. The CSC is the “M. Bufalini” hospital in Cesena; EVT is performed only in the CSC. The PSCs are the “Infermi” hospital in Rimini (38 km/40 min away from the CSC) and the “Morgagni-Pierantoni” hospital in Forlì (29 km/35 min away from the CSC). During the COVID-19 pandemic in 2020, the PSCs were converted to mainly COVID-hospitals. Hence, on the 15th March 2020, the stroke network shifted toward a MS model 24/7 h for Rimini province and overnight for Forlì province until the 15th June 2020. We excluded direct transportation to the CSC patients with a

mRS  $\geq$  4 or whose symptoms onset was  $>$  24 h. 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.

### 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 15th March–15th June 2019–2020 were included. We considered as spoke-district patients all EVT patients from Rimini province (24/24 h) and Forlì area (on night shift only). EVTs carried out on spoke-district patients from 15th March to 15th 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 OGT without affecting the 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 3 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), CNT, and CGT between cohorts, and (2) we analyzed time logistics 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 nonparametric 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 evaluate the effect of baseline covariates better. We calculated the propensity score considering these variables: age, sex, night shift presentation, NIHSS score, ASPECTS score, TICI score, atrial fibrillation, hypertension, diabetes, and treatment (EVT alone or combined EVT + IVT).

Statistical analysis was performed using SPSS version 25. Anonymized datasets are available at <https://doi.org/10.7910/DVN/BROSVG>. The study received approval from the local Ethical Committee.

## Results

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 1). Demographic characteristics, cardiovascular risk factors, and stroke severity were similar between groups. 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 48 h. 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 min [IQR 106] vs

**Table 1** Treatments and demographics

	DS (2019)	MS (2020)	<i>p</i>
<i>N</i> of cases	24	26	
EVT ( <i>n</i> , %)	11 (45.8%)	4 (15.4%)	
EVT+IVT ( <i>n</i> , %)	13 (54.2%)	22 (84.6%)	0.030
Spoke-district			
Forlì ( <i>n</i> ,%)	3 (12.5%)	3 (11.5%)	
Rimini ( <i>n</i> ,%)	21 (87.5%)	23 (88.5%)	1
Demographics			
Sex ( <i>F</i> , %)	50%	54%	0.786
Age, years (mean, SD)	75.9 (11.9)	75.9 (11.1)	0.993
mRS pre 0–1 (%)	95.8%	100%	0.480
Risk factors			
Previous stroke or TIA (%)	12.5%	11.5%	0.627
Hypertension (%)	83.3%	80.8%	0.554
Atrial fibrillation (%)	25%	23.1%	0.874
Diabetes (%)	8.3%	23.1%	0.250
Dyslipidemia (%)	50%	34.6%	0.208
Stroke severity and outcome			
NIHSS (median, IQR)	12 (12)	16.5 (14)	0.147
ASPECTS (median, IQR)	9 (2)	9 (2)	0.944
TICI 2b/3 (%)	87.5%	80.8%	0.704
Anterior circulation (%)	91.7%	96.2%	0.602
Careggi collateral score ≥ 3 (%)	54.5%	54.6%	0.931
mRS 3 month 0–1 ( <i>n</i> , %)	8 (33.3%)	10 (38.5%)	0.706
mRS 3 month 6 [death] ( <i>n</i> , %)	1 (4.2%)	7 (26.9%)	0.050
Onset-to-call time, min (median, IQR)	163 (376)	29 (101)	0.016

269 min [IQR 320],  $p=0.001$ ) without significantly affecting the median ONT (140.5 min [IQR 84] vs 136 min [IQR 105],  $p=0.853$ ).

### 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%];  $p=0.030$ ). In most DS model patients (63.7%), IVT was not administered due to wake-up stroke or unknown stroke onset. Details are shown in Supplementary Table 1.
2. MS model showed a significantly longer transport time from the site intervention to the hospital (median CDT difference: 23 min,  $p<0.005$ ). However, the management of AIS patients in the CSC was quicker than in PSCs. Median DCT decreased by 11.5 min ( $p=0.017$ ), median CT-to-needle decreased by 20.5 min ( $p=0.001$ ), and median CT-to-groin decreased by 78 min ( $p<0.005$ ). Altogether, DNT and DGT significantly decreased with the MS model (DNT: DS median 74 min [IQR 27], MS median 43 min [IQR 26],

$p=0.001$ ; DGT: DS median 144.5 min [IQR 55], MS median 62 min [IQR 23],  $p= <001$ ). Figure 1 shows the detailed median time intervals of every out-of-hospital and in-hospital step in AIS patient management.

- We found no effects of the stroke network model (MS or DS) on the 3-month mRS category (adjusted odds ratio 0.787, 95% CI 0.178–3.489,  $p=0.753$ ; Fig. 2). Full details of the logistic regression model can be found in Supplementary Table 2. At 3-month, the proportion of patients in mRS 0–1 category is 33.3% for spoke-district DS patients and 38.5% for spoke-district MS patients, a non-significant difference ( $p=0.706$ ).

Repeated analysis after propensity-score weighting (IPTW) confirmed no difference in the distribution of 3-month mRS ( $p=0.533$ ) nor in the rate of 3-month mRS 0–1 category ( $p=0.761$ ).

In 2020, a significantly higher proportion of patients died during the 3-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, and 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, the median OCT was significantly shorter in 2020 (Table 1,  $p < 0.016$ ), 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

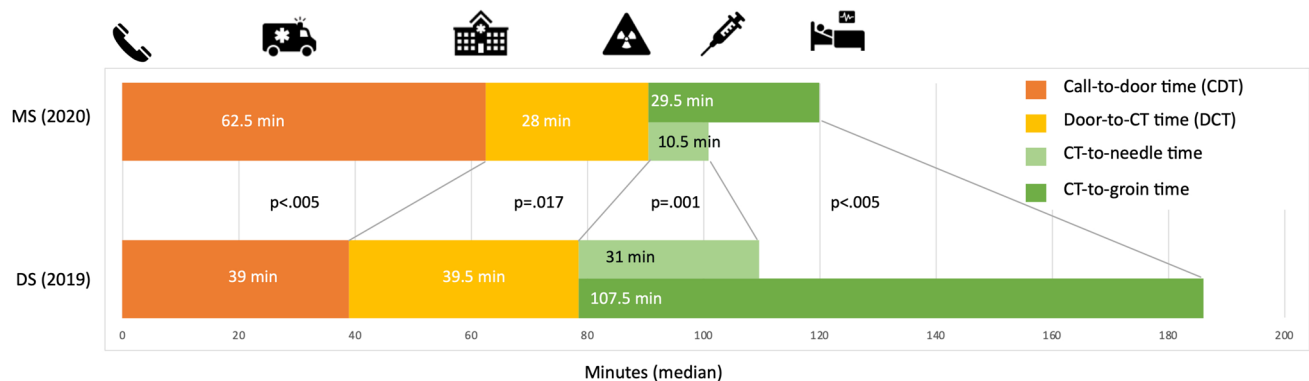
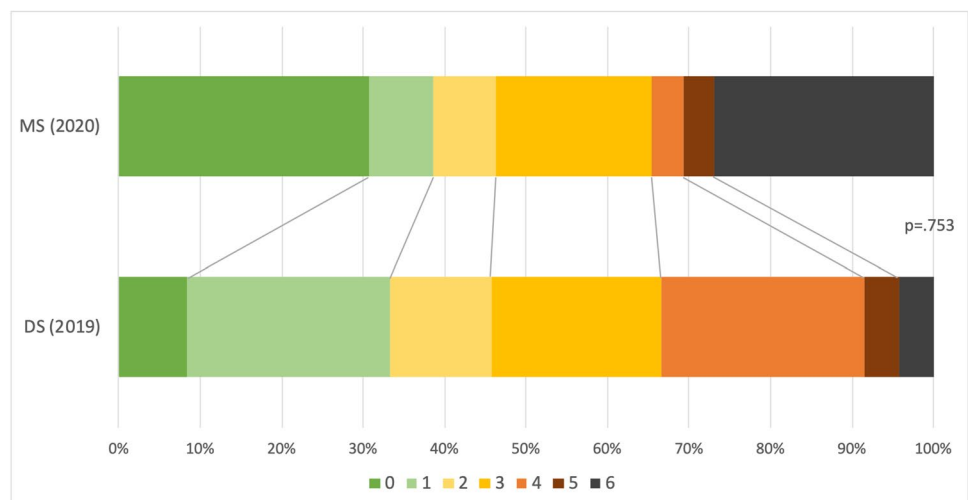


Fig. 1 Median diagnostic and intervention times for DS and MS groups

Fig. 2 Three-month mRS for DS and MS groups



in-hospital management efficiency since delays in calls 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 min,  $p < 0.005$ ) without significant differences in CNT ( $p = 0.324$ ).

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 ( $p = 0.182$ ) (Supplementary Table 3). 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,  $p = 0.033$ ).

### 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 3-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 both for sex ( $p = 0.603$ ) and age ( $p = 0.216$ ). The mortality rate (3-month mRS category = 6) was similar between groups (7/26 [26.9%] in MS, 6/24 in DS 2 [25%];  $p = 0.567$ ) (Fig. 3). However, a significantly lower number of patients was

treated with IVT in DS 2 (9/24 [37.5%] vs 22/26 [84.6%],  $p = 0.001$ ). 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%],  $p = 0.385$ ). In the DS 2 group, the median DNT was 84 min (IQR 42), and the median DGT was 166 (IQR 58). Again, an ordinal logistic regression found no effects of the stroke network model (MS or DS 2) on the 3-month mRS category ( $p = 0.182$ ; Fig. 3). 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;  $p = 0.147$ ), no patients in the DS 2 group reached mRS = 0.

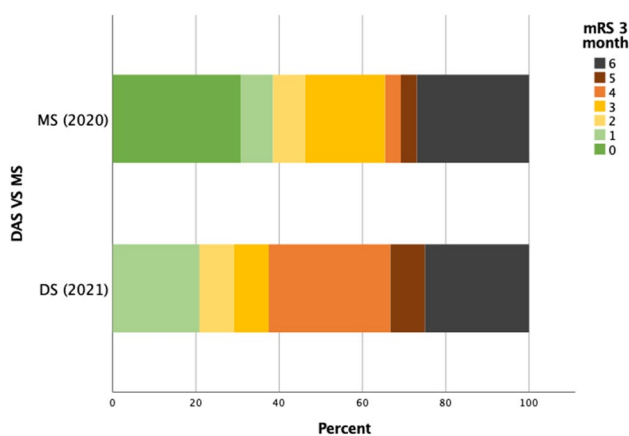
## Discussion

Our retrospective analysis on the performances of the 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 intrahospital 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 emerging in treatment timing, no significant difference was found in good clinical outcomes (3-month mRS).

A shorter interval from OCT for help 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 the MS model on 3-month functional independence compared to DS [3]. The theoretical advantage of the DS model is the shorter interval of IVT administration from stroke onset ONT since PSCs are the nearest centers. However, CSCs usually have shorter intrahospital intervals from the entrance to IVT starting DNT, leading to shorter ONT in CSCs than PSCs, despite longer transport time [3]. A decision-analytic model based on data from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke (HERMES) trial meta-analysis confirmed that MS is the leading strategy when transportation time to both the PSC and CSC is short (respectively, 30 min and 93 min) [4].



**Fig. 3** Three-month mRS between MS group and DS 2020–21 group (pandemic)



Similarly, other mathematical models concluded that MS is generally preferable over DS, except for rural areas [5, 6]. Ongoing trials (RACECAT, PRESTO-F, SWIFT DIRECT, TRIAGE) could add some insights in the next future. New insights may also 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 [7]. However, the application of this model is not widespread but has been applied in limited settings. 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 km<sup>2</sup> 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 [8] and are in line with the results of the mothership-based Bologna stroke network [9]. 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 [10].

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 [9] were more severe than 2019 patients, as was noticed worldwide during the first pandemic [11]. 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 the COVID-19 pandemic (DS = 12; MS = 16.5;  $p = 0.147$ ). 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. 3). 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 hemorrhagic 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 [12]. 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 3 months. Hence, we can conclude that the MS model is not responsible for the higher mortality but instead favors 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 manage the risk of the hub over triage better and reduce the risk of delaying the IVT access for people with a low probability of LVO stroke.

This work presents some limitations. The main limitation is the retrospective design of the study. 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 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.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10072-022-05903-5>.

**Author contribution** MP and ML conceived the study, were involved in protocol development, gaining ethical approval. MP, SB, FC, and MR were involved in data gathering. MP was involved in data analysis. MP wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

## Declarations

**Ethical approval** As this is an observational study, the Institution Review Board has been notified as requested by Italian law.

**Informed consent** Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

**Guarantor** ML

**Conflict of interest** The authors declare no competing interests.

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