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Geographical differences in thrombolysis treatment for acute ischaemic stroke

ORIGINAL ARTICLE

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Background

Administering intravenous thrombolysis (IVT) as soon as possible after symptom onset impacts on the functional outcome for patients with acute ischaemic stroke. The study aimed to assess whether the distance from hospital impacts on the access to IVT for acute ischaemic stroke at the University Hospital of North Norway in Tromsø (UNN Tromsø).

Material and method

This prospective quality study included 231 patients admitted with acute ischaemic stroke to UNN in the period 1 January 2019–31 December 2019. The patients were divided into two groups based on vehicle transport time by road to the hospital at symptom onset: the urban cohort (≤ 30 minutes) and the rural cohort (> 30 minutes). Information on patient characteristics, IVT administration and functional status was retrieved from the Norwegian Stroke Registry, and prehospital timelines were retrieved from the Acute Medical Information System (AMIS). Outcome measures were the proportion of patients treated with IVT, and the time from symptom onset to thrombolysis.

Results

At symptom onset, 108 of the 231 patients were in an urban area and 123 were in a rural area. The urban cohort included fewer men (54 % vs. 68 %), a lower proportion with good functional status (a score of 0–1 on the Modified Rankin Scale) before symptom onset (58 % vs. 73 %) and fewer patients admitted via the local out-of-hours medical centre (10 % vs. 28 %) than the rural cohort. The proportion of patients treated with IVT in the urban cohort was 38 %, compared to 23 % in the rural cohort. On average, the urban cohort received the treatment 75 minutes sooner than the rural cohort.

Interpretation

The findings indicate that patients who are further from the hospital at symptom onset receive IVT less frequently and with a greater delay, and therefore have a lower likelihood of a favourable treatment outcome. Direct access to decentralised IVT could improve the treatment provision for ischaemic stroke patients.

Main findings

Intravenous thrombolysis (IVT) was administered to 41/108 (38 %) of the patients who were in an urban area at symptom onset, and 28/123 (23 %) of the patients who were in a rural area.

Patients with symptom onset in a rural area received IVT an average of 75 minutes later than patients from an urban area (95 % CI 29–129, $p = 0.002$).

In Norway, approximately 10,000–11,000 people suffer an acute stroke each year, of which 86 % are ischaemic strokes and the remainder are cerebral haemorrhages (1). Where there are no contraindications, intravenous thrombolysis (IVT) should be administered for ischaemic strokes as soon as possible, in accordance with current guidelines (2, 3). Prior to treatment, brain imaging must be performed to rule out cerebral haemorrhages, typically using computed tomography (CT) (2–4). All patients who can be treated within 4.5 hours of symptom onset should be considered for IVT. This can also be considered for individual patients up to nine hours after symptom onset and in strokes occurring during sleep (wake-up stroke), based on findings from magnetic resonance imaging (MRI) or CT perfusion (3). Patients whose ischaemic stroke was caused by a thrombus in a major cerebral artery should also be considered for thrombectomy (2).

The key factor for successful IVT is minimising the time from symptom onset to the initiation of treatment (5–7). In recent years, several measures have been implemented to streamline the pre-hospital treatment process for strokes. In the period 2016–17, the Norwegian Directorate of Health conducted the public awareness campaign, FAST (Face drooping, Arm weakness, Speech difficulty Time to call 113), aimed at raising awareness among the population of stroke symptoms and encouraging people to call the medical emergency service on 113 if they experience such symptoms. The national clinical guidelines for stroke treatment recommend that calls regarding suspected acute stroke go directly to the Emergency Medical Communication Centre (AMK) via 113, without contact with a local out-of-hours medical centre (2). Time-saving measures have also been implemented internally in hospitals. Stroke patients who are considered for IVT or thrombectomy are taken directly to the CT lab and assessed there by a dedicated stroke response team.

However, data from the Norwegian Stroke Registry show that only 45 % of ischaemic stroke patients arrive at the hospital within four hours (1). The proportion of patients treated with IVT, and the proportion who receive this within 40 minutes, are two key national quality indicators for acute ischaemic stroke treatment (1). An IVT rate in excess of 20 % among ischaemic stroke patients is considered a high level of achievement (1). In the period 2019–2022, 20–22 % of acute ischaemic stroke patients received IVT in Norway as a whole, compared to 15–20 % in the Northern Norway Regional Health Authority region (1). Geographical distances in Northern Norway are vast, and the vehicle transport time to hospital is part of the reason why patients in rural areas can miss the treatment window for IVT. The Norwegian Stroke Registry reports the proportion of thrombolysed patients at the hospital level, but there is no documentation of how this varies within the catchment area of a hospital. The University Hospital of North Norway in Tromsø (UNN Tromsø) also serves as a local hospital for several municipalities in the county of Troms. In this study, we aimed to examine how geographic location at symptom onset impacts on the access to IVT for acute ischaemic stroke.

Material and method

The study is a quality study based on prospectively registered data from UNN Tromsø in the Norwegian Stroke Registry. This national quality register for stroke treatment requires the reporting of all hospitalised patients with acute stroke in Norwegian hospitals, as mandated by law. Informed consent is not required. Entries in the Norwegian Stroke Registry are based on information from electronic patient records and in-person check-ups or phone calls with the patient or their next of kin three months after the stroke.

Patients admitted to UNN Tromsø and registered with the ICD-10 diagnostic code I63 (Cerebral infarction) in the Norwegian Stroke Registry in the period 1 January 2019 to 31 December 2019 (n = 343) met the criteria for inclusion in the study. The coverage rate of the Norwegian Stroke Registry for 2019 was 91 %. To ensure that all relevant patients were included, a double check was performed by comparing entries in the Norwegian Stroke Registry with local administrative data for patients registered with the ICD-10 diagnostic code I63 at the hospital during the relevant period. Information on patients' location at symptom onset was obtained retrospectively by reviewing the electronic medical records. Patients who were outside the local catchment area of UNN Tromsø when the stroke occurred (n = 10), patients transferred from other local hospitals for potential thrombectomy or neurosurgical intervention (n = 50), and patients with incorrectly registered diagnostic codes (n = 4) were excluded from the study (Figure 1). Since the purpose of the study was to investigate whether the distance from the hospital impacted on the access to IVT and time to treatment, we also excluded patients with intrahospital symptom onset (n = 48).

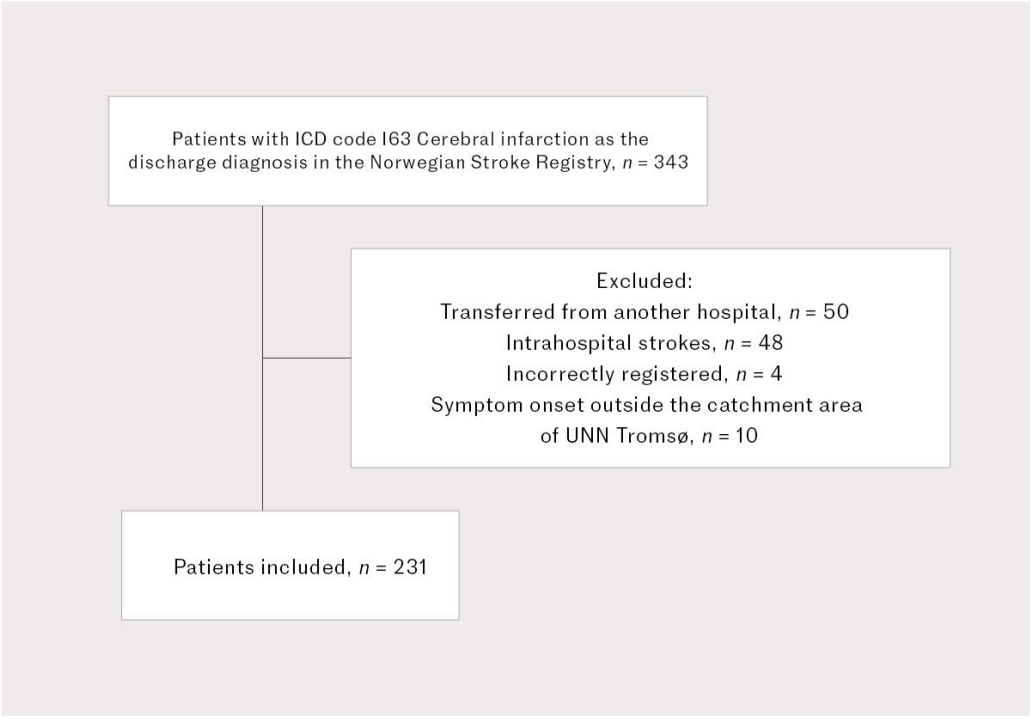

Figure 1 Flowchart for the study sample consisting of patients admitted with ischaemic stroke from the local catchment area of UNN in 2019, based on location at

symptom onset.

The sample consisted of 231 patients who were divided into two groups: the urban cohort (n = 108), consisting of patients whose symptom onset occurred within areas with a vehicle transport time by road to UNN Tromsø of 30 minutes or less, based on the applicable speed limit, and the rural cohort (n = 123), consisting of patients whose symptom onset occurred in areas with a vehicle transport time to hospital of more than 30 minutes (Figure 2).

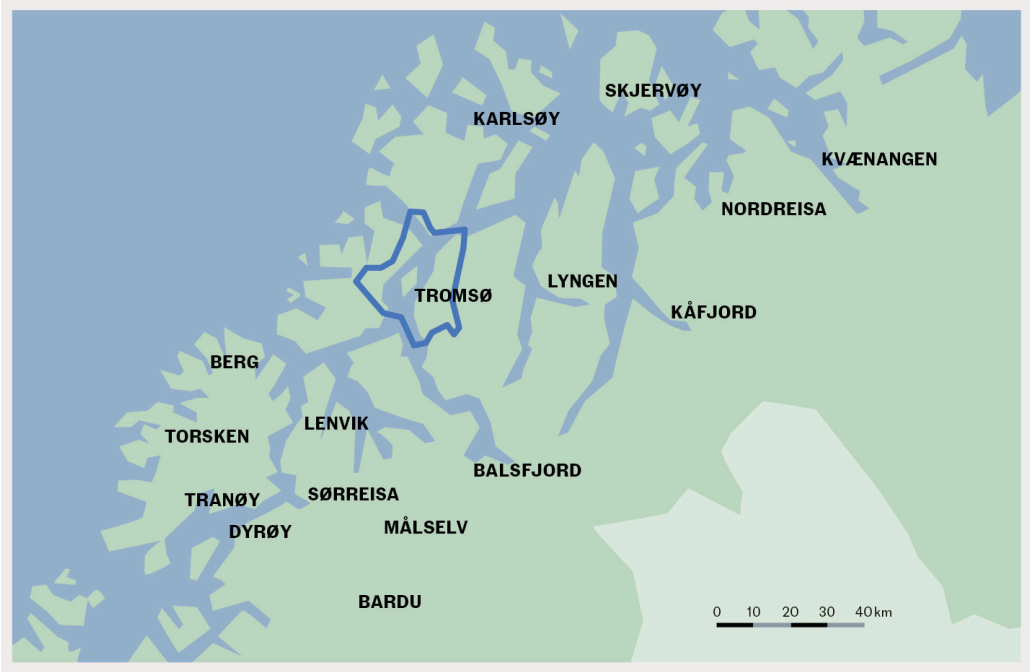

Figure 2 Map of the municipalities included in the study according to the municipal division in 2019 and the defined geographical boundaries for the urban cohort and the rural cohort. Google Maps was used to determine the area covered by a 30-minute driving time from UNN Tromsø in all directions, based on the applicable speed limit and including all main roads out of Tromsø city centre. Points were marked on the map, and lines were drawn between the points. Patients who were located within the marked area at symptom onset were defined as the urban cohort.

Information on age, sex, risk factors, functional status prior to the stroke, symptoms and findings on admission (including severity according to the National Institutes of Health Stroke Scale (NIHSS) (8), treatment, as well as functional status according to the Modified Rankin Scale (mRS) at a three-month check-up after the stroke, was obtained from UNN Tromsø's entries in the Norwegian Stroke Registry. Information on smoking status was missing for 42 patients (18 %, 20/108 in the urban cohort and 22/123 in the rural cohort), information on consultations with a local out-of-hours medical centre was missing for 52 patients (23 %, 27/108 in the urban cohort and 25/123 in the rural cohort), while the mRS score at the three-month check-up was missing for 4 patients (2 %, all in the urban cohort). Information on pre-hospital timelines was obtained from Norway's Acute Medical Information System (AMIS). For patients with wake-up stroke, the time of symptom onset is unknown, and in the Norwegian Stroke Registry, symptom onset is set to midnight the preceding night.

The Modified Rankin Scale is a measure of functional status and assistance needs for activities of daily living (ADLs). The scale ranges from 0 to 6, where 0 represents no symptoms and 6 means the patient has died (9). Based on previous IVT studies (7, 10, 11), a 'good outcome' in this study, three months after the stroke, was defined as an mRS score of 0–1 (no or minimal disability) or an unchanged mRS score compared to the pre-stroke status, for patients with a premorbid mRS score > 1.

The study was a quality project and was not considered to require approval from the Regional Committees for Medical and Health Research Ethics (REK). The study was approved by the data protection officer at UNN (ref. 2020/4772).

Statistical analyses were performed using SPSS software (version 29.0, Armonk, NY). Categorical variables are presented as absolute numbers/totals with percentages in parentheses (*n/N* (%)), and continuous variables were assessed for normality of distribution and presented either as the mean with standard deviation in parentheses or as the median with the interquartile range in parentheses.

The groups were compared in terms of the outcome measures 'proportion of patients treated with IVT' and 'time from symptom onset to IVT' using binary logistic and linear regression analyses, respectively, adjusted for age, sex and stroke severity (NIHSS score) on admission. The 'time from symptom onset to IVT' variable met the requirement for linear regression analysis due to the normal distribution of residuals. A p-value < 0.05 was set as the significance level. The rural cohort was used as the reference group. The study was not sufficiently powered to examine differences in functional status after three months, so these results are presented as unadjusted percentages without formal significance testing.

Results

The sample consisted of 231 patients, of whom 108 had symptom onset in an urban area and 123 in a rural area. The urban cohort had fewer men (58/108 (54 %) vs. 84/123 (68 %) in the rural cohort), a lower proportion with good functional status before symptom onset (mRS score of 0–1: 63/108 (58 %) vs. 90/123 (73 %) in the rural cohort), a higher proportion with a history of myocardial infarction (22/108 (20 %) vs. 13/123 (11 %) in the rural cohort), and more nursing home patients (9/108 (8 %) vs. 4/123 (3 %) in the rural cohort) (Table 1).

Table 1

Characteristics of patients admitted with ischaemic stroke from the local catchment area of UNN in 2019, by location at symptom onset. Number (%) unless otherwise specified.

	Urban (N = 108)	Rural (N = 123)
Median age, years (interquartile range)	79 (65–83)	73 (62–81)
Men	58 (53.7)	84 (68.3)
Risk factors		
Diabetes	24 (22.2)	30 (24.4)
Atrial fibrillation	24 (22.2)	37 (30.1)
Hypercholesterolemia[1]	47 (43.5)	56 (45.5)
Hypertension[1]	70 (64.8)	83 (67.5)
Previous stroke	33 (30.6)	26 (21.1)
Previous transient ischaemic attack	15 (13.9)	15 (12.2)
Previous myocardial infarction	22 (20.4)	13 (10.6)
Anticoagulant treatment[2]	10 (9.3)	18 (14.6)
Smoking[3]		
Never smoked	30 (34.1)	39 (38.6)
Former smoker	44 (50.0)	36 (35.6)
Current smoker	14 (15.9)	26 (25.7)
Living situation prior to stroke		
Own home without municipal assistance	67 (62.0)	94 (76.4)
Own home with municipal assistance	25 (23.1)	20 (16.3)
Nursing home	9 (8.3)	4 (3.2)
Sheltered housing	7 (6.5)	5 (4.1)
Functional status prior to stroke		
No disability (mRS[4] score 0–1)	63 (58.3)	90 (73.2)
Slight to moderate disability (mRS score 2–3)	37 (34.3)	31 (25.2)
Moderately severe to severe disability (mRS score 4–5)	8 (7.4)	2 (1.6)

[1]Defined as hypercholesterolemia/hypertension for which medication was being taken.

[2]Defined as the use of anticoagulants or INR > 1.7 on admission.

[3]Information on smoking status was missing for 20/108 in the urban cohort and 22/123 in the rural cohort. The percentages are calculated based on 88 and 101 patients, respectively.

[4]Functional status was assessed using the Modified Rankin Scale (mRS) (mRS score 0 = no symptoms; 1 = no significant disability; 2 = slight disability; 3 = moderate disability; 4 = moderately severe disability; 5 = severe disability; 6 =

died).

The median time from symptom onset to AMK notification was 79 minutes (interquartile range: 19–463) in the urban cohort and 190 minutes (20–619) in the rural cohort (Table 2). The proportion of patients with wake-up stroke and unknown symptom onset time was lower in the urban cohort (10/108 (9 %) vs. 28/123 (23 %) in the rural cohort), and when excluding these patients (Table 3) there was a smaller difference in time from symptom onset to AMK notification (urban cohort: median time was 63 minutes (13–253); rural cohort: 94 minutes (16–501)). The time from symptom onset to hospital arrival was shorter in the urban cohort, where 55/108 (51 %) arrived at the hospital within 4 hours, compared to 41/123 (33 %) in the rural cohort. The median time from AMK notification to hospital arrival was 38 minutes (31–55) in the urban cohort and 130 minutes (88–210) in the rural cohort. In the rural cohort, more patients were admitted via a local out-of-hours medical centre than in the urban cohort (27/98 (28 %) vs. 8/81 (10 %)), but this information was missing for 52/231 (23 %) of the patients.

Table 2

Time from symptom onset until AMK responds after a 113 call, from AMK's response to hospital arrival, and from symptom onset to IVT in patients admitted with ischaemic stroke from the local catchment area of UNN in 2019, according to location at symptom onset. Time is presented as median number of minutes (interquartile range).

	Urban (N = 108)	Rural (N = 123)
From symptom onset[1] until AMK responds		
All patients[2]	79 (19–463)	190 (20–619)
Patients with known symptom onset[3]	63 (13–253)	94 (16–501)
Patients who received IVT[4]	30 (7–86)	23 (11–93)
From AMK's response to hospital arrival		
All patients	38 (31–55)	130 (88–210)
From symptom onset to IVT		
Patients who received IVT[5]	100 (65–153)	204 (149–247)

[1]Symptom onset is calculated from the known time of symptom onset or when the patient was last observed to be healthy.

[2]Patients who contacted AMK, 83 in the urban cohort and 97 in the rural cohort.

[3]Patients who contacted AMK *and* had a known time of symptom onset, 76 in the urban cohort and 77 in the rural cohort.

[4]Patients who contacted AMK *and* received IVT, 38 in the urban cohort and 28 in the rural cohort.

[5]All patients who received IVT, 41 in the urban cohort and 28 in the rural cohort.

Table 3

Symptoms, treatment process and functional outcomes in patients admitted with ischaemic stroke from the local catchment area of UNN in 2019, by location at symptom onset. Number (%) unless otherwise specified.

	Urban (N = 108)	Rural (N = 123)
Symptoms		
FAST symptoms[1]	79 (73.1)	88 (71.5)
Other focal neurological deficits[2]	85 (78.7)	89 (72.4)
NIHSS score on admission. median (interquartile range)	3 (2–5)	2 (1–5)
Unknown time of symptom onset/wake-up stroke	10 (9.3)	28 (22.8)
Consultation with a local out-of-hours medical centre[3]	8 (10)	27 (28)
Transport		
Ambulance	83 (76.9)	46 (37.4)
Air ambulance (helicopter/plane. Or in combination with regular ambulance)	0 (0.0)	51 (41.5)
Private car, taxi or other form of transport	25 (23.1)	26 (21.1)
Treatment process		
Admitted by the stroke response team directly at the CT lab	66 (61.1)	59 (48.0)
Treated in the stroke unit	100 (92.6)	120 (97.6)
IVT	41 (38.0)	28 (22.8)
Thrombectomy	7 (6.5)	9 (7.3)
Functional status three months after stroke		
Good functional status[4]	47/104 (45.2)[5]	73 (59.3)
mRS[6] score 0–1	37/104 (35.6)	63 (51.2)
mRS score 0–2	59/104 (56.7)	90 (73.2)
Died	24/108 (22.2)	10 (8.1)

[1]Facial paralysis, arm paresis, dysarthria, aphasia

[2]One or more of the following symptoms: leg paresis, sensory loss, dysphagia, ataxia, neglect, double vision, visual field loss, vertigo, with or without FAST symptoms.

[3]Information was missing for 27/108 in the urban cohort and 25/123 in the rural cohort. The percentage is calculated based on 81 and 98 patients, respectively.

[4]Defined as a functional score from the Modified Rankin Scale (mRS) of 0–1 or unchanged mRS score from before the stroke.

[5]The functional score from the Modified Rankin Scale after three months was missing for four patients in the urban cohort. Information from the hospital record system DIPS indicated that they were not deceased at the time of follow-up. The percentage is calculated from 104 patients, except for the deceased proportion, which is based on 108 patients.

[6]Functional score from the Modified Rankin Scale (0 = no symptoms; 1 = no significant disability; 2 = slight disability; 3 = moderate disability; 4 = moderately severe disability; 5 = severe disability; 6 = died).

A stroke response team was used for 66/108 (61 %) patients in the urban cohort and 59/123 (48 %) in the rural cohort (Table 3). The urban cohort had a median NIHSS score of 3 (2–5) upon arrival at hospital, while the median in the rural cohort was 2 (1–5). Overall, 69/231 (30 %) received IVT: 41/108 (38 %) in the urban cohort and 28/123 (23 %) in the rural cohort. Binary logistic regression analysis, adjusted for age, sex and NIHSS score on admission, showed that patients in the urban cohort had a significantly higher likelihood of receiving IVT, with an adjusted odds ratio of 2.2 (95 % confidence interval [CI]: 1.2–4.1; p = 0.014) compared to the rural cohort. The median time from symptom onset to IVT was 100 minutes (65–153) for the urban cohort and 204 minutes (149–247) for the rural cohort (Table 2). Linear regression analysis, adjusted for other explanatory variables, revealed a significant difference, with patients in the urban cohort receiving IVT on average 75 minutes sooner (95 % CI: 29–129; p = 0.002) than those in the rural cohort.

In the rural cohort, a larger proportion had an mRS score of 0–1 both before and after the stroke, with 90/123 (73 %) before and 63/123 (51 %) after. The corresponding figures for the urban cohort were 63/108 (58 %) and 37/104 (36 %). A larger proportion of the rural cohort achieved a good outcome (mRS score of 0–1 and/or unchanged mRS score from before symptom onset) after the stroke, with 73/123 (59 %) in the rural cohort compared to 47/104 (45 %) in the urban cohort (Table 3). The proportion who died within three months was lower in the rural cohort than in the urban cohort (10/123 (8 %) vs. 24/108 (22 %)).

Discussion

The rural cohort was less likely to receive IVT compared to the urban cohort and, on average, the treatment was administered 75 minutes later.

Our findings are consistent with a US study showing that stroke patients living in and treated in rural areas were less likely to receive reperfusion therapy and that they experienced longer delays in treatment compared to those in urban

areas (12). In the US study, rural patients were treated at small local hospitals with no stroke specialists or dedicated stroke units. The results are therefore not directly comparable to our study. Nevertheless, the findings suggest that patients in sparsely populated areas or those located further from hospitals experience longer delays in treatment, which reduces the likelihood of a good treatment effect. A more recent study has shown that the disparity in the treatment provision between central and rural areas is increasing (13).

The time from symptom onset to AMK notification was longer for the rural cohort, and a higher proportion of this group visited a local out-of-hours medical centre before hospital admission compared to the urban cohort. However, data on the timing of the initial contact with the health service is incomplete. For patients who first sought care at a local out-of-hours medical centre, AMK was likely notified following the primary care doctor's assessment. Previous studies have shown that patients who contacted the ambulance service directly were admitted to hospital sooner than those who first consulted a primary care doctor (14). A higher proportion of patients in the rural cohort presented with wake-up stroke and an unknown time of symptom onset. The rural cohort also had milder symptoms, which potentially could have created more uncertainty about whether to seek medical attention. Overall, differences in patient delays, prehospital factors and symptom severity may have contributed to variations in the time from symptom onset to treatment and the proportion of patients treated with IVT in the two patient cohorts.

The proportion of women, nursing home residents and patients with a history of cardiovascular disease was lower in the rural cohort than the urban cohort. This selection bias may have contributed to a higher proportion in the rural cohort achieving good functional status at three months and to the lower mortality rate. The longer distances in rural areas may also have raised the threshold for hospitalising patients with low functional status and stroke symptoms.

The study lacks the statistical power to detect a difference in IVT-related treatment effects between the urban and rural cohorts; however, a strong body of evidence in the literature shows that IVT and early intervention are associated with good functional outcomes (5–7). Although both the urban and rural cohorts met the national target of an IVT rate in excess of 20 % at UNN Tromsø in 2019, our findings suggest that fewer patients residing in rural areas receive acute treatment for ischaemic stroke and that treatment is administered later than for their urban counterparts. New approaches are needed to counteract these undesirable geographical variations in access to treatment. The use of ambulances equipped with a CT scanner (mobile stroke unit) was found to be effective in densely populated areas (15). Introducing stationary CT scanners at rural medical centres and potentially other strategic sites outside the hospital setting that are quickly accessible by ambulance, combined with stroke telemedicine, could be a suitable solution in sparsely populated areas (16). Decentralised solutions implemented at the Rural Medical Centre in Mid-Troms and a local medical centre in Ål, Hallingdal, have shown promising results in providing earlier IVT for ischaemic stroke patients in rural areas (17).

One of the strengths of our study is that UNN has sole responsibility for the geographical area in question. A limitation of the study is that some of the data from the Norwegian Stroke Registry is based on a retrospective review of medical records, which increases the risk of incorrectly registered and incomplete data. Reliability was, however, good for most variables in the Norwegian Stroke Registry, including medical history and premorbid functional status (18). Nevertheless, poorer quality in some time-related variables cannot be ruled out, and information about prehospital timelines was therefore obtained from AMIS. Due to the limited sample size, it was not possible to compare differences in functional status after IVT between urban and rural patients. Larger-scale studies are needed to investigate whether differences in acute stroke treatment between urban and rural patients affect post-stroke functional outcomes.

The article has been peer-reviewed.

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