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Telemedicine in neurology, in stroke patient care and treatment

volume III

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Telemedicine in neurology, volume III: In stroke patient care and treatment

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BRIEF RESEARCH REPORT
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A Case for the Non-Neurologist Telestroke Provider

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Introduction: Telestroke networks have effectively increased the number of ischemic stroke patients who have access to acute stroke therapy. However, the availability of a dedicated group of stroke subspecialists is not always feasible. We hypothesize that rates of tPA recommendation, sensitivity of final diagnosis, and post-tPA hemorrhagic complications do not differ significantly between neurologists and an emergency-medicine physician during telestroke consultations.

Methods: Retrospective review of all telestroke consults performed at a comprehensive stroke center over 1 year. Statistical analysis: Chi squared test.

Results: Three hundred and three consults were performed among 6 spoke sites. 16% (48/303) were completed by the emergency medicine physician; 25% (76/303) were performed by non-stroke-trained neurologists, and 59% (179/303) were completed by a board-certified Vascular Neurologist. Overall rate of tPA recommendation was 40% (104/255), 38% (18/48), 41% (73/179), and 41% (31/76) among the all neurology-trained, emergency medicine-trained, stroke neurology-trained and other neurology- trained provider groups, respectively ($p = 0.427$). Sensitivity of final stroke diagnosis was 77% (14/18) and 72% (75/104) in the emergency-medicine trained and neurology-trained provider groups ($p = 0.777$) No symptomatic hemorrhagic complications following the administration of tPA *via* telestroke consultation occurred in any group over this time period. One asymptomatic intracerebral hemorrhage was observed (0.96% or 1/104) in the neurology-trained provider group.

Discussion/Conclusion: Our results did not illustrate any statistically significant difference between care provided by an emergency medicine-trained physician and neurologists during telestroke consultation. While our study is limited by its relatively low numbers, it suggests that identifying a non-neurologist provider who has requisite clinical experience with acute stroke patients can safely and appropriately provide telestroke consultation. The lack of formerly trained neurologists, therefore, may not need to serve as an impediment to building an effective telestroke network. Future efforts should be focused on illuminating all strategies that facilitate sustainable telestroke implementation.

Keywords: telestroke, telemedicine, stroke, telestroke program, emergency & critical care

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INTRODUCTION

Stroke remains a leading cause of death and disability in the United States, especially in rural, geographically isolated areas (1, 2). Although outcome-changing therapies such as thrombolysis with tissue plasminogen factor (tPA) and endovascular thrombectomy (EVT) are available, these interventions are time-sensitive and limited by patients' proximity to adequately equipped centers (3). Telestroke, usually with neurologist evaluation, has been a critical tool used to make these therapies accessible to patients despite being far from stroke centers. While advances in technology have markedly increased access to audiovisual communication, access to specialists with neurologic expertise continue to be in short supply nationally with insufficient numbers of graduating neurologists only projected to worsen by 2025 (4). However, considering the algorithmic nature of emergency stroke management, how essential is subspecialty care in telestroke evaluation? No formal requirements for the practice of telestroke currently exist, however, the American Telemedicine Association recently advocated that consults be performed by vascular neurologists (5). Previous research has focused on demonstrating the reliability of delivering neurologic care *via* telemedicine as opposed to evaluating the reliability of non-stroke practitioners delivering that care (6).

To bridge the gap between the supply of neurologists and the demand for stroke care, we included an emergency medicine-trained physician in our pool of telestroke providers. The purpose of this article is to determine if a non-neurologist provider with adequate clinical experience with acute stroke can safely and effectively provide telestroke consultation without subspecialist intervention.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at West Virginia University (WVU). Written informed consent was waived and therefore was not required for this study in accordance with national legislation and institutional requirements. A retrospective review of all telestroke consults performed over a 1-year period by our comprehensive stroke center across all six spoke sites was conducted. Spoke sites initiate consults by directly calling the on-call telestroke provider. Following a brief discussion of the relevant clinical details and a review of the patient's computed tomography (CT) scan *via* a cloud-based radiology platform, the telestroke physician conducts an audio-visual consult using a mobile-based encrypted platform with the help of the originating site provider or nurse at bedside. Recommendations regarding patient treatment and disposition are then made. Each formal telestroke evaluation is documented in the hub's electronic medical record. Basic information is collected, including demographic data, location of call, providers involved, relevant time metrics, provisional diagnosis, administration of thrombolytic, or transfer for EVT. Patients are subsequently entered into an internally managed database where outcome information is recorded. Outcomes are obtained *via* the electronic medical record or from information obtained directly from the originating sites during periodic data collection timepoints mandated in the telestroke service contract. This entire process is managed by the telestroke program's coordinator and medical director.

Consults were categorized by three board-certified physician groups: (1) Vascular Neurology, (2) Neurology, or (3) Emergency Medicine. The frequency of tPA use, any radiographic, or clinical evidence of hemorrhage following lytics and sensitivity of initial stroke diagnosis were recorded. Symptomatic intracranial hemorrhage was defined as any acute intracranial hemorrhage on follow-up imaging accompanied by neurologic worsening as defined by an increase of ≥ 4 points on the National Institutes of Health Stroke Scale (NIHSS). Sensitivity of stroke diagnosis was determined based on final ischemic stroke diagnosis at discharge as documented in the medical record. The authors (AA, JC who abstracted this data) were blinded to the identity of the telestroke physician initially involved in the case. Following abstraction, author AP analyzed the results and correlated with the telestroke provider group. In addition to descriptive statistics, we used the Fisher's exact test to calculate *p*-values for any statistically significant findings.

RESULTS

Three hundred and three telestroke consults were performed over six spoke sites during the study period. 59% (179) of consults were completed by board-certified vascular neurologists, 25% (76) of consults were completed by neurologists, and 16% (48) of consults were completed by an emergency medicine physician. The overall rate of tPA administration was similar between all three provider groups; 41% (73), 41% (31), and 38% (18) in the vascular neurologist, neurologist, and emergency medicine groups, respectively ($P = 0.427$). The sensitivity of final ischemic stroke diagnosis among those who received tPA was also similar between the neurology-trained and emergency medicine-trained provider groups; 72% (75), and 77% (14), respectively ($P = 0.777$). No symptomatic or fatal hemorrhages were observed among patients administered tPA by any of the groups. One non-fatal, asymptomatic intracerebral hemorrhage was observed among the patients administered tPA by the neurology-trained provider group. No radiographic or clinical evidence of hemorrhage occurred among patients given tPA by the emergency medicine-trained provider group.

DISCUSSION/CONCLUSION

The rate of tPA in acute ischemic stroke has nearly doubled from the early 2000's and telestroke has been a considerable basis for its expanded use (7, 8). However, a rural-urban disparity persists with urban stroke patients eligible for thrombolysis at least twice as likely to receive it as compared to their rural counterparts (2). Although, recent rural telestroke networks have demonstrated significant impact in tPA use, the evaluating telestroke physician has traditionally been a neurologist (5, 9). In fact, lack of access to a neurologist has been identified as a significant barrier to the use of tPA in ischemic stroke, initially setting the stage for

telestroke network creation (10). However, there are currently only 60 neurologists practicing in our state, approximately half of the 145 estimated by the American Academy of Neurology needed to adequately serve this population by 2025 (4, 11). The demand for neurologists already exceeds supply in most states, and this is only projected to worsen by 2025 in the face of the aging US population and the increasing utilization of neurologic services (4). In the face of this growing demand in an increasingly neurologist-strapped environment, we must design a system of care that allocates our limited resources wisely while still delivering safe and effective care to isolated, rural populations far from stroke centers. The benefit of advanced nurse practitioners with subspecialty expertise is well-established and similar models in vascular neurology have been identified but large-scale adoption is lagging (12).

Mobile Stroke Units (MSU) are ambulances equipped with a CT scanner (and in some cases can also perform advanced CT angiography and perfusion) outfitted for thrombolysis administration. In efforts to increase the efficiency of acute stroke treatment, this model brings tPA to the stroke patient in the field. MSU implementation studies have repeatedly demonstrated both feasibility and a reduction in time to treatment (13). They also may be cost effective, at least in densely populated urban settings where multiple tertiary stroke care centers are available (14–16). Their role in rural and resource-limited settings, however, has not been systematically evaluated (17). Furthermore, MSUs are still dependent on a *neurologist* present and staffing these stroke calls in the ambulance. Given these inherent challenges, they are unlikely to be widely adopted in rural settings where effective telestroke and pre-hospital triage systems have been demonstrated to be more impactful (17).

Our results failed to demonstrate statistically significant differences in tPA administration rates, sensitivity of ischemic stroke definitive diagnosis, and hemorrhagic complications between care provided by neurologists and care provided by an emergency medicine physician during telestroke consultation. This suggests that, with adequate clinical experience in management of acute stroke patients and familiarity with thrombolytic inclusion and exclusion criteria, non-neurologist providers can provide safe, and equally effective consultation *via* telestroke. The lack of formerly trained neurologists, therefore, may not necessarily be a fixed barrier to building an effective telestroke network going forward.

It is important to note the several limitations of this study, including its retrospective nature which introduces a risk of selection bias. Also, only one non-neurologist provider was included on the telestroke team for this study, and their training in emergency medicine, a field with significant experience and training in the diagnosis and management of acute ischemic stroke, may have contributed to the similarities between provider groups. Our results, therefore, cannot serve as definitive evidence supporting the broader application of non-neurologists providing telestroke services; rather, they challenge us to seek innovative solutions for the common yet critical clinical field of acute stroke care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JC made substantial contributions to analyzing and interpreting data for the work, drafting the work, and revising the work to be published. AA made substantial contributions to the conception and design of the work, the acquisition and analysis of data for the work, and the drafting and revision of the work to be published. AP made substantial contributions to the acquisition and interpretation of data for the work, and the revision of the work to be published. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Content Analysis of Stroke Teleconsultation Recordings in the Moravian-Silesian Region, Czech Republic

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Background: Direct teleconsultations between emergency medical services (EMS) crews and hospital-based stroke neurologists are mandated in the Czech Republic as triage and prenotification tool in acute stroke patients. The main aim of this study was to analyze the efficacy as well as quality of such teleconsultations in daily clinical practice.

Methods: This is a descriptive analysis of teleconsultations between EMS paramedic crews and hospital-based neurologists in a geographically defined region of the Czech Republic (Moravian-Silesian region) between October 2018 to December 2018. All teleconsultations were analyzed for length and content. Content analysis included the following information: date, age, sex, prehospital neurological deficit(s), known/unknown time of symptom onset, anticoagulation status, vital signs, premorbid disability, and patient ID/insurance company number.

Results: Within the study period, paramedics conducted 522 calls across 6 stroke centers. Of these, 334 (64%) calls were conducted because patients met pre-established prehospital criteria for suspected acute stroke. Median call duration was 1 min 44 s ± 56 s (minimum 50 s, maximum 5 min 5 s). Amongst the analyzed prehospital teleconsultations, stroke onset time was reported in 95% of cases, neurological deficit in 96%, significant co-morbidities in 53%, premorbid disability in 37%, and anticoagulation status in 53%.

Conclusion: Teleconsultations between paramedics and hospital-based neurologists are not time-consuming. Stroke onset time and severity of neurological deficit are consistently communicated, however other important information such as comorbidities, premorbid disability, and anticoagulation status are reported inconsistently.

Keywords: ischemic stroke, prehospital care, emergency medical service, prenotification, teleconsultation

INTRODUCTION

Acute ischemic stroke is a medical emergency with effective but time-limited treatment including intravenous thrombolysis and/or endovascular (mechanical) thrombectomy. The sooner therapy is provided, the better clinical outcome (1, 2). Every minute of delay in treatment initiation results in an average of 1.8 days of healthy life lost (3).

Prenotification by EMS has been associated with decreased prehospital (4–6) as well as in-hospital times (4, 5, 7–10) and increased thrombolytic administration rates (5, 9, 10). Prenotification by EMS can further facilitate early activation of stroke interventional teams.

Teleconsultation could serve as both a prehospital triage tool (11) and a prenotification (12). Advantages of teleconsultation include the provision of expert guidance for paramedic teams in the prehospital environment, more accurate decision-making for patient transportation decisions, and early activation of ED and stroke interventional teams to reduce treatment delays upon arrival at destination. Proposed disadvantages of teleconsultation include the potential time burden of teleconsultation calls and the inconsistent quality of communicated information. The main goal of this study is to assess the efficacy and measure teleconsultation quality in the management of acute stroke patients.

MATERIALS AND METHODS

This is a descriptive observational study of all available teleconsultation events for suspected acute ischemic stroke cases involving prehospital teleconsultations between EMS and stroke neurologists within the geographically defined Moravian-Silesian region [1 comprehensive stroke center (CSC), 5 primary stroke centers (PSC), catchment area: 1.2 million inhabitants] between October 2018 to December 2018. This study assessed audio-recordings of all recorded prehospital communications between the EMS and hospital-based neurologists. The Ethics Committee of the University Hospital Ostrava approved the study.

Organization of Stroke Services in the Czech Republic

There are currently 13 comprehensive stroke centers (CSC) performing endovascular therapy and 32 primary centers capable of administering intravenous thrombolysis (IVT) in the Czech Republic.

Based on legislation in the Czech Republic, every suspected stroke case must be tele-consulted with a hospital-based neurologist. EMS providers are trained to activate stroke protocols if a patient meets the following criteria: sudden onset of neurological deficit (1 major symptom—hemiparesis/plegia, facial droop or speech disturbances or 2 following minor symptoms—hemihypesthesia, dysarthria, hemianopsia, loss of consciousness, diplopia, atypical "worst-ever" headache, meningism, or vertigo with nausea and vomiting) with sudden onset and last seen normal in the past 24 h. EMS providers are trained regularly by stroke physician (i.e., PowerPoint presentation/webinar with testing of knowledge at the end of session. Ideally, EMS personnel should convey all relevant information to primary treating physician (i.e., stroke neurologist) in order to make patient-centered decisions about transport and treatment strategy (13). Teleconsultation represents a critical opportunity to provide expert-guided, individualized care to every stroke patient.

Each of the 14 regions within the Czech Republic has one EMS headquarter. In 2016, the validated prehospital stroke scale called FAST PLUS was implemented in the Moravian-Silesian region to test for potential large vessel occlusion strokes (14). The FAST PLUS test positivity helps to guide the EMS crew and to initiate a teleconsultation with the hospital-based neurologist at the designated comprehensive stroke center (CSC). The stroke team then determines whether the patient is to be transported directly to a CSC or is first to be directed to a PSC. If patient is directed to PSC, EMS prenotification call (i.e., secondary call—for details see the **Figure 1**) is provided in advance of patient arrival to the receiving stroke team at PSC. Patients with a negative FAST PLUS are teleconsulted with the nearest PSC and this teleconsultation serves also as prenotification. For this study, all available data from the Moravian-Silesian EMS teleconsultations were analyzed.

Teleconsultations Between EMS and Hospital-Based Neurologist

All teleconsultations between EMS and a hospital-based neurologist are connected via EMS dispatchers and recorded. For the purpose of this study, recorded teleconsultations between EMS crews and hospital-based neurologists from all stroke centers in the Moravian-Silesian region were stored on an encrypted compact disc (CD). Personal data was handled in accordance with Article XIII of the GDPR Regulation.

Analysis of Teleconsultations

Content analysis was performed by a trained neurologist (L.K). Incomplete (interrupted calls)/low quality calls (calls with technical problems), calls which did not fulfill the criteria of suspected acute stroke (i.e., stroke onset/last seen normal > 24 h or no major stroke sign or only 1 minor stroke sign) and secondary calls (subsequent PSC prenotifications) were excluded (**Figure 1**). Date and length of calls were recorded. The presence or absence of the following information was collected: age, sex, neurological deficit (1 major symptom—hemiparesis/plegia, facial droop or speech disturbances or 2 minor symptoms—hemihypesthesia, dysarthria, hemianopsia, loss of consciousness, diplopia, atypical "worst-ever" headache, meningism or vertigo with nausea and vomiting), FAST PLUS test positivity (if severe unilateral hemiparesis/hemiplegia is present), stroke onset time/last seen normal/wake-up stroke or unknown stroke onset, pre-morbid status (independent, dependent or modified Rankin Scale, if available), anticoagulation therapy (warfarin or new oral anticoagulation), significant co-morbidities (e.g., prior stroke, history of epilepsy, severe trauma/surgery within last 2 weeks, gastrointestinal bleeding within 3 weeks, cancer), all other co-morbidities (if available), insurance identification number, vital functions measured by paramedics (including blood pressure, level of glycemia, level of consciousness, heart rate, oxygen

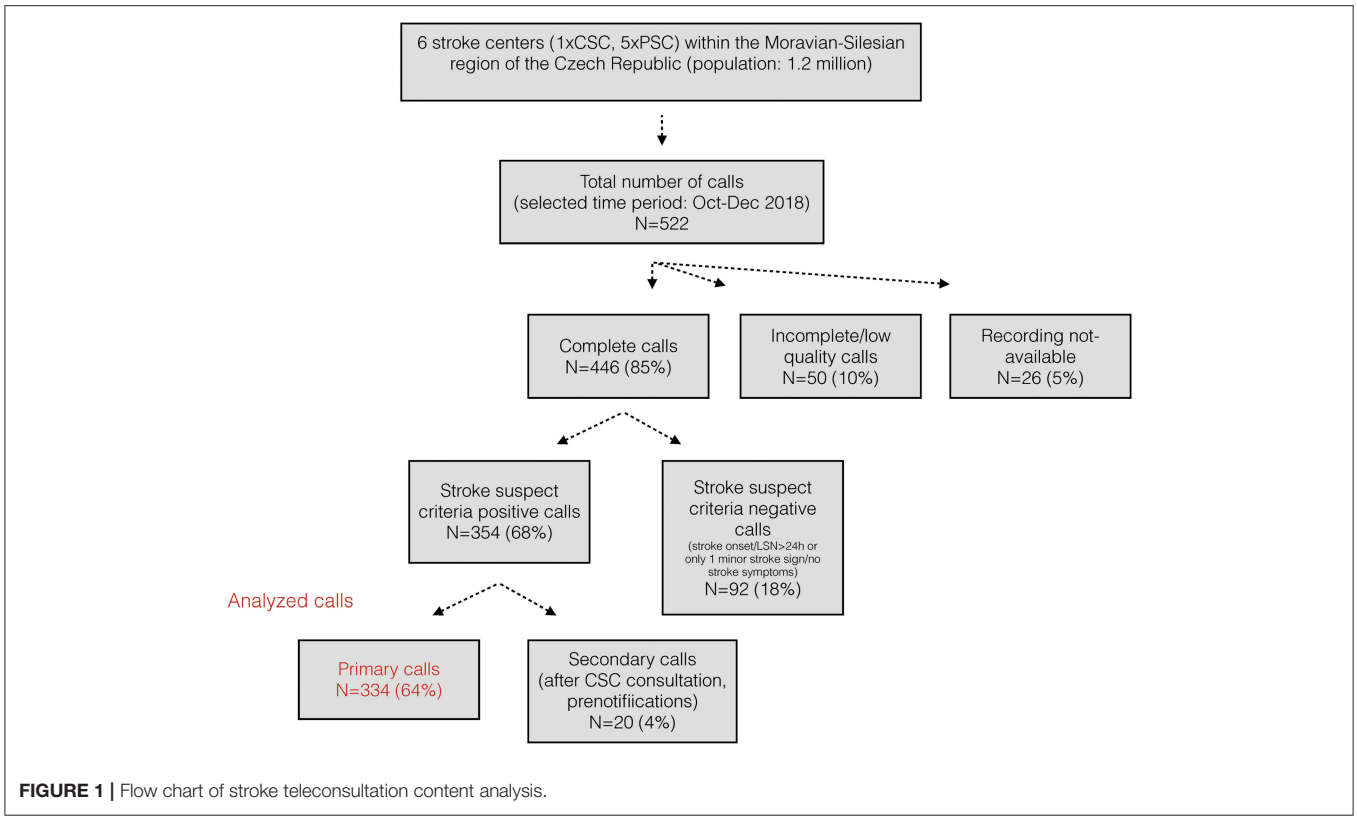

FIGURE 1 | Flow chart of stroke teleconsultation content analysis.

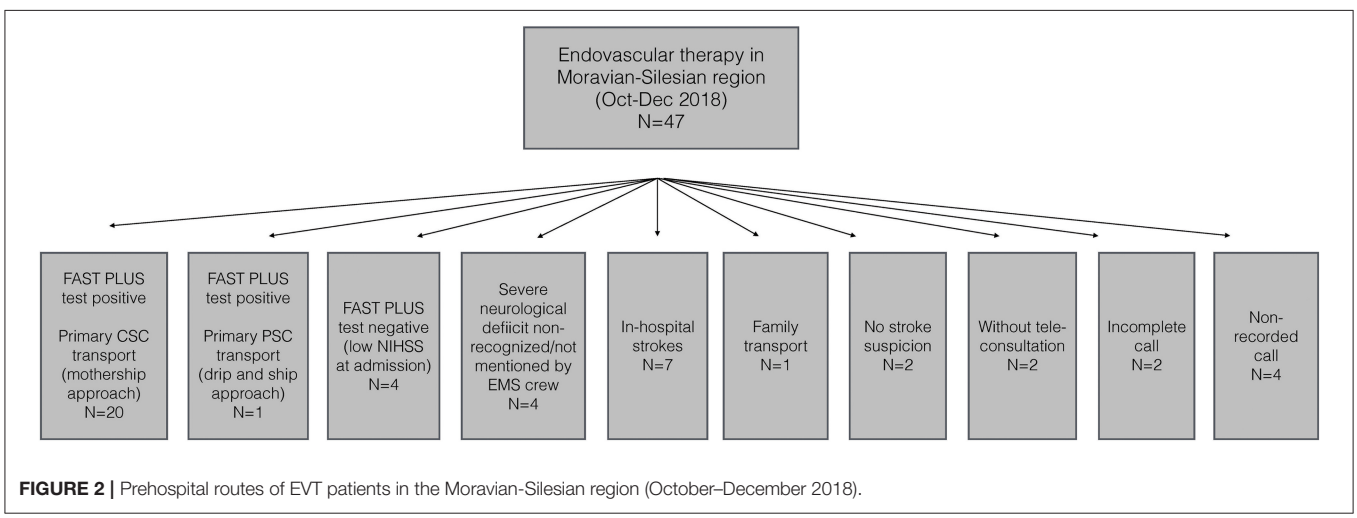

FIGURE 2 | Prehospital routes of EVT patients in the Moravian-Silesian region (October–December 2018).

saturation, heart rhythm). Final diagnosis and treatment of patients transported to the CSC was also collected. Standard descriptive statistics were used to measure the central tendency and variability of baseline characteristics.

RESULTS

Within study period, there were 889 hospital admissions in the Moravian-Silesian region with diagnosis of any (acute and non-acute) ischemic stroke or TIA. Altogether 522 teleconsultations were recorded during the study period. Of these, 334 (64%) calls were triggered by correct identification of patients meeting pre-established prehospital stroke triage criteria (i.e., stroke onset/last seen normal <24 h or no major stroke sign or only 1 minor stroke sign (please see **Figure 1**).

Altogether 152 (17%) were treated with IVT and 47 (5%) patients underwent EVT. **Figure 2** summarizes prehospital routes of EVT patients within study period.

Of 87 patients who were transported directly to a CSC, hospital discharge diagnosis was ischemic stroke in 76%,

TABLE 1 | Teleconsultation content analysis.

		Primary calls
Total No. of calls		334
Duration of call, median (IQR)		01:44 (01:20–02:30)
Timing of call		
Weekday	Working hours	76%
	After working hours (>17:00)	24%
Weekend/holidays		27%
Identification of the patients		
	Reported vs. non-reported	46 and 54%
Identification reported	ID (full name and/or patient identification number)	46%
	Sex, male (%)	49%
	Age, yes/no	100%
Patients factors	Initial major and non-major deficit	96 and 4%
	Percentage of FAST PLUS positive patients	19%
	Stroke onset/last seen normal/wake-up stroke symptoms/unknown, yes/no	95%
	Comorbidities mentioned, yes/no	53%
	Premorbid status mentioned, yes/no	37%
	Anticoagulation therapy, yes/no	53%
	Insurance company, yes/no	4%
Vital functions	Blood pressure	48%
	Glycemia	27%
	Level of consciousness	7%
	Heart rate	8%
	Oxygen saturation level	8%
	Heart rhythm	3%

hemorrhagic stroke in 14%, and stroke mimic in 10%. Twenty-five patients with acute ischemic stroke (AIS) were treated with IVT, another 18 with both EVT and IVT, 2 patients underwent only EVT and 21 patients were treated conservatively.

Median call duration was 1 min 44 s ± 56 s (minimum 50 s, maximum 5 min 5 s). Six percent of calls lasted <1 min and 86% <3 min. Seventy-three percent of calls were conducted during weekdays and 67% during working hours (7:00–17:00).

Stroke onset time was reported in 95% of cases, neurological deficit in 96%, significant co-morbidities in 53%, premorbid disability affecting patient activities of daily living in 37%, and active anticoagulation therapy in 53%. Blood pressure was reported in 48%, level of glycemia in 27%, oxygen saturation level in 8%, heart rate in 8%, level of consciousness in 7%, and heart rhythm in 3% (**Table 1**).

DISCUSSION

Our study analyzed teleconsultations between EMS crews and hospital-based neurologists for all suspected stroke cases. One major finding of our study is that teleconsultation itself does not contribute substantially to any pre-hospital delay in stroke management. The duration of the majority (59%) of calls was between 1 and 2 min, and the most critical elements (stroke symptom onset or last seen normal time and stroke severity) were consistently reported in a manner allowing enhancing decision-making. Teleconsultation between EMS crews and neurologists is likely to aid with more efficient transportation decisions (i.e., PSC vs. CSC destination) and early activation of stroke intervention teams when indicated and feasible.

Median door-to-needle time (DNT) from all stroke centers within study period was 23 min (IQR 23 min−30 min). Undoubtedly, teleconsultations also contribute to this result.

Accurate decision-making depends on the quality of information provided during the calls. In our study, we found that certain critical pieces of information were provided in the majority of cases (e.g., onset time, severity of neurological deficit, age). However, other important elements, such as anticoagulation status, significant co-morbidities, and premorbid disability were provided inconsistently. Information quality was not associated with the length of teleconsultation.

Communication between paramedics and hospital-based teams is a common practice in medicine. For example, in STEMI cases, EKGs are often transmitted to the hospital and prenotification is provided prior to patient arrival to ensure early mobilization of cardiac catheterization teams, thereby reducing the treatment delays (15). EMS-stroke teleconsultations were highly variable in terms of the quality of provided information. This might be explained by the fact that EMS crews are often faced with certain challenges, including time limitations, environmental factors, and patient factors that can make it difficult to gather and report all relevant information. Similarly, neurologists may have their own "habits" of how they ask for information that may impact if important information is elicited or not. For a future we plan to develop, implement structured checklist-style tool which might be useful to standardize and make these conversations more effective.

The strength of our study is that majority of acute stroke cases is teleconsulted (the least number would be 59% but we conclude from our observations that is much more). On the other hand, the limitation is that we are unable to track disposition endpoint based on the available data and unable to determine how many decisions were "altered" directly due to the teleconsultation itself—largely because this is an established protocol assessed by observational study, so we didn't have a "non-consult" cohort to compare outcomes against.

CONCLUSION

In conclusion, teleconsultations represent a feasible tool for stroke triage in prehospital settings. However, inconsistent quality of communicated information presents a potential barrier to optimizing this strategy. Implementation of structured checklist-style communication tool may enhance teleconsultation efficiency by ensuring that all the key information is conveyed and captured. Additional prospective studies examining the utility, cost-effectiveness, and benefit on patients outcomes are needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University Hospital Ostrava, Czech Republic. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LK, KL, OV, RM, MB, and MH: conceptualization. LK, KL, MC, and DH: formal analysis, data curation, and writing—original draft. OV, RM, and MB: writing—review and editing. OV, MH, MB, and RM: supervision. All authors contributed to the article and approved the submitted version.

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Staff and Facility Utilization in Direct Patient Transfer to the Comprehensive Stroke Center: Testing a Real-Time Location System for Automatic Patient Pathway Characterization

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Introduction: Starting reperfusion therapies as early as possible in acute ischemic strokes are of utmost importance to improve outcomes. The Comprehensive Stroke Centers (CSCs) can use surveys, shadowing personnel or perform journal analysis to improve logistics, which can be labor intensive, lack accuracy, and disturb the staff by requiring manual intervention. The aim of this study was to measure transport times, facility usage, and patient–staff colocalization with an automated real-time location system (RTLS).

Patients and Methods: We tested IR detection of patient wristbands and staff badges in parallel with a period when the triage of stroke patients was changed from admission to the emergency room (ER) to direct admission to neuroradiology.

Results: In total, 281 patients were enrolled. In 242/281 (86%) of cases, stroke patient logistics could be detected. Consistent patient–staff colocalizations were detected in 177/281 (63%) of cases. Bypassing the ER led to a significant decrease in median time neurologists spent with patients (from 15 to 9 min), but to an increase of the time nurses spent with patients (from 13 to 22 min; $p = 0.036$). Ischemic stroke patients used the most staff time (median 25 min) compared to hemorrhagic stroke patients (median 13 min) and stroke mimics (median 15 min).

Discussion: Time spent with patients increased for nurses, but decreased for neurologists after direct triage to the CSC. While lower in-hospital transport times were detected, time spent in neuroradiology (CT room and waiting) remained unchanged.

Conclusion: The RTLS could be used to measure the timestamps in stroke pathways and assist in staff allocation.

Keywords: triage, quality—hospital staff, logistics, nursing & care, telemedicine

INTRODUCTION

Stroke is a major source of morbidity and mortality and is now the second leading cause of death worldwide, accounting for 5.5 million deaths in 2016 (1). For every minute passing after a proximal middle cerebral artery occlusion without reperfusion therapy, 2 million brain neurons die (2). Therefore, when someone suffers from a stroke, it is critical to reach the hospital quickly and medical staff needs to act fast. For best functional outcome, an ischemic stroke victim with a large vessel occlusion needs to be treated in hospitals with access to endovascular thrombectomy (EVT) (3, 4).

The Karolinska University Hospital and the Stockholm Region developed and implemented the Stockholm Stroke Triage System, a three-step prehospital evaluation for primary stroke center (PSC) bypass for patients with suspected stroke and a moderate-to-severe hemiparesis. Bypass was initiated following teleconsultation between ambulance staff and a stroke physician at the Comprehensive Stroke Center (CSC) (5). Those approved for PSC bypass was directly transferred from the ambulance to the CSC department of neuroradiology, bypassing the emergency room (ER), if cardiorespiratory stable and not unconscious (5). The main goal of the Stockholm Stroke Triage System was to reduce the time from symptom onset to initiation of EVT without delaying intravenous thrombolysis (IVT), which is currently the central goal of acute stroke triage (6, 7). In parallel with the implementation of the new triage system, we conducted an observational study where the timestamps of the care pathway were automatically recorded by a real-time location system (RTLS), tracking patients and staff without direct observation by researchers and without interfering with the new pathway workflow. The principal aim of this study was to characterize the changes in logistics and staffing following PSC and ER bypass. We hypothesized that: (1) PSC and ER bypass of patients with severe symptoms to a CSC would result in an increase of the time spent by medical staff with more severely disabled patients (suspected to have large vessel occlusions) and (2) time patients spent at the neuroradiology department before a treatment decision for EVT was made would increase because initial medical assessment shifted from the ER to the neuroradiology unit. The impact of this study results could potentially be used for the changes in staffing and resource allocation.

PATIENTS AND METHODS

The study was conducted jointly by the Department of Neurology at the Karolinska University Hospital and by Philips Research between May 2017 and September 2018.

Hardware Equipment

The RTLS system (CenTrak®, Newtown, Philadelphia, USA) based on IR and radiofrequency (RF) technology was installed at the Karolinska University Hospital in Solna (**Supplementary Material**, RTLS diagram). The choice of IR in detriment of other technologies such as low-energy based Wi-Fi, ultrasound, or Bluetooth was made to offer room-level accuracy, since signal leaking outside room range was more frequent in all the latter. The hardware system consists of tags, monitors, and virtual walls. Tags with IR sensors were applied to staff (badges) and patients (wrist bands), which interacted with monitors when they acquire line of sight. Monitors were placed on room ceilings and mapped to a location, so that when a tag reported to a specific monitor, the system could identify in which room it occurred. Finally, virtual walls acted similarly to monitors in that they were tied to a location; however, they were used to delimitate rooms.

Patient Care Pathway Detection

To study and track the stroke patient pathway, IR monitors and virtual walls were installed in every location where a stroke patient would be transported. In total, 23 locations were equipped with monitors including ambulance bays, the ER, elevator halls, neuroradiology entry door, CT scan rooms, stroke unit entry door, and corridors where patients were transported. In addition, a wristband tag was placed on each patient and all the staff members were given a badge tag, which would report their location to the monitors. Wristbands were placed on patients at their arrival, if a stroke was suspected. The medical staff participating in this study consisted of neurologists, stroke nurses, neuroradiologists, and radiology nurses. Only staff instructed and delegated to participate in the study could include patients (about two-thirds of the stroke team workforce). The remaining workforce not participating in the study consisted of short term or shift workers who did not attend training or did not provide consent. Most often, a location would be enough in detecting a pathway step; however, there were some exceptions. For example, while the RTLS data indicate when a patient enters a CT room, it is unable to identify the specific procedures that occur inside the room, e.g., physical examination, administration of IVT. The RTLS had no connection to medical records of patients and, therefore, lacked context. To solve this challenge, some patient-level data were gathered in the form of a handwritten logbook filled by nurses along with manually retrieved electronic health record (EHR) data to double-check both the automatically generated RTLS data and the logbook. The main data points used for this purpose were the stroke type (ischemic, hemorrhagic) or if the patient had a stroke mimic and whether they were transferred from the ER or from another hospital (secondary transfer). The main pathways that the RTLS would cover were: (1) time elapsed between hospital arrival at ER or arrival at neuroradiology ambulance bay until exiting the CT room after imaging; (2) transport times between arrival point of entry and reaching the holding room at neuroradiology; (3) time spent waiting for a CT scan (on holding outside the CT room) and time elapsed in the CT room; (4) total time spent in the neuroradiology department (including time spent in CT scanning, clinical evaluation, IVT, and endovascular treatment at the neurointerventional suite); and (5) time measured when a nurse colocalized with the patient in the same room. The Department of Neuroradiology is equipped with two CT rooms and two conventional neuroendovascular rooms.

Case Filtering Algorithm

The RTLS system continually reported every few seconds while a tag was moving and dropped down to every 5 min if the tag had been stationary for sometime. In addition, there was a

period where the nurse was transporting the tag, which contained reports that were not relevant to the patient care pathway. To overcome this, we used a simple algorithm to filter out unnecessary data. First, we only kept tags that had a patient associated with them in the logbook and only the data for the day of patient arrival. Finally, we filtered out every report before one of the starting locations (either triage room or neuroradiology reception) was detected. Finally, we also checked the presence of the end location (elevators near neuroradiology reception) of the patient pathway. If all the conditions were met, the patient case was kept for further analysis.

Analysis of Missing Data

Patient tags and staff badges always needed to be uncovered to be detected by IR sensors. Clothes, blankets, or other material sometimes obscured the tags and resulted in temporary loss of location. For instance, if CT room location was missing in one patient with a consistent stroke pathway, the patient was excluded from the "time in CT room" measurement.

Phases of the Study

The trial was divided into two phases. Phase I ran from 1 May, 2017 until 10 October, 2017 and phase II started on 10 October, 2017, immediately after phase I, and ran until 31 September, 2018.

Baseline Pathway (Phase I)

During baseline, the stroke care pathway was organized as follows (**Figure 1,** Left): the ambulance delivered all the suspected stroke patients to the ER after prehospital assessment using the Face, Arm, Speech, and Time (FAST) test without stroke physician prenotification. The neurologist on call (staffing the ER) immediately examined the patient to make an initial diagnosis at the ER including the National Institutes of Health Stroke Scale (NIHSS) assessment. Patient registration in the EHR, printing of ID tags, history taking, current medication check, vital signs, blood work (if indicated) and intravenous medication were also performed at the ER by a local nurse. An electrocardiogram (EKG) performed in the presence of angina pectoris was also performed by the local nurse. If the condition of the patient was assessed as a stroke, they were transported to the neuroradiology department passing two elevators and a corridor. Specific tasks for the stroke nurse at this stage were to collect personal belongings of the patient, assist with bed transport to neuroradiology, opening doors, move the patient to the CT board, communicate brief clinical information to the CT nurse, recheck the intravenous routes of the patient, change oxygen supply from portable to general, recheck vital signs at the CT room, calculate the dose for thrombolysis (alteplase) based on visual weight estimation, and prepare for and/or administer alteplase or intravenous medication when required. A CT scan was performed to determine the type of stroke. If the stroke was ischemic, then IVT was administered to eligible patients. CT angiography (CTA) and CT perfusion (CTP) were performed in all ischemic stroke patients to assess EVT indication and eligibility. During image postprocessing and multidisciplinary discussion between the neurologist, neuroradiologist, and interventional neuroradiologist, the patients and the stroke team moved to the neurointerventional suite on the same floor. Patients with hemorrhagic stroke were also evaluated with CTA unless contraindicated because of renal failure or in the presence of typical small vessel, small volume hemorrhage coincident with severe hypertension on arrival. Hemorrhagic stroke patients were either transferred directly to the stroke unit, to intensive care, or emergency neurosurgery, all located on the different floors. Patients assessed as having a stroke mimic in the ER would be referred to neuroradiology if their condition necessitated further radiological investigation (e.g., first seizure, suspected tumor) acutely or after admission to an in-patient ward.

New Triage Pathway (Phase II)

The stroke care pathway was reorganized as follows (**Figure 1,** Right): the ambulance nurses performed an initial assessment using the FAST test. If the patient was FAST test positive, an additional test was performed. If the patient scored $\geq$ 2 NIHSS points each in both the ipsilateral arm and leg (called the A2L2 test), the ambulance nurse teleconsulted the neurologist at the CSC. Conversely, in A2L2-negative cases, the ambulances prenotified the nearest PSC. During the CSC teleconsultation, the prehospital suspicion of stroke was confirmed, information on the premorbid level of function and comorbidities of patient was gathered, and a final triage decision was made, whether PSC bypass was indicated or not. Triage positive (A2L2 and teleconsult positive) cases were directly delivered to the neuroradiology department through a dedicated ambulance bay, eliminating ER assessment (otherwise conducted in a separate building). During ambulance transport, the stroke nurse at the stroke unit registered the patient in the EHR, printed ID tags, informed the ward team about the patient, prepared blood typing requests, checked the weight of the patient in the EHR and calculated the dose for thrombolysis, and loaded the pump for intravenous administration of thrombolysis. The neurologist checked current medication and previous medical history in the EHR. After patient arrival, vital signs, blood work, or EKG, when indicated, were then performed by the stroke nurse in the CT room or during holding time waiting for a CT scan. The neurologist examined the patient and performed the NIHSS assessment in the CT room. Specific tasks performed by the stroke nurse that followed in the CT room were then similar to the tasks in the baseline pathway. In both study phases, the neurologist and the stroke nurse were deployed to arrival of patient at the same time and the stroke nurse inserted a urinary catheter in all the patients selected for thrombectomy.

Statistical Analysis

Descriptive statistics such as the one-way and two-way ANOVA with the Tukey's *post-hoc* tests were used to describe and detect the significant differences between the groups. Data are presented as median and interquartile ranges (IQRs). The RStudio software (Boston, MA, USA) was used for facility pathway analyses.

Ethical Approval

This study was approved by the Stockholm Regional Ethical Council (nr 2017/511-31/4). Oral informed consent was obtained by a nurse or a physician immediately at arrival from patients

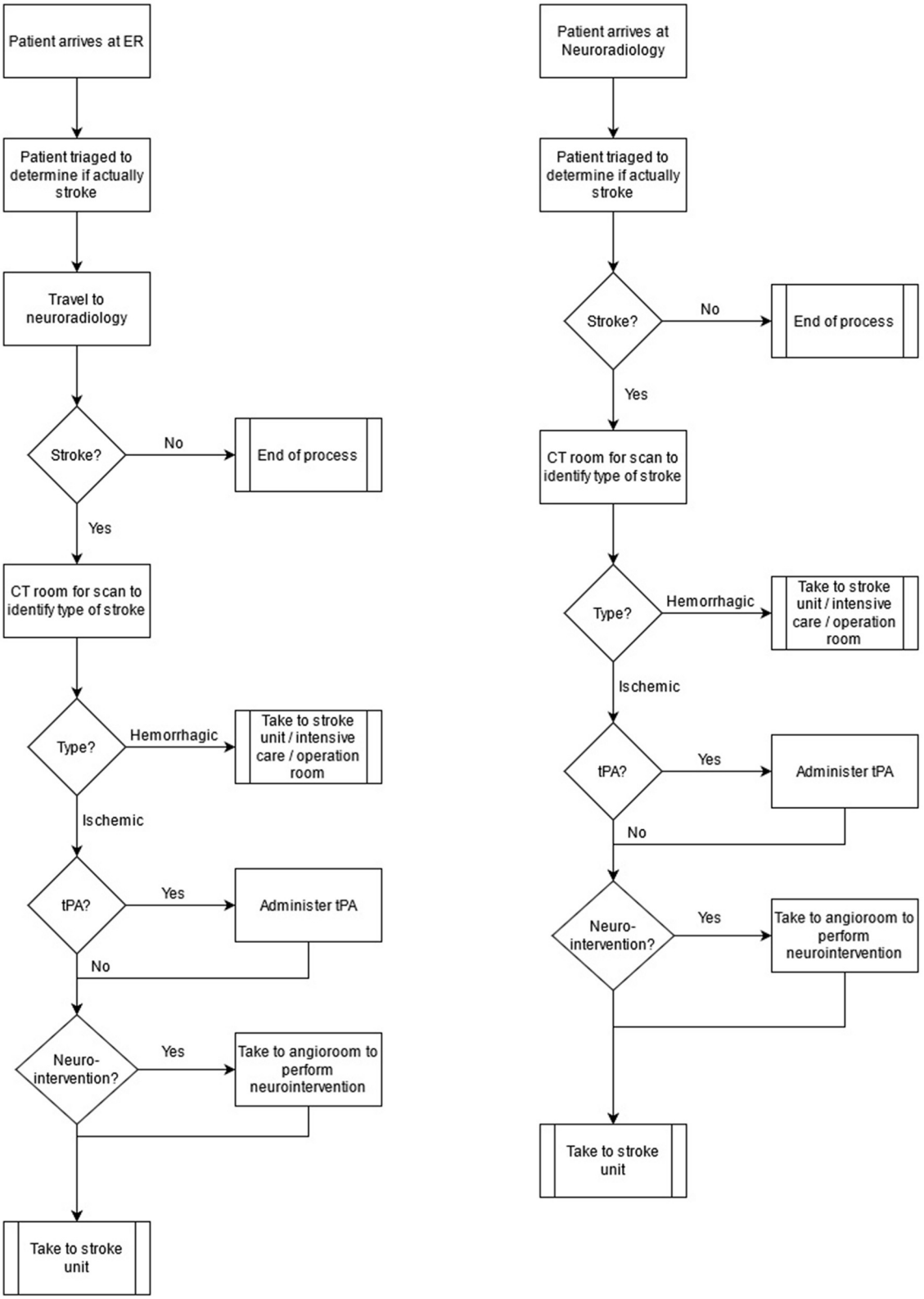

FIGURE 1 | Stroke workflow, baseline (left) and new triage (right).

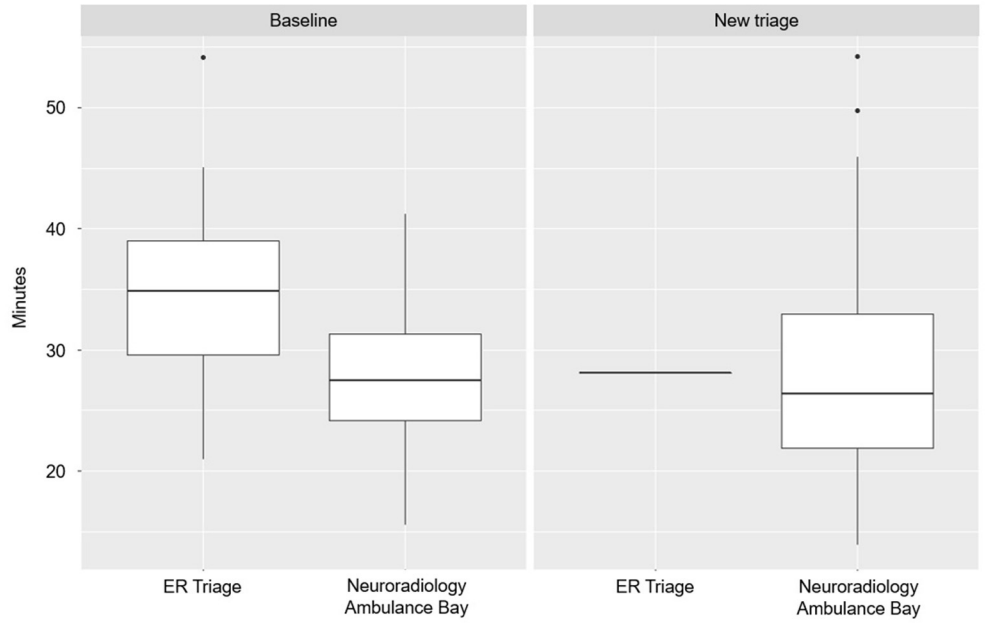

FIGURE 2 | Time from hospital arrival to leaving the CT room comparing entry points (ER emergency room or neuroradiology ambulance bay).

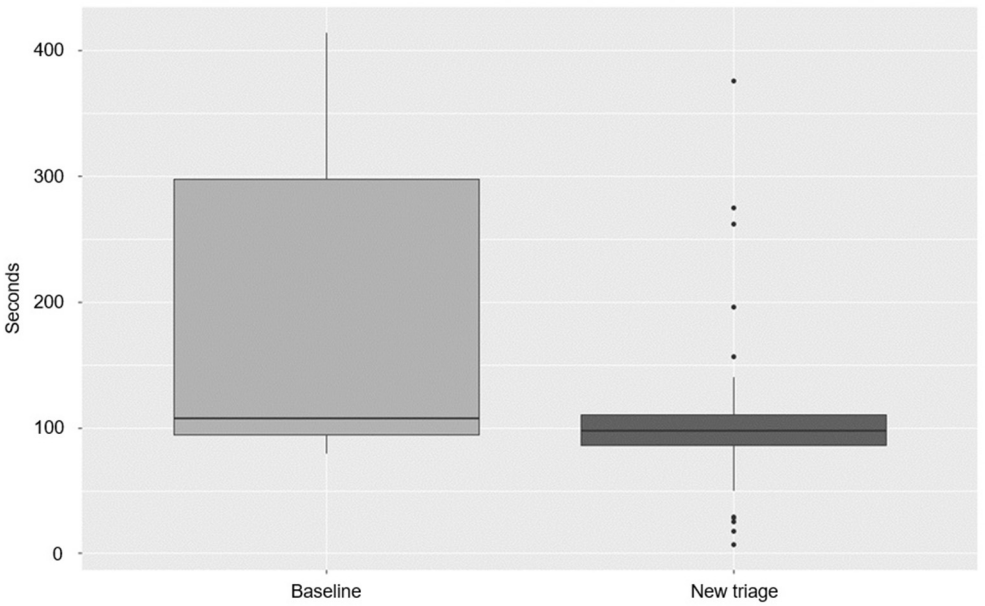

FIGURE 3 | Transport time per study phase ($p < 0.01$).

without aphasia, able to understand the study information and to follow instructions. The wrist band was applied to the healthy arm. If able to use a pen, patients would sign the informed consent form as soon as possible and without delay to the acute stroke pathway. When written informed consent could not be obtained, the ethics approval still allowed the patients to be included in the study by the treating physician. Patients were contacted for providing their informed consent if they regained understanding of study consent during hospital stay. Staff members also provided informed consent for anonymized time and position tracking in the aforementioned locations.

Patient and Public Involvement

Only patients were involved in this study, starting with May 7, 2017. In the informed consent form, patients were informed both orally and in writing, when able to read and sign, about

TABLE 1 | Time spent in holding in the CT room per study phase and stroke type, time spent in neuroradiology per stroke, and transfer types.

Phase/Stroke type	Patients, *n*	Median (IQR)	*P* value
Time in holding (s)			n/s
Baseline	29	13 (6)	0.813
New triage	71	13 (45)	0.813
Hemorrhagic stroke*	15	14 (3.5)	0.414
Ischemic stroke*	84	13 (6)	0.414
Stroke mimic*	13	13 (5)	0.414
Time in CT room (min)			n/s
Baseline	34	17.5 (8.3)	0.422
New triage	94	19.3 (9.3)	0.422
Hemorrhagic stroke	17	19.5 (7.9)	0.796
Ischemic stroke	113	17.4 (8.7)	0.796
Stroke mimic	13	16.9 (7.1)	0.796
Time in neuroradiology (min)			n/s
Hemorrhagic stroke	18	35.1 (17.3)	0.283
Ischemic stroke	108	50.6 (86.7)	0.283
Stroke mimic	13	38.7 (12.5)	0.283
Direct transfer	96	38.5 (35)	0.232
Secondary transfer	44	107.4 (103.6)	0.232

IQR, interquartile range; n/s, non-significant.
**Time on holding per stroke type was compared after acquiring the postimaging diagnoses.*

the aims of the study. They also received information about the duration, individual risk/benefit of participation, handling of confidential personal data, insurance policy, and funding of the study. Thereafter, they also followed details on the technical aspects. The patients were also informed that they could stop participating in the study at any time. Neither patients nor the public were involved in the design and conduction of the study or the choice of outcome measures.

Funding

The Philips Research Team provided hardware equipment, installation, and the RTLS data analysis.

RESULTS

The number of stroke code patients directly admitted from an ambulance to our stroke team was on average 350 patients per year during the study period. Over 17 months, a total of 281 patients were tagged with IR-sending wrist bands and in the EHR (55 patients in phase I and 226 patients in phase II). The total number of patients with acute ischemic stroke and intracerebral hemorrhage was 216 (77%) and 38 (13.4%), respectively. An additional 27 patients (9.6%) were stroke mimics (10 patients had epileptic seizures, four patients had migraine, two patients had tension headache, two patients had head trauma, two patients had confusion, and seven patients had other diagnoses). A total of 11 additional patients had been tagged with wrist bands, but not registered in the EHR and were, therefore, excluded.

Occurrences Automatically Detected by the RTLS

The RTLS system could automatically detect 242 (86%) occurrences as possible stroke pathway patients. Of these, 65 (23%) had to be excluded related to the following: *system downtime* (5.7%)—the patient arrived during a period of the RTLS downtime when no movements were recorded, *likely a nurse* (5.3%)—the movement pattern in the data (e.g., multiple visits to the CT control room) suggested the tag was on a nurse rather than on the patient themselves, *missing data* (8.3%)—too much relevant data are missing from the pathway of patient. This could happen due to, for example, covering the tag with a blanket making the IR sensor unable to communicate with the monitors, and *data-log mismatch* (2.3%)—the RTLS data did not detect that a designated tag was attached to a patient or staff member, although being handwritten in the logbook. For example, on the supposed date of a patient having worn the tag, it was only detected in a single room. The total number of stroke pathway patients correctly detected by the RTLS was 177 (63% of all the tagged patients).

Facility Pathway Analysis

Time Elapsed Between Hospital Arrival at ER or Neuroradiology Ambulance Bay Until Exiting the CT Room After Imaging (Arrival-To-CT Exit)

At baseline, median time between hospital arrival to leaving the CT room was 35 min if patients were first admitted to the ER and 27.5 min if patients were admitted directly to neuroradiology (**Figure 2**). During the new triage system, all patients were admitted directly to neuroradiology with median time of hospital arrival-to-leaving the CT room of about 25 min.

Transport Times per Trial Phase

The RTLS could measure the amount of time traveled through the hospital between leaving the arrival point of entry and reaching the holding room at neuroradiology (**Figure 3**).

There was a significant difference between the median baseline (107.5 s) and new triage (97.5 s) transport times ($p < 0.01$).

Holding and CT Room Times per Trial Phase and Stroke Type

In total, the RTLS detected time spent waiting before entering the CT room (time in holding), the time spent in the CT room, and the total time spent in neuroradiology (**Table 1**). There were no significant differences between time in holding and time in the CT room when baseline, new triage, and stroke types were compared. Patients presenting without stroke required the same amount of time as stroke patients.

Time in Neuroradiology per Stroke Type and in Direct vs. Secondary Transfer

Longer times spent in neuroradiology were observed for the ischemic strokes and patients arriving as secondary transfers from the primary stroke centers (**Table 1**), but not reaching statistical significance. Patients without stroke spent the same amount of time in neuroradiology as hemorrhagic stroke patients.

Patient–Staff Pathway Analysis

After implementation of the new triage system, neurologists spent less time (from 15 ± 2.4 to 9 ± 1.3 min), whereas nurses spent significantly more time with patients (an increase from 13 ± 2.9 to 22 ± 5.1 min; $p = 0.036$, **Figure 4**). There was no influence of stroke type or of nonstroke diagnosis in the time staff spent with patients (**Figure 5**).

DISCUSSION

The RTLS was shown to measure the facility usage and patient–staff interaction times. The yield of automatic detection with complete accuracy was seen in 63% of cases over the course of 17 months.

Facility Usage

Transport time is influenced by, among other factors, hospital layout. The significant pathway shift, including ER bypass, caused by the new triage system, had a visible impact on the time, while the patient is being moved through the hospital. Direct triage to neuroradiology resulted in a significant decrease in transport time by about 2 min (**Figure 3**). Time in holding waiting for a CT examination did not significantly vary over time and was in the order of 10–20 s in both the phases (**Table 1**). Usually, the CT rooms need to be prepared by the staff before usage (e.g., cleaning and setting up the machine). Therefore, we would expect that holding times would be shorter in phase I since transport time was longer and staff has more time to prepare the room. On the contrary, patients were almost never required to wait for a CT examination most likely because the staff at neuroradiology was well prepared and notified in advance in both the phases. Similarly, time in the CT room did not vary between the study phases (**Table 1**). The CT scan duration is fixed and the time corresponding to the actions performed in the CT room (e.g., administration of IVT or deciding where to transfer next) did not appear to be influenced by direct triage ($p = 0.42$). There was also a nonsignificant trend ($p = 0.23$) for longer times spent in neuroradiology for patients secondarily transferred from another hospital compared to directly triaged patients. The secondarily transferred patients were exclusively candidates for endovascular treatment after initial CT/CTA in the referring hospital. According to the previous local guidelines at our center (until 2019), they were re-evaluated with native CT, multiphase CTA, CTP, and discussed with the neurointerventionist before a decision was made for thrombectomy. This is to be expected since patients who are secondarily transferred usually have more severe strokes and large vessel occlusions (8, 9). This pathway was shown to be time-consuming in this study (107.4 min, neurointervention time included). On the other hand, some of these patients are re-evaluated with CT perfusion or multiphase CT and do not proceed to thrombectomy if the infarct size is too large, but this is also time-consuming (including time waiting for an available bed or transport back to the referring hospital) (10, 11). In our recently updated local guidelines, patients secondarily referred for thrombectomy with stroke onset times < 6 h proceed directly to neurointervention in the absence of early neurological deterioration or complete recovery, thus decreasing the time spent in clinical and neuroradiological assessment. Median time spent in the CT room was slightly, but not significantly higher for hemorrhagic stroke patients. Most of these patients are evaluated with acute CTA, on-site consultation with the neurosurgeon, and eventual acute blood pressure management before transfer to another unit. Stroke mimics use slightly less CT room time in comparison, but still require clinical and imaging assessment before transfer, increasing the total time in neuroradiology to the same level of hemorrhagic stroke patients.

Patient–Staff Interaction

Measuring how often staff and patients colocalize is potentially useful due to its ability to more realistically estimate resource allocation costs involved in certain workflows and procedures, a concept known as time-driven activity-based costing (12). In this study, the stroke nurse spent the most time with patients (**Figure 5**), which is expected since the stroke nurse has to attend to the patient through the care pathway. However, after changing triage of moderate-to-severe hemiparesis patients directly to neuroradiology, neurologists spent significantly less time with patients, while nurses spent more time as the study progressed. At baseline, neurologists spent more time with patients because the majority arrived at the ER, where they were examined by the neurologist, who also followed the patient during transport to the CT room. With direct triage, the preliminary diagnosis at the prehospital stage is more robust, since a dialog between the ambulance staff and receiving neurologist has already taken place, with the benefit of the region-wide EHR immediately available to the neurologist during the call. Upon arrival, the neurologist, thus, knows much more about the patient and the bedside history and examination take less time because of the time saved by previous teleconsultation and the EHR review. The need for keeping door-to-needle times short requires quick examination before decision on IVT or thrombectomy is made. In direct triage, stroke nurses also take over some of the tasks from ER nurses and need to stand by the patients longer also because they are more severely neurologically impaired. After implementing the new stroke pathway, stroke nurses spent a median time of 21 min in the first 5 months (compared to 13 min at baseline) and this still increased to 22 min in the last 7 months of the study, even if they had more experience and were trained in the new pathway. This likely reflects the increased number of tasks being performed and the increased stroke severity requiring more nursing. Interestingly, patient–staff interaction time was the same for stroke mimics and hemorrhagic stroke patients. Deciding on stroke mimic diagnosis and treatment for other disorders (e.g., epilepsy) is also time-consuming for the staff and the facility.

The RTLS offers an option for long-term assessments of bottlenecks in stroke care pathways instead of consuming staff and time resources for short-term audits, surveys, or shadowing exercises. Common bottlenecks in stroke pathways are ambulance dispatch and arrival to the correct hospital, distances from door-to-treatment (hospital layout, elevators, etc.), history taking, current medication check, team availability, patient history communication between teams, and resource management (imaging requests, CT room

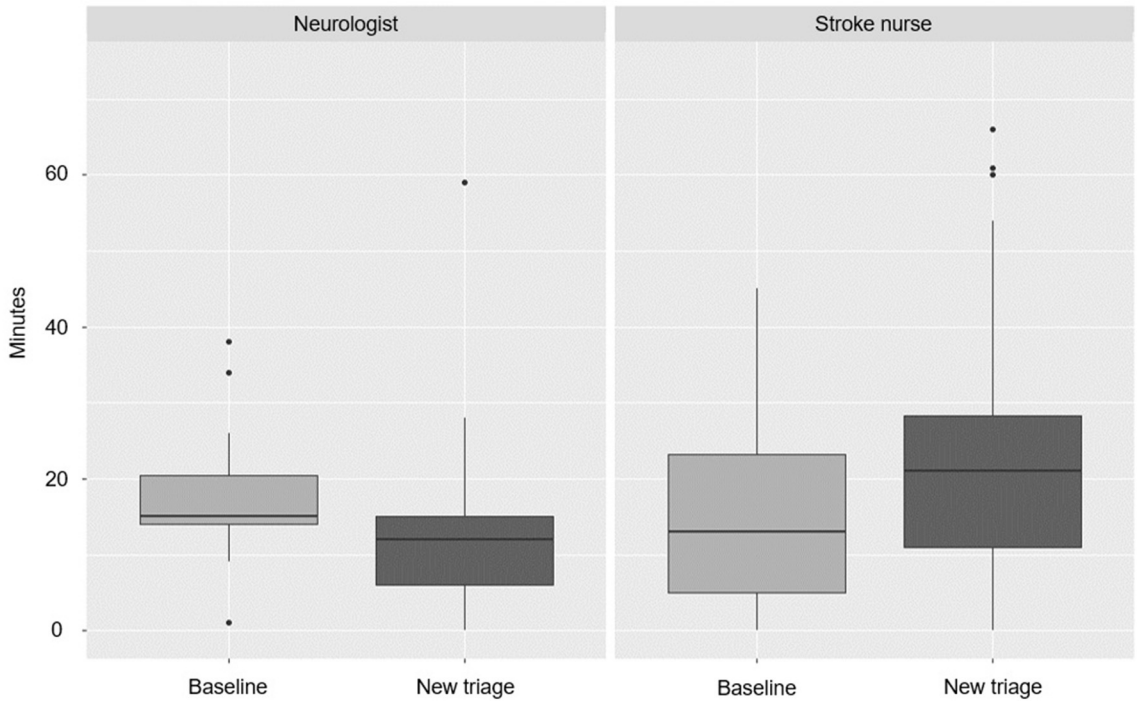

FIGURE 4 | Time spent with patients per study phase and role ($p = 0.036$).

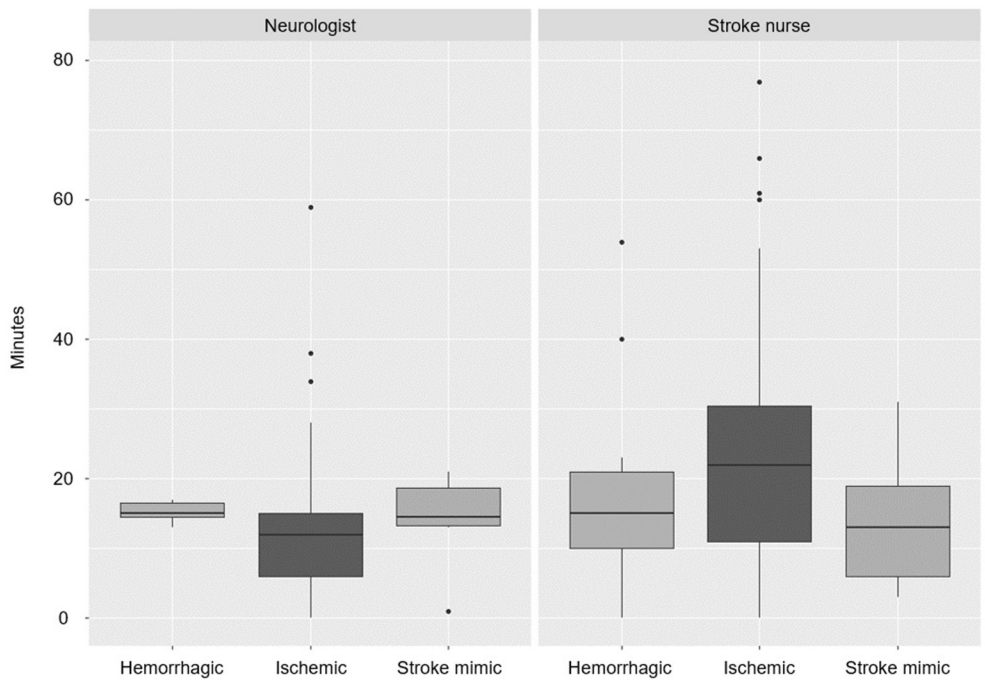

FIGURE 5 | Time spent with patients per stroke type and role ($p > 0.5$).

preparations, thrombolysis, anesthesia availability, and blood sampling). Typically, manually collected times during these exercises are not always registered immediately and often filled in later because the acute treatment has priority. This leads to a higher chance of misreporting times. The RTLS analytics, albeit only focusing on bottlenecks related to distance

times, facility, and resource/staffing usage, can alleviate the burden of the staff to allow focus on treatment. The major advantage of this innovation is that it allows further description of time and staff logistics in more detail and at different areas where the stroke care is taking place, which cannot be analyzed from compact total door-to-needle or door-to-groin puncture times.

Cost-Effectiveness

The installation costs of the RTLS are dependent on accuracy desired, number of rooms/zones to be covered, and use cases (for example, equipment, patients). The estimated infrastructure cost per room-level accuracy is about 500 Euro and the total cost for this study (equipment, personnel, installation, and training) was about 25,000 Euro. Data from the system can spare about 2–3 weeks of data collection, analysis, and reporting per year (conservative cost savings of about 3,000 Euro in salaries per year and releasing additional time for clinical work and production). With the current room installation, any clinical pathway from the ER to neuroradiology (e.g., neurotrauma, meningitis) can be analyzed by switching the tags to the different personnel and patient groups. Net turnover could be achieved after 3–5 years of usage. The results of this study also stressed the importance of having a backup nurse to the principal stroke nurse at neuroradiology, since the latter was busier with more tasks to perform, which has been implemented. Thus, reorganizing staff can lead to time savings in door-to-treatment times and to improve outcomes in the long term.

Limitations

Several technical limitations resulted in missing data, which could be improved by changing the placement of patient tags and backup systems. Patient recruitment could not be made consecutively owing to refusal to consent and staffing rotation. Inferences based on characteristics such as age, sex, and stroke severity were not possible due to privacy restrictions and scope of study. The RTLS alone cannot make measurements of important metrics for stroke care pathways such as door-to-needle time. With only location data available, the closest metric that could be inferred would approximately be the time from patient arrival to leaving the CT room. We did not report the exact time when the neurologist and the stroke nurse arrived to the patient but, according to study design and usual clinical practice, the stroke nurse and the neurologist were deployed to the patient at the same time during the baseline and new pathway phases. Some exceptions may have occurred, but these would be expected in both the study phases and to be of short duration (for instance with busy, parallel stroke cases or telephone calls). Thus, the extra time spent by the nurse indicates that the nurse stayed longer with the patient, which is what we have observed.

CONCLUSION

After changing the stroke triage system, median times of hospital arrival to leaving the CT room were cut by about 10 min. The RTLS was able to demonstrate that direct triage of moderate-to-severe hemiparesis patients increased stroke nurse–patient interaction times. The teleconsultation with the ambulance led to a decrease in the neurologist–patient interaction times. The RTLS can be useful for automatic identification of bottlenecks in stroke pathways and assist in staff management. Further technical improvements and interaction with the EHR can increase detection yield and workflow characterization in more detail.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stockholm Regional Ethical Council (nr 2017/511-31/4). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.741551/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Intravenous Thrombolysis by Telestroke in the 3- to 4.5-h Time Window

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Background: While intravenous thrombolysis (IVT) in ischemic stroke can be safely applied in telestroke networks within 3 h from symptom onset, there is a lack of evidence for safety in the expanded 3- to 4. 5-h time window. We assessed the safety and short-term efficacy of IVT in acute ischemic stroke (AIS) in the expanded time window delivered through a hub-and-spoke telestroke network.

Methods: Observational study of patients with AIS who received IVT at the Stroke Eastern Saxony Telemedical Network between 01/2014 and 12/2015. We compared safety data including symptomatic intracerebral hemorrhage (sICH; according to European Cooperative Acute Stroke Study II definition) and any intracerebral hemorrhage (ICH) between patients admitted to telestroke spoke sites and patients directly admitted to a tertiary stroke center representing the hub of the network. We also assessed short-term efficacy data including favorable functional outcome (i.e., modified Rankin Scale ≤ 2) and National Institutes of Health Stroke Scale (NIHSS) at discharge, hospital discharge disposition, and in-hospital mortality.

Results: In total, 152 patients with AIS were treated with IVT in the expanded time window [spoke sites, $n = 104$ (26.9%); hub site, $n = 48$ (25.9%)]. Patients treated at spoke sites had less frequently a large vessel occlusion [8/104 (7.7) vs. 20/48 (41.7%); $p < 0.0001$], a determined stroke etiology ($p < 0.0001$) and had slightly shorter onset-to-treatment times [210 (45) vs. 228 (58) min; $p = 0.02$] than patients who presented to the hub site. Both cohorts did not display any further differences in demographics, vascular risk factors, median baseline NIHSS scores, or median baseline Alberta stroke program early CT score ($p > 0.05$). There was no difference in the frequency of sICH (4.9 vs. 6.3%; $p = 0.71$) or any ICH (8.7 vs. 16.7%; $p = 0.15$). Neither there was a difference regarding favorable functional outcome (44.1 vs. 39.6%; $p = 0.6$) nor median NIHSS [3 (5.5) vs. 2.5 (5.75); $p = 0.92$] at discharge, hospital discharge disposition ($p = 0.28$), or in-hospital mortality (9.6 vs. 8.3%; $p = 1.0$). Multivariable modeling did not reveal an association between telestroke and sICH or favorable functional outcome ($p > 0.05$).

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Conclusions: Delivery of IVT in the expanded 3- to 4.5-h time window through a telestroke network appears to be safe with equivalent short-term functional outcomes for spoke-and-hub center admissions.

Keywords: telemedicine, thrombolysis, stroke, acute stroke therapy, stroke network

INTRODUCTION

Although the implementation of endovascular therapy (EVT) in the treatment of acute ischemic stroke (AIS) has a largely improved prognosis of the disease, intravenous thrombolysis (IVT) using tissue plasminogen activator continues to be the mainstay of acute care of patients with AIS and remains of great importance for prevention of long-term disability (1, 2). The efficacy and safety of IVT are primarily time-dependent and the benefit increases the earlier and faster the therapy is initiated (3).

The widespread availability of evidence-based stroke therapies, regardless of geographical barriers, is still a challenge of acute stroke care (4). It has been shown that telemedicine can overcome this challenge and improve the care of patients with stroke through the identification of patients in need of IVT or EVT and further rescue therapies (5–7). This is reflected by the fact that telestroke networks meanwhile achieve similar rates of IVT and transfers for EVT compared with neurological stroke centers (8).

We have recently shown that IVT delivered through telestroke network is not inferior in terms of safety and efficacy to tissue-type plasminogen activator (tPA) provided at specialized stroke centers for the treatment of AIS in the 3-h time window (9). However, while recent data even suggest a benefit of IVT up to 9 h from symptom onset using advanced imaging techniques that are commonly reserved to dedicated stroke centers, there is still a lack of evidence regarding its safety and efficacy in the regularly approved 3- to 4.5-h therapeutic time window in the telestroke setting (9–12). In view of these considerations, we aimed to investigate the safety and short-term efficacy of IVT in the 3- to 4.5-h time window for treatment of AIS in a telestroke network.

METHODS

Study Design and Telestroke Network

We performed an observational study using prospectively collected data from a large hub-and-spoke telestroke network in Saxony, Germany. The Stroke Eastern Saxony Telemedical Network (SOS-TeleNET) founded in 2007 comprises 13 spoke sites and provides telestroke care to ∼1.000 patients per year (**Figure 1**). The Department of Neurology of the University Hospital Carl Gustav Carus in Dresden serves as the main hub for each of the spokes. At the time of the study period (01/2014–12/2015), the SOS-TeleNET also included two secondary care hospitals, which served as additional Neurology hub sites. One site performed teleconsultations 3 days per month, the other site provided neurosurgical care of patients with stroke, but no teleconsultation service. The distance between the main hub and the surrounding spoke sites is between 15 km (about 10 mi) and up to 120 km (about 75 mi).

The video-based evaluation of the neurological status and immediate review of the cerebral imaging transmitted *via* virtual private network was performed 24/7 by a stroke neurologist at the main hub site using either a stationary telemedical unit (VIMED® DOC, MEYTEC GmbH Medizinsysteme, Werneuchen) or wireless Universal Mobile Telecommunications System (VIMED® UMTS 2, MEYTEC GmbH Medizinsysteme, Werneuchen) outside working hours. Neuroimages were transmitted in DICOM (Digital Imaging and Communications in Medicine) format and temporarily stored on a certified PACS (Picture Archiving and Communication System) server. Imaging findings and stroke cases potentially amenable to interventional therapies were discussed with a neuroradiologist who was available 24/7. At spoke sites, a mobile telemedical system (VIMED® TELEDOC, MEYTEC GmbH Medizinsysteme, Werneuchen) located in the emergency room was used for teleconsultations. Indications for telestroke consultations comprised suspected stroke within a therapeutic time window up to 24 h from symptom onset, intracranial hemorrhage, brainstem symptoms, unclear qualitative or quantitative disturbances of consciousness, unclear clinical or diagnostic status, and progressive stroke.

All spoke sites followed standard operating procedures provided by the SOS-TeleNET and were guided by current stroke guidelines (13, 14). Also, annual quality assurance audits were conducted at all spoke sites to ensure evidence-based and high-quality stroke care.

As the standard of care, serial National Institutes of Health Stroke Scale (NIHSS) scores and Alberta stroke program early CT score (ASPECTS) on baseline CT scan were obtained in all patients. Guided by clinical and imaging findings, stroke neurologists ultimately gave recommendations regarding treatment with IVT and transfer to the hub site for further treatment evaluation. Patient data, namely, demographical information, medical history, stroke-related information, and treatment specifics and characterization of stroke etiology were retrieved from prospective teleconsult summaries and the institutional stroke care quality registry. Additional information was extracted retrospectively from all available sources, namely, the hospitals' electronic patient databases and admission, follow-up, and discharge summaries.

Patient Outcomes

To evaluate the safety and short-term efficacy of IVT with tPA in patients with telestroke, we compared data from patients presented to the spoke sites with that of patients primarily presented to the hub site. Safety outcomes included symptomatic intracerebral hemorrhage (sICH), defined as any intracerebral hemorrhage (ICH) on 12- to 36-h follow-up

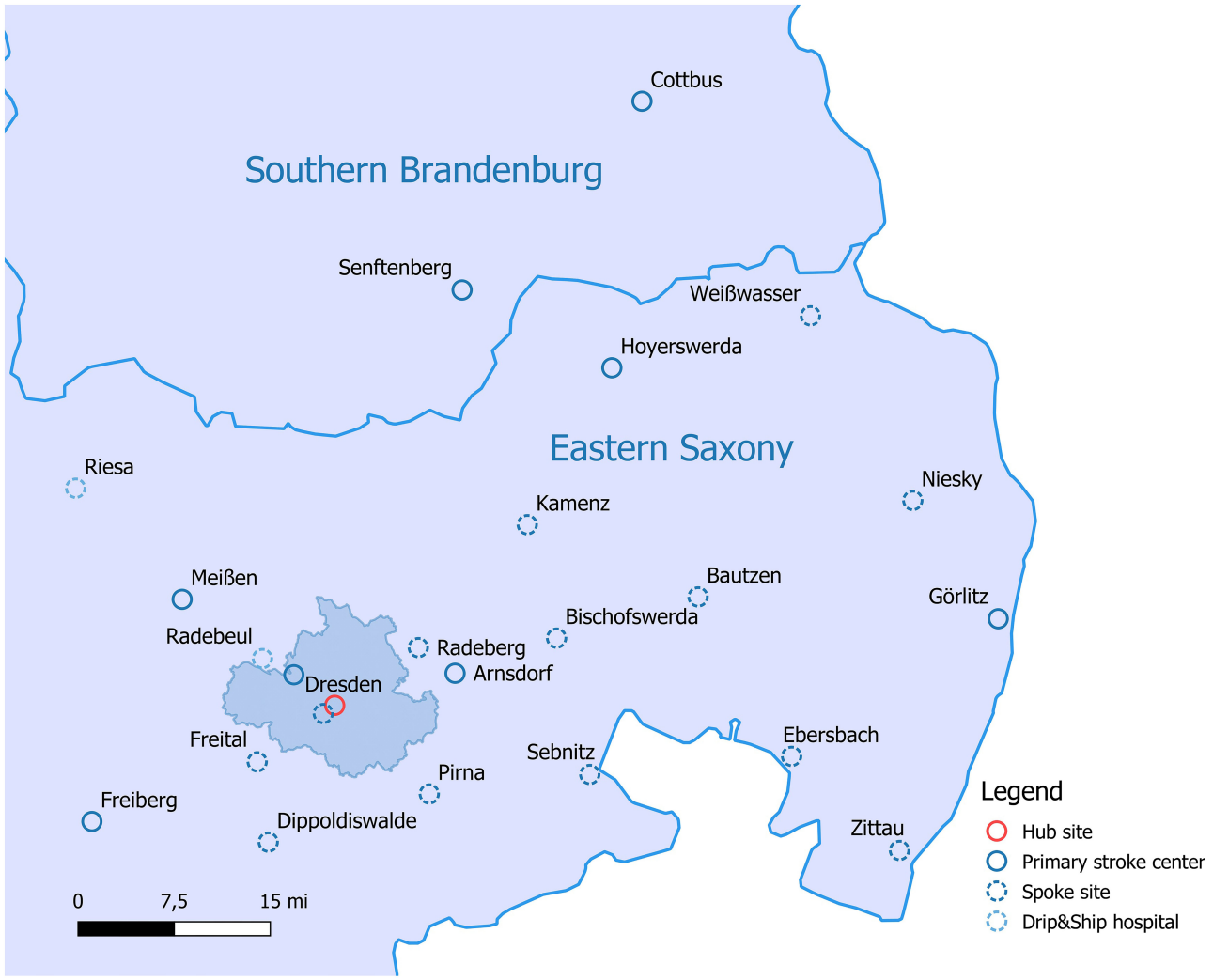

FIGURE 1 | Map of the Stroke East Saxony Telemedical Network in the eastern part of Saxony, Germany.

CT scan that was causatively associated with a four-point worsening of NIHSS, and any ICH according to the radiographic hemorrhagic transformation classification (15). For this purpose, all imaging data were prospectively reviewed by a board-certified neuroradiologist (A.A.) who was blinded to group allocation and clinical information. We also assessed favorable (i.e., modified Rankin Scale, mRS $\leq$ 2) functional outcome at discharge, NIHSS at discharge, in-hospital mortality, and hospital discharge disposition.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD and non-continuous variables as median (interquartile range, IQR) or percentage. Between-group comparisons were conducted with the use of *t*-test, Mann-Whitney-*U*-test, chi-squared-test, and Fisher's exact-test,where appropriate.

A multivariable logistic regression analysis with a stepwise forward selection procedure was conducted to explore the association between telestroke and sICH or favorable functional outcome. Candidate variables were *a priori* selected according to their known predictive association with ICH (i.e., age, history of atrial fibrillation, concomitant therapeutic anticoagulation or antiplatelet therapy, onset-to-treatment time, admission glucose, baseline systolic blood pressure, baseline ASPECTS, and baseline NIHSS) or functional outcome (i.e., age, baseline NIHSS, baseline ASPECTS, onset-to-treatment time, and large vessel occlusion), and entered in the final model at $p < 0.2$. We also performed a sensitivity analysis, considering only variables that emerged significantly different in the between-group comparisons.

Available case analysis was used for any missing data on baseline parameters. *p*-value was considered significant at <0.05. Adjusted odds ratios (ORs) are presented with corresponding 95% CI. All analyses were computed with SPSS (Statistical Package for Social Sciences, version 20.0, IBM, Armonk, New York).

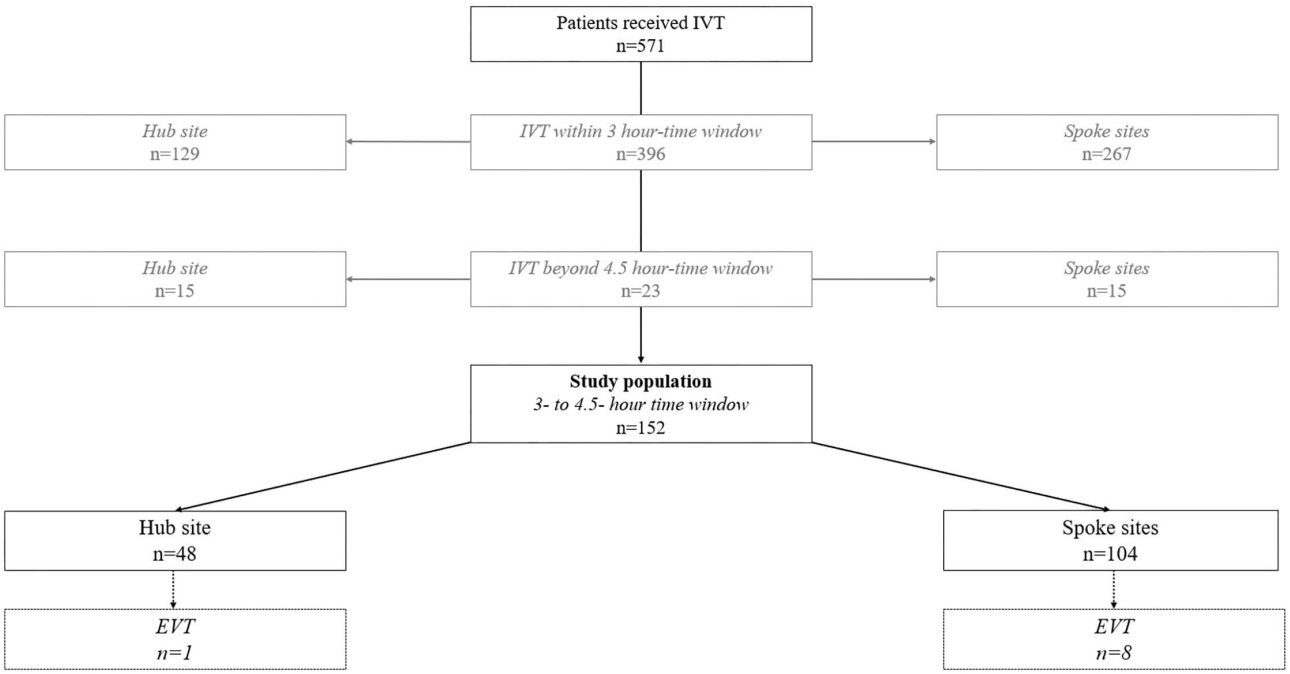

FIGURE 2 | Flow chart of the study population. IVT, intravenous thrombolysis; EVT, endovascular therapy.

RESULTS

Study Population

During the 2-year study period, a total of 571 patients with ischemic stroke received IVT within the SOS-TeleNET (spoke sites, $n = 386$; hub site, $n = 185$). Of these patients, 396 were treated within the 3-h time window [spoke sites, $n = 267$ (69.2%); hub site, $n = 129$ (69.7%)] and 23 beyond the 4.5-h time window [spoke sites, $n = 15$ (3.9%); hub site, $n = 8$ (4.3%)]. The final study population consisted of 152 patients with AIS who were treated in the 3- to 4.5-h time window [spoke sites, $n = 104$ (26.9%); hub site, $n = 48$ (25.9%)]. Eight of 104 (7.7%) patients with telestroke were subsequently transferred for potential EVT or advanced stroke care to the hub site (two eventually underwent EVT). In the stroke center cohort, 1/48 (2.1%) patients underwent EVT (**Figure 2**).

The mean age of the study population was 74 ± 12.3 years, 50% were men, baseline NIHSS scores was 7 (IQR, 8) points and baseline ASPECTS 10 (IQR, 1) points. Patients treated at spoke sites less frequently exhibited a large vessel occlusion [8/104 (7.7) vs. 20/48 (41.7%); $p < 0.0001$] and well-defined stroke etiology ($p < 0.0001$), and had slightly shorter onset-to-treatment times [210 (45) vs. 228 (58) min; $p = 0.02$] than patients who presented to the hub site. Further baseline characteristics, namely, demographics, vascular risk factors, and clinical and imaging parameters were well-balanced among both groups. **Table 1** illustrates the corresponding baseline data of the study population.

Intracerebral Hemorrhage

There were no differences concerning sICH following IVT between patients who primarily presented to the spoke sites and those who presented to the hub site [5/104 (4.9) vs. 3/48 (6.3%); $p = 0.71$]. Neither there was a difference in the radiographic evidence of any ICH [9/104 (8.7%) vs. 8/48 (16.7%); $p = 0.15$]. Data on follow-up CT scans were missing in one patient who was treated at the spoke site and who died before follow-up CT. Applying the worst-case scenario, there was still no difference in terms of sICH between both groups [6/104 (5.8) vs. 3/48 (6.3%); $p = 1.0$].

Three of 48 (6.25%) patients treated at the hub site experienced subarachnoid hemorrhage, one of which was considered symptomatic and occurred in addition to ICH. When we considered these bleeding complications in the bivariate analysis, there were fewer intracranial hemorrhages following IVT in patients treated at the spoke sites than in patients treated at the hub site [9/104 (8.7) vs. 10/48 (20.8%); $p = 0.037$].

The multivariable model did not reveal an association between telestroke consultation and sICH following IVT ($p = 0.5$). The results remained the same when we considered only variables that were unbalanced among the study groups ($p = 0.84$). Only atrial fibrillation was associated with sICH (OR: 20.57, 95% CI: 2.38–178.1; $p = 0.006$).

Short-Term Efficacy Outcomes

Functional outcome data was missing in two patients treated at the spoke sites. No differences were evident in terms of favorable

TABLE 1 | Clinical characteristics, process times, and stroke etiologies of the study population.

	Telestroke ($n = 104$)	Stroke center ($n = 48$)	*p*-value
Demographics			
Gender, male, *n* (%)	52 (50)	24 (50)	1.0
Age, years, mean ± σ	73.3 ± 12.7	75.5 ± 11.4	0.32
Initial stroke severity, median (IQR)			
NIHSS	8 (9)	6.5 (6.8)	0.28
ASPECTS	10 (1)	10 (1)	0.99
Clinical baseline values, $\bar{x} \pm \sigma$			
Serum glucose, mmol/L	7.1 ± 2.7	7.1 ± 2.4	0.85
Initial systolic blood pressure	167 ± 31.3	170 ± 34	0.55
Initial diastolic blood pressure	87 ± 27	89 ± 21.5	0.36
Pre-IVT systolic blood pressure	160 ± 29	156 ± 26	0.24
Pre-IVT diastolic blood pressure	83 ± 19	81 ± 15.8	0.55
Vascular risk factors, *n* (%)			
Previous ischemic stroke	23 (22.1)	13 (27.1)	0.50
Arterial hypertension	92 (88.5)	44 (91.7)	0.55
Diabetes mellitus type II	44 (42.3)	23 (47.9)	0.52
Hyperlipidemia	78 (75)	39 (81.3)	0.40
Atrial fibrillation	29 (27.9)	15 (31.3)	0.67
Smoking	17 (16.3)	5 (12.5)	0.54
Pre-medication, *n* (%)			
Antiplatelet therapy	44 (42.7)	14 (29.2)	0.11
Anticoagulation	3 (2.9)	4 (8.3)	0.21
Large vessel occlusion, *n* (%)			
Any	8 (7.7)	20 (41.7)	<0.0001
Terminal internal carotid artery	3 (2.9)	4 (8.3)	
Middle cerebral artery	4 (3.9)	12 (25)	
Basilar artery	0 (0)	1 (2.1)	
Other	1 (1)	3 (6.3)	
Process times, median (IQR)			
Door-to-imaging, min	17 (24)	18 (20)	0.40
Door-to-needle, min	74 (57)	67 (39.5)	0.20
Onset-to-treatment, min	210 (45)	228 (58)	0.02
Door-to-consult, min	18 (23)	–	
Teleconsult duration, min*	10 (13)	–	
Stroke etiology, *n* (%)			
Toast classification			<0.0001
Large-artery atherosclerosis	8 (7.7)	20 (41.7)	
Small-vessel occlusion	9 (8.7)	4 (8.3)	
Cardioembolism	20 (19.2)	17 (35.4)	
Other determined etiology	1 (1)	1 (2.1)	
Undetermined etiology	66 (63.5)	2 (4.2)	
Stroke mimics	3 (2.9)	-	0.55

σ, standard deviation; $\bar{x}$, mean; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.
**According to data from 42 telestroke patients.*

functional outcome at discharge between patients receiving IVT at the spoke sites and the hub site [45/102 (44.1) vs. 19/48 (39.6%); $p = 0.6$].

TABLE 2 | Safety and short-term efficacy parameters.

	Telestroke ($n = 104$)	Stroke center ($n = 48$)	*p*-value
Safety, *n* (%)			
Symptomatic intracerebral hemorrhage[a]	5 (4.9)	3 (6.3)	0.71
Any intracerebral hemorrhage[a]	9 (8.7)	8 (16.7)	0.15
HI1	2 (1.9)	1 (2.1)	
HI2	5 (4.8)	1 (2.1)	
PH1	1 (1.0)	2 (4.2)	
PH2	1 (1.0)	4 (8.3)	
Any intracranial hemorrhage[a]	9 (8.7)	10 (20.8)	0.04
Short-term efficacy			
NIHSS at discharge, median (IQR)	3 (5.5)	2.5 (5.75)	0.92
mRS at discharge, median (IQR)[b]	3 (3)	3 (2.75)	0.92
mRS 0-2, *n* (%)	45 (44.1)	19 (39.6)	0.6
Discharge disposition, *n* (%)[b]			0.28
Home	43 (42.2)	15 (31.3)	
Acute rehabilitation	31 (30.4)	23 (47.9)	
Nursing facility	15 (14.7)	4 (8.3)	
Hospital transfer	3 (2.9)	2 (4.2)	
In-hospital mortality, *n* (%)	10 (9.6)	4 (8.3)	1.0

[a] *One telestroke patient died before follow-up CT.*
[b] *Missing data on discharge location in two telestroke patients.*
IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; HI, hemorrhagic infarction; PH, parenchymal hemorrhage.

After adjusting for known covariates in the logistic regression model, age (OR: 0.93, 95% CI: 0.89–0.97; $p = 0.001$), baseline NIHSS (OR: 0.76, 95% CI: 0.67–0.86; $p < 0.001$) and baseline ASPECTS (OR: 1.93, 95% CI: 1.04–3.57; $p = 0.036$) emerged as predictors of favorable functional outcome at discharge, but not telestroke consultation ($p = 0.68$). The results remained the same when we kept all covariates in the model.

Patients treated at the spoke sites appeared to be more frequently discharged to home and less frequently discharged to acute rehabilitation than patients treated at stroke center [43/102 (42.2) vs. 15/48 (31.3%) and 31/102 (30.4) vs. 23/48 (47.9%), respectively]; however, this trend did not reach statistical significance.

At discharge, 10/104 (9.6%) patients in the telestroke group and 4/48 (8.3%) patients in the stroke center group were deceased with no differences in bivariate analysis ($p = 1.0$). **Table 2** provides a summary of patient outcomes.

DISCUSSION

The findings of this observational study suggest that IVT delivered through a hub-and-spoke telestroke network is safe in the expanded 3- to 4.5-h time window. sICH rate of 4.9% at spoke sites was comparatively low in our network and equivalent to the rates of 5.3% reported in the randomized controlled European Cooperative Acute Stroke Study (ECASS) III study and of 3.9% in the SITS-UTMOST and 4.5% in the SITS-ISTR registries

(12, 16, 17). Moreover, any intracerebral bleeding occurred less frequently in patients with telestroke and was quite low (i.e., 8.7%) when compared with the incidence rate reported in the population of the ECASS III study (i.e., 27.0%).

The median door-to-needle time at the telestroke spoke sites (i.e., 74 min) was slightly longer than that achieved at the hub site. Longer in-hospital treatment times have also been observed in general patients with stroke who were treated in the expanded 3- to 4.5-h window compared with the 3-h window (16, 17). Potential loss of time at the spoke sites could yet be still attributed to the teleconsultation itself including video-consult initiation and completion. However, with a median of 10 min, teleconsult time was shorter than reported in other large telestroke networks ranging between 14 and 35 min (18–20). Moreover, disregarding the teleconsult duration, door-to-needle times at spoke sites appeared to be comparable to that at the hub site suggesting that in-hospital operational processes of patients eligible to IVT can be established at telestroke units, just as it is for in-person treatment at dedicated stroke centers. Most patients with telestroke in our study also met the proposed door-to-imaging goal of 25 min or less for suspected patients with stroke (21).

As recommended by current AHA guidelines, continuous quality improvement activities are expected to facilitate quality, performance, and outcomes of stroke care provided at telestroke sites (4). In our hub-and-spoke telestroke network, data on stroke quality measures are continuously collected and analyzed and stroke-specific care procedures such as adequate diagnostic and medical treatment, dysphagia screening, and early implementation of rehabilitation are audited regularly by in-person visits at the spoke sites. Lastly, data reported in this observational study originates from the years 2014 and 2015 and increasing on-site stroke experience at spoke sites may have further led to improvement in telestroke process metrics as we were able to show in a recent publication (5). Door-to-needle times improved to an average of 52 min that complies with the 60-min target recommended by current stroke guidelines (13, 14).

Comparability of functional outcome and thus efficacy of IVT is limited by the mRS availability in our telestroke network. Patient outcomes were regularly measured using mRS at discharge and in-hospital mortality, which have been still recommended as short-term proxies for the functional outcome (4). By that, a favorable functional outcome was observed in almost every second patient with telestroke exposed to IVT that was comparable to the corresponding rate in patients directly treated at the hub site. Moreover, given the fact that the ECASS III study and the SITS-ISTR and SITS-UTMOST registries obtained modified Rankin scores at 3 months (mRS $\leq$ 2: 66.5, 65, and 62.7%, respectively), the frequency of favorable functional outcome seen in our telestroke cohort appears realistic (12, 16, 17). The same applies for in-hospital mortality in our study that was between that in ECASS III (i.e., 6.7%), SITS-ISTR (i.e., 11.1%), and in SITS-UTMOST (i.e., 12%).

Large vessel occlusion was detected more frequently in patients directly admitted to the stroke center than in patients with telestroke (41.7 vs. 7.7%). Considering similar baseline stroke severity in both groups, this difference might be rather related to the infrequent performance of CT angiography at spoke sites during the study period. Acute vessel imaging in patients with acute stroke potentially eligible for reperfusion therapies was not implemented as standard of care in our telestroke network until the first efficacy data for EVT were presented in 2015 (1). We, therefore, do not assume that this imbalance in vessel occlusion status has confounded our findings on ICH or functional outcomes, which is also supported by the results of our multivariable model. In the meantime, routine implementation of CT angiography in the acute stroke workup has led to equivalent large vessel occlusion detection rates and allows proper identification of those potentially amenable to EVT (5).

Our study has limitations that largely arise from its observational design. However, aside from slightly longer onset-to-treatment times in patients directly admitted to the hub center, there was homogeneity in terms of demographics, vascular risk factors, baseline stroke severity and initial radiographic extend of early ischemic changes providing a sufficient degree of comparability across both cohorts. Moreover, a randomized controlled trial of IVT in the expanded time window in the telestroke setting would potentially compromise treatment times and there is still the notion that IVT should be initiated at the nearest hospital equipped with tPA (13). There was a substantial amount of missing data regarding the duration of the teleconsultation; however, we do not expect that this has influenced outcomes chosen in this study. Also, our findings are not generalizable to telestroke networks other than hub-and-spoke models.

In conclusion, our observational data supports the equivalence of safety and short-term efficacy of IVT in the expanded 3- to 4.5-h times window between telestroke units and a dedicated stroke center. Considering recent data on further expansion of the treatment window, there is a need to explore the delivery of IVT through telestroke networks using advanced imaging modalities (10, 11).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee (EK) of the Technische Universitaet Dresden. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KB and JB: conceptualization and supervision. MF, KB, and JB: methodology. MF and KB: statistical analysis. CW, HR, VP, KB, and JB: resources. ES, MF, AA, SW, CW, KB, and

JB: data curation. ES: writing—original draft preparation. ES, L-PP, TS, HR, VP, KB, and JB: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Telestroke Assessment With Perfusion CT Improves the Diagnostic Accuracy of Stroke vs. Mimic

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Background and Purpose: CT perfusion (CTP) has been implemented widely in regional areas of Australia for telestroke assessment. The aim of this study was to determine if, as part of telestroke assessment, CTP provided added benefit to clinical features in distinguishing between strokes and mimic and between transient ischaemic attack (TIA) and mimic.

Methods: We retrospectively analysed 1,513 consecutively recruited patients referred to the Northern New South Wales Telestroke service, where CTP is performed as a part of telestroke assessment. Patients were classified based on the final diagnosis of stroke, TIA, or mimic. Multivariate regression models were used to determine factors that could be used to differentiate between stroke and mimic and between TIA and mimic.

Results: There were 693 strokes, 97 TIA, and 259 mimics included in the multivariate regression models. For the stroke vs. mimic model using symptoms only, the area under the curve (AUC) on the receiver operator curve (ROC) was 0.71 (95% CI 0.67–0.75). For the stroke vs. mimic model using the absence of ischaemic lesion on CTP in addition to clinical features, the AUC was 0.90 (95% CI 0.88–0.92). The multivariate regression model for predicting mimic from TIA using symptoms produced an AUC of 0.71 (95% CI 0.65–0.76). The addition of absence of an ischaemic lesion on CTP to clinical features for the TIA vs. mimic model had an AUC of 0.78 (95% CI 0.73–0.83)

Conclusions: In the telehealth setting, the absence of an ischaemic lesion on CTP adds to the diagnostic accuracy in distinguishing mimic from stroke, above that from clinical features.

Keywords: stroke, telestroke, imaging—computed tomography, transient ischaemic attack (TIA), CT perfusion (CTP), stroke mimic

INTRODUCTION

Access to reperfusion therapy for stroke is largely related to the timely and accurate diagnosis of stroke (1). However, the availability of reperfusion therapy is still largely limited in rural areas of many countries, such as Australia (2). Telestroke with multimodal CT (mCT) imaging, which includes non-contrast CT brain, CT angiography (CTA), and CT perfusion (CTP), has been demonstrated to be an effective way of increasing thrombolysis in these regions and has also been used to select patients who are likely to benefit from transfer to a comprehensive stroke centre for endovascular thrombectomy (3).

Accurate diagnosis of stroke mimics from stroke and transient ischaemic attack (TIA) is required to avoid unnecessary treatment and transfer of patients in the telestroke setting. However, there has been little research into the accuracy of identifying mimics from ischaemic events in the telestroke setting. Most of the research differentiating ischaemic events from mimics has focused primarily on face-to-face clinical assessment in the Emergency Department (4–8). Common predictors of mimics include younger age, lower National Institutes of Health Stroke Scale (NIHSS), lack of stroke risk factors (such as atrial fibrillation and hypertension), lack of lateralising weakness, loss of consciousness, confusion, paraesthesia, or previous diagnosis of migraine or epilepsy (4–7, 9). There are fewer studies, which examine imaging factors to differentiate stroke from mimic. Chang et al. (7) assessed CTA in improving the diagnostic accuracy of strokes from mimics, and their logistic regression model using clinical features and evidence of atherosclerosis on CTA yielded an overall accuracy of 91.4%.

There have been a few studies looking at clinical predictors to develop risk prediction tools for distinguishing between stroke and mimic in the telestroke population (10–12). In a recent study by Tu et al. (13), which externally validated four existing stroke mimic prediction scales, the scale with the highest discrimination for stroke mimics had an area under the receiver operator curve value of 0.75. Similar to the studies which focused on face-to-face clinical evaluation in the Emergency Department, studies of telestroke assessment found that mimic patients had lower NIHSS scores, were younger in age, usually had a history of seizure, migraine or psychiatric illness, were less likely to have atrial fibrillation or hypertension, and had a lack of localising symptoms (10–12). However, none of these studies evaluated the utility of including imaging in predictive models.

The aim of the current study was to determine the clinical features that distinguish mimic from stroke and TIA in a telestroke setting, and whether mCT, in particular, CTP improves diagnostic accuracy.

MATERIALS AND METHODS

We retrospectively analysed consecutively recruited patients assessed by the Northern New South Wales Telestroke service from the time of introduction of telestroke to the area from April 2013 to March 2020. There were five spoke hospitals in total. The distance between the spoke sites and the hub ranged from 167 to 386 km. At each spoke hospital, cameras for consultation were provided, and training was provided to physicians for the use of the Face Arm Speech Time (FAST) scale (13).

Radiology technicians were trained to perform an mCT imaging protocol which included non-contrast brain CT, CTA, and CTP at baseline, with either non-contrast brain CT or MRI performed at 24–48 h. MIStar (Apollo Medical Imaging Technology) was used to process perfusion CT to generate cerebral blood volume, cerebral blood flow (CBF), mean transit time, delay time (DT) maps, summary ischaemic core, and penumbra maps. Tissue with DT >3 sec and relative CBF >30% of normal tissue were defined as the penumbra, and tissue with DT >3 sec and relative CBF <30% of the contralateral hemisphere were defined as the ischaemic core. More detailed information on the imaging protocol has been previously published (3).

The criteria for stroke call were defined as FAST scale positive neurological symptoms presenting within 4.5 h of symptom onset from April 2013 to November 2017, after which the time window was expanded to 24 h given the findings of the Diabetes Autoimmunity Withdrawn in New Onset Patients (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-UP and Late Presenting Strokes Undergoing Neurointervention with Trevo) trial (14). The Northern New South Wales Telestroke service is staffed by stroke neurologists from the John Hunter and Gosford District Hospitals and was responsible for clinical telestroke assessment and interpreting the mCT scans in the acute phase.

The following patient characteristics were collected: demographic data (age and sex), the record of symptoms (hemiparesis, dysphasia, visual disturbance, paraesthesia, isolated facial palsy, isolated limb weakness, dysarthria, ataxia, dizziness, decreased level of consciousness, disorientation, headache, seizure, and non-localising symptoms), and NIHSS score at presentation. Imaging findings, such as the presence of vessel occlusion on CTA, volume of automated CTP lesions (core and penumbra), and follow-up imaging results, were also recorded. The final diagnosis was reviewed by a telestroke neurologist and based upon all clinical and imaging findings, such as subsequent imaging and clinical assessments. Stroke was defined as symptoms consistent with a stroke syndrome with the presence of infarction on follow-up imaging or persisting beyond 24 h. TIA was defined as typical stroke symptoms lasting <24 h with no infarction on follow-up imaging. Mimics were defined as an atypical stroke presentation with the absence of infarction on follow-up CT or MRI, and/or if symptoms were explained by a clinically determined alternative aetiology (excluding intracranial haemorrhage). Uncertain cases were decided by consensus between two stroke neurologists. Patients who did not have acute CTP were excluded from this study. Ethics approval was obtained from the Hunter New England Human Research Ethics Committee (HNEHREC reference no: 2019/ETH13062).

Patient characteristics were summarised by percentage and group differences and were tested by Pearson Chi-squared test. Logistic regression was performed to assess the significance of patient characteristics in differentiating mimic from stroke, followed by receiver operation characteristic (ROC) curve analysis with the area under curve (AUC) indicating diagnostic accuracy. Five models were constructed to examine the

TABLE 1 | Predictors used in logistic regression models for stroke vs. mimic and transient ischaemic attack vs. mimic.

Stroke vs. Mimic	
Model	Predictors
A1	Symptoms
A2	Symptoms, NIHSS score, age, sex
A3	Symptoms, NIHSS score, age, sex, CTA (no occlusion)
A4	Symptoms, NIHSS score, age, sex, CTP (ischaemic lesion of 0 mL)
A5	Symptoms, NIHSS score, age, sex, CTA (no occlusion), CTP (ischaemic lesion of 0 mL)
TIA vs. Mimic	
Model	Predictors
B1	Symptoms
B2	Symptoms, NIHSS score, age, sex
B3	Symptoms, NIHSS score, age, sex, CTA (no occlusion)
B4	Symptoms, NIHSS score, age, sex, CTP (ischaemic lesion of 0 mL)
B5	Symptoms, NIHSS score, age, sex, CTA (no occlusion), CTP (ischaemic lesion of 0 mL)

NIHSS, National Institutes of Health Stroke Scale; CTA, computed tomography angiography; CTP, computed tomography perfusion; TIA, transient ischaemic attack.

diagnostic accuracy of using clinical features only and then with the addition of imaging findings to differentiate the additional benefit in diagnostic accuracy with CTA and/or CTP. The core volume on the summary CTP maps was used as the CTP ischaemic lesion volume in the statistical analysis. Only the symptoms, which were significant as a univariate predictor, were included in the models. Please see **Table 1** for further detail regarding the models and the variables included as predictors. Similarly, logistic regression and ROC analysis were also performed to assess the diagnostic accuracy in differentiating mimic from TIA, and five analogous models were also created (**Table 1**). All statistical analysis was done using STATA 13.0 (Stata Corp, College Station, TX, USA), with CI set at 95% and a significant level set at 0.05.

RESULTS

In total, 1,513 patients were assessed over this time period by the Northern New South Wales Telestroke service, and 1,074 patients assessed had CTP and were included in this study. The most common reasons for not proceeding with mCT included evidence of established stroke, bleed, or tumour on non-contrast CT brain (121 patients, 28%), minor symptoms (119, 27%), or presentation deemed unlikely to be stroke (79 patients, 18%). Stroke was diagnosed in 693 (64%) patients, 97 patients (9%) were diagnosed with TIA, 259 (24%) patients were classified as mimics, and 25 (2%) patients were found to have an intracranial bleed. The diagnosis of stroke was confirmed on MRI imaging in 288 (42%) patients, 326 (47%) cases were confirmed on CT imaging, and 79 (11%) cases were clinical diagnoses. With regards to the aetiology of the cases classified as a mimic, there were 47 (18%) seizures, 28 (11%) were diagnosed with a functional neurological syndrome, 25 (10%) with syncope or hypotension, 22 (8%) with migraine, 22 (8%) with delirium or metabolic encephalopathy, 20 (8%) with peripheral vestibulopathy, 11 (4%) with infection, 10 (4%) with peripheral nerve lesion, 10 (4%) with drug intoxication or medication side effect, and 7 (3%) with intracranial tumour. There were 28 (11%) cases of mimics that had an identified cause, but <5 cases for each cause, and 29 (11%) cases where the aetiology of the mimic could not be further determined.

There were considerable differences between the stroke and mimic groups (**Table 2**). In terms of demographics, those with stroke tended to be older than the stroke mimics, with 73% over age 65 in the stroke group compared to 50% in the mimics ($p < 0.001$). There was a higher proportion of male patients in the stroke group than the mimic group (64 vs. 44%, $p < 0.001$). The mimic group had lower NIHSS scores, 65% having an NIHSS score ≤4 in the mimic group vs 42% in the stroke group ($p < 0.001$). Hemiparesis, aphasia, the visual disturbance were more common in the stroke group compared to the mimic group (**Table 2**). Clinical features, which were more common in the mimic group, were vertigo, decreased level of consciousness, non-localising symptoms, disorientation, headache, and seizures (**Table 2**). The symptom of paraesthesia did not differ between the two groups (**Table 2**).

The diagnostic accuracy of an absent CTP core/penumbra lesion in a univariate regression model for distinguishing stroke from stroke mimic produced an AUC of 0.79 (95% CI 0.77–0.81), and this was higher than the diagnostic accuracy of no vessel occlusion on CTA, which had an AUC of 0.72 (95% CI 0.70–0.74). Multivariate regression models for differentiating stroke from mimics were created using symptoms that were significant in univariate analysis (**Table 2**), acute NIHSS score, age, sex, and CT imaging findings (**Table 3**). The first multivariate regression model, A1, using symptoms only, produced an AUC of 0.71 (95% CI 0.67–0.75; **Figure 1**). In the second model, A2, with the addition of acute NIHSS score, age, and sex to the initial model, the AUC improved to 0.80 (95% CI 0.77–0.84). In the third model, A3, with the addition of the absence of CTA occlusion to the same clinical features used in model A2, the AUC was improved to 0.88 (95% CI 0.86–0.90). In the fourth model, A4, with the addition of an absent CTP core/penumbra lesion to clinical features, the AUC was improved to 0.90 (95% CI 0.88–0.92). In the fifth model, A5, the addition of both absence of occlusion on CTA and absence of CTP core/penumbra lesion yielded the model with the highest diagnostic accuracy, AUC of 0.91 (95% CI 0.89–0.93).

With regards to the differentiating between TIA and mimics, there was no significant difference between the two groups in terms of sex (**Table 2**). Older age, lower NIHSS scores (≤4), hemiparesis, dysarthria, and paraesthesia were more common in those with TIA compared to mimic (**Table 2**). Decreased levels of consciousness, disorientation, and seizure were more likely to be present in mimics than in patients with TIA (**Table 2**). Other individual clinical features, such as vertigo, and non-localising symptoms, did not distinguish between mimic and TIA (**Table 2**).

In the initial multivariate regression model for distinguishing mimic from TIA using symptoms only (B1), the AUC was 0.71 (95% CI 0.65–0.76; **Figure 2**). The AUC was improved to 0.77 (95% CI 0.72–0.82) when age and NIHSS score were added to the model (B2). With the addition of no occlusive lesion on CTA to the model (B3), the AUC did not improve, AUC

TABLE 2 | Predictors for stroke vs. mimic and TIA vs. mimic.

	Stroke ($n = 693$)	Mimic ($n = 259$)	TIA ($n = 97$)	P value for stroke vs. mimic	P value for TIA vs. mimic
CTP ischaemic lesion = 0 ml	246 35.5%	245 94.6%	86 88.7%	<0.001	0.051
Age>65	510 73.6%	129 49.8%	64 65.9%	<0.001	0.007
Male	449 64.8%	115 44.6%	51 52.6%	<0.001	0.178
Baseline NIHSS score ≤4	296 42.9%	164 65.1%	83 85.6%	<0.001	<0.001
Clinical feature					
Hemiparesis	444 64.1%	102 40.2%	54 56.3%	<0.001	0.007
Aphasia	222 32.0%	57 22.4%	N/A	0.004	N/A
Dysarthria	N/A	20 7.9%	17 17.7%	N/A	0.008
Visual disturbance	110 15.9%	20 7.9%	N/A	0.002	N/A
Paraesthesia	36 5.2%	21 8.3%	17 17.7%	0.078	0.011
Vertigo	12 1.7%	22 8.7%	3 3.1%	<0.001	0.073
Decreased level of consciousness	17 2.5%	35 13.8%	1 1.0%	<0.001	<0.001
Non-localising symptoms	6 0.9%	14 5.5%	1 1.0%	<0.001	0.065
Disorientation	12 1.7%	19 7.5%	0 0%	<0.001	0.006
Headache	6 0.9%	19 7.5%	N/A	<0.001	N/A
Seizure	4 0.6%	12 4.7%	0 0%	<0.001	0.03

TIA, transient ischaemic attack; CTP, computed tomography perfusion, NIHSS, National Institutes of Health Stroke Scale.

TABLE 3 | Multivariate regression model for predicting mimic vs. stroke.

Mimic vs. stroke	Odds ratio	*P* value	95% CI	
CTP lesion = 0 ml	31.28	<0.001	16.43	59.54
Age > 65	0.33	<0.001	0.22	0.50
Male	0.40	<0.001	0.27	0.59
NIHSS score ≤ 4	1.53	0.048	1.00	2.33
Aphasia	1.35	0.207	0.84	2.16
Visual disturbance	0.92	0.826	0.46	1.84
Paraesthesia	0.82	0.576	0.41	1.64
Vertigo	4.67	0.001	1.82	11.98
Decreased LOC	12.82	<0.001	5.04	32.58
Non-localising symptoms	6.61	0.007	1.67	26.09
Disorientation	7.62	<0.001	2.90	19.99
Headache	4.17	0.017	1.29	13.49
Seizure	9.57	0.004	2.07	44.09

CTP, computed tomography perfusion; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval.

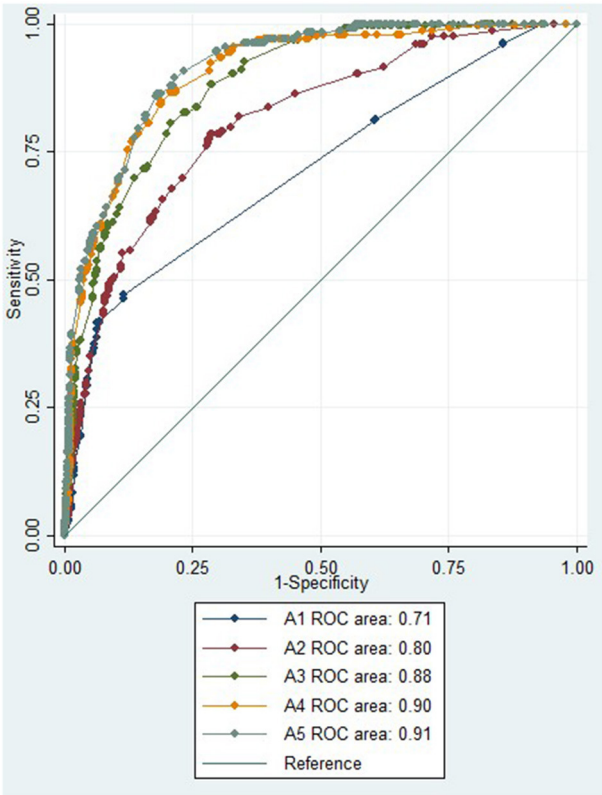

FIGURE 1 | ROC for multiple regression model to distinguish between stroke and mimic. ROC, receiver operator curve; NIHSS, National Institutes of Health Stroke Scale; CTA, computed tomography angiography; CTP, computed tomography perfusion.

0.77 (95% CI 0.72–0.83; **Figure 2**). Similarly, with the addition of absence of CTP lesion in the B4 model, the AUC did not significantly improve, AUC 0.78 (95% CI 0.73–0.83; **Figure 2**), even though the absence of a CTP lesion was a borderline significant independent variable in the multivariate equation ($p = 0.054$, **Table 4**). The addition of both CTA and CTP findings of no lesion in model B5 has a similar AUC of 0.77 (95% CI 0.72–0.82).

DISCUSSION

The results are consistent with previous studies in non-telestroke and telestroke populations showing that there are a number of clinical features that can help differentiate between stroke and mimics (4, 6, 11). Patients with stroke tended to be older, have lateralising symptoms, and have higher NIHSS scores compared to mimics (4, 6, 11). In contrast, symptoms which occurred more commonly in mimic, such as vertigo, decreased level of consciousness, confusion, headache, and seizure, were less likely to be strokes and tended to be the common presentation of mimic conditions, such as migraine, seizures, and metabolic disturbances (11). The diagnostic accuracy of our model using clinical features to differentiate between stroke and mimic was

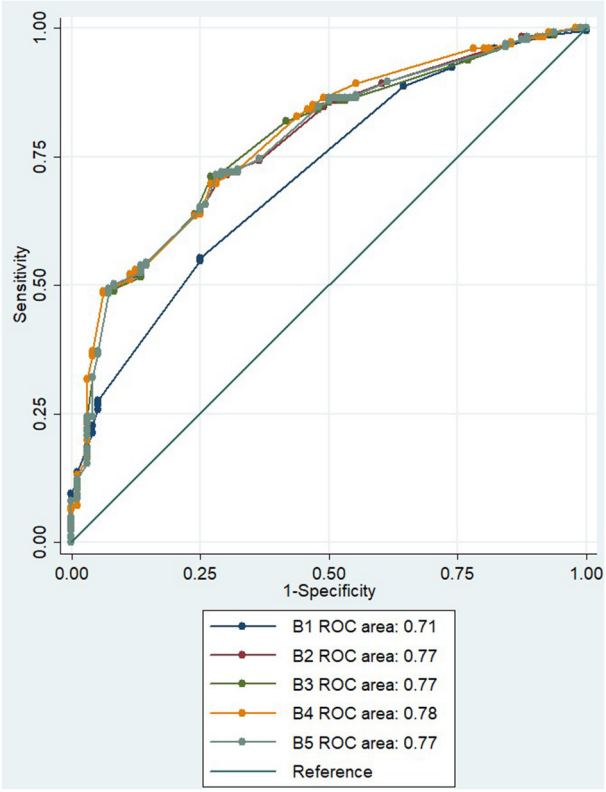

FIGURE 2 | ROC for multiple regression model to distinguish between TIA and mimic. ROC, receiver operator curve; NIHSS, National Institutes of Health Stroke Scale; CTA, computed tomography angiography; CTP, computed tomography perfusion.

TABLE 4 | Multivariate regression model for predicting mimics vs. TIA.

Mimics vs. TIA	Odds	*P*	95% CI	
CTP lesion = 0 ml	2.84	0.054	0.98	8.22
Age > 65	0.33	<0.001	0.18	0.59
NIHSS score ≤ 4	0.34	0.003	0.16	0.70
Hemiparesis	0.58	0.065	0.33	1.03
Dysarthria	0.29	0.007	0.12	0.71
Vertigo	4.21	0.031	1.14	15.53
Paraesthesia	0.33	0.009	0.15	0.76
Decreased LOC	15.22	0.009	1.95	118.43
Non-localising symptoms	2.60	0.386	0.29	22.58
Disorientation	1	(omitted)		
Seizure	1	(omitted)		

TIA, transient ischaemic attack; CTP, computed tomography perfusion, NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval.

similar to that of Ali et al. (12) who had a result of 0.72, using age, NIHSS, history of atrial fibrillation, hypertension, and facial weakness as predictors in their model. Similar to other studies looking at the primary presentation of stroke, the rate of mimics was about 24% (4, 5, 8, 11).

Regression analysis to distinguish between stroke and mimic showed that the presence of a CTP lesion in isolation was as accurate as clinical features in diagnosis. This is particularly important in a telestroke setting, where it can be difficult to appreciate nuances in clinical features remotely. When adding the absence of a CTP lesion to the clinical features, the ROC area of 0.9 was extremely high. Whilst there are no comparable studies using a telehealth population and CTP in their regression models, the accuracy of our model is as least as accurate as studies where face-to-face clinical assessment occurred and included CTA findings (but not CTP) in their models (6). Our model using CTP in addition to clinical features is considerably more accurate than that of previous stroke mimic prediction scales used in the telestroke context, which have only included clinical features (12). Our findings support the use of CTP in improving diagnostic confidence when attempting to distinguish stroke from mimics in the telehealth setting.

With regards to differentiating between TIA and mimic, as expected, decreased level of consciousness was more likely to occur in mimic than TIA, given that decreased level of consciousness is more commonly associated with metabolic disturbances and seizures than ischaemic pathology (7). Interestingly, lower NIHSS scores were more common in those with TIA compared to mimic. One possible explanation of this finding is that the conditions which mimic stroke can present with generalised weakness which may be scored highly on the NIHSS, compared to TIA which usually presents with minor or rapidly resolving focal neurological symptoms. Whilst not as many of the symptoms were statistically significant to differentiate between mimics and TIA individually in comparison to the stroke vs. mimic model, collectively, as demonstrated in the multivariate regression model, the AUC was 0.71 and comparable to that using symptoms alone for distinguishing between stroke and mimic. This model is comparable to the AUC of the Dawson Model and slightly less than the diagnosis of TIA (DOT) model previously described to differentiate between TIA and TIA mimics (7).

The use of mCT did not improve the diagnostic accuracy of differentiating between TIA and mimic in this study and this could be due to limited power from the small number of patients diagnosed with TIA (9%) and the possibility of misclassification in the final diagnosis between those in the TIA and mimic groups given the inherent difficulties to accurately and reliably apply the operationalised definitions. Interestingly, ischaemic core/penumbra lesions were seen in a subset of patients with TIA, and there was a strong trend for the absence of core/penumbra lesion to predict mimic from TIA in multivariate analysis (**Table 4**). It was not expected that the absence of an ischaemic lesion on automated CTP maps would be useful to differentiate between TIA and mimic, because neither conditions are expected to have a core/penumbra lesion on CTP. This raises the possibility that assessment of the individual perfusion maps might also assist in distinguishing between mimic and TIA (15–17). This potentially provides an avenue of further investigation to aid the clinically difficult task of differentiating TIA from mimic, especially via telemedicine.

A limitation of the current study is its retrospective analysis which exposes it to the possibility of information bias. There is a small proportion of patients diagnosed with stroke clinically who did not have subsequent imaging to confirm the diagnosis. It is possible that a subset of these patients were mimics who were incorrectly classified. To improve the external validity of the study, patients referred to the telestroke service but who did not proceed to have CTP were excluded from the analysis to reflect the clinical practice that patients diagnosed with the established stroke, bleed, or tumour on non-contrast CT brain, or minor symptoms, are generally ineligible for reperfusion therapy. We limited our analysis to the patients presenting with stroke-like symptoms being considered for reperfusion therapy, to provide evidence whether CTP could be used as a tool to improve diagnostic confidence between strokes and mimic. However, selecting this particular population and excluding those with minor symptoms or a syndrome clinically inconsistent with stroke may have potentially affected the analysis of differentiating TIA vs. mimics.

The results of this study support the use of CTP to improve the accuracy of differentiating between stroke and mimics in a telehealth setting for patients being considered for reperfusion therapy. Whilst it is generally not harmful to give thrombolysis to mimics (18), when one does, it can falsely elevate rates of good outcome (as the mimics generally have an excellent natural history). Further, the cost-effectiveness of using a relatively expensive medication and more intensive (and expensive) post-lysis inpatient care, unnecessary investigations, and/or patient transfer has yet to be properly assessed. The feasibility of using CTP in rural areas with expert stroke input via telehealth for improving access to stroke-specific therapy, such as thrombolysis, has been demonstrated in a previous study with a similar population (3).

In summary, patients presenting with an acute stroke-like presentation assessed via telemedicine for reperfusion therapy, such as acute CTP, can help reliably distinguish strokes from mimics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hunter New England Human Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. An opt-out consent form was available for participants who did not wish to participate.

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CG-E, BC, LT, and LL organised the database. LL performed the statistical analysis and wrote sections of the manuscript. LT and MP wrote the initial draft of the manuscript. All authors contributed to the revision of the manuscript, approved the final manuscript for publication, contributed to the conceptualisation, and design of the study.

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Feasibility of Telemedical HINTS (Head Impulse-Nystagmus-Test of Skew) Evaluation in Patients With Acute Dizziness or Vertigo in the Emergency Department of Primary Care Hospitals

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Background: Acute dizziness, vertigo and imbalance are common symptoms in emergency departments. Stroke needs to be distinguished from vestibular diseases. A battery of three clinical bedside tests (HINTS: Head Impulse Test, Nystagmus, Test of Skew) has been shown to detect stroke as underlying cause with high reliability, but implementation is challenging in primary care hospitals. Aim of this study is to prove the feasibility of a telemedical HINTS examination *via* a remotely controlled videooculography (VOG) system.

Methods: The existing video system of our telestroke network TEMPiS (Telemedic Project for Integrative Stroke Care) was expanded through a VOG system. This feature enables the remote teleneurologist to assess a telemedical HINTS examination based on inspection of eye movements and quantitative video head impulse test (vHIT) evaluation. ED doctors in 11 spoke hospitals were trained in performing vHIT, nystagmus detection and alternating cover test. Patients with first time acute dizziness, vertigo or imbalance, whether ongoing or resolved, presented to the teleneurologist were included in the analysis, as long as no focal neurological deficit according to the standard teleneurological examination or obvious internal medicine cause was present and a fully trained team was available. Primary outcome was defined as the feasibility of the telemedical HINTS examination.

Results: From 01.06.2019 to 31.03.2020, 81 consecutive patients were included. In 72 (88.9%) cases the telemedical HINTS examination was performed. The complete telemedical HINTS examination was feasible in 46 cases (63.9%), nystagmus detection in all cases (100%) and alternating covert test in 70 cases (97.2%). The vHIT was recorded and interpretable in 47 cases (65.3%). Results of the examination with the VOG system yielded clear results in 21 cases (45.7%) with 14 central and 7 peripheral lesions. The

main reason for incomplete examination was the insufficient generation of head impulses.

Conclusion: In our analysis the telemedical HINTS examination within a telestroke network was feasible in two thirds of the patients. This offers the opportunity to improve specific diagnostics and therapy for patients with acute dizziness and vertigo even in primary care hospitals. Improved training for spoke hospital staff is needed to further increase the feasibility of vHIT.

Keywords: dizziness, vertigo, telemedicine, emergency department, stroke, HINTS, video head impulse test

INTRODUCTION

Vertigo and dizziness are among the most common symptoms in the emergency department (ED) with about 4% of emergency patients suffering from it (1). Lifetime prevalence of medium and intense vertigo and dizziness is about 30% (2). About 4.4 million annual visits to emergency rooms in the United States of America are due to vertigo and dizziness (3). A relevant portion of patients with dizziness and vertigo are misdiagnosed in the ED (4). In particular, failing to identify stroke as a cause of dizziness/vertigo has fatal consequences (5). According to recent estimates about 4% to 10% of ED patients with dizziness and vertigo as leading symptoms have a stroke (6, 7) and misdiagnosis of peripheral vestibular failure is estimated to account for up to 60% of stroke cases during the initial classification of patients in the ED (5, 8, 9).

The quick differentiation between a central and a peripheral cause of dizziness/vertigo is crucial to start appropriate therapy in time, e.g., stroke unit therapy including thrombolysis in selected cases. In order to differentiate central and peripheral causes, the HINTS (Head Impulse test, Nystagmus, Test of Skew) is the best known clinical test battery in cases of acute dizziness/vertigo (10). The HINTS examination is a battery of bedside clinical tests and consists of three examinations: the head impulse test, characterization of nystagmus and test of skew. It has been shown to be more reliable than a cranial MRI (Magnetic Resonance Imaging) in the first 48 h after the onset of vertigo symptoms in patients with acute vestibular syndrome (AVS) (11). Within the HINTS examination, the single best predictor for stroke is the clinically assessed horizontal head impulse test (HIT). A bilaterally normal result increases the odds of a stroke and an abnormal HIT is predictive for a peripheral vestibulopathy (9). HIT is also the most challenging to perform and to interpret, and the expertise of the examiner affects results with sensitivity of maximum 70% [compared to video head impulse test (vHIT)] even in experienced neuro-otologists (12, 13). This is, amongst other reasons, due to the fact that in a relevant proportion of individuals early corrective saccades in eye movements or so-called covert saccades are clinically not detectable. Clinically visible saccades with later onset are referred to as overt saccades. The clinical differentiation of correcting saccades from Nystagmus might therefore be difficult (14). Furthermore, HIT is a subjective test without an objective verifiable approach. The quantitative analysis of HIT, called vHIT overcomes these limitations (10, 15–17). It has already been shown in various studies that, compared to clinical bedside HIT, vHIT improves the HINTS examination (10, 17). Moreover, HINTS examination's sensitivity and specificity are higher when tests are performed and interpreted by a trained neurologist rather than by emergency physicians (18). Those specialists are mostly not available in the ED of primary care hospitals and due to lack of expertise HINTS examinations are often not performed at all (9). In our study we built on those experiences and performed HINTS examinations *via* a VOG system. The technical examinations were included in a standard videoconferencing system to be assessed remotely by an experienced teleneurologist. Our telemedicine-supported project to examine patients with dizziness and vertigo (called TeleVertigo) may offer improved acute care in patients with acute dizziness, vertigo or imbalance in EDs of primary care hospitals (19). This study aims to analyze the feasibility of a telemedical HINTS examination.

MATERIALS AND METHODS

This study was based on our telemedical stroke network cohort. The Telemedic Project for Integrative Stroke Care (TEMPiS) is a telestroke unit network in South East Bavaria, Germany, with two comprehensive stroke centers (hubs) and 24 primary stroke centers (spokes) (20). Within this network any patient with suspicion of acute stroke admitted to the ED in one of the spokes is presented to a teleneurologist provided there is no consultant neurologist on site. In addition to the evaluation of computed tomography (CT) scans (or MRI) hyperacute treatment, e.g., recanalization therapies and stroke unit care, can be recommended. In the network more than 7.000 teleconsultations are performed annually.

Since November 2018, the TeleVertigo project has been implemented on the already existing structure of the TEMPiS network in 11 spokes so that any patients presented within the TEMPiS network could be telemedically examined concerning dizziness and vertigo (19). A VOG system plugged into the existing video conferencing system was established. This feature enables the remote teleneurologist to see even subtle eye movements and to instruct and evaluate the vHIT.

Abbreviations: AVS, acute vestibular syndrome; CT, computed tomography; ED, emergency department; HINTS, Head Impulse Test, Nystagmus, Test of Skew; HIT, head impulse test, IQR, inter-quartile range; MRI, magnetic resonance imaging; ms, millisecond; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation; TEMPiS, Telemedic Project for Integrative Stroke Care; TIA, transient ischemic attack; vHIT, video head impulse test; VOG, videooculography; VOR, vestibulo-ocular reflex.

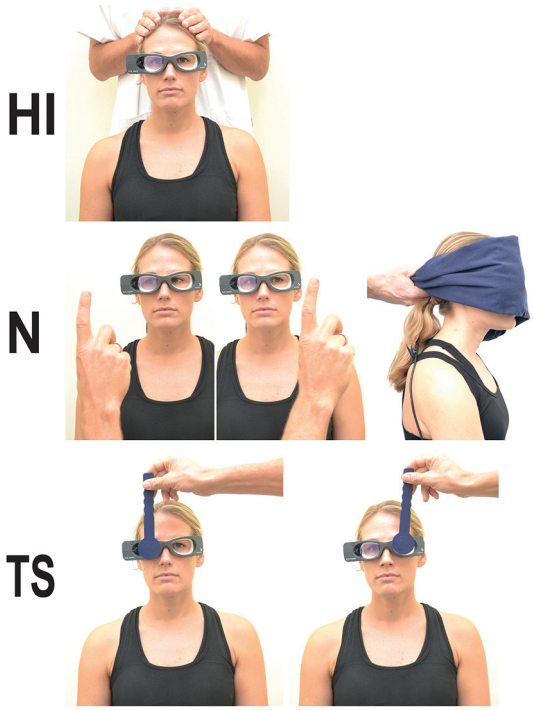

FIGURE 1 | Performance of the three-step HINTS test battery: (HI) head impulse test, (N) nystagmus detection and (TS) test of skew. Nystagmus detection is performed in primary gaze position with and without fixation as well as looking about 20°–30° to the right and to the left.

According to the standard TEMPiS procedure, any patient examined *via* videoconference first undergoes medical history screening (including pre-existing conditions and medication) and stroke assessment including National Institute of Health Stroke Scale (NIHSS) classification. In dizzy and vertiginous patients and those with acute balance disturbance a more detailed neurological examination is performed provided it is possible *via* standard camera. In this study, according to a consensus statement of the Barany Society, we defined dizziness as "the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion" and vertigo as "the sensation of self-motion when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement" (21). If there are clear signs of either a central origin (mostly concomitant focal neurological deficits) or a primary internal disease in history, clinical examination, laboratory results or imaging explaining the patients' symptoms, they are admitted either to the stroke unit or to internal medicine ward respectively. If standard teleneurological examinations reveal no conclusive signs concerning the symptoms' etiology, examination with the VOG system is added. An algorithm for the HINTS examination for dizzy/vertiginous patients aimed at differentiating peripheral vs. central origin was implemented. Further detail can be found in an already published account on this system (19). This study exclusively evaluates the telemedical HINTS examination.

Standard Operating Procedures and Teaching

As a first step, standard operating procedures for performance and interpretation of the TeleVertigo examination as well as for treatment options were implemented. A training program was set up for spoke staff members to perform vHIT, nystagmus detection and the alternating cover test (see **Figure 1**). This included 15 central training courses with 3.5 h of theoretical training and 2.5 h of practical training for doctors, nursing staff and therapists, on-site sessions for each hospital and also one-to-one online teachings per request. Furthermore, trained personnel were instructed to share knowledge with colleagues. All sessions were performed by the neuro-otologists and specialized physiotherapists of the two centers (Munich Clinic Harlaching and InnKlinikum Altötting). Teleneurologists in one hub hospital (Munich Clinic Harlaching) underwent individual training regarding the operation and interpretation of the acute examination. When necessary, supervision by a neuro-otologist was carried out during core working hours. At regular ongoing intervals, quality circles were organized for all participating hospitals.

Technical Device

The additional TeleVertigo examination is performed using a VOG system (video goggles; ICS Impulse Type 1085 in combination with the OTOsuite Vestibular software, version 4.10 Build 1341, Natus Medical Denmark ApS, Taastrup, Denmark) as described elsewhere (19). These lightweight video goggles include a light, small and very fast infra-red camera, a half-silvered mirror reflecting infra-red light and small sensors measuring head movement velocity. Video goggles are secured to the patient's head with adjustable straps to minimize slippage. They were especially developed to document and quantify the vestibulo-ocular reflex (VOR). In the telemedical setting, those video goggles are used additionally as a second camera during videoconferencing for detection of nystagmus and skew deviation. This allows teleconsultants to explore even subtle eye movements, which is not possible with a standard camera. The video goggles are plugged into the videoconferencing system on demand. The teleconsultant operates the video goggle software and camera, and the doctor in the spoke hospital carries out examinations on the patient (e.g., giving head impulses, covering the eye, etc.).

Hints Examination and Decision Rules

The telemedical HINTS examination was performed after a regular neurological examination and comprises oculography for nystagmus detection and test of skew as well as vHIT. According to the definition of the HINTS examination, we classified the result as peripheral vestibular lesion in case of direction fixed nystagmus, pathological vHIT and lack of skew deviation (each criterion must be met). A central vestibular lesion was assumed in case of direction-changing nystagmus and/or skew deviation or the combination of any nystagmus with a physiological vHIT. All cases without nystagmus were classified as unclear.

Oculography for Nystagmus Detection

The patient is placed at 1 m distance from a fixation dot (on the wall). In order to perform an eye movement calibration of the VOG system, the patient is asked to stare at a projected dot. Gaze examination is performed to test for spontaneous and gaze evoked nystagmus. Therefore, the patient is instructed to look center, left and right (both about 20°-30°), first with fixation, then with fixation block. This latter is performed by covering the patient's eyes with an opaque towel. Nevertheless, the camera of the video goggles still enables the examination of eye movements. Each position is held for 15–30 s. Nystagmus analysis is carried out by the teleneurologist in the hub based on the evaluation of the video frame of the right eye. A direction changing gaze nystagmus strongly indicates a central lesion (22).

Test of Skew Deviation

Skew deviation is tested through alternating cover test. The patient is instructed to stare at the dot on the wall again. The ED physician starts covering the right eye with one hand, then moves the hand to the left to cover the left eye, and back again to cover the right eye. Each eye is covered for about 5 s. This is repeated until each eye was covered at least five times. Through the camera the covered right eye is still visible to the teleneurologist. The teleneurologist evaluates whether there is a vertical adjustment movement of the right eye when covering or uncovering it. Skew deviation commonly indicates a vertebrobasilar pathology, especially brainstem strokes, but can also be caused by a peripheral vestibular pathology (9, 23, 24). A recent publication casts doubt on this interpretation (25).

Video Head Impulse Test

During vHIT patients remain seated on the bed (or a stationary chair) at about 1 m distance from the dot on the wall which they are supposed to stare at. It is especially important that the straps of the video goggles are fixed tightly on the patient's head. The ED physician is standing behind the patient holding the patient's head with both hands above or below the straps. The ED physician rotates the patient's head horizontally at a small angle (about 10°-20°) in a random direction. In each direction (leftward and rightward) rotation is performed until 10–15 interpretable impulses are detected on both sides. Velocity of the stimulus (head movement) and velocity of the response (eye movement) are measured, displayed and processed by the OTOsuite software. Gain as ratio of eye movement velocity to head movement velocity is calculated. Individual gain of every single movement is displayed as well as the mean gain of all impulses on one side and shown on a diagram (gain vs. head velocity). Furthermore, head movement and eye movement velocity and possible catch-up saccades are displayed in a graph. Unilateral gain values <0.8 together with catch-up saccades are considered pathological, mostly indicating an unilateral vestibulopathy (16). A normal vHIT in the setting of AVS is a strong predictor of a central origin, mostly indicating stroke (22).

Study Population

This study included consecutive patients who were admitted to EDs in the 11 participating primary care hospitals (TEMPiS stroke network spokes) and presented to the teleneurologist with acute dizziness, vertigo or imbalance of new quality within the last 72 h, without a new focal neurological deficit in the standard teleneurological examination and without any other obvious reason for the symptoms. Furthermore, fully trained staff in the spoke was mandatory, as well as fully trained teleneurologists in the hub. As only one teleneurologist team was trained, only those weeks in which the hub hospital in Munich Clinic Harlaching was on duty were included. Patients who had paroxysmal symptoms or completely resolved symptoms at time of consultation were included as well. Exclusion criteria were the unavailability of the examination *via* VOG system in the ED.

Study Protocol

All variables were predefined. The following variables were collected prospectively from examinations stored in the software of the video goggles: vHIT parameters and duration of the examination. The other variables were retrieved from documentation of the telemedical consultations: age, sex, vascular risk factors, history of stroke/transient ischemic attack (TIA), peripheral vestibular disorder or dizziness/vertigo of unknown origin, symptoms which led to presentation in the emergency room, onset of dizziness/vertigo/imbalance, results of examination of nystagmus, skew deviation and side effects. Overall evaluation of telemedical HINTS examination (feasibility and categorization to peripheral or central cause), and reasons why tests were not feasible were documented. Primary outcome was the feasibility of the telemedical HINTS examination. Secondary outcomes were the feasibility and results of the single tests as well as categorization to peripheral or central cause. Additionally, we investigated why testing with video goggles was incomplete in some cases. All data were stored in an anonymized quality register, for which no patient consent is required according to German legislation.

Statistical Analysis

As our primary and secondary outcomes of interest were descriptive in nature, we performed qualitative data analysis and used descriptive statistics.

RESULTS

From 01.06.2019 to 31.03.2020, 81 patients met the inclusion criteria for this study. 9 of them did not undergo an examination with the video goggle because of acute technical problems with the video goggles ($n = 5$), discharge against medical advice ($n = 2$) or language barrier with missing collaboration of the patient ($n = 2$) (see **Figure 2**).

In the remaining 72 cases an examination with the video goggles was performed. More female patients ($n = 49$; 68.1%) than male ($n = 23$; 31.9%) were included; mean age was 64.9 years. Median duration of dizziness/vertigo symptoms was 313 (IQR 231–653) minutes with almost half of the patients suffering from nausea ($n = 32$; 44.4%). For detailed baseline characteristics see **Table 1**. The median examination time for the

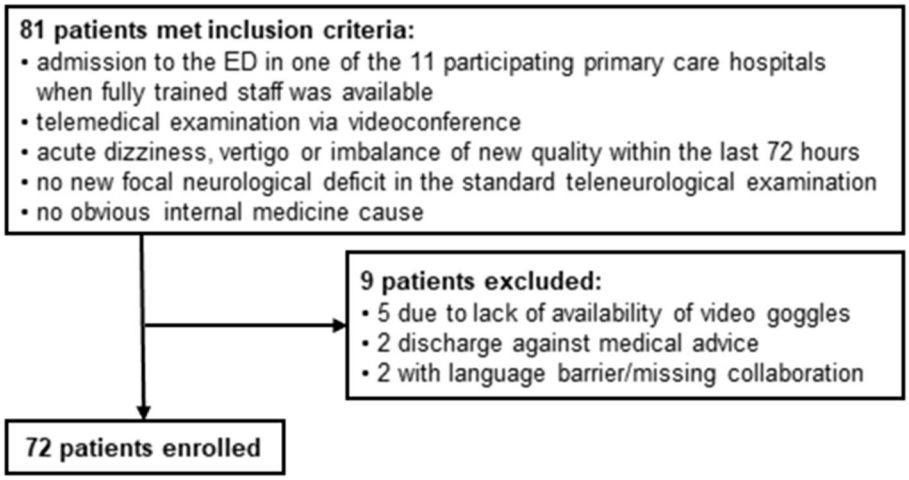

FIGURE 2 | Study design.

TABLE 1 | Baseline characteristics of all patients enrolled.

	***n* = 72**
Age, years (mean, SD)	64.9 (15.4)
Sex	
Male	23 (31.9%)
Female	49 (68.1%)
Duration since onset of symptoms, minutes (median, IQR)	313 (231–653)
Symptoms	
Gait instability	23 (31.9%)
Nausea	32 (44.4%)
Oscillopsia	3 (4.2%)
Vascular risk factors	
Hypertension	40 (55.6%)
Hypercholesterinemia	5 (6.9%)
Diabetes	8 (11.1%)
Current/former smoking	4 (5.6%)
History of	
Previous peripheral vestibular disease	4 (5.6%)
Previous vertigo/dizziness of unknown origin	7 (9.7%)
Previous stroke/TIA	13 (18.1%)
Atrial fibrillation	4 (5.6%)
Coronary artery disease	8 (11.1%)

IQR, interquartile range; SD, standard deviation.

TABLE 2 | Intended and completed telemedical HINTS examinations.

	Intended examinations	**Examinations fully completed with interpretable results**
vHIT	72	47 (65.3%)
Nystagmus	72	72 (100%)
Test of skew	72	70 (97.2%)
HINTS overall	**72**	**46 (63.9%)**

vHIT, video head impulse test; HINTS, Head Impulse Test, Nystagmus, Test of Skew.

telemedical HINTS examination and positional testing by Dix-Hallpike maneuver (results on that test are not reported in this manuscript) was 10 (IQR 6–15) minutes.

Successful evaluation of all three steps of the telemedical HINTS examination was feasible in 46 patients (63.9%) (**Table 2**). An investigation for nystagmus could be carried out in all patients ($n = 72$; 100%). The alternating covert test for search of skew was feasible in 70 (97.2%) and the vHIT in 47 (65.3%) patients. Mean peak velocity of head impulses was 213±37°/s on the right side and 209 ± 39°/s on the left side. Side effects, e.g., nausea and vomiting, during the examination occurred in 5 patients (6.9%).

In two patients, the alternating cover test was not possible due to lack of cooperation. vHIT could not be carried out successfully in 25 patients mainly due to insufficient generation of evaluable impulses ($n = 18$; 72%). Further reasons were vomiting, acute technical problems and the lack of patient cooperation.

In 46 patients, all parts of the telemedical HINTS examination were performed successfully. In 21 of those cases (45.6%) a conclusive result could be determined by application of the HINTS rule. A peripheral vestibular lesion was identified in 7 cases (15.2%) with an abnormal gain (mean gain 0.45 ± 0.18) and correcting saccades (mean number of overt saccades 0.73 ± 0.13, latency 257 ± 61 ms, amplitude 213 ± 62°/s; mean number of covert saccades 0.20 ± 0.15, latency 119 ± 23 ms, amplitude 151 ± 92°/s) on one side and a normal gain on the other side (mean gain 0.93 ± 0.15). Peak velocity of head impulses in these 7 patients was 210 ± 35°/s on the right side and 209 ± 50°/s on the left side. A central vestibular lesion was diagnosed in 14 cases (30.4%) due to direction changing nystagmus in 4 cases (8.7%) and direction-fixed nystagmus in combination with normal vHIT in 10 cases (21.7%). Peak velocity of head impulses in these 14 cases was 220 ± 42 on the right side and 204 ± 31 on the left side with a mean gain of 1.02 ± 0.13 and 0.96 ± 0.15, respectively.

TABLE 3 | Results of successful telemedical HINTS examinations ($n = 46$).

vHIT	Nystagmus	Skew	Number	Interpretation
Pathological	Direction-fixed nystagmus	No	7 (15.2%)	Peripheral cause
Physiological	Direction-fixed nystagmus	No	10 (21.7%)	Central cause
Physiological	Direction-changing nystagmus	No	4 (8.7%)	Central cause
Physiological	No nystagmus	No	25 (54.3%)	Unclear (HINTS not applicable due to missing nystagmus)

vHIT, video head impulse test; HINTS, Head Impulse Test, Nystagmus, Test of Skew.

In 25 cases (54.3%) the HINTS rule was not applicable as no nystagmus was detectable. For the application of the HINTS rule a nystagmus as part of a vestibular syndrome is required. Therefore, we classified these cases without any nystagmus as unclear with respect to the underlying etiology. For details see **Table 3**.

DISCUSSION

Our prospective evaluation shows that telemedical HINTS examination can be performed successfully by trained staff *via* telemedicine in a relevant proportion of 63.9%. This study is the first evaluating a telemedical HINTS examination in ED patients of primary care hospitals. Our findings suggest that extensive area-covering and an 24/7 availability approach for the adequate workup of patients with acute dizziness and vertigo in hospitals without specialized neuro-otological care is possible. It may lead to a faster classification of these highly prevalent symptoms and may therefore be a relief not only for the patients but also regarding the socioeconomic burden. Reports are available on management improvements concerning dizzy patients *via* telemedicine. Zee et al. describe first experiences in the classification of patients with dizziness and vertigo in the ED by a "Tele-Dizzy consultation service" (26). Greater diagnostic accuracy *via* a telemedical connection to the neuro-otological department in the same academic center is reported. Similarly to our project, a VOG device was employed. All other published reports about telemedicine in dizzy/vertiginous patients focus on aspects others than the acute management in the emergency department (27–33).

Most challenging to perform but the single best predictor of a stroke is the vHIT. The full interpretability of almost two thirds of telemedical vHIT examinations in our cohort is therefore a remarkable result. Furthermore, based on the analysis of peak velocities of telemedical vHITs, peak velocities of head impulses of around 210°/s were reached, which is within recommended ranges (15). Nystagmus detection as well as test of skew were evaluated by clinical assessment of the transmitted video. The employed VOG system also allows a quantitative evaluation of these tests and may further improve diagnostic accuracy.

The time delay for an additional telemedical HINTS examination was <10 mins on average. This delay seems adequate for optimized triage with these symptoms.

In cases with successful telemedical HINTS examination, 46% could be classified as peripheral or central, leaving 54% of cases without classification according to the HINTS rule. Absence of a nystagmus in all those cases, made the HINTS rule non-applicable, and criteria for AVS were not met. AVS is a clinical syndrome of severe vertigo, nausea and vomiting, spontaneous nystagmus and postural instability (34). Recent studies estimate a proportion of AVS in all ED cases with acute dizziness/vertigo of about 10–20% (7). The higher proportion in our sample of 46% may be explained by case selection, as we did not include cases with obvious internal medicine cause, focal neurological deficit (explored in the teleneurological examination) and recurrent vertigo/dizziness symptoms of known quality. Nevertheless, with 54% of unclassifiable cases, the telemedical HINTS examination alone is of limited value for ED triage when criteria for AVS are not met. This is in line with recent publications (18). The addition of further symptom characteristics and tests may be of value. Further extensions of HINTS or new approaches to dizzy/vertiginous patients include addition of a bedside hearing test to HINTS (HINTS plus) to differentiate posterior fossa stroke from peripheral origin of vertigo (35), a more extended access including symptom timing, triggers and bedside eye examination (TiTrATE) (36) or adding standing examination and search for positional vertigo (STANDING) (37). Most of these items are integrated in the algorithm suggested by Venhovens et al. (38). Improved approaches to vertigo and dizziness with well-defined algorithms and further developed technology may offer new telemedical approaches (19, 39).

The most common reason in our study for not interpretable vHIT was the fact that not enough evaluable impulses could be generated. This difficulty may be overcome by more training and experience.

Twice as many cases suggesting a central lesion as cases with peripheral lesions (14 vs. 7) have been recorded in our sample when the telemedical HINTS examination was successful. Of note, among unsuccessful telemedical HINTS examinations in our sample, another 17 cases displayed direction-fixed nystagmus while vHIT was not interpretable. Most of these cases might have had a peripheral etiology, which, if identified, could have led to proportionally fewer central lesions in our findings. Once again, the rate of central lesions is higher than expected based on the available literature (6) and may be explained, in particular, by the generally more restrictive case selection criteria of our sample.

Strengths of our study are that it is a prospective and real-world analysis with data collection in multiple network spokes. This made it possible to collect a relevant number of consecutive patients ($n = 81$) over a 10-month-period. The disadvantage

of a multicenter study concerning data collection and data interpretation was compensated in part by a central evaluation in one single center (Munich Clinic Harlaching).

There are some *limitations* to our study. First, telemedical HINTS examinations were not assessed by one single neuro-otologist, but we ensured an intensive training of all the involved teleneurologists. Furthermore, we cannot exclude some convenience sampling as it is just within the discretion of the treating ED physician of the spoke hospital to decide which cases are presented to the teleconsultation service and therefore included in the study.

To summarize, we showed that the telemedical HINTS examination is feasible within a telestroke network if close cooperation as well as intensive and ongoing training are established, and if continuous telemedical supervision by a neuro-otologist is available. The telemedical application of oculomotor tests in primary care hospitals offers the opportunity to improve acute hospital care of patients with acute dizziness and vertigo. For a full evaluation of the efficacy of this approach further studies are needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

RM, CL, PM-B, NH, and GH contributed to conception and design of the study. RM, CL, and PM-B organized the database and performed the statistical analysis. RM and CL wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Identification of Stroke and TIA in Patients With Acute Dizziness, Vertigo or Imbalance in Emergency Departments of Primary Care Hospitals: Early Experiences With a Network-Based Telemedical Approach

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Background: Acute dizziness, vertigo, and imbalance are frequent and difficult to interpret symptoms in the emergency department (ED). Primary care hospitals often lack the expertise to identify stroke or TIA as underlying causes. A telemedical approach based on telestroke networks may offer adequate diagnostics and treatment.

Aim: The aim of this study is to evaluate the accuracy of a novel ED algorithm in differentiating between peripheral and central vestibular causes.

Methods: Within the Telemedical Project for Integrative Stroke Care (TEMPiS), a telemedical application including a videooculography (VOG) system was introduced in 2018 in 19 primary care spoke hospitals. An ED triage algorithm was established for all patients with acute dizziness, vertigo, or imbalance of unknown cause (ADVIUC) as a leading complaint. In three predefined months, all ADVIUC cases were prospectively registered and discharge letters analyzed. Accuracy of the ED triage algorithm in differentiation between central and peripheral vestibular cases was analyzed by comparison of ED diagnoses to final discharge diagnoses. The rate of missed strokes was calculated in relation to all cases with a suitable brain imaging. Acceptance of teleconsultants and physicians in spoke hospitals was assessed by surveys.

Results: A total number of 388 ADVIUC cases were collected, with a median of 12 cases per months and hospital (IQR 8–14.5). The most frequent hospital discharge diagnoses are vestibular neuritis (22%), stroke/TIA (18%), benign paroxysmal positioning vertigo (18%), and dizziness due to internal medicine causes (15%). Detection of a central vestibular cause by the ED triage algorithm has a high sensitivity (98.6%), albeit poor

specificity (45.9%). One stroke out of 32 verified by brain scan was missed (3.1%). User satisfaction, helpfulness of the project, improvement of care, personal competence, and satisfaction about handling of the VOG systems were rated consistently positive.

Discussion: The concept shows good acceptance for a telemedical and network-based approach to manage ADVIUC cases in the ED of primary care hospitals. Identification of stroke cases is accurate, while specificity needs further improvement. The concept could be a major step toward a broadly available state of the art diagnostics and therapy for patients with ADVIUC in primary care hospitals.

Keywords: dizziness, vertigo, telemedicine, emergency medicine, stroke, diagnostic method, acute vestibular syndrome

INTRODUCTION

Acute dizziness and vertigo are frequent and difficult to diagnose symptoms in the emergency department (ED) (1–3). Since stroke is the underlying cause in about 5% of these cases (4, 5) but missed in about 35% of stroke cases, especially when symptoms are mild and transient (6–9), a specific concept is required. Therefore, a workflow in the ED is desirable which identifies all stroke cases correctly for rapid admission to a stroke unit and applies immediate therapy such as intravenous thrombolysis if indicated. The most promising approach seems to use a battery of different oculomotor tests like the HINTS (head impulse – nystagmus – test of skew) or the HINTS plus exam (10–14), which identify strokes based on clinical examinations better than an initial MRI (9, 12). Adding the video head impulse test (vHIT) to quantify the vestibular ocular reflex further improves the effectiveness of the algorithm (15–17).

As those tests are applied by trained neurootologists, our challenge is to bring the necessary expertise to the bedside in ED of primary care hospitals, which mostly do not employ a neurologist in the ED. Our favored solution is telemedicine, as is already used with success in treating stroke, known as telestroke (18, 19). A telemedical consultation program for acutely dizzy patients bringing neurootological expertise in the ED of the same hospital reported higher diagnostic accuracy and lower employment of computed tomography scans (20). The employment of smartphones for vHIT measurement may facilitate this development in the future (21). A clinical trial comparing video-oculography (VOG) guided care to standard care in EDs is ongoing (Acute Video-Oculography for Vertigo in Emergency Rooms for Rapid Triage [AVERT] trial) (22).

Current telestroke networks seem ideal for the additional implementation of telemedical care for acutely dizzy patients, as there are close synergies to be expected (medically – because of the underlying etiology of stroke – and technically – because of the similar infrastructure needed). The logistics developed for telestroke could be extended for dizzy patients, regarding teleconsultation workflow, specific treatment standards, training, and quality management. Additional resources needed are mainly one expert neurootologist and one vestibular rehabilitation therapist in the network center, VOG systems in all spokes and sufficient resources for training and quality management (23).

This study evaluates our telematic approach to diagnose acute dizziness, vertigo, and imbalance in our telemedical stroke network TEMPiS in Bavaria, Germany, with the main focus on the diagnostic accuracy of the ED algorithm in differentiating between peripheral and central vestibular diseases. Results of the remote VOG examination including telemedical HINTS and vHIT are reported in another paper (24).

MATERIALS AND METHODS

As telestroke is already implemented in our region of South-East Bavaria, we built our concept on this telematic system. The Telemedical Project for Integrative Stroke Care (TEMPiS) is a stroke network consisting of two hubs and 24 spokes and was implemented in 2003 (18, 19). A total of 7,427 and 7,337 teleconsultations were performed in 2019 and 2020, respectively. TeleVertigo was introduced in 2018 in 19 spoke hospitals as an add-on to the preexisting telestroke collaboration (**Figure 1**). The detailed concept was already published (23). The catchment area of the 19 hospitals sums up to a population of 1,987,414 inhabitants (25). Six of these spokes have a neurology department on-site with 24/7 availability of a neurologist.

In brief, our innovative telemedical concept addresses all patients who were admitted to an ED of the participating primary care hospitals due to acute dizziness, vertigo, or imbalance of unknown cause (ADVIUC) as a leading complaint (**Figure 2**). The key technical diagnostic tool is a VOG system embedded in a standard videoconferencing system. In contrast to standard videoconferencing systems (26), the added VOG system enables vestibular testing by telemedicine. The concept comprises three stages: (1) telemedical triage in the ED (including vHIT and fast track VOG; **Figure 3**) for reliable and rapid decision-making on acute treatment, including stroke treatment if indicated: This triage uses a telemedical examination of oculomotor signs, the vHIT and the diagnostic Dix-Hallpike-maneuvers for

Abbreviations: ADVIUC, acute dizziness, vertigo, or imbalance of unknown cause; BPPV, benign paroxysmal positional vertigo; HINTS, head impulse – nystagmus – test of skew; IQR, interquartile range; TEMPiS, Telemedical Project for Integrative Stroke Care; TiTrATE, timing, triggers, and targeted bedside eye examinations; TIA, transient ischemic attack; vHIT, video head impulse test; VOG, videooculography.

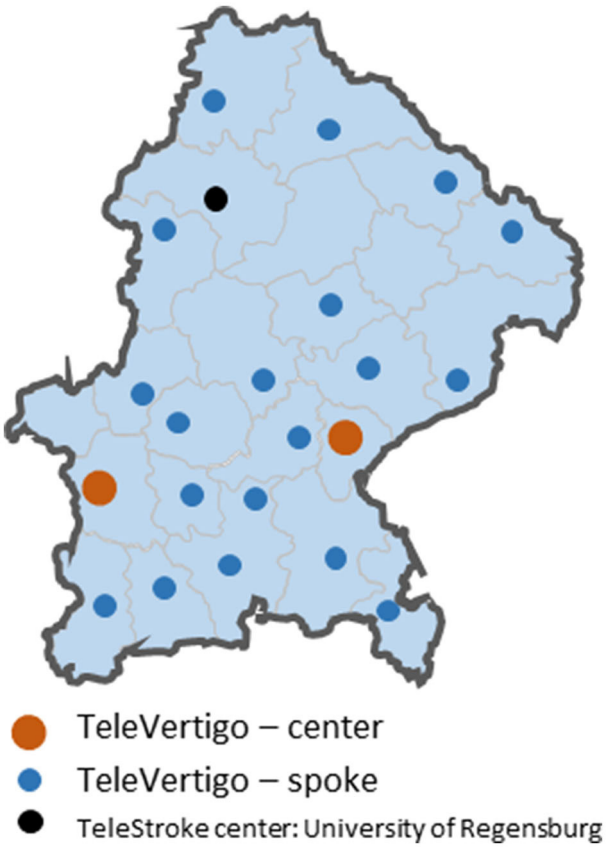

FIGURE 1 | Map of the southeastern part of Bavaria, Germany with all TeleVertigo hospitals.

benign paroxysmal positional vertigo (BPPV) of the posterior semicircular canals. For this purpose, a VOG system ("video goggles"; ICS Impulse Type 1085 in combination with the OTOsuite Vestibular software, version 4.10 Build 1341, Natus Medical Denmark ApS, Taastrup, Denmark) was included in the videoconferencing system in all participating hospitals; (2) elective clinical examination including quantitative VOG and finding of the causal diagnosis: In cases of ADVIUC, an elective neurological examination by the vascular neurologist is done next day. Vascular neurologists are thoroughly trained within this project in diagnosing dizziness and vertigo. Additionally, a VOG including nystagmus detection, tests for skew deviation, visually guided saccades, smooth pursuit eye movements, vHIT, and Dix-Hallpike-maneuvers is performed by trained technicians or physical therapists. On demand, a neurootologist of the network center evaluates this VOG remotely and supports spoke physicians in diagnosis and therapy. (3) Adequate treatment including vestibular rehabilitation and canalith repositioning procedures: Physiotherapy was established for all patients with ongoing dizziness, vertigo, or imbalance, including canalith repositioning maneuvers and vestibular rehabilitation. To obtain high standards, a physical therapist of the network center specialized in vestibular disorders offers regular training to the physical therapists in the spoke hospitals.

In 2018, we developed project standards for acute and elective diagnosis and treatment of patients with dizziness, vertigo, and imbalance, and also specific diagnostic and treatment standards for benign paroxysmal positional vertigo, vestibular neuritis, and dizziness of central origin, based on the criteria of the Bárány Society (27–29). We trained 180 physicians, therapists, and technicians of the participating hospitals in these standards in 15 sessions lasting 6 h each, consisting of 3.5 h of theoretical training and 2.5 h of practical training. An exit test or any other credential was not collected.

Study Protocol

For project evaluation, evaluation periods with full documentation of all admitted patients in the EDs of the participating hospitals were predefined. In compliance with the capacity of participating primary care hospitals, we tailored the evaluation effort to 3 months (11/2019, 3/2020, and 10/2020). A screening registry was designed, and all participating hospitals were asked to register all patients with the leading symptom of acute dizziness, vertigo, or imbalance of unknown cause (ADVIUC) in screening lists. "Unknown cause" was defined as follows: (1) In the ED, no history of episodic vertigo or dizziness with the same quality of symptoms like in the actual presentation was reported, and (2) in the first short triage done by ED physicians, an underlying reason for the acute dizziness symptom is not obvious. This triage includes a short internal medicine and neurological examination and also the assessment of vital parameters (heart rate, blood pressure, temperature, oxygen saturation), an ECG and basic blood parameters (small blood count, natrium, potassium and, if necessary, inflammation parameters, and D-dimer). Therefore, patients with an obvious hemiparesis or dyspnea were excluded, whereas patients with a subtle focal neurological deficit or mild internistic symptoms were included. In the ADVIUC analysis, all cases with symptoms lasting more than 72 h were excluded.

For all ADVIUC cases, discharge letters were requested, and relevant information was extracted by neurootologists in the stroke center (CL, PMB). Base data collected are as follows: age, sex, relevant risk factors, relevant symptoms, and hospital discharge diagnoses.

Accuracy of the triage algorithm was focused on cases with vestibular disorders. We compared the ED diagnoses to final discharge diagnoses for all central and peripheral vestibular cases according to the final discharge diagnosis. ED diagnoses were categorized as peripheral if diagnostic criteria for vestibular neuritis or BPPV were fulfilled. Cases with central signs (e.g., a direction-changing nystagmus or a skew deviation) or constellations suggestive for a central lesion (e.g., direction-fixed horizontal nystagmus, but physiological vHIT) or unclear constellations (e.g., no peripheral and central vestibular symptoms) were categorized as central.

In most ADVIUC cases without clear evidence for peripheral or internal medicine cause, a CT scan was performed in the ED. In all ADVIUC cases suspicious for a central etiology, cranial MRI was recommended between days 3 and 5. The written results

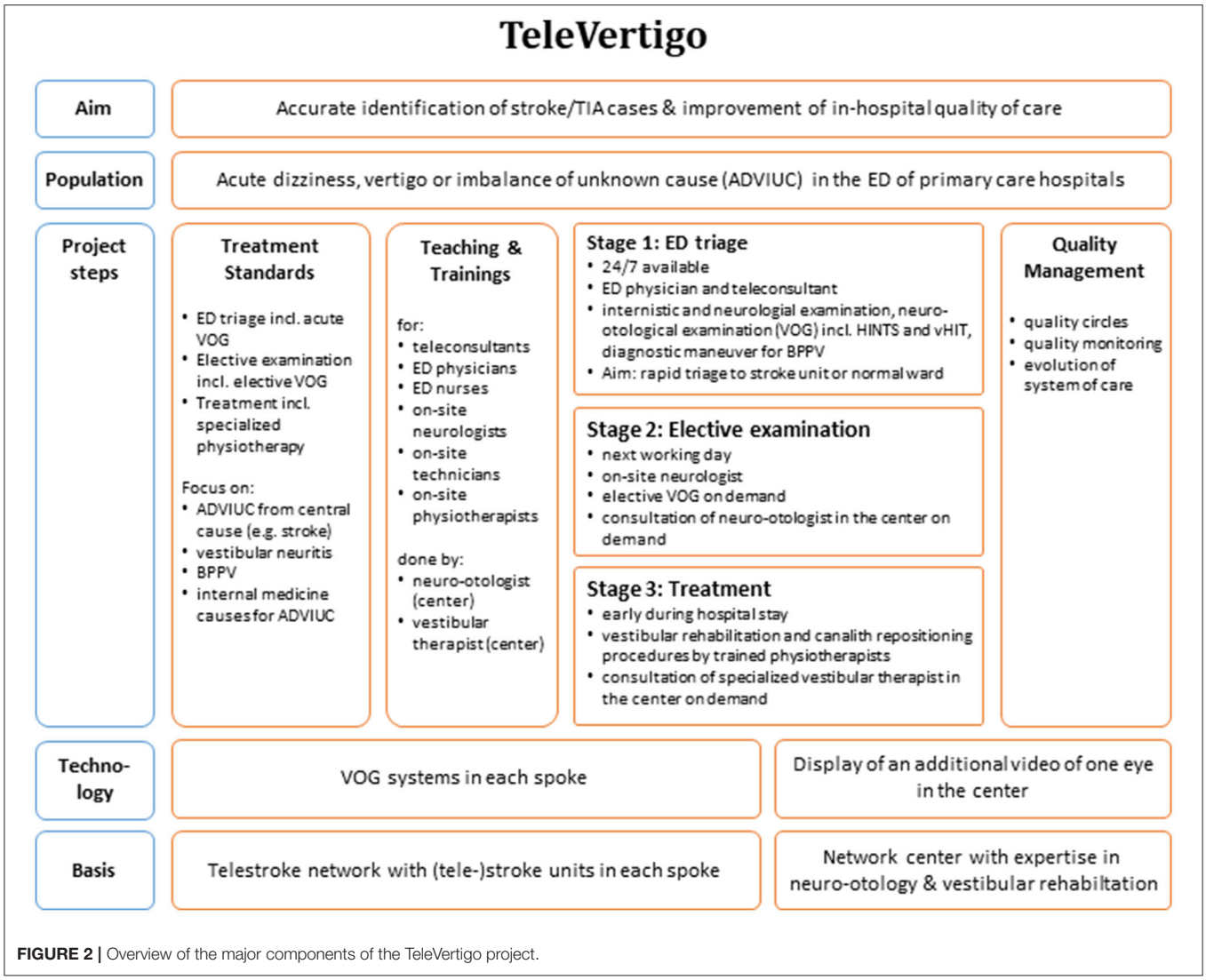

FIGURE 2 | Overview of the major components of the TeleVertigo project.

of all brain scans performed were collected and evaluated by experienced vascular neurologists centrally (CL, PMB). For the evaluation of missed strokes, all ADVIUC cases with an adequate brain imaging were considered. All MRI scans were considered as adequate, whereas CT scans were counted only if pathologic. All cases in the spoke hospitals with CT or MRI evidence of stroke, which were not primarily admitted to stroke units, were counted as missed strokes.

For all acute telemedical ED triage examinations, subjective satisfaction and added value were documented by the teleconsultants. Accordingly, the same items were documented for all elective VOGs by the physicians who made the finding. For further project evaluation, an online questionnaire was sent to all participating hospitals at the end of the project phase in November 2020. We wrote to our medical contact persons and also to therapists and technicians with the request to forward the questionnaire to their colleagues. The questionnaire asked for the subjective assessment of how helpful measures within the project were perceived, whether the care of patients with dizziness in their own hospital was improved, whether their own competence could be expanded, how satisfactory the implementation of the VOG was perceived, and whether a continuation of the application was desired. Answers were given anonymously.

Outcomes and Statistics

Primary outcome of this evaluation is the accuracy of the ED triage algorithm in differentiation between peripheral and central vestibular disease. Secondary outcomes are rate of missed strokes in acutely dizzy patients, improvement of diagnostic quality, and acceptance of physicians in spoke hospitals.

We applied descriptive statistics. Due to non-normal distribution of cases, data are presented as median and interquartile range. All patient data are derived from our anonymized and project-related quality register. According to German legislation, no patient consent is required for documentation in routine observational quality registries.

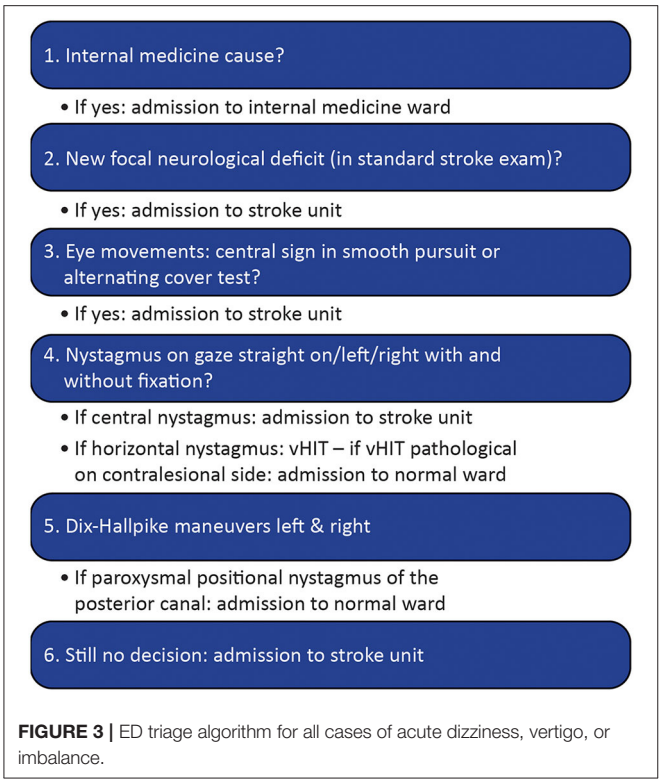

FIGURE 3 | ED triage algorithm for all cases of acute dizziness, vertigo, or imbalance.

TABLE 1 | Number of cases per hospital and evaluation month with acute (<72 h from onset) dizziness, vertigo, or imbalance of unknown cause (ADVIUC) as a leading symptom for ED admission.

	Month 1	Month 2	Month 3	Cases per year
Agatharied	10	12	14	144
Bad Reichenhall	9	8	7	96
Bad Tölz	7	11	13	124
Burglengenfeld		8	12	120
Cham		12		144
Ebersberg		10	5	90
Eggenfelden			25	300
Erding			12	144
Freising		12	16	168
Mühldorf		7	12	114
Rosenheim	16	17	17	200
Rotthalmünster		12	6	108
Traunstein	18	20	24	248
Vilsbiburg			8	96
Wasserburg	13	9	6	112
Total	73	138	177	2,208
Median (IQR)		12 (8–14.5)		124 (110–184)

Annual number of cases are extrapolated from monthly numbers.

RESULTS

Screening lists were expected from all 19 hospitals in all of the three evaluation months (total $n = 57$) and provided from 18 hospitals in 40 evaluation months (40/57 = 70%). We had to exclude 8 lists due to implausible data, with 32 remaining lists from 15 hospitals (32/57 = 56%) and a total of 469 cases with the leading symptom of dizziness, vertigo, or imbalance in the ED. Response rate improved gradually over time from 6 to 12 to 14 hospitals with valid screening lists. The median number of cases was 13.5 per month and hospital [interquartile range (IQR) 10–21]. After exclusion of 81 cases with symptoms lasting more than 72 h, a total number of 388 ADVIUC cases remained with a median number of 12 per month and hospital (IQR 8–14.5; see **Table 1**).

Baseline characteristics, risk factors, and symptoms of the 388 acute cases are given in **Table 2**. In 11.9% of cases, there is a history of dizziness or vertigo, but of different symptom quality. In most cases (87.9%), onset was reported as hyperacute. Nystagmus was detected in 51.0% of cases.

Distribution of hospital discharge diagnoses of these cases is displayed in **Table 3** with vestibular neuritis, stroke/TIA and BPPV (each about 20%), and dizziness of internal medicine causes (15%) as the most frequent diagnoses.

Accuracy of the ED triage algorithm was calculated in vestibular cases compared to the final discharge diagnosis (see **Figure 4**). Sensitivity for detecting a central lesion was 73/74 (98.6%) and specificity 83/181 (45.9%). The positive predictive value is 73/171 (42.7%) and the negative predictive value 83/84 (98.8%) (see **Table 4**).

In 196 cases, an adequate brain imaging (MRI in 192 cases and CT in 4 cases) was performed with a brain lesion matching the symptoms in 36 cases (36/196 = 18.4%). In four cases, lesions were not due to stroke: 1 acoustic neurinoma, 1 inflammatory lesion, 1 cerebral tumor, and 1 PICA aneurysm with compression of the brainstem. Three out of 32 stroke lesions were detected in CT scans (two ischemic cerebellar and one ischemic brainstem lesion), the remaining by MRI scans. A number of 16 out of 32 strokes were located predominantly in the cerebellum, 11/32 strokes in the brainstem, and 5/32 strokes in the cortex. One stroke was a cerebellar hemorrhage, the remaining ischemic. With the ED triage algorithm, 31/32 (96.9%) strokes confirmed by imaging were detected correctly in the ED. One stroke was missed (3.1%).

User satisfaction, the subjective sensation of safety in the clinical examination and diagnostic interpretation and the subjective added value in the concrete case by application of the acute and elective VOG are generally high, as stated by the teleconsultants and on-site physicians (see **Figure 5**). A total of 32 colleagues responded to our anonymous online questionnaire in November 2020. The total of 59% of them are physicians, 34% therapists and 6% technicians. Questions about helpfulness of the project, improvement of care on ADVIUC patients, and personal competence and also satisfaction about handling of the elective VOGs were rated consistently positive (for details see **Figure 6**). Slightly lower rates (80% positive) were recorded concerning helpfulness and satisfaction with the handling of acute VOGs. All responders voted for a continuation of the project.

TABLE 2 | Baseline characteristics of all cases with an acute leading symptom of dizziness, vertigo, or imbalance of unknown cause (ADVIUC).

	n	*N*	%
Age [median; IQR (years)]	65 (54–78)		
Female sex	210	388	54.1%
Risk factors			
Arterial hypertension	224	388	57.7%
Diabetes mellitus	68	388	17.5%
Hypercholesterinemia	146	388	37.6%
(ex-)smoker	59	388	15.2%
Atrial fibrilation	46	376	12.2%
Osteoporosis	17	359	4.7%
History of dizziness/vertigo	43	360	11.9%
Symptoms			
Hyperacute onset	340	387	87.9%
Dizziness or vertigo	386	388	99.5%
Vertigo only	206	370	55.7%
Imbalance	235	359	65.5%
Nystagmus	197	386	51.0%
Nausea	246	343	71.7%
Vomiting	153	340	45.0%
New neck pain or headache	49	263	18.6%
Known headache	22	388	5.7%
New tinnitus	21	214	9.8%
New hearing disturbance	14	211	6.6%
New ear symptoms (others)	20	211	9.5%
New phono- or photophobia	8	163	4.9%

Missing cases are due to missing information in available hospital discharge letters.

TABLE 3 | Distribution of hospital discharge diagnoses of all cases ($n = 388$) with an acute leading symptom of dizziness, vertigo, or imbalance of unknown cause (ADVIUC).

Diagnosis	*n*	%
Vestibular neuritis	87	22.4%
Vertebrobasilar stroke or TIA	68	17.5%
BPPV	68	17.5%
Dizziness of internal medicine cause	57	14.7%
Meniere's disease	26	6.7%
Functional disorder	7	1.8%
Vestibular migraine	7	1.8%
Inflammatory CNS disease	6	1.5%
Others*	3	0.8%
Unclear	59	15.2%

*Others include one case of bilateral vestibulopathy, vestibular paroxysm, and polyneuropathy each.

DISCUSSION

We report on our experience of a telemedical approach to improve quality of care in patients with acute dizziness, vertigo, or imbalance in primary care hospitals. The approach is based on telestroke networks and comprises multiple components including the implementation of standards, training of ED physicians, on-site neurologists, on-site therapists and teleconsultants, telemedical examinations, and implementation of VOG including vHIT (see **Figure 2**). The implementation is challenging and needs relevant resources and time, but our data demonstrate its feasibility. The approach distinguishes central (mostly stroke) from peripheral vestibular disorders with high sensitivity, albeit poor specificity. The vast majority of colleagues involved report subjective satisfaction and added diagnostic value and also the desire to continue the project.

The median monthly number of ADVIUC cases in the EDs of our primary care hospitals is 12 (IQR 8 – 14.5). Our data allow us to estimate an incidence, because catchment areas of our primary care spoke hospitals correspond largely to the correlating county, as we know from earlier evaluations of stroke cases (30). An extrapolated annual number of 2,208 ADVIUC cases correspond to a population of 1,987,414 inhabitants, resulting in an annual incidence of 111 cases per 100,000 inhabitants. This is in line with population-based studies performed by retrospective medical record reviews. A study from Sweden (4) reports an incidence of acute vestibular syndrome in the ED of 92 per 100,000 inhabitants per year, and another from Texas (6), reports 1,297 isolated dizziness symptoms as the principal presenting complaint in a 3.5-year period in proportion to about 300,000 inhabitants, and therefore resulting in an incidence of 123.5 cases per 100,000 inhabitants per year.

Our ADVIUC cases in ED of primary care hospitals resulted in the final diagnosis of vestibular neuritis, stroke/TIA and BPPV in about 20% of cases each, and dizziness of internal medicine cause in about 15%. These figures differ relevantly from other publications. Ljungren report 10% stroke/TIA in their sample of acute vertigo in the ED (4). However, it must be mentioned that only 45% of cases got a medical diagnose, whereas 55% were coded with a symptom diagnose. In an US sample of dizziness presentations in the ED, 4% resulted in a diagnosis of stroke/TIA, 33% otologic/vestibular, 21% cardiovascular, and 11% respiratory and metabolic (5). Noteworthy is again that only 49% of cases got a medical diagnose and the sample was not restricted to acute cases without an obvious underlying reason for the chief complaint of dizziness. Therefore, we believe that differences are explained by a selection bias due to different sampling definitions and an additional coding bias (in our sample in 15% of cases the final diagnosis remained unclear). Data for acute vertigo/dizziness from the ED of a tertiary referral center seem to match our data quite well-considering that recurrent manifestations of episodic syndromes are not excluded and medical disorders may be included more frequently (31).

The high proportion of 20% of stroke/TIA diagnoses in our sample underlines the importance for rapid and accurate triage of dizzy patients in the ED. Our approach (**Figure 3**) is highly sensitive (98.6%), but of poor specificity (45.9%). Only one stroke out of 32 verified by brain scan was missed, which outperforms misdiagnosis rates of 35% and more reported earlier (6–9). One reason is our conservative approach in unclear cases in the ED: until a peripheral cause is not proven, a central cause is assumed. Therefore, two-thirds of the cases were primarily admitted to stroke units (171/255 cases). Retrospectively, this was

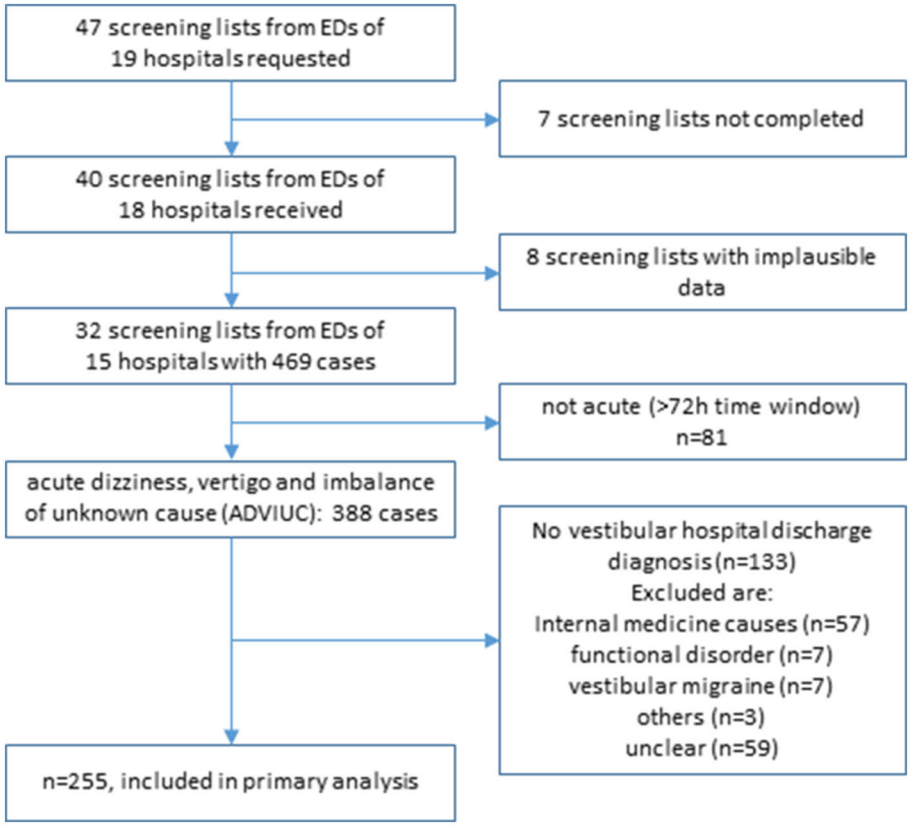

FIGURE 4 | Flowchart of the study cohort.

TABLE 4 | Accuracy of ED triage algorithm in vestibular cases.

ED diagnosis final diagnosis	Central vestibular	Peripheral vestibular	Total
Central or unclear	73	98	171
Peripheral	1	83	84
Total	74	181	255
Sensitivity:	98.6%		
Specificity:	45.9%		
Positive predictive value:	42.7%		
Negative predictive value:	98.8%		

ED diagnoses compared to final discharge diagnoses.

unnecessary in 57% of cases (98/171). Further improvement in triage tools is mandatory to reduce overadmission to stroke unit.

During planning and implementation of our TeleVertigo project, a strong feeling for the need of a specific concept for the management of dizzy patients in the ED of primary care hospitals evolved. Spectrum of diagnoses, training and experience of ED physicians and on-site neurologists, and diagnostic resources differ relevantly from other settings like at the general practitioner, in outpatient clinics, and in academic and specialized vertigo centers. Therefore, data and approaches cannot be transferred easily between these settings. In the literature, we could not find a commonly accepted definition for the relevant symptoms in our ED setting. There are various and substantially different definitions for acute vestibular syndrome (AVS) (4, 5, 12, 32), mostly requiring a persistence of symptoms over at least 24 h and a nystagmus. There is not an accepted definition for acute vertigo. Furthermore, vertigo and dizziness are different symptoms by definition (29), but cannot be distinguished by anamnesis in the ED in a relevant percentage of cases (33, 34). Therefore, we suggest a new definition for use in the ED setting, which focuses on the diagnostically challenging cases. These are all patients with acute dizziness, vertigo, or imbalance of unknown cause (ADVIUC). We defined "acute" as symptoms persisting <72 h. The reason for this is the consideration that for strokes with onset > 72 h stroke unit treatment usually is no longer indicated and therefore rapid triage to stroke unit or normal ward is unnecessary. "Unknown cause" means without an obvious reason for these symptoms detectable in the first medical check by ED physicians at admission (like an obvious focal neurological deficit, acute respiratory distress or relevant tachycardia). This excludes also recurrent manifestations of an already diagnosed episodic disorder, as long as the acute symptoms are preknown. In our cohort of ADVIUC cases in the ED, any nystagmus was detected in 51% of cases only. Cases without nystagmus (n = 189) correspond mostly to cases with dizziness of internal medicine cause (52/189),

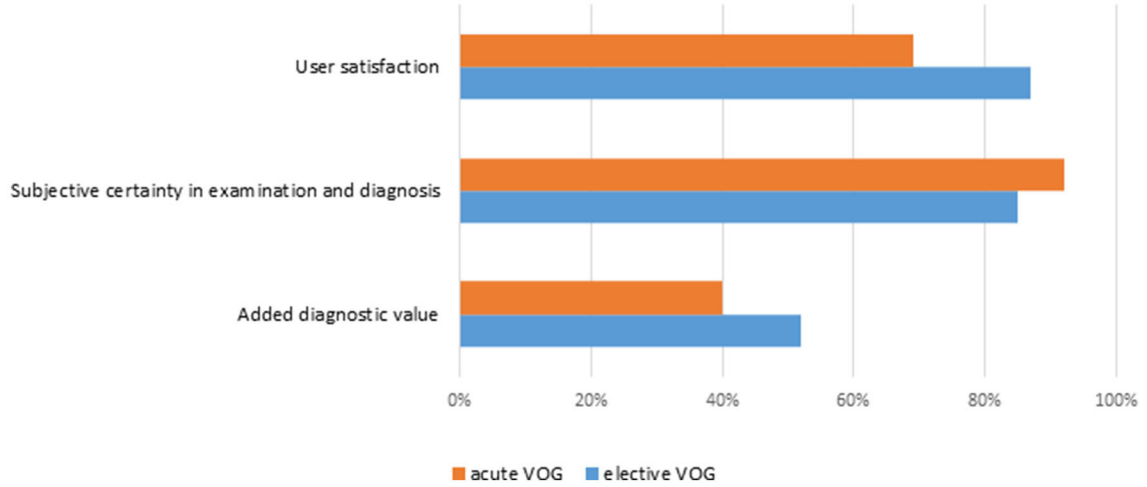

FIGURE 5 | Subjective user assessment for acute and elective videooculographies. Rates of positive answers.

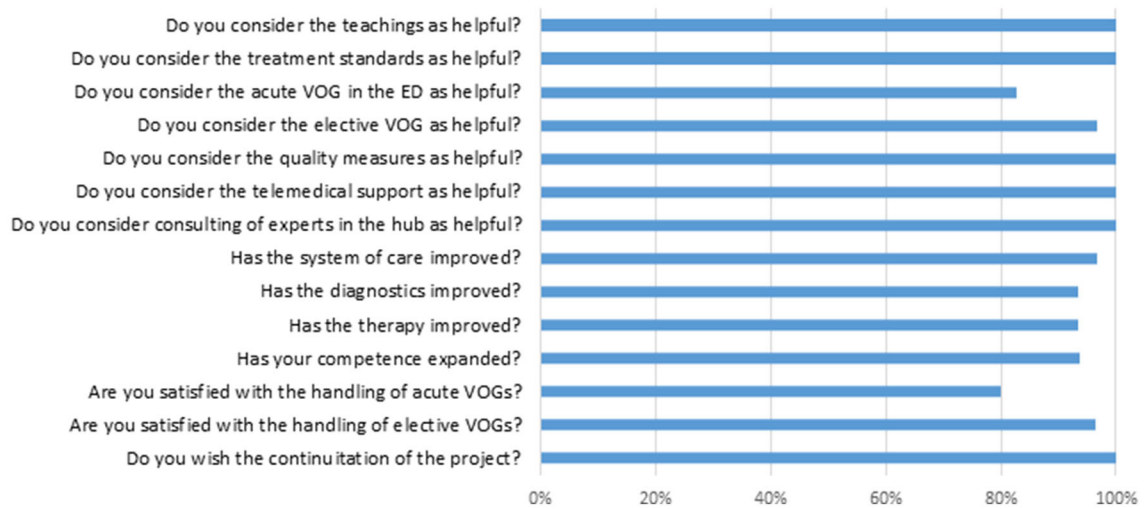

FIGURE 6 | Results of online survey in November 2020. Rates of positive answers.

stroke/TIA (42/189), and unclear cases (44/189) and emphasize the difference between AVS and ADVIUC.

We believe that for these ADVIUC patients in this setting, a comprehensive approach for adequate diagnostic and therapy is required. The diagnostic approaches based on the HINTS rule alone do not seem sufficient and feasible. Diagnostic accuracy has only been shown in highly selected patients due to tight inclusion criteria (35). The HINTS rule does not work at all in cases with completely resolved symptoms such as TIA or BPPV. The generalizability of the positive study results to less selective cohorts appears problematic. Furthermore, in our experience, an independent application and interpretation of the HINTS rule by ED physicians in primary care hospitals rarely yields reliable results. Nevertheless, HINTS is a precious diagnostic tool and is implemented in our ED triage algorithm as well (see **Figure 3**). Essentially, it is embedded in a telemedically supported and network-based application to assure specific feasibility. Moreover, questions about internal medicine cause and Dix-Hallpike maneuvers are added, and the workflow is optimized. The teachings and trainings for teleconsultants, ED-physicians, on-site neurologists, technicians, and physiotherapists are focused on history-taking [especially about timing and triggers according to the TiTrATE concept (36, 37)], the examination of subtle focal neurological symptoms and central oculomotor signs and also the four major diagnoses involved (vertigo/dizziness of central cause, vestibular neuritis, BPPV and, internal medicine causes of dizziness). We assume that this knowledge is important to understand diagnostic and treatment standards and therefore improves adherence to standards and quality of care.

One strength of this study is the prospective data sampling with active screening of all ED cases. Consequently, we can report

reliable numbers of cases of difficult dizziness presentations in the ED of primary care hospitals and also a reliable diagnostic spectrum. Hospital discharge diagnoses in the spokes were made thoroughly based on the established treatment standards and under supervision of the network center. Accuracy of the ED triage algorithm was prospectively analyzed.

Some limitations have to be addressed. First, although hospital discharge diagnoses in the spokes were made in the best way possible, the diagnostic quality does not reach standards of specialized academic centers and leaves room for misdiagnoses. MRI scans were only conducted on cases with suspicion for a central etiology; therefore, some central lesions may have been missed. Furthermore, analysis of accuracy of the ED triage was restricted to cases with a vestibular final discharge diagnosis, as the major challenge in the ED is the correct identification of stroke and TIA cases in ongoing but also resolved dizziness symptoms. Finally, we did not verify the proficiency of all staff members involved and did not systematically survey the quality of VOG examinations and diagnoses in the spoke hospitals. This system is aimed to improve quality of care in a large area with a clearly defined protocol to serve as many patients as possible. This expansion of competence into the area may be at the expense of the competence of the individual actors – a conflict you often face when setting up large scale systems of care. In diagnoses with potentially time dependent treatment (such as acute stroke), this strategy has been proven to be effective (18). The overall system, which includes the protocol and proficiency of all staff involved, seems very reassuring regarding the most important aim, the detection of an acute central cause.

In conclusion, the concept evaluated shows good acceptance for a complex telemedical and network-based approach to manage patients with acute dizziness, vertigo, or imbalance of unknown cause in the ED of primary care hospitals. Identification of stroke cases is accurate, whereas specificity needs further improvement. The concept could be a major step toward a broadly available evidence-based and state of the art diagnostics and therapy for patients with ADVIUC, especially in primary care hospitals of rural areas.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PM-B, CL, NH, and GH contributed to conception and design of the study. CL and PM-B organized the database and performed the statistical analysis. PM-B wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Telemedicine for Stroke: Quantifying the Long-Term National Costs and Health Benefits

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Objective: Few countries have established national programs to maximize access and reduce operational overheads. We aimed to use patient-level data up to 12 months to model the potential long-term costs and health benefits attributable to implementing such a program for Australia.

Methods: A Markov model was created for Australia with an inception population of 10,000 people with stroke presenting to non–urban or suburban hospitals without stroke medical specialists that could receive stroke telemedicine under a national program. Seven Markov states represented the seven modified Rankin Scale (mRS) scores (0 no disability to 6 dead) plus an absorbing state for all other causes of death. The literature informed inputs for the model; for the telemedicine program (including program costs and effectiveness) and patients, these were extrapolated from the Victorian Stroke Telemedicine (VST) program with the initial status of patients being their health state at day 365 as determined by their mRS score. Costs (2018 Australian dollars, healthcare, non–medical, and nursing home) and benefits were reported for both the societal and healthcare perspectives for up to a 25 years (lifetime) time horizon.

Results: We assumed 4,997 to 12,578 ischemic strokes would arrive within 4.5 h of symptom onset at regional hospitals in 2018. The average per person lifetime costs were $126,461 and $127,987 from a societal perspective or $76,680 and $75,901 from a healthcare system perspective and benefits were 4.43 quality-adjusted life years (QALYs) and 3.98 QALYs gained, respectively, for the stroke telemedicine program and practice without such program. The stroke telemedicine program was associated with a cost saving of $1,526 (from the societal perspective) or an additional $779 (from the healthcare system perspective) and an additional 0.45 QALY gained per patient over the lifetime. The incremental costs of the stroke telemedicine program ($2,959) and management poststroke ($813) were offset by cost savings from rehospitalization (–$552), nursing home care (–$2178), and non–medical resource use (–$128).

Conclusion: The findings from this long-term model provide evidence to support ongoing funding for stroke telemedicine services in Australia. Our estimates are conservative since other benefits of the service outside the use of intravenous thrombolysis were not included.

Keywords: stroke telemedicine, cost-effectiveness analysis, thrombolysis (tPA), long-term, ischemic stroke

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INTRODUCTION

Despite dramatic improvements in the treatment of acute stroke over the past 5 years, stroke remains the leading cause of disability and death of an adult in Australia (1) and worldwide, contributing to 5.5 million deaths (2). With timely access to evidence-based treatment, including intravenous thrombolysis and endovascular thrombectomy, the morbidity and mortality poststroke can be significantly reduced. However, the dispersed distribution of the Australian population, similar to other large countries, disadvantages people who live outside metropolitan areas in terms of access to diagnosis and treatment (3). For example, as a standard treatment for acute ischemic stroke, intravenous thrombolysis is generally considered and applied for patients presenting within 4.5 h of symptom onset (4). However, meeting such strict onset to needle times remains a challenge for patients residing in regional areas of Australia due to longer transport times to a hospital with thrombolysis capability. Moreover, the incidence of stroke is greater (117 vs. 100 per 100,000 population) among people living in regional areas than those in metropolitan Australia (2), which creates a strong need for improving access to specialist stroke care in regional areas.

One method for increasing access to stroke specialists in regional areas is *via* the use of telemedicine programs (5). Telestroke (or stroke telemedicine) programs aim to improve stroke outcomes for people living in regional areas by providing access to neurologists *via* real-time consultations to expedite diagnosis and treatment decisions in partnership with local clinical teams (6). A recent systematic review of eight economic evaluations of stroke telemedicine programs conducted in different countries suggested that such programs are generally cost-effective with favorable health gains (5). The limitation of the past study is that it has usually relied on simulation modeling using indirect sources of data. In our recent study, we have shown that the Victorian Stroke Telemedicine (VST) program in Australia is cost-effective [nominally lower costs telemedicine $98,777 vs. control $110,861 and greater benefits in terms of quality-adjusted life year (QALY) gains 0.53 vs. 0.38, per patient] within the first 12 months of stroke using patient-level data collected from 2014 to 2017 (7). The long-term benefits of the stroke telemedicine programs have been explored for the US and Europe (8) and for Australia, it remains unknown. Given the objective of scaling-up the stroke telemedicine programs nationally, quantifying the potential long-term costs and health benefits is needed to inform funding decisions and ensure rational resource allocation.

This research study aims to provide an economic evaluation of the potential long-term cost and benefits of an established stroke telemedicine program using the data-rich VST program as the case study.

METHODS

Population

The modeled population was defined according to the original VST study (7). This was a primarily historical controlled, real-world cohort study, which compared a 12-months period prior to implementation to the first 12 months of implementation of the stroke telemedicine program in 16 participating hospitals in Victoria. We prospectively collected 3- and 12-month resource utilization and health outcome data from a sample of the control and intervention groups to inform the cost-effectiveness model. A detailed description of the study population has been reported elsewhere (6, 9). In brief, patients with a mean age of 74 years, 55% being male, were defined accordingly for the long-term simulation starting from the first day of the index stroke symptoms.

Long-Term Simulation Model

A Markov model was constructed to evaluate the long-term cost-effectiveness of the stroke telemedicine program vs. the care provided to patients with stroke in the absence of such a program (10, 11). Seven Markov states represented the seven modified Rankin Scale (mRS) scores (0 to 6) plus an absorbing state for all other causes of death. The initial status of patients in the model was their health state at day 365, as determined by their mRS score, informed by the VST study (7). From day 366 onward over the rest of their lifetime, patients who survived the first 365 days after their index stroke could experience a recurrent stroke or background mortality. Those who experienced recurrent stroke assumed that they could only transit to a health state that was equal to, or worse than, their current one and were unable to return to a better health state (e.g., moving from mRS 2 to mRS 1 was excluded). A similar model structure has been adopted for other economic evaluations of stroke treatments and the health states considered capturing the long-term costs and health outcomes associated with stroke (12). The long-term modeling was conducted using TreeAge software (Williamstown, Massachusetts, USA). The model structure is shown in **Figure 1**. The reference sources for long-term events are given in **Table 1** and additional details are provided below.

Model Inputs

Transition Probabilities

The mRS scores at day 365 post the index stroke by the telestroke group or control (no telestroke access) were sourced from the original study (7). The only difference in transition probabilities between the two groups was the proportion of patients commencing the long-term simulation in each of the six health states (i.e., the mRS scores of 0–5; patients who died in the first 365 days were excluded from the long-term modeling, but their initial costs up to 12-months were included) as defined by the patient-level data. The annual probability of recurrent stroke (13, 14) and background mortality (15) was identical for the two treatment arms but was adjusted by the occurrence of recurrent events (i.e., experiencing a recurrent stroke leads to the increased risk of a subsequent one) (16).

The transition probabilities for both groups are shown in **Table 1**.

Costs

All the costs related to medical care, nonmedical care (i.e., nonmedical including accommodation changes, community services, home modifications, special equipment, informal care, etc.), and formal care (i.e., institutional care) were considered

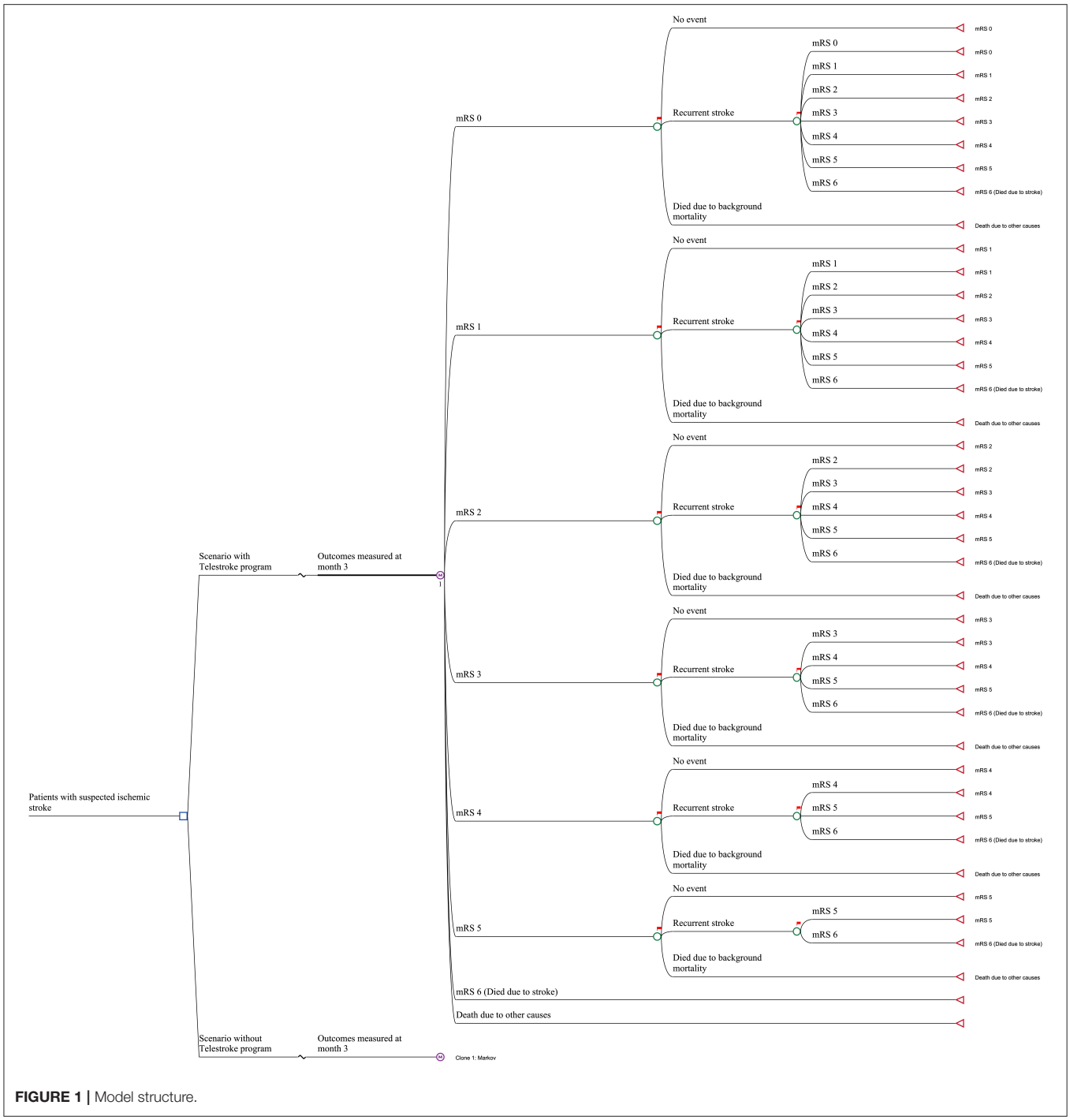

FIGURE 1 | Model structure.

in the model (**Table 1** and **Supplementary Table 1**) from a societal perspective starting from day 1 of the index stroke, while the medical care costs were included in the healthcare system perspective (10, 17–19). Productivity losses (i.e., paid work) were not considered, given the average age of the modeled population was 74 years and the retirement age set at 66 years in Australia (20). Costs associated with each health state, including the first 12 months (informed by the original study), recurrent hospitalizations, outpatient care (consultations, pharmaceuticals, and examinations), nursing home care (for patients with the mRS score 4 to 5), and non–medical care, were sourced from published literature (10). All the costs were valued in 2018 Australian dollars.

Utility Weights

Utility weights are preference weights representing the strength of desirability toward different health states (i.e., more preferred health states will have greater weight such as perfect health).

TABLE 1 | Inputs for the long-term cost-effectiveness analysis.

Variable	Base case value	Reference
Transition probabilities		
Probability of recurrent stroke	Year 1: 0.0649; Year 2+: 0.0201	Mohan et al. (13)
		Pennlert et al. (14)
Probability of death following a recurrent stroke^	0.1783	Fagan et al. (43) Chen et al. (44)
Relative risk of having recurrent stroke*	1.48	Park et al. (16)
Probability of utilizing non-medical care		Gao et al. (19)
mRS 1	0.9138	
mRS 2	0.8431	
mRS 3	0.9070	
mRS 4	0.8963	
mRS 5	0.9232	
HR of background mortality		Hong et al. (45)
mRS 0	1.53	
mRS 1	1.52	
mRS 2	2.17	
mRS 3	3.18	
mRS 4	4.55	
mRS 5	6.55	
Costs		
Cost of rehospitalisation		IHPA 2018-19
mRS 0	$10,886	
mRS 1	$10,086	
mRS 2	$16,662	
mRS 3	$16,662	
mRS 4	$22,086	
mRS 5	$22,086	
mRS 6	$10,886	
Cost of management		
mRS 0	Year 1: $10,499; Year 2: $1,431	Arora et al. (10); Gloede et al. (17); Baeten et al. (18)
mRS 1	Year 1: $13,230; Year 2: $1,814	
mRS 2	Year 1: $15,943; Year 2: $1,814	
mRS 3	Year 1: $17,540; Year 2: $1,814	
mRS 4	Year 1: $20,772; Year 2: $1,814	
mRS 5	Year 1: $24,169; Year 2: $1,814	
Cost of non-medical care		Gao et al. (19)
mRS 1	$1,318	
mRS 2	$2,231	
mRS 3	$5,430	
mRS 4	$6,552	
mRS 5	$24,420	
Cost of nursing home care		Government website (46)
mRS 4	$40,689	
mRS 5	$40,689	
Utility weights		
mRS 0	0.836	Kim et al. (7)
mRS 1	0.777	
mRS 2	0.694	
mRS 3	0.437	
mRS 4	0.242	
mRS 5	0.064	

mRS, modified Rankin Scale; $, Australian dollars; IHPA, Independent Hospital Pricing Authority Australia.
^0.11, for sensitivity analysis.
**The average RR was used.*

They are measured on a cardinal scale of 0–1, where 0 indicates a health state equivalent or equal to death and 1 indicates perfect health (negative values represent a health state worse than death) (21). In this study, utility weights associated with being in the poststroke health states defined by the mRS score were directly informed by the VST participants measured using EQ-5D−3L at 12 months and were assumed to remain unchanged over the long term (22). The utility weights applied are shown in **Table 1**.

Cost-Effectiveness Analysis

In the base case, 10,000 patients with stroke from regional/rural areas of Australia arriving within 4.5 h of symptom onset were simulated. A societal perspective was taken to provide a broader range of costs and health benefits (QALYs) over a 25 years time horizon. In addition, a healthcare system perspective was adopted to estimate the direct healthcare costs only and benefits for the same time horizon. Utility weights were used from the published literature to estimate the QALYs gained (21). In addition, life years lived were estimated to measure the survival gains. The primary outcome for the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER) per QALY gained, which is calculated as the ratio between incremental cost and incremental QALYs gained (intervention vs. control). Costs and benefits were discounted at a rate of 3% per annum (23). The often-quoted willingness to pay (WTP) per QALY threshold of AU$50,000 was adopted to assess the potential cost-effectiveness of the stroke telemedicine program against a scenario with the no stroke telemedicine program (24).

Sensitivity Analyses

One-way deterministic sensitivity analyses were conducted by varying one model parameter at a time within a plausible range to examine the robustness of base case results (**Table 1**). The results of a range of individual deterministic sensitivity analyses are combined and presented in the form of a tornado diagram (i.e., by showing the range of change in ICER). The probabilistic sensitivity analyses (PSAs), which determined the distribution of

key uncertain parameters, were run to further explore the results. Additionally, the mRS outcomes at 1 year for the participants of the stroke telemedicine program were tested with a Dirichlet distribution. The Australian Telestroke Network study informed the distribution of the cost related to the stroke telemedicine program delivery (**Supplementary Table 2**). A key assumption made in the PSA was that the distributions for each parameter were not correlated (i.e., the variation in one parameter was not associated with the change in another parameter). An incremental cost-effectiveness plane was generated to illustrate the results of the PSA.

In order to identify the cutoff for the population size enabling the cost-effective implementation of the stroke telemedicine program, a threshold analysis was undertaken. The intervention cost was defined as the total intervention implementation cost ($1,762,892 from the primary study where all the costs for equipment in the first year operational model are incurred) divided by the population in a region.

Impact of the National Implementation

The VST program directly informed the cost of stroke telemedicine delivery. The per capita intervention cost was conservatively assumed to remain the same during the national implementation even though the scaling-up is likely to result in lower per capita cost from improved efficiency. In order to quantify the long-term implications of implementing the national stroke telemedicine program, the annual numbers of patients were estimated for Australia in 2018 [the total number of strokes was 38,055 in 2018 (1)]. Based on the latest national acute stroke audit in Australia, of 4,176 patient case notes audited, 83% of strokes were ischemic (25). Among the ischemic strokes, approximately 60% were among people residing in the metropolitan area, while the balance of 40% comprised people from either inner regional or outer regional areas (26). We examined scenarios where 20%, 50%, and 100% of patients from inner regional (people from inner regional areas may be transferrable to a metropolitan hospital directly) would be eligible for the stroke telemedicine program, in addition to 100% of people from outer regional areas.

RESULTS

Cost-Effectiveness Analysis

Overall, implementing the stroke telemedicine program for patients with ischemic stroke from regional Australia in the long term was a dominant strategy (more health gains and cost saving) from the societal perspective or highly cost-effective (ICER of $1,736 per QALY gained) from the healthcare system perspective.

The base case cost-effectiveness analysis showed that implementing stroke telemedicine in the long term was associated with lower costs and greater benefits. In particular, the average per patient lifetime costs for the stroke telemedicine program vs. the no stroke telemedicine program were $126,461 and $127,987 from a societal perspective or $76,680 and $75,901 from the healthcare system perspective. Corresponding benefits were 4.43 QALYs and 3.98 QALYs gained or 7.68 life years and 7.15 life years for the stroke telemedicine program and practice without such program, with a cost saving of $1,526 (from the societal perspective) or an additional $779 (from the healthcare system perspective) in cost and an addition 0.45 QALY gained per patient. The incremental cost of the stroke telemedicine program ($2,959) and management poststroke ($813) was partially offset by the cost savings arising from reduced rehospitalization (–$552), nursing home care (–$2178), and non–medical resource use (–$128) costs (**Table 2**).

TABLE 2 | The results of base cost-effectiveness analysis.

	Intervention	Control	Difference
Total QALYs	4.428	3.979	0.449
Total LYs	7.687	7.145	0.542
Societal perspective			
Total costs	$152,209	$152,607	–$397
		ICER (per QALY)	**Dominant**
Healthcare system perspective			
	$102,429	$100,520	$1,908
		ICER (per QALY)	**$4,252**
Number of patients received nursing home care*	2861	2962	101
Cost components			
First 12-month cost	$78,859	$76,954	$1,904
Management cost	$11,267	$10,454	$813
Rehospitalisation cost	$12,303	$13,113	-$809
Nursing home cost	$46,590	$48,769	-$2,178
Non-medical cost	$3,190	$3,318	-$128

QALY, quality-adjusted life year; LY, life year; ICER, incremental cost-effectiveness ratio.
**Per 10,000 patients over the lifetime. Dominant means less costs and more benefits.*

In addition, the stroke-related disability prevented due to the stroke telemedicine program was associated with a reduced probability of utilizing nursing home care poststroke, with a corresponding reduction of 101 nursing home residents per 10,000 patients.

Sensitivity Analysis

The one-way deterministic sensitivity analysis results showed that the base case results were robust to the variation in key model inputs (variation in all the inputs did not alter the conclusion of cost-effectiveness of the stroke telemedicine program). However, the changes in costs of the first-year stroke management (patients with the 3-months mRS scores of 1, 2, and 3), background mortality, time horizon, and probability of recurrent stroke contributed to the variation in ICER (**Figure 2**).

The PSAs showed that the probability of the stroke telemedicine program being the dominant option is high (100%) by incorporating the distribution of key variables (**Figure 3**).

The cutoff value for the population size to implement the cost-effective stroke telemedicine program was 67 (e.g., a region with a minimum 67 suspected strokes, equivalent to $26,312 per person, over 1 year could sustain the cost-effectiveness of the stroke telemedicine program) (**Supplementary Figure 1**).

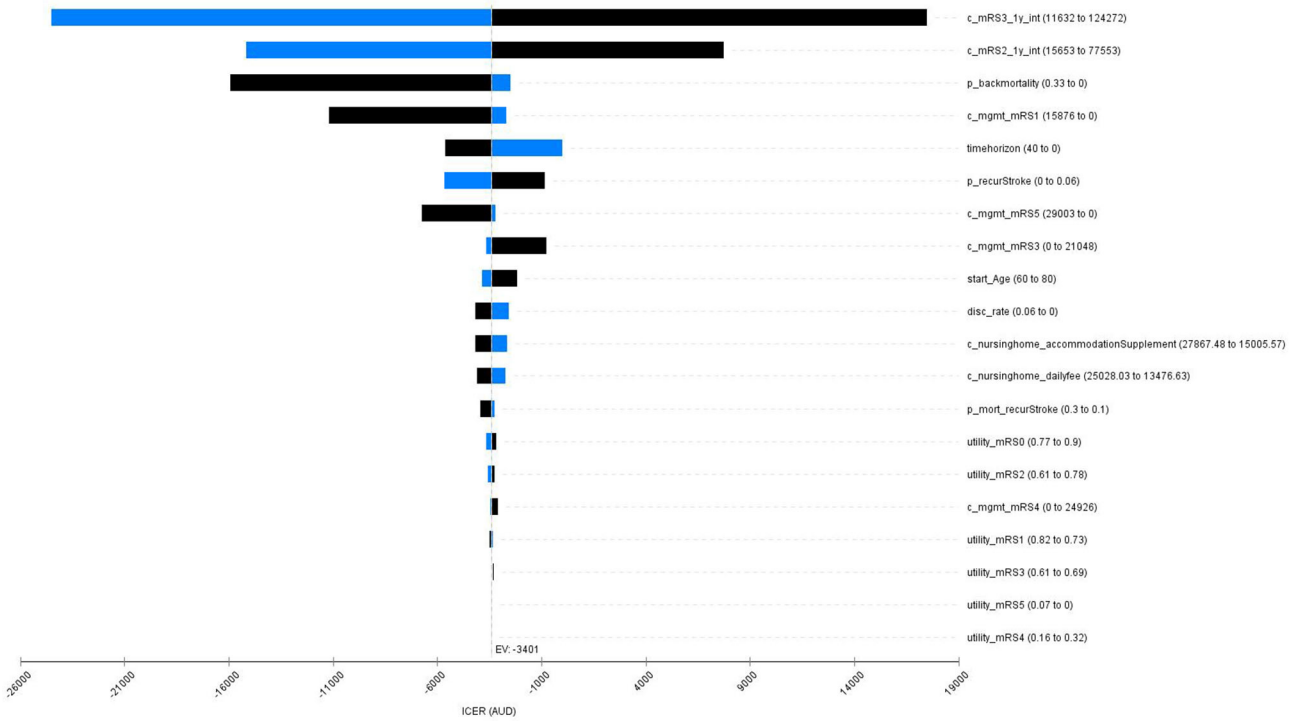

FIGURE 2 | A Tornado diagram for the one-say sensitivity analyses. Red bar means the value increases from the base case; blue bar represents the value decreases from the base case. mRS, modified Rankin Scale; mgmt, management; mort, mortality; c_mRS3_1y_int, cost of management for the intervention group for the first year post stroke (mRS3); c_mRS2_1y_int, cost of mangement for the intervention group for the first year post stroke (mRS2); p_backmortality, probability of background mortality; c_mgmt_mRS1, cost of long-term management post stroke (mRS1); timehorizon, modeled time horizion; p_recurStroke, probability of having recurrent stroke; c_mgmt_mRS5, cost of long-term management post stroke (mRS5); c_mgmt_mRS3, cost of long-term management post stroke (mRS3); start_Age, onset age of the index stroke; disc_rate, discount rate for both costs and QALYs; c_nursinghome_accommodationSupplement, cost of nursing home care for the accommodation supplement; c_nursinghome_dailyfee, cost of nursing home care for the daily fee; utility_mRS0, utility weights post stroke (mRS0); utility_mRS2, utility weights post stroke (mRS2); c_mgmt_mRS4, cost of long-term management post stroke (mRS4); p_mort_recurStroke, probabiltiy of death following a recurrent stroke; utility_mRS1, utility weights post stroke (mRS1); utility_mRS3, utility weights post stroke (mRS3); utility_mRS5, utility weights post stroke (mRS5); utility_mRS4, utility weights post stroke (mRS4).

Impact of the National Implementation

Implementing the stroke telemedicine program Australia-wide was associated with cost savings and more health gains. A single year implementation could lead to a maximum of $19 million savings and 5,646 additional QALY gained over a lifetime compared to current practice where such a program does not exist. The savings could completely offset the implementation cost of $37 million from reduced need for nursing home care combined with reduced costs of acute hospitalization for the index stroke (**Table 3**).

DISCUSSION

We provide evidence that the implementation of the national stroke telemedicine program for patients with ischemic stroke from regional Australia in the long term provides more health gains and cost savings from the societal perspective or is highly cost-effective (ICER of $1,736 per QALY gained) from the healthcare system perspective and is a worthwhile objective to achieve. The model-based cost-effectiveness analysis extending the short-term patient-level results to the long-term patient-level indicated that implementing the stroke telemedicine program in Victoria was associated with lower costs and greater health benefits from a societal perspective or higher costs and benefits from a healthcare system perspective. The cost savings exceeded the cost of implementing the stroke telemedicine program from any subsequent hospitalizations, nursing home care, and non–medical care. Moreover, the long-term model also suggested that the stroke telemedicine program could potentially avoid the need for nursing home care (101 cases avoided per 10,000 patients).

Our short-term individual patient-level data-based economic evaluation of the stroke telemedicine program reported that using telemedicine technology to diagnose and treat patients with acute stroke was most likely to be cost-effective at 12 months poststroke within Australia (7). However, during the acute phase of the index stroke, greater acute costs were observed for participants of the stroke telemedicine program, probably due to the increased frequency of transfer following specialist recommendations (averaging $1,866 per trip for people from regional/rural areas by Ambulance Victoria).

A recent systematic review of the economic evaluations (cost-effectiveness and cost-utility analyses) of telemedicine/telestroke identified eight economic evaluations worldwide (5). It was

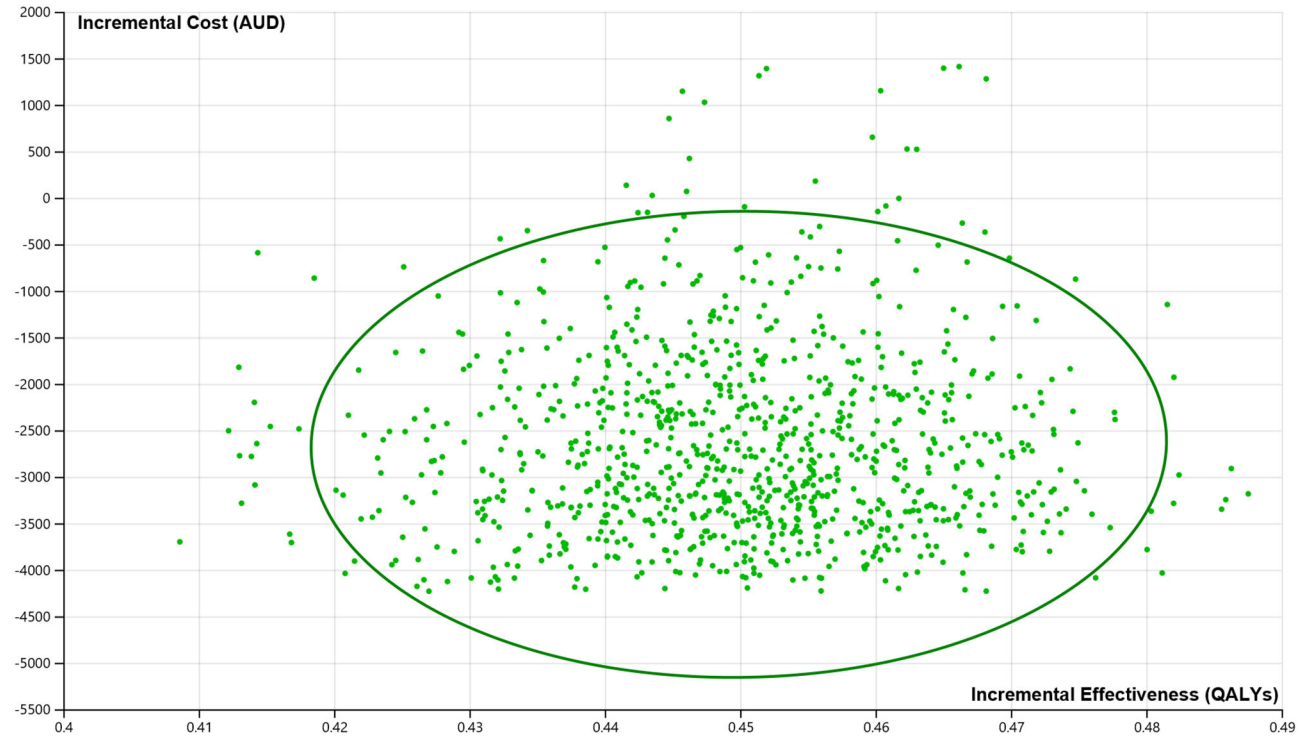

FIGURE 3 | Incremental cost-effectiveness plane from the probabilistic sensitivity analysis. AUDs, Australian dollars; QALYs, quality-adjusted life years. 100% of all the iterations suggest that the stroke telemedicine program is cost saving and more effective over the lifetime of patients.

TABLE 3 | Results from the national implementation.

	National impact*		
	Scenario 1 (20%)	**Scenario 2 (50%)**	**Scenario 3 (100%)**
Total costs	–$1,985,002	–$3,114,400	–$4,996,729
Total QALYs	$2,243	$3,519	$5,646
Management cost	$4,062,273	$6,373,567	$10,225,722
Rehospitalisation cost	–$4,042,645	–$6,342,771	–$10,176,313
Nursing home cost	–$10,883,496	–$17,075,830	–$27,396,386
Non-medical cost	–$637,245	–$999,816	–$1,604,100
First 12-month cost	$9,516,111	$14,930,450	$23,954,349

**Scenarios 1 to 3 assumed that 20% (n = 4997), 50% (n = 7840), and 100% (n = 12578) of inner regional population (plus 100% of outer regional population) would be eligible for the VST program of 38,055 stroke Australia-wide.*
QALY, quality-adjusted life year.

reported that there was heterogeneity in the design across the reviewed studies. It is worth mentioning that the cost-effectiveness of the stroke telemedicine program generally varied according to the time horizon of the analysis. For example, the high upfront costs of implementing such a program (i.e., infrastructure and equipment to deliver the services, etc., totaling over $1.8 million in the VST) cannot be offset by the subsequent cost saving from treatment/management in the short term. In the reviewed articles, cost savings arose primarily from decreased nursing home care required or avoided interhospital transfer.

The results from this long-term model-based cost-effectiveness analysis were comparable with prior long-term studies. Generally, all the studies found that the stroke telemedicine program improved quality of life outcomes [ranging from 0.02 (27) to 1.3 (28) QALYs gained; the incremental QALYs (0.449) from our modeling fell within this range]. However, the cost results were slightly inconsistent: incremental costs over short timeframes from the stroke telemedicine programs ranged between cost savings of US$ 4,241 (29) to additional costs of US$ 3,006 (30) per patient, while for long-term horizons, they varied from cost savings of US$ 19,888 (30) to an additional cost of US$ 3,184 (28) per patient.

In this study, the benefits from the stroke telemedicine program were mainly driven by the proportion of patients who arrived < 4.5 h from stroke onset and received intravenous thrombolysis (i.e., increased from 17 to 26%), which has a demonstrated effectiveness in reducing poststroke disability (6). The 12-month mRS outcomes post the index stroke were directly informed by patient-level data from the primary data collection. All the event rates, event-related costs, and utility weights were identical for both the stroke telemedicine and non–stroke telemedicine scenarios in the long-term model. The disability avoided by timely intravenous thrombolysis was then extrapolated over the remaining life course. The potential benefit to the stroke telemedicine program of endovascular

thrombectomy (EVT), which was introduced in Australia in 2015, was not fully captured in the current data collection (due to time lag). Large vessel occlusion (LVO) stroke, although only accounting for 10–15% of all the strokes, represents a disproportionate share of the disease burden. Without EVT, LVO stroke is associated with more than 50% mortality or major disability at 3 months (31). The stroke telemedicine program provides rapid access to stroke specialists. Thus, eligible patients can be accurately identified and transferred in a timely manner to a metropolitan hospital with EVT capability (only four metropolitan hospitals have the facility for EVT procedure 24/7 in Victoria); the milestone trials have demonstrated that EVT led to the significantly higher rate of functional independence and decreased mortality at the 3-month post the index stroke (32–38). It is highly probable that the potential cost saving and health benefits from the stroke telemedicine program would be further expanded if the combined benefits from both the intravenous thrombolysis and endovascular thrombectomy could have been measured.

In, 2017–2018, the Australian government spent over $18 billion on aged care with 67% of total expenditure on residential care ($12 billion) (39). This study indicates that when modeled for the national population, the stroke telemedicine program was associated with substantial savings in terms of nursing home care. It is also worth noting that the productivity cost was not included in the current long-term model due to the mean age of the simulated population. However, a recent report on the burden of heart valve disease in Australia suggests that the elderly population contributes substantially to the economy through unpaid productivity by providing childcare for grandchildren, caring for family members, and volunteering (40). The cost saving of the stroke telemedicine program from a societal perspective could be further increased if such unpaid productivity costs were considered.

This is the first study in Australia that translated the short-term benefits of a stroke telemedicine program into long-term cost savings and health outcomes. The patient-level data directly informed the costs and outcome for the first year following program implementation. However, this study is not without limitations. First, the long-term model only simulated the events related to recurrent stroke, whereas, in reality, other cardiovascular (heart attack) or non–cardiovascular (such as cancer) events may occur. This does not favor the intervention under evaluation given the higher probability of other cardiovascular events with advanced disability poststroke (41). Second, it was assumed that the functional status at 12-months poststroke could not be improved (i.e., patients with the mRS 3 cannot enhance to mRS 2) over the remaining life course, which is not necessarily the case. Third, while the cost-effectiveness results from this study cannot be directly transferred to another jurisdiction for funding decision-making, they can be adapted (with local costs and utility weights) for timely use. Lastly, the results from the long-term model are likely to be conservative, given not all the benefits related to the stroke telemedicine service were able to be captured. In particular, patients with suspected stroke get earlier diagnosis and treatment, if being hemorrhagic or stroke mimics. In addition, intangible benefits from better coordination of stroke care, improved capacity building through enhanced training and experience, reduced caregiver burden from lowered transport costs, and improved quality of life are not measured and valued in the current estimation. Also, since the stroke incidence is projected to increase (42), the benefit from the national implementation may have been underestimated. The cost of potentially more treatment (i.e., transferring patients timely for thrombectomy) due to the application of the stroke telemedicine program was not incorporated in the current estimation due to the study timeframe (2010–2016). Moreover, the change in the cost of thrombolysis and telemedicine staff salaries is not factored into account.

CONCLUSION

The findings from this long-term model provide evidence to support ongoing funding for stroke telemedicine services in Australia. Our estimates are conservative since other benefits of the service outside the use of intravenous thrombolysis were not included, e.g., optimal management of patients with intracerebral hemorrhage.

DATA AVAILABILITY STATEMENT

The data that support this study cannot be publicly shared due to ethical or privacy reasons and may be shared upon reasonable request to the corresponding author if applicable.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Monash University Human Research Ethics Committee (2014-2482-2291). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LG, DC, and MM designed the study. LG, ET, and JK undertook the analysis. LG, ET, JK, DC, and MM interpreted the results. LG drafted the manuscript. LG, ET, JK, CB, HD, KB, DC, and MM provided critical input for the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.804355/full#supplementary-material

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BRIEF RESEARCH REPORT
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Human vs. Machine Learning Based Detection of Facial Weakness Using Video Analysis

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Background: Current EMS stroke screening tools facilitate early detection and triage, but the tools' accuracy and reliability are limited and highly variable. An automated stroke screening tool could improve stroke outcomes by facilitating more accurate prehospital diagnosis and delivery. We hypothesize that a machine learning algorithm using video analysis can detect common signs of stroke. As a proof-of-concept study, we trained a computer algorithm to detect presence and laterality of facial weakness in publically available videos with comparable accuracy, sensitivity, and specificity to paramedics.

Methods and Results: We curated videos of people with unilateral facial weakness ($n = 93$) and with a normal smile ($n = 96$) from publicly available web-based sources. Three board certified vascular neurologists categorized the videos according to the presence or absence of weakness and laterality. Three paramedics independently analyzed each video with a mean accuracy, sensitivity and specificity of 92.6% [95% CI 90.1–94.7%], 87.8% [95% CI 83.9–91.7%] and 99.3% [95% CI 98.2–100%]. Using a 5-fold cross validation scheme, we trained a computer vision algorithm to analyze the same videos producing an accuracy, sensitivity and specificity of 88.9% [95% CI 83.5–93%], 90.3% [95% CI 82.4–95.5%] and 87.5 [95% CI 79.2–93.4%].

Conclusions: These preliminary results suggest that a machine learning algorithm using computer vision analysis can detect unilateral facial weakness in pre-recorded videos with an accuracy and sensitivity comparable to trained paramedics. Further research is warranted to pursue the concept of augmented facial weakness detection and external validation of this algorithm in independent data sets and prospective patient encounters.

Keywords: cerebrovascular disease, stroke, infarction, access to care, diagnostic test, computer vision, machine learning

INTRODUCTION

Inaccurate detection of common neurologic signs, such as facial weakness, can lead to delays in diagnosis and treatment for a variety of neurological diseases, particularly time-sensitive conditions such as stroke. For instance, emergency medical service (EMS) providers may fail to detect stroke in over half of cases, even when using standard prehospital stroke detection screening tools such as the Cincinnati Prehospital Stroke Scale (CPSS) (1, 2). The CPSS and other screening tools rely heavily on provider experience and training to accurately hone the identification of neurologic deficits, which is most challenging for non-neurologist providers (3). Additionally, neurologic deficits are not easily quantifiable and therefore their interpretation is highly subjective. In one study, paramedics failed to identify facial weakness in 17% of stroke patients and incorrectly interpreted facial weakness as present when it was absent in an additional 33% of cases (4). In a study of over 8,000 raters of the NIH Stroke Scale (NIHSS), including neurologists, nurses, and emergency providers, facial weakness had the second poorest agreement (0.25) of all the scale items (5). Weak inter-operator variability contributes to the wide range of CPSS stroke scale sensitivity and specificity observed in the prehospital setting (1, 6, 7). As a result, many stroke patients go unrecognized or are inappropriately triaged delaying or missing the opportunity for timely acute stroke treatment with thrombolysis. Concomitantly, common stroke mimics are often over triaged unnecessarily expending emergency resources.

Most current, the challenge of stroke screening in the field has been accentuated in the endovascular era, in which the accurate detection of large vessel occlusion (LVO) stroke could inform triage to a thrombectomy capable center (8, 9). Thus, numerous second generation LVO stroke scales have been derived and internally validated but lack consistent performance and generalizability across multiple regions. Additionally, no single scale has demonstrated proven superiority and further external validation and accuracy in real world practice is needed (10).

Computer vision analysis through machine learning has the potential to enhance clinical diagnosis of visually observable diseases, such as diabetic retinopathy and skin cancer (11). Since stroke is a clinical diagnosis reliant on visually observable neurologic signs, we believe that AI can be developed to augment the detection of stroke through recognition and differentiation of focal deficits. Specifically in regards to facial analysis, machine learning algorithms can differentiate between deliberate and spontaneous smiles by analyzing distinct patterns of facial muscle activation (12). Similarly, machine learning can identify subtle facial asymmetry in expressions suggestive of negative emotional valence (13).

Given that gross facial asymmetry is the hallmark of localized facial weakness with impaired muscle contraction. In the current study, we aimed to develop a machine learning algorithm to identify pathological facial weakness using computer based video analysis. Specifically, we hypothesized that a machine learning algorithm can detect asymmetric facial weakness with a similar or better accuracy than trained paramedics.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

All study procedures were in alignment with the Declaration of Helsinki and approved by the institutional review board of the University of Virginia (#20021), which waived the need for informed consent as retrieved videos came from open access (public) repositories.

Convenient Population Sample

Videos voluntarily submitted by people demonstrating unilateral facial weakness were conveniently collected from open access repositories such as YouTube and Google (14). Videos that contained only one individual with the same individual smiling normally with or without unilateral facial weakness were eligible for inclusion in this study. Videos of people smiling were collected to assure the possibility for an assessment of the presence of pathological asymmetry. There were no additional exclusion criteria in order to achieve a wide range of unilateral facial weakness presentations mirroring real life encounters. As an exploratory proof of concept study, a formal sample size was not estimated prior to sampling videos to be rated.

Reference Standard

There is no higher gold standard for facial weakness detection other than by clinical assessment. Since vascular neurologists receive specialized training in the accurate and rapid diagnosis of stroke of which facial weakness is a common sign, we assumed that vascular neurologists are the best candidate to be the "ground truth" for detecting the presence or absence of pathological unilateral facial weakness for the purposes of this study. Thus three board-certified vascular neurologists blinded to the type of video independently rated each one denoting the presence or absence of facial weakness.

The study employed a rating scale similar to a Likert scale in order to capture possible rater uncertainty brought on by facial weakness subtlety. The rating scale ranged from 1 to 5 equating to Pathology is: 1) Likely absent, 2) Somewhat likely absent, 3) Indeterminate, 4) Somewhat likely present, and 5) Likely present. If the neurologist rated a video a 4 or 5, then he or she was asked to denote the laterality or side of the facial weakness as either "Left" or "Right."

After the initial rating of each video by the vascular neurologists, we collapsed the facial weakness ratings down to: 1) Absent, 2) Indeterminate, and 3) Present. This allowed us to establish the "ground truth" that facial weakness is absent, present, or unknown as the mode (most common) of the ratings of the three vascular neurologists. The same manner was used for laterality of facial weakness. This approach is equivalent to majority voting which we believe to be better approach for determine the presence of facial weakness than the traditional approach of using the NIH stroke scale facial palsy item which has a reported interrater reliability kappa as low as 0.25 (5). To note, none of the ground truth ratings of fascial weakness or laterality received a final rating of "unknown"; thus all fascial video had

a ground truth rating of absent or present and if present, then laterality was either left or right.

Three blinded paramedics independently classified the videos using the same protocol as the vascular neurologists. The relative experience of the three paramedics included an EMT with 7 years of experience total and 5 years of experience as an advanced life support provider, a nationally registered paramedic with over 10 years of experience, and an entry level EMT with 1 year of experience.

Computer Vision Algorithm

The computer vision algorithm aims to classify the input video as normal, left deficit, and right deficit, by exploiting the Histogram of Oriented Gradients (HoG) (15) feature sets and the penalized Linear Discriminant Analysis (pLDA) technique (16). Detailed description of the algorithm is described in Zhuang et al. (14). To be specific, given a given input video, the framework decomposes the video into a sequence of individual frames, extracts the corresponding facial landmarks, and performs face normalization to remove different translation, scaling, and rotation variations. After preprocessing the video, the HoG features are extracted for each individual frame. We prefer the HoG features over landmarks features, which are commonly done for vision based facial weakness analysis, due to the fact that landmark-based methods can suffer from inaccuracies in face landmarks localization (17, 18), while the HoG features are able to handle local misalignment and capture the detailed gradient features exhibited by facial weakness (15). Since HoG features are high-dimensional, to increase computation efficiency and avoid overfitting, the principal component coefficients are computed from the training dataset to reduce the dimensions of the HoG features to the components that can cover 95% of the variance. Using the principal component coefficient of HoG features as the input, then a supervised pLDA predictive model classifies each individual frame by searching the most discriminant information related to facial weakness. One prominent advantage of the pLDA approach is that it provides visualizable and interpretable results. A detailed formulation and discussion regarding modeling the pathological meaningful texture variations for facial weakness using the pLDA predictive model can be found in Zhuang et al. (17, 19). In the current study, we evaluated the computer vision algorithm developed in Zhuang et al. (14) on a board-certified neurologist verified video dataset used in Zhuang et al. (19), specifically focusing on the comparison between human raters' assessment and the performance of computer vision algorithm from the clinical perspective. Finally, a voting classifier aggregates the individual classification results and outputs discrete classification results: normal, left facial weakness, and right facial weakness (**Figure 1**). In addition, an ensemble of regression trees based facial landmark extractor (20) is used in our study because of its accurate and robust performance (18). The configurations for HoG features are set as follows: the number of orientation bins in a cell is nine, a cell consists of eight by eight pixels, and each block contains four cells in each block is four. Performance of the algorithm was tested using a 5-fold cross-validation scheme and calculating sensitivity, specificity, and accuracy. The dataset was randomly divided into five groups with balanced samples. Four groups of samples were used for the training process and one group served as the testing dataset. The process was then repeated five times.

Data Analysis

For the paramedic ratings, individual and the group average sensitivity, specificity, and accuracy were obtained. A false negative was defined as either 1) the failure to identify right facial weakness (3R) when right facial weakness was the ground truth, or 2) the failure to identify left facial weakness (3L) when left facial weakness was the ground truth. A false positive was defined as denoting the presence of facial weakness when normal smile was the ground truth. The algorithm and paramedic groups' sensitivity, specificity, and accuracy were compared and confidence intervals were constructed by 10,000 bootstraps at the patient level and balanced between videos with and without facial weakness, which accounts for repeated measures on patients. This method allows for the estimation of variability for each paramedic as well. To further analyze performance, the identification of unilateral facial weakness was divided into two components: 1) identifying the presence of weakness and 2) identifying the correct laterality of the weakness. Laterality designations (L or R) were initially excluded from video classification. To assess identification of correct laterality, we looked at all reviews where an error was made, and compared whether the rater was human or not with whether or not the error was in laterality using Fisher's exact test with a p-value threshold of 0.05 to assign significance.

Comparison to Prior Work

The present study utilizes the same data set from Zhuang et al. (14), detailed in Section 2.2, and a similar rating schema described in Zhuang et al. (19), in order to compare the current algorithm's performance in detecting facial weakness to trained paramedics. In contrast to these prior studies, the current analysis explores the variability among paramedics and how this variability, as seen in real life practice, compares to the algorithm's performance. We also seek to determine the accuracy of identifying the correct laterality of facial weakness by the algorithm vs. paramedics, which is a key skill in evaluating patients with facial weakness in clinical practice.

RESULTS

Demographics

A total of 202 videos were collected: 13 videos were excluded due to failure to detect facial landmarks due to variations in lighting and head position. Of the 189 remaining videos (117 females), 96 demonstrated a normal smile (58% women), and 93 demonstrated unilateral facial weakness (61% women). Of the videos with facial weakness, 50 were with right sided weakness and 43 with left sided weakness. Based on skin-tone, 155 videos had light-skinned individuals and 34 individuals were dark-skinned. All videos were standardized to a rate of 30 frames per second. Overall the videos had a median (range) number of frames of 60 (12 to 260). Videos with normal smiles had a median

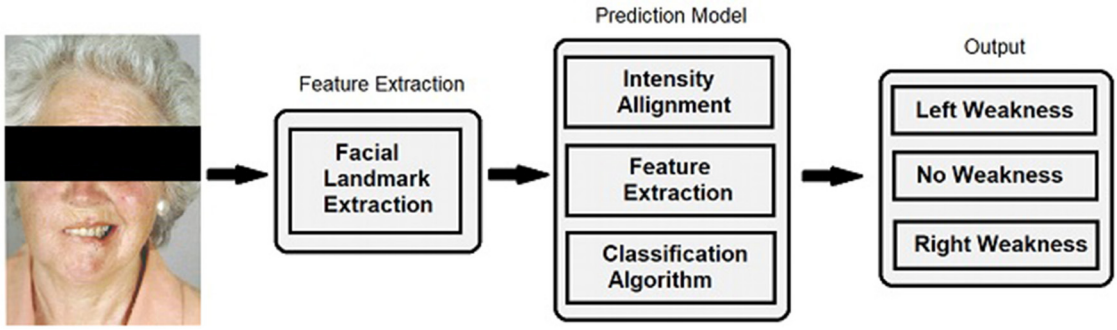

FIGURE 1 | Facial landmark extraction and classification. For algorithm training and performance, videos were decomposed into individual frames and facial landmarks were extracted. Normalization was performed by aligning the extracted landmarks of current input sequences to a template to handle different head scales, location, and orientation. The same transformation was applied to the pixel intensity information to remove these variations. A predictive model computed the classification result for each individual frame and a voting classifier reduced the output into discrete classifications comprised of no weakness, left facial weakness, and right facial weakness categories.

(range) number of frames 48 (13 to 157), while those with facial weakness had a median of 79 (23 to 260).

Accurate information on age, race, and ethnicity from the videos was not possible to obtain. However, descriptively the videos exhibited a wide range of facial characteristics including glasses, beards, tattoos, and cultural-specific facial painting or adornment. The faces of the individuals ranged from adolescent to elderly in appearance. Solely based on visual inspection to assess ethnicity, the videos encompassed a multi-ethnic sample including people of African, Europe, and South-East Asia ancestry. To provide information about the degree of difficulty of rating the videos for the board-certified vascular neurologists, we calculated the Fleiss Kappa as a measure of agreement (21). The neurologists showed almost perfect agreement (0.8–1.0) for the presence of facial weakness (0.90), for laterality of weakness (0.91), and combined (0.89).

Algorithm and Paramedic Diagnostic Comparison

As previously reported, the paramedics had a mean accuracy, sensitivity and specificity of 92.6% [95% CI 90.1–94.7%], 87.8% [95% CI 83.9–91.7%] and 99.3% [95% CI 98.2–100%], respectively (19). This study's algorithm had an accuracy, sensitivity and specificity of 88.9% [95% CI 83.5–93%], 90.3% [95% CI 82.4–95.5%] and 87.5 [95% CI 79.2–93.4%]; see **Table 1**. While there was no difference in accuracy and sensitivity between the paramedics and the algorithm, paramedic assessments were more specific. Overall, the performance of the algorithm to detect the presence of facial weakness was similar to paramedics ($p = 0.074$).

On the other hand, the paramedic group showed notable variability in the sensitivity of facial weakness detection, **Table 1**. Paramedic sensitivity ranged from 78.5% (69.9–86.5%) to 95.70% (97–99%), a large 17.2% difference. This was not the case for specificity which had a non-significant 6.2% point difference. **Figure 2** exhibits the ROC curves for the algorithm and each paramedic.

As a sensitivity analysis, we excluded laterality designations. This did not change the performance metrics of the algorithm. In contrast, the exclusion of laterality improved the average paramedic sensitivity to 92.5 [89.5–95.2%] from 87.8%, but not for specificity. Paramedics made more laterality errors than the algorithm (**Table 2**) (13 vs. 0, p-value = 0.044).

DISCUSSION

In this preliminary study, we demonstrate that a machine learning algorithm using computer vision analysis can detect facial weakness in recorded videos with an accuracy and sensitivity comparable to trained paramedics. However, the average paramedic ratings had better specificity than the algorithm (99 vs. 88%). Just last year, our team has shown that this approach can achieve higher accuracy (94.3%), sensitivity (91.4%), and specificity (95.7%) performance in comparison to paramedics (19), especially when juxtaposing the enhanced algorithm to several state-of-the art methods. Unlike our previous work (19), we show in this analysis the inter-rater variability among paramedics; see **Table 1** and **Figure 2**. The variability in performance among the paramedic was related to differences in sensitivity. This may reflect real-life interactions between paramedics and patients suffering from a stroke in the field. Paramedics have varying years on the job, training programs, and local stroke incidence rates that affect their individual ability to detect stroke. To further this point, Brandler and colleagues observed that ambulance-based paramedics had 83% sensitivity and 66% specificity to detect facial weakness (6). When laterality designations were excluded in our sensitivity analysis, we found that EMS provider ratings had an average sensitivity and specificity of 92.5 and 99%, respectively. The higher specificity as compared to sensitivity may be due, in part, to our pre-specified definitions of false negatives and false positives. Accordingly, laterality errors were designated as false negatives rather than false positives. Given that the EMS providers made several laterality errors, these errors decreased

TABLE 1 | Performance metrics of the correct identification of facial weakness and its laterality among all raters.

Facial weakness detection performance						
	Paramedics Overall		**Algorithm**		**ZeroR**	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	
Accuracy	92.60%	90.1–94.7%	88.90%	83.5–93%	49%	
Sensitivity	87.80%	83.9–91.7%	90.30%	82.4–95.5%	100%	
Specificity	99.30%	98.2–100%	87.50%	79.2–93.4%	0%	
	Paramedic 1		**Paramedic 2**		**Paramedic 3**	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Accuracy	94.70%	91.5–97.9%	94.20%	90.5–97.4%	88.90%	84.1–93.1%
Sensitivity	95.70%	91–99%	89.20%	82.6–95%	78.50%	69.9–86.5%
Specificity	93.80%	88.5–98%	99.00%	96.6–100%	98.90%	96.6–100%

95% Confidence intervals are the result of 10,000 boot-straps via the percentile method. ZeroR shows. the expected diagnostic performance based on random selection of the presence of facial weakness.

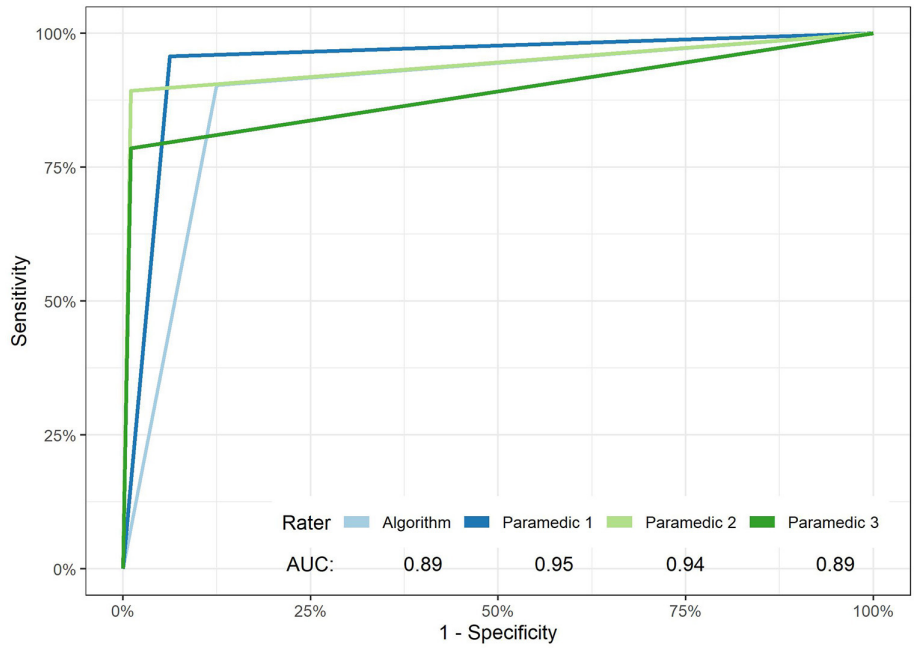

FIGURE 2 | ROC curves of facial weakness and laterality detection of the algorithm and each paramedic. The overall performance of paramedics vs. the algorithm in the detection of unilateral facial weakness failed to reach significance (*p*-value 0.074).

the sensitivity but not the specificity of the paramedic group. However, we did not make this comparison with our updated algorithm (19). It is encouraging that our algorithm's facial detection accuracy (89%) can be improved to 94.5% (19).

An interesting note, the algorithm made no laterality errors compared to paramedics. A possible explanation is that human examiners may make two independent decisions: 1) a more global assessment of facial asymmetry and the presence of pathology followed by 2) closer inspection and selection of the side that appears abnormal. There is no evidence of such dissociation for computer-based detection of unilateral facial weakness. More research is needed to further explore this hypothesis. As a pilot observational study, there are several limitations to consider. As a publically available repository, the dataset was quite heterogeneous with varying video length, quality and formatting. Given the lack of available medical information and dedicated exam maneuvers, particularly to assess the upper facial muscles, we did not seek to classify facial weakness as peripheral vs. central in origin (e.g., Bell's palsy vs. stroke). The inclusion of both younger individuals with peripheral patterns of facial

TABLE 2 | Cross tabulation ratings of presence and laterality of unilateral facial weakness by paramedics as a group vs. the machine learning algorithm.

	Presence of unilateral facial weakness		
	Present	**Absent**	**Total (n = 189)**
Paramedics			
Present	82	1	83
Absent	11	95	106
Algorithm			
Present	84	12	96
Absent	9	84	93
	Side of facial weakness		
	Correct laterality	**Incorrect laterality**	
Paramedics	245	13	
Algorithm	84	0	

Three independent and blinded board-certified vascular neurologists determined the ground truth labeling for the presence or absence of unilateral facial weakness and the affected side of the face. For the presence of facial weakness, there was no significant differences between Paramedics (as a group) and the algorithm, p-value 0.074. The Paramedics, however, had significantly more laterality errors compared to the algorithm, p-value 0.044. Both comparisons utilized Fisher's exact test.

weakness and older individuals with no visible evidence of upper facial weakness suggests that multiple disease processes are represented in the dataset. While patient heterogeneity may broaden the generalizability of the algorithm, further validation in well-curated datasets and live patient encounters is underway.

Another limiting factor of our study is that sensitivity and specificity of the paramedic assessments were higher than expected and much more so than reported by Brandler and colleagues (6). One possible explanation is that our video dataset included an overrepresentation of more severe and obvious cases of facial weakness, as individuals are more likely to upload extreme examples rather than subtle facial asymmetry. In real world practice, many stroke patients will present with more subtle facial weakness, indicated by flattening of the nasolabial fold or slight asymmetry in facial expressions. In these incidences, a computer algorithm applying quantifiable landmark extraction, rather than gross visual inspection, might perform better by comparison.

Although the landmarks extraction approach performed well in terms of localization accuracy and computation efficiency (17), approximately 6% of videos were excluded from analysis due to failure of the algorithm to detect landmarks. The reasons are likely 2-fold. First, we reported a previous study (17) suggesting that the accuracy of the facial landmark extraction approach is insufficient in some cases, where the patients demonstrate severe facial weakness symptoms. This is because modern landmarks detection systems are typically trained and calibrated using normal facial configuration while facial weakness subjects may demonstrate a more pathological configuration. Second, performing facial landmarks detection in an uncontrolled dataset, such as our publically curated videos, is a challenging task (22). Variations arise not only from different denvironmental settings (e.g., indoor vs. outdoor), but also from individual appearance variations (e.g., glasses, mustaches, wrinkles, makeup). This is why we sampled a diverse set of public videos for this study as detailed in the results section. These factors contribute to variability in facial landmarks detection, but they are representative of the same issues one would encounter with real patients in the emergency setting.

Future approaches will seek to first train a dedicated facial landmark extractor for real world patients with facial weakness, and second to explore whether an interactive interface that gives corrective commands to the user can decrease such errors by limiting variability in variables such as head position and lighting.

The ability to detect facial weakness through computer vision analysis is a proof of concept that computer vision methods can be applied to detect other visually observable neurologic signs that could help specify not only stroke, but various stroke subtypes such as large vessel occlusions (e.g., gaze preference, hemiplegia, neglect) or posterior circulation stroke (e.g., nystagmus, dysconjugacy, limb ataxia). Further, we believe machine learning techniques could be applied to non-visual neurologic signs such as aphasia and dysarthria through alternative means such as natural language auditory processing. In a future state, our goal would be to integrate these ML algorithms into an automated version of the NIHSS (i.e., eNIHSS) that could be deployed on mobile devices and expedite the accurate diagnosis and differentiation of stroke for non-neurology providers. The greatest potential for a future at scale implementation of this technology could be the integration into telemedicine or telestroke consults. This possibility is especially poignant due to the rapid advancement and acceptance of telemedicine technology in recent years.

SUMMARY/CONCLUSIONS

This study offers initial proof-of-principle that a computer vision machine learning algorithm can detect lateralized facial weakness with similar accuracy to trained paramedics. We are currently applying similar methods for automated detection of other focal neurological signs common in stroke. External validation is needed in independent datasets and prospective patient encounters.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Virginia Internal Review Board (IRB). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CA: drafting/revision of the manuscript for content, including medical writing for content, analysis or interpretation of data, additional contributions, manuscript preparation, and formatting for submission. MM: drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, study concept or design, and analysis or interpretation of data. MW: drafting/revision of the manuscript for content and including medical writing for content and major role in the acquisition of data. YZ: drafting/revision of the manuscript for content, including medical writing for content and analysis or interpretation of the data. OU: drafting/revision of the manuscript for content, including medical writing for content, study concept or design and analysis or interpretation of data. TM: analysis or interpretation of data. IL: major role in the acquisition of data. HP and BS: major role in the acquisition of data. WD, JC, SC, and BW: drafting/revision of the manuscript for content and including medical writing for content. GR: drafting/revision of the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data. AS: drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, study concept or design, and analysis or interpretation of data. All authors contributed to the article and approved the submitted version.

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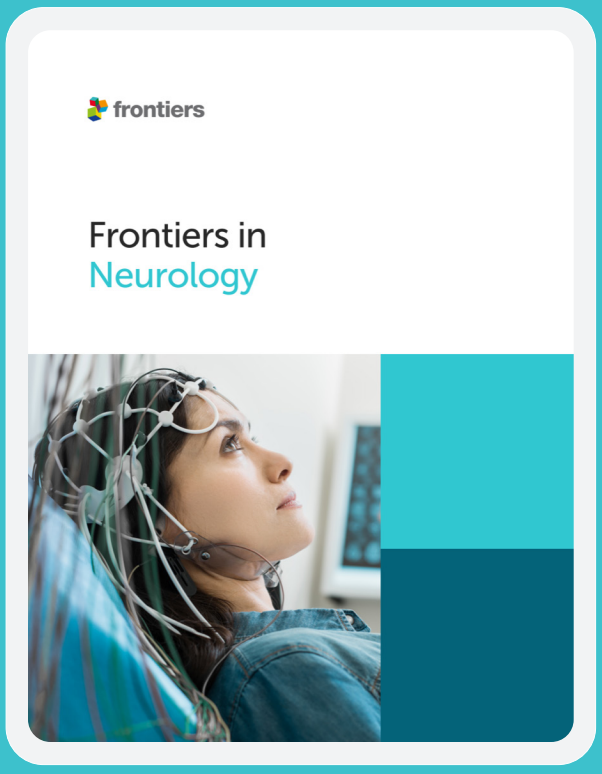

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