Received: 6 August 2021 | Accepted: 9 September 2021

DOI: 10.1111/ene.15107

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Relationship between primary stroke center volume and time to endovascular thrombectomy in acute ischemic stroke

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Funding information
The MR CLEAN Registry was funded and performed by Erasmus MC University Medical Center, Amsterdam UMC, and Maastricht University Medical Center. The MR CLEAN Registry was additionally funded by the TWIN Foundation, which played no role in the study design and patient enrollment nor in data collection, analysis, or writing of the article

Abstract

Background and purpose: We investigated whether the annual volume of patients with acute ischemic stroke referred from a primary stroke center (PSC) for endovascular treatment (EVT) is associated with treatment times and functional outcome.

Methods: We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) registry (2014–2017). We included patients with acute ischemic stroke of the anterior circulation who were transferred from a PSC to a comprehensive stroke center (CSC) for EVT. We examined the association between EVT referral volume of PSCs and treatment times and functional outcome using multivariable regression modeling. The main outcomes were time from arrival at the PSC to groin puncture (PSC-door-to-groin time), adjusted for estimated ambulance travel times, time from arrival at the CSC to groin puncture (CSC-door-to-groin time), and modified Rankin Scale (mRS) score at 90 days after stroke.

Results: Of the 3637 patients in the registry, 1541 patients (42%) from 65 PSCs were included. Mean age was 71 years (SD ± 13.3), median National Institutes of Health Stroke Scale score was 16 (interquartile range [IQR]: 12–19), and median time from stroke onset to arrival at the PSC was 53 min (IQR: 38–90). Eighty-three percent had received intravenous

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thrombolysis. EVT referral volume was not associated with PSC-door-to-groin time (adjusted coefficient: −0.49 min/annual referral, 95% confidence interval [CI]: −1.27 to 0.29), CSC-door-to-groin time (adjusted coefficient: −0.34 min/annual referral, 95% CI: −0.69 to 0.01) or 90-day mRS score (adjusted common odds ratio: 0.99, 95% CI: 0.96–1.01).
Conclusions: In patients transferred from a PSC for EVT, higher PSC volumes do not seem to translate into better workflow metrics or patient outcome.

KEYWORDS
high-volume hospitals, low-volume hospitals, ischemic stroke, thrombectomy, workflow

INTRODUCTION

Intravenous thrombolysis (IVT) with alteplase followed by endovascular thrombectomy (EVT) is the standard treatment for patients with acute ischemic stroke caused by a large-vessel occlusion of the anterior circulation [1,2]. Although IVT with alteplase can be given in all hospitals that provide acute stroke care, EVT can only be performed in more specialized hospitals, so-called comprehensive stroke centers (CSCs). In most countries, the majority of patients with a suspected stroke are brought to the nearest primary stroke center (PSC) to undergo diagnostic tests and treatment with IVT. Patients with a large-vessel occlusion who are potentially eligible for EVT are subsequently transferred to a CSC. The proportion of patients who are treated according to this drip-and-ship paradigm varies between 45% and 83%, depending on the region [3–6]. For both IVT and EVT, timely start of treatment is important, because shorter treatment times improve the functional outcome of patients [7,8].

For a number of neurological diseases, including glioblastoma, subarachnoid hemorrhage, and amyotrophic lateral sclerosis, it has been shown that treatment in high-volume, specialized hospitals improves patient outcomes [9–11]. Regarding treatment of acute ischemic stroke, multiple studies have shown that hospitals with higher annual IVT volumes achieve lower door-to-needle times [12–14]. For EVT, a similar association has been found for the annual number of cases in CSCs [15–17]. However, little is known about the relationship between the volume of EVT-eligible patients who present to a PSC (EVT referral volume) and time to treatment. We hypothesized that higher EVT referral volume may positively affect treatment times, because it may be associated with more streamlined care pathways within the PSC, more experienced physicians when it comes to acute stroke treatment, and better facilities for acute stroke imaging. We aimed to investigate the association between the EVT referral volume of PSCs and treatment times and clinical outcomes in patients with an acute ischemic stroke who were transferred from a PSC for EVT.

METHODS AND MATERIALS

Study design and population

We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN Registry) Registry, which is a nationwide, prospective cohort study in which data from all adult patients who underwent EVT for an acute ischemic stroke in the Netherlands since completion of the MR CLEAN trial (March 2014–December 2018) have been registered. Detailed methods of the MR CLEAN Registry have previously been reported [18]. Permission to carry out the registry was granted by the medical ethics committee of Erasmus Medical Center, University Medical Center in Rotterdam, the Netherlands. The requirement for informed consent was waived.

For the current study, we used data collected from March 2014 until November 2017 (registry parts I and II). We included adult patients with an acute ischemic stroke of the anterior circulation who had initially presented to a PSC and subsequently were transferred to a CSC that had participated in the MR CLEAN trial to undergo EVT. Patients who had primarily presented to a CSC or to a PSC outside the Netherlands were excluded from the analysis. Furthermore, because during the study period EVT was not standard care in the Netherlands for patients with a large-vessel occlusion stroke who were presented more than 6 h after onset, and median door-to-groin time in patients transferred for EVT in the Netherlands is approximately 30 min[19], we excluded patients with an onset-to-groin time >390 min. In-hospital strokes were also excluded.

Definitions and outcomes

A CSC was defined as a hospital that offers both IVT and EVT. A PSC was defined as a hospital that routinely offers IVT and performs computed tomography angiography (CTA) to identify patients with a large-vessel occlusion stroke but does not provide EVT. To verify whether hospitals provided IVT during the study period, data from the public Health Care Quality registration of the National Health Care Institute (in Dutch: Zorginstituut Nederland) were used [20]. All hospitals are obliged to report IVT-related benchmarks in this annual registration. For hospitals that reported IVT benchmarks only for part of the study period, we assumed that IVT for acute ischemic stroke was only offered in the years in which these benchmarks were reported, and the EVT referral volume was calculated for this period only. For hospitals with multiple locations, each location was treated as a separate PSC. If the specific location of a hospital with multiple locations from which a patient was referred was unknown, we used the patient's postal code to determine which of the hospital locations was located closest to the patient's home, and it was assumed that this was the referring PSC.

The annual EVT referral volume of a PSC was defined as the mean number of patients per year who had primarily presented to that PSC and who ultimately underwent EVT during the study period. For comparison of baseline characteristics and illustrative purposes, we categorized PSCs into low, medium, or high volume. Low annual EVT referral volume was defined as <6 referrals per year, medium as 6–12 referrals per year, and high as >12 referrals per year. However, for our regression analyses, annual EVT referral volume was assessed as a continuous variable. EVT was defined as arterial puncture in the angiography suite, with the objective to perform mechanical thrombectomy. The actual EVT strategy was at the discretion of the interventionist.

Our primary outcome measure was time from PSC arrival to arterial puncture in the CSC (PSC door-to-groin time [PSC DTGT]). Other workflow-related outcome measures were time from arrival at the PSC to arrival at the CSC (door-to-door time) and time from arrival at the CSC to arterial puncture (CSC door-to-groin time [CSC DTGT]). Clinical outcomes were modified Rankin Scale (mRS) score and mortality at 90 days after stroke.

Statistical analysis

We compared baseline characteristics, treatment times, and clinical outcomes of patients referred from low-volume PSCs, medium-volume PSCs, and high-volume PSCs, using one-way analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for nonnormally distributed continuous variables, and χ^2 test for categorical variables.

We examined the effect of EVT referral volume at the hospital level on treatment times and clinical outcome using multilevel regression modeling. For these analyses, annual EVT referral volume was assessed as a continuous variable. For our analyses of PSC DTGT and door-to-door time, we used multilevel linear regression, adjusting for the following preselected variables on patient level (unless reported otherwise, baseline characteristics were measured upon arrival at the CSC): referring PSC as a random effect, and age, history of hypertension, prestroke mRS, baseline systolic blood pressure, baseline National Institutes of Health Stroke Scale (NIHSS) score, location of occlusion on CTA, treatment with IVT, onset-to-first-door time, estimated time of travel by ambulance from PSC to CSC, and the receiving CSC as fixed effects. The estimated ambulance travel times were provided by the Dutch National Institute for Public Health and the Environment and calculated using their proprietary model, assuming the ambulance driving with the highest level of emergency and daytime circumstances outside of rush hour [21]. When analyzing CSC DTGT, we also used multilevel linear regression, adjusting for the following patient-level variables: referring PSC as a random effect and age, history of hypertension, prestroke mRS, baseline systolic blood pressure, baseline NIHSS score, location of occlusion on CTA, time from onset to arrival at the CSC, and the receiving CSC as fixed effects. For our analysis of the 90-day mRS score we used multilevel ordinal logistic regression, and for our analysis of mortality we used multilevel binary logistic regression. Both analyses were adjusted for the following variables on patient level: referring PSC as a random effect and age, history of hypertension, prestroke mRS score, baseline systolic blood pressure, baseline NIHSS score, location of occlusion on CTA, treatment with IVT, onset-to-first-door time, and the receiving CSC as fixed effects. For all regression analyses, we imputed missing data using multiple imputation, using the following covariates: age, sex, history of stroke, history of hypertension, history of diabetes mellitus, history of atrial fibrillation, prestroke mRS score, baseline blood pressure (systolic and diastolic), baseline NIHSS score, location of occlusion on CTA, treatment with IVT, onset-to-first-door time, estimated time of travel by ambulance from PSC to CSC, PSC DTGT, door-to-door time, CSC DTGT, expanded Treatment in Cerebral Ischemia score after EVT, symptomatic intracranial hemorrhage, and 90-day mRS score. All analyses were performed using SPSS (version 25; IBM, Armonk, NY).

RESULTS

Between March 2014 and November 2017, 3637 patients were included in the MR CLEAN Registry. We excluded 2096/3637 patients (58%) because they had not primarily presented to a PSC ($n = 1474$), underwent EVT in a CSC that had not participated in the MR CLEAN trial ($n = 177$), had an acute ischemic stroke of the posterior circulation ($n = 172$), had an in-hospital stroke ($n = 149$), had an onset-to-groin time of >390 min ($n = 99$), or had presented to a PSC outside the Netherlands ($n = 16$; Figure 1). Therefore, 1541/3637 patients (42%) were included in the study.

Patients had primarily presented to one of 65 PSCs and were treated with EVT in one of 16 CSCs. Annual EVT referral volume was low (<6 per year) for 35/65 PSCs (54%), medium (6–12 per year) for 20/65 PSCs (31%), and high (>12 per year) for 10/65 PSCs (15%). Of all patients, 435/1541 (28%) had presented to a low-volume PSC, 583/1541 (38%) to a medium-volume PSC, and 523/1541 (34%) to a high-volume PSC. For one patient, it was unknown which of two hospital locations was the referring PSC, so the hospital location located closest to the patient's postal code was assumed to be the referring PSC.

Baseline characteristics categorized by low-, medium-, and high-PSC volume are reported in Table 1. Patients who presented to high-volume PSCs more often had a history of hypertension (low: 48%, medium: 54%, high: 57%; $p = 0.03$) and had slightly lower NIHSS scores at baseline (low: median 16 [IQR: 12–20], medium: 16 [IQR: 12–20], high: 15 [IQR: 11–19]; $p = 0.01$). Estimated ambulance travel times between PSC and receiving CSC were shorter for patients who presented to high-volume PSCs (low: median 22 min [IQR: 15–28], medium: 22 min [IQR: 15–33], high: 17 min [IQR: 9–30]; $p < 0.01$). Other baseline characteristics did not differ between groups.

When comparing treatment times between low-, medium-, and high-volume PSCs, we found that patients who had presented to

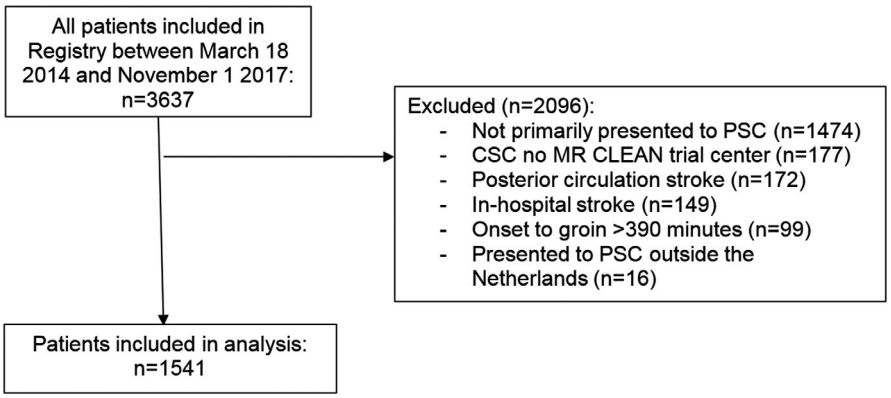

FIGURE 1 Flowchart of patient inclusion. CSC, comprehensive stroke center; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; PSC, primary stroke center; Registry, MR CLEAN Registry

TABLE 1 Baseline characteristics

		Annualized EVT referral volume			
Characteristic[a]	**All patients**	**Low, <6**	**Medium, 6–12**	**High, >12**	***p* value**[b]
No. of hospitals (no. of patients)	65 (1541)	35 (435)	20 (583)	10 (523)	NA
Age, years, mean ± SD	70.8 ± 13.3	70.0 ± 13.3	71.4 ± 13.5	70.9 ± 13.1	0.27
Male sex, *n*/total (%)	795/1541 (52%)	220/435 (51%)	301/583 (52%)	274/523 (52%)	0.86
History of hypertension, *n*/total (%)	798/1502 (53%)	205/426 (48%)	304/566 (54%)	289/510 (57%)	0.03
Diabetes mellitus, *n*/total (%)	241/1528 (16%)	70/430 (16%)	86/578 (15%)	85/520 (16%)	0.76
Atrial fibrillation, *n*/total (%)	366/1519 (24%)	105/430 (24%)	143/571 (25%)	118/518 (23%)	0.67
Previous stroke, *n*/total (%)	236/1524 (15%)	68/429 (16%)	96/576 (17%)	72/519 (14%)	0.43
Prestroke mRS score, median (IQR)[c]	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.07
Systolic blood pressure, median (IQR)[d]	150 (132–166)	148 (131–166)	150 (134–168)	150 (132–165)	0.34
Diastolic blood pressure, median (IQR)[e]	80 (71–91)	80 (71–90)	81 (72–92)	80 (70–90)	0.13
NIHSS score, median (IQR)[f]	16 (12–19)	16 (12–20)	16 (12–20)	15 (11–19)	0.01
Intracranial occlusion site on CTA, *n*/total (%)					
Intracranial ICA	406/1468 (28%)	113/419 (27%)	165/545 (30%)	128/504 (25%)	0.21
M1	876/1468 (60%)	267/419 (64%)	311/545 (57%)	298/504 (59%)	
M2	177/1468 (12%)	37/419 (9%)	68/545 (12%)	72/504 (14%)	
A1	2/1468 (0%)	0/419 (0%)	1/545 (0%)	1/504 (0%)	
Other	4/1468 (0%)	1/419 (0%)	0/545 (0%)	3/504 (1%)	
None	3/1468 (0%)	1/419 (0%)	0/545 (0%)	2/504 (0%)	
Presentation outside office hours, *n*/total (%)	1030/1541 (67%)	284/435 (65%)	387/583 (66%)	359/523 (69%)	0.52
Time from stroke onset to arrival at PSC, min, median (IQR)[g]	53 (38–90)	53 (40–94)	50 (36–83)	56 (37–90)	0.38
Estimated ambulance travel time between PSC and receiving CSC, median (IQR)	19 (12–32)	22 (15–28)	22 (15–33)	17 (9–30)	<0.01
Treatment with IVT, *n*/total (%)	1280/1533 (83%)	353/434 (81%)	489/577 (85%)	438/522 (84%)	0.52

Abbreviations: A1, first segment of anterior cerebral artery; CSC, comprehensive stroke center; CTA, computed tomography angiography; EVT, endovascular thrombectomy; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; PSC, primary stroke center.

[a]All baseline characteristics were measured on arrival at the CSC unless reported otherwise.

[b]The *p* value is for comparison between patients who were referred from low, medium, and high annual referral volume PSCs.

[c]Missing values = 44.

[d]Missing values = 55.

[e]Missing values = 60.

[f]Missing values = 19.

[g]Missing values = 438.

high- and medium-volume PSCs had shorter PSC DTGT (low: median 150 [IQR: 123–186], medium: 145 [IQR: 120–173], high: 146 [IQR: 124–178]; $p = 0.03$) and lower door-to-door times (low: median 109 [IQR: 84–135], medium: 102 [IQR: 83–124], high: 106 [IQR: 85–128]; $p < 0.01$), compared to patients who presented to low-volume PSCs (Table 2). However, when we analyzed EVT referral volume as a continuous variable and adjusted for potential confounders, there was no association between annual EVT referral volume and PSC DTGT (Figure 2a) or door-to-door time (Figure 2b). CSC DTGT did not differ between groups (Table 2), and there was no statistically significant association between EVT referral volume as a continuous variable and CSC DTGT after adjustment (Figure 2c).

The mRS score and mortality at 90 days after stroke did not differ between patients who presented to low-, medium-, and high-volume PSCs (Table 2). After adjustment, there was also no association between annual EVT referral volume and 90-day mRS score (unadjusted common odds ratio [cOR]: 0.98, 95% confidence interval [CI]: 0.96–1.01; adjusted common OR: 0.99, 95% CI: 0.96–1.01), or mortality (unadjusted OR: 1.02, 95% CI: 0.99–1.04; adjusted OR: 1.02, 95% CI: 0.98–1.06].

DISCUSSION

In this cohort study, we examined the relationship between the EVT referral volume of PSCs and treatment times and clinical outcomes. We observed that PSCs with high or medium EVT referral volume had shorter PSC DTGT compared to low-volume PSCs. However, after adjustment, there was no association between PSC volume and workflow times or functional outcome of patients.

The consonance of previous studies when it comes to the benefits of treatment in high-volume, specialized hospitals has led many to plead for increasing centralization of care for several neurological diseases [9–11], including acute ischemic stroke [12–17,22–25]. In light of this, it is somewhat surprising that our findings indicate that high PSC volumes do not translate into better workflow metrics or patient outcome. We defined high PSC volume as >12 EVT referrals per year based on the distribution of our data; only 15% of PSCs had >12 annual EVT referrals. Although few previous studies have reported on EVT referral volumes, average PSC volumes in our study seem relatively high compared to those found in regions in Germany and Australia (six annual EVT referrals per PSC in our study vs. four in both Germany and Australia) [26,27]. Nonetheless, it is possible that for even higher EVT referral volumes, an association with shorter time to treatment would exist. Bray et al. [13] found a similar trend for the association between hospital volume and time to initiation of IVT; only hospitals with >50 IVT cases per year achieved lower door-to-needle times, whereas no difference was found between hospitals with <25 annual cases and hospitals with 25–50 annual cases. However, because the number of PSCs with very high EVT referral volumes was low in our cohort, we could not test this hypothesis. Another potential explanation for the absence of an association between PSC volume and treatment times in our study could be the fact that the Netherlands has a well-developed health care system. Stroke workflow in the Netherlands, including emergency medical services and PSC and CSC logistics, is generally well organized, resulting in relatively short treatment times [19]. Within such a system it may be more difficult to discern the potential effect modifying variables such as PSC volume.

Two baseline imbalances should be noted. First, estimated ambulance travel times between PSC and receiving CSC were shorter for patients presented to high-volume PSCs. PSCs that are located in an area with low population density, and therefore have lower annual patient volumes, are likely to be located further away from the nearest CSC than PSCs in densely populated regions. This makes a comparison of treatment times inherently biased in favor of patients presented to a PSC in a more densely populated area, and thus in favor of high-volume PSCs. To account for this bias, we adjusted our

TABLE 2 Treatment times and clinical outcomes for patients presented to low-, medium-, and high-volume primary stroke centers

		Annualized EVT referral volume			
	All patients, *n* = 1541	**Low, <6, *n* = 435**	**Medium, 6–12, *n* = 583**	**High, >12, *n* = 523**	***p* value**
PSC DTGT, min, median (IQR)[a]	146 (122–178)	150 (123–186)	145 (120–173)	146 (123–177)	0.03
Door-to-door time, min, median (IQR)[b]	105 (84–129)	109 (84–135)	102 (83–124)	106 (85–128)	<0.01
CSC DTGT, min, median (IQR)[c]	39 (27–57)	36 (25–55)	40 (27–56)	40 (28–60)	0.18
mRS score at 90 days, median (IQR)[d]	3 (2–6)	3 (2–6)	3 (2–6)	3 (2–6)	0.19
Mortality at 90 days, *n*/total (%)[d]	445/1541 (29%)	121/435 (28%)	162/583 (28%)	162/532 (30%)	0.37

Note: Number of imputed values: [a]432, [b]481, [c]71, and [d]138. Numbers of imputed values did not differ between groups for the time intervals ([a]$p = 0.12$, [b]$p = 0.18$, [c]$p = 0.97$). The *p* value is for comparison between patients who were referred from low, medium, and high annual referral volume PSCs.

Abbreviations: CSC DTGT, time from arrival at the comprehensive stroke center to arterial puncture; door-to-door time, time from arrival at the PSC to arrival at the CSC; EVT, endovascular thrombectomy; IQR, interquartile range; mRS, modified Rankin Scale; PSC DTGT, time from arrival at the primary stroke center to arterial puncture.

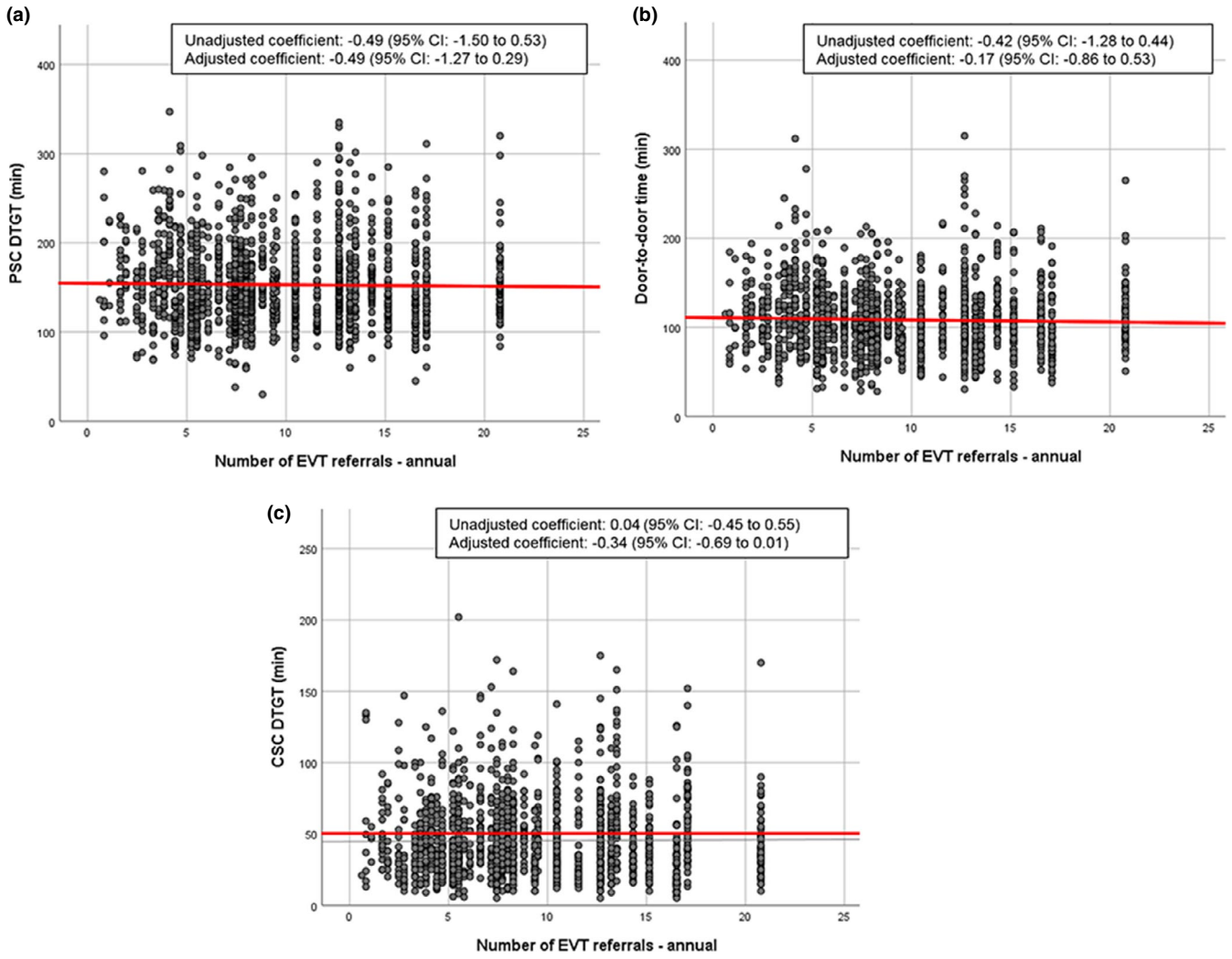

FIGURE 2 Plots of treatment times by annual EVT referral volumes. The treatment times (y-axis) and the annual endovascular thrombectomy (EVT) referral volume (x-axis) are shown for each patient (imputed data). Each dot represents a single patient. Vertically aligned dots represent the data of a single hospital with the corresponding number of annual EVT referrals. In case multiple hospitals had the same annual EVT referral volume, they were plotted on the same vertical axis. Both the adjusted and unadjusted coefficients are shown. For adjustment variables, see the Methods and Materials section. (a) PSC DTGT. (b) Door-to-door-time. (c) CSC DTGT. CI, confidence interval; CSC, comprehensive stroke center; CSC DTGT, time from arrival at the comprehensive stroke center to arterial puncture; door-to-door time, time from arrival at the primary stroke center to arrival at the comprehensive stroke center; EVT, endovascular thrombectomy; PSC, primary stroke center; PSC DTGT, time from arrival at the primary stroke center to arterial puncture [Colour figure can be viewed at wileyonlinelibrary.com]

analyses of treatment times for the estimated ambulance travel time between the PSC and the receiving CSC. Second, patients presented to high-volume PSCs had slightly lower NIHSS scores upon arrival at the CSC. A potential explanation for this could be that low-volume PSCs, due to possible lack of around-the-clock availability of stroke imaging facilities, may not have routinely performed CTA in patients with a suspected stroke and mild neurological deficits, causing these patients to less often be referred for EVT. Alternatively, more distal occlusions, such as M2 occlusions, may have been overlooked more often in low-volume PSCs because of less experienced readers.

There are several limitations to our study. First, the analysis of hospital performance is inherently influenced by variation by chance across hospitals, which especially affects low-volume hospitals. We used multilevel regression analysis, because such models can take clustering effects and variation by chance into account, contrary to regular fixed-effects models. However, it is possible that the effects of PSC volume were slightly underestimated by our random-effects model, because the observed variation across the hospitals may have been diluted, especially for low-volume PSCs [28–30]. Second, data collection for our study took place in the Netherlands, which is a densely populated country in which hospitals are located relatively close to one another, and there is overall good infrastructure [31]. Furthermore, in our study, the median PSC DTGT was short (144 min) compared to existing literature, in which median PSC DTGTs ranging from 153 to 191 min have been reported [3,32–34]. This was also the case for ambulance travel times; median ambulance

travel time in our study was 19 min compared to 23–95 min in other studies [3,5,32,33,35]. Our median CSC DTGT (39 min) was within the range, although on the lower end, of previously reported median CSC DTGTs for transferred patients (35–81 min) [3,7,33]. As data for this study were collected in a country with an advanced health care system, and time intervals were relatively short compared to those found in other countries, our findings should be extrapolated to other countries with caution. Third, we did not have data of patients who were referred to a CSC for EVT and were ultimately deemed ineligible for EVT, because these patients were not included in the MR CLEAN Registry. Therefore, the true annual number of patients referred from the PSCs for EVT may have been higher than reported in our study, and the frequency with which futile transfers occurred could not be assessed. Finally, we had relatively high numbers of missing values for three variables: door-to-door time (31%), PSC DTGT (28%), and time from stroke onset to arrival at the PSC (28%). To minimize the impact of these missing values on our analyses, we used multiple imputation. Time between arrival at the PSC and departure from the PSC (door-in-door-out time), which would have been an outcome measure of interest in our study, was not available in our dataset.

In conclusion, we did not observe an association between the EVT referral volume of PSCs and the PSC DTGT or the 90-day mRS score of patients who were transferred from a PSC for EVT. Based on the data in our study, PSC volumes do not seem to translate into better overall workflow metrics or patient outcome.

CONFLICT OF INTERESTS

B.J.E. reports funding from ZonMW (Leading the Change) and Health Holland paid to the institution, and has received grants paid to the institution from Stryker Neurovascular in the past and personal fees from Dekra and Novartis outside the submitted work. C.B.L.M.M. reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation, Stryker, and Health Evaluation Netherlands, all outside the submitted work (paid to the institution), and is a shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Y.B.W.E.M.R. is a minor shareholder of Nico.lab. H.B.v.d.W. has received speaker's fees from Boehringer Ingelheim, has served as a consultant to Boehringer Ingelheim, and is the recipient of unrestricted grants from the Dutch Heart Foundation and the European Union for the conduct of trials on acute treatment for stroke, all outside the submitted work. D.W.D. reports fees for consultations by Stryker and Bracco Imaging; grants from the Dutch Heart Foundation, Brain Foundation Netherlands, Netherlands Organisation for Health Research and Development, and Health Holland Top Sector Life Sciences & Health; and unrestricted grants from AngioCare BV, Covidien/EV3, MEDAC Gmbh/LAMEPRO, Top Medical/Concentric, Stryker, Stryker European Operations BV, Penumbra Inc., Medtronic, Thrombolytic Science, LLC, and Cerenovus, all paid to the institution. J.M.C. received unrelated research support from the Dutch Heart Foundation, Bayer, Boehringer, and Medtronic. All fees were paid to his employer. The other authors report no conflicts.

AUTHOR CONTRIBUTIONS

Laura C. C. van Meenen: Conceptualization (equal), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), writing–original draft (lead), writing–review & editing (lead). **Sanne J. den Hartog:** Data curation (supporting), formal analysis (supporting), writing–review & editing (supporting). **Adrien E. Groot:** Writing–review & editing (supporting). **Bart J. Emmer:** Writing–review & editing (supporting). **Martin D. Smeekes:** Writing–review & editing (supporting). **Arjen Siegers:** Writing–review & editing (supporting). **Geert Jan Kommer:** Formal analysis (supporting), writing–review & editing (supporting). **Charles B. L. M. Majoie:** Writing–review & editing (supporting). **Yvo B. W. E. M. Roos:** Conceptualization (equal), writing–review & editing (supporting). **Adriaan C. G. M. van Es:** Writing–review & editing (supporting). **Diederik W. Dippel:** Writing–review & editing (supporting). **H. Bart van der Worp:** Writing–review & editing (supporting). **Hester F. Lingsma:** Methodology (supporting), writing–original draft (supporting), writing–review & editing (supporting). **Bob Roozenbeek:** Methodology (supporting), writing–original draft (supporting), writing–review & editing (supporting). **Jonathan M. Coutinho:** Conceptualization (equal), methodology (supporting), supervision (lead), writing–original draft (supporting), writing–review & editing (supporting).

DATA AVAILABILITY STATEMENT

Individual patient data cannot be made available under Dutch law because we did not obtain patient approval for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Appendix S1

How to cite this article: van Meenen LCC, den Hartog SJ, Groot AE, et al; the MR CLEAN Registry Investigators. Relationship between primary stroke center volume and time to endovascular thrombectomy in acute ischemic stroke. *Eur J Neurol*. 2021;28:4031–4038. https://doi.org/10.1111/ene.15107