A Managed Care System with Telemedicine Support for Neurological Emergencies

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Objectives: Telemedicine is frequently used to provide remote neurological expertise for acute stroke workup and was associated with better functional outcomes when combined with a stroke unit system-of-care. We investigated whether such system-of-care yields additional benefits when implemented on top of neurological competence already available onsite.

Methods: Quality improvement measures were implemented within a "hub-and-spoke" teleneurology network in 11 hospitals already provided with onsite or telestroke expertise. Measures included dedicated units for neurological emergencies, standardization of procedures, multiprofessional training, and quality-of-care monitoring. Intervention effects were investigated in a controlled study enrolling patients insured at 3 participating statutory health insurances diagnosed with acute stroke or other neurological emergencies. Outcomes during the intervention period between November 2017 and February 2020 were compared with those pre-intervention between October 2014 and March 2017. To control for temporal trends, we compared outcomes of patients with respective diagnoses in 11 hospitals of the same region. Primary outcome was the composite of up-to-90-day death, new disability with the need of ambulatory or nursing home care, expressed by adjusted hazard ratio (aHR).

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Results: We included 1,418 patients post-implementation (55% female, mean age 76.7 ± 12.8 year) and 2,306 patients pre-implementation (56%, 75.8 ± 13.0 year, respectively). The primary outcome occurred in 479/1,418 (33.8%) patients post-implementation and in 829/2,306 (35.9%) pre-implementation. The aHR for the primary outcome was 0.89 (95% confidence interval [CI]: 0.79–0.99, $p = 0.04$) with no improvement seen in non-participating hospitals between post- versus pre-implementation periods (aHR 1.04; 95% CI: 0.95–1.15).
Interpretation: Implementation of a multicomponent system-of-care was associated with a lower risk of poor outcomes.

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Introduction

Organized inpatient care for stroke (or care on dedicated stroke units) improves outcome in acute stroke patients.[1] Because this concept requires neurological expertise, stroke units were first implemented in larger hospitals staffed with neurologists or stroke physicians, which made stroke unit implementation challenging for smaller hospitals, particularly in rural areas with a limited number of medical disciplines. Telemedicine networks offer rapid neurological expertise in facilities without specialist neurologists onsite, facilitating state-of-the-art acute stroke assessment and management.[2–5] Telemedicine networking was associated with more frequent and appropriate use of intravenous thrombolysis and better functional outcomes when combined with a stroke unit system of care.[6–9] However, it has never been investigated whether a managed-care system yields additional benefit when implemented on top of existing onsite or telemedically provided neurological competence.

Previous studies almost exclusively included patients with acute stroke diagnosis although patients with other neurological emergencies are frequently assessed via telemedicine as differential diagnoses in acute stroke workup.[5] Because delays in initiating specific therapies often lead to irreversible neurological damage, stroke and non-stroke neurological emergencies typically share the close association of therapeutic effects with time-to-treatment initiation.[10,11] Hence, inclusion of patients with status epilepticus, coma of unclear etiology, meningitis, encephalitis, and acute spinal cord injury/paraplegia offers a broader perspective for the assessment of clinical effectiveness of teleneurology networks.

The current study, therefore, aimed to estimate the effect of a managed-care system with the implementation of a dedicated unit for neurological emergencies and comprehensive quality management in rural hospitals which had neurological competence either onsite or via telemedicine already available.

Methods

Study Design

This is a multicenter, controlled, open-label, 2-arm intervention study assessing primary and secondary outcomes before and after implementation of the Acute Neurological care in Northeast Germany with TeleMedicine support (ANNOTeM) network. The ANNOTEM intervention started on July 2, 2017, and was funded for evaluation until July 31, 2020. The design and analysis plan has been registered at the German Clinical Trials Register DRKS00013067 (date of registration: November 16, 2017. URL: http://www.drks.de/DRKS00013067) and the protocol of the study has been published previously.[12]

Network

The intervention was carried out in a hospital network in Northeast Germany, including 3 comprehensive neurocenters, 1 comprehensive epilepsy center, and 11 rural hospitals (see Figure 1 for a map of participating hospitals). None of the latter hospitals participated in a quality-managed network before. Before the intervention, these 11 rural hospitals delivered neurological care for their patients in different settings:

- One hospital had a neurology department, including a stroke unit certified by the German Stroke Society, but did not provide endovascular treatment for stroke patients with large vessel occlusions. An additional telestroke service was not present at this hospital.
- In 4 hospitals, a single neurologist was available onsite as a permanent employee during daytime every weekday and as needed during daytime on weekends. Three of these hospitals also had an additional telestroke service (24/7/365).
- In another 4 hospitals, neurologists were available onsite as consultants during daytime on specific weekdays or when requested. All 4 of these hospitals also had an additional telestroke service (24/7/365).
- In 2 hospitals, neurologists were not available onsite at all. However, these 2 hospitals had a 24/7/365 telestroke service.

Nine of the 11 rural hospitals were already using a telestroke cooperation with comprehensive neurocenters before the start of the intervention program. However, this did not include comprehensive quality management measures and was restricted to suspected stroke patients

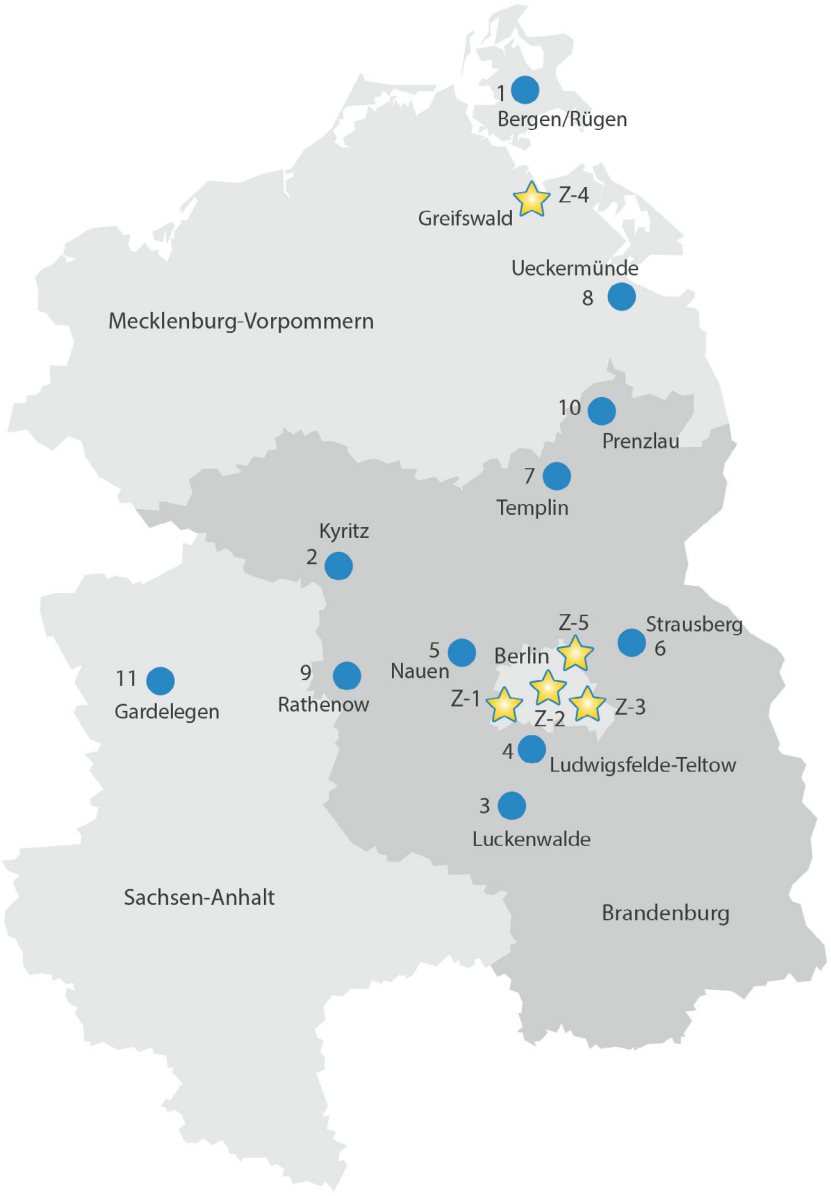

FIGURE 1: Map of participating hospitals. (1) Sana-Krankenhaus Bergen/Rügen, (2) KMG-Klinikum Kyritz, (3) KMG-Klinikum Luckenwalde, (4) Evangelisches Krankenhaus Ludwigsfelde-Teltow, (5) Havelland-Kliniken Nauen, (6) Krankenhaus Märkisch-Oderland Strausberg, (7) Sana-Krankenhaus Templin, (8) AMEOS-Klinik Ueckermünde, (9) Havelland-Kliniken Rathenow, (10) Kreiskrankenhaus Prenzlau, (11) Altmark-Klinikum Krankenhaus Gardelegen. Z1–Z5 depict the hubs of the network (Z1 + Z2: Charité – Universitätsmedizin Berlin, Z-3: Unfallkrankenhaus Berlin, Z-4: Universitätsmedizin Greifswald, and Z-5: Epilepsieklinik Tabor Bernau). [Color figure can be viewed at www.annalsofneurology.org]

only. Table 1 presents the characteristics of the participating hospitals before start of the intervention. The ANNOTeM intervention program was gradually implemented in participating hospitals from July 2, 2017, to November 12, 2018.

Intervention

The intervention consisted of implementing a quality managed teleneurology network for hospitals in rural areas treating patients with neurological emergencies. The intervention has been described in detail in the published ANNOTeM protocol:[12] Core elements of the intervention included:

- 24/7 ("around the clock on every day") teleneurology service offering board-certified neurologist standards. Compared to the pre-existing telestroke service at the rural hospitals, the indications for teleconsultations were expanded beyond suspected stroke and also included other neurological emergencies. Indications for teleconsultations as being part of the contracts between

TABLE 1. Characteristics of Intervention and Control Hospitals

	Intervention Hospitals										
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
Bed capacity	116	177	165	122	185	250	218	312	206	253	332
Index event cases 2016	120	131	165	188	274	295	318	336	435	448	493
Department of neurology	No	No	No	No	No	No	No	No	No	No	Yes
Pre-existing telemedicine service	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
	Control Hospitals										
	L	**M**	**N**	**O**	**P**	**Q**	**R**	**S**	**T**	**U**	**V**
Bed capacity	71	195	174	171	129	155	354	154	200	500	488
Index event cases 2016	91	109	154	158	177	261	298	310	385	456	604
Department of neurology	No	No	No	No	No	No	No	No	No	Yes	No
Pre-existing telemedicine service	No	No	No	No	No	No	No	No	No	No	No

neurocenters and rural hospitals included the following leading symptoms/syndromes or suspected diagnoses: focal neurological deficits with suspected stroke, severe headache with sudden onset, seizures, status epilepticus, higher-grade disturbance of consciousness (stupor, coma), delirium of unknown origin, headache with fever (suspected meningitis/encephalitis), and acute incomplete or complete paraplegia.

- Implementation of dedicated neuro-acute units based on the concept of telestroke units for specialized treatment of acute neurological emergencies and establishing interdisciplinary teams (including physicians, nurses, and allied health professionals).[13] In contrast to prior care at the participating hospitals, patients with neurological emergencies in the intervention period were supposed to be treated at these neuro-acute units only.
- Training all members of the interdisciplinary neuro-acute teams in intervention hospitals to optimally treat patients according to standardized and up-to-date diagnostic and therapeutic recommendations. The training was organized by the comprehensive neurocenters. It included onsite joint ward rounds for nurses led by stroke nurses of the comprehensive neurocenters (5 times per year at each intervention hospital), onsite joint ward rounds for allied health professionals (physiotherapists, speech therapists, and occupational therapists) led by allied health professionals of the comprehensive neurocenters (5 times per year at each intervention hospital), and also onsite interdisciplinary education of physicians, nursing staff, and allied health professionals by expert neurologists of the comprehensive neurocenters (twice a year at each intervention hospital). The intervention also included full-day interdisciplinary education sessions and workshops at the comprehensive neurocenters (twice a year). There was no managed continuous training and education program for neurological emergencies prior to the intervention at the participating hospitals.
- A new quality management program with participation of all intervention hospitals in a cross-regional stroke register[14] and in a newly established register for non-stroke neurological emergencies within the ANNOTeM network with regular counseling of hospital teams (twice a year at each intervention hospital). Counseling included for example, improvement of data assessment for quality management, improving specific quality indicators for stroke, and implementation of new or updated diagnostic and therapeutic recommendations.
- Optimization of interhospital transfers by identifying patients with transfer indications, avoiding not-indicated transfers, providing digital transmission of neuroimaging, and monitoring transfer processes based on a newly established register for interhospital transports for thrombectomies.

Study Objectives

We hypothesized that the described multicomponent intervention reduces the combined outcome of death, new disability with the need for ambulatory care nursing, or

new disability with the need for nursing home care within 90 days of hospital admission compared to the pre-existing standard of care in the participating hospitals.

Participants

We enrolled patients between October 1, 2014, and March 31, 2017 (control period) and between November 16, 2017, and July 31, 2020 (intervention period). Recruitment of patients in the intervention period started at each hospital after a 3-month roll-in phase after the first teleconsultation. Patients were included if diagnosed with 1 of the pre-specified acute neurological emergency diagnoses (stroke, status epilepticus or coma, meningitis/encephalitis, or acute spinal cord injury/paraplegia) and if insured by 1 of the 3 statutory health insurance providers (AOK Nordost, BARMER, Techniker Krankenkasse) that participated in this health care innovation project. Patients being insured by 1 of these large health insurances are expected to be representative of patients with statuary health insurances in the Northeast of Germany. Patients with acute neurological emergencies insured with other health insurance providers were also cared for within the network. They received telemedicine support, but their baseline and outcome data were not available for evaluation.

To investigate potential influences of non-intervention-related changes in the health care system over time (temporal trends), a secondary analysis was conducted for patients with identical inclusion criteria treated in hospitals not participating in the network ("control hospitals") in the same region of Northeast Germany during the same time of the intervention. These hospitals were similar to the network hospitals according to geographical location, size, and number of acute neurological cases per yr.[12] Their characteristics are shown in Table 1.

Patients admitted to the evaluated hospitals more than once were only evaluated for their first admission.

Outcomes

The composite primary outcome was time to (1) death, (2) new disability with the need for ambulatory care nursing or, (3) new disability with the need for nursing home care within 90 days after the index hospital admission, whichever occurred first. These outcomes were routinely collected and provided by the statutory health insurers, which are also responsible for paid nursing care services in Germany.

Secondary outcomes included: (1) Frequency of evidence-based therapies for acute stroke such as Stroke Unit treatment and intravenous thrombolysis (all assessed via the "operation and procedure codes" of the German Diagnoses Related Groups system). (2) Single outcomes for time to death, new disability with the need of ambulatory care nursing, and new disability with the need of nursing home care within 90 days after hospital admission. Hospital transfers for endovascular thrombectomy and hemicraniectomy were a planned outcome in the study protocol but not available in the data provided by health insurers.

Sample Size

Based on the results of the Telemedical Project for integrative Stroke Care (TEMPiS) study,[6] the sample size was calculated, assuming a reduction of dependency by one-fifth in the intervention hospitals. Given the number of patients in the participating hospitals known before implementing the network, a sample size of 1,820 patients per group was calculated; this sample size ensured a power of 80% and an alpha of 5% for a 2-sided test. A pre-planned interim analysis without significance testing was performed after completing 50% of patient follow-ups to inform the funder about the progress of the scientific evaluation and possible options for transition into regular care. Further details regarding sample size are described in detail in the published study protocol.[12]

Statistical Analysis

Baseline characteristics of the intervention and the control group were compared with descriptive statistics. Cox proportional hazards models were computed to compare the 2 groups in the pre- and post-implementation period, adjusting for age and sex. Hazard ratios and their 95% confidence intervals were calculated for the composite outcome. Pre-specified subgroup analyses[12] included the occurrence of the composite primary outcome according to age, sex, index diagnosis (ischemic stroke, hemorrhagic stroke, other neurological emergencies), and paid nursing care before the index hospital admission. Furthermore, we assessed the occurrence of the composite primary outcome in an extended follow-up period of 120 days after hospital admission. Additionally, separate Cox models were set up for each outcome of the composite primary outcome: death, new ambulatory care nursing, and new nursing home care. In a further secondary analysis, Cox regression models adjusted for age and sex were computed to compare the pre- and post-implementation period in non-participating hospitals. To test for statistically significant interactions, we included an interaction term to the regression models.

We estimated the adjusted absolute risk reduction in analogy to the stratification rationale of the Cochran–Mantel–Haenszel test. For each of the 8 strata (defined as the possible combinations of 4 age groups (<65, 65–74, 75–84, ≥85 years of age) and 2 sexes), we calculated the

difference in the absolute risks in the intervention and control populations first. We then averaged these differences into the adjusted (or stratified) absolute risk reduction estimate.

All tests were performed at a 2-sided significance level of alpha = 0.05. All analyses were performed using R (version 3.7).

Deviation from the Original Study Protocol

In many health care systems, including the German one, the early phase of the coronavirus disease 2019 (COVID-19) pandemic was associated with increased average severity of the stroke patients population admitted to hospitals, likely caused by avoidance of hospitalization by patients with transient or mild stroke symptoms as reported elsewhere and also from the ANNOTeM network.[15–17] However, an adjustment according to stroke severity was not possible within the framework of the planned primary analysis due to missing documentation of stroke severity in the data collected by the participating health insurances. To avoid potential selection bias in the comparison of patients admitted before and after the start of the intervention program, the original evaluation plan was modified before study data were received from health insurers, and the primary analysis was conducted with a shortened intervention period ending on February 15, 2020 – before the main effects of the pandemic were observed. For a sensitivity analysis comparing intervention hospitals with non-participating hospitals, the evaluation was run for the full initially planned intervention period (until July 31, 2020, including the first months of the COVID-19 pandemic) because pandemic related effects were assumed to be equal for both hospital groups.

Ethics Approval

The ANNOTeM study has been approved by the ethics committee (Charité Campus Mitte; Berlin/Germany; no. EA1/078/10 and subsequently by the responsible ethics committees in Brandenburg (AS 90(bB)/2018) and Mecklenburg-Western Pomerania (BB 057/18)) and the Data Protection Department of the Charité. According to the favorable votes of the ethics committees, informed consent for participation in this study was not necessary.

Results

Patients

A total of 2,306 patients were included in intervention hospitals before the implementation of the ANNOTeM network between October 1, 2014, and March 31, 2017. A total of 1,418 patients were included in intervention hospitals between November 16, 2017, and February 15, 2020, after the implementation of the program. For details, see Figure 2.

Table 2 shows baseline characteristics of the study populations. Compared to the pre-implementation period, patients of the intervention hospitals were slightly older (76.7 years, ±12.8 vs. 75.8 years, ±13.0) during the post-implementation period and had more often ambulatory care nursing (41.0% vs. 36.9%) or nursing home care (11.1% vs. 9.5%) before their index event. In both the post-implementation and the pre-implementation periods, the most frequent diagnosis was stroke (90% and 92%, respectively). Non-stroke diagnoses consisted of status epilepticus/coma (8.0% in the post-implementation period vs. 6.3% in the pre-implementation period), meningitis/encephalitis (1.8% vs. 1.3%), and acute spinal cord injury/paraplegia (0.6% vs. 0.6%).

Primary Outcome

The primary composite outcome occurred in 829/2,306 (35.9%) patients during the pre-implementation period and in 479/1,418 (33.8%) patients during the post-implementation period. After adjusting for age and sex, patients of the post-implementation period had a statistically significantly lower relative hazard for the primary composite outcome (adjusted hazard ratio [HR], 0.89; 95% CI: 0.79–0.99; $p = 0.04$). This corresponded to an adjusted relative risk reduction of −3.2%. Table 3 shows the results for the primary composite outcome.

Subgroup analyses revealed no statistically significant interaction between subgroups for the primary outcome (Table 4). In the extended observation period of 120 days within hospital admission, the primary composite outcome occurred in 884/2,305 (38.4%) patients before implementation of the intervention program and 516/1,417 (36.4%) patients after implementation (adjusted HR, 0.89; 95% CI: 0.80–1.00).

Secondary Outcomes

The operation and procedure code for treatment ≥24 hours on a stroke unit in all patients with ischemic stroke was significantly more often fulfilled during the post-implementation period compared to the pre-implementation period (322/1,545 (20.8%) vs. 219/1,636 (13.4%); $p < 0.001$). Intravenous thrombolysis was given more often in the post-implementation period compared to pre-implementation (160/1,545 (10.4%) patients vs. 147/1,636 (9.0%) patients), but the difference was not significant ($p = 0.19$). The results with adjusted absolute risk reductions for each component of the primary composite outcome (death, new disability with ambulatory care nursing, and new disability with nursing home care) are shown in Table 3.

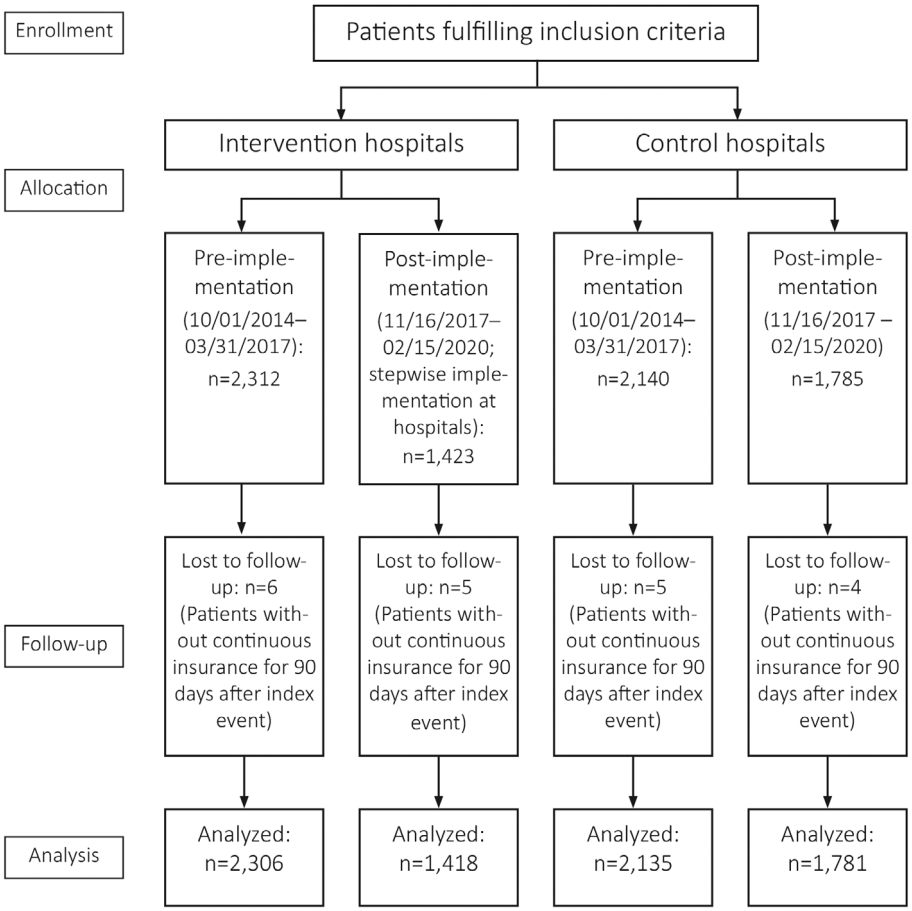

FIGURE 2: CONSORT diagram.

Secondary Analysis

In the group of hospitals without implementation of the ANNOTeM program (control hospitals), patients were, on average older and more likely to be female compared with patients in intervention hospitals both in the pre- and the post-implementation periods. In contrast, the distributions of index diagnoses and paid nursing care before the index event were similar in both hospital groups. Table 2 shows baseline characteristics of patients in both hospital groups.

In the control hospitals, the primary composite outcome occurred in 869/2,135 (40.7%) patients in the pre-implementation period and 757/1,781 (42.5%) patients in the post-implementation period. The adjusted hazard ratio was 1.04 (95% CI: 0.95–1.15), indicating no improvement in the primary composite outcome in the post-implementation period in control hospitals.

In a sensitivity analysis using the full time of the observation including the early COVID-19 pandemic until July 31, 2020, the primary composite outcome occurred in 829/2,306 (35.9%) patients in the pre-implementation period (same as in the primary analysis) and 594/1,761 (33.7%) patients during the post-implementation period (adjusted HR, 0.91; 95% CI: 0.81–1.01) in the intervention hospitals. In control hospitals, the primary composite outcome occurred in 869/2,135 (40.7%) patients in the pre-implementation period and 873/2,069 (42.2%) patients in the post-implementation period (adjusted HR, 1.03; 95% CI: 0.94–1.13).

Discussion

In patients with neurological emergencies admitted to rural hospitals in Northeast Germany, the ANNOTeM intervention program was associated with an improved composite outcome of death, new disability with the need for ambulatory care nursing, or new disability with the need for nursing home care. Similarly, lower risks were also observed in every single outcome. While there were no significant treatment-effect interactions in all subgroups, including stroke and non-stroke patients, the number of patients with hemorrhagic stroke and non-stroke emergencies was small. Therefore, no firm conclusions can be made on the effect of the intervention beyond acute ischemic stroke. As no temporal

TABLE 2. Baseline Characteristics of the Study Populations in the Intervention Hospitals and Control Hospitals, Respectively

	Intervention Hospitals		Control Hospitals	
	Pre-implementation Period	Post-implementation Period	Pre-implementation Period	Post-implementation Period[a]
Patients	2,306	1,418	2,135	1,781
Age (mean ± SD)	75.8 (13.0)	76.7 (12.8)	76.9 (12.4)	77.9 (12.7)
Female sex	1,289 (55.9%)	778 (54.9%)	1,214 (56.9%)	1,018 (57.2%)
Diagnosis				
Stroke	2,118 (91.8%)	1,270 (89.9%)	1,955 (91.6%)	1,594 (89.5%)
Status epilepticus/coma	145 (6.3%)	114 (8.0%)	137 (6.4%)	147 (8.2%)
Meningitis/encephalitis	30 (1.3%)	26 (1.8%)	23 (1.1%)	19 (1.1%)
Acute spinal cord injury/ paraplegia	13 (0.6%)	8 (0.6%)	20 (0.9%)	21 (1.2%)
Care status before index event				
Ambulatory care nursing	850 (36.9%)	581 (41.0%)	829 (38.8%)	724 (40.7%)
Nursing home care	220 (9.5%)	158 (11.1%)	185 (8.7%)	178 (10.0%)

[a]"Post-implementation period" in control hospitals corresponds to the same post-implementation period in intervention hospitals; there was no intervention at control hospitals.
Abbreviation: SD = standard deviation.

TABLE 3. Results, ARRS, aARR, and aHRs with 95% CI for the Primary Composite Outcome and Every Single Outcome

	Pre-implementation Period $n = 2{,}306$		Post-implementation Period $n = 1{,}418$		ARR	aARR	aHR	95% CI
Composite outcome	829/2306	35.9%	479/1418	33.8%	−2.1	−3.2	0.89	0.79–0.99
Death	454/2306	19.7%	263/1418	18.5%	−1.2	−1.8	0.89	0.76–1.03
New disability with ambulatory care nursing	333/1427	23.3%	187/837	22.3%	−1.0	−2.4	0.91	0.76–1.09
New disability with nursing home care	204/2079	9.8%	110/1260	8.7%	−1.1	−1.8	0.82	0.65–1.03

Abbreviation: ARR = absolute risk reduction; aARR = absolute risk reduction adjusted for age and sex; aHR = hazard ratio adjusted for age and sex; CI = confidence interval; HR = hazard ratio.

trends for outcome improvement were seen in hospitals not participating in the ANNOTeM network, the observed effects are very likely the consequence of the intervention.

The ANNOTeM intervention program implemented a quality managed teleneurology network for patients with neurological emergencies in rural hospitals. In contrast to prior studies like TEMPiS,[14] all participating hospitals in our current study already had onsite neurological expertise and/or received expert consultation for stroke via telemedicine (telestroke) before start of the intervention. The intervention contained a bundle of new measures with equal focus on continuous onsite training and education delivered by expert neurologists, up-to-date recommendations for diagnosis and therapy of neurological emergencies, and a quality management program with assessment and improvement of quality

TABLE 4. Results and adjusted HRs for the primary composite outcome according to subgroups and interaction analysis

Subgroups	Pre-implementation Period	Post-implementation Period	Adjusted HR (95% CI)	*p*-Value for Interaction
Age				0.92
<65 yr	53/420 (12.6%)	24/248 (9.7%)	0.77 (0.47–1.24)	
65–74 yr	82/381 (21.5%)	49/227 (21.6%)	1.00 (0.70–1.42)	
75–84 yr	361/914 (39.5%)	181/500 (36.2%)	0.92 (0.77–1.10)	
>84 yr	333/591 (56.3%)	225/443 (50.8%)	0.87 (0.73–1.03)	
Sex				0.98
Female	528/1,289 (41%)	294/778 (37.8%)	0.89 (0.77–1.03)	
Male	301/1,017 (29.6%)	185/640 (28.9%)	0.88 (0.73–1.06)	
Diagnosis				0.71
Ischemic stroke	656/1881 (34.9%)	371/1,154 (32.1%)	0.87 (0.76–0.99)	
Hemorrhagic stroke	128/237 (54%)	70/116 (60.3%)	1.16 (0.87–1.55)	
Other neurological emergencies[a]	45/188 (23.9%)	38/148 (25.7%)	0.95 (0.61–1.47)	
Care status before index event				0.45
Paid nursing care at home	441/1,427 (30.9%)	248/837 (29.6%)	0.96 (0.82–1.12)	
No paid nursing care	375/850 (44.1%)	231/581 (39.8%)	0.88 (0.88–1.03)	

[a]Including status epilepticus, coma, meningitis, encephalitis, acute spinal cord injury/paraplegia.
Abbreviation: HR = hazard ratio.

indicators. Our results indicate that such a quality managed teleneurology network may yield additional benefits for patients even in pre-existing telestroke settings.

The effect size of our intervention may seem, despite the statistical significance, modest and less robust at first glance compared to other interventions like intravenous thrombolysis or mechanical thrombectomy.[18–20] However, the ANNOTeM intervention program was applied to a broad population of patients with stroke and also to patients with other neurological emergencies, whereas thrombolytic therapy and – even more so – endovascular therapy are applied only to a minority of stroke patients.[21] The adjusted absolute risk reduction of 3.2% for this population compares favorably with the estimated absolute risk reductions in all ischemic strokes of 2.6% by intravenous thrombolysis (13% for treated patients but only ~20% eligible) and of 2.6% by thrombectomy (26% for treated patients but only ~10% eligible). Thus, the ANNOTeM intervention program – which can also be regarded as a health care intervention focused on the implementation of evidence-based recommendations in rural areas – was associated with improved outcomes on a broad general population level.

Despite the higher frequency of the operation and procedure code for treatment ≥24 h on a stroke unit in patients with ischemic stroke during the post-implementation period (20.8%) compared to pre-implementation (13.4%), the frequency remained low. This is attributable to strict requirements for this operation and procedure code in the German diagnosis related groups (DRG) system, which includes, for example, (a) bed-side consultations by neurologists from day 1 on after admission or (b) speech therapy or occupational therapy no later than the day after admission if indicated.[22] Because of the shortage of neurologists and speech therapists/occupational therapists in rural hospitals, these strict requirements could only be fulfilled in a minority of patients.

This study has several strengths but also limitations. Strengths included the provision of outcome data by the statutory health insurances, which allowed for completely

investigator-independent assessment of outcomes and very low lost-to-follow-up rates. The outcomes analyzed in this study are both clinically and economically important. Although paid nursing care is usually closely related to dependency in activities of daily living,[23] some patients and relatives may not have applied for paid nursing care from their insurance providers in the observed time period of 90 days after the index hospital admission despite new disabling deficits. Therefore, the observed frequency of paid nursing care may underestimate the real burden of dependency in patients who have experienced a neurological emergency.

The main limitation of this study is the non-randomized design with comparisons between pre- and post-implementation periods and hospitals participating or not participating in the network. However, we adjusted for age and sex and performed a secondary (parallel) analysis analyzing outcomes of patients in similar hospitals of the same region that did not participate in the intervention program. While there was no significant interaction in the subgroup analysis for individual diagnoses (ischemic stroke, hemorrhagic stroke, and the group of other neurological emergencies, that is, status epilepticus, coma, meningitis, encephalitis, acute spinal cord injury/paraplegia), the number of patients with non-stroke emergencies was small, and the confidence intervals do not allow firm conclusions on the effects of the program in patients with other diagnoses than ischemic stroke. Nevertheless, the results can still be interpreted in a way that the ANNOTeM intervention program was associated with improved outcomes of patients with a broad spectrum of neurological emergencies in rural hospitals. The number of patients in the post-implementation period was smaller than initially planned. First, the intervention was implemented gradually at participating hospitals. Second, the study period was shortened because of the changes in patient composition due to pandemic-related avoidance of hospital admission observed in many areas, including ANNOTeM hospitals.[15–17] However, even with the reduced sample size, the primary outcome analysis confirmed the study hypothesis of better outcome after implementing the ANNOTeM intervention program. ANNOTeM poses a multifaceted intervention concept combining elements of managed care, telemedicine, and quality assurance. Similar to the (Tele-) Stroke Unit concept, the used study methods do not allow to delineate the effect size of each part of the multifaceted intervention. Regarding acute teleconsultations, the StrokeDOC trial has shown superiority of real-time, 2-way audio and video telemedicine compared to telephone consultations in acute stroke decision-making.[7] When assessing neurological emergencies other than stroke via telemedicine, local medicolegal regulations regarding ethical and safety aspects have to be considered. In Germany, the legal basis of such approaches is that higher quality of care can be expected if more specialized expertise is involved in clinical management. However, in other countries medicolegal regulations may be stricter regarding expansion of teleneurology beyond stroke, limiting the generalizability of our intervention program. Disparities in acute stroke care between rural and urban areas with a shortage of neurological expertise, absence of specialized facilities and lower utilization of evidence-based treatments in rural areas have been reported from different regions.[24–26] Hence, improving quality of care in time critical neurological emergencies using concepts like ANNOTeM is likely to improve outcomes in different settings. Finally, costs of implementing a managed care network have to be considered. A previous analysis of the TEMPiS project with a similar multidimensional network concept but only applied to patients with acute stroke resulted in complete cost compensation by savings in medium and long-term care.[23] A detailed cost-effectiveness analysis of the ANNOTeM projects is currently in preparation.

Conclusions

The ANNOTeM multicomponent intervention improved outcomes in patients with acute stroke or non-stroke neurological emergencies in rural hospitals with already partially available neurological expertise (either onsite and/or via telemedicine). Enhanced cooperation of tertiary neurological care centers with rural hospitals in a quality managed teleneurology network may improve health outcomes in underserved regions with a shortage of specialist neurologists. In future research, the effects of such multicomponent interventions should be investigated with the inclusion of larger groups of patients with non-stroke neurological emergencies.

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Author Contributions

Hebun Erdur, Joachim E. Weber, Stefanie Ernst, Sarah Theen, Matthias Endres, Tobias Kurth and Heinrich J. Audebert contributed to the conception and design of the study; Hebun Erdur, Joachim E. Weber, Farid I. Kandil, Sarah Theen, Matthias Endres, Tobias Kurth and Heinrich J. Audebert contributed to the acquisition and analysis of data; all authors contributed to drafting the text or preparing the figures.

Potential Conflict Of Interest

Beata Hennig, Katrin C. Reber, and Udo Schneider are employees of the participating statutory health insurances (BARMER, AOK Nordost, and Techniker Krankenkasse, respectively) which may be affected if regulatory authorities in Germany recommend funding the costs of teleneurology or telestroke networks. The other authors declare that they have nothing to report.

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