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Development of stroke systems of care across the globe

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Development of stroke systems of care across the globe

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Editorial: Development of stroke systems of care across the globe

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Editorial on the Research Topic
Development of stroke systems of care across the globe

Stroke, a leading cause of disability and death worldwide, knows no boundaries, affecting individuals, families, and communities globally and imposing immense challenges on healthcare systems (1). To address this, stroke care encompasses a continuum of services, ranging from prevention and acute treatment to rehabilitation and long-term support, highlighting the importance of effective stroke systems of care to ensure optimal patient outcomes.

The Research Topic "*Development of stroke systems of care across the globe*" includes 21 manuscripts: 14 original research articles, one systematic review, one study protocol, two reviews, one prospective, and two brief research reports. These articles provide valuable insights into stroke care delivery across different regions and healthcare settings. They cover early identification and assessment of stroke patients, innovative technologies for acute stroke management, the impact of telestroke programs on specialized care access, and comprehensive rehabilitation strategies.

Despite the universal impact of stroke, substantial inequalities exist between countries and regions. High-income countries often possess well-established stroke networks, specialized stroke centers, and comprehensive rehabilitation programs. In contrast, low- and middle-income countries face significant challenges in terms of limited resources, inadequate infrastructure, and a shortage of healthcare professionals (2). As an example of these inequalities in a middle-income country, the SAMBA study, an analysis of stroke in multiple Brazilian areas, addresses the significant impact of stroke in Brazil with a remarkable social and financial burden (Santos et al.). The study registered 932 stroke cases in 1 year, revealing different incidence rates among the cities. Sobral, with the lowest socioeconomic indexes and no stroke service in the city, exhibited the worst results in terms of lethality (49% in hospital mortality) and functional status. In this context, Matuja et al. conducted a study in Tanzania to assess the prevalence and outcomes of presumed large vessel occlusion (LVO) in ischemic stroke patients, with a particular focus on a region where definitive vessel imaging is not readily available. The study revealed a high burden of presumed LVO, resulting in significant 1-year morbidity and mortality rates, emphasizing the need for good epidemiological data before advocating for evidence-based acute stroke interventions in resource-limited settings. These studies highlight the importance of improved resource allocation based on regional health priorities to improve stroke care and outcomes in vulnerable populations.

Disparities in stroke care are not only limited to income levels but also emerge between rural and urban regions, as demonstrated by Llanos-Leyton et al.. In a prospective cohort study conducted in Colombia, stroke patients from diverse areas were examined, and their functional outcomes were evaluated based on sociodemographic factors and healthcare access. The study revealed that rural patients had a higher likelihood of experiencing severe strokes and unfavorable functional outcomes at discharge and during the 3-month follow-up, in contrast to urban patients with similar risk factors. Importantly, these disparities could not be solely attributed to poverty rates or barriers in healthcare access. Gender differences in stroke outcomes and treatment access also require attention. Naveed et al., using Qatar stroke database data, discovered gender disparities in stroke care. Women had delayed presentation, more severe strokes, lower thrombolysis rates, increased complications, and longer hospital stays. Long-term outcomes were unfavorable for women, with fewer achieving good outcomes at 90 days, lower medication use, and higher rates of major adverse cardiovascular events.

Yang et al. provides an essential addition to the discourse on stroke care challenges. The results gleaned from the study indicate that pre-stroke frailty is an independent risk factor for 28-day mortality and for 28-day or 1-year severe disability post-stroke. Analyzing data from international aging surveys involving 3,432 participants with stroke history, Gil-Salcedo et al. found that individuals with higher pre-stroke disability experienced less pronounced increases in limitations in activities of daily living (ADL) 1 year after the stroke. However, over time, ADL limitations increased for all pre-stroke disability levels, particularly in those aged 75 or older at stroke onset. This highlights the necessity of adopting an inclusive approach to stroke care that not only takes into account clinical variables but also considers patients' pre-existing conditions. In conjunction with the disparities mentioned earlier, these findings further accentuate the significance of implementing stroke care systems attuned to the diverse needs of populations across varying healthcare contexts.

Addressing these inequalities requires a multi-faceted approach involving targeted funding, capacity building, and knowledge transfer. A well-coordinated stroke network is essential for efficient healthcare delivery, including hospitals, emergency medical services (EMS), and rehabilitation centers. EMS utilization among acute ischemic stroke has been proven to significantly shorten prehospital delay and enhance prenotification of the receiving hospital (3). Ding K. et al. conducted an analysis of medical records from 2018 to 2021 in Beijing, uncovering that 46.1% of acute ischemic stroke patients were transported to hospitals via EMS. This study identified significant disparities in EMS usage, with a notable preference for urban areas. Nasreldein et al. investigated factors contributing to pre- and in-hospital delays in the use of intravenous thrombolysis (IVT) for acute ischemic stroke patients in both urban and rural areas of Egypt. Rural patients experienced longer delays from symptom onset to hospital arrival, emphasizing the need for improved educational initiatives and enhanced EMS accessibility, particularly in rural regions and for individuals at an elevated risk of stroke.

Accurate prehospital triage for acute ischemic stroke (AIS) patients is crucial to ensure timely and appropriate care, preventing the misallocation of resources. Sjöö et al. evaluated the characteristics and diagnosis distribution among patients presenting with suspected stroke and stroke mimics within the newly implemented Stockholm Stroke Triage System. The study showed the importance of accurately triaging stroke mimics to avoid inappropriate resource allocation. Recently, studies have shown that mobile stroke units (MSU) care expedites intravenous thrombolysis compared to standard emergency medical services. In this context, Ellens et al. conducted a study to establish standard metrics for reporting MSU operational efficiency, considering that MSU operations require significant personnel and material resources, and the cost-effectiveness and viability of these units will vary according to local circumstances.

At its core, the stroke network emphasizes swift identification and diagnosis, rapid transport of patients to designated stroke centers, and seamless communication among medical professionals. This cohesive approach ensures that stroke patients receive the most appropriate treatment promptly, leading to a higher likelihood of successful recovery (4). Bonifacio-Delgadillo et al. present a remarkable stroke network program, *the ResISSSTE Cerebro,* which was established in 2019 as Mexico's first stroke network in the public health system. This program features one advanced stroke center and seven essential stroke centers using a modified hub-and-spoke model to deliver acute stroke care and showcases positive clinical outcomes. Schaefer et al. conducted a retrospective analysis using data from the German Stroke Registry to compare outcomes between two models of endovascular therapy (EVT) for AIS patients with large-vessel occlusion: the "drip-an-ship" model and direct transfer to a thrombectomy center. Their findings indicated that secondary transfers in the DS model resulted in poorer outcomes when compared to the direct-to-center EVT approach, emphasizing the need to optimize EVT workflows to reduce time delays.

The organization of stroke services within hospitals assumes a pivotal role in optimizing patient outcomes and fostering recovery. Rapid and efficient triage, accurate diagnosis, and effective treatment pathways collectively contribute to a significant reduction in the impact of strokes, thereby enhancing survival rates. Sahakyan et al. present a contemporary evaluation of the implementation of acute stroke care services in Armenia, subsequent to the establishment of the National Stroke Program in 2019. Among the 385 patients included in the analysis, 155 underwent reperfusion therapies, primarily arriving at the hospital via ambulance. Notably, 79.2% exhibited neurological improvement upon discharge, and 60.6% achieved a favorable modified Rankin score of 0–2 at the three-month mark. The study highlights the substantial progress achieved in the performance of acute stroke services through the implementation of organized protocol-driven care, serving as a model for enhancing structured stroke care in resource-limited settings. During the COVID-19 pandemic, numerous challenges emerged in maintaining stroke patient care in hospitals, including issues related to access, infection control, and resource allocation. Klu et al. conducted a study in Brazil, demonstrating the feasibility of reducing the door-to-needle time for acute stroke patients. Importantly, their research highlights that despite the challenges posed by the pandemic, acute stroke care remained a priority. Also, the study emphasizes the continuous monitoring of service times to enhance stroke center quality and improve functional outcomes for stroke patients.

Furthermore, a well-structured system ensures the delivery of appropriate post-acute care and rehabilitation services, which are integral in reinstating functional capabilities and augmenting overall quality of life. Su et al. conducted a meta-analysis of telerehabilitation's impact on stroke patients during the pandemic, showing its effectiveness. Equally vital is the establishment of robust follow-up mechanisms for stroke patients subsequent to their initial hospitalization. Illustratively, Yi et al. examined a cohort of 2,893 individuals at high risk of stroke in China. The study revealed that over a span of 4.7 years, the rates of persistence with various medications ranged from 38.0 to 59.8%. Notably, the study observed a direct correlation between increased adherence to antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics, and a reduced incidence of new ischemic strokes and composite vascular events. These findings underscore the imperative of augmenting the persistence of drug therapy through public education, particularly among high-risk populations. Technology plays a crucial role in identifying high-risk patients, enabling timely interventions and regular monitoring, which can significantly improve long-term health outcomes. Gong et al. demonstrate the cost-effectiveness evaluation of implementing a primary care-based and technology-enabled model of intervention, which is centered on stroke secondary prevention and management in rural China. Sustained continuity of care, facilitated by regular follow-up appointments, empowers healthcare providers to closely monitor the patient's progress and manage risk factors, ultimately culminating in the diminishment of recurrent stroke risks.

Also, effective stroke care systems require continuous learning, knowledge exchange and government support. Ding G. -B. et al. assessed stroke knowledge among primary healthcare providers in the context of acute stroke care and found that only 39.7% of healthcare providers surveyed were aware of the time window for stroke management. These findings highlight the importance of implementing strategies to enhance stroke-related knowledge and awareness of healthcare professionals. The field of stroke care has witnessed significant advancements in recent years, driven by the collective efforts of researchers, clinicians, and policymakers globally. Amorín et al. showed that Uruguay's National Stroke Plan serves as a prime example of successful collaboration, supported by financial incentives to adhere to stroke management guidelines, to improve quality of stroke care, even during the pandemic. The authors demonstrate that by focusing on these key aspects, better outcomes, improved quality of life for stroke survivors, and reduced healthcare costs can be achieved. Stroke registries have been implemented for quality improvement, resulting in an increased thrombolysis rate. Wada et al. explore the establishment and significance of the Japan Stroke Data Bank in the context of the Japanese National Plan for the Promotion of Measures Against Cerebrovascular and Cardiovascular Diseases. They emphasize the importance of improving the registry's quality through meticulous data collection, integration with external databases, enhancing treatment quality via benchmarking, and securing ongoing support from governmental and academic institutions. Collantes et al. described the gaps in stroke care and the development of stroke systems of care in the Philippines. The Stroke Society of the Philippines has collaborated with the government to address these issues by providing nationwide and regional stroke training, establishing acute stroke-ready hospitals and units, and adapting stroke protocols. Other low- and middle-income countries can learn valuable lessons from these studies by utilizing technology for outreach, training non-neurologists to assist stroke patients, expanding insurance coverage for reperfusion therapies, improving stroke infrastructures, and bolstering community awareness about stroke.

In conclusion, effective stroke systems of care require global collaboration, continuous learning, and innovative strategies tailored to diverse regional needs. Addressing disparities, promoting knowledge exchange, and implementing early interventions are essential steps in reducing the global burden of stroke and improving outcomes for patients.

Author contributions

SM: Conceptualization, Writing—review and editing. TS: Writing—original draft, Writing—review and editing. CM: Writing—review and editing. RN: Writing—review and editing.

Conflict of interest

The 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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Mobile Stroke Unit Operational Metrics: Institutional Experience, Systematic Review and Meta-Analysis

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Background: The available literature on mobile stroke units (MSU) has focused on clinical outcomes, rather than operational performance. Our objective was to establish normalized metrics and to conduct a meta-analysis of the current literature on MSU performance.

Methods: Our MSU in upstate New York serves 741,000 people. We present prospectively collected, retrospectively analyzed data from the inception of our MSU in October of 2018, through March of 2021. Rates of transportation/dispatch and MSU utilization were reported. We also performed a meta-analysis using MEDLINE, SCOPUS, and Cochrane Library databases, calculating rates of tPA/dispatch, tPA-per-24-operational-hours ("per day"), mechanical thrombectomy (MT)/dispatch and MT/day.

Results: Our MSU was dispatched 1,719 times in 606 days (8.5 dispatches/24-operational-hours) and transported 324 patients (18.8%) to the hospital. Intravenous tPA was administered in 64 patients (3.7% of dispatches) and the rate of tPA/day was 0.317 (95% CI 0.150–0.567). MT was performed in 24 patients (1.4% of dispatches) for a MT/day rate of 0.119 (95% CI 0.074–0.163). The MSU was in use for 38,742 minutes out of 290,760 total available minutes (13.3% utilization rate). Our meta-analysis included 14 articles. Eight studies were included in the analysis of tPA/dispatch (342/5,862) for a rate of 7.2% (95% CI 4.8–9.5%, $I^2 = 92\%$) and 11 were included in the analysis of tPA/day (1,858/4,961) for a rate of 0.358 (95% CI 0.215–0.502, $I^2 = 99\%$). Seven studies were included for MT/dispatch (102/5,335) for a rate of 2.0% (95% CI 1.2–2.8%, $I^2 = 67\%$) and MT/day (103/1,249) for a rate of 0.092 (95% CI 0.046–0.138, $I^2 = 91\%$).

Conclusions: In this single institution retrospective study and meta-analysis, we outline the following operational metrics: tPA/dispatch, tPA/day, MT/dispatch, MT/day, and utilization rate. These metrics are useful for internal and external comparison for institutions with or considering developing mobile stroke programs.

Keywords: mobile stroke unit (MSU), ambulance, mechanical thrombectomy (MT), tissue plasminogen activator (tPA), operational performance

INTRODUCTION

Since mobile stroke units (MSU) were first described in 2003 in Germany, numerous studies have shown MSU care expedites intravenous thrombolysis and mechanical thrombectomy compared to standard emergency medical services (1–7). Recently, two large, prospective controlled trials have shown improved clinical outcomes 90 days after presentation with acute ischemic stroke in patients receiving MSU care as compared to traditional emergency medical services (8, 9). These compelling data have raised the question, "Does My District Need a Mobile Stroke Unit?" (10).

Because MSU operations require significant personnel and material resources, cost-effectiveness and viability will vary with local circumstances (11). The decision to establish a mobile stroke unit must be made in consideration of local case volume, geography, and infrastructure. The purpose of this manuscript was to establish standard metrics for reporting MSU operational efficiency and to benchmark those numbers using our institutional experience and a meta-analysis of the current literature.

METHODS

Retrospective Single Center Cohort Analysis

The authors performed a retrospective analysis of a prospective database of stroke patients at the University of Rochester, from October 2018 through March 2021. At our institution, the mobile stroke unit services a population of ∼741,770 people in the greater Rochester area. The MSU is available on weekdays for 8 h per day and is staffed by a registered nurse and a CT technician, each with specialized training, along with a paramedic and emergency medical technician (EMT) (12). Our MSU is dispatched along with a separate emergency medical service (EMS) unit for all 911 calls identified as suspected stroke (Card 28) as defined by the Medical Priority Dispatch System (version 13.1, International Academies of Emergency Dispatch, Salt Lake City, UT). Accuracy of code 28 dispatches in our catchment is consistent with national standards with approximately one-third representing patients ultimately diagnosed with transient ischemia or stroke. Our MSU can be dispatched by first responder request but is not permitted to self-attach after hearing of possible stroke over EMS communications. The MSU works with an on-call teleneurologist. Each eligible patient undergoes a formal evaluation on-scene using a National Institutes of Health Stroke Scale (NIHSS), followed by non-contrast head CT. A decision is then made regarding immediate tPA administration and, when clinically indicated, patients are transferred to a comprehensive stroke center for mechanical thrombectomy.

Institutional review board approval was obtained to collect and report the data at our institution. Operational metrics were collected and included dispatches, transport, tPA administration, mechanical thrombectomy (MT), and operational hours in service. Utilization was calculated by dividing the duration of time from dispatch to return to service for all MSU dispatches, by the total time the MSU was available. The authors also performed a systematic review and meta-analysis to determine the operational metrics reported in the literature for MSUs. This was performed up to May of 2021, according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

Meta-Analysis Eligibility Criteria and Study Selection

All studies that were identified and analyzed fit the following criteria: the paper was written in English and reported operational metrics of a mobile stroke unit that consisted of dispatches, transports, intravenous tPA administration, MT, and operational hours in service. We included studies of a prospective and retrospective nature, in addition to large case series. Case reports were excluded. Local, regional, and international studies were included. Data was abstracted from publications and/or supplementary data in all cases except BEST-MSU, which consists of 7 sites (8). BEST-MSU investigators provided details regarding launch dates, operational hours, and site-specific enrollment to enable accurate determination of pooled tPA/day.

Information Sources, Literature Search, and Data Collection

Relevant studies were identified by searching the MEDLINE, SCOPUS and Cochrane Library databases up to May of 2021 using the following terms: (mobile stroke unit), (mobile stroke) AND (efficiency), (mobile stroke program), (mobile stroke) AND (dispatch), (mobile stroke) AND (utilization). Any duplicates that were identified within this search were then removed (**Figure 1**). The initial screening process was performed by reading the article title, followed by the abstract. If there was still uncertainty regarding the article's relevance, the full article manuscript was read. Two independent reviewers rigorously reviewed all final manuscripts to confirm their relevance and the decision for inclusion. Any cases of disagreement were resolved by consensus with the remainder of the authors. All studies that passed the above criteria were included within this meta-analysis.

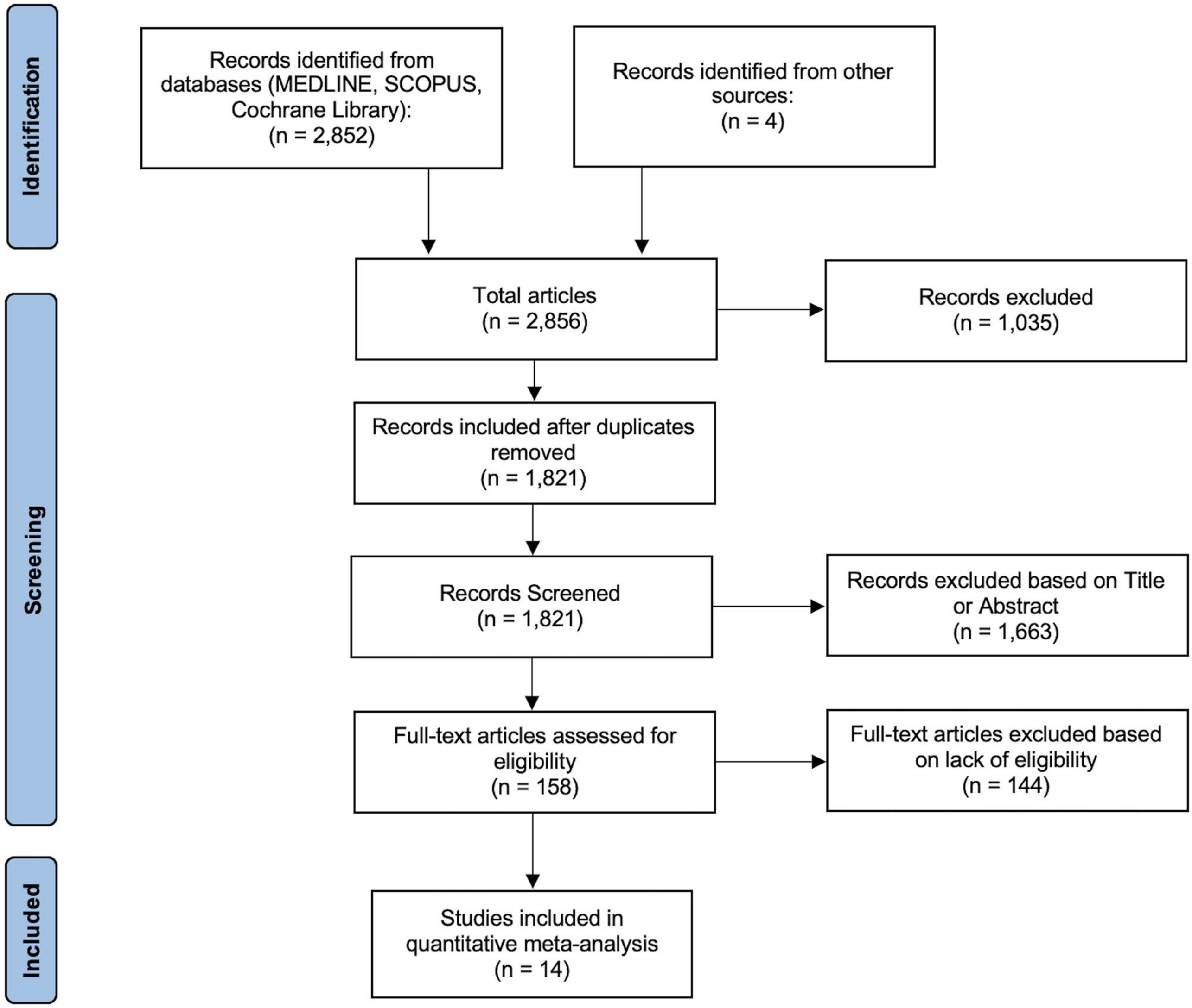

FIGURE 1 | PRISMA flow diagram. This diagram demonstrates the systematic method used for the identification, screening, and inclusion of articles that met criteria for inclusion within the meta-analysis.

Results Synthesis and Statistical Analysis

Forest plots depicting the pooled proportion for the transportations/dispatch, tPA/dispatch, tPA/day, MT/dispatch, and MT/day analyses were generated along with 95% confidence intervals (CI) using a random effects model. "Per day" is used to mean "per 24 operational hours" and reflects the fact that individual programs run different shift lengths. Pooled, meta-analytic rates were calculated from weighted proportions of the included studies and are not derived simply from the composite rates. Individual studies were weighted by the inverse variance of their estimated variances to account for inter-study variation (DerSimion Laird). All forest plots and corresponding statistical analysis, were generated using the OpenMeta[Analyst] from Brown University (http://www.cebm.brown.edu/openmeta/).

Statistical heterogeneity was assessed using Cochran's Q statistic and described using the I^2 measure. An I^2 of 50 and 75% were used as benchmarks for moderate and high heterogeneity among the included studies, respectively. A P value of under 0.05 was used as a benchmark for significance within the heterogeneity assessment. Assessment of potential publication bias was also completed for each analysis using funnel plots and Egger's regression test, implemented with MedCalc statistical software (https://www.medcalc.org). A $P > 0.05$ was used to indicate non-significant bias.

RESULTS

Retrospective Single Center Cohort Analysis

The MSU at our institution was dispatched 1,719 times over a period of 606 days for an average rate of 8.5 dispatches/24-hour-day. Of these 1,719 dispatches, 324 patients (18.8%) were

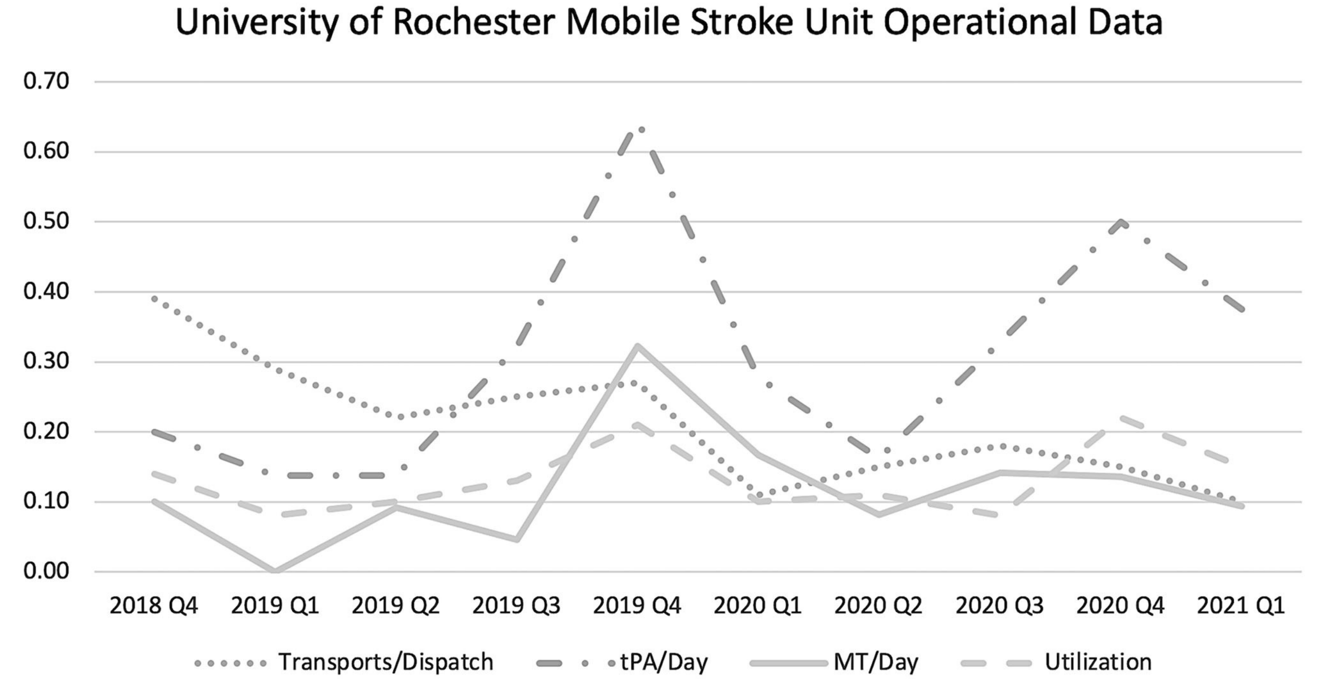

FIGURE 2 | University of Rochester Medical Center Mobile Stroke Unit Operational Data. The data shown here outlines the mobile stroke unit experience at the University of Rochester from its inception in October of 2018, through March of 2021. tPA, tissue plasminogen activator; MT, mechanical thrombectomy.

transported to a nearby hospital. Systemic intravenous tPA was administered in 64 patients (3.7% of all dispatches) and the rate of tPA administration per day was 0.317 (95% CI 0.150–0.567). Twenty-four patients were found to have large vessel occlusions and underwent mechanical thrombectomy (1.4% of dispatches) for an MT/day rate of 0.119 (95% CI 0.074–0.163). Of the 290,760 total minutes the MSU was available, it was in use for 38,742 mins (13.3% utilization rate).

Our MSU launched in October of 2018, serving the downtown Rochester population of 206,284. For the first 3 quarters, we noted a tPA/day rate of 0.159 and an MT/day rate of 0.064. We then expanded to serve the greater Rochester area in June of 2019, increasing our catchment population to 741,770 for quarters 4 through 10. Our tPA/day and MT/day rates increased to 0.373 and 0.141, following this expansion. As our institution gained experience, we also noticed a trend of increasing dispatches/24-h-day, with a rate of 6.4 during the first five quarters, and a rate of 10.7 during the second five quarters. There was a mild decrease in rates of tPA/dispatch (4.2% decreased to 3.4%) and MT/dispatch (1.5 to 1.4%). Average utilization rates remained relatively stable (13%) between the first and second half of our study experience (**Figure 2**).

Systematic Literature Search

Using the MEDLINE, SCOPUS, and Cochrane databases we identified 2,856 total articles, which consisted of 1,821 unique articles after removing duplicates. 1,663 articles were then removed after reading the titles and abstracts, leaving a total of 158 articles. The full text of each article was read and 14 of these articles fit the criteria and were included in the analysis. Each of these articles were reviewed independently by two authors (NE and MB) to confirm that they fit the inclusion criteria.

Meta-Analysis of Proportion

There were 8 studies, including the authors' current data, which met the inclusion criteria for pooled analysis of tPA administration per dispatch (4, 5, 13–18). In these studies, there were 5,862 dispatches, of whom 342 were administered tPA for an average rate of 7.2% (95% CI 4.8–9.5%). Seven unique studies met inclusion criteria for analysis of MT/dispatch (4, 13, 14, 16, 17, 19). These seven studies reported a total of 102 patients who underwent mechanical thrombectomy out of a total of 5,335 dispatches. The pooled average rate was 2.0% (95% CI 1.2–2.8%). Eleven studies reported information regarding rates of tPA administration based on time of MSU availability (4, 5, 8, 9, 13–16, 18, 20, 21). Collectively, tPA was administered 1,858 times over 4,961 available days (defined as 24-h period), for a rate of 0.358 (95% CI 0.215–0.502) (**Figure 3**). Seven studies met the inclusion criteria for pooled analysis of thrombectomy per day (4, 13, 14, 19, 21, 22). In these studies, there were 103 thrombectomies over 1,249 available days, for a rate of 0.092 (95% CI 0.046–0.138) (**Figure 4**). The authors present the only reported utilization rate in the literature thus far, at 13.3%.

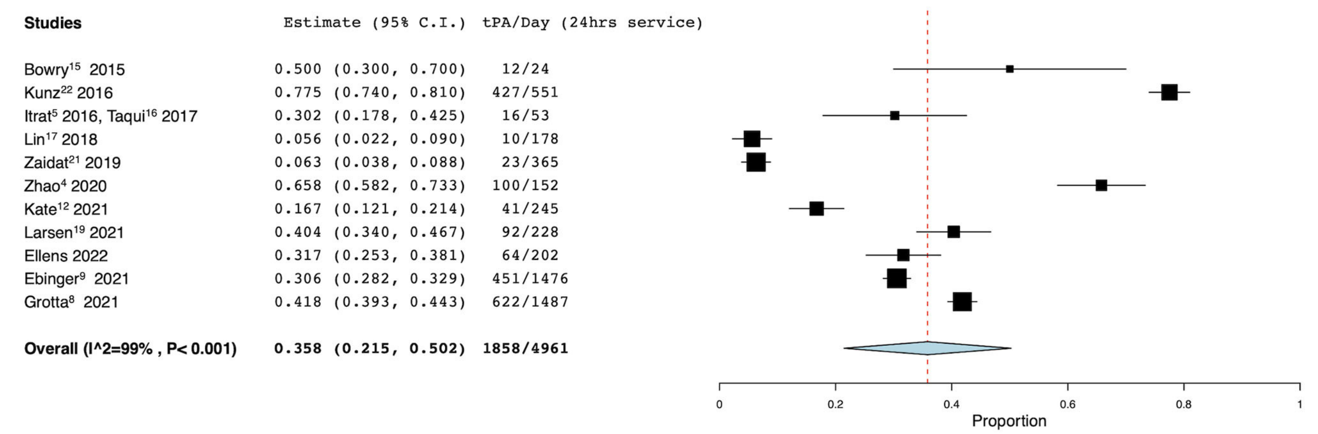

FIGURE 3 | Rate of tPA administration per day. Forest plot demonstrating the results from the meta-analysis of rates of tPA administration per day. tPA, tissue plasminogen activator; CI, confidence interval.

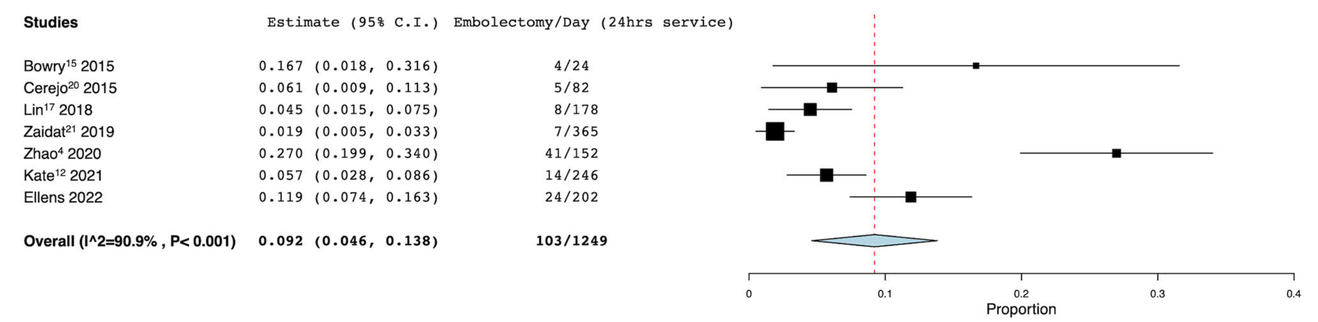

FIGURE 4 | Rate of mechanical thrombectomy per day. Forest plot demonstrating the results from the meta-analysis of the rate of mechanical thrombectomy per day. CI, confidence interval.

Assessment of Heterogeneity and Bias

I^2 values for tPA administration per dispatch and per day were 92 and 99% which both corresponded to $p < 0.001$. I^2 values for MT/dispatch and MT/day were 67 and 91%, which corresponded to $p = 0.005$ and $p < 0.001$ respectively. Together, this indicated a moderate to high degree of interstudy heterogeneity within each analysis (**Supplementary Table 1**). Egger's test was also utilized to assess for publication bias, with significant bias observed within the transportations per dispatch analysis ($p = 0.0097$). No significant bias was found within the tPA administration per dispatch ($p = 0.1976$), MT/dispatch analysis ($p = 0.0817$), tPA administration per day ($p = 0.738$), and MT per day ($p = 0.283$) (**Supplementary Table 2**).

DISCUSSION

This was a single-institution retrospective observational study of mobile stroke unit operational performance as well as a meta-analysis of the literature on MSU operations. Our MSU was dispatched 8.5 times per 24-h-day and intravenous tPA was administered to 3.7% of dispatches while 1.4% underwent mechanical thrombectomy. Our rates of intravenous tPA administration and thrombectomy per day were 0.317 and 0.119 per day, which were similar to the meta-analysis benchmarks of 0.358 and 0.092 per day, respectively. The data for these metrics was abstracted from existing manuscripts but was not explicitly reported in this format. We introduce the metric "MSU utilization rate," the percentage of operational minutes in which the MSU was deployed on a call, which was 13.3% at our institution over the study period. Operational performance will be an area of increased focus as mobile stroke units increase in number.

THROMBOLYSIS METRICS

The first standardized metric used to assess MSU operations was tPA administration per 24 h in service. The PHANTOM-S trial in Berlin reported the highest rate at 0.775, followed by Zhao et al. in Melbourne. Notably, these MSU programs service large populations, with Berlin and Melbourne each servicing populations over 1 million people. We report a tPA administration per day rate of 0.317 (95% CI 0.150–0.567), which is similar to the rate of 0.358 (95% CI 0.150–0.567) observed in the meta-analysis. Not surprisingly, this increased as we expanded our catchment area, as larger catchment areas were noted to typically have higher rates of tPA administration per day (4, 20).

The BEST-MSU group, which contributed 30% of service time to our meta-analysis of tPA/day, illustrates the variability and potential of MSU thrombolysis. The pooled rate across the seven programs included in BEST-MSU was 0.418 tPA/day but ranged from 0.040 in Los Angeles to 1.053 tPA/day in Houston, TX (8). The latter, the oldest program in BEST-MSU which accounted for 25% of BEST-MSU service days, may represent a ceiling of thrombolysis productivity that less mature programs can target. Houston uses several strategies to increase volume and enhance dispatch specificity, including monitoring EMS radio for "active pursuit" opportunities and having first responders add the MSU to high-probability calls not originally identified as a stroke. As a result, Houston is dispatched more often than our MSU in Rochester (13.5 vs. 8.5 times/day) and with a higher thrombolysis yield (10 vs. 3.7% tPA/dispatch). Capacity is preserved by deferring to EMS to transport patients that have obvious exclusions for thrombolysis prior to CT scanning: the fraction of transported patients who received tPA was 60% in Houston as compared with 20% at our program. It is important to acknowledge that BEST-MSU data reflects only those patients who met criteria for enrollment in a controlled trial and excludes a small number of patients who received thrombolysis outside the trial.

Prior to settling on intravenous tPA administration per 24 h in service as a performance metric, we first focused on tPA per MSU dispatch. This figure was 3.7% at our institution and 7.2% in the meta-analysis (range 3.6–26.3%). We came to believe time is a better denominator than dispatches, however, since dispatch criteria vary significantly across programs, often based on urban/rural setting. Kate et al. (13) reported the highest rate of tPA administration per dispatch at 26.3%, while serving rural Alberta, a community with a radius of 250 km. Larsen et al. (18) services rural Norway with an MSU using an air-ambulance and rendezvous model, and reports a tPA/dispatch rate of 12.3%. Given the increased time and resource utilization associated with longer dispatches, rural programs may benefit from more selective MSU dispatch to patients more likely to receive thrombolysis. Conversely, Weinberg et al. (17) demonstrated the lowest rate of tPA administration per dispatch at 3.6%, and they service an area of only 83 square miles in Philadelphia.

Additional Metrics: Embolectomy and Utilization

A small percentage of MSU dispatches will be candidates for endovascular intervention and this is a second important standardized metric to assess MSU operations. Our MSU transported an average of 0.119 MT/day and meta-analysis revealed a range from 0.019 to 0.270, with an average rate of 0.092 (95% CI 0.046–0.138). Rates of MT/day follow a similar pattern to tPA administration per day, and also increase with catchment size and population density. Zhao et al. and the BEST MSU trial had the highest rates at 0.270 and 0.168, and they served the largest cohorts of the seven studies included (4, 14). Kate et al. (13) covers rural Alberta, with a very low population density, and reported lower rates of MT/day at 0.057. The Alberta program represents an instance in which MT/day and MT/dispatch offer conflicting portrayals of MSU activity, as the more specific dispatch criteria required in a rural setting raise the MT/dispatch rate to the higher end of the spectrum (9.0% compared to the average of 2.0% and range of 0.9–9.0%) (13). Rural programs often have smaller populations and longer drive times, which increase the difficulty of administering time sensitive therapies such as tPA and endovascular thrombectomy.

Two metrics that can be useful for internal comparison to evaluate the developmental stage of a mobile stroke program are dispatches/day and transportations/dispatch. Over the duration of this study, our program averaged 8.5 dispatches/day, ranging as low as 3.9 in the beginning and plateauing around 12.0/day. Transportation/dispatch rate was 18.8% (95% CI: 17.0–20.7%) at our institution, which decreased over the period of the study. These metrics lack external validity because of variable dispatch and transport criteria. To illustrate, Grunwald et al. had the highest rate of transportation/dispatch but transported a much lower percentage of patients with a final cerebrovascular diagnosis (39.7%) than we have previously reported (59%) (7, 23).

Utilization rates have not been previously reported but may serve as a metric for MSU programs to ensure efficiency and optimal resource utilization. Determining the ideal number of physicians, ambulances, and other resources to devote to an MSU program, requires an awareness of the frequency with which these resources are being utilized. In population-dense environments, MSU programs may progress to a utilization threshold at which they are unable to attend stroke alerts. The PHANTOM-S cohort in Berlin reported an inability to deploy their mobile stroke team to 1,288 patients, because the MSU was already in operation (2). They have since added two new MSUs to the Berlin region, resulting in expanded availability and coverage (9). The average utilization rate for our MSU was 13.3%, with a peak quarter of 21.9%. We believe this indicates there is capacity remaining within the system. Our utilization rate remained relatively stable since the inception of our MSU, despite increasing dispatch/day. We recommend monitoring utilization rates to ensure efficiency in maturing mobile stroke programs. Utilization rates as a function of operational time of day could be an avenue for future research.

Context

Currently benchmarks are utilized for multiple clinical outcomes for stroke, including "door to needle" time and "door to groin puncture" time. However, little attention has been given to MSU operational performance. The data for these metrics was abstracted from existing manuscripts but was not reported in this format. The data we report may provide a preliminary benchmark for new or inexperienced programs looking to improve MSU operational efficiency.

Establishing these operational performance metrics will also increase transparency between institutions. A successful MSU utilizes significant healthcare resources, including a specialized ambulance equipped with a CT scanner and a comprehensive stroke team. The standardized reporting of these performance metrics may allow for better comparison of MSUs and their utilization across different centers, while providing valuable information to institutions attempting to maximize cost-effectiveness and minimize resource utilization.

This study has several limitations. Although the data we reported was collected prospectively, it was analyzed in a retrospective fashion. Many of the studies included in the meta-analysis were also retrospectively analyzed. Therefore, these studies are subject to the typical biases associated with retrospective studies including confounding and selection bias. This is consistent with the publications bias that we observed within the transportations/dispatch analysis. This could suggest that the data within the literature is reported by high utilizers, and this should be considered when interpreting the results of this study. BEST-MSU and Berlin were prospective, controlled trials with data that was largely concordant with the other included studies (8, 9). This systematic review and meta-analysis included a variety of institutions which varied in experience, acuity, volume, and patient population. Each of these differences increased the observed heterogeneity between each group. This significant degree of heterogeneity suggests variability of utilization metric reporting and study design within the current literature and argues for better standardization and reporting.

CONCLUSION

In this retrospective single institution analysis and meta-analysis, we propose and benchmark the following metrics for MSU operations: tPA/dispatch, tPA/day, MT/dispatch, MT/day, and utilization rate. These metrics are useful for internal and external comparison for institutions with or considering developing mobile stroke programs.

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 Rochester Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NE and DS contributed to the project conception, design, data collection, meta-analysis, manuscript drafting, review, and submission. RR and SA contributed to the project data collection, analysis, and manuscript revisions. AK and CB contributed to critically reviewing and revising the manuscript. SP contributed by providing additional data from other medical centers and reviewing the manuscript. JB, DP, WP, and TM contributed to data analysis, reviewed the manuscript, and provided critical revisions. JG contributed to the project conception, provided additional data from other medical centers, and reviewed and critically revised the manuscript. TB contributed to the project conception and reviewed and critically revised the manuscript. MB contributed to the project conception, design, data collection, meta-analysis, manuscript drafting, review, submission, and overseer of project. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

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BRIEF RESEARCH REPORT
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Disparities Influencing Functional Outcomes Between Rural and Urban Patients With Acute Stroke

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Introduction: There is scarce information in Latin America about factors related to stroke patient outcomes in rural areas compared to urban ones.

Objective: To evaluate functional outcomes of stroke code patients from rural and urban areas and their relationship with socioeconomic disparity.

Methods: Prospective cohort study included patients of urban, semi-urban, and rural origin with stroke code from a high complexity hospital in southwestern Colombia between 2018 and 2019. Demographic, clinical data modified Rankin at discharge, and 3-month follow-up were analyzed. The poverty index, barriers to health access and availability of ambulances by the municipality was assessed at an ecological level.

Results: Five hundred and fifty five stroke patients were registered, 21.2% from rural areas, 432 (77.98%) had an ischemic stroke. There were no significant differences in sociodemographic factors and medical background. Urban patients had lower reperfusion therapies rates (23.25%). Favorable mRS at discharge (<3) was higher in urban areas (63.03%) and mortality was superior in rural patients (13.56%). The ambulance rate in semi-urban and rural areas was as low as 0.03 per 100.000 inhabitants, the poverty index was 11.9% in urban areas vs. 23.3% in semi urban and rural areas.

Conclusions: Rural patients treated in our center were more likely to present with severe strokes and unfavorable mRS at hospital discharge and 3-month follow-up compared to urban, despite having similar risk factors. There is an inverse relationship, which is not related to the poverty rate or the percentage of people with barriers to access to health. There is a need for further studies that assess barriers inherent in rural patients and establish a regional stroke network.

Keywords: ischemic stroke, health inequities, rural, urban, outcomes

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INTRODUCTION

In high-income countries, stroke mortality has decreased during recent years using treatments such as systemic thrombolysis and mechanical thrombectomy. However, there are some population groups in which lethality could be significantly higher. Patients from rural areas seem to suffer more severe strokes, although this relationship could be moderated by a higher incidence rate (1). In particular, more than 600,000 stroke patients per year in the United States do not receive adequate treatment in rural areas, mainly due to longer times to obtain a specialized neurological evaluation which implies an increase in mortality of up to 20% compared to that registered in patients from large cities (1).

According to the ESENCIA study, in 2017, there was a prevalence of 158 (CI 95% 157-160) cases per 100,000 inhabitants of ischemic stroke in Colombia. The prevalence was higher in patients affiliated to the contributory insurance regime (financed by employee-employer contributions) (62.11%, OR 1.488, 95% CI 1.454-1.523, $p < 0.001$). The highest stroke prevalence was registered in the regions of Bogotá (438, 431-444), Cundinamarca (407, 396-419), and Chocó (312, 277-350) (2). According to the Global Burden of Disease, ischemic stroke in Colombia caused 8,295 deaths (6,266-10,477) and an absolute number of 137,162 *DALYs (11,328-166,980) in 2019 (3).

There is evidence that the most critical disparity in Latin America is related to the differential access to medical services among rural and urban patients, which leads to biased epidemiology information and an underestimation of the current public health problem (4). The prehospital care for stroke in low and middle-income countries (LMICs) is underdeveloped, and there is a poor pre-notification system associated with longer door-to-image, door-to-needle, and door-to-groin times and, consequently, worse prognosis (5). Pre-hospital recognition of a neurovascular syndrome is key as the rates of intravenous thrombolysis could rise from 23 to 42% (4).

In Colombia, only 13 cities out of the 1,103 municipalities have thrombectomy centers and, of the 34 hospitals enabled to perform this intervention, only 14 provide 24/7 services (6). According to the World Health Organization (WHO), a city should have one ambulance for every 25.000 inhabitants (7) to improve and guarantee pre-hospital care.

Given the high prevalence of the diseases and the lack of knowledge about the geographical barriers in acute stroke patients accessing health services, it is necessary to clarify how these characteristics are associated with their clinical outcomes. Therefore, this study aims to compare the pre- and intra-hospital care received by acute stroke patients from rural, semi-urban, and urban areas treated in a comprehensive stroke center located in southwestern Colombia and determine potential differences in outcomes related to patients' precedence.

METHODS

This is a prospective cohort study of acute stroke patients based on demographic and clinical data collected between January 2018 and January 2020 who were admitted in a high complexity hospital from Southwestern Colombia as part of a pilot stroke network, consisting of rural primary centers without the capacity of imaging or thrombolysis and a mothership hospital.

The included subjects were patients over 18 years old who attended Hospital Universitario Fundación Valle del Lili within a stroke code context. Confirmation of ischemic and hemorrhagic strokes was based on computer tomography or magnetic resonance imaging, and a vascular or trained general neurologist diagnosed transient ischemic attacks (TIA) according to the clinical manifestations and current guidelines. We excluded patients who underwent extra-institutional reperfusion therapy, those without institutional diagnostic images, stroke mimics, or those who presented the cerebrovascular event during hospitalization. We considered each stroke code consultation as a separate registry.

Mode of arrival at the stroke center, timing, clinical characteristics, interventions, and modified Rankin scale (mRS) for ischemic stroke patients at onset, discharge, and 3-months follow-up were assessed. mRS was considered favorable if <3. Distance from rural and semi-urban facilities to the mothership center was extracted from Google Maps (8) and generally set as 11 Km for urban patients (half of the city's maximum extension).

In Colombia, according to the *Departamento Administrativo Nacional de Estadística* (DANE), a metropolitan area is defined as the administrative entity formed by a set of two or more municipalities. The metropolitan area of Cali comprises Palmira, Yumbo, Jamundí y Candelaria (semi-urban municipalities). Urban areas are limited to the set of buildings and blocks that configures adjacent group structures. On the contrary, the rural area has a dispersed disposition of houses and farms, without nomenclature of streets (9).

Ecological variables of municipalities (total population, poverty index, percentage of inhabitants with evident healthcare barriers, and the number of total, primary, and medicalized ambulances) were extracted from their most recent Health Situation Analysis (ASIS, 2017-2020) and compared with the change in mRS between onset and discharge/3-months follow-up (primary outcome) and total length of in-hospital and ICU stay.

Statistical Analysis

According to their distribution, qualitative variables were described with absolute and relative frequencies and numerical features with medians and interquartile ranges. Differences between urban, semi-urban, and rural areas were analyzed using multiple comparisons χ^2 test and Kruskal-Wallis statistic with Dunn's *post-hoc* method and Sidak correction (*p*-values reported for rural vs. urban only). Wilcoxon test was implemented for identifying significant changes between mRS at discharge/3-months follow-up and onset.

Poisson multivariate regression models were built using the change in mRS between onset and discharge/3-months follow-up as the primary outcome and selecting independent variables through a stepwise backward method. Different models were defined for total, rural, and urban code-stroke patients. An additional logistic model was proposed for differentiating rural and urban populations after excluding patients from semi-urban areas. The odds ratio and 95% confidence intervals were calculated. Correlations of ecological variables of municipalities with the outcomes were assessed using Spearman's rank coefficient. Significance was set as $p < 0.05$. Statistical analysis was performed in Stata v.15.0 (StataCorp, College Station, TX, USA).

Institutional review board approval was granted for this study as part of the continuous prospective registry of stroke patients

(No. 422/2019). An abstract of a preliminary analysis was recently published (10).

RESULTS

Patients and Neurovascular Events Features at Arrival

All the 555 code-stroke patients who attended the emergency department were included in the study: 357 (64.3%) from the urban area, 80 (14.4%) from semi-urban locations, and 118 (21.2%) from rural sites. Baseline mRS was favorable (0-2) in the majority of patients from urban areas (91.92%) semi-urban (89.18%), and rural (88.8%).

According to the geographical origin, there were no significant differences in age, gender, or medical background, except for previous TIA, which was more common in urban patients 7.84% vs. semiurban 0.00% vs. rural 5.08%; global $p = 0.0260$, *post-hoc* $p = 0.3140$. In detail, rural and semi-urban individuals had a similar absolute prevalence of arterial hypertension; however, the frequency of atrial fibrillation, dyslipidemia, and previous myocardial infarction was numerically higher in urban subjects (**Table 1**). Additionally, rural patients reported mildly lower use of statins (23.73%) than semi-urban (32.50%) and urban areas (31.93%). Semi-urban patients tended to be prescribed anticoagulants more frequently than urban and rural individuals, but the intake of antiplatelet agents was equivalent among all groups.

Symptoms commonly started between 8:00 and 15:50 h (46.37%). Urban patients (38.74%) were less likely to be transported by ambulance than those from semi-urban (83.54%) and rural areas (92.31%). The median distance to the mothership hospital was 14 Km (IQR 14-14) for semi-urban subjects and 45 Km (IQR 45-53) for rural patients. Consequently, there was a higher median time window: for the urban area 230 min (IQR 1487.50-417.5) 165 min for semi-urban locations (IQR 89-314), and 151min (IQR 80-328) for rural sites (global $p = 0.0001$, *post-hoc* $p < 0.0000$).

Clinical Characteristics During the In-hospital Stay

Rural (98.30%) and semi-urban (95%) patients were more likely to be classified as triage 1 and 2 (global $p = 0.0010$, *post-hoc* $p = 0.000$). Urban patients (18%) less frequently presented NIHSS scores compatible with a moderate-severe stroke ($\geq$16) compared with semiurban (30%) and rural subjects (43%).

Door-to-image time was higher for urban patients (30 min, IQR 15-78) in comparison to semiurban (20 min, IQR 11-37) and rural subjects (22 min, IQR 12-40). Four hundred and thirty two (77.98%) patients had an ischemic stroke, with no significant differences according to patients' origin. The median score on the ASPECTS scale was lower in rural patients (8, IQR 7-10), while semi-urban (9, IQR 8-10) and urban (9, IQR 8-10) subjects exhibited a less extensive compromise (global $p = 0.0114$, *post-hoc* $p = 0.0093$).

There were significant global differences ($p = 0.0021$, *post-hoc* $p = 0.0830$) regarding the chosen treatment. In particular, as the percentage of ischemic stroke patients with an adequate window time (<4.5 h) was higher in semi-urban (68.75 %) patients compared with patients from urban (60.22 %) and rural areas (52.14 %), the use of intravenous thrombolysis (alone or combined with thrombectomy) was also higher in the semi-urban group (32.5%). Rural patients were treated more often with thrombectomy (alone or combined) (17.8%) (**Table 2**).

TABLE 1 | Baseline characteristics of patients.

Characteristic	No (%) Urban (*N* = 357)	Semi-urban (*N* = 80)	Rural (*N* = 118)	*P*-value
Median age (IQR), years	70 (60-81)	71 (61-80)	71 (60-81)	0.9324
Female	192 (53.78)	37 (46.25)	56 (47.46)	0.3020
BMI (Kg/m2) IQR	26.5 (23.9-29.1)	25.4 (23.1-28.4)	27 (25-29.4)	0.363
Arterial hypertension	243 (68.07)	65 (81.25)	86 (72.88)	0.0560
Diabetes mellitus	86 (24.09)	20 (25)	31 (26.27)	0.8900
Atrial fibrillation	34 (9.52)	9 (11.25)	10 (8.47)	0.8080
Previous smoking	15 (4.2)	3 (3.75)	4 (3.39)	0.9210
Current smoking	30 (8.4)	8 (10)	12 (10.17)	0.7990
Dyslipidemia	45 (12.61)	6 (7.5)	7 (5.93)	0.0790
Myocardial infarction	64 (17.93)	12 (15)	17 (14.41)	0.6080
Deep venous thrombosis	4 (1.12)	1 (1.25)	3 (2.54)	0.5260
Prior ischaemic stroke	67 (18.77)	11 (13.75)	25 (21.19)	0.4120
Prior hemorrhagic stroke	8 (2.24)	0 (0)	0 (0)	0.1050
Prior transitory ischemic attack	28 (7.84)	0 (0)	6 (5.08)	0.0260
mRs premorbid (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.9266

BMI, body mass index; AF, atrial fibrillation; mRs, modified rankin scale.

TABLE 2 | Acute ischemic stroke treatment.

	Urban (*N* = 356)	Semi-urban (*N* = 80)	Rural (*N* = 118)	Global *P*-value	*Post-hoc P*
Time window					
<4.5 h	215 (60.22)	55 (68.75)	61 (52.14)	0.062	
>24 h	31 (8.69)	7 (8.75)	11 (9.4)	0.972	
Arrival by ambulance	117 (38.74)	66 (83.54)	108 (92.31)	0.000	
Door-to-image (IQR)	30 (15-78)	20 (11-37)	22 (12-40)	0.0004	0.0053
ASPECTS (IQR)	9 (8-10)	9 (8-10)	8 (7-10)	0.0114	0.0093
Medical treatment	274 (76.75)	52 (65)	80 (67.8)		
Thrombolysis	50 (14.01)	21 (26.25)	17 (14.41)		
Thrombectomy	14 (3.92)	2 (2.5)	9 (7.63)		
Combined	19 (5.32)	5 (6.25)	12 (10.17)		
Door-to-needle (IQR)	60 (47-85)	55 (45-81)	57 (45-70)	0.5486	
Door-to-groin (IQR)	132 (90-203)	116 (85-160)	157.5 (116.5-183)	0.6363	
In-hospital stay (days)	4 (2-9)	6 (2-12)	4 (2-11)	0.4927	
ICU stay (days)	3 (2-5)	3 (2-5)	3 (2-6)	0.8342	

IQR, interquartile range; ICU, intensive care unit.

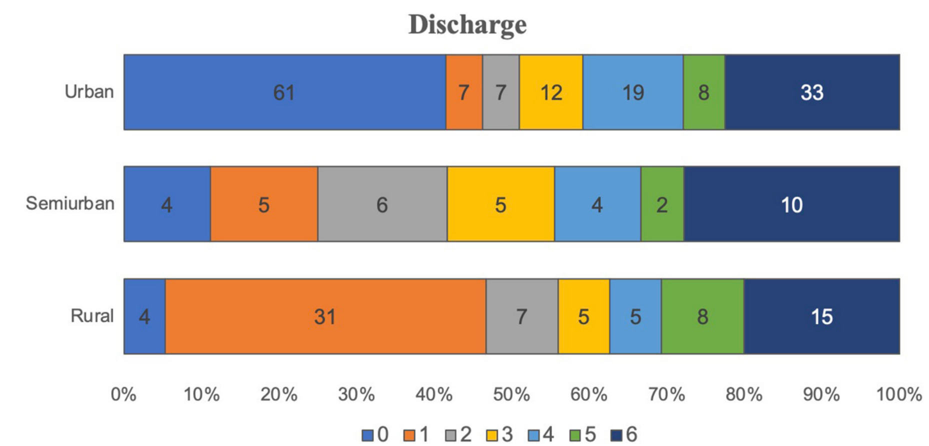

FIGURE 1 | mRs scale at discharge.

Conservative management was offered to patients with lower NIHSS (5, IQR 2-12 vs. 12, IQR 8-20; $p = 0.000$), and the best empirical cut-point for deciding reperfusion therapy was found at 16.5. Subsequently, median door-needle time was higher in urban patients, differing from rural subjects (global $p = 0.054$). There were no relevant differences related to the door-groin time ($p = 0.6363$).

There were no significant differences between the groups in the length of in-hospital and ICU stay.

Differential Functional Outcomes by Patients' Origin

Three hundred and thirty seven patients could be contacted to assess the telephonic rankin follow-up, among them 68.06% urban, 52.5% semi-urban, and 44.06% rural patients. Quantitative evaluation of mRS at discharge and 3-months follow-up showed significant differences (global $p = 0.0001$, *post-hoc* $p = 0.0002$). The percentage of patients with favorable mRS at discharge was higher in urban areas (63.03%) than in semi-urban (48.75%) and rural areas (31.35%) (global $p = 0.0000$, *post-hoc* $p = 0.0000$). Lethality (mRS 6) was higher in rural (13.56%) and semi-urban individuals (15%) compared with urban patients (10.64%) (**Figures 1**, **2**).

Multivariate association model for higher mRS increase at discharge and 3-months follow-up in the whole ischemic stroke sample can be accessed in the **Supplementary File**. Higher NIHSS scores were associated with a worse decline in functionality for rural and urban patients at both time points. In subjects living in the city, previous myocardial infarction, more extended in-hospital stay, and receiving bridging therapy were also more common in those with poorer outcomes at discharge. Initial blood glucose levels and previous smoking showed similar associations at 3-months

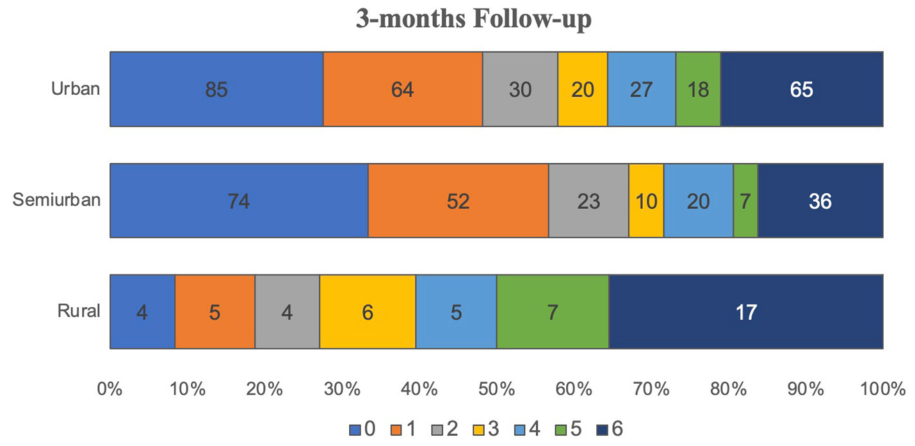

FIGURE 2 | mRs scale at 3-months follow up.

follow-up. Finally, patients' origin was associated with mRS variation at 3-months follow-up after multivariate adjustment by blood systolic and medium pressures, respiratory rate, use of statins, and triage classification (**Supplementary File**).

Ecological Correlation of Municipality Conditions With Outcomes

Cali's urban area has a lower poverty index (11.9%) compared with semi-urban and rural populations (23.33%, IQR 15.68-63.87) and a higher number of ambulances (0.15 vs. as low as 0.03 per 100.000 inhabitants). There are 363 ambulances (11) in Cali for 2,496,442 inhabitants (12), leaving one ambulance for every 6,877 inhabitants. The ambulance rate in semi-urban and rural areas could be as low as 0.03. Patients from the city exhibited an mRS increase at the discharge of 1 point (IQR 0-3) vs. 3 points (IQR 2-3.5) in rural subjects. For instance, six patients from Buenos Aires (Cauca), a rural municipality located 53 Km from the mothership hospital, demonstrated a 3.5 points increase between baseline and discharge mRS. This municipality has a high prevalence of poverty (82.28%) and healthcare access barriers (43.83%).

The studied municipalities adhered to the WHO recommendations regarding the number of ambulances, except from three rural populations (Buenaventura, Guapi, and Corinto) located at 50-175 Km from Cali. Total ($\rho = -0.3973$, $p = 0.0492$) and basic ($\rho = -0.4061$, $p = 0.0440$) ambulance indexes were inversely correlated with the increase of mRS at discharge and 3 months follow-up (**Figure 3**).

DISCUSSION

To our knowledge, this is an innovative prospective study in Latin America comparing the pre-hospital and intra-hospital care of code-stroke patients, characterizing and differentiating their clinical outcomes based on their origin (rural, semi-urban or urban areas).

Patients from rural Southwestern Colombia were more likely to present severe stroke despite the registry of lower cardiovascular risk factors. Once arrived at the stroke center, the final diagnosis was reached faster, but disability was higher at discharge and 3-months follow-up. In agreement with previous studies (13–15), age and gender were similar among the three areas, and overweight, hypertension, diabetes mellitus were the most prevalent modifiable stroke risk factors. A previous history of ischemic stroke was more prevalent in rural patients, which increases the risk of a new stroke (16). Studies have shown that cumulative risk of stroke recurrence can vary from 7 to 20% in up to 5-year follow-up (17). History of myocardial infarction and dyslipidemia was higher in urban patients, probably because of an undiagnosed and underreporting of dyslipidemia in rural patients. Previous TIA was less prevalent in rural patients than the other groups, perhaps because they do not present to the emergency department when experiencing minor symptoms (18). Most of the subjects were overweight, mainly rural patients, who also had less prescription of statins; this is contradictory with other studies in which overweight is more prevalent in urban patients (19, 20).

In our study, patients had favorable mRs at baseline (global mRS median 0 (0-1). Patients from rural areas had higher window time than semi-urban and urban patients. This can be associated with longer distances and a lower education level about stroke symptoms, which is catastrophic in a pathology where treatment depends on timing (21). Consequently, these patients were more likely to have more severe strokes with higher NIHSS scores and lower ASPECTS, consistent with Kapral et al. study (22).

A higher percentage of rural patients arrived by ambulance outside the traditional and extended therapeutic window. In our study, only 38% of urban patients arrived by ambulance while other research studies have evidenced that urban patients are most likely to use this mode of transport within the therapeutic window (1, 22). This result is likely to occur because patients believe that there is someone else is greater need or unaware of the urgency (22). Also, literature reported the lack of public

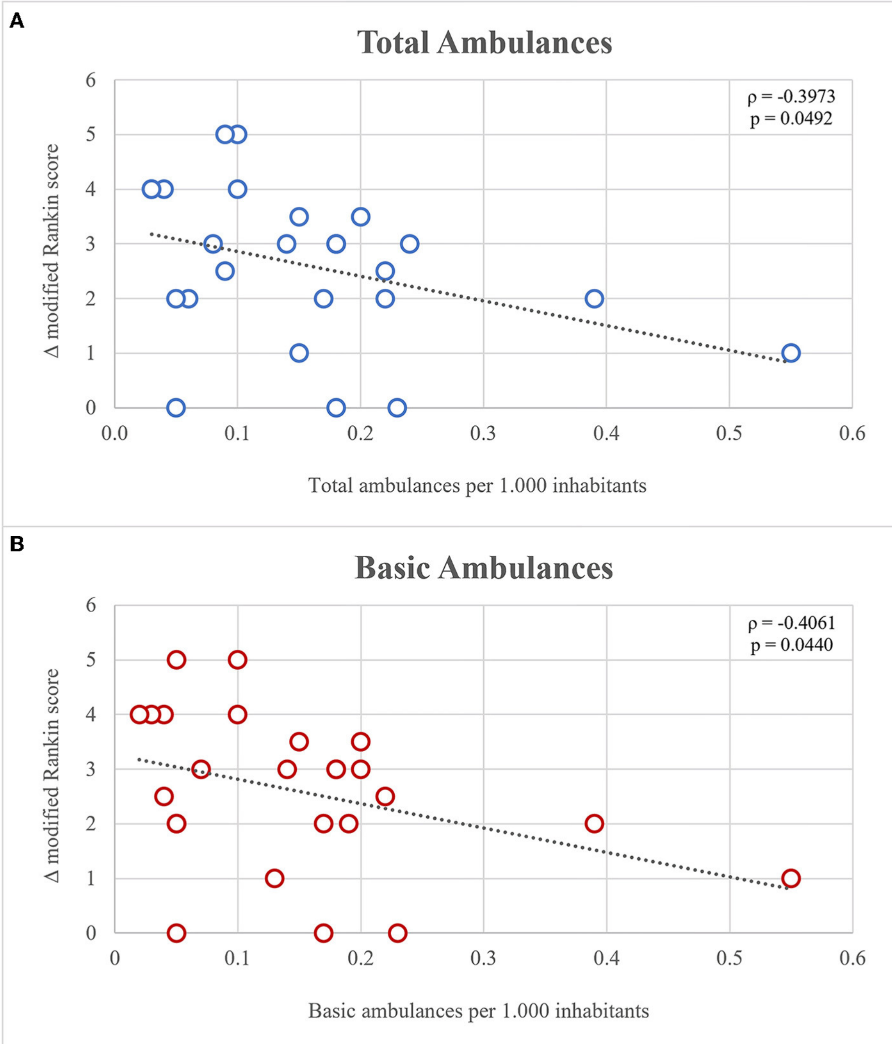

FIGURE 3 | (A,B) Correlation of ambulance index and mRs and discharge.

awareness about the need for an ambulance and the common perception of patients that a taxi or private car is faster than an ambulance. In a low-middle income country such as Colombia, there is an inefficient emergency medical service (EMS) in the cities, probably due to a lack of funding, roads, and traffic volume (23). Upon arrival at the stroke center, the diagnosis was reached faster for rural patients because their primary health centers usually refer them to confirm a severe stroke, making it easy to suspect the pathology (24). Even though, disability was higher at discharge and 3-months follow-up.

At the hospital, a non-contrast CT scan was the chosen image for most of the patients. Urban patients had longer window-times probably due to lack of pre-notification and less severe strokes (TIA). The most affected vessel in ischemic stroke was the MCA, according to the literature (5). Thrombectomy was more likely to be done in rural patients because of their longer window times, excluding patients to receive intravenous thrombolysis. Urban and semi-urban patients were more likely to receive rt-PA treatment than rural patients, which is consistent with the literature (25, 26).

Patients who lived in towns with a low ambulance index had worse mRs at discharge. This could be explained by differences in the opportunity for timely transportation, treatment, and rehabilitation, being worse in rural patients, and this might deleteriously impact their functional results. According to other studies, a rural residence has also been associated with a higher mRS and mortality rate (27).

Regarding the in-hospital stay observed in our study, there were no differences with the data reported by other authors (28, 29). Lethality rates were higher in rural and semi-urban patients compared to urban's. We suggest this happened because of patients' difficulties in identifying symptoms and delays in the ambulance services which are inefficient when pursuing reperfusion therapy (24).

Related Factors With Functional Outcomes at 3-Months Follow-Up

In the multivariate association model, blood glucose levels, heart rate, and blood pressure were associated with mRS variation at 3 months follow up, which correlates with the literature. Autonomic nervous system dysfunction occurs after acute stroke and correlates with stroke severity and outcomes through increased blood pressure variability, impaired cerebral autoregulation, hyperglycemia, and blood-brain barrier dysfunction (30).

Non-urban patients who arrived by ambulance had higher mRs scores at discharge and 3 months follow-up than patients who arrived by private transportation due to more severe stroke. The unfavorable mRS score at 3-months follow-up could be due to fewer possibilities to obtain physical rehabilitation and other post-stroke services; this is clearly inadequate and far below evidence-based standards (31).

Although the significance is borderline, we observed that the municipalities with a fewer rate of ambulances demonstrated a higher increase in mRS at discharge (loss of functionality). An inverse relationship is not explained by the poverty rate or the percentage of people with healthcare access barriers. In that sense, the public administrations must create a pre-hospital care protocol and increase the ratio of ambulances per 1.000 habitants.

These findings support the need for further studies to understand additional variables that may contribute to the mortality of rural stroke patients. Our findings are likely to generalize to Colombia because of a similar demographic distribution where larger cities are surrounded by many small municipalities (semi-urban and rural areas). Patients are often referred from these rural territories to anywhere with a high-complexity healthcare center. Thus, the strategy of the godfather/mothership hospital can be strengthened to improve the detection and treatment rates of stroke patients, using telemedicine tools in a stroke network, generating better clinical outcomes.

Strengths and Limitations

The sample of this study is small compared to international studies. As far as we know, this type of study has not been carried out in Latin America; however, studies from the region describe the prevalence and clinical outcomes of rural populations with stroke without comparing them with their urban counterparts (32). We also found studies comparing rural with urban populations, but these were carried out by applying questionnaires and did not consider treatment variables (33). We consider that the number of patients is adequate for the results obtained from this first experience.

Given the type of study, certain limitations should be mentioned. First, the collection of prospective information could have been biased after the creation of the institutional code-stroke and the standardization of treatments. Second, an important limitation comprises the loss in the follow-up of patients due to changes in their telephone number or because they did not answer. However, the follow-up rate was high. Another significant limitation was that the study was conducted in a single center in southwestern Colombia because we are starting a pilot program to create the stroke network. We need to create a local registry that includes all stroke centers to provide information about the incidence and prevalence of stroke in the city and the rural areas. Another limitation is the lack of data in rural hospitals about stroke cases.

In general, patients from rural areas had lower rates of dyslipidemia, taking into account that not all patients underwent a lipid profile, which could generate underdiagnosis and information biases. Rural patients presented more severe strokes compared to semi-urban and urban. However, we considered that it could be partly explained since the referred patients have a longer time window in the worst conditions. These patients also had worse functional outcomes at 3 months. There might be a smaller opportunity for access to post-stroke services considering that the probability is markedly influenced by the distance between healthcare centers and patients' houses and the state of the roads (1). These factors could not be studied as they are difficult to estimate from the perspective of the mothership hospital.

Relevance to Our Region

Considering the findings obtained and the limitations presented in the study, we plan to develop strategies that could improve the disparities in care according to the origin of the patients. Our University hospital has been a pioneer in the region and the country by sponsoring rural hospitals through educational programs for fighting the lack of awareness of the disease. We also have promoted the activation of code-stroke by rural physicians who received personalized advice by a neurologist. We firmly believe that many rural patients could benefit from this sponsorship program by obtaining faster stroke care that results in better clinical outcomes. We need to work in an urban EMS program to increase the number of patients arriving in ambulance.

According to our institutional data, 45% of code-stroke patients come from rural areas. The study of differential clinical factors could favor the future design of strategies with a positive impact on prevention and early recognition of the disease, effective/comprehensive treatment, and the reduction of mortality and long-term disability.

CONCLUSIONS

There is a lack of information in Latin America about the clinical outcomes of stroke patients according to their place of origin. We found a low percentage of patients from urban areas transferred by ambulance, needing to reinforce a pre-hospital care system in the city. Patients from rural areas of Southwestern Colombia were more likely to present with severe strokes and exhibited unfavorable mRS at hospital discharge and 3-month follow-up compared to their urban counterparts, despite having similar risk factors. Further studies should specifically assess the existence of barriers inherent to the place of origin, such as socioeconomic status, healthcare access, limited public transportation, inadequate pre-hospital emergency services, difficulties in accessing rehabilitation therapies, little knowledge of stroke symptoms, among others. Establish a regional stroke network could help to increase the access of the patients to a comprehensive stroke center.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

PA, NL-L, and CP: study conception and design. PA, AA, JV, NL-L, CP, and GP-M: data collection. GP-M, PA, NL-L, and CP: analysis and interpretation of results. PA, NL-L, CP, GP-M, AA, JV, and IP: draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.869772/full#supplementary-material

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ORIGINAL RESEARCH
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Association of Pre-stroke Frailty With Prognosis of Elderly Patients With Acute Cerebral Infarction: A Cohort Study

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Background: Frailty is a state of cumulative degradation of physiological functions that leads to adverse outcomes such as disability or mortality. Currently, there is still little understanding of the prognosis of pre-stroke frailty status with acute cerebral infarction in the elderly.

Objective: We investigated the association between pre-stroke frailty status, 28-day and 1-year survival outcomes, and functional recovery after acute cerebral infarction.

Methods: Clinical data were collected from 314 patients with acute cerebral infarction aged 65–99 years. A total of 261 patients completed follow-up in the survival cohort analysis and 215 patients in the functional recovery cohort analysis. Pre-stroke frailty status was assessed using the FRAIL score, the prognosis was assessed using the modified Rankin Scale (mRS), and disease severity using the National Institutes of Health Stroke Scale (NIHSS).

Results: Frailty was independently associated with 28-day mortality in the survival analysis cohort [hazard ratio (HR) = 4.30, 95% *CI* 1.35–13.67, $p = 0.014$]. However, frailty had no independent effect on 1-year mortality ($HR = 1.47$, 95% *CI* 0.78–2.79, $p = 0.237$), but it was independently associated with advanced age, the severity of cerebral infarction, and combined infection during hospitalization. Logistic regression analysis after adjusting for potential confounders in the functional recovery cohort revealed frailty, and the NIHSS score was significantly associated with post-stroke severe disability (mRS > 2) at 28 days [pre-frailty adjusted odds ratio (a*OR*): 8.86, 95% *CI* 3.07–25.58, $p < 0.001$; frailty a*OR*: 7.68, 95% *CI* 2.03–29.12, $p = 0.002$] or 1 year (pre-frailty a*OR*: 8.86, 95% *CI* 3.07–25.58, $p < 0.001$; frailty a*OR*: 7.68, 95% *CI* 2.03–29.12, $p = 0.003$).

Conclusions: Pre-stroke frailty is an independent risk factor for 28-day mortality and 28-day or 1-year severe disability. Age, the NIHSS score, and co-infection are likewise independent risk factors for 1-year mortality.

Keywords: frailty, frailty index, stroke, cerebral infarction, mRS, NIHSS

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INTRODUCTION

Stroke has become the second largest cause of death and the third largest cause of disability after ischemic heart disease and is an important factor in disability-adjusted life-years (DALYs) lost in people over 50 years old (1). In China, the prevalence of stroke exceeds that of ischemic heart disease, with more than 2 million new cases per year, making stroke the most DALYs lost among all diseases (2). Although measures such as endovascular intervention and the establishment of stroke centers have significantly reduced the mortality of the cerebrovascular disease, surviving patients have also increased the social disability burden (3). Functional recovery tended to stabilize at 3–6 months after stroke, but the recovery of different patients still showed individual differences, and some patients had accelerated accumulation of disabilities over time (4–6).

Frailty status is a meaningful manifestation of aging in the population, characterized by a decline in function across multiple physiological systems. This decline is a disproportionate change in health status caused by small stress events accompanied by an increased vulnerability to stressors (7). Frailty is more prone to negative outcomes and is a predictor of all-cause mortality (8, 9). Acute cerebral infarction produces a major impact on the body and makes patients more prone to adverse events, such as poststroke pneumonia (10), persistent disability (11), and neurocognitive disorders (12).

Shanghai, the country's most populous city, has 3,824,400 registered residents aged 65 years and above in 2020, nearly 25.9% of the population (13). There are 40 large-scale general hospitals in Shanghai. A cross-sectional study based on Fried's frailty phenotype was used to assess frailty status was performed in 780 Shanghai suburban older adults aged 65–74 years in 2019. The percentages of robust, pre-frail, and frail were 48.46, 47.69, and 3.85% (14).

This study aimed to establish the relationship between pre-stroke frailty and outcomes after acute ischemic stroke. We divided participants into survival and functional recovery cohorts and explored 28-day and 1-year post-stroke outcomes.

METHODS

Study Design and Participants

This cohort study enrolled 314 consecutive older adult patients with acute cerebral infarction at Huadong Hospital affiliated with Fudan University from September 2019 to September 2020. The inclusion criterion was patients between 65 and 99 years. All patients underwent CT/MRI after the symptoms occurred, and lesions of acute ischemic stroke were found on CT/MRI. Exclusion criteria included (1) stroke symptom onset for more than 1 week, (2) only clinical symptoms without imaging evidence, (3) functional impairment prior to the onset of stroke [modified Rankin Scale (mRS) $\geq$ 3], and (4) living alone and unable to complete the questionnaire independently. Furthermore, 32 patients who had consciousness disorders (n = 15), severe cognitive dysfunction (n = 11), and aphasia (n = 6) would not provide the medical history, and the relevant information would be provided by the guardian or caregiver. If the caregiver was unable to remember illnesses completely, the researchers would get supplementary medical history through the test report.

Participants or guardians were fully informed of the purpose and content of the study in written and oral form, and this study was approved by the Ethics Committee of the Huadong Hospital affiliated with Fudan University.

Clinical and Demographic Data

Patient clinical characteristics, such as age, sex, body mass index (BMI), lesion side of stroke, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, National Institutes of Health Stroke Scale (NIHSS), comorbidities (previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, and smoking), stroke treatment (antiplatelet therapy, intravenous thrombolysis, or thrombolysis), and concurrent infection during hospitalization (co-infection).

Prognostic Assessment

The WHO recommends the mRS (15) to assess post-stroke prognosis, defined as follows: (1) mRS = 0 (no symptoms at all); (2) mRS = 1 (no significant disability): despite symptoms, able to carry out all usual duties and activities; (3) mRS = 2 (slight disability): unable to perform all previous activities but able to look after own affairs without assistance; (4) mRS = 3 (moderate disability): requiring some help but able to walk without assistance; (5) mRS = 4 (moderately severe disability): unable to walk without assistance and unable to attend to own bodily needs without assistance; (6) mRS = 5 (severe disability): bedridden, incontinent, and requiring round-the-clock nursing care and attention; (7) mRS = 6 (death) (16). An mRS score of $\leq$2 was considered to have a favorable prognosis (no symptoms or slight disability), while mRS > 2 was considered to have a worse prognosis (severe disability). An mRS score of 6 is equivalent to death. Survival outcome and functional recovery status were assessed using mRS at 28 days and 1 year after disease onset.

Assessment of Pre-stroke Frailty Status

The two main frailty assessment instruments are the frailty phenotype and the frailty index (deficit accumulation) (17). Since routine measurement tools require tests such as grip strength or walking speed, these are difficult to evaluate in patients with limb hemiplegia due to cerebral infarction. Instead, this study used the FRAIL scale to assess pre-stroke frailty status, a scale based on self-report that does not require activities affected by the disease itself (18). Existing studies confirm that the FRAIL scale has high sensitivity and specificity compared with the phenotype criteria (18), which is the same scale usually applied in the Chinese population (19, 20). The FRAIL scale consists of five components: fatigue, resistance, ambulation, illness, and loss of weight. It involves asking about the frequency of fatigue occurrence during the past 4 weeks, resistance by asking whether one can climb a staircase independently, ambulation by asking whether one can walk for 100 m independently, illness by asking whether one has more than five or more diseases, and weight loss by asking whether one lost 5% of their weight or more within 6 months. We collected details of fatigue from caregivers whether the patient

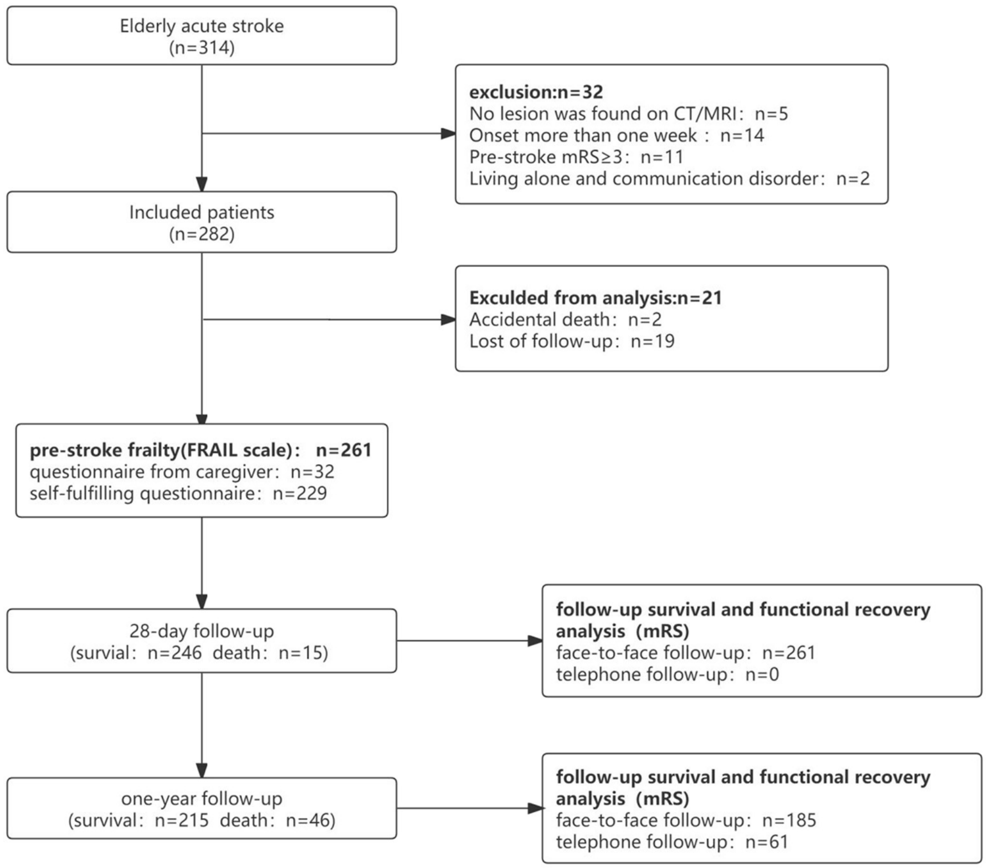

FIGURE 1 | Diagram of the study design.

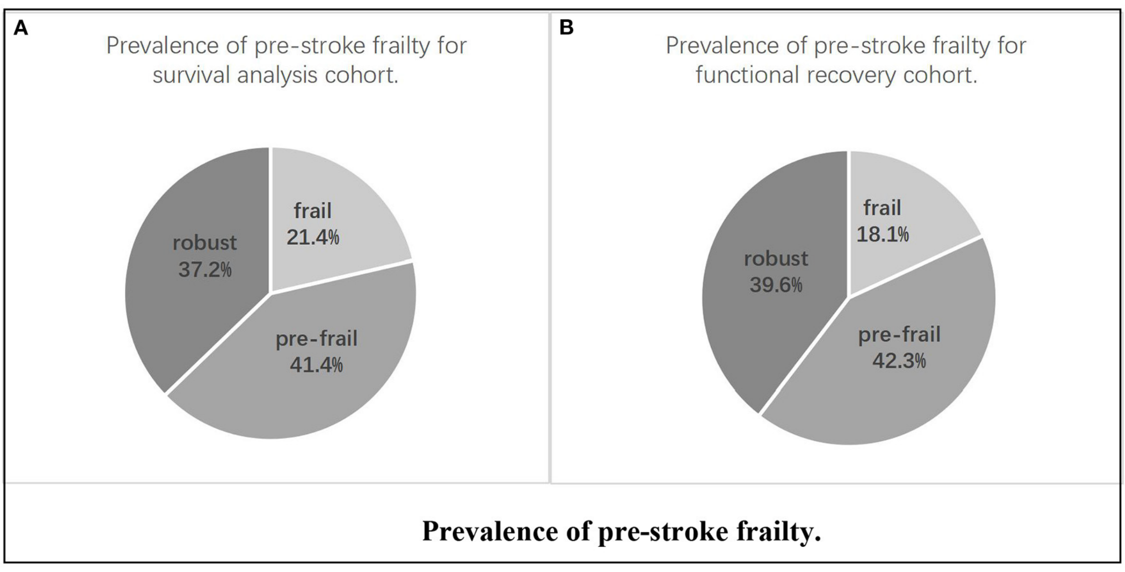

FIGURE 2 | Prevalence of pre-stroke frailty. **(A)** Prevalence of pre-stroke frailty for survival analysis cohort. **(B)** Prevalence of pre-stroke frailty for functional recovery cohort.

complained of six somatic symptoms more than half the time in the past 4 weeks. They included the presence of muscle pain or tired muscles after activity, the need to sleep longer, poor sleep, prolonged tiredness after activity, and poor concentration (21). The FRAIL scale scores range from to 0–5 (0 = best to 5 = worst) and represent frailty (3–5), pre-frailty (1, 2), and robust (0) health status (22).

Follow-Up and Outcome Events

Follow-up visits were conducted face-to-face or *via* telephone, with telephone follow-up being done by professionally trained personnel. Follow-up was performed at 28 days and 1 year after the stroke. Then, 1-year follow-up was allowed with an error of not more than 7 days. All patients received face-to-face follow-up at 28 days. In addition, 61 patients or their respective caregivers received telephone follow-up and others visited the clinic at 1 year. The characteristics of patients who did not arrive at the clinic for follow-up were as follows: died ($n = 31$), bedridden ($n = 22$), and others ($n = 8$). All patients who completed the follow-up visit were included in the survival cohort analysis, and those who survived at 1 year were included in the functional recovery cohort analysis.

Statistics

We divided our study population into two non-interfering groups according to survival status at 1 year. Between-group differences in baseline were obtained using the Kruskal–Wallis test or the Pearson X^2 test. All variables significantly associated with outcome in the univariate analysis were included in a multivariable binary Cox or logistic regression analysis, and the hazard ratio (*HR*) or the adjusted odds ratios (a*OR*) and 95% confidence intervals (95% *CI*s), where the 1-year functional improvement rate was determined, were calculated using the Pearson X^2 test and pair comparisons were performed. The level of significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 25.0.

TABLE 1 | Demographics and clinical characteristics of the participants for survival analysis.

	Non-frail (*n* = 205)	Frail (*n* = 56)	*P*-value
Age [year, median (IQR)]	74(70–80)	78(72–86)	<0.001*
BMI [kg/m^2,median (IQR)]	24.6(22.2–26.2)	24.4(22.3–26.6)	0.686
NIHSS score [median (IQR)]	3(1–5)	3(1–7)	0.032
Sex			0.130
Male (%)	122(46.7)	27(10.4)	
Female (%)	83(31.8)	29(11.1)	
TOAST classification			0.004*
Atherosclerotic (%)	48(18.4)	15(5.7)	
Lacunar (%)	72(27.6)	10(3.8)	
Cardioembolic (%)	40(15.3)	18(7.0)	
Unknown (%)	43(16.5)	9(3.4)	
Other (%)	2(0.8)	4(1.5)	
Side of lesion			0.587
Left (%)	96(36.8)	27(10.3)	
Right (%)	77(29.9)	18(6.9)	
Both (%)	30(11.5)	11(4.2)	
Stroke treatment			0.835
Antiplatelettherapy (%)	185(70.9)	52(19.9)	
Intravenous thrombolysis (%)	15(5.8)	3(1.1)	
Thrombectomy (%)	5(1.9)	1(0.4)	
Previous stroke (%)			
Smoking	58(22.2)	20(7.6)	0.282
Former (%)			0.047*
Current (%)	33(12.6)	2(0.8)	
Never (%)	25(9.6)	9(3.4)	
Hypertension (%)	147(56.4)	45(17.2)	
Diabetes mellitus (%)	161(61.7)	50(19.2)	0.070
Hyperlipidemia (%)	87(33.3)	25(9.6)	0.175
Atrial fibrillation (%)	54(20.7)	15(5.7)	0.947
Concurrent infection (%)	45(17.2)	19(7.3)	0.065
	43(16.5)	22(8.4)	0.005*

**Indicates a signicant difference (p < 0.05) between non-frail and frail.*

RESULTS

Study Process and Grouping Based on Frailty Status

Clinical data of 314 patients with acute cerebral infarction aged 65–99 years were included. In total, 261 completed follow-up visits were entered into the survival cohort analysis, and 215 were included in the functional recovery cohort analysis (**Figure 1**). In the survival cohort, the prevalence of frailty status before stroke was as follows: 97 (37.2%) were robust, 108 (41.4%) were pre-frail, and 56 (21.4%) were frail. Due to sample size limitations, we combined robust and pre-frail status as non-frail. The 261 patients were further divided into two groups according to the frailty dichotomy: 205 (78.6%) were non-frail and 56 (21.4%) were frail. In the functional recovery cohort, the prevalence of frailty status was as follows: 85 (39.6%) were robust, 91 (42.3%) were pre-frail, and 29(18.1%) were frail (**Figure 2**).

Demographic Data in the Survival Analysis Cohort

Demographic data from the survival analysis cohort were recorded. The frail group had significantly higher age ($p < 0.001$), NIHSS scores ($p = 0.032$), and possibility of co-infection ($p = 0.005$) than the non-frail group (**Table 1**). There were 15 patients who died within 28 days, with 6 patients (2.9%) in the non-frail group and nine patients (16.1%) in the frail group (X^2-value = 14.030, $p < 0.001$), while 46 patients died within 1 year, 29 (14.1%) in the non-frail group and 17 (30.4%) in the frail group (X^2-value = 7.962, $p = 0.005$) (**Table 2**).

Risk Factors for Mortality in the Survival Analysis Cohort

Factors with intergroup differences $p < 0.1$ in the survival analysis cohort were included in the Cox regression, such as

TABLE 2 | Survival status for 28-day and 1-year follow-up for survival analysis.

	All	Non-frail	Frail	X^2-test	
	(n = 261)	(n = 205)	(n = 56)	X^2-value	p-value
28-day survival status					
Survival	246	199(97.1%)	47(83.9%)	14.030	<0.001*
Death	15	6(2.9%)	9(16.1%)		
One-year survival status					
Survival	215	176(85.9%)	39(69.6%)	7.962	0.005*
Death	46	29(14.1%)	17(30.4%)		

NIHSS, National Institutes of Health Stroke Scale.
Values are shown as median (interquartile range) or ordinal variables and counts (%) for categorical variables.
Non-frail includes robust and pre-frail.
Indicates a significant difference (p < 0.05) between non-frail and frail.

TABLE 3 | Cox regression for 28-day and 1-year follow-up survival status for survival analysis.

	28-day survival status		One-year survival status	
	HR(95%CI)	P-value	HR(95%CI)	P-value
Age	1.09(0.95–1.10)	0.616	1.07(1.03–1.12)	0.001*
Sex	0.73(0.24–2.25)	0.582	0.73(0.37–1.46)	0.374
Concurrent infection	0.32(0.06–1.67)	0.178	0.18(0.08–0.41)	<0.001*
NIHSS	1.09(1.02–1.18)	0.019*	1.07(1.02–1.12)	0.006*
Frailty status	4.30(1.35–13.67)	0.014*	1.47(0.78–2.79)	0.237
Atrial fibrillation	1.46(0.26–8.26)	0.672	0.95(0.29–3.07)	0.931
Hypertension	1.15(0.28–4.67)	0.845	1.35(0.65–2.79)	0.420
Smoking				
Former	Reference	-	Reference	-
Smoking current	0.82(0.80–8.37)	0.867	0.86(0.24–3.06)	0.819
Smoking never	0.00(0.00–2.43)	0.935	0.50(0.11–2.20)	0.356
TOAST classification				
Atherosclerotic	Reference	-	Reference	-
Lacunar	0.00(0.00–5.99)	0.967	0.21(0.03–1.77)	0.152
Cardioembolic	2.04(0.32–13.22)	0.453	1.01(0.29–3.46)	0.991
Unknown	4.25(0.60–30.00)	0.147	2.30(0.85–6.28)	0.102
Other	1.63(0.13–20.47)	0.706	0.90(1.88–4.36)	0.899

Indicates a significant difference (p < 0.05)between the groups.

age, co-infection, frailty status, hypertension, atrial fibrillation, NIHSS score, TOAST classification, smoking history, and sex (23). In the 28-day survival analysis, frailty status (HR = 4.30, 95% CI 1.35–13.67, p = 0.014) and NIHSS score (HR = 1.09, 95% CI 1.02–1.18, p = 0.019) were independently associated with mortality. Frailty had no independent association with mortality within 1 year (HR = 1.47, 95% CI 0.78–2.79, p = 0.237), and those independently associated with mortality within 1 year were age (HR = 1.07, 95% CI 1.03–1.12, p = 0.001), NIHSS score (HR = 1.07, 95% CI 1.02–1.12, p = 0.006), and co-infection (HR = 0.18, 95% CI 0.08–0.41, p < 0.001) (**Table 3**).

Demographic Data of the Functional Recovery Cohort

Demographic data from the functional recovery cohort were recorded (**Table 4**). The prognosis of acute cerebral infarction was assessed by mRS (scored from 0 to 5). NIHSS score and frailty status were significantly different between groups (robust, pre-frail, and frail) at 28 days (X^2 = 38.180, p < 0.001) or 1 year (X^2 = 56.091, p < 0.001) (**Table 5**).

TABLE 4 | Demographics and clinical characteristics of the participants for functional recovery analysis.

	Robust (n = 85)	Pre-frail (n = 91)	Frail (n = 39)	P-value
Age [year, median (IQR)]	75(70–79)	74(69–80)	78(73–86)	0.005*
BMI [kg/m^2, median (IQR)]	24.8 (23.3–26.1)	24.4 (22.1–25.8)	24.6 (22.8–26.1)	0.181
NIHSS score[median (IQR)]	2(1–6)	4(2–7)	4(2–10)	0.005*
Sex				0.297
Male (%)	54(25.1)	53(24.7)	19(8.8)	
Female (%)	31(14.4)	38(17.7)	20(9.3)	
TOAST classification				0.022*
Atherosclerotic (%)	15(7.0)	23(10.7)	9(4.2)	
Lacunar (%)	32(14.9)	39(18.1)	10(4.7)	
Cardioembolic (%)	14(6.5)	12(5.6)	13(6.0)	
Unknown (%)	24(11.2)	15(7.0)	5(5.2)	
Other (%)	0(0.0)	2(0.9)	2(0.9)	
Side of lesion				0.148
Left (%)	49(22.8)	36(16.7)	19(8.8)	
Right (%)	30(14.0)	41(19.1)	16(7.4)	
Both (%)	6(2.8)	14(6.5)	4(4.2)	
Stroke treatment				0.092
Antiplatelet therapy (%)	77(35.8)	82(38.1)	35(16.3)	
Intravenous Thrombolysis (%)	8(3.7)	5(2.3)	4(1.9)	
Thrombectomy (%)	0(0.0)	4(1.9)	0(0.0)	
Previous stroke (%)	18(8.4)	33(15.3)	15(7.0)	0.049*
Smoking				
Former (%)	5(2.3)	3(1.4)	3(1.4)	0.248
Current (%)	18(8.4)	27(12.6)	5(2.3)	
Never (%)	62(28.8)	61(28.4)	31(14.4)	
Hypertension (%)	69(32.1)	71(35.8)	36(16.7)	0.150
Diabetes mellitus (%)	31(14.4)	44(20.5)	2(9.3)	0.175
Hyperlipidemia (%)	25(11.6)	23(10.7)	12(5.6)	0.753
Atrial fibrillation (%)	18(8.4)	13(6.0)	15(6.9)	0.009*
Concurrent infection (%)	4(1.9)	17(7.9)	10(4.6)	0.003*

Indicates a signicant difference (p < 0.05) between non-frail and frail.

Influencing Factors of Functional Recovery Analysis

Factors analyzed at p < 0.1 in the functional recovery cohort included multivariate logistic regression analysis for 28-day and 1-year functional recovery. These include age, NIHSS score, previous history of stroke, atrial fibrillation, co-infection, frailty status, TOAST classification, stroke treatment, and sex (23). An mRS score ≤2 was considered to have a favorable prognosis (no symptoms or slight disability), and an mRS score >2 was considered to have a worse prognosis (severe disability).

After adjusting for confounding variables (age, sex, and stroke risk factors), the presence of pre-stroke frailty and NIHSS score remained an independent predictor of negative prognosis at 28

TABLE 5 | The modified Rankin Scale (mRS) for each group of frailty status for a 28-day functional outcome and a 1-year follow-up functional outcome for functional recovery analysis.

	All subjects (*n* = 215)	Robust (*n* = 85)	Pre-frail (*n* = 91)	Frail (*n* = 39)	X^2	*P*-value
28-day functional outcome (%)					38.180	<0.001*
mRS = 0	18	14(6.5)	4(1.9)	0(0.0)		
mRS = 1	32	16(7.4)	10(4.7)	6(2.8)		
mRS = 2	52	30(14.0)	17(7.9)	5(2.3)		
mRS = 3	44	11(5.1)	23(10.7)	10(4.7)		
mRS = 4	36	9(4.2)	20(9.3)	7(3.3)		
mRS = 5	33	5(2.3)	17(7.9)	11(5.1)		
One-year functional outcome(%)					56.091	<0.001*
mRS = 0	57	40(18.6)	13(6.0)	4(1.9)		
mRS = 1	48	25(11.6)	20(9.3)	3(1.4)		
mRS = 2	32	7(3.3)	17(7.9)	8(3.7)		
mRS = 3	31	6(2.8)	17(7.9)	8(3.7)		
mRS = 4	22	5(2.3)	12(5.6)	5(2.3)		
mRS = 5	25	2(0.9)	12(5.6)	11(5.1)		

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.
Values are shown as median (interquartile range) or ordinal variables and counts (%) for categorical variables.
*Indicates a significant difference ($p < 0.05$) between the groups.

TABLE 6 | Logistic regression for a 28-day functional outcome for functional recovery analysis.

	Unadjusted OR(95%CI)	*P*-value	Adjusted OR(95%CI)	*P*-value
Age	1.02(0.97–1.06)	0.230	1.02(0.95–1.08)	0.595
Sex	1.39(0.80–2.39)	0.242	1.72(0.70–4.22)	0.240
Concurrent infection	0.06(0.01–0.25)	<0.001*	0.81(0.08–8.28)	0.861
Stroke history	1.60(0.89–2.89)	0.117	1.34(0.55–3.27)	0.512
Atrial fibrillation	0.40(0.21–0.81)	0.011	0.17(0.02–1.63)	0.125
NIHSS	1.90(1.58–2.29)	<0.001*	2.06(1.63–2.60)	<0.001*
Frailty status				
Robust	Reference	–	Reference	–
Pre-frail	4.65(2.46–8.78)	<0.001*	8.86(3.07–25.58)	<0.001*
Frail	6.11(2.64–14.14)	<0.001*	7.68(2.03–29.12)	0.003*
TOAST classification				
Atherosclerotic	Reference	–	Reference	–
Lacunar	0.03(0.12–0.53)	<0.001*	1.82(0.50–6.66)	0.368
Cardioembolic	1.20(0.47–3.02)	0.709	0.50(0.37–6.86)	0.607
Unknown	0.43(0.18–1.00)	0.051	3.44(0.78–15.09)	0.102
Other	–	0.999	–	0.999
Stroke treatment				
Antiplatelet therapy	Reference	–	Reference	–
Intravenous thrombolysis	1.63(0.57–4.66)	0.360	1.52(0.26–9.02)	0.654
Thrombectomy	–	0.999	–	0.999

*Indicates a signicant difference ($p < 0.05$) between non-frail and frail.

days and 1 year. In the 28-day functional recovery analysis, the NIHSS score had an a*OR* of 2.06 (95% *CI* 1.63–2.60, $p < 0.001$), pre-frailty a*OR* of 8.86 (95% *CI* 3.07–25.58, $p < 0.001$), and frailty a*OR* of 7.68 (95% *CI* 2.03–29.12, $p = 0.003$) (**Table 6**), while in the 1-year analysis, the NIHSS score a*OR* of 1.43 (95% *CI* 1.24–1.63, $p < 0.001$), pre-frailty a*OR* of 5.14 (95% *CI* 2.00–13.20, $p = 0.001$), and frailty a*OR* of 9.28 (95% *CI* 2.85–30.18, $p < 0.001$) (**Table 7**).

Functional Improvement Within 1 Year in the Functional Recovery Analysis Cohort

Of the 215 patients in the functional recovery cohort, 123 had a worse prognosis (mRS > 2), with 27 in the robust group, 64 in the pre-frail group, and 32 in the frail group at 28 days. If the functional status was assessed as mRS ≤ 2 at 1-year follow-up, it will be considered a significant functional improvement. As the degree of frailty increased, the likelihood of functional improvement after 1 year was low, with 13 (48.14%) considered robust, 21 (32.81%) considered pre-frail, and 5 (15.65%) considered frailty ($X^2 = 7.2$, $p = 0.27$) after 1 year (**Table 8**).

DISCUSSION

This cohort study revealed the relationship between pre-stroke frailty status and acute cerebral infarction prognosis and found that pre-stroke frailty was an independent influencing factor for 28-day mortality but not for 1-year mortality. Besides, 1-year mortality was independently associated with advanced age, NIHSS score, and co-infection. Pre-stroke frailty status was associated with severe disability at 28 days and 1 year, suggesting possible negative functional improvement for those with frailty.

Previous studies have confirmed that pre-stroke frailty status is associated with adverse outcomes, such as stroke severity (24), mortality (25), short-term functional outcome (26), lower daily activity ability (27), discharge location (28), and post-stroke cognitive impairment (29). This study confirmed that pre-stroke frailty status exacerbated the risk of short-term mortality but had no independent effect on long-term mortality. Long-term mortality outcomes after stroke are largely caused by diseases other than stroke (30). Our study also confirmed that the main causes of mortality in patients with early death were cerebral infarction and related complications, such as major seizures and cerebral hernias, while post-stroke pneumonia and heart failure occur beyond the acute phase.

The pathophysiology of frailty is a decline in the physiological regulatory systems. This results in dynamic imbalance and impaired resilience, accompanied by an increased vulnerability to stressors. When a certain amount of dysregulation occurs, clinical manifestations of frailty occur with increased mortality and disability (31). When stress events occur (such as, in acute cerebral infarction), the functional ability of pre-frail or frail people deteriorates rapidly (17), increasing the risk of short-term mortality and acute disease severity (32).

Frailty after stroke is common, and the prevalence of post-stroke frailty is two times that of non-stroke patients (33). Approximately one out of four patients with acute stroke develop frailty, and four more patients develop frailty if their pre-stroke status is pre-frail (34). Our study found that pre-stroke frailty was not an independent influencing factor for 1-year

TABLE 7 | Logistic regression for 1-year follow-up on functional outcomes for functional recovery analysis.

	Unadjusted OR(95%CI)	*P*-value	Adjusted OR(95%CI)	*P*-value
Age	1.04(1.00–1.08)	0.053	1.03(0.97–1.09)	0.311
Sex	1.15(0.66–2.02)	0.622	1.13(0.51–2.54)	0.757
Concurrent infection	0.08(0.03–0.21)	<0.001*	0.59(0.15–1.41)	0.464
stroke history	1.33(0.73–2.41)	0.348	1.02(0.46–2.28)	0.887
Atrial fibrillation	0.54(0.28–1.05)	0.068	2.40(0.23–25.13)	0.853
NIHSS	1.30(1.20–1.41)	<0.001*	1.43(1.24–1.63)	<0.001*
Frailty status				
Robust	Reference	-	Reference	-
Pre-frail	4.54(2.21–9.34)	<0.001*	5.14(2.00–13.20)	0.001*
Frail	8.86(3.70–21.25)	<0.001*	9.28(2.85–30.18)	<0.001*
Tostal system				
Atherosclerotic	Reference	-	Reference	-
Lacunar	0.24(0.11–0.52)	<0.001*	1.01(0.33–3.03)	0.991
Cardioembolic	1.12(0.48–2.62)	0.797	2.87(0.23–35.32)	0.411
Unknown	0.40(0.17–0.95)	0.039	1.25(0.38–4.13)	0.712
Other	–	0.999	–	0.999
Stroke treatment				
Antiplatelet therapy	Reference	-	Reference	-
Intravenous thrombolysis	0.58(0.18–1.86)	0.357	0.18(0.03–1.04)	0.057
Thrombectomy	2.60(0.42–15.92)	0.302	1.34(0.21–7.67)	0.069

**Indicates a significant difference ($p < 0.05$) between the groups.*

TABLE 8 | Functional improvement after 1 year follow-up for functional recovery analysis.

	All	No improvement(%)	Improvement(%)	X^2-text	
	(*n* = 123)	(*n* = 84)	(*n* = 39)	X^2-value	*P*-value
Robust	27	14(51.86%)	13(48.14%)	7.2	0.027*
Pre-frail	64	43(67.19%)	21(32.81%)		
Frail	32	27(84.37%)	5(15.63%)		

**Indicates a significant difference ($p < 0.05$) between the groups.*

mortality. A study with a mean follow-up time of 1.6 years shows older adults over 80 years had a significantly attenuated association between pre-stroke frailty and long-term survival after stroke, which may be associated with heterogeneity in older adults (27). Older adults usually combined with higher NIHSS and infection rates after acute cerebral infarction, which aggravates the deterioration of previous frailty status (33). Previous studies have shown that factors, such as advanced age, co-infection, and higher NIHSS score have a correlation with post-stroke long-term mortality (35–37), which may reduce the predictive effect of pre-stroke frailty on post-stroke long-term mortality. Therefore, paying attention to the prevention and treatment of infection in the acute phase can effectively reduce long-term mortality (38, 39).

Our findings emphasize that frailty was strongly associated with functional recovery, whether at 28 days or 1 year. Functional improvement was significantly reduced with pre-stroke frailty deterioration. This study did not exhibit post-stroke rehabilitation exercise as all patients underwent rehabilitation guidance and training during hospitalization at our center. There is a vicious cycle as well because pre-stroke frailty was significantly associated with stroke severity (26) and post-stroke neurologic impairment exacerbated deterioration to frailty (40). High frailty risk was independently associated with a decreased likelihood of favorable 3-month outcomes in patients with acute ischemic stroke who underwent endovascular stroke treatment (41). Simultaneously, in participants with mild stroke, health-related quality-of-life was impaired and continued to deteriorate among patients with in-hospital frailty from 3 to 18 months post-stroke (42).

Frailty is highly prevalent and is associated with adverse outcomes and increased healthcare costs. Pre-frailty is a dynamic process from quantitative to qualitative change between robust and frail individuals, who have adverse risk factors but are not yet undergoing severe physical and physiological changes associated with frailty (31). The transition time between pre-frailty to frailty in this study is uncertain. It may be that frailty and vascular changes are already associated before the onset of an overt cerebrovascular event (33) and the acute shock exacerbated further the patient's frailty status. Of note, it is clear that prolonged bouts of sedentary lifestyle and anorexia increase the incidence of frailty in the elderly (31, 43–45). Primary care interventions that promote physical activity and nutrition may arrest the progression of pre-frailty to frailty (46), reducing the likelihood of adverse outcomes after stroke.

This study cannot determine whether morbidity in cerebral infarction is greater in frail than non-frail patients, but existing studies have demonstrated that frailty is a high-risk factor for severe stroke and increased frailty severity (47, 48). Advocating for the elderly to increase physical activity, conduct moderate exercise, and increase intake of high-quality protein and trace elements is a powerful measure to prevent acute cerebrovascular events and reduce mortality and severe disability (49, 50).

There were several limitations in interpreting the results of this cohort study. First, this was a single-center study with a small sample size. Second, the applied frailty research tool was the FRAIL score. This puts the study at risk of notification error because subjects who can answer questions independently are prone to recall bias, while some patients who cannot express themselves provide relevant information through their guardians or caregivers, which is also prone to recall bias. Patients were likely to exaggerate the feelings of fatigue because of the illusion of temporary fatigue before the onset. It may increase the prevalence of fatigue and frailty before the stroke. Third, this study did not investigate the incidence of frailty after the stroke, and further research is needed to investigate the effect of pre-stroke frailty on post-stroke frailty.

CONCLUSION

In conclusion, our study suggests that pre-stroke frailty status is directly associated with poor outcomes after acute cerebral infarction. It was an independent influencing factor for 28-day mortality but not for 1-year mortality and was associated with severe disability at 28 days and 1 year. More evidence-based studies are needed to develop interventions that may reverse pre-frailty.

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 the Ethics Committee of Huadong Hospital. The patients/participants provided their written informed consent to participate in this study. 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

FY, WW, and AY conceived the project and designed the study. FY, NL, LY, and WW contributed to participant recruitment, data collection, and data analysis. FY, NL, JC, and AY wrote the article. 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.2022.855532/full#supplementary-material

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Pre-stroke Disability and Long-Term Functional Limitations in Stroke Survivors: Findings From More of 12 Years of Follow-Up Across Three International Surveys of Aging

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Background: Almost 50% of the post-stroke disabled population already have a premorbid disability before stroke. These patients may be offered a different care pathway in the acute and subacute phase than those without pre-morbid disability. Therefore, the aim of this study was to assess the association of the severity of premorbid disability with change of limitations in basic and instrumental activities of daily living (ADL/IADL) 1 year after stroke and over the following decade.

Methods: Among 3,432 participants from HRS, SHARE and ELSA cohorts with a first stroke, ADL/IADL limitations were measured at 1–2 years prior to stroke, at 1 year post-stroke, and during the chronic phase. Modified Ranking Scale (P-mRS) was used to categorize the participants by level of premorbid disability (1–2 years pre-stroke). Change in ADL/IADL limitations by P-mRS level (0–1, 2–3, and 4–5) was assessed using a piecewise linear mixed model with a breakpoint set at 1 year post-stroke, stratified by median age groups.

Results: Increase in ADL limitations at 1 year post-stroke was less pronounced in P-mRS $\geq$2 ($p < 0.005$). After years of relative stability, limitations of ADL increased for all P-mRS levels ($p = 0.003$). In those aged $\geq$75 years at stroke event, the increase was similar irrespective of P-mRS ($p = 0.090$). There were no significant differences in IADL trajectories between P-mRS levels ($p \geq 0.127$).

Conclusion: These results suggest similar trajectories of functional limitations between P-mRS levels up to 9 years post-stroke, highlighting the possible benefit of including patients with pre-morbid disability to certain treatments during the acute phase.

Keywords: stroke, chronic phase, premorbid disability, functioning, limitation

INTRODUCTION

Stroke is one of the leading causes of long-term disability in the world (1, 2). More than 20% of stroke survivors experience some limitations in activities of daily living (ADL) (3, 4) and 30% experience limitations in instrumental activities of daily living (IADL) (4, 5), with prevalence of limitations increasing with age (6). As populations age (1, 4) and stroke events occur at more advanced ages, some patients have functional limitations before stroke event (premorbid disability). The care pathway for these patients differs during the acute and sub-acute phase compared to those without premorbid disability. In international reports (7, 8) and a previous study (9) it was reported that only 1 out of 10 patients treated with intravenous thrombolysis had a premorbid disability and in one study (10) only 3 out of 10 patients with premorbid disability accessed a full rehabilitation service during acute care following stroke, despite lack of evidence to support such differential treatment (10, 11). These disparities in the care pathway between those with and without premorbid disability might contribute to increase health inequalities between these groups (11, 12).

Long term studies have reported that about 50% of patients with disability after stroke had a premorbid disability (13–15). Studies suggested after stroke, persons with premorbid disability have higher rates of mortality, institutionalization, and healthcare costs (13, 14), higher severity ratios (14, 16) and a lower probability of achieving favorable outcomes (9) compared to those without premorbid disability. As a result, healthcare professionals tend to develop cognitive biases during acute care of patients with premorbid disability (11, 14). In particular, *fragility* refers to the tendency of physicians to assign pessimistic prognoses to patients with premorbid disability (11, 17) and therefore withhold certain treatments.

Most long-term studies so far [with a maximum of 10 years of follow-up in one study (18)] use the premorbid modified Rankin scale (P-mRS) in dichotomous form) (no-disability [levels 0–1 or 0–3] vs. disability [levels >2 or >3]) (14, 15). Although the P-mRS has been shown to be a predictor of prognosis in its dichotomous form (15, 19), this scale could provide additional information on the influence of the severity of premorbid disability on the functional outcome of stroke patients if a broader categorization (no disability, mild or moderate disability, and severe disability) was used. In addition, there is no evidence of its impact on change in a more graded disability scale, such as limitations in ADL and IADL (20), following stroke event while differentiating the post-stroke subacute and chronic phases (21).

In order to address these gaps in the literature, we examined the association between premorbid disability severity and ADL/IADL limitations after stroke both 1 year after stroke (after the subacute phase) and in the long term, using data spanning 20 years from three large-scale cohort studies conducted in Europe and the United States.

METHODS

Study Population

The study population was drawn from three related surveys (22) of persons aged over 50 from the United States and Europe: the Health and Retirement Study (HRS) (23), the Survey of Health, Aging and Retirement in Europe (SHARE) (24) and the English Longitudinal Study of Ageing (ELSA) (25). Details of these studies are provided elsewhere (23–25). For the present study, HRS data from 1996 to 2018 (12 waves), SHARE data from 2004 to 2016 (6 waves; no data in 2008), and ELSA data from 2002 to 2018 (9 waves) were used. The study sample included all participants who reported having been diagnosed by a physician as having suffered a stroke from the three studies and with data on limitations and covariates before stroke onset (1–2 years pre-stroke) and at least one wave post-stroke. Participants who reported a prevalent stroke at baseline were excluded because no data prior to stroke were available. Participants with recurrent stroke have different prognosis and care than individuals with a single stroke event (26, 27), and were therefore excluded.

ADL and IADL Limitations and Follow-Up

ADL and IADL data were collected similarly in the three surveys (28). Participants (or proxies) reported whether they had experienced any difficulty with ADLs or IADLs lasting longer than 3 months due to a "physical, mental, emotional or memory problem." ADLs included dressing, walking across a room, bathing/showering, eating, getting in/out of bed, using the toilet, and urinary continence, leading to an ADL score ranging from 0 to 7 (29). IADLs included using a map, preparing a hot meal, shopping for groceries, using the telephone, taking medications, and managing money, leading to an IADL score ranging from 0 to 6 (30). Scores equal to 0 indicated no limitations and a score of 7 (for ADLs) or 6 (for IADLs) indicated respondents were fully limited. Follow-up of participants started at year of premorbid stroke status (1 or 2 years pre-stroke) and ended at the last wave of ADL/IADL data, using all information available at waves in between. ADL/IADL limitations show important short-term changes during the acute phase (first year post-stroke) (31) and given that data were collected every 2 years, data in the year following stroke were not considered in the analysis.

Premorbid Disability Level

Premorbid disability level was evaluated based on the P-mRS using self-reported limitations at the last wave before stroke, allowing a maximum of 2 years before stroke event. The P-mRS is a scale for determining levels of disability prior to stroke and has been shown to be a strong predictor of prognosis (19). Three levels of P-mRS were estimated using ADLs and IADLs at the last wave before stroke: 0–1 (no symptoms or significant disability: no limitations in ADLs or IADLs); 2–3 (slight-to-moderate disability: some limitations in ADLs and/or IADLs but able to walk across a room); and 4–5 (moderately severe and severe disability: multiple limitations in ADLs and/or IADLs including an inability to walk across room) (32, 33).

Covariates

Sociodemographic factors included sex, age, education (below secondary, secondary, and above secondary level based on a previously harmonized education category) (34) and marital status ("married or cohabiting" vs. "single, divorced or widowed") and were drawn from the closest wave before stroke event. Other covariates were drawn concurrently with measures of ADL/IADL limitations at each wave. Health behaviors included smoking status (non-smoking and current smoking), alcohol consumption over the last 6 months [abstainers (<once a month), moderate drinkers (≥once per month to <5 days/week) and frequent drinkers (≥5days/week)], and practice of moderate-to-vigorous physical activity at least three times a week. Body mass index (BMI) was estimated based on self-reported weight and height and categorized as <18.5–25, 25–30, and >30 kg/m². In ELSA information on BMI was available every 2 waves and data were carried forward for missing waves. Morbidities included self-report of medical diagnosis of heart problems, high blood pressure, diabetes, lung diseases, arthritis, cancer, chronic pain, and sleep disorders. The number of morbidities was categorized as 0, 1, 2, or ≥3.

Statistical Analysis

Characteristics of the population as a function of P-mRS level (0–1, 2–3, and 4–5) at the closest interview before stroke (pre-stroke status) were presented. Pearson's chi-squared test was used to assess differences between groups in sociodemographic factors, health behaviors, BMI categories, and the number of morbidities. For continuous scores of ADL/IADL limitations, analysis of variance was used to describe differences by P-mRS level groups. In addition, a multivariate logistic model was used to compare participants with "no symptoms or significant disability" (P-mRS 0–1) vs. premorbid disability (P-mRS ≥2), and stratified by age group (50–74 and ≥75 years) defined using median age.

Main Analysis

Change in ADL/IADL limitation scores, at 1 year post-stroke and in the long-term, was assessed using piecewise linear mixed models. The origin of the timeline in the analysis was the year of stroke. The start of the timeline was set at 1 year before stroke using data from the last wave before stroke (allowing a maximum of 2 years before stroke event). The next measure included in the analysis was the first in the data assessed after 1 year post-stroke (after subacute phase). The breakpoint in the model was set at 1 year post-stroke to examine change in limitations following the subacute phase. Random effects were included for intercept at survey-level (HRS, SHARE, and ELSA) and intercept and slope at the individual level to account for variations between surveys and individuals. Analysis were adjust sequentially, initially including time, P-mRS level, sociodemographic variables, and year of stroke. Time squared and lower order interactions between covariates and time terms (time, time squared) were included in the model if they were significant based on the likelihood ratio test. The model was then further adjusted for health behaviors, BMI and number of morbidities as time-dependent variables.

A significant interaction was found between age of stroke as a continuous term and P-mRS both for ADL [both at the intercept ($p < 0.001$) and over time ($p = 0.001$)] and IADL limitations (intercept $p < 0.001$). Exploratory analysis stratified in 6 age bands (**Supplementary Figure 1**) led us to stratify the analysis into two age groups (individuals aged 50–74 years at stroke year and those aged ≥75 years) using the median age of the sample to ensure sufficient numbers in each group. No further interaction was found within these age groups.

To facilitate interpretation of the results, we plotted the adjusted mean ADL/IADL limitation score as a function of time from stroke event estimated in fully adjusted models with 95% confidence intervals (95%CI). These results were plotted over a period of 16 years for the age group 50–74 years, and 12 years for age group ≥75 years, representing the maximum period for which the number of participants in each level of P-mRS was at least 5.

All statistical analyses were carried out using STATA statistical software version 15.1 (Stata-Corp, College Station, Texas).

Sensitivity Analysis

We undertook several sensitivity analyses to test the robustness of our results. First, analyses were carried out separately in HRS, SHARE, and ELSA to evaluate the influence of each survey. Second, imputation of ADL/ADL limitations at 1 year before stroke was performed for participants with limitation data only at 2 years before stroke. We imputed values based on predictions from a fully adjusted linear mixed model with data from 1 and 2 years before stroke, and then repeated the main analysis to evaluate whether limitations increased during the year before stroke where limitation data were missing. Third, because the follow-up period differed between surveys [means (range): HRS = 5.7 (0–21), SHARE = 3.4 (0–11), ELSA = 5.8 (0–16)], the analyses were repeated restricting the follow-up to 6 years (median of total follow-up) to evaluate the influence of follow-up periods of different lengths. Finally, premorbid disability was associated with a high risk of mortality after stroke, potentially impacting estimates of change in limitations in stroke survivors; thus, we replicated the analysis excluding participants who died during follow-up to assess the effect of mortality on results.

RESULTS

Population Characteristics

Of the 189,653 participants from the 3 surveys, 16,252 individuals reported a history of stroke. 6,804 participants were excluded due to prevalent stroke at study baseline ($N = 6{,}043$) or multi-stroke event over the follow-up period ($N = 761$). Of 9,448 participants with first-ever stroke, 3,545 did not participate 1–2 years pre-stroke or had missing ADL/IADL limitation or covariate data at this wave. Finally, 2,471 participants were excluded due to non-participation following the subacute phase, leading to an analytic

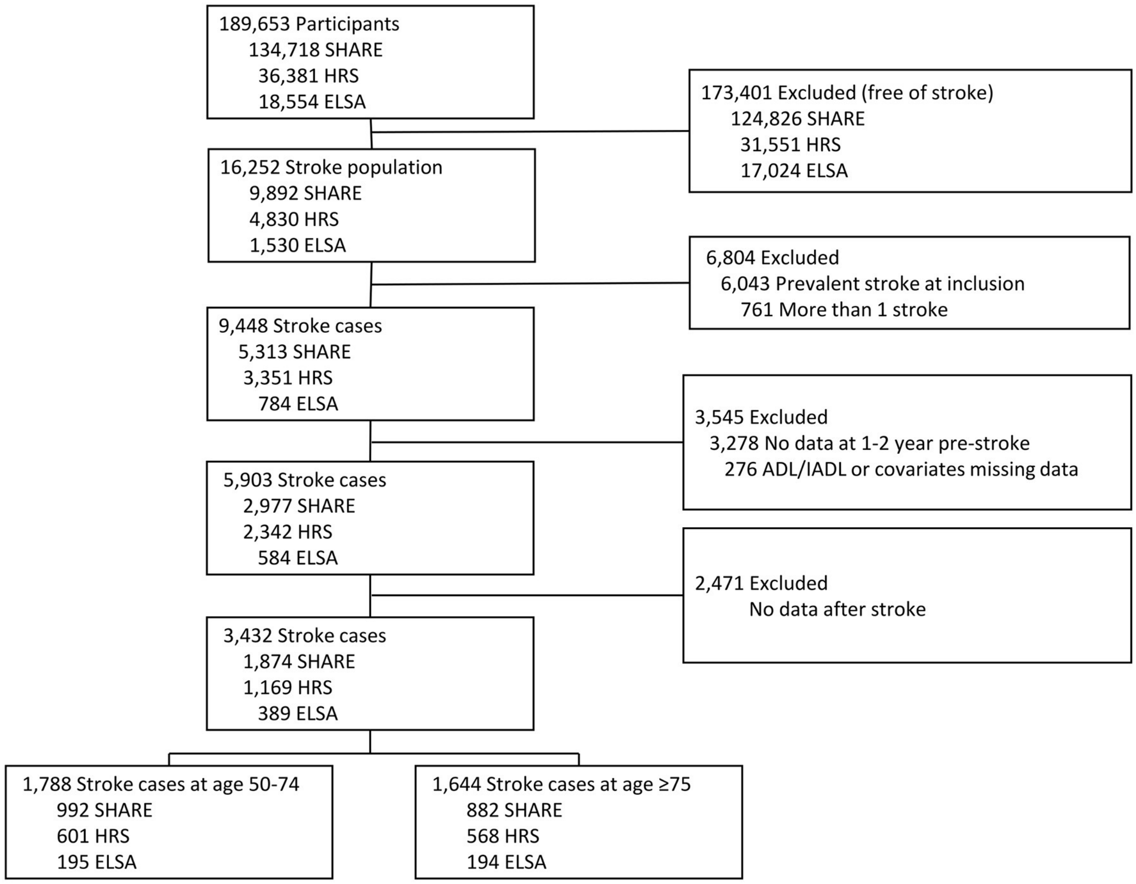

FIGURE 1 | Flowchart of the study samples.

sample of 3,432 first-ever stroke cases (1,169 in HRS; 1,874 in SHARE; 389 in ELSA) (**Figure 1**).

At the last interview before stroke (1,541 1 year before stroke and 1,891 2 years before stroke), the mean age of participants was 73.5 (SD = 9.7) years, 55% were female, 54% reported no limitation, 27% reported slight-to-moderate disability (P-mRS 2–3), and 18% reported moderately-severe and severe disability (P-mRS 4–5). Participants in the slight moderate (P-mRS 2–3) and moderate severe and severe (P-mRS 4–5) disability groups compared to those with no limitations (P-mRS 0–1), were older, more likely to be women, with lower educational level, single/divorced/widowed, non-smokers, non-drinkers, obese (BMI $\geq$ 30 kg/m^2) and less likely to take part in moderate and vigorous physical activities; they also tended to have a higher number of comorbidities (all $p <$ 0.001; **Table 1**). These differences were evident in both age groups (**Supplementary Tables 1**, **2**).

In the multivariate logistic model comparing participants with no premorbid disability (P-mRS 0–1) to those with premorbid disability (P-mRS $\geq$2, 38% for those aged 50–74 and 53% for those aged $\geq$75), participants who were women, with lower educational level and more comorbidities were more likely to have a premorbid disability (all $p <$ 0.05) in both age groups. Age and obesity were associated with higher odds of premorbid disability only for participants aged $\geq$75, and single/divorced/widowed participants were more likely to have disability only in those aged 50–74 (**Supplementary Table 3**).

Change in the Number of ADL Limitations

The mean follow-up was 5.1 (SD = 3.9) years for all levels of premorbid disability in the group aged 50–74 years and 3.6 (SD = 2.7) years in the group aged $\geq$75 years. The change in the number of ADL limitations between pre-stroke and 1 year post-stroke differed as a function of premorbid disability levels ($p <$ 0.005). At 1 year post-stroke, participants aged 50–74 years with no premorbid limitations (P-mRS 0–1) showed a 9% increase (ΔADL = 0.64, 95%CI = 0.54–0.75, out of a maximum of 7 limitations) in ADL limitations compared to their pre-stroke ADL limitations score (**Figure 2**, **Supplementary Table 4**). This increase was 4% among those with slight-to-moderate premorbid limitation (P-mRS 2–3; ΔADL = 0.30, 95%CI = 0.15–0.46) and 0.6% among those with premorbid moderately severe to severe limitation levels (P-mRS 4–5; ΔADL = 0.04, 95%CI = −0.14–0.24; **Figure 2**, **Supplementary Table 4**). Among participants aged $\geq$75 years at stroke event, individuals with no limitation or slight-to-moderate premorbid disability levels had a similar

TABLE 1 | Characteristics of the study sample at last[a] interview before stroke onset according to premorbid disability level using modified Rankin scale (P-mRS)[b].

Characteristics	Premorbid Disability Level			p
	P-mRS 0–1 (N = 1,872)	P-mRS 2–3 (N = 925)	P-mRS 4–5 (N = 635)	
Sex				
Men	984 (52.6)	344 (37.2)	215 (33.9)	<0.001
Women	888 (47.4)	581 (62.8)	420 (66.1)	
Age (years)				
50–65	547 (29.2)	220 (23.8)	137 (21.6)	<0.001
66–74	553 (29.5)	211 (22.8)	120 (18.9)	
75–81	457 (24.4)	232 (25.1)	161 (25.4)	
>81	315 (16.8)	262 (28.3)	217 (34.2)	
Education level				
Low	543 (29.0)	366 (39.6)	317 (49.9)	<0.001
Middle	917 (49.0)	415 (44.9)	241 (38.0)	
High	412 (22.0)	144 (15.6)	77 (12.1)	
Marital status				
Single/divorced/widowed	695 (37.1)	412 (44.5)	349 (55.0)	<0.001
Married/Cohabiting	1,177 (62.9)	513 (55.5)	286 (45.0)	
Smoking status				
Non-smoking	889 (47.5)	578 (62.5)	404 (63.6)	<0.001
Current smoking	983 (52.5)	347 (37.5)	231 (36.4)	
Alcohol consumption				
Non-drinkers	900 (48.1)	586 (63.4)	506 (79.7)	<0.001
Moderate drinkers	636 (34.0)	208 (22.5)	69 (10.9)	
Heavy drinkers	336 (18.0)	131 (14.2)	60 (9.5)	
MVPA at least 3 times a week				
No	700 (37.4)	564 (61.0)	544 (85.7)	<0.001
Yes	1,172 (62.6)	361 (39.0)	91 (14.3)	
BMI (kg/m²)				
<25	608 (32.5)	289 (31.2)	167 (26.3)	
25–30	779 (41.6)	354 (38.3)	215 (33.9)	
>30	485 (25.9)	282 (30.5)	253 (39.8)	
Number of comorbidities				
0	322 (17.2)	50 (5.4)	25 (3.9)	<0.001
1	567 (30.3)	166 (18.0)	66 (10.4)	
2	449 (24.0)	243 (26.3)	113 (17.8)	
3 or more	534 (28.5)	466 (50.4)	431 (67.9)	
ADL limitation Score (0–7)[c]				
Mean (SD)	0.0 (0.0)	1.0 (0.9)	2.8 (1.8)	<0.001
IADL limitation Score (0–6)[c]				
Mean (SD)	0.0 (0.0)	1.0 (1.2)	1.7 (1.9)	<0.001

[a]Interview maximum 2 years before stroke. [b]Values are numbers (percentages). [c]Score corresponds to number of ADL or IADL limitations. Percentages are reported in column. ADL, Activities of daily living; IADL, Instrumental ADL; P-mRS, premorbid modified Ranking Scale; MVPA, moderate-to-vigorous physical activity.

increase (15.7% [ΔADL = 1.10 95%CI = 0.94–1.26] and 17.2% [ΔADL =1.21 95%CI = 1.02–1.39] respectively; $p = 0.388$) in ADL limitations pre-stroke and 1 year post stroke while those with moderate-to-severe premorbid disability tended to experience a lower increase in ADL limitations (11%[ΔADL = 0.77 95%CI = 0.56–0.98], $p < 0.001$).

When examining the long-term trajectories of ADL limitations (after 1 year post-stroke), in participants aged 50–74 at stroke event, only P-mRS 2–3 showed a significant 5.0% increase (ΔADL =0.35 95%CI = 0.11–5.85, $p = 0.004$) between years 1 and 7. Then, between 7 and 16 years post-stroke, those with premorbid disability level 0–1 and 4–5 showed a significant increase of 17.0% (ΔADL =1.23 95%CI = 0.59–1.86, $p < 0.001$) and 23.0% in ADL limitations score respectively (ΔADL =1.61 95%CI = 0.76–2.46, $p < 0.001$), while those with premorbid disability level of 2–3 showed no

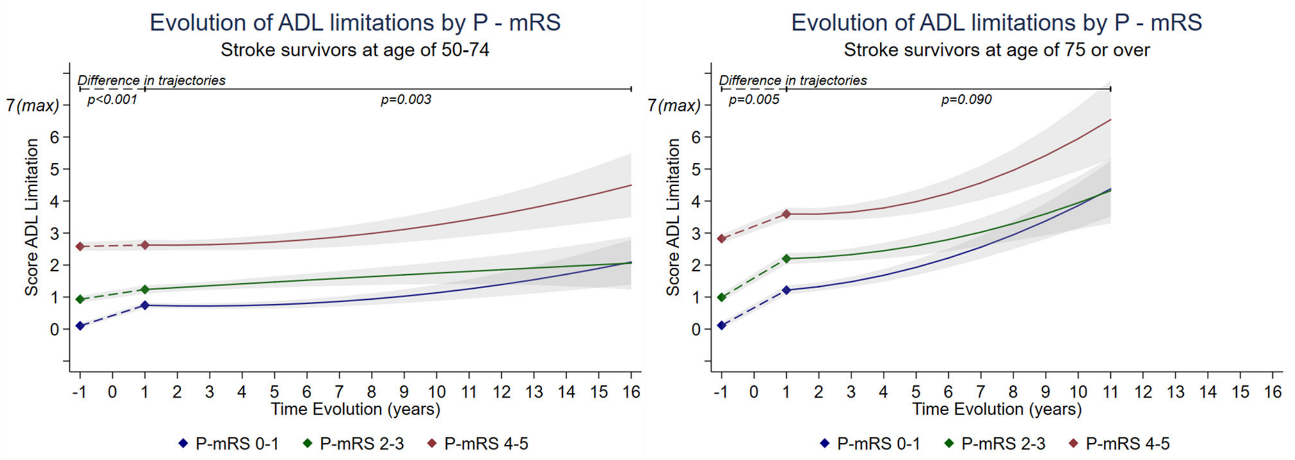

FIGURE 2 | Long-term trajectories of score of ADL limitations in stroke survivors by premorbid modified Rankin scale (P-mRS) stratified by age*. *Estimated from piecewise linear mixed model adjusted for socioeconomic variables, pre-stroke wave data collection, heath behaviors, BMI, and number of comorbidities. Breakpoint was set at 1 year post-stroke. Detailed changes in limitations between pre-stroke and 1 year post-stroke could not be modeled due to lack of information and was assumed linear for the sake of the analysis. ADL score range from 0 = no limitation to 7 = maximum limitation. Estimations are presented for a 16 year follow-up (corresponding to maximum follow-up with at least 5 participants by level of mRS) for population aged 50–74 years and a 11 year follow-up for those aged ≥75 years. **Supplementary Table 4**.

significant increase. In participants aged ≥75 years at stroke event, there were no significant differences in ADL change 1 year post-stroke between premorbid disability levels ($p = 0.090$, **Figure 2**, **Supplementary Table 4**). Between post-stroke years 1 and 4, individuals with p-mRS levels at 0–1 and 2–3 had a mean increase in ADL score of 6.6% (ΔADL = 0.46 95%CI = 0.26–0.66, $p < 0.001$) and 3.5% (ΔADL = 0.25 95%CI = 0.01–0.49, $p = 0.050$), respectively, while those with level 4–5 had a non-significant increase of 2.7% (ΔADL = 0.19 95%CI = −0.11 to 0.48, $p = 0.211$). Between 4 and 12 years post-stroke, all levels of P-mRS showed a similar increase in ADL limitations: 46.7% (ΔADL =3.27 95%CI = 2.26–4.28, $p < 0.001$) for level 0–1, 32.8% (ΔADL = 2.29 95%CI = 1.11–3.48, $p < 0.001$) for level 2–3 and 48.8% (ΔADL = 3.42 95%CI = 1.99–4.84, $p < 0.001$) for level 4–5.

Change in the Number of IADL Limitations

The trajectories of IADL limitations over the follow-up did not differ by premorbid disability level for both age groups (**Figure 3**, **Supplementary Table 5**). Among participants aged 50–74 years at stroke event, at 1 year post-stroke, increase in IADL limitation score was similar whether the premorbid disability level was 0–1 (7.9% increase, ΔIADL = 0.47 95%CI = 0.37–0.57 out of a maximum of 6 limitations), 2–3 (5.4%, ΔIADL = 0.32 95%CI = 0.19–0.46), or 4–5 (5.4%, ΔIADL = 0.32 95%CI = 0.15–0.50; comparison ΔIADL for 0–1 vs. 2–3, $p = 0.07$; for 0–1 vs. 4–5, $p = 0.146$). Changes of IADL limitations did not differ by premorbid disability levels for those aged ≥75 at 1 year post-stroke ($p = 0.166$). The increase in IADL score was 15.1% (ΔIADL = 0.95 95%CI = 0.80–1.10) for level 0–1, 15.8% (ΔIADL = 0.90 95%CI = 0.72–1.08) for level 2–3 and 11.9% (ΔIADL = 0.71 95%CI = 0.51–0.91) for level 4–5.

Long-term trajectories showed no significant differences between levels of premorbid disability. Between post-stroke years 1 and 7 in participants aged 50–74 years, there was no evidence of change in ADL limitations irrespective of premorbid disability level (ΔIADL<3% and p>0.115 for all levels). A significant increase in IADL limitations was then observed between years 7 and 16 post-stroke in all levels: 21.0% (ΔIADL = 1.29 95%CI = 0.71–1.87, $p < 0.001$) for level 0–1, 18.6% (ΔIADL = 1.11 95%CI = 0.45–1.78, $p = 0.001$) for level 2–3, and 28.6% (ΔIADL = 1.72 95%CI = 0.94–2.49, $p < 0.001$) for level 4–5. In participants aged ≥75 years, the increase of IADL limitations was observed from 1 year post-stroke; level 0–1 and 4–5 showed an increase of 7.0% (ΔIADL = 0.44 95%CI = 0.25–0.62, $p = 0.001$; ΔIADL = 0.45 95%CI = 0.18–0.73, $p = 0.001$ respectively) and level 2–3 showed an increase of 4.0% (ΔIADL = 0.24 95%CI = 0.13–0.47, $p = 0.001$) during a follow-up between year 1 and 4 post-stroke. Then, between years 4 and 12 post-stroke a more pronounced increase was observed irrespective of premorbid disability levels; 41.2% (ΔIADL = 2.48 95%CI = 1.53–3.41, $p < 0.001$) for those in level 0–1, 51.6% (ΔIADL = 3.10 95%CI = 2.00–4.20, $p = 0.001$) for those in level 2–3, and 44.5% (ΔIADL = 2.67 95%CI = 1.35–3.99, $p = 0.001$) for those in level 4–5.

Sensitivity Analysis

In the analyses stratified by survey, the results at 1 year post-stroke showed similar findings as the main analysis. Long-term trajectories were found to be similar to the main results, except for ADL changes in SHARE and IADL in ELSA, possibly due to absence of data with long follow-up (**Supplementary Figures 2**, **3**). Second, in analyses with imputation of ADL/IADL limitations score at 1 year pre-stroke,

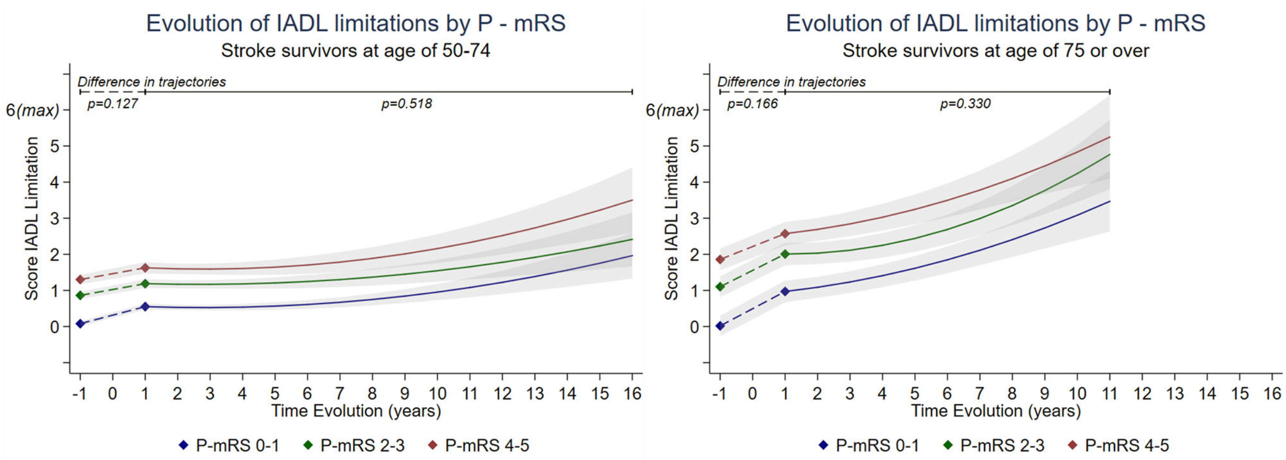

FIGURE 3 | Long-term trajectories of score of IADL limitations in stroke survivors by premorbid modified Rankin scale (P-mRS) stratified by age*. *Estimated from piecewise linear mixed model adjusted for socioeconomic variables, pre-stroke wave data collection, heath behaviors, BMI, and number of comorbidities. Breakpoint was set at 1 year post-stroke. Detailed changes in limitations between pre-stroke and 1 year post-stroke could not be modeled due to lack of information and was assumed linear for the sake of the analysis. IADL score range from 0 = no limitation to 6 = maximum limitation. Estimations are presented for a 16 year follow-up (corresponding to maximum follow-up with at least 5 participants by level of mRS) for population aged 50–74 years and a 11 year follow-up for those aged ≥75 years. **Supplementary Table 5**.

the results were similar to the main analysis suggesting that possible increase in limitations between 2 and 1 years pre-stroke did not influence the change in limitations during post-stroke follow-up (**Supplementary Figure 4**). Third, analyses repeated with period of follow-up limited to 6 years post-stroke showed similar results to the main analysis suggesting that results were not influenced by the length of follow-up (**Supplementary Figure 5**). Finally, removal from analysis of participants who died during the follow-up period (P-mRS 0–1 = 213, 2–3 = 200, 4–5 = 198, **Supplementary Table 6**) did not alter findings, suggesting mortality did not influence findings (**Supplementary Figure 6**).

DISCUSSION

In this observational study of 3,432 stroke participants with a premorbid disability measure drawn from three international longitudinal surveys, premorbid disability was observed in around 45% of participants. The increase of ADL limitations at 1 year post-stroke was less pronounced in cases with premorbid disability (P-mRS levels 2–5 for those aged 50–74 years and 4–5 for those aged ≥75 years) compared with those reporting none. In the long term, relative stability in ADL limitations was observed between 1 and 7 year post-stroke for those aged 50–74 years and between 1 and 4 years for those aged ≥75 years. Thereafter, a similar increase was observed irrespective of the premorbid disability level, with the exception of those aged 50–74 years with moderate to severe prémorbide disability (P-mRS levels 4–5) where the increase was slightly more pronounced. The trajectories of IADL limitations did not differ between premorbid disability levels.

Comparison With Previous Studies

In agreement with previously reported studies with long-term follow-up undertaken in populations with premorbid disability (14, 15, 18), we observed a high proportion of participants reporting limitations prior to stroke, especially older participants. Previous studies showed that long-term outcomes in participants with premorbid disability tended to be less favorable with age (13–15, 35, 36); the present study adds to evidence that trajectories of ADL limitations post-stroke differed by premorbid disability levels, particularly among participants with stroke at younger age. In addition, our analyses accounting for pre-stroke ADL limitations allowed us to observe an increase in ADL limitations at 1 year post-stroke that was less pronounced for those with slight to severe premorbid disability (P-mRS 2–5). This finding is consistent with a previous study that showed a higher increase in mRS 3 months post-stroke among individuals with no premorbid limitations (14). Finally, a recent study showed that patients with premorbid disability treated with thrombectomy had no functional differences with patients who did not have premorbid disability 3 months after stroke (37). This contrasts with our results, in which the trajectories of ADL limitations differed according to P-mRS levels at 1 year post-stroke, however this difference ceases to be significant after several years.

Strengths and Limitations

This observational study has several strengths including a large number of participants with multi-country data on premorbid disability status assessed prospectively before stroke onset. This allowed us to stratify the analysis by age and examine the differences in the trajectories of limitations by levels of premorbid disability maintaining a sufficient number of participants over the follow-up period to ensure robust results. The use of a piece-wise mixed model allowed the examination of two different periods (pre-stroke to 1 year, and 1 to 16 years after stroke) in the same model taking into account the association with both the end of the sub-acute post-stroke phase and long-term trajectory of functional limitations (38).

Our results should be considered in light of the following limitations: (1) subtype of stroke information was not available and stroke was self-reported or reported by a proxy, introducing a possible recall bias. Nevertheless, in previous studies it was observed that prevalence of self-report of chronic conditions such as stroke is close to prevalence obtained from linkage to electronic medical records with agreement of 96% (39), Even so, previous studies show a range of sensitivities between 36 and 98% and a specificity between 96 and 99% (40). Inclusion of false positive (confusion with stroke synonyms) (41) might have affected the trajectory of those with no significant disability (P-mRS 0–1). (2) Data on premorbid status was collected in a period of maximum 2 years before the stroke onset, thus participants measured 2 years pre-stroke may present a different premorbid state at stroke onset compared to participants with measure at 1 year pre-stroke. To assess potential selection bias, an analysis with data imputed for those measured at 2 years pre-stroke was conducted and results were consistent with main findings. (3) Previous studies reported an association between premorbid disability level and mortality, and long-term results may be influenced by the death of participants with a higher level of disability (38, 42). To address this limitation, the analysis was repeated excluding all cases with a report of death during follow-up; the results were consistent with the main findings. (4) We used three different surveys which might increase heterogeneity in the measures; however, previous studies showed good concordance between cohorts and sensitivity analyses stratified by survey suggest that our results were similar across cohorts (28). (5) The P-mRS was derived from the count of ADL and IADL limitations, this scale will require further validation in the premorbid population, although it is beginning to be commonly used to assess the pre-stroke disability level retrospectively in research and clinical settings; the P-mRS was used to categorize the premorbid disability level of stroke participants giving a more clinically significant and comprehensive characterization of premorbid disability than the simple count of ADL and IADL limitations.

Clinical Implications and Future Research

The clinical care of stroke patients may be different when the patient has a premorbid disability, because of the tendency to establish a pessimistic prognosis for patients with a disability (*fragility* bias) (11, 17). However, our findings suggest that after 1 year post-stroke the increase in limitations is less pronounced for participants with premorbid disability and in the long term all levels showed several years of relative stability. In addition, change in IADL limitations does not differ by severity level of premorbid disability. These findings should be confirmed in future prospective studies, and may encourage healthcare professionals to treat patients with premorbid disability more rigorously during the acute phase of stroke. Our findings suggest the importance of future research aimed at understanding the impact of premorbid disability in acute illness, and addressing possible bias in health care. In addition, future studies should consider trajectories of different types of disability (physical, sensory, or cognitive) after an acute event. Further studies are also needed in low-income countries, where access to preventive and rehabilitative health services may be more restricted.

CONCLUSION

The present study may indicate that premorbid disability is present in more than 1/3 of stroke survivors and the trajectories of ADL limitations may be influenced by premorbid disability after several years of relative stability. After the stable period, an increase in ADL limitations is more pronounced in those with severe premorbid disability levels. IADL limitations have a similar trajectories regardless of the level of premorbid disability. These results highlight the importance of adapting health and social care for stroke survivors toward greater inclusion of patients with premorbid disability.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: Health and Retirement Study (HRS), https://hrsdata.isr.umich.edu/data-products, Survey of Health, Aging and Retirement in Europe (SHARE), http://www.share-project.org/ data-access/share-conditions-of-use.html and English Longitudinal Study of Aging (ELSA), https://www.elsa-project.ac.uk/accessing-elsa-data.

AUTHOR CONTRIBUTIONS

AG-S and AS: conceptualization, data curation, and writing—original draft preparation. AG-S, SS, AD, and AF: methodology. SS, AD, AF, and AS: validation. AG-S, AD, and AF: formal analysis and visualization. AD, AF, LJ, MB, and BL: writing—review and editing. AS: supervision. 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.2022.888119/full#supplementary-material

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Ischemic Stroke at a Tertiary Academic Hospital in Tanzania: A Prospective Cohort Study With a Focus on Presumed Large Vessel Occlusion

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Background: Large vessel ischemic strokes account for more than one-third of all strokes associated with substantial morbidity and mortality without early intervention. The incidence of large vessel occlusion (LVO) is not known in sub-Saharan Africa (SSA). Definitive vessel imaging is not routinely available in resource-limited settings.

Aims: We aimed to investigate the burden and outcomes of presumed LVO among patients with ischemic stroke admitted to a large tertiary academic hospital in Tanzania.

Methods: This cohort study recruited all consenting first-ever ischemic stroke participants admitted at a tertiary hospital in Tanzania. Demographic data were recorded, and participants were followed up to 1 year using the modified Rankin Scale (mRS). A diagnosis of presumed LVO was made by a diagnostic neuroradiologist and interventional neurologist based on contiguous ischemic changes in a pattern consistent with proximal LVO on a non-contrast computed tomography head. We examined factors associated with presumed LVO using logistic regression analysis. Inter-observer Kappa was calculated.

Results: We enrolled 158 first-ever ischemic strokes over 8 months with a mean age of 59.7 years. Presumed LVO accounted for 39.2% [95% confidence interval (CI) 31.6–47.3%] and an overall meantime from the onset of stroke symptoms to hospital arrival was 1.74 days. Participants with presumed LVO were more likely to involve the middle cerebral artery (MCA) territory (70.9%), $p < 0.0001$. Independent factors on multivariate analysis associated with presumed LVO were hypertension [adjusted odds ratio (aOR) 5.74 (95% CI: 1.74–18.9)] and increased waist-hip ratio [aOR 7.20 (95% CI: 1.83–28.2)]. One-year mortality in presumed LVO was 80% when compared with 73.1% in participants without presumed LVO. The Cohen's Kappa inter-observer reliability between the diagnostic neuroradiologist and interventional neurologist was 0.847.

Conclusion: There is a high burden of presumed LVO associated with high rates of 1-year morbidity and mortality at a tertiary academic hospital in Tanzania. Efforts are needed to confirm these findings with definitive vessel imaging, promoting cost-effective preventive strategies to reduce the burden of non-communicable diseases (NCDs), and a call for adopting endovascular therapies to reduce morbidity and mortality.

Keywords: ischemic stroke, large vessel occlusion, thrombectomy, morbidity and mortality, Tanzania

INTRODUCTION

Stroke is a leading cause of death and disability, particularly in low and middle-income countries (LMICs), contributing to 80% of all incident cases, 87% of all deaths, and 89% of stroke-related disability-adjusted life years (DALYs) (1, 2). According to the 2019 Global Burden of Disease (GBD) report, there were 12.2 million stroke incident cases, 6.55 million stroke fatal cases, and 143 million stroke DALYs (3). Globally, the proportions of ischemic strokes (62.4%) are higher as compared to intracerebral hemorrhages (27.9%) and subarachnoid hemorrhages (9.7%) (3). In LMIC, ischemic stroke accounts for approximately 7 million cases (63%) and 1.5 (57%) million deaths as a proportion of all strokes and deaths, respectively (4). A similar trend is observed in sub-Saharan Africa (SSA), where ischemic strokes account for 68% of all strokes as compared to 32% of hemorrhagic strokes (5).

Large vessel occlusions (LVOs) account for 20–40% of all ischemic strokes associated with substantial morbidity and mortality (6, 7). In high-income countries (HICs), the incidence of LVO is estimated at 24 per 100,000-person years, summing up to 80,000 cases annually (8). In the pre-endovascular era, mortality was two times (64% vs. 24%) among those with LVO as compared to those without, respectively (6). This eventually led to the adoption of endovascular interventions that have proven cost-effective in preventing mortality and disability from a stroke in HIC based on previous pivotal clinical trials (9, 10). Notably, such resources are limited in the vast majority of facilities sub-serving people living in SSA contributing to increased stroke mortality. In addition, it is unusual for patients to arrive in the early time window for stroke intervention. Little is known about the true burden and outcomes of LVO among patients with ischemic stroke in SSA. We therefore aimed to investigate the prevalence and outcomes of first-ever ischemic strokes, with a particular focus on presumed LVO in patients admitted to a tertiary academic hospital in Tanzania.

MATERIALS AND METHODS

Study Design and Population

This cohort study was conducted at Muhimbili University of Health and Allied Sciences Academic Medical Center (MAMC), medical wards in Dar es Salaam, Tanzania. This is a tertiary academic hospital that receives referral patients from both public and private hospitals and offers specialized medical care for all medical subspecialties in Tanzania.

Consecutive participants aged ≥18 years admitted at MAMC with a diagnosis of first-ever ischemic stroke according to the World Health Organization definition (WHO) (11) between June 2018 and January 2019 were recruited. Written informed consent was obtained from either the participants or their next of kin if the participant was unable to consent before study enrollment.

Data Collection

An interviewer-based structured questionnaire was administered to all study participants or their caregivers capturing the following: demographic information, date of onset of stroke symptoms, date of admission, contact details, and premorbid stroke risk factors (e.g., hypertension, diabetes mellitus (DM), and HIV infection). Medication history for hypertension, DM, HIV, and hormonal contraception for women was also obtained. We also inquired about smoking and alcohol consumption.

Clinical Measurements

Physical examination included measurement of blood pressure (BP) using a standard digital BP machine, AD Medical Inc. Three BP readings were collected spaced 5-min apart, while the participant was at rest, and an average BP was computed. Participants were regarded as hypertension when the average BP readings for systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or if the participant was on anti-hypertensive therapy according to the Joint National Committee 7 (JNC-7) definition (12). All participants had their waist and hip circumference measured using a tape measure and recorded in centimeters. The waist-hip ratio was interpreted according to the WHO guidelines; in men, the ratio of ≥0.90 and in women, the ratio of ≥0.85 were regarded as substantially increased (13). The examination also included precordial and neck carotid auscultation.

Laboratory Investigations

Capillary fingertip blood samples were collected to check for random blood glucose (RBG) levels and HIV rapid testing using a glucometer GLUCOPLUS™ and SD Bioline, respectively. A fasting blood glucose (FBG) sample was collected the following morning for participants with RBG levels of ≥11.1 mmol/l (equivalent to ≥200 mg/dl). DM diagnosis was defined as an RBG reading of ≥11.1 mmol/l (equivalent to ≥200 mg/dl) or an FBG reading of ≥7 mmol/l (equivalent to ≥126 mg/dl). HIV testing was performed using sequential rapid test SD Bioline,

Abbreviations: AF, Atrial Fibrillation; DALYS, Disability Adjusted Life Years; DWI, Diffusion Weighted Imaging; FBG, Fasting Blood Glucose; HIV, Human Deficiency Virus; LVO, Large vessel occlusion; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SSA, sub-Saharan Africa; WHO, World Health Organization.

followed by Unigold Biotech – these are both rapid immune-chromatographic antibody assays for HIV 1/2 antibodies.

We aseptically collected 5 ml of venous blood from each study participant. We analyzed random total cholesterol, triglycerides (TGA), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) using machine model A15 of BioSystems. Cutoffs for total cholesterol >240 mg/dl were regarded as hypercholesterolemia, TGA >200 mg/dl as hypertriglyceridemia, LDL >129 mg/dl as increased, and HDL <35 mg/dl as reduced levels.

Brain Imaging

A non-contrast brain computed tomography (NCCT) using GE Healthcare Optima was performed on all the study participants only at baseline, and images were independently interpreted by a diagnostic neuroradiologist (FL) and an interventional neurologist (FS). Ischemic stroke was defined based on a clinical stroke syndrome and objective evidence of focal cerebral ischemia in a vascular territory by an NCCT (14) (**Figure 1**). Presumed LVO was defined as occlusion of the proximal segments of the MCA (i.e., M1 or proximal M2), anterior cerebral arteries, posterior cerebral arteries, vertebral arteries, and basilar arteries that were determined radiographically based on contiguous hypo-density noted on NCCT that can be attributed to the involved vascular territory with or without the presence of additional findings, such as hyperdense MCA or basilar signs (15, 16). Hemorrhagic transformation was defined as per European Cooperative Acute Stroke Study (ECASS II) (17). Hemorrhagic infarction type 1 (HI1) was defined as petechial hemorrhages at the infarct margins. Hemorrhagic infarction type 2 (HI2) was defined as petechial hemorrhages throughout the infarct and no mass-effect was attributable to the hemorrhages. Parenchymal hematoma type 1 (PH1) was defined as ≤30% of the infarcted area and minor mass effect attributable to the hematoma. Parenchymal hematoma type 2 (PH2) was defined as >30% of the infarct zone and substantial mass effect attributable to the hematoma. Midline shift was defined as any measurable shift of midline cerebral structures seen on axial images of an NCCT, specifically the septum pellucidum and/or the pineal gland (18).

Cardiovascular Assessment

Transthoracic echocardiography (ECHO) using GE Medical Systems was performed by a trained cardiologist, and interpretation was based on European Society of Cardiology/American Society of Echocardiography guidelines for evidence of any structural heart abnormalities and other cardiac risk factors for stroke, such as mitral stenosis, presence of vegetations and thrombus (19). A 12-lead electrocardiogram (ECG) using a machine of Bionet was performed on the study participants to look for evidence of atrial fibrillation.

Stroke Outcomes

Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) on admission (11). Stroke outcomes were categorized using the modified Rankin Scale (mRS) (11) at 24 h, 30 days, and 1 year from admission, with scores ranging from 0 (no symptoms) to 6 (death).

Study Variables

The dependent variable was presumed LVO. The independent variables included demographic characteristics, risk factors (hypertension, DM, smoking, cardiac disease, alcohol consumption, increased waist-hip ratio, hypercholesterolemia, and increased LDL), vascular territories, and stroke outcomes (death or survival with/without disabilities).

Data Analysis

Data were analyzed using SPSS version 20.0. Continuous variables were summarized and presented as means and standard deviation (SD) or medians with interquartile range [IQR]. Categorical variables were summarized as frequencies and proportions. Comparisons between proportions were done using Pearson's Chi-square test or Fisher's exact test. The logistic regression technique was used to determine independent factors associated with presumed LVO. All covariates with a p-value of < 0.2 in the bivariable analysis were included in the multivariable analysis model. Unadjusted and adjusted odds ratios (OR), 95% confidence intervals (CI), and corresponding p-values were obtained from the models. A two-tailed significance level was set as a p-value of ≤ 0.05. Inter-observer Kappa between the diagnostic neuroradiologist (FL) and interventional neurologist (FS) was also calculated.

RESULTS

Between June 2018 to January 2019, there were 1,403 medical admissions, out of which 408 (29.1%) participants met the WHO clinical definition of first-ever ischemic stroke. We excluded 250 (15.9%) participants for the following reasons: inability to consent, those who did not complete brain imaging, those with stroke mimics based on brain imaging, intracranial hemorrhage, normal brain CT scans, indeterminate CT scans (those with artifacts or poor imaging quality), and those with mixed lesions. We recruited the remaining 158 (38.7%) participants with a confirmed diagnosis of ischemic stroke, as shown in **Figure 2**. The proportion of ischemic strokes over total admissions was 158 of 1,403 [(11.3%) (95% CI 9.7–13.0%)]. Of these, 62 of 158 [(39.2%) (95% CI 31.6–47.3%)] had presumed LVO.

The overall mean age ± SD of the recruited participants was 59.7 ± 16.6 years, and the majority resided in Dar-es-Salaam (72.8%), a former capital city. A quarter possessed health insurance (25.9%). The overall meantime from the onset of stroke symptoms to hospital arrival was 1.74 days with no statistically significant difference in the meantime from the onset of stroke symptoms to hospital arrival in the presumed LVO vs. non-LVO groups (1.87 days vs. 1.83, respectively, $p < 0.32$.). Overall, 29 (18.3%) participants were observed to arrive at the hospital within 24 h from stroke symptom onset with no participant arriving in <4.5-h and <8-h windows.

The MCA was the predominant major vascular territory involved. It was statistically seen more frequently in the presumed LVO group as compared to those with non-LVO, i.e., 44 (71.0%)

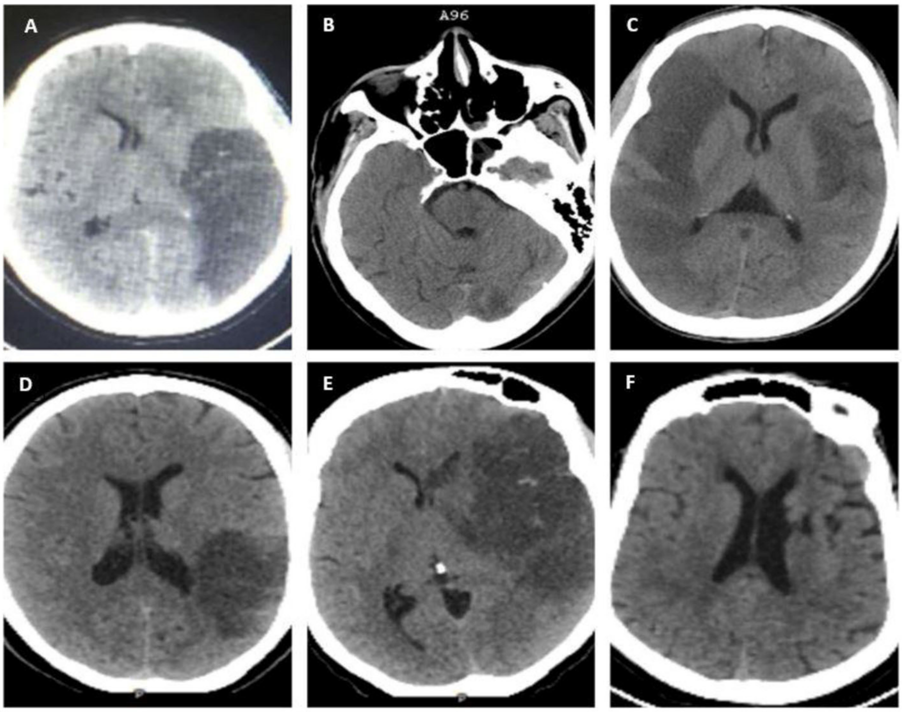

FIGURE 1 | Non-contrast brain computed tomography (NCCT) scans showing evidence of ischemic infarcts in various vascular territories; **(A)** left distal middle cerebral artery (MCA) M1 with HI 1; **(B)** basilar and left posterior cerebral artery (PCA) infarction with a hyperdense basilar sign; **(C)** bilateral MCA: right M1 and left distal M1/ proximal M2; **(D)** inferior division M2 MCA with HI 1; **(E)** left proximal M1 with HI 1; and **(F)** left Lacunar infarct (non-LVO).

vs. 32 (33.3%), $p < 0.0001$, respectively. Similarly, participants with presumed LVO were statistically more likely to have the following cardiovascular risk factors as compared to those with non-LVO: increased waist-hip ratio 54 (87%) vs. 56 (58.3%), $p < 0.001$, hypertension 49 (79.0%) vs. 47 (48.9%), $p < 0.001$, mean total cholesterol of 220.1 ± 95.9 mg/dl vs. 188.9 ± 56.2 mg/dl, $p < 0.001$, and mean TGA 138.4 ± 103.2 mg/dl vs. 117.1 ± 56.9 mg/dl, $p < 0.001$, respectively (**Table 1**).

Predictors of presumed LVO are summarized in **Table 2**. In univariate analysis, factors that were significantly associated with presumed LVO were medical co-morbidities, such as hypertension, atrial fibrillation, increased waist-to-hip ratio, total cholesterol, and TGA. In multivariate analysis, presumed LVO was independently associated with hypertension [adjusted OR (aOR) 5.74 (95% confidence interval (CI): 1.74–18.9)] and increased waist-hip ratio [adjusted OR 7.20 (95% CI: 1.83–28.2)].

Table 3 describes the outcomes of the study participants. At 30 days, there were 3 participants who were lost to follow-up and were excluded from the analysis. Overall, the 30-day mortality was 89/155 (57.4%), with no statistically significant difference in mortality in the presumed LVO and non-LVO groups, 36/62 (58.1%) vs. 53/93 (57%), $p = 0.51$, respectively. At 1 year, there were 5 participants who were lost to follow-up and were excluded from the analysis. The overall 1-year mortality was 116/153 (75.8%), 48/60 (80%) in the presumed LVO group vs. 68/93 (73.1%) in the non-LVO group, $p = 0.25$. Those with presumed LVO were statistically more likely to have a hemorrhagic transformation on the NCCT head as compared to those with non-LVO, 29 (46.7%) vs. 5 (5.20%), $p < 0.001$, respectively. The Cohen's Kappa inter-observer reliability between the diagnostic neuroradiologist and interventional neurologist was calculated at 0.847.

DISCUSSION

This is the first study looking at the burden and outcomes of presumed LVO among all presenting ischemic strokes in Tanzania, an East African nation representative of many LMICs located in SSA. The present study was conducted at a tertiary specialized academic hospital and found a proportion of 39.2% of presumed LVO. This is a large proportion of all presenting ischemic strokes and is comparable to a previously reported global prevalence of 31% in a large meta-analysis (20). Our findings are of particular importance given the high burden of ischemic strokes in Tanzania (21) and the need for good epidemiological data before advocating for evidence-based acute stroke interventions in resource-limited settings. There is currently no data on the prevalence of LVO ischemic strokes in SSA.

The mechanisms for LVO include intracranial artery atherosclerosis, cardioembolism, artery to artery embolism (from extracranial atherosclerosis or dissection), and unknown/cryptogenic causes (22). Our study found that risk factors for presumed LVO on the univariate analysis

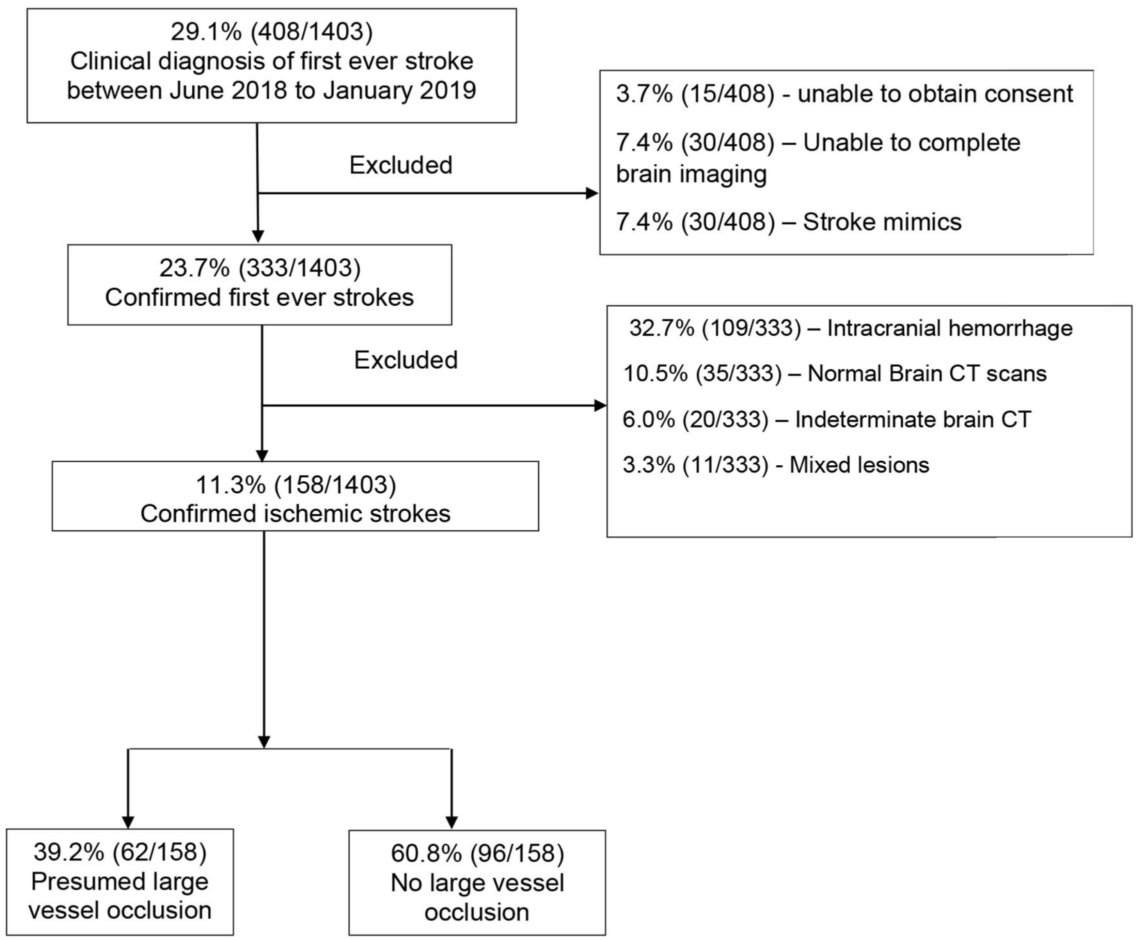

FIGURE 2 | Consort diagram showing the flow of participants.

included hypertension, increased waist-to-hip ratio (a surrogate for obesity), increased total cholesterol, triglycerides, and atrial fibrillation. On multivariate analysis, only hypertension and increased waist-to-hip ratio remained statistically significant, which are known risk factors for both intracranial and extracranial vessel atherosclerosis (23). It is notable that our study showed a relatively lower prevalence of atrial fibrillation of 16.6% in the presumed LVO group and 5.3% in the non-LVO group when compared to a meta-analysis of 5 randomized trials that looked at the efficacy of endovascular thrombectomy over standard medical care where the prevalence of atrial fibrillation was noted to be 33% (24). A similar high prevalence of atrial fibrillation was noted in the DAWN trial with 40% in the mechanical thrombectomy arm and 24% in the medical therapy arm (25). Several factors might explain the lower prevalence of atrial fibrillation in this setting that included genetic predisposition, under surveillance resulting in lower detection of occult or paroxysmal atrial fibrillation using conventional resting ECG that was utilized as a part of routine clinical care and poor access to healthcare (26, 27). Stroke is preventable in SSA by ensuring early detection and control of modifiable risk factors, related to urbanization and lifestyle changes. Therefore, efforts need to be centered on promoting low-cost interventions to reduce this looming epidemic of non-communicable diseases (NCDs) since a stroke in Tanzania is associated with substantial morbidity and mortality, impacting the country's economy (28). The involvement of the MCA as the most common site for presumed LVO is in concordance with global trends (29).

The mainstay for the management of LVO is through endovascular interventions, which have been associated with improved outcomes; however, the majority of these clinical trials on the efficacy of thrombectomy have been done in HIC (9, 10). The barriers in LMIC that lead to inequity in endovascular care are mainly due to the high cost of the procedure, lack of endovascular specialists, and late times to presentation, among others. This was shown in the Mexican Endovascular Reperfusion Registry (MERR), which supported the effectiveness of thrombectomy but noted that treatment was mainly feasible in private hospitals (30). Similarly, the RESILIENT trial conducted in Brazil was the first clinical trial that evaluated the benefits of thrombectomy in patients with LVO

TABLE 1 | Comparison of baseline characteristics and risk factors.

Variable	Presumed LVO (*n* = 62)	Non-LVO (*n* = 96)	*p*-value
Age (mean ± SD)	62.1 ± 17.4	58.0 ± 15.9	0.44
Female	39 (40.6%)	57 (59.3%)	0.81
Admission NIHSS (mean ± SD)	21.9 ± 8.4	20.4 ± 8.7	0.50
Vascular territory			
MCA	44 (70.9%)	32 (33.3%)	–
ACA	2 (3.22%)	3 (3.12%)	
ACA + MCA	5 (8.06%)	0	
Basilar/PCA	11 (17.7%)	8 (8.33%)	
Vertebral/PICA	0	2 (2.08%)	
Multiple	0	6 (6.25%)	
Lenticulostriate	0	11 (11.4%)	
Other**	0	34 (35.4%)	
Vascular territory			
MCA	44 (71.0%)	32 (33.3%)	<0.0001*
Other vascular territories	18 (29.0%)	64 (66.0%)	
Last seen normal to hospital arrival (in days)	1.71 ± 1.68	1.80 ± 1.81	0.52
Last seen normal to picture (in days)	1.87 ± 1.80	1.83 ± 2.0	0.32
Glucose - RBG in mmol/l	8.20 ± 2.55	7.55 ± 2.41	0.63
Lipids - Total cholesterol (mg/dl)	220.1 ± 95.9	188.9 ± 56.2	<0.0001*
Low-density lipoproteins (mg/dl)	89.6 ± 55.6	74.7 ± 54.0	0.80
High-density lipoproteins (mg/dl)	48.1 ± 25.5	52.2 ± 21.6	0.19
Triglycerides (mg/dl)	138.4 ± 103.2	117.1 ± 56.9	<0.0001*
Waist-to-hip ratio Increased	54(87.0%)	56 (58.3%)	<0.0001*
Hypertension	49 (79.0%)	47 (48.9%)	<0.0001*
Diabetes	10 (16.1%)	19 (19.7%)	0.55
Atrial fibrillation	9 (16.6%)	4 (5.26%)	0.05
HIV	1 (1.61%)	7 (7.29%)	0.16
Mitral stenosis	1 (1.66%)	1 (1.04%)	0.76
Carotid bruit	2 (3.22%)	2 (2.08%)	0.67
Cigarette smoking	5 (8.1%)	7 (7.29%)	0.85
Alcohol	18 (29.0%)	16 (16.6%)	0.08
Oral contraceptives	5 (13.5%)	16 (27.5%)	0.08

**Statistically significant p-value; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; RBG, random blood glucose. **Watershed infarcts, pontine perforator infarct, thalamoperforator infarct and bilateral thalamic infarcts.*

TABLE 2 | Predictors of presumed large vessel occlusion.

Variable	Unadjusted OR (95% CI)	*p*-value	Adjusted* OR (95% CI)	*p*-value
Hypertension	3.93 (1.87–8.24)	0.0004	5.74 (1.74–18.9)	0.004
Atrial fibrillation	3.60 (1.025–12.6)	0.04	2.75 (0.28–27.1)	0.38
waist-to-hip ratio	4.82 (2.04–11.4)	0.0004	7.20 (1.83–28.2)	0.005
Triglycerides	0.997 (0.992–1.001)	0.12	0.998 (0.990–1.007)	0.71
Total cholesterol	0.994 (0.990–0.999)	0.02	0.993 (0.985–1.001)	0.08

**Model adjusted with age, gender, vascular territory, and statistically significant medical comorbidities: hypertension, atrial fibrillation, waist-to-hip ratio, total cholesterol, and triglycerides.*

TABLE 3 | A comparison of outcomes among participants with and without presumed LVO.

Outcomes	Presumed LVO	Non-LVO	*p*-value
Midline shift	10 (6.32%)	0	–
Hemorrhagic transformation categories			–
Hemorrhagic infarction type 1 (HI1)	23 (37.0)	3 (3.1%)	
Hemorrhagic infarction type 2 (HI2)	5 (8.0%)	2 (2.1%)	
Parenchymal hematoma type 1 (PH1)	1 (1.61%)	0	
Parenchymal hematoma type 2 (PH2)	0	0	
Overall Hemorrhagic Transformation	29 (46.7%)	5 (5.20%)	<0.0001
mRS* categories at 24 h			
0–3	(1.61%)	4 (4.16%)	0.33
4–6	61 (98.3%)	92 (95.8%)	
mRS* categories at 30-days	Frequency Missing: 3		
0–3	8 (12.9%)	17 (18.3%)	0.50
4–6	54 (87.1%)	76 (81.7%)	
mRS* categories at 1-year	Frequency Missing: 5		
0–3	9 (15%)	23 (24.7%)	0.12
4–6	51 (85%)	70 (75.3%)	

**mRS, modified Rankin Scale.*

in LMIC presenting within 8 h from stroke symptoms (31). Their results showed a better functional outcome at 90 days among the LVO group receiving endovascular therapy. Muhimbili National Hospital (MNH) and MAMC, where this study was conducted, can administer IV thrombolysis to patients presenting with an acute coronary syndrome, which will potentially translate to IV thrombolysis for acute ischemic stroke; however, we currently do not have mechanical thrombectomy capability in Tanzania. The poor functional outcomes in this cohort could be attributed to the severity of the stroke. It is notable that both groups had similar NIHSS scores (mean NIHSS score >20), which is a matter of concern, especially in the non-LVO group. One possible explanation for the severe symptoms in the non-LVO group is the anatomical location of the infarcts, which included watershed infarcts, pontine perforator infarcts, thalamoperforator infarcts, and bilateral thalamic infarcts. Further, reports have indicated that NIHSS scores can predict the presence of LVO among patients with ischemic stroke arriving at an early time window (within the first hours) but predicts less in late presenting patients (32). The latter was the case for this study and given the fact that our study did not use angiographic techniques to confirm the diagnosis of LVO; this could be another possible explanation for this discrepancy. Nonetheless, the severity of stroke also has multifactorial explanations that include lack of stroke readiness in the healthcare infrastructure and referral networks and lack of community awareness regarding stroke symptoms and signs translating into delays and progression of stroke syndromes. In our cohort, the time from stroke onset to presentation was suboptimal in both groups, with a mean of 1.87 days in the presumed LVO group vs. 1.83 days in the non-LVO group, $p < 0.32$ and no patients arriving within the first 8 h. This delay represents a critical barrier to adopting endovascular interventions and IV thrombolysis in our setting. Therefore, it is a call for prehospital referral strengthening approaches to facilitate transferring potential strokes to a stroke-capable facility.

Also importantly, there were high rates of hemorrhagic transformation on CT head statistically seen more in participants with presumed LVO (46.7% vs. 5.2%, $p < 0.0001$, respectively), even though most of these patients were not parenchymal hematomas (HI 1 and 2). This high rate is multifactorial and could represent the severity of reperfusion injury and uncontrolled hypertension; this highlights the need for specialized stroke units for peri-procedural management of these high-risk patients regardless of whether they undergo mechanical thrombectomy. This also highlights the need for a multidisciplinary approach with the involvement of neurosurgeons to facilitate decompressive hemicraniectomy to manage malignant cerebral edema and hemorrhagic transformation (33).

Finally, there was a higher rate of poor outcomes at 1 year (defined as mRS 4–6) in the presumed LVO group (85%) when compared with the non-LVO group (75.3%; $p = 0.12$), which is concerning but representative of global trends (1, 2). Similarly, 1-year mortality was higher in the presumed LVO group at 80% when compared with the non-LVO group at 73.1%. The overall high rate of poor outcomes in both groups represents a more significant problem with regard to post-stroke care and lack of rehabilitation in LMIC, particularly in SSA. Studies in SSA have previously demonstrated a low implementation of secondary preventive measures following stroke and limited access to rehabilitation services impacting the overall quality of life of these patients (34, 35).

Our study had the following strengths: it provides actionable information given the lack of similar data regarding the burden of presumed LVO in local and regional stroke demographics in LMIC in general and Tanzania as a representative country in SSA in particular. With the development of the MAMC, a state-of-the-art academic hospital sub-serving East and Central Africa, there is potential for more acute therapies for ischemic stroke reperfusion to be introduced into the local neurological landscape. Therefore, the results of this study show important challenges that need to be overcome, as highlighted above. Our study compared presumed large vessel and non-large vessel strokes enabling a unique analysis between these two entities in SSA, while previous data have only looked at overall ischemic strokes.

Finally, the high inter-rater Kappa boosts confidence in the reproducibility of these findings. Given previous infrastructural unavailability of CT/MR angiographic techniques to diagnose and manage LVOs, this study uses the next best method to provide preliminary data that will be the necessary stepping stone to generate discussions among different stakeholders to establish the mechanisms for introducing non-invasive and invasive angiography to diagnose and treat acute ischemic strokes.

This study is limited by the fact that the diagnosis of LVO was made without the use of angiographic techniques, which is the gold standard for this diagnosis. There are reliable data to suggest that the diagnosis of LVO can be inferred from non-angiographic CT studies based on contiguous hypodensity that can be attributed to the involved vascular territory and a compatible clinical syndrome (15, 16). In addition, given later times to presentation/imaging in our cohort, the reliability of NCCT findings increases with time (36, 37). However, it is entirely possible that there were patients in the non-LVO group that had not yet developed contiguous lobar hypodensities due to slow infarct progression; this technique, therefore, has the potential to underdiagnose LVO. Despite the late presentation of our patients (time from the onset of stroke symptoms to hospital arrival of (1.74 days), excluding the 35 patients with normal NCCT head might have underestimated the proportion of presumed LVO. Additionally, our study did not record specific neurological characteristics of these patients.

CONCLUSION

There is a high burden of presumed LVO associated with high rates of 1-year morbidity and mortality. Concerted efforts are required to promote cost-effective preventive strategies to combat the looming epidemic of non-communicable diseases and a call for adopting endovascular interventions to reduce morbidity and mortality.

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 Muhimbili University of Health and Allied Sciences Institutional Review Board approval number DA.287/298/01A/. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM, RA, FL, MM, and FS conceptualized and designed the study and drafted the initial manuscript. MC carried out the data analysis and interpreted the results. SM, RA, MC, MM, FS, PM, KK, KT, FL, GR, VG, and AM critically reviewed and revised the final manuscript. All authors contributed to the article and approved the submitted version.

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Persistence of drug therapy is associated with ischemic stroke and other vascular events in high-risk stroke population

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The high-risk stroke populations are significantly associated with an increased risk of stroke or other vascular events. Although proven primary and secondary stroke prevention medications are available, persistent use is required to be effective. However, the persistence of drug therapy and its association with outcomes in the high-risk stroke population have received limited study in China. Hence, according to the China National Stroke Screening Survey (CNSSS) program in 2015, we performed this multicenter population-based cross-sectional survey and prospective cohort study in Sichuan of southwestern China. The residents aged $\geq$ 40 years volunteered to participate in a face-to-face survey in 8 communities. Subjects with at least three of eight stroke-related risk factors or a history of stroke were defined as high-risk stroke population. The interviewers recorded individuals' medications at a face-to-face survey, and all the high-risk stroke population was followed up for 4.7 years. The persistence of antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics for stroke was evaluated. The primary outcome was new stroke. Secondary outcomes included new composite vascular events of stroke, myocardial infarction, and death during follow-up periods. Among 16,892 participants, 2,893 (17.1%) participants were high-risk stroke population and 2,698 (93.3%) participants completed to follow-up. The 4.7-year persistence of therapy rate of antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics was 38.0%, 39.9%, 43.9%, and 59.8%, respectively. The total persistence of therapy rate for antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics was 47.6% (136/286) in patients with hypertension, diabetes, dyslipidemia, and stroke at the same time. During the 4.7-year follow-up, there were 118 (4.4%) new ischemic stroke, 24 (0.9%) hemorrhagic stroke, 53 (2.0%) myocardial infarctions, and 33 (1.2%) deaths. After adjusting for the covariates, 4.7-year persistence of antihypertensives, hypoglycemics, lipid-lowering therapy, antithrombotics, and total persistence was independently associated with less new ischemic stroke and less new composite vascular events. Thus, more effective public education and efforts to understand and enhance the persistence of drug therapy are crucial to improve population health and decrease stroke and other vascular events for the high-risk stroke population.

KEYWORDS

high risk stroke population, stroke, risk factors, health care, medication compliance, outcomes

Introduction

Stroke is a leading cause of adult mortality and disability, and it has the greatest stroke burden in the world with a 39.3% risk of lifelong stroke for people over 25 years in China (1, 2). In the past few decades, the incidence of stroke has decreased because of good health services and effective prevention of risk factors for stroke in developed countries. However, the incidence of stroke has increased because of insufficiently good health services and strategies for primary prevention of stroke in developing countries (3). According to the report from the World Health Organization (WHO), the incidence of stroke is still increasing with an annual rate of 8.7% in China (4). There are approximately 3 million new stroke cases every year in China (1, 5).

In the last three decades, China has experienced rapid sociodemographic changes and health transitions, and the epidemiological features for stroke have likely changed in China (1, 5, 6). There was a large increase in the prevalence of hypertension, dyslipidemia, and diabetes mellitus (5–8), these were very common and modifiable risk factors for stroke, and all of these may affect stroke burden (1, 6). The incidence of stroke is significantly higher in the high-risk stroke population (multiple risk factors for stroke) than in those individuals with health or low-risk stroke population (1–3, 7); this indicates that the primary prevention and control of risk factors for stroke are very important to decrease the incidence of stroke.

Hypertension, dyslipidemia, diabetes mellitus, and history of stroke are the most important risk factors for stroke. Several medications, such as antihypertensives, lipid-lowering medications, hypoglycemics, and antithrombotics, had been demonstrated to reduce the risk of stroke among specific patient subgroups (9). However, the treatment rate, standard-reaching rate, and persistence of drug therapy rate for hypertension, diabetes mellitus, and dyslipidemia are significantly lower in China than in high-income countries (10, 11). Drugs don't work in patients who don't take them (12), and medications' non-persistence is very common and is associated with adverse outcomes in patients with coronary artery disease (13). Studies from secondary prevention for stroke have shown that implementation and persistence of secondary prevention medications after acute ischemic stroke are effective for preventing recurrent stroke (14, 15). In 2003, a WHO statement suggested that improved medication adherence "may have a far greater impact on the health of the population than any improvement in specific medical treatments" (13). Thus, effective control of risk factors requires more effective public education and greater responsibilities of individuals. These may increase the awareness of risk factors for stroke and the persistence of drug therapy (7, 11). However, the persistence of drug therapy and its association with outcomes in the high-risk stroke population have received limited study in China.

According to the China National Stroke Screening Survey (CNSSS) program (1), we performed a community-based high-risk stroke population survey in 8 communities in Sichuan of southwestern China (6). Using the data from the survey, we aimed to (1) investigate the persistence of drug therapy in high-risk population for stroke and (2) identify the association between persistence of drug therapy and outcomes during follow-up.

Methods

Study design and participants

This multicenter population-based cross-sectional survey and prospective cohort study was part of the CNSSS and was carried out in the Sichuan of southwestern China from May 2015 to January 2020. The study protocol was reviewed and approved by the Ethics Committee of participating hospitals (People's Hospital of Deyang City, the Affiliated Hospital of Southwest Medical University, and Suining Central Hospital), and informed consent was obtained from each participant during recruitment.

The cross-sectional survey was conducted in 8 communities of Sichuan from May 2015 to September 2015. The 8 communities were selected using the cluster randomization method. The detailed procedures for recruitment of participants and evaluation of risk factors are described in our previous article (6, 16) and Figure 1. In brief, all residents who aged $\geq$ 40 years and had lived in the county for at least

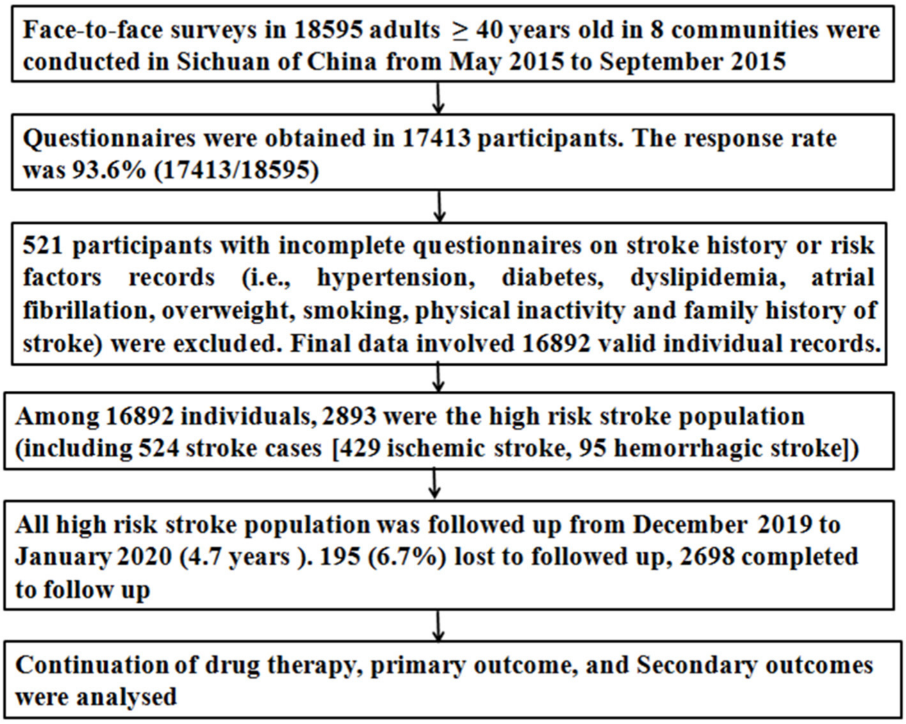

FIGURE 1
Flowchart in this study.

6 months were initially screened using a structured face-to-face questionnaire by interviewers. The questionnaire included demographic characteristics [e.g., age, gender, education level, employment, payment pattern of health insurance (urban basic medical insurance schemes, new rural cooperative medical schemes, and commercial insurance), and income], stroke-related behavioral factors (drinking, smoking, exercise habits, and diet), personal and family medical history of stroke, chronic diseases [hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation (AF)], current medications (antihypertensives hypoglycemics, lipid-lowering medications, and antithrombotics), and physical examination (height, weight, and resting blood pressure). Stroke history and stroke types (ischemic stroke and hemorrhagic stroke) were established by a combination of self-reporting and the judgment of a physician or neurologist according to neuroimaging. The eight risk factors for stroke, including overweight/obesity, smoking, physical inactivity, family history of stroke, hypertension, diabetes mellitus, dyslipidemia, and AF, were evaluated (6, 16). Subjects with at least three of the aforementioned eight stroke-related risk factors or a history of stroke were classified as high-risk population for stroke (6, 16, 17), otherwise, defined as low-risk population for stroke.

Assessment of persistence of drug therapy

The interviewers asked the individuals who were taking medicines to continue medications at a face-to-face survey. The persistence of drug therapy was evaluated in the high-risk stroke population. In this study, we focused on several evidenced-based prevention medications including antihypertensives for hypertension (e.g., calcium-channel blockers, beta-blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and diuretics), hypoglycemics for diabetes mellitus (i.e., oral diabetic agents or insulin), antithrombotics for stroke (antiplatelet and anticoagulants), and lipid-lowering medications (statins or fibrates). Medication information at a face-to-face survey was used as the reference anchor for evaluating the persistence of drug therapy. To ensure proper persistence of drug therapy, trained research nurses were assigned to supervise the individuals' medication taking and advise the individuals to continue medications during follow-up periods once a year by telephone. The individuals in the high-risk stroke population were contacted from December 2019 to January 2020 (4.7 years after the face-to-face survey) using the telephone by trained research nurses or personnel.

The persistence of drug therapy was evaluated at 4.7 years after the face-to-face survey. In this study, 4.7-year persistence of drug therapy was defined as medication(s) continuation from a face-to-face survey to 4.7 years after the face-to-face survey (18, 19). Subjects who were prescribed an individual medication at a face-to-face survey but failed to take that medication at 4.7 years after the face-to-face survey or at every single point of telephone call each year were defined as "non-persistence." The patients who had not received treatment at the survey but then received treatment during follow-up were also defined as "non-persistence." However, subjects were considered "persistence," if there was a switch of medication within the same class. The medication class included antihypertensives, hypoglycemics, antithrombotics, and lipid-lowering medications.

Outcomes

All the high-risk stroke population was followed up from December 2019 to January 2020 by telephone interview and by reviewing the medical charts of each participant. The follow-up period was 4.7 years after the face-to-face survey. The primary outcome was new ischemic or hemorrhagic stroke during the follow-up. Stroke was defined as an acute focal neurological deficit that lasted for more than 24 h and was confirmed by brain computed tomography scan or magnetic resonance imaging scan. Secondary outcomes included new composite vascular events of stroke, myocardial infarction, or death from cardio-cerebral vascular cause during follow-up. Myocardial infarction was confirmed by the symptom of prolonged angina (>30 min), creatine kinase elevation, and electrocardiographic evidence of infarction (20). The researchers for outcome assessment were blinded to the status of persistence of drug therapy. For those individuals who reached at least one of the outcomes, a medical chart review was initiated to determine whether the event met the definitions described earlier.

Statistical analysis

The sample size necessary for this study was calculated, and the detailed calculation for the sample size was described in our previous article (6). Finally, 18,595 participants aged $\geq$ 40 years participated in this survey (Figure 1).

Descriptive analyses were conducted to determine the distribution of the demographic data and risk factors in the study population using SPSS version 17.0 (SPSS Inc. New York, New York, United States). Categorical variables were presented as percentages and were compared using χ^2 tests between groups. If continuous variables were normally distributed, they were expressed as mean $\pm$ standard deviation and were compared using the Student's *t*-test between groups. Otherwise, they were analyzed by the Wilcoxon rank-sum test. A multivariate logistic regression model was used to analyze the influence of the persistence of drug therapy on ischemic stroke and secondary outcomes. The variables that were statistically significant at $P < 0.2$ between patients with and without outcomes in the univariate analysis were entered into the multivariate logistic regression models. The results were reported as odds ratio (OR) with 95% confidential intervals (CIs).

All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of the high-risk stroke population

A total of 18,595 participants volunteered to participate in a face-to-face survey, questionnaires were obtained from 17,413 participants [the response rate was 93.6% (17,413/18,595)], and final data involved 16,892 valid individual records (Figure 1). Among 16,892 individuals, 2,893 (17.1%) were the high-risk stroke population. All the 2,893 high-risk stroke population was followed up at 4.7 years after a face-to-face survey, 2,698 completed to follow-up, and 195 (6.7%) lost to follow-up. The baseline characteristics of the 2,698 high-risk stroke population in a face-to-face survey are shown in Table 1. In the 2,698 high-risk stroke population, 1,949 (72.2%) had hypertension, 721 (26.7%) had diabetes mellitus, 751 (27.8%) had dyslipidemia, 487 (18.1%) had a history of stroke (399 were ischemic stroke and 88 were hemorrhagic stroke), and 378 had hypertension, diabetes, dyslipidemia, and stroke at the same time at a face-to-face survey.

Persistence of drug therapy in the high-risk stroke population

At a face-to-face survey, 996 (51.1%) patients with hypertension received antihypertensive treatment, 444 (61.6%) patients with diabetes mellitus received hypoglycemics, and 374 (49.8%) patients with dyslipidemia received lipid-lowering therapy; however, all patients with a history of stroke received antithrombotics. Among the 378 participants with hypertension, diabetes, dyslipidemia, and stroke at the same time, 286 (75.7%) received antihypertensives, hypoglycemic, lipid-lowering therapy, and antithrombotics at the same time. At 4.7 years after the survey, only 378 (19.4%) patients with hypertension continued taking antihypertensives, 177 (24.5%) patients with diabetes mellitus continued taking hypoglycemics, 164 (21.8%) patients with dyslipidemia continued taking lipid-lowering medications, 291 (75.2%) patients with a history of stroke continued taking antithrombotics, and 136 (36.%) patients with hypertension, diabetes, dyslipidemia, and

TABLE 1 Baseline characteristics of the 2,698 high-risk stroke population at a face-to-face survey.

Characteristics	$N = 2{,}698$
Age ≥ 60 y (*n*, %)	1755 (65.0)
Male (*n*, %)	1,288 (47.7)
Rural (*n*, %)	1,456 (54.0)
Education (*n*, %)	
Junior middle school or below	2,345 (86.9)
Senior middle school or above	353 (13.1)
Overweight/obesity (*n*, %)	1,436 (53.2)
Smoking (*n*, %)	714 (26.5)
Physical inactivity (*n*, %)	1,647 (61.0)
Hypertension (*n*, %)	1,949 (72.2)
Diabetes (*n*, %)	721 (26.7)
Dyslipidemia (*n*, %)	751 (27.8)
Atrial fibrillation (*n*, %)	71 (2.6)
Family history for stroke (*n*, %)	479 (17.8)
History of ischemic stroke (*n*, %)	399 (14.8)
History of hemorrhagic stroke (*n*, %)	88 (3.3)
Hypertension, diabetes, dyslipidemia and stroke at same time	378 (14.0)

stroke continued taking antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics at the same time prescribed at a face-to-face survey. The persistence of therapy rate of antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics was 38.0% (378/996), 39.9% (177/444), 43.9% (164/374), and 59.8% (291/478), respectively (Table 2). The total persistence of therapy rate for antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics was 47.6% (136/286) in patients with hypertension, diabetes, dyslipidemia, and stroke at the same time (Table 2).

Outcomes and their association with persistence of drug therapy

In a total of the 2,893 high-risk stroke population, 2,698 (93.3%) completed a 4.7-year follow-up, and there were 118 (4.4%) new ischemic stroke, 24 (0.9%) hemorrhagic stroke, 53 (2.0%) myocardial infarctions, and 33 (1.2%) deaths. Compared with the patients without outcomes, the patients with outcomes were older and had a higher history of stroke and a lower rate of antihypertensive therapy ($P < 0.05$, Table 3). However, there was no significant difference in other risk factors between patients with and without outcomes ($P > 0.05$, Table 3).

The association between 4.7-year persistence of drug therapy and clinical outcomes is shown in Table 4. Compared with patients with 4.7-year non-persistence, patients with 4.7-year persistence of antihypertensives had a significantly lower rate of new ischemic stroke (persistence vs. non-persistence: 1.3% vs. 4.2%, $P = 0.013$) and total new composite vascular events (persistence vs. non-persistence: 3.2% vs. 8.4%, $P = 0.001$). Compared with patients with 4.7-year non-persistence of lipid-lowering medications, patients with 4.7-year persistence had a significantly lower rate of total new composite vascular events (persistence vs. non-persistence: 3.7% vs. 10.0%, $P = 0.017$). Compared with patients with 4.7-year non-persistence of antithrombotics, patients with 4.7-year persistence had a significantly lower rate of new ischemic stroke (persistence vs. non-persistence: 5.8% vs. 15.8%, $P < 0.001$) and total new composite vascular events (persistence vs. non-persistence: 14.8% vs. 27.0%, $P < 0.001$). Furthermore, the total persistence of antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics in patients with hypertension, diabetes, dyslipidemia, and stroke at the same time was significantly associated with a lower rate of new ischemic stroke (persistence vs. non-persistence: 0.74% vs. 6.7%, $P = 0.009$) and total new composite vascular events (persistence vs. non-persistence: 2.2% vs. 12.7%, $P < 0.001$). However, there was no significant difference in outcomes between patients with compliance and non–compliance of hypoglycemics by univariate analysis ($P > 0.05$, Table 4).

Effect of persistence of drug therapy on outcomes by multivariable regression analysis

The effect of 4.7-year persistence of drug therapy on new ischemic stroke and new total composite vascular events was evaluated using multivariable regression analysis. Variables entered the models were the variables showed a significant association ($P < 0.2$) with new ischemic stroke and total new composite vascular events on univariate analysis. After adjusting for these covariates, 4.7-year persistence of antihypertensives, hypoglycemics, lipid-lowering therapy, antithrombotics, and total persistence was significantly independently associated with less new ischemic stroke (OR, 0.81, 95% CI: 0.66–0.94, $P < 0.001$; OR, 0.92, 95% CI: 0.76–0.97, $P = 0.029$; OR, 0.90, 95% CI: 0.82–0.95, $P = 0.029$; OR, 0.69, 95% CI: 0.64–0.89, $P < 0.001$; OR, 0.69, 95% CI: 0.62–0.87, $P < 0.001$, respectively, Table 5) and less total new composite vascular events (OR, 0.76, 95% CI: 0.63–0.92, $P < 0.001$; OR, 0.92, 95% CI: 0.75–0.97, $P = 0.027$; OR, 0.85, 95% CI: 0.77–0.95, $P = 0.015$; OR, 0.73, 95% CI: 0.62–0.92, $P < 0.001$; OR, 0.70, 95% CI: 0.61–0.89, $P < 0.001$, respectively, Table 6).

Discussion

In this study, using our data from a community-based study in Sichuan of southwestern China (6, 16, 21), we

TABLE 2 Persistence of medications in the 2,698 high-risk stroke population.

	Hpertension ($n = 1,949$)	Diabetes ($n = 721$)	Dyslipidemia ($n = 751$)	History of stroke ($n = 487$)	Hpertension, diabetes, dyslipidemia and stroke at same time ($n = 378$)
Treatment at survey (*n*, %)	996 (51.1)	444 (61.6)	374 (46.2)	487 (100.0)	286 (75.7)
Treatment at 4.7 years after survey (*n*, %)	378 (19.4)	177 (24.5)	164(21.8)	291(59.8)	136 (36.0)
Persistence of therapy rate (*n*, %)	38.0 (378/996)	39.9 (177/444)	43.9 (164/374)	59.8 (291/487)	47.6 (136/286)

TABLE 3 Comparison of patients with and without outcomes during follow-up periods.

Characteristics	Patients with outcomes ($n = 192$)	Patients without outcomes ($n = 2,506$)	*P* value
Age ≥60y (*n*, %)	138 (71.9)	1,617 (64.5)	0.041
Male (*n*, %)	89 (46.3)	1,199 (47.8)	0.705
Rural (*n*, %)	104 (54.2)	1,352 (54.0)	0.983
Education (*n*, %)			
Junior middle school or below	169 (88.0)	2,176 (86.8)	0.664
Senior middle school or above	23 (12.0)	330 (13.2)	
Overweight/obesity (*n*, %)	107 (55.7)	1,329 (53.0)	0.512
Smoking (*n*, %)	57 (29.7)	657 (26.2)	0.294
Physical inactivity (*n*, %)	114 (59.4)	1,533 (61.2)	0.641
Hypertension (*n*, %)	136 (70.8)	1,813 (72.3)	0.672
Antihypertensive drugs (*n*, %)	52 (27.1)	944 (37.7)	0.003
Diabetes (*n*, %)	59 (30.7)	662 (26.4)	0.203
Hypoglycemic drugs (*n*, %)	37 (19.3)	407 (16.2)	0.986
Dyslipidemia (*n*, %)	57 (29.7)	694 (27.7)	0.571
Lipid lowering therapy (*n*, %)	23 (12.0)	351 (14.0)	0.148
Atrial fibrillation (*n*, %)	4 (2.1)	67 (2.7)	0.641
Family history for stroke (*n*, %)	40(20.8)	439 (17.5)	0.246
History of stroke (*n*, %)	82(42.7)	405(16.2)	<0.001

found that the treatment rate for hypertension, diabetes mellitus, and dyslipidemia was very low, and the persistence of antihypertensives, hypoglycemics, lipid-lowering drugs, and antithrombotics was significantly associated with a decreased risk of new ischemic stroke and total new composite vascular events in the high-risk stroke population.

Hypertension, diabetes mellitus, dyslipidemia, and stroke are the most important risk factors for stroke or stroke recurrence in China (1, 6, 7). Antihypertensives, hypoglycemics, lipid-lowering therapy, and antithrombotics (for stroke) had been demonstrated to reduce the risk of stroke or other vascular events (9). However, the treatment rate and standard-reaching rate for hypertension, diabetes mellitus, and dyslipidemia are significantly lower in China than in high-income countries (10, 11). The proportion of people whose hypertension is controlled is under 20% in China; similarly, dyslipidemia and diabetes are poorly controlled in China (10, 11, 22). In this survey, we found that the proportion of treatment for the patients with hypertension, diabetes mellitus, and dyslipidemia was 51.1%, 61.6%, and 46.2% in a face-to-face survey, respectively, which was considerably lower than in the United Kingdom or the United States (23). Thus, improved control of these factors requires more effective public education and greater responsibilities of individuals in China.

"Drugs don't work in patients who don't take them" (13). The persistence of drug therapy is critical and is a common and refractory problem. Medication non-persistence is very common and is associated with adverse outcomes and higher costs of care in the world (12, 13, 24). Improved medication adherence may have a far greater impact on the health of the population than any improvement in specific medical treatments (12). Previous studies on the persistence of

TABLE 4 Persistence of drug therapy with outcomes (*n*, %).

	Ischemic stroke	Hemorrhagic stroke	Myocardial infarction	Death	Total
Hypertension					
No (*n* = 749)	32 (4.3)	7 (0.9)	19 (2.5)	6 (0.8)	64 (8.5)
Yes (*n* = 1,949)	86 (4.4)	17 (0.9)	34 (1.74)	27 (1.4)	164 (8.4)
P value	0.943	0.951	0.197	0.211	0.910
Non-treatment (*n* = 953)	55 (5.8)	11 (1.2)	20 (2.1)	14 (1.5)	100 (10.5)
Treatment (*n* = 996)	31 (3.1)	6 (0.6)	14 (1.4)	13 (1.3)	64 (6.6)
P value	0.004	0.190	0.243	0.757	0.002
Non-persistence (*n* = 618)	26 (4.2)	5 (0.8)	11 (1.8)	10 (1.6)	52 (8.4)
Persistence (*n* = 378)	5 (1.3)	1 (0.3)	3 (0.8)	3(0.8)	12 (3.2)
P value	0.013	0.417	0.271	0.390	0.001
Diabetes					
No (*n* = 1,977)	81 (4.1)	18 (0.9)	37 (1.9)	22 (1.1)	158 (8.0)
Yes (*n* = 721)	37 (5.1)	6 (0.8)	16 (2.2)	11 (1.5)	70 (9.7)
P value	0.707	0.976	0.573	0.397	0.167
Non-treatment (*n* = 277)	15 (5.4)	3 (1.1)	5 (1.8)	4 (1.4)	27 (9.7)
Treatment (*n* = 444)	22 (5.0)	3 (0.7)	11 (2.5)	7 (1.6)	43 (9.7)
P value	0.785	0.680	0.614	0.100	0.999
Non-persistence (*n* = 267)	17 (6.4)	2 (0.7)	7 (2.6)	5 (1.9)	31 (11.6)
Persistence (*n* =1 77)	5 (2.8)	1 (0.6)	4 (2.3)	2 (1.1)	12 (6.8)
P value	0.118	0.100	0.100	0.708	0.091
Dyslipidemia					
No (*n* = 1,947)	81 (4.2)	18 (0.9)	36 (1.8)	23 (1.2)	158 (8.1)
Yes (*n* = 751)	37 (4.9)	6 (0.8)	17 (2.3)	10 (1.3)	70 (9.2)
P value	0.394	0.768	0.495	0.722	0.304
Non-treatment (*n* = 377)	23 (6.1)	4 (1.1)	11 (2.9)	5 (1.3)	43 (11.4)
Treatment (*n* = 374)	14 (3.7)	2 (0.5)	6 (1.6)	5 (1.3)	27 (7.2)
P value	0.136	0.686	0.226	0.100	0.046
Non-persistence (*n* = 210)	11 (5.2)	2 (1.0)	5(2.4)	3(1.4)	21(10.0)
Persistence (*n* = 164)	3 (1.8)	0 (0.0)	1(0.6)	2(1.2)	6(3.7)
P value	0.102	0.505	0.234	0.100	0.017
Antithrombotics					
Non-persistence (*n* = 196)	31 (15.8)	3 (1.5)	12 (6.1)	7 (3.6)	53 (27.0)
Persistence (*n* = 291)	17 (5.8)	8 (2.7)	11 (3.8)	7 (2.4)	43 (14.8)
P value	<0.001	0.378	0.211	0.473	<0.001
Total persistence for antihypertensives, hypoglycemics, lipid lowering medications and antithrombotics at same time					
Yes (*n* = 136)	1 (0.74)	0 (0.0)	1 (0.74)	1 (0.74)	3 (2.2)
No (*n* = 150)	10 (6.7)	2 (1.3)	4 (2.7)	3 (2.0)	19 (12.7)
P value	0.009	0.192	0.223	0.391	<0.001

secondary prevention medications after acute ischemic stroke or transient ischemic attack (TIA) in the Chinese population have been reported (15, 25). The study from the China National Stroke Registry (CNSR) showed that only 63.6% of patients with acute ischemic stroke or TIA continued taking all the secondary prevention medications prescribed at hospital discharge for 3 months after discharge. By medication class, 3-month compliance was found highest for diabetic medications (82.7%), followed by antiplatelet agents (80.4%) and antihypertensives (79.2%), and lowest for warfarin (31.7%) (15). Another study from China found that antihypertensive use was well-maintained, whereas the compliance rate of antiplatelet was 66% at 12 months after stroke (25). These studies from China were in accordance with other international studies (26, 27).

TABLE 5 Multivariable regression analysis of risk factors for new ischemic stroke during follow-up.

Factor	OR	95% CI	*P* value
Age ≥ (60 years)	1.04	0.77–1.62	0.235
Antihypertensives for hypertension	0.94	0.88–1.21	0.362
Persistence of antihypertensives	0.81	0.66–0.94	<0.001
Persistence of hypoglycemic	0.92	0.76–0.97	0.029
Lipid lowering therapy for dyslipidemia	0.95	0.93–1.19	0.422
Persistence of lipid lowering therapy	0.90	0.82–0.95	0.029
History of stroke	2.23	1.37–5.18	<0.001
Persistence of antithrombotics for stroke	0.69	0.64–0.89	<0.001
Total persistence for antihypertensives, hypoglycemics, lipid lowering medications and antithrombotics	0.68	0.62–0.87	<0.001

OR, odds ratio; CI, confidence interval.

TABLE 6 Multivariable regression analysis of risk factors for total new composite vascular events during follow-up.

Factor	OR	95% CI	*P* value
Age ≥ (60 years)	1.13	0.94–2.56	0.118
Antihypertensives for hypertension	0.91	0.86–1.24	0.257
Persistence of antihypertensives	0.76	0.63–0.92	<0.001
Diabetes	1.12	0.92–3.13	0.214
Persistence of hypoglycemic	0.92	0.75–0.97	0.027
Lipid lowering therapy for dyslipidemia	0.95	0.89–1.08	0.214
Persistence of lipid lowering therapy	0.85	0.77–0.95	0.015
History of stroke	2.52	1.61–6.06	<0.001
Persistence of antithrombotics for stroke	0.73	0.62–0.92	<0.001
Total persistence for antihypertensives, hypoglycemics, lipid lowering medications and antithrombotics	0.70	0.61–0.89	<0.001

OR, odds ratio; CI, confidence interval.

The adherence evaluation after ischemic stroke longitudinal (AVAIL) study showed that nearly one-quarter and one-third of patients with acute ischemic stroke discontinued one or more of their prescribed secondary prevention medications at 3- and 12-months postdischarge, respectively (26). An inner-city population study reported that the adherence rate was 70% for antihypertensive therapy, 75% for antiplatelet therapy, and 41% for anticoagulation therapy for 3 months after ischemic stroke (27). In this study, we found that a 4.7-year compliance rate for antithrombotics was not ideal (59.8%) in patients with stroke, and it was significantly lower compared with other previous studies (15, 25–27). The reason may be related to the long follow-up time of this study (4.7 years). To the best of our knowledge, this study is the longest follow-up to identify compliance for antithrombotics after stroke.

Till present, few studies investigated the persistence of drug therapy and its association with outcomes in the high-risk stroke population. In this study, the results showed that the 4.7-year persistence of therapy rate for antihypertensives, hypoglycemics, and lipid-lowering medications was 38.0%, 39.9%, and 43.9%, respectively, indicating the persistence of drug therapy is very low in the high-risk stroke population in China. A study from Systolic Blood Pressure Intervention Trial (SPRINT) data reported that 21.2% had low antihypertensives adherence, 40.0% had medium adherence, and 38.8% had high adherence for patients with hypertension, and medium or above compliance was significantly associated with lower systolic blood pressure (SBP) (28), and this was agreed with this study.

Numerous studies have shown that the persistence of secondary prevention medications, including antiplatelet, warfarin, statins, antihypertensive, and antidiabetic medications was associated with a lower hazard of recurrent stroke, composite events, death, and lower OR of disability in patients with ischemic stroke or TIA (15, 29, 30). In this study, we found that the 4.7-year persistence of antithrombotics in patients with stroke was independently associated with less recurrent ischemic or hemorrhagic stroke and less total new composite vascular events, and the results were agreed with other previous studies (15, 29, 30). There are few studies to evaluate the association between persistence of drug therapy and outcomes in the high-risk stroke population. Studies from patients with coronary artery disease have shown that medication non-persistence for coronary artery disease is associated with poor blood pressure control and subsequent adverse outcomes (12, 13). Studies from SPRINT data showed that medium or above compliance with antihypertensives was significantly associated with lower SBP (28) but was not associated with primary outcomes (a composite of myocardial infarction, other acute coronary syndromes, heart failure, stroke, or death from cardiovascular causes) (31). In this study, the results showed that the 4.7-year persistence of antihypertensives, hypoglycemics, and lipid-lowering therapy was significantly associated with less new ischemic stroke and total new composite vascular events in the high-risk stroke population. Thus, more effective public education, greater responsibilities of individuals, and efforts to understand and enhance the persistence of drug therapy are crucial to improve population health and decrease stroke or other vascular events for the high-risk stroke population (7), and fixed-dose combination options for polypill products would be more eligible for secondary and primary prevention of stroke (32).

There are several limitations in our study. First, because numerous previous studies have evaluated the influence factors of persistence of drug therapy, the main aim of this study was to investigate the association between persistence of drug therapy and outcomes in the high-risk stroke population. Thus, we did not assess the influence factors of persistence of drug therapy in this study. Second, this study was a multicenter, cross-sectional survey, and prospective cohort study in southwestern China, and there may have a recall bias because of the self-reported questionnaire and follow-up by telephone. Third, we only screened residents aged ≥ 40 years in 8 communities in southwestern China. Thus, the results of this study may not represent the full spectrum of the Chinese population. The findings must be validated in larger, multicenter studies in China. Fourth, some studies showed that the standard-reaching rate for hypertension, diabetes mellitus, and dyslipidemia (embodied in blood pressure, glucose, and lipids) was very low, and was associated with outcomes (10, 11). However, some studies thought that blood pressure, blood glucose, and lipids, as the intermediate markers during medication treatment, were not associated with susceptibility to stroke and outcomes (33, 34). In this study, although we investigated the persistence of antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics in the high-risk stroke population, the relevant data such as blood pressure, glucose, and lipids at 4.7 years after a face-to-face survey were not collected. Thus, future studies are needed to evaluate the effect of blood pressure, blood glucose, and lipids on outcomes. Furthermore, as the prevalence of cardiogenic stroke was very low in the survey, we did not stratify the compliance with anticoagulation therapy and its effect on outcomes. Finally, our measure of the persistence of drug therapy was telephone self-reported compliance. Although the excellent agreement between telephone self-reported compliance and analysis of pharmaceutical data has been previously reported (35), such data might be biased by patients' subjective response (information bias and recall bias). The 8-item Morisky Medication Adherence Scale (MMAS-8) is an 8-question self-reported instrument that has proven to be a valid and reliable assessment tool for compliance (28, 31). Further studies are needed to determine the association between medication compliance and outcomes using MMAS-8 in the high-risk stroke population.

Conclusion

In this study, we found that the 4.7-year persistence of antihypertensives for hypertension, hypoglycemics for diabetes, lipid-lowering medications for dyslipidemia, and antithrombotics for stroke was very low, and the persistence of antihypertensives, hypoglycemics, lipid-lowering medications, and antithrombotics was independently associated with less new ischemic stroke and total new composite vascular events in the high-risk stroke population. Thus, more effective public education and efforts to understand and enhance the persistence of drug therapy are crucial to improve population health and decrease stroke and other vascular events for the high-risk stroke population.

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 of People's Hospital of Deyang City. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XY and HC: designed the study and acquired funding. MY, HL, and JZ: performed this survey and follow-up.

WW, YW, and XC: analyzed the results and drafted the figures. XY, MY, and HL: drafted manuscript and the tables. XY, HC, MY, and HL: supervised the project. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Prehospital stroke mimics in the Stockholm Stroke Triage System

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Introduction: In 2017, Stockholm implemented a new prehospital stroke triage system (SSTS) directing patients with a likely indication for thrombectomy to the regional comprehensive stroke center (CSC) based on symptom severity and teleconsultation with a physician. In Stockholm, 44% of patients with prehospital code stroke have stroke mimics. Inadvertent triage of stroke mimics to the CSC could lead to inappropriate resource utilization.

Aims: To compare the characteristics between (1) triage-positive stroke mimics and stroke (TP mimics and TP stroke) and (2) triage-negative stroke mimics and stroke (TN mimics and TN stroke) and to (3) compare the distribution of stroke mimic diagnoses between triage-positive and triage-negative cases.

Methods: This prospective observational study collected data from October 2017 to October 2018, including 2,905 patients with suspected stroke who were transported by code-stroke ambulance to a Stockholm regional hospital. Patients directed to the CSC were defined as triage-positive. Those directed to the nearest stroke center were defined as triage-negative.

Results: Compared to individuals with TP stroke ($n = 268$), those with TP mimics ($n = 55$, median 64 vs. 75 years, $P < 0.001$) were younger and had lower NIHSS score (median 7 vs. 15, $P < 0.001$). Similarly, those with TN mimics ($n = 1{,}221$) were younger than those with TN stroke (n = 1,361, median 73 vs. 78 years, $P < 0.001$) and had lower NIHSS scores (median 2 vs. 4, $P < 0.001$). Functional paresis was more common in those with TP mimics than in those with TN mimics, 18/55 (32.7%) vs. 82/1,221 (6.7%), $P < 0.001$. Systemic infection was less common in those with TP mimics than in those with TN mimics, 1/55 (1.8%) vs. 160/1,221 (13.1%), $P < 0.011$. There was a trend toward "syncope, hypotension, or other cardiovascular diagnosis" being less common in those with TP mimics than in those with TN mimics, 1/55 (1.8%) vs. 118/1,221 (9.7%), $P < 0.055$.

Conclusions: In the SSTS, those with triage-positive and triage-negative stroke mimics were younger and had less severe symptoms than patients with stroke. All patients with TP mimics who had hemiparesis but overall exhibited less severe symptoms against true stroke but more severe symptoms than those with TN mimics were triaged to the nearest hospital. Over-triage of functional paresis to the CSC was relatively common. Meanwhile, a large majority of cases with minor symptoms caused by stroke mimics was triaged correctly by the SSTS to the nearest stroke center.

KEYWORDS

acute ischemic stroke, stroke mimics, prehospital triage, telemedicine, thrombectomy

Introduction

In acute ischemic stroke (AIS), treatment with endovascular thrombectomy (EVT) and intravenous thrombolysis (IVT) has the greatest effect when initiated within the first h to several h after onset (1, 2). EVT availability is limited to comprehensive or thrombectomy-ready stroke centers (CSCs or TSCs), while IVT can be administered in all stroke centers, including primary stroke centers (PSCs). Interhospital transfer from PSCs to CSCs delays treatment and is associated with worse outcomes (3). However, mass bypass of PSCs could overwhelm CSC capacity with EVT-ineligible cases. This highlights the need for an accurate prehospital triage system.

In the prehospital setting, clinical algorithms are used to detect signs of stroke and large artery occlusion (LAO). However, diagnosing AIS in the prehospital setting is challenging, and frequently, other conditions, so called stroke mimics, are mistaken for stroke.

Prior to the Stockholm Stroke Triage Project, prehospital guidelines mandated triage using a Swedish, modified, version of the Face-Arm-Speech-Time (FAST) test, allowing for both arm or leg weakness (4). Patients with suspected stroke were transported with first-priority ambulance to the nearest hospital for initial assessment and treatment. Patients potentially eligible for thrombectomy were subsequently transported to the CSC in the Stockholm region. A new workflow, the Stockholm Stroke Triage System (SSTS), was implemented in October 2017. This combines the assessment of hemiparesis with ambulance-hospital teleconsultation to direct patients with high likelihood of LAO and EVT indication directly to the CSC, bypassing PSCs.

The SSTS has a high accuracy for predicting LAO and indication for EVT (5, 6). The implementation of SSTS has resulted in a 69-min reduction of symptom onset to arterial puncture time in EVT and improved patient outcomes (7). However, 44% of all suspected stroke cases managed in the SSTS are ultimately diagnosed with a stroke mimic (5).

To assess if resource utilization could be optimized and care pathways for patients with stroke mimic in the SSTS could be improved, we wanted to identify which types of stroke mimics tend to be routed to the CSC. By assessing differences in prehospital characteristics between stroke mimics and true stroke triaged to the CSC and the nearest PSC, we hoped to find any patterns helpful for improvement of the teleconsultation. Improving mimic triage is not only important for patients with stroke mimic but could also indirectly benefit those with true stroke. Over-triage could lead to increased patient volume routed to CSC, which could lead to resource conflicts and delay in treatment if the capacity to manage parallel cases is exhausted (8).

We aimed to compare characteristics between (1) triage-positive stroke mimics and stroke (TP mimics and TP stroke) and (2) triage-negative stroke mimics and stroke (TN mimics and TN stroke), and (3) compare the distribution of stroke mimic diagnoses between triage-positive and triage-negative cases.

Materials and methods

This was an observational cohort study using prospectively collected data between 10 October 2017 and 9 October 2018. The inclusion criteria were prehospital suspicion of stroke and transport with code-stroke ground ambulance to a hospital in the Stockholm region, and patients aged 18 years or above. The exclusion criteria were transport to a hospital by means other than a priority one ambulance or transport from outside the Stockholm region and stroke during in-hospital care for another condition.

The Swedish Ethical Review Authority (ERA) gave approval for the project. Need for active consent was waved. Patients or family were informed in writing of the right to opt out of study data collection.

The SSTS was implemented on 10 October 2017 in the Stockholm region (population 2.3 M, area 6,519 km^2), which is served by six primary stroke centers (PSCs) and one comprehensive stroke center (CSC). The triage process starts with an ambulance nurse suspecting stroke as a potential cause of symptoms either *via* the FAST test or for any other clinical reason. The next step is to assess for hemiparesis using the motor items of the NIH Stroke Scale (NIHSS), where $\geq$2 points in each of the affected extremities are considered positive. This test is named the A2L2 test (arm two or more, leg two or more). If the patient cannot keep an arm and ipsilateral leg raised for 10

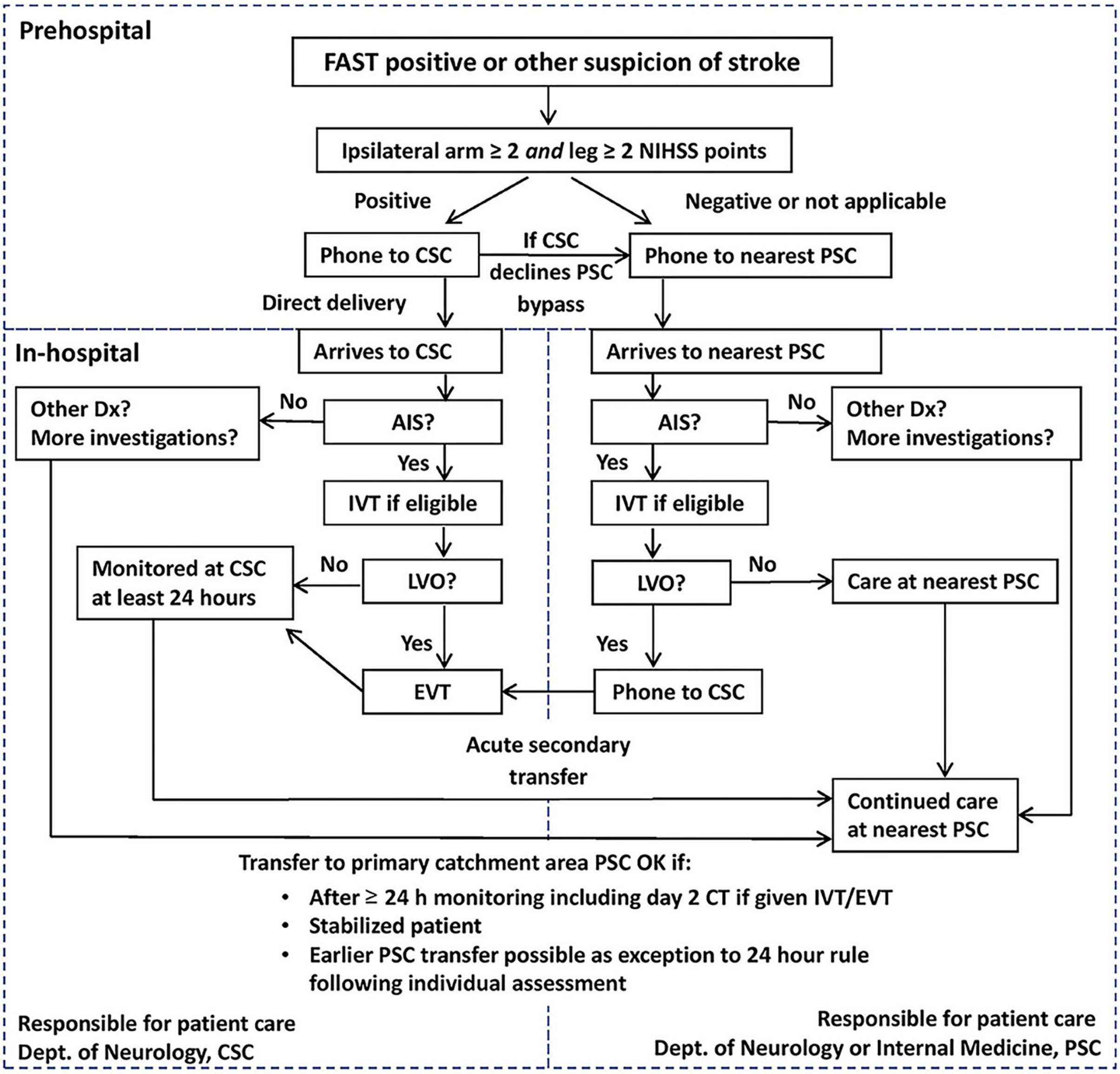

FIGURE 1
Flowchart of the Stockholm Stroke Triage System.

and 5 s, respectively, the A2L2 test is positive. The test is not applicable to patients with seizures, unconsciousness, or bilateral paresis. The final step is teleconsultation between the ambulance nurse and a stroke neurologist at the CSC in A2L2-positive cases or a pre-notification to the nearest PSC in A2L2-negative or inapplicable cases. A flowchart of the triage system is shown in Figure 1.

In the Stockholm region, all ambulances are operated by a crew of two, with at least one specialist ambulance nurse with 3 years of university education and 1 year of specialist training in either prehospital care or anesthesia. Prior to the implementation of the SSTS, ambulance nurses were educated by web-based training and live lectures on the SSTS and stroke scales used.

Data were collected on baseline demographics, imaging and clinical parameters, treatments, time measures, and final diagnosis. Data sources were the region-wide electronic health record systems for emergency health services and for in-hospital, outpatient, and primary care services along with the regional radiological picture archiving and communication system.

Triage-positive (TP) cases were defined as patients with a positive A2L2 test and those who were, after teleconsultation, triaged to the CSC with suspected LAO and no EVT contraindications. Triage-negative (TN) cases were defined as

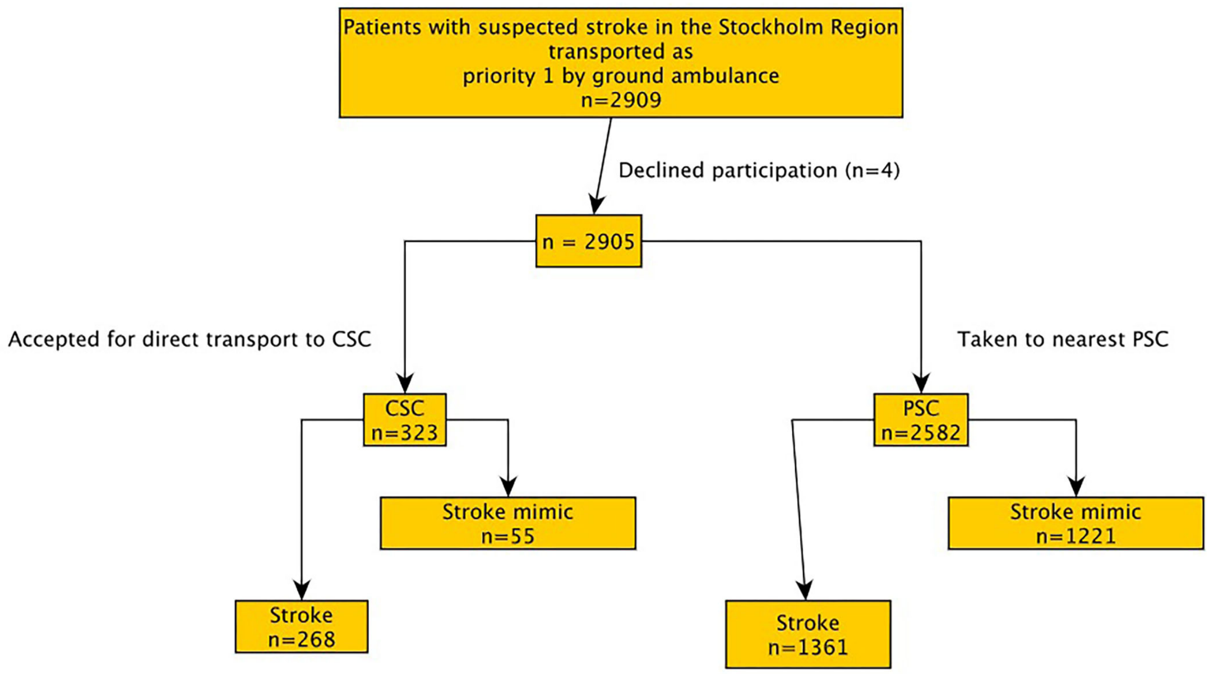

FIGURE 2
Patient distribution per study group.

patients with a negative A2L2 test or patients with a positive A2L2 test who, after teleconsultation, were directed to a PSC because of EVT contraindications. In cases where the closest hospital was the CSC, patients were still triaged the same way, by the A2L2 test and teleconsultation. If the patient was triage-negative they were still taken to the CSC, as it was the nearest hospital. Meanwhile, for the purposes of the study, they were still classified as triage negative. Contraindications for EVT were: >24 h since time of last known well, severe co-morbidity with a pre-stroke life expectancy less than 3 months, and pre-stroke mRS of 4–5.

Stroke mimics were defined as a main discharge diagnosis other than stroke or transient ischemic attack (TIA). These were classified into standardized categories: epileptic seizure, functional neurological disorder, primary headache disorder, etc. The final diagnosis of stroke was made on discharge by synthesis of clinical and radiological findings including CT or MR as deemed clinically appropriate on a case-by-case basis.

Continuous and ordinal variables were reported as medians with the interquartile range (IQR). Statistical significance of differences was assessed by the Mann-Whitney U test. Statistical significance of differences between proportions was assessed by the Pearson chi-square test or Fisher's exact test as appropriate. A difference with a p-value <0.05 was considered statistically significant. SPSS version 27 (IBM, Armonk, NY, United States) was used for data analysis.

Results

Of 2,909 eligible patients, four declined to participate. Out of the remaining 2,905 patients, 1,276 (43.9%) received a stroke mimic diagnosis. Of the 1,276 patients with stroke mimic, 55 (4.3%) were triage-positive and 1,221 (95.7%) were triage-negative (Figure 2). As reported previously, the proportion of mimics among triage-positive patients was 55/323 (17%) and among triage-negative cases was 1,221/2,582 (47.3%) ($P < 0.001$) (5).

Table 1 shows baseline characteristics comparing TP mimics and TP stroke. Patients with TP mimic were younger than those with TP stroke (median age 64 vs. 75 years). There was a difference in gender distribution, 63.6% women vs. 44.8% men in the TP mimics and TP stroke, respectively. Patients with TP mimics had lower NIHSS scores (median seven) than those with TP stroke (median 15). In the FAST test, the patients with TP mimic less frequently had findings in face (38.2 vs. 72.4%) and speech (40 vs 78.7%) items compared to those with TP stroke.

As for patients with TN (Table 2), those with TN mimic were younger than those with TN stroke (median 73 vs. 78 years) and had lower NIHSS scores (median 2 vs. 4). TN Mimics and TN stroke differed significantly on all the FAST items: face (24.7 vs. 42.4%), arm (31.7 vs. 50.3%), leg (27.8 vs. 41.9%), and speech (50 vs. 62.2%).

TABLE 1 Comparison of triage-positive stroke mimics vs. triage-positive stroke.

	Triage positive stroke mimics *N* = 55		Triage positive stroke *N* = 268		
	N	% or median(IQR)	N	% or median(IQR)	*P*-value
Demographics					
Age	55/55	64 (45–74)	268	75 (66–82)	<0.001
Sex, women	35/55	63.6%	120/268	44.8%	0.011
Baseline characteristics					
NIHSS Score	54/55	7 (3–10)	266/268	15 (9–19)	<0.001
FAST test status					
Positive face	21/55	38.2%	194/268	72.4%	<0.001
Positive arm	55/55	100%	268/268	100%	1
Positive leg	55/55	100%	267/268	99.6%	1
Positive speech	22/55	40%	211/268	78.7%	<0.001
A2L2 status					
A2L2 positive	55/55	100%	268/268	100%	1
A2L2 negative	0/55	0%	0/268	0%	1
A2L2 N/A	0/55	0%	0/268	0%	1
Known onset	42/55	76.4%	183/268	68.3%	0.235
Woke up with symptoms	14/55	25.5%	85/268	31.7%	0.359
ODT, min	52/55	86 (58–243)	265/268	86 (58–246)	0.88
Stroke subtype					
Cerebral infarction	N/A		190/268	70.9%	
ICH	N/A		68/268	25.4%	
SDH	N/A		3/268	1.1%	
TIA	N/A		7/268	2.6%	

A2L2, Arm 2-Leg 2-test; FAST, Face-Arm-Speech-Test; ICH, intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; ODT, onset-to-first-hospital-door time; SDH, subdural hematoma; TIA, transient ischemic attack.

All patients with TP were, by definition, A2L2-positive; however, this was also seen in 56 (4.6%) of the TN mimic and 151 (11.1%) of TN stroke cases. Additionally, in 215/1,221 (17.6%) of the TN-mimic and 135/1,361 (9.9%) of the TN stroke cases, the A2L2 test was not applicable, indicating that they had a witnessed seizure, were unconscious, or had paresis of all the four limbs.

As seen in Table 3, the overall distribution of mimic diagnoses differed between the TP and TN mimic cases. We found significant differences in the occurrence of functional or other psychiatric disorders (more common in the TP group at 32.7 vs. 6.7%) and systemic infection (less common in the TP group, 1.8 vs. 13.1%) and a trend toward significance in syncope, hypotension, or other circulatory disorders (less common in the TP group, 1.8 vs. 9.7%).

Discussion

This observational study aimed to evaluate differences between triage-positive stroke mimics and stroke and triage-negative stroke mimics and stroke. We also aimed to establish whether the occurrence of specific stroke-mimicking conditions varies between triage-positive and triage-negative mimic groups.

An important finding was that the patients with stroke mimic were younger and had less severe symptoms, regardless of the triage status. While this pattern is well-established for mimics vs. true stroke (9), we were somewhat surprised that patients with TP stroke mimics and patients with TP stroke would have such a large difference in median NIHSS at 7 vs. 15. However, cases with occlusions of the M1 MCA segment or intracranial carotid artery in many studies have a median NIHSS of around 15–17 (10). The positive A2L2 test, being one of the requirements for TP status, would in itself generate an NIHSS subtotal of 4–8 points. It is clear from our findings that most patients with TP mimic had only these motor symptoms in isolation or with relatively minor additional symptoms. In terms of differences in distribution of stroke mimic diagnoses, functional neurological symptoms were common in TP mimics, while infections and syncope or hypotension were the more common causes of stroke mimics in TN mimics. The finding that functional neurological disorders (FNDs) were the most common diagnosis in the TP mimic group could be explained by the fact that

TABLE 2 Comparison of triage-negative stroke mimics vs. triage-negative stroke.

	Triage negative stroke mimics $N = 1{,}221$		Triage negative stroke $N = 1{,}361$		
	N	% or median (IQR)	N	% or median (IQR)	*P*-value
Demographics					
Age	1,221/1,221	73 (59–83)	1,361	78 (70–85)	<0.001
Sex, female	621/1,221	50.9%	644/1,361	47.3%	0.072
Baseline characteristics					
NIHSS Score	935/1,221	2 (0–6)	1,264/1,361	4 (2–9)	<0.001
FAST test status					
Positive face	281/1,138	24.7%	552/1,302	42.4%	<0.001
Positive arm	361/1,138	31.7%	655/1,302	50.3%	<0.001
Positive leg	316/1,138	27.8%	546/1,302	41.9%	<0.001
Positive speech	569/1,138	50%	811/1,303	62.2%	<0.001
A2L2 status					
A2L2 positive	56/1,221	4.6%	151/1,361	11.1%	<0.001
A2L2 negative	950/1,221	77.8%	1,075/1,361	79%	0.47
A2L2 N/A	215/1,221	17.6%	135/1,361	9.9%	<0.001
Known onset	626/1,221	51.3%	780/1,361	57.3%	0.002
Woke up with symptoms	518/1,221	42.4%	514/1360	37.8%	0.017
ODT, min	1,188/1,221	206 (81–625)	1,328/1,361	139 (69–467)	<0.001
Stroke subtype					
Cerebral infarction	N/A		825/1,361	60.7%	
ICH	N/A		174/1,361	12.8%	
SAH	N/A		30/1,361	2.2%	
SDH	N/A		57/1,361	4.2%	
TIA	N/A		269/1,361	18.7%	

A2L2, Arm 2-Leg 2-test; FAST, Face-Arm-Speech-Test; ICH, intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; ODT, onset-to-first-hospital-door time; SAH, subarachnoid hemorrhage, SDH, subdural hematoma; TIA, transient ischemic attack.

patients with functional neurological symptoms often present with acute severe hemiparesis (11, 12), which is what the A2L2 test screens for. Moreover, our results indicate that the functional hemiparesis is a largely isolated symptom. Meanwhile, it is apparently difficult for ambulance staff to differentiate between FND and stroke even with the help of the mandatory teleconsultation with a stroke neurologist. In fact, FNDs are difficult to diagnose not only for ambulance staff but for physicians as well, making functional paresis the most common stroke mimic type to be inadvertently treated with IVT (13).

Our results are encouraging insofar that the 55 triage-positive stroke mimic cases directed to the CSC (i e, on average one per week) are unlikely to have caused serious bed capacity issues. Conversely, a large majority of mimics were correctly triaged to the nearest hospital, usually a PSC. One could consider whether our results could inform the teleconsultation process. We suggest that the finding of isolated hemiparesis commonly found in the FND group is insufficient to warrant a decline for direct CSC transport in such patients. This assessment is reinforced by a recent analysis by our group, which conducted a decision curve analysis to evaluate whether the triage algorithm could be improved using combinations of variables routinely available in the prehospital setting during the study period. This showed that classifying patients with isolated hemiparesis as triage-negative would not improve the precision of the system for LAO stroke or EVT (14). Cases with TP mimics had the same onset to hospital door time as TP stroke at just 86 min. Cases with dramatic symptoms and a short time from onset to alert of emergency services might have been difficult to decline for CSC routing. Meanwhile, the onset-to-first-hospital-door time (ODT) was more than 1 h longer in TN mimics than in TN stroke. Possibly, with longer time for the patient and bystanders to witness and observe early prehospital evolution and possibly additional symptoms, it might have been easier for a teleconsulted physician to correctly suspect a mimic in TN mimic cases even with hemiparesis ($n = 56$) and route them to a PSC instead of a CSC.

Regarding the higher frequency of infectious and circulatory stroke mimics among TN vs. TP mimics, this finding appears to reflect our clinical experience, as such mimic

TABLE 3 Comparison of diagnostic category distribution between patients with triage-positive mimic and those with triage-negative stroke mimic.

Diagnostic category	Triage positive stroke mimics *N* = 55 (4.3%) *N* (%)	Triage negative stroke mimics *N* = 1,221 (95.7%) *N* (%)	*P*-value	All stroke mimics *N* = 1,276 *N* (%)
FND or other psychiatric diagnosis	18 (32.7%)	82 (6.7%)	<0.001	100 (7.8%)
Epileptic seizure	15 (27.3%)	264 (21.6%)	0.319	279 (21.9%)
Peripheral neuropathy	4 (7.3%)	75 (6.1%)	0.772	79 (6.2%)
Brain tumor	4 (7.3%)	50 (4.1%)	0.287	54 (4.2%)
Sequelae of previous stroke or other previous brain injury	3 (5.5%)	52 (4.3%)	0.511	55 (4.3%)
Primary headache disorder	2 (3.6%)	66 (5.4%)	0.765	68 (5.3%)
Other neurological diagnosis	2 (3.6%)	43 (3.5%)	1	45 (3.5%)
Musculoskeletal	2 (3.6%)	39 (3.2%)	0.696	41 (3.2%)
Systemic infection	1 (1.8%)	160 (13.1%)	0.011	161 (12.6%)
Syncope, hypotension, or other cardiovascular diagnosis	1(1.8%)	118 (9.7%)	0.055	119 (9.3%)
Drugs and alcohol	1 (1.8%)	82 (6.7%)	0.256	83 (6.5%)
Metabolic/endocrinological	1 (1.8%)	69 (5.7%)	0.361	70 (5.5%)
Peripheral vertigo	1 (1.8%)	47 (3.8%)	0.719	48 (3.8%)
Dementia	0	34 (2.8%)	0.397	34 (2.7%)
Head trauma	0	15 (1.2%)	1	15 (1.2%)
Other (miscellaneous) diagnosis	0	11 (0.9%)	1	11 (0.9%)
Transient global amnesia	0	8 (0.7%)	1	8 (0.6%)
Meningitis/encephalitis	0	6 (0.5%)	1	6 (0.5%)

FND, functional neurological disorder.

categories appear to relatively seldom generate major focal neurological syndromes.

There is an interesting pattern pertaining to sex differences in our study. The finding that female sex was overrepresented among the TP mimic group when compared to the TP stroke group could have been expected, as this has been seen in studies on IVT-treated stroke mimics (13). It appears that TP mimic cases were hard to distinguish from stroke in the prehospital setting even with a neurological teleconsultation. Meanwhile, the TN mimic and TN stroke groups did not have a significant sex difference. Importantly, we have previously shown that the SSTS performs equally between women and men, despite mimics being more common, overall, among women (15).

An important limitation of the study is the low number of individuals in the TP mimic group. This gives a limited statistical power for comparisons of this group vs. others. The low number in the TP group is in line with the previously reported high LAO and EVT specificity of the triage system (5). Furthermore, the limited number of variables describing clinical characteristics is a limitation, since it increases the risk of confounding factors not being identified and considered. This was due to the fact that the clinical characteristic data were collected from routine prehospital documentation, which prioritizes high data completeness over granularity.

Conclusions

In the SSTS, those with triage-positive and those with triage-negative stroke mimics were younger and had less severe symptoms than patients with stroke. All patients with TP mimics had a hemiparesis but overall exhibited less severe symptoms against true stroke but more severe symptoms than those with TN mimics. Over-triage of functional paresis to the CSC was relatively common. Meanwhile, a large majority of the cases with minor symptoms experienced by stroke mimics and were triaged correctly by the SSTS to the nearest stroke center.

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 the Swedish Ethical Review Authority approval 2017/374. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

AB and MM collected the dataset. MM designed and supervised the study. MS performed all the data processing, statistical analysis, and wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Endovascular treatment for ischemic stroke with the drip-and-ship model—Insights from the German Stroke Registry

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Background: Endovascular therapy (EVT) in acute ischemic stroke has been widely established. Globally, stroke patients are transferred either directly to a thrombectomy center (DC) or a peripheral stroke unit with a "drip-and-ship" (DS) model. We aimed to determine differences between the DS and DC paradigms after EVT of acute stroke patients with large-vessel-occlusion (LVO) in the database of the German Stroke Registry (GSR).

Methods: We performed a retrospective analysis of GSR patients between June 2015 and December 2019 in 23 German centers. Primary outcome was an ordinal shift analysis of modified Rankin Scale (mRS) 90 days after index event. Secondary endpoints included time from symptom onset to recanalization and complications. Tertiary endpoint was the association of imaging strategies in DS admissions with outcome.

Results: 2,813 patients were included in the DS and 3,819 in the DC group. After propensity score matching mRS after 90 days was higher in DS than DC admissions (OR 1.26; 95%-CI 1.13–1.40). Time from symptom-onset to flow-restoration was shorter in DC than DS (median 199.0 vs. 298.0 min; $p < 0.001$). DS patients undergoing magnetic resonance imaging (MRI; n=183) before EVT had a lower 90-day mRS than without ($n = 944$) (OR 0.63; 95%-CI 0.45–0.88). ASPECTS assessed on MRI correlated with 90-day mRS ($\rho = -0.326$; $p < 0.001$).

Conclusions: Clinical outcome was worse for EVT-eligible patients in the DS setting, even though patients were in a better state of health prior to stroke. A potentially mutable factor was the time delay of 99 min from symptom-onset to successful recanalization. Performing MRI before thrombectomy was associated with good outcome and MRI-ASPECTS was negatively correlated with mRS after 90 days.

KEYWORDS

ischemic stroke, endovascular treatment, mechanical thrombectomy, drip-and-ship, direct-to-center

Introduction

"Time is brain" has guided stroke care since its inception and equally applies to thrombolysis and endovascular treatment (EVT)(1, 2). Since EVT is oftentimes limited to comprehensive stroke centers the question has emerged whether patients suspected to suffer from acute ischemic strokes should primarily be transferred to hospitals with EVT capabilities ("direct-to-center", DC) or the nearest peripheral hospital for rapid thrombolysis and in case of large vessel occlusions (LVO) to a thrombectomy center thereafter ("drip-and-ship", DS). Results from the DAWN and DEFUSE 3 trials provided a framework for EVT in a time window of up to 24 h from symptom onset, rendering secondary transfer feasible in many cases (3, 4). However, the ensuing time delay might negatively influence the eventual outcome. On the contrary, long transportation times to EVT centers are likely to postpone the start of intravenous thrombolysis. Several studies have compared these concepts, some of which have suggested that bypassing stroke units, which only offer intravenous thrombolysis, might confer the benefit of more rapid revascularization and improve outcomes (5). In 2020, a systematic review and meta-analysis of 18 pertinent studies with 7,017 patients demonstrated more functional independence after DC treatment compared to DS (6). Additionally, to save time, patients transferred for EVT from a peripheral center are predominantly directed to angiography without repeat imaging. Recent studies have suggested that foregoing secondary imaging is associated with shortened treatment times and better clinical outcome, but there might be a rationale for additional diagnostic work-up after transport delays (7, 8).

We aimed to analyze the influence of secondary transfers of acute stroke patients and investigate strategies to improve the DS model. To this end, large-scale registries of real-wold data can provide essential insights, and statistical computations such as multivariable regression analysis and propensity score matching can reduce confounding.

Methods

We retrospectively analyzed data from the German Stroke Registry (GSR, https://www.clinicaltrials.gov identifier NCT0335639), which prospectively collects data on treatment practices, safety and outcome after EVT for ischemic strokes (9, 10). Patients ≥18 years old with acute ischemic stroke in anterior and posterior circulation are enrolled in all participating centers and followed-up for 90 days. No exclusion criteria were defined. Consent is obtained either by the patient or a legal representative. If no consent can be obtained before death, inclusion was based on presumed consent to reduce selection bias. Baseline and treatment data are recorded as part of routine care. Clinical outcome is assessed *via* telephone interview 90 days after stroke. The study protocol was centrally approved by the local Ethics Committee of the Ludwig-Maximilian University Munich (689-15).

Primary endpoint was an ordinal shift analysis of 90-day modified Rankin Scale (mRS) after propensity score matching with multivariable regression analyses (adjusted for age, sex, NIHSS at admission, comorbidities and thrombolysis) (11). Secondary endpoints were a dichotomous analysis of favorable outcome, time delay between DC and DS admissions, correlation between the absolute reduction in National Institute of Health Stroke Scale (NIHSS) from admission to discharge and time from symptom onset and complications in both groups. Tertiary endpoint was the influence of additional imaging [computed tomography (CT), magnetic resonance imaging (MRI)] on treatment times and outcome.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS, version 27.0.1.0, Armonk, N.Y., USA) and R (R package version 3.363) for propensity score matching. Categorical data were evaluated for differences by χ^2-tests, ordinal and metric data without normal distribution were assessed by Mann-Whitney-*U*-test. According to recommendations of the European Stroke Organization outcome was primarily measured by ordinal logistic regression of mRS as common odds ratios (OR) with adjustment for age, sex, pre-stroke mRS, admission NIHSS, comorbidities and thrombolysis (11, 12). Propensity score matching was performed with 1:1 matching based on the nearest-neighbor algorithm with a caliper width of 0.2 of the propensity score for age, pre-stroke mRS, NIHSS on admission and thrombolysis. The significance level was set to $P < 0.05$, and all tests of hypotheses were two-sided.

Results

Study population

Between June 2015 and December 2019, 6,632 patients from 23 centers were enrolled. Of them, 3,819 were treated in the primary admitting center (DC) and 2,813 were transferred after initial treatment in a peripheral hospital (DS). Clinical parameters at baseline for both groups are demonstrated in Table 1. DS patients were more likely to be living unassisted at home ($p < 0.001$) and had lower mRS scores before stroke (median 0 vs. 0; $p < 0.001$). Distribution of comorbidities (arterial hypertension, diabetes, atrial fibrillation, dyslipidemia) did not differ significantly between groups. LVO was more proximal in the DS compared to DC group (extracranial internal carotid artery 7.0 vs. 5.4%; M1-segment 34.1 vs. 32.2%; $p <$ 0.001). Clinical outcome after 90 days was available for 2,266 DS and 3,172 DC patients (80.6 vs. 83.1%, $p = 0.010$).

TABLE 1 Baseline, treatment and outcome characteristics for direct-to-center and drip-and-ship admission status, analyzed by χ^2-test[a] for categorical data and Mann-Whitney-*U*-test[b] for continuous, non-Gaussian data.

	Direct-to-center	Drip-and-ship	*p*-value
n	3,819	2,813	
Age (years, mean ± SD, minimum, maximum)	73.2 ± 13.2 (20–100)	73.0 ± 12.9 (17–100)	0.411[b]
Sex, female, *n* (%)	1,947 (51.0%)	1,414 (50.3%)	0.568[a]
mRS before stroke (median, IQR)	0 (0–1)	0 (0–1)	<0.001[b]
Living status before stroke			
Home	3,074 (80.5%)	2,364 (84.0%)	<0.001[a]
Nursing at home	186 (4.9%)	83 (3.0%)	
Nursing home	277 (7.3%)	170 (6.0%)	
Unknown	282 (7.4%)	196 (7.0%)	
Risk factors			
Arterial hypertension	2,779 (72.8%)	2,063 (73.3%)	0.689[a]
Diabetes	770 (20.2%)	609 (21.6%)	0.241[a]
Atrial fibrillation	1,490 (39.0%)	1,120 (39.8%)	0.876[a]
Dyslipidemia	1,423 (37.3%)	1,044 (37.1%)	0.564[a]
Antithrombotic medication			
Antiplatelets	1,124 (31.8%)	802 (30.4%)	0.251[a]
VKA	263 (7.4%)	218 (8.3%)	0.230[a]
DOAC	480 (13.6%)	350 (13.3%)	0.459[a]
NIHSS on admission (median, IQR)	14.0 (9–18)	15.0 (10–19)	0.003[b]
Vessel occlusion			
ICA extracranial	207 (5.4%)	198 (7.0%)	<0.001[a]
ICA intracranial	753 (19.8%)	617 (20.8%)	
MCA M1	1,228 (32.2%)	960 (34.1%)	
MCA M2	786 (20.6%)	552 (19.6%)	
ACA	86 (2.3%)	63 (2.2%)	
PCA	121 (3.2%)	47 (1.7%)	
BA	385 (10.1%)	276 (9.8%)	
VA	79 (2.1%)	45 (1.6%)	
Stroke etiology			
Cardioembolic	1,822 (47.7%)	1,379 (49.0%)	<0.001[a]
Large-vessel-disease	867 (22.7%)	639 (22.7%)	
ESUS	588 (15.4%)	486 (17.3%)	
Dissection	68 (1.8%)	45 (1.6%)	
Other	180 (4.7%)	98 (3.5%)	
Unknown	294 (7.7%)	166 (5.9%)	
Thrombolysis	1,767 (46.3%)	1,556 (55.3%)	<0.001[a]

Mean and standard deviation (SD) or median and interquartile range (IQR) are shown as appropriate. mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery; ESUS, embolic stroke of unknown source.

Primary endpoint

After multivariable regression analysis mRS after 90 days was higher in DS than DC admissions [odds ratio (OR) 1.26; 95%-confidence interval 1.13–1.40; $p < 0.001$; Figure 1A]. Propensity score matching balanced the baseline characteristics of both groups (Table 2), but OR for higher mRS scores after 90 days was still significantly lower in DC compared to DS admissions (DC $n = 2{,}234$; DS $n = 2{,}114$; OR 1.26; 95%-CI 1.13 to 1.40; $p < 0.001$; Figures 1B, 2B).

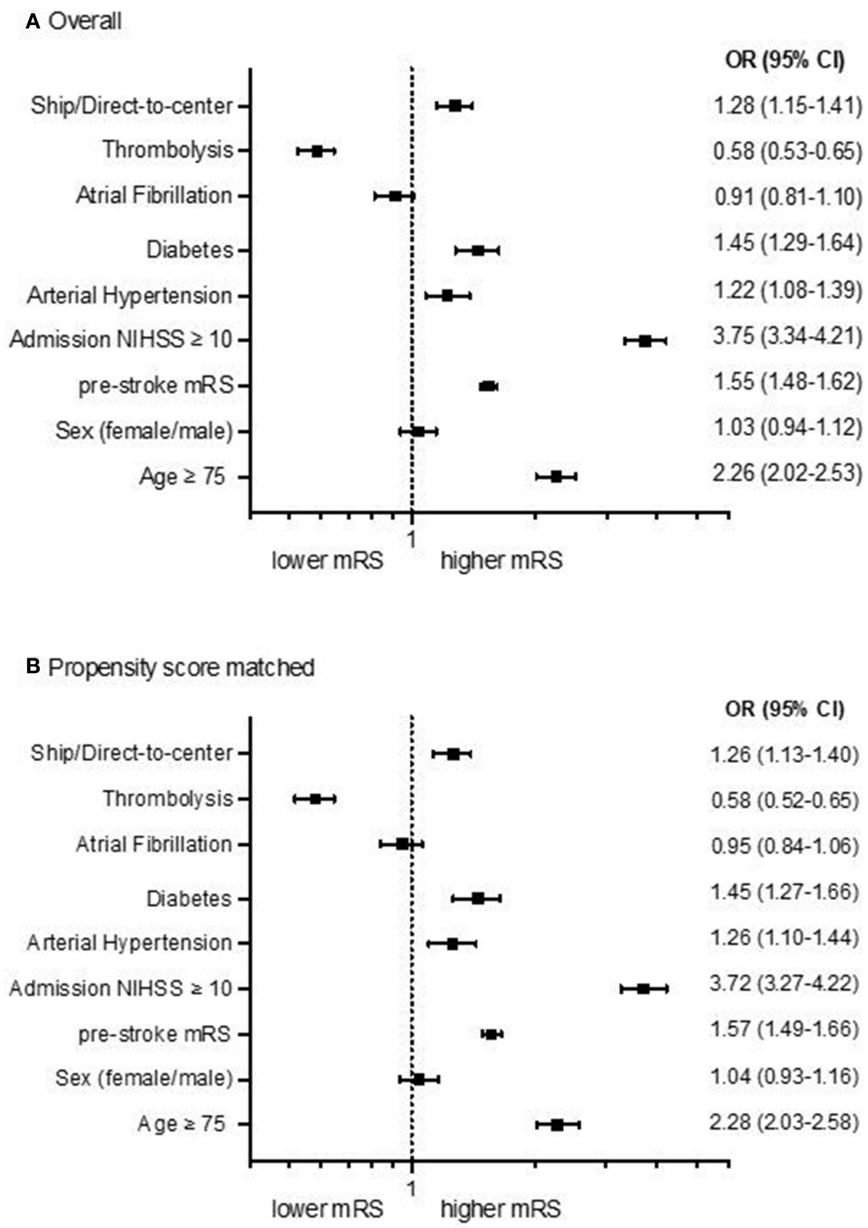

FIGURE 1
Forest plots showing multivariable ordinal regression analyses of the adjusted common odds ratio (OR) of modified Ranking Scales (mRS) 90 days after stroke for DC/DS admission status, sex, age, admission NIHSS, comorbidities and thrombolysis in all patients [**(A)**, $n = 5{,}107$] and after propensity score matching [**(B)**, $n = 4{,}348$]. The OR is presented logarithmically with 95%-confidence intervals.

Secondary endpoints

A favorable clinical outcome after 90 days, defined as mRS 0–2, was less frequent in the DS compared to the DC group (34.9 vs. 38.7%; OR 0.73; 95%-CI 0.64–0.83; $p < 0.001$). After intravenous thrombolysis favorable outcomes were more frequently observed, however still less so in the DS than the DC group (39.1 vs. 46.9%; $p < 0.001$; Figures 2A–D). Without thrombolysis, no significant difference in favorable outcome could be detected between DS and DC (29.5 vs. 31.4%; OR 0.87; 95% CI 0.72–1.05; $p = 0.149$).

After propensity score matching, median time interval between symptom onset and flow restoration was 199.0 min (IQR 160.0–258.0 min) for DC and 298.0 min (IQR 239.8–370.0

TABLE 2 Results from baseline characteristics, treatment procedures and outcome of direct-to-center and drip-and-ship patients after propensity score matching for age, pre-stroke mRS, NIHSS at admission and thrombolysis.

Propensity score matched analysis

	Direct-to-center	Drip-and-ship	*p*
N	2,556	2,555	
Mean age (years ± SD, minimum, maximum)	73.1 ± 13.1 (21–100)	72.8 ± 12.9 (17–99)	0.417[b]
Sex, female (*n*, %)	1,293 (50.6%)	1,282 (50.2%)	0.780[a]
mRS before stroke (median, IQR)	0 (0–1)	0 (0–1)	0.557[b]
Risk factors			
Arterial hypertension	1,969 (77.3%)	1,959 (77.2%)	0.920[a]
Diabetes	527 (20.7%)	569 (22.4%)	0.152[a]
Atrial fibrillation	1,044 (41.1%)	1,056 (41.5%)	0.754[a]
Dyslipidemia	1,006 (39.6%)	992 (39.1%)	0.730[a]
NIHSS on admission (median, IQR)	15.0 (10–19)	15.0 (10–19)	0.910[b]
Imaging (*n*, %)			
CT	2,373 (93.0%)	2,291 (92.0%)	0.198[a]
MRI	239 (9.4%)	208 (8.4%)	0.216[a]
Stroke etiology			
Cardioembolic	1,301 (51.4%)	1,316 (51.9%)	0.373[a]
Large-vessel-disease	626 (24.7%)	618 (24.4%)	
ESUS	56 (2.2%)	45 (1.8%)	
Dissection	429 (16.9%)	463 (18.2%)	
Other	117 (4.6%)	93 (3.7%)	
Thrombolysis	1,407 (55.0%)	1,430 (55.9%)	0.518[a]
Symptom onset—admission in center (minutes, median, IQR)	63.0 (45.0–103.0)	195.0 (149.0–255.0)	<0.001[b]
Symptom onset—thrombolysis (minutes, median, IQR)	90 (70.0–120.0)	95 (71.0–180.0)	0.083[b]
Symptom onset—flow restoration (minutes, median, IQR)	199.0 (160.0–258.0)	298.0 (239.8–370.0)	<0.001[b]
NIHSS after 24 h (median, IQR)	10 (4–19)	11 (5–19)	0.001[b]
ICH after 24 h	267 (10.4%)	329 (12.9%)	0.007[b]
ICH between 24 h and discharge	77 (3.0%)	99 (3.9%)	0.107[b]
NIHSS on discharge (median, IQR)	5 (1–13)	6 (2–14)	<0.001[b]
mRS on discharge (median, IQR)	4 (2–5)	4 (2–5)	<0.001[b]
mRS after 90 days (median, IQR)	3 (1–6)	4 (2–6)	0.001[b]

Analysis was performed by χ^2-test[a] for categorical data and Mann-Whitney-U-test[b] for continuous, non-Gaussian data. Mean and standard deviation (SD) or median and interquartile range (IQR) are shown as appropriate.

min) for DS admissions ($p < 0.001$). Overall, there was a weak albeit significant correlation between the time from stroke onset to successful endovascular recanalization and the net clinical benefit as measured by the difference of NIHSS from admission to discharge ($n = 2,366$; Spearman's $\rho = 0.27$; $p < 0.001$) (Figure 3).

Complications were more common in the DS than the DC group (any adverse event: 39.6 vs. 34.1%; $p < 0.001$) (Table 3). Notably, intracranial hemorrhages were recorded more frequently in the DS group during EVT (3.2 vs. 2.4%; $p = 0.039$) and 24 h after intervention (12.6 vs. 10.0%; $p = 0.001$). Contrarily, early recurrent strokes were less frequent in the DS than the DC group (2.1 vs. 5.3% vs.; $p < 0.001$).

Tertiary endpoint

DS patients with MRI were more likely to achieve a lower mRS score after 90 days, as evidenced by multivariable regression analysis with adjustment for pre-stroke mRS, gender, Alberta Stroke Program Early CT Score (ASPECTS) and thrombolysis ($n = 183$ vs. $n = 944$ without MRI; OR 0.634; 95%-CI 0.46–0.88; $p = 0.006$) (Figure 4). CT-ASPECTS correlated weaker with the 90-day mRS ($n = 1,480$, Spearman's $\rho = -0.139$; $p < 0.001$) than MRI-ASPECTS ($n = 108$, Spearman's $\rho = -0.326$; $p < 0.001$). Any secondary imaging led to a median delay of 28 min between admission and groin puncture, and MRI increased this interval compared to CT from 60 min to 82 min ($p < 0.001$; Table 4).

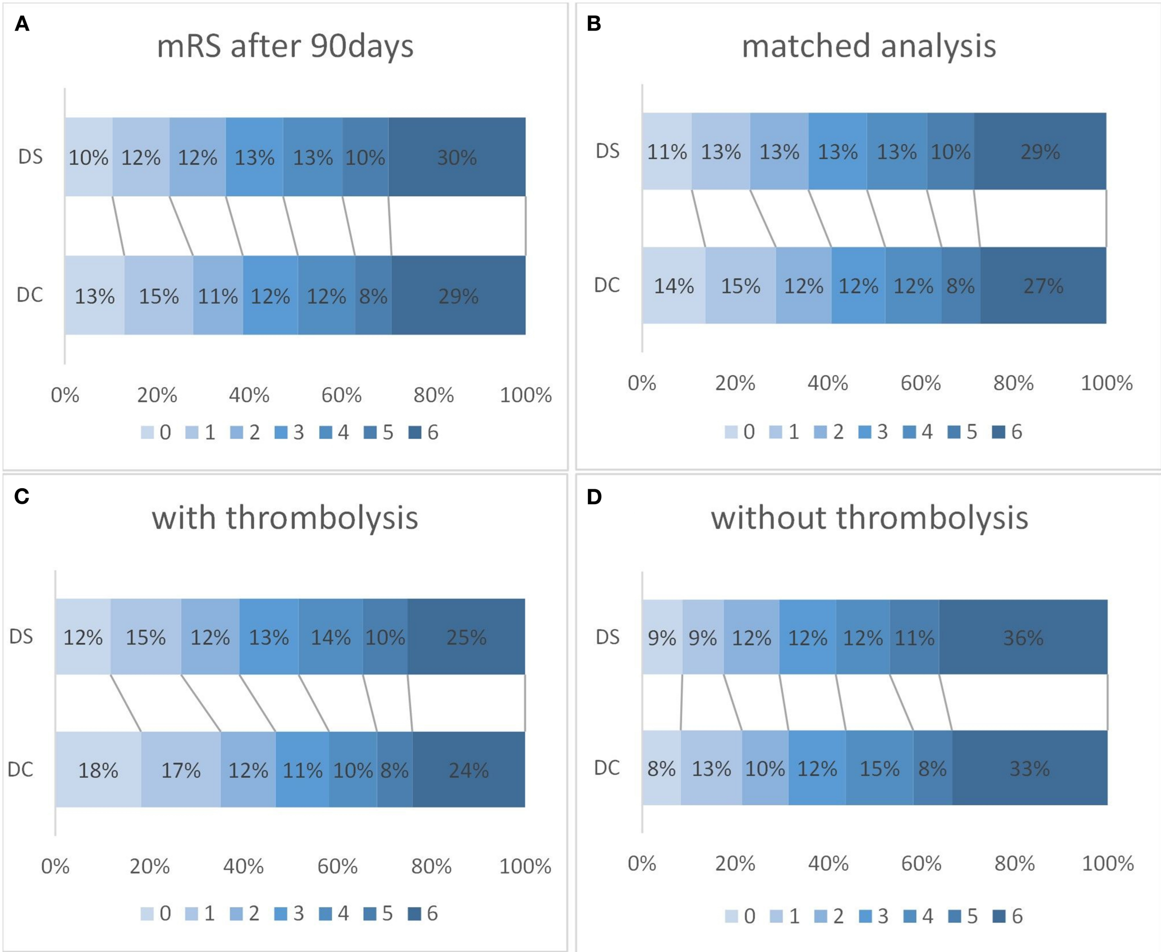

FIGURE 2
The outcome on modified Rankin Scale (mRS) after 90 days for drip-and-ship (DS) and direct-to-center (DC) in all patients [**(A)**; DS $n = 2{,}266$; DC, $n = 3{,}172$; OR 1.28; 95%-CI 1.15–1.41; $p < 0.001$] and after a propensity score matched analysis [**(B)**; DS $n = 2{,}114$; DC $n = 2{,}993$; OR 1.28; 95%-CI 1.15–1.41; $p < 0.001$]. Favorable outcome (mRS 0–2) was also significantly more likely in DC than DS admissions after thrombolysis [**(C)**; DS $n = 1{,}273$, DC $n = 1{,}485$; OR 0.73; 95%-CI 0.64–0.83; $p < 0.001$], but not if thrombolysis was not administered [**(D)**; DS $n = 977$, DC $n = 1{,}663$; OR 0.87; 95%-CI 0.72–1.05; $p = 0.149$].

Discussion

In this retrospective analysis DS patients fared worse in terms of functional neurological outcome 90 days after stroke compared to DC admission. This difference persisted after propensity score matching and adjustment for confounding factors. The most likely causative factor was a median time delay from symptom onset to reperfusion of 99 min between DC and DS. The risk of intracranial hemorrhages after recanalization was also higher in DS than DC (19.6 vs. 15.4%), a finding which might be attributed to more reperfusion injury after delayed recanalization. Other stroke registries have already stressed the time advantage of the DC strategy with a median delay of 109 and 96 min from symptom onset to recanalization, respectively (5, 13). A median time delay of 99 min as in our study would correspond to the loss of roughly 188 million neurons per patient according to a modeled analysis (14).

Considering these disadvantages of DS, should ambulances be instructed that "routing is brain" or is there potential for improvement of the paradigm? Based on clinical data, statistical models have been developed to determine which proximity of EVT centers and procedure times would justify bypassing thrombolysis-only hospitals (15). A probabilistic sensitivity analyses suggest that bypassing peripheral stroke units may achieve better functional outcomes, unless it delays thrombolysis by more than 30 min in urban and 50 min in rural areas (16).

This strategy has been put to test in the recently published RACECAT trial (17). Here, neurological disability of patients,

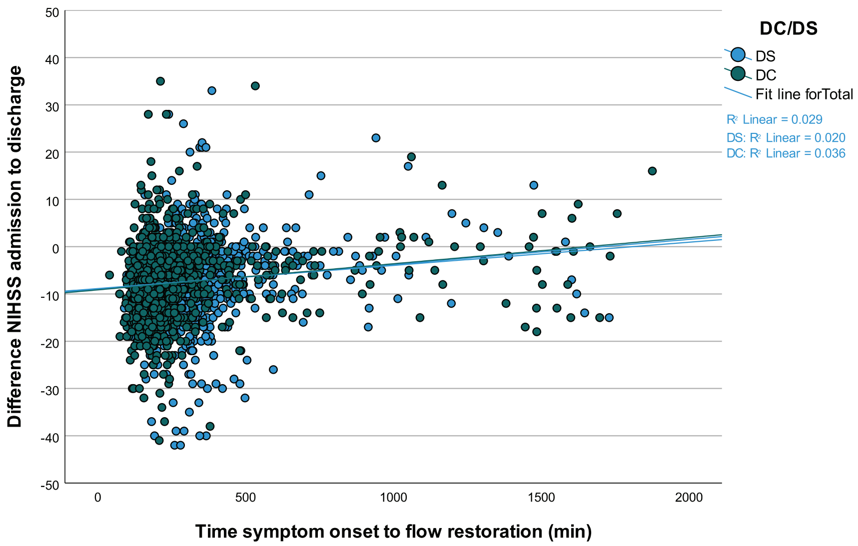

FIGURE 3
Correlation between the time from symptom onset to successful endovascular recanalization and the absolute difference of NIHSS scores at hospital admission and discharge. Values <0 signify a benefit from thrombectomy and values ≥ 0 suggest lack of benefit, which becomes more likely along with passing time in minutes for drip-and-ship (DS) and direct-to-center treated patients ($n = 2,366$; $\rho = 0.27$; $p < 0.001$).

who were preclinically randomized to either be transported directly to a thrombectomy center or the closest stroke unit based on a clinical score indicating LVO, was not different after 90 days. However, mRS > 2 and admission > 7 h from symptom onset were exclusion criteria, which differs from real-world data and would exclude about 40% of patients in our study (18).

In general, time delay is a modifiable by logistic optimization. Pre-hospital delays have an influence in both settings, as evidenced by a GSR analysis with focus on treatment times, which showed an increase in unfavorable outcome with every additional hour from onset to admission for DC- and DS-treated patients (absolute risk difference +0.7 vs. +1.3%) (19). An analysis of a federal stroke registry in Germany demonstrated onset-to-EVT times in DS patients were considerably shortened by approximately 100 min since 2012, most likely allowing for better clinical outcomes in the future (20).

However, even with shortened transport-to-center times, many patients are still likely to arrive in a late time window, i.e., >6 h after symptom onset or >2 h after initial imaging, prompting the question whether to repeat imaging. Our results suggest that DS patients undergoing MRI before EVT were more likely to achieve a good outcome despite longer intervals between symptom onset and recanalization. This appears likely to represent a selection bias by excluding patients who subsequently did not receive EVT due to presumed lack of salvageable tissue. The approximate intrahospital time delay caused by MRI was 22 min compared to CT and 48 min to no secondary imaging. Hence, it is important to consider whether the associated loss of salvageable tissue can be legitimized by cases, in which patients can be spared an unnecessary thrombectomy with inherent intra- and post-procedural risks (21). Such futile interventions could possibly be reduced by MRI and ASPECTS can guide prognostication, which might then outweigh the disadvantage of time consumption (22). Considering the recently published RESCUE-JAPAN results, even patients with a MRI-ASPECTS of 3–5 can benefit from EVT compared to medical treatment alone, but it is important to note that in a time window of >6 h after symptom onset MRI mismatch between diffusion-weighted-imaging and fluid attenuation inversion recovery was utilized (23). Besides MRI, mismatch imaging with CT-perfusion might also provide clinical information as a basis for decision-making. A comprehensive registry or prospective studies of secondary imaging after transfer regardless of whether subsequent EVT was performed would certainly provide better evidence for clinical decision making.

There are several limitations to this study. Firstly, only EVT was included, therefore no definite conclusion on transfer strategies for all stroke patients can be formed. Due to the voluntary nature of participation in the GSR a possible selection bias cannot be excluded. However, compared to other registries which are limited to preformed stroke networks, the GSR resembles real-world conditions more closely due to decentralization. No distances between the patient's location and admitting stroke center were recorded, but the time between

TABLE 3 Results from baseline characteristics, treatment procedures and outcome of direct-to-center and drip-and-ship patients after propensity score matching.

	Direct-to-center	Drip-and-ship	*p*-value
Final TICI			
0	308 (8.1%)	223 (7.9%)	0.035[b]
1	51 (1.3%)	44 (1.6%)	
2a	205 (5.4%)	156 (5.5%)	
2b	1,189 (31.1%)	978 (34.8%)	
3	1,954 (51.2%)	1,369 (48.7%)	
ICH during MT	90 (2.4%)	90 (3.2%)	0.039[a]
ICH after 24 h	381 (10.0%)	354 (12.6%)	0.001[a]
ICH between 24 h and discharge	118 (3.1%)	106 (3.8%)	0.132[a]
Recurrent stroke after 24 h	203 (5.3%)	59 (2.1%)	<0.001[a]
Recurrent stroke between 24 h and discharge	62 (1.6%)	37 (1.3%)	0.357[a]
Malignant media infarction after 24 h	118 (3.1%)	108 (3.8%)	0.100[a]
Malignant media infarction between 24 h and discharge	98 (2.6%)	91 (3.2%)	0.117[a]
Median NIHSS after 24 h (IQR)	10 (4–19)	12 (5–19)	<0.001[b]
NIHSS on discharge (median, IQR)	5 (2–14)	6 (1–13)	<0.001[b]
NIHSS admission-discharge (median, IQR)	−6 (−11 to −1)	−5 (−10 to 0)	0.003[b]
mRS on discharge (median, IQR)	3 (2–5)	4 (2–5)	<0.001[a]
mRS after 90 days (median, IQR)	3 (1–5)	3 (1–5)	0.003[a]
Symptom onset—admission in center (minutes, median, IQR)	65 (49.0–107.0) ($n = 2{,}052$)	195.0 (149.0–254.0) ($n = 1{,}738$)	<0.001[b]
Admission—groin puncture (minutes, median, IQR)	82.0 (61.0–159.0) ($n = 3{,}415$)	48.0 (31.0–114.0) ($n = 2{,}624$)	<0.001[b]
Groin puncture—flow restoration (minutes, median, IQR)	41.0 (26.0–101.0) ($n = 3{,}137$)	41.0 (26.0–98.0) ($n = 2{,}429$)	0.758[b]
Symptom onset—flow restoration (minutes, median, IQR)	201.0 (160.0–380.0) ($n = 1{,}740$)	297.5 (240.0–477.0) ($n = 15{,}05$)	<0.001[b]
Symptom onset—thrombolysis (minutes, median, IQR)	90.0 (72.0–175.0) ($n = 1{,}186$)	95.0 (71.0–180.0) ($n = 897$)	0.220

Analysis was performed by χ^2-test[a] for categorical data and Mann-Whitney-*U*-test[b] for continuous, non-Gaussian data. Mean and standard deviation (SD) or median and interquartile range (IQR) are shown as appropriate. ICH, intracranial hemorrhage.

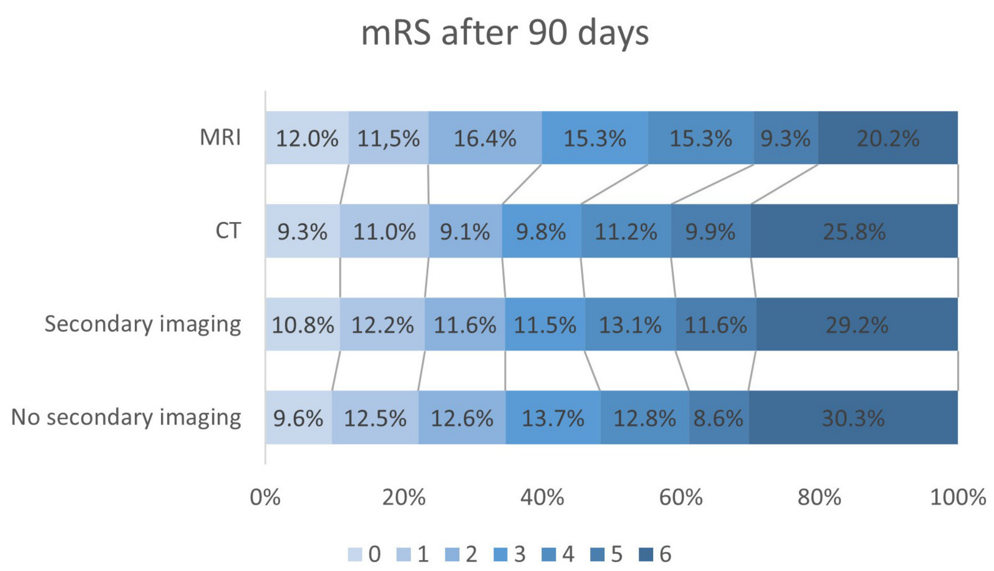

FIGURE 4
Modified Ranking scale (mRS) outcome data after 90 days in all drip-and-ship (DS) patients without secondary imaging ($n = 1{,}171$), with secondary imaging in interventional center ($n = 1{,}045$), only CT-imaging ($n = 944$) and MRI ($n = 183$). Secondary imaging in general did not significantly affect mRS compared to only initial imaging in peripheral centers ($p = 0.206$). After multivariable adjustment DS patients undergoing MRI before EVT had lower mRS scores than those without (OR 0.63; 95%-CI 0.46–0.88; $p = 0.006$).

TABLE 4 Baseline characteristics and procedure times of drip-and-ship admissions according to whether secondary imaging was performed and if there was CT only or MRI available.

	No secondary imaging	Secondary imaging	*p*	CT only	MRI	*p*
n	1,171	1,045		944	183	
Mean age (years ± SD)	73.9 ± 12.5	72.2 ± 13.0	0.020[b]	72.7 ± 12.7	70.6 ± 13.6	0.060[b]
Sex (female; *n*; %)	606 (51.8%)	510 (48.9%)	0.173[b]	468 (49.6%)	86 (47.0%)	0.519[b]
Median mRS before stroke (IQR)	0 (0–1)	0 (0–1)	0.032[a]	0 (0–1)	0 (0–1)	0.580[b]
NIHSS on admission (median, IQR)	15.0 (10.0–19.0)	15.0 (9.0–19.0)	0.007[b]	15.0 (9.0–19.0)	12.0 (7.0–17.0)	0.004[b]
ASPECTS (median, IQR)	9.0 (8.0–10.0)	9.0 (7.0–8.0)	<0.001[b]	8.0 (7.0–9.0)	7.5 (6.0–9.0)	0.027[b]
Thrombolysis (*n*; %)	653 (56.4%)	588 (56.3%)	0.996[a]	544 (57.6%)	90 (49.5%)	0.050[a]
Symptom onset—admission in center (minutes, median, IQR)	187.0 (145.0–242.8)	198.0 (148.0–255.0)	0.035[b]	194.0 (147.0–250.5)	240.0 (190.0–316.0)	<0.001[b]
Admission—groin puncture (minutes, median, IQR)	34.0 (25.0–48.0)	62.0 (46.0–86.0)	<0.001[b]	60.0 (44.0–81.0)	82.0 (50.0–117.0)	<0.001[b]
Admission—flow restoration (minutes, median, IQR)	77.0 (57.0–109.0)	113.0 (87.0–148.0)	<0.001[b]	111.0 (85.0–143.0)	130.0 (96.0–180.0)	<0.001[b]
Groin puncture—flow restoration (minutes, median, IQR)	38.0 (25.0–61.0)	43.0 (28.0–70.0)	0.001[b]	43.0 (27.0–70.0)	40.0 (27.0–69.0)	0.761[b]
Symptom onset—flow restoration (minutes, median, IQR)	270.0 (219.0–345.0)	313.0 (260.0–386.3)	<0.001[b]	310.0 (255.0–375.0)	381.0 (334.8–517.8)	<0.001[b]

Analysis was performed by χ^2-test[a] for categorical data and Mann-Whitney-*U*-test[b] for continuous, non-Gaussian data. Mean and standard deviation (SD) or median and interquartile range (IQR) are shown as appropriate.

onset and admission is likely to be a more relevant factor considering different transport mechanisms. Another difference in baseline parameters between our DC and DS group were more proximal vessel occlusions in the latter, which could partly explain the less favorable results. Lastly, there was a difference in the availability of follow-up information after 90 days between groups, for which possible factors such as death cannot be ruled out.

Conclusions

Secondary transfer led to worse outcome compared to direct-to-center EVT. Considering the similar correlation between time to recanalization and NIHSS reduction in both groups, optimizing EVT workflows to reduce time delay remains a crucial factor to improve the DS paradigm. Despite late recanalization, patients with MRI showed favorable outcomes compared to no secondary imaging and MRI-ASPECTS correlated negatively with mRS after 90 days, suggesting that in certain settings (e.g., after prolonged transfer) MRI could augment prognostic accuracy, which in turn could facilitate a better definition of the patient collective most likely to benefit despite delayed EVT and thus reduce futile interventions.

Data availability statement

The raw data supporting the conclusions of this article can be provided upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Ludwig-Maximilian University Munich (689-15). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JS, WP, and FB researched literature and conceived the study. JS, NK, and FB gathered and analyzed the data. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Conflict of interest

Author FB reports receiving research grant from Stryker Neurovascular and Boehringer Ingelheim and speaker's honoraria from Alexion, Medtronic and Laerdal. Author WP reports speaker's honoraria from Laerdal.

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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Emergency medical service utilization among acute ischemic stroke patients in Beijing: An observational study

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Objective: To investigate emergency medical service (EMS) utilization and its associated factors in patients with acute ischemic stroke (AIS), and further explore the urban-rural differences.

Methods: Medical records for AIS in all emergency departments in Beijing were obtained from the Beijing Emergency Care Database from January 2018 to December 2021. EMS utilization was described and factors associated with EMS use were examined by multivariable logistic regression models with the generalized estimating equations. Results were compared between urban and rural districts.

Results: A total of 24,296 AIS patients were included in the analysis, and 11,190 (46.1%) were transported to hospitals by EMS. The percentage of EMS usage in urban areas was significantly higher than that in rural areas (53.6 vs. 34.4%, $P < 0.001$). From 2018 to 2021, EMS utilization was on the increase (P-value for trend <0.001) with a higher average annual growth rate in rural areas (12.6%) than in urban (6.4%). Factors associated with EMS utilization were age (OR: 1.20 per 10-year increase, 95% CI: 1.17–1.23), NIHSS scores, off-hour arrival (OR: 1.32, 95% CI: 1.23–1.37), treatment in tertiary hospitals (OR: 1.75, 95% CI: 1.60–1.92), and possessing comorbidities such as coronary artery disease (OR: 1.15, 95% CI: 1.17–1.24), atrial fibrillation (OR: 1.56, 95% CI: 1.41–1.73), prior stroke (OR: 0.84, 95% CI: 0.78-0.90) or dyslipidemia (OR: 0.78, 95% CI: 0.71–0.85).

Conclusion: This study demonstrated an inadequate use of EMS among AIS patients in Beijing, especially in rural areas, and revealed several associated factors. Enhanced education programs and EMS accessibility are necessary particularly for high-risk individuals and regions.

KEYWORDS

emergency medical services, acute ischemic stroke, risk factors, urban-rural disparities, prehospital delay

Introduction

Acute ischemic stroke (AIS) is one of the leading causes of mortality and disability in China and around the world (1–4). Early diagnosis and timely treatment are paramount to achieve maximal functional recovery (5). Emergency medical services (EMS) utilization among AIS has been proven to significantly shorten prehospital delay and enhance prenotification of the receiving hospital (5), and rapid thrombolytic treatment was observed subsequently (6–8). Many studies have shown that the main challenges in stroke management in China are pre-hospital delays and a relatively low thrombolysis rate, while the main benefits of EMS are quicker triage and higher rates of thrombolysis (9, 10). However, the rate of EMS utilization (12.5%) is currently low among Chinese AIS patients in a national study in 2018 (7). Among other regional studies in China, the prevalence of EMS utilization shows a difference due to various distributions of medical resources and patient awareness in space and time (11–13). To improve the management of AIS acute care in China it is important to monitor the use of pre-hospital EMS and respond to changing patterns. Equally considerable is that such adequate care should be delivered in both urban and rural regions. Yet the use and determinants of health and emergency services likely differ between rural and urban regions, on account of different healthcare infrastructure, characteristics, and preferences of patients (14).

A program targeted at streamlining AIS care processes in prehospital and stroke facilities has been implemented in Beijing since January 2018 (15). Using the data acquired by this program, we aimed to describe the pattern of EMS utilization, identify associated factors with EMS activation, and compare them between urban and rural areas. The results may provide valuable information to achieve appropriate EMS planning and develop effective interventions to reduce delays and improve outcomes for AIS patients.

Methods

Data source and study population

An observational study was conducted based on historical data from Jan. 2018 to Dec. 2021. Data were obtained from the Beijing Emergency Care Database (16). The database keeps records of medical information for several conditions (acute stroke, heart attack, injury, and gynecological diseases) in the EMS system and emergency departments in secondary and tertiary hospitals in Beijing. This prospective registry was established in January 2018 and has been updated in real-time since then (15). For acute stroke, patients from all the 74 hospitals eligible for AIS acute care, included in the First Aid Treatment Map for Stroke (FATMS) published by Beijing Health and Family Planning Commission (Figure 1; Supplementary Table 1), were all recorded by a standard platform. Paramedics, physicians, and nurses in all eligible centers were trained to streamline the AIS emergency management processes by using this platform. For patients transported by the ambulance, once the paramedics identified a suspected IS patients, the nearest qualified hospital will be prenotified to clear a fast pathway for the coming patients. During transportation, paramedics initiated the patient's records on the platform. For patients who arrivied the hospitals by themselevs, nurses in the emergency departments would notify the AIS acure care team and start the records on the platform directively (15). Records of patients who arrived at the hospital within 4.5 h of onset were kept in the database. The main variables included demographic information, comorbidities, ways of transportation, types of treatment, diagnosis at discharge, hospital information, and so on. Patients with the primary diagnosis of AIS from January 2018 to December 2021 were included in this study. After excluding in-hospital stroke and transferred patients, a total of 24,296 AIS patients were included in the analysis.

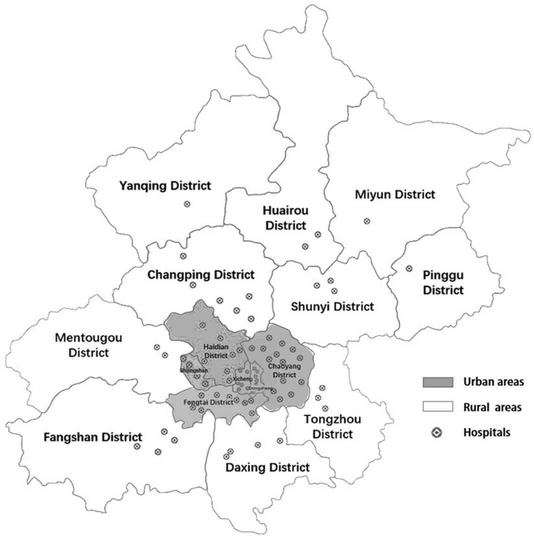

FIGURE 1
Seventy four hospitals in the First Aid Treatment Map for Stroke (FATMS) in Beijing.

Outcome measure and key variables

Patients who were transported to hospitals by ambulance were identified as using EMS. The main outcome of interest was the percentage of EMS use in AIS patients. Other key variables included in the analysis were demographic features (age and sex), stroke severity, time of hospital arrival, comorbidity, the level of receiving hospitals, and district (urban or rural areas). Stroke severity was determined by the National Institutes of Health Stroke Scale (NIHSS) score and stratified as <6, 6 to 15, and >15. Time of hospital arrival was defined as on-hour arrival (8 am to 6 pm) or off-hour arrival (6 pm to 8 am). Comorbidity was concerned with the presence of vascular-related diseases, including hypertension, dyslipidemia, diabetes mellitus, prior stroke, heart failure (HF), atrial fibrillation, coronary artery disease, carotid stenosis (CS), and peripheral vascular disease (PVD) (7). The receiving hospitals were classified as secondary hospitals or tertiary hospitals, according to the Beijing Municipal Health Commission. The district variable (urban or rural areas) depended on where the patient lives according to the classification of the National Bureau of Statistics of China. Six districts of Beijing were classified as urban (including Dongcheng district, Xicheng district, Chaoyang district, Haidian district, Shijingshan district and Fengtai district), while the remaining ten districts were classified as rural (Figure 1). The differences in the accessibility and effectiveness of the urban and rural health services were striking according to previous studies (17).

Statistical analysis

Characteristics of AIS patients were first described by frequencies and percentages for categorical variables, mean and standard deviation (SD) for continuous variables with normal distribution, and median and interquartile range (IQR) for continuous variables with skewed distribution. Characteristics of patients between urban and urban areas were then compared by the chi-square test, Student's *t*-test, or Wilcoxon test. Factors associated with EMS utilization were further examined by fitting multivariable logistic regression models with the generalized estimating equations to account for within-hospital clustering. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported after adjusting for individual and hospital characteristics, including age, sex, baseline NIHSS group, comorbidities, time of hospital arrival, and level of receiving hospital. Besides, the calendar year was added as an adjustment variable in the sensitivity analysis. All analyses were conducted by different districts. Statistical significance was set at a *P*-value of 0.05. All analyses were conducted in R (v.4.1.0).

Results

Characteristics of AIS patients

A total of 24,296 AIS patients were analyzed with a mean age of 65.6 (SD: 12.8) years and 68.4% of males. The average baseline NIHSS score was 7.9 (SD: 6.9). Over three-quarters of patients had one or more vascular-related comorbidities. Two-fifths of patients arrived at the hospital from 6 pm to

TABLE 1 Characteristics of AIS patients.

	Overall (*N* = 24,296)	Urban (*N* = 14,766)	Rural (*N* = 9,530)	*P*-value
Age, years, mean (sd)	65.6 (12.8)	66.6 (13.1)	64.1 (12.1)	<0.001
Male, *n* (%)	16,620 (68.4)	10,059 (68.1)	6,561 (68.8)	0.242
NIHSS score				<0.001
0–5	11,587 (47.7)	6,702 (45.4)	4,885 (51.3)	
6–16	98,74 (40.6)	6,221 (42.1)	3,653 (38.3)	
>16	28,35 (11.7)	1,843 (12.5)	992 (10.4)	
Comorbidity, *n* (%)				
Hypertension	14,240 (58.6)	8,556 (57.9)	5,684 (59.6)	0.009
Diabetes mellitus	6,111 (25.2)	3,952 (26.8)	2,159 (22.7)	<0.001
Prior stroke	6,036 (24.8)	3,810 (25.8)	2,226 (23.4)	<0.001
Coronary artery disease	4,505 (18.5)	2,882 (19.5)	1,623 (17.0)	<0.001
Dyslipidemia	2,917 (12.0)	1,955 (13.2)	962 (10.1)	<0.001
Atrial fibrillation	2,672 (11.0)	1,874 (12.7)	798 (8.4)	<0.001
HF/CS/PVD*	330 (13.6)	189 (12.8)	141 (14.8)	0.209
Off-hour arrival, *n* (%)	9,950 (41.0)	6,209 (42.0)	3,741 (39.3)	<0.001
Weekend arrival, *n* (%)	6,706 (27.6)	4,055 (27.5)	2,651 (27.8)	0.555
Level of hospitals, *n* (%)				<0.001
Secondary hospitals	2,752 (11.3)	1,039 (7.0)	1,713 (18.0)	
Tertiary hospitals	21,544 (88.7)	13,727 (93.0)	7,817 (82.0)	

*HF, heart failure; CS, carotid stenosis; PVD, peripheral vascular disease.

8 am and a quarter of patients arrived on weekend. The characteristics of the patients were shown in Table 1. There were 14,766 (60.8%) and 9,530 (39.2%) patients treated in urban and rural areas, respectively. Patients in urban areas were older, had higher NIHSS scores, were more likely to present face drooping or slurred speech, arrive at hospitals on off-hour, possess comorbidities, and be treated in tertiary hospitals (Table 1).

EMS utilization

Among all AIS patients, 11,190 (46.1%) were transported to hospitals by EMS, and the percentage of EMS usage in urban areas was significantly higher than in rural areas (53.6 vs. 34.4%, $P < 0.001$). From 2018 to 2021, EMS utilization was on the increase in both areas (both *P*-values for trend <0.001), with a higher rate in urban areas each year (Figure 2). The average annual growth rate in rural areas was higher than in urban areas (12.6 vs. 6.4%, $P < 0.001$). The higher percentages of EMS usage in urban areas were shown in patients with different characteristics, except for those treated in secondary hospitals (Table 2).

Compared with patients in the non-EMS groups, patients in the EMS group were older, more likely to be females, more severe, more likely to possess comorbidities, and more likely to be received intravenous thrombolysis therapy with door-to-needle time ≤60 min (Supplementary Table 2).

Factors associated with EMS utilization

Factors associated with the use of EMS were older age (OR: 1.20 per 10-year increase, 95% CI: 1.17–1.23), higher baseline NIHSS scores, off-hour arrival (OR: 1.30, 95% CI: 1.23–1.37), treatment in tertiary hospitals (OR: 1.75, 95% CI: 1.60–1.92), and possessing comorbidities such as coronary artery disease (OR: 1.15, 95% CI: 1.07–1.24) and atrial fibrillation (OR: 1.56, 95% CI: 1.41–1.73). Factors associated with not use of EMS were possessing comorbidity of prior stroke (OR: 0.84, 95% CI: 0.78–0.90) or dyslipidemia (OR: 0.78, 95% CI: 0.71–0.85).

When further stratified by district, factors associated with EMS utilization were similar in rural and urban regions except for sex, off-hour arrival, possessing HF/CS/CVD, and treatment in tertiary hospitals (Table 3). The association between sex and EMS usage was only observed in urban areas but not in rural areas. Possessing HF/CS/CVD was significantly associated with the tendency of EMS utilization only in the rural area but not in the urban area, while the association between EMS utilization and treatment in tertiary hospitals was only significant in the urban area. The association between EMS utilization and off-hour arrival was stronger in the urban area than in the rural area. The results were similar when added calendar year as an adjustment variable in the sensitivity analysis (Supplementary Table 3).

Discussion

Timely delivery of reperfusion therapies is paramount for the neurological recovery of AIS patients. EMS utilization is reportedly the most significant and consistent factor associated

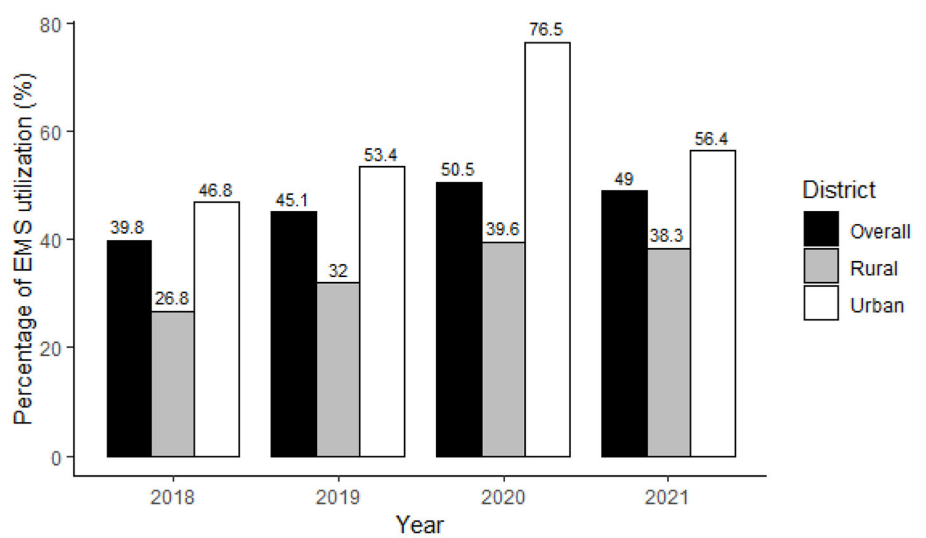

FIGURE 2
Percentage of EMS utilization in AIS patients in Beijing, 2018–2021.

TABLE 2 Percentage of EMS utilization in AIS patients with different characteristics.

	Urban, *n* (%)		Rural, *n* (%)		*P*-value
	EMS	non-EMS	EMS	non-EMS	
Age					
18–59	1,992 (45.0)	2,431 (55.0)	922 (27.6)	2,423 (72.4)	<0.001
60–74	3,136 (52.0)	2,893 (48.0)	1,414 (33.4)	2,824 (66.6)	<0.001
75+	2,782 (64.5)	1,532 (35.5)	944 (48.5)	1,003 (51.5)	<0.001
Sex					
Male	5,174 (51.4)	4,885 (48.6)	2,217 (33.8)	4,344 (66.2)	<0.001
Female	2,736 (58.1)	1,971 (41.9)	1,063 (35.8)	1,906 (64.2)	<0.001
NIHSS group					
0–5	2,283 (34.1)	4,419 (65.9)	943 (19.3)	3,942 (80.7)	<0.001
6–16	4,050 (65.1)	2,171 (34.9)	1,637 (44.8)	2,016 (55.2)	<0.001
>16	1,577 (85.6)	266 (14.4)	700 (70.6)	292 (29.4)	<0.001
Comorbidity					
Hypertension	4,638 (54.2)	3,918 (45.8)	1,987 (35.0)	3,697 (65.0)	<0.001
Diabetes mellitus	2,086 (52.8)	1,866 (47.2)	724 (33.5)	1,435 (66.5)	<0.001
Prior Stroke	1,912 (50.2)	1,898 (49.8)	782 (35.1)	1,444 (64.9)	<0.001
Coronary artery disease	1,756 (60.9)	1,126 (39.1)	674 (41.5)	949 (58.5)	<0.001
Atrial fibrillation	1,376 (73.4)	498 (26.6)	458 (57.4)	340 (42.6)	<0.001
Dyslipidemia	875 (44.8)	1,080 (55.2)	276 (28.7)	686 (71.3)	<0.001
HF/CS/PVD*	127 (67.2)	62 (32.8)	40 (28.4)	101 (71.6)	<0.001
Off-hour arrival	3,631 (58.5)	2,578 (41.5)	1,363 (36.4)	2,378 (63.6)	<0.001
Weekend arrival	2,230 (55.0)	1,825 (45.0)	932 (35.2)	1,719 (64.8)	<0.001
Level of hospital					
Secondary hospital	342 (32.9)	697 (67.1)	571 (33.3)	1,142 (66.7)	0.854
Tertiary hospital	7,568 (55.1)	6,159 (44.9)	2,709 (34.7)	5,108 (65.3)	<0.001

*HF, heart failure; CS, carotid stenosis; PVD, peripheral vascular disease.

with reduced prehospital delays among AIS patients. To approve the probabilities of timely treatment, activation of EMS after a stroke attack is recommended by recent guidelines (18). Since January 2018, a program aimed at streamlining the AIS care processes in prehospital has been implemented in Beijing including promoting the use of ambulances. Based on a 4-year observation, we investigate EMS utilization and its associated factors in patients with acute ischemic stroke (AIS) and further explored the urban-rural difference.

According to the results, less than half (46.1%) of AIS patients were transported *via* ambulance in Beijing. Previous studies revealed the EMS utilization rates in other provinces and cities in China were only 9.1–32.9% (11–13), with a national reported rate of 12.5% in 2018 (7). The percentage of patients who use EMS in Beijing was higher than in other places in China. Even though, the percentage of EMS usage in this study was much lower than the reported 63.7% in the United States (6), 78.8% in England (19), and 72.0% in Germany (20). Insufficient prehospital EMS resources and the lack of awareness of stroke symptoms may partially explain the fewer EMS usage in China, which justifies specific stroke education strategies and proper EMS infrastructure planning for the targeted regions and population (21).

Consistent with previous studies (14, 22, 23), the EMS utilization differed between urban and rural regions, with significantly higher rates in urban areas. However, the prevalence, incidence, and mortality of stroke in China were significantly higher in rural than in urban areas (3). The disease burden of stroke consistently increased over the past 30 years, especially in the rural area. The imbalance in vascular risk factors, economic development, access to healthcare, and so on (22, 24, 25) may contribute to the urban-rural disparities in EMS utilization. Despite it, increasing year-on-year utilization of EMS over the past 4 years in both urban and rural areas has been observed in our study. Besides, the average annual growth rate in rural areas was nearly two times the rate in urban areas (12.6 vs. 6.4%, $P < 0.001$). It was worth noting that although rural residents were underutilizing EMS when compared to their urban counterparts, the significant decrements in urban-rural disparities reflect the positive effect of

TABLE 3 Factors associated with EMS utilization*.

	Total		Urban		Rural		Interaction
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	*P*-value
Age per 10 years	1.20 (1.17, 1.23)	<0.001	1.18 (1.15, 1.22)	<0.001	1.19 (1.14, 1.24)	<0.001	0.650
Sex							
Female	ref		ref		ref		
Male	1.06 (1.00, 1.13)	0.059	1.00 (0.92, 1.08)	0.974	1.12 (1.01, 1.24)	0.025	0.076
NIHSS group							
0–5	ref		ref		ref		
6–16	3.19 (3.01, 3.39)	<0.001	3.14 (2.90, 3.41)	<0.001	3.26 (2.95, 3.60)	<0.001	0.622
>16	7.98 (7.18, 8.88)	<0.001	8.46 (7.30, 9.81)	<0.001	7.95 (6.77, 9.33)	<0.001	0.306
Comorbidity							
Hypertension	1.02 (0.96, 1.08)	0.522	1.04 (0.96, 1.12)	0.377	1.07 (0.97, 1.18)	0.154	0.889
Diabetes mellitus	1.03 (0.96, 1.10)	0.462	1.00 (0.92, 1.09)	0.956	0.98 (0.88, 1.10)	0.768	0.979
Prior stroke	0.84 (0.78, 0.90)	<0.001	0.79 (0.72, 0.86)	<0.001	0.88 (0.79, 0.98)	0.025	0.125
Coronary artery disease	1.15 (1.07, 1.24)	<0.001	1.17 (1.06, 1.29)	0.002	1.14 (1.00, 1.29)	0.044	0.716
Atrial fibrillation	1.56 (1.41, 1.73)	<0.001	1.49 (1.31, 1.69)	<0.001	1.50 (1.26, 1.77)	<0.001	0.785
Dyslipidemia	0.78 (0.71, 0.85)	<0.001	0.74 (0.66, 0.83)	<0.001	0.77 (0.65, 0.91)	0.002	0.582
HF/CS/PVD	0.91 (0.71, 1.17)	0.463	1.26 (0.89, 1.79)	0.192	0.65 (0.44, 0.98)	0.038	0.012
Off-hour arrival	1.30 (1.23, 1.37)	<0.001	1.37 (1.27, 1.47)	<0.001	1.16 (1.05, 1.27)	0.002	0.003
Weekend arrival	1.03 (0.97, 1.10)	0.321	1.04 (0.96, 1.13)	0.297	1.02 (0.92, 1.14)	0.649	0.832
Level of hospital							
Secondary hospital	ref		ref		ref		
Tertiary hospital	1.75 (1.60, 1.92)	<0.001	2.04 (1.76, 2.37)	<0.001	1.07 (0.95, 1.21)	0.286	<0.001

*HF, heart failure; CS, carotid stenosis; PVD, peripheral vascular disease. OR and 95% CI were obtained by multivariable logistic regression models with the generalized estimating equations to account for within-hospital clustering. Variables included in multivariable models were age, sex, baseline NIHSS group, comorbidities, time of hospital arrival, and level of receiving hospital.

implementing a uniform stroke management model across the whole region.

We identified several factors associated with seeking EMS, including older age, more severe stroke, possessing atrial fibrillation or coronary artery disease, off-hour hospital arrival, and treatment in tertiary hospitals. The results could be used as a crucial basis for improving education strategies and EMS planning. The facilitators of EMS use in this study were similar to previous studies (6, 7, 12, 26, 27). A possible explanation is that patients with these characteristics are more likely to access EMS and realize the need for urgent stroke treatment. Older patients tend to be vulnerable and have more severe symptoms at the onset, which may prompt patients and bystanders to activate EMS as soon as symptoms manifest in case of more serious consequences (6, 26). Similarly, patients with higher NIHSS baseline scores presented with more severe and acute symptoms, which may prompt patients and bystanders to recognize stroke-related episodes and initiate EMS (6, 12). Consistent with another Chinese study that found that strong predictors of EMS use were cardiovascular disease (7), patients with atrial fibrillation or coronary artery disease in this study were more likely to activate EMS. The likely explanation is that these patients and their co-residents are well educated to use EMS, or even have used EMS multiple times. Patients with AIS onset outside of working hours may have difficulty using public transport or taxis after operating hours, raising the possibility that EMS will be selected. Treating in tertiary hospitals might indicate a higher level of income and health awareness and access to adequate EMS resources and in-hospital education, thus promoting recognition of stroke and decisions using EMS (28). In addition, consistent with what has been reported in other studies (6, 29, 30), we found that patients with prior stroke were less likely to use EMS, indicating potential missed opportunities to educate stroke or TIA patients on the need for EMS transportation at future symptom onset, and suggesting that in-hospital education should be strengthened due to the high recurrence rate of stroke. Previous studies have confirmed that patient knowledge regarding stroke is still lacking at the time of discharge (31, 32). It has also shown that awareness does not necessarily translate into appropriate actions to use the EMS immediately at stroke onset (32, 33). Therefore, not only should discharge education on stroke recognition be improved but timely EMS usage should also be vigorously advocated to reduce prehospital delays when suffering a relapse.

Public education remains imminently reinforced, especially toward high-risk populations, such as individuals with advanced age, hypertension, prior stroke, and their families, to improve their ability to identify initial symptoms as stroke-related and recognize the urgency of contacting EMS.

In the stratification analysis, off-hour arrival and treatment in tertiary hospitals were more strongly correlated with EMS usage in urban areas than in rural areas. The underlying reasons for these characteristics cannot be determined right now. However, the various distributions of medical resources among regions and different levels of health literacy among populations may be an explanation for the disparities in the EMS utilization (34, 35). The association between sex and EMS usage was only observed in urban areas but not in rural areas, which may suggest the gap in awareness of seeking medical care related to socioeconomic status (36–38). The significant difference in EMS utilization between urban and rural areas suggests that special attention should be paid to rural areas to promote equal access to basic public health services and safeguard public welfare (39). Existing or newly developed stroke education programs need to expand their coverage and ensure efficient delivery of stroke knowledge to vulnerable high-risk people in rural areas (40, 41).

There are some limitations in the study. First, the research was carried out in Beijing with relatively rich medical resources, which could not represent other places lacking medical resources. As mentioned above, the EMS utilization rate in Beijing was significantly higher than that in other regions. The extrapolation of the results should be cautious. Second, the urban-rural division of Beijing based on administrative functions differed from the classical definition of urbanization. Nevertheless, previous studies have found significant differences between urban and rural residents in their use of chronic medical services (17), as well as the urban-rural differences in EMS use in our study. Third, based on the historical data from an administrative database, some factors such as economic status, health literacy, attitude to activate EMS, the performances of EMS on the therapy outcome and the long-term health should be evaluated when data are available.

Conclusion

This study demonstrated an inadequate use of EMS among AIS patients in Beijing, especially in rural areas. Several factors were identified to be associated with EMS utilization including older age, more severe stroke, first stroke, possessing atrial fibrillation or coronary artery disease, off-hour hospital arrival, treating in tertiary hospitals, and living in urban communities. Enhanced education programs and EMS accessibility are still necessary, particularly for high-risk individuals and regions.

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 the Ethics Committee of Peking University Health Science Center, Beijing, China. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YWu and WenZ contributed to the study concept and had full access to all the data in the study. KD, YWu, and HC take responsibility for the integrity of the data, interpreted the findings, and drafted the article. KD, YWa, HL, and BC contributed to the data analysis. WeiZ, LG, GD, and TS interpreted the data. WenZ and YWu attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All the authors contributed to the critical revision of the article for important intellectual content and approved the submitted version.

Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.969947/full#supplementary-material

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Incidence, lethality, and post-stroke functional status in different Brazilian macro-regions: The SAMBA study (analysis of stroke in multiple Brazilian areas)

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Background: Stroke is the second leading cause of death in Brazil. The social and financial burden of stroke is remarkable; however, the epidemiological profile remains poorly understood.

Objective: The aim of this study was to report the incidence, lethality, and functional status at 30 and 90 days post-stroke in the cities of different Brazilian macro-regions.

Methods: This is an observational, prospective, and population-based study, led in Canoas (South), Joinville (South, reference center), Sertãozinho (Southeast), and Sobral (Northeast) in Brazil. It was developed according to the three-step criteria recommended by the World Health Organization to conduct population-based studies on stroke. Using different sources, all hospitalized and ambulatory patients with stroke were identified and the same criteria were kept in all cities. All first events were included, regardless of sex, age, or type of stroke. Demographic and risk factor data were collected, followed by biochemical, electrocardiographic, and radiological test results. Functional status and lethality were obtained using the mRankin scale through telephonic interview (validated Brazilian version).

Results: In 1 year, 932 stroke cases were registered (784 ischemic stroke, 105 hemorrhagic stroke, and 43 subarachnoid hemorrhage). The incidence rates per 100,000 inhabitants, adjusted for the world population, were 63 in Canoas, 106 in Joinville, 72 in Sertãozinho, and 96 in Sobral. The majority (70.8%) were followed for 90 days. Kaplan–Meier curves showed that 90-day survival was different among cities. Sobral, which has the lowest socioeconomic indexes, revealed the worst results in terms of lethality and functional status.

Conclusion: This study expands the knowledge of stroke epidemiology in Brazil, a middle-income country with enormous socioeconomic and cultural diversity. The discrepancy observed regarding the impact of stroke in patients from Joinville and Sobral highlights the need to improve the strategic allocation of resources to meet the health priorities in each location.

KEYWORDS

stroke, epidemiology, incidence, lethality, functional status

Introduction

Since 2005, the prevalence of stroke has increased considerably, and more than 104 million people live with its consequences worldwide (1). The social and financial burden of stroke is remarkable (2). Acute stroke interventions, such as stroke units and reperfusion therapy, have the potential to improve outcomes. In addition, primary prevention is essential to reduce its incidence, prevalence, lethality, and life years lost due to disability (DALYs) (3).

In 2018, the first Latin American Stroke Ministerial Meeting gathered the health ministries from 13 different countries in Brazil to discuss and identify ways to cooperate on reducing stroke charges in the region (4). Meta-regression data showed that the incidence of stroke in Latin America decreased by 25% from 1990 to 2017 (4).

One-third of the Latin America's population is in Brazil, where the stroke incidence per 100,000 inhabitants was reduced from 146 (95% CI: 130–163) in 1990 to 136 (95% CI: 122–153) in 2019 (5). However, the improvements were not enough to eliminate health inequities, and the number of stroke cases usually remains higher in the North and Northeast than in the South and Southeast regions (6). As in other middle-income countries, stroke care follows the social disparities that divide Brazil into two different "countries": the wealthier part, which shares the same profile as developed countries and can afford high-quality stroke care resources, and the majority of the population, who have various limitations in accessing stroke prevention, acute treatment, and rehabilitation (7). The Brazilian Stroke Society points out that population-based studies are needed in all major regions of the country, from the Amazon to the South, in order to provide more reliable information about the impact of stroke care policies (7).

Given all these worries and social inequality, yet significant in Brazil, this study aimed to report the post-stroke incidence, lethality, and functional status in different macro-regions, comparing population data from Joinville (the reference stroke center in Brazil) vs. other studied cities.

Methods

Study framing and planning

The Health Ministry (HM) ordered the Brazilian Stroke Society to expand the knowledge on stroke incidence and prognosis outside the reference centers, so that the influence of socioeconomic diversity could be considered. Joinville Stroke Registry (JOINVASC) was defined as the coordinator of the study due to its population-based databank in progress since 1995, supported by municipal law since 2013 (8, 9). Initially, the HM defined that the study should represent each of the five macro-regions of the country. The cities included in the study had as prerequisites the availability of more than 100,000 inhabitants and the availability of 24-hour access to a cranial tomography (CT), laboratory for biochemical analysis, electrocardiogram (ECG), and conventional radiology. The chosen cities were Canoas (South), Joinville (South), Sertãozinho (Southeast), Sobral (Northeast), and Campo Grande (Midwest). None of the northern cities met the initial inclusion criteria.

A JOINVASC team was sent to the selected cities to lead meetings with hospital managers and municipal health departments. Face-to-face meetings were held to train the local teams according to the three-step criteria recommended by the World Health Organization (WHO) to conduct population-based studies on stroke (10).

Study design

This is an observational, population-based, prospective, and multicenter study. The events were registered consecutively in Sertãozinho (April 2015 to March 2016), Sobral (January to December 2015), Campo Grande (June 2015 to May 2016), Canoas (January to December 2016), and Joinville (January to December 2016), covering all seasons. The detailed methods regarding population-based studies on stroke have been previously reported (8, 11). Stroke was defined according to WHO criteria (12). The stroke investigation routine followed the Brazilian Society of Cerebrovascular Diseases guidelines (13) and adapted to each hospital's resources and reality. Supplementary Table 1 shows the demographics and aging-related indexes of attending cities.

Using different sources, all hospitalized and ambulatory patients with stroke were identified (14). The same criteria were followed in all cities. To evaluate the hospitalized cases daily, the local research nurse registered all stroke cases with the diagnosis made by a neurologist and confirmed by a head CT. By using the electronic registries of diagnoses listed according to the tenth International Classification of Diseases (CID-10) revision, all death certificates that had any reference to the CID-10 codes related to stroke (161–169), or death for unknown cause (R99), were analyzed every month. The non-identified death causes were investigated through medical records; in this sense, we excluded all patients with sudden death at home, no CT confirming the diagnosis, no medical history or incompatible with the one extracted by the nurse, and patients codified with R99 who were still inconclusive after the medical record revision. To identify mild stroke cases among those who did not seek hospital assistance, general clinicians, cardiologists, neurologists, and neurosurgeons were personally invited to notify the study team of these cases. The local health departments sent a formal declaration of adhesion to highlight the study's importance to the assistance network and the public interest in the data by the HM. It did not perform a direct search of patients at stroke risk, like those with carotid and coronary investigation for diagnostic and therapeutic purposes.

All patients diagnosed with any type of ischemic stroke (IS), hemorrhagic stroke (HS), or subarachnoid hemorrhage (SAH) and residents in one of the studied cities, regardless of age, were included. Permanent residents who had an event outside the city limits were confirmed retrospectively and included in the study. Stroke cases who died within the first 24 h of symptom onset, without having a brain scan confirming the event, were excluded. Additionally, there were excluded patients with subdural and epidural hemorrhages, whether traumatic or not; intracerebral hemorrhages secondary to rupture of arteriovenous malformation; hemorrhages secondary to bleeding by use of oral anticoagulants or by tumor bleeding. Patients without brain images were classified as indeterminate cases and coded as IS (15).

The at-risk population data during 2015 and 2016 were extracted from the Department of Informatics of the Unified Health System (DATASUS/MS) (16) of HM and the municipal health department of each city. Permanent residents were defined as those who lived for at least 12 months in the city before study enrollment.

Diagnostic and evaluation criteria

Demographic and risk factor data were collected, followed by biochemical, electrocardiographic, and radiological test results. The research nurses registered the cardiovascular risk factors during face-to-face meetings with patients or family members. The neurologist assistant informed the nurse about the clinical stroke syndrome according to the Oxfordshire Community Stroke Project (OCSP) classification (17). The assistant also informed about the corresponding pathophysiological diagnosis according to "Trial of Org 10172 in Acute Stroke Treatment" (TOAST) criteria, used to classify ischemic stroke into five subtypes, namely, atherosclerosis of large arteries (atherothrombotic), cardioembolism (cardioembolic), small vessel occlusion (lacunar), stroke of other determined etiology, and stroke of undetermined etiology (18). The clinical severity of the events was measured by the "National Institutes of Health Stroke Scale" (NIHSS) at hospital admission, stratified into minor (0–3), moderate (4–10), and severe (>10) (19). All criteria were maintained throughout the study.

The education level of patients was stratified on complete school years and skin color by self-definition, according to categories–black, brown, indigenous, white, and yellow – of the Brazilian Institute of Geography and Statistics (IBGE). The economic strata were based on the Brazilian Association of Research Companies classification (20).

The Modified Rankin Scale (mRS) was used to evaluate post-stroke functional dependency and lethality, stratifying patients into three categories: independent (0–2), dependent (3–5), and dead (6) (21). Each nurse, in their respective city, reported the functional status of patients during the first month. After 3 months of the event, a JOINVASC nurse contacted all patients (or family members), using a validated Brazilian version of mRS, to evaluate the functional status through telephonic interview (20).

Statistical analysis

Results of descriptive analyses are presented as average and standard deviations for quantitative variables and as frequencies, expressed in percentages, for qualitative variables. To calculate incidence and corresponding confidence intervals (CI) of 95%, the Poisson distribution was used for the number of events. The incidence specified by age and sex was adjusted by the direct method for the Brazilian population and for the WHO standard population. The incidence rates were compared using the epidemiological calculator OpenEpi (7, 8). For comparisons among cities, we applied the chi-square test for qualitative variables and the ANOVA test, with Bonferroni correction, for quantitative variables, with $p < 0.05$ considered significant. To analyze the survival rate, Kaplan–Meier curves were plotted (log-rank test). For all these analyses, the statistical software SPSS version 23.0 was used.

Ethical aspects

This study was approved by the Brazilian Research Ethics Commission, under opinion 759670, on 29 April 2014. The Ethics Committees from each involved city have also approved it locally. Written informed consent was obtained from all study participants or their legal representatives.

Results

A total of 932 new cases of stroke met the inclusion and exclusion criteria of the study from Joinville – reference center ($n = 527$), Canoas ($n = 217$), Sertãozinho ($n = 70$), and Sobral ($n = 118$). The city of Campo Grande (Midwest macro-region) was excluded from the intended analysis as it was not possible to achieve a significant coverage of stroke cases. The 30-day post-event follow-up was carried out in 911 cases. In 90 days, this amount was reduced to 659 cases (Figure 1). Table 1 shows baseline demographic and socioeconomic data of patients, as well as the main risk factors and access to stroke assistance.

The obtained stroke incidence rates per 100,000 inhabitants, adjusted for the Brazilian population, were 54.3 (95% CI: 49.3–64.3) in Canoas; 85 (95% CI: 77.9–92.5) in Joinville; 58.7 (95% CI: 49.1–78.2) in Sertãozinho; and 77 (95% CI: 63.7–92.2) in Sobral, with no significant difference between sexes. The stroke incidence stratified by city, age group, and sex, as well as considering adjustment for the world population, is presented in Table 2 and Figure 2. Table 3 shows the relative incidences by age group, comparing the reference center with the other participating cities.

The incidence of IS ($n = 784$) per 100,000 inhabitants, adjusted for the Brazilian population, varied significantly ($p = 0.006$) among participant cities, being 45 (95% CI: 37–52) in Canoas; 81 (CI 95%: 74–89) in Joinville; 44 (95% CI: 38–58) in Sertãozinho, and 60 (95% CI: 48–73) in Sobral. The detailed data regarding IS cases are shown in Table 4, Supplementary Table 2, Figure 1. Cases of undetermined etiology were more frequent (41–67%) than other IS subtypes, but showed a significant difference among cities ($p < 0.001$). Considering IS subtypes of defined etiology, according to the TOAST criteria, the cardioembolic subtype was significantly more common ($p < 0.001$) in Joinville, while the lacunar subtype was more common in Sobral ($p = 0.02$). Atherothrombotic stroke cases were not significantly different among participating cities. Regarding the Bamford clinical classification applied to IS cases, significant differences were identified related to the frequencies of all subtypes. Canoas reported a higher frequency of cases classified as partial anterior circulation stroke (PACS) (65.6%, $p < 0.001$), while Sertãozinho had the highest number of total anterior circulation strokes (TACS) (36.5%, $p = 0.001$). Sobral stood out for presenting the highest number of cases of lacunar stroke (LACS) (40.9%, $p < 0.001$) since there were no cases of posterior circulation syndrome (POCS) ($p = 0.002$).

The proportion of functionally independent individuals at 30 days of the IS event, evaluated by mRS, was significantly higher ($p = 0.003$) in Canoas and Joinville. However, this difference in functional status relative to the other cities was not maintained at 90 days after the stroke ($p = 0.055$).

The lethality of IS in 30 and 90 days after event was higher in Sobral (37 and 49%, respectively) and Sertãozinho (23% and 35%), being significantly superior ($p < 0.001$) than observed in the reference center – Joinville (10% and 18%). However, when considering the severity of the stroke, Sobral and Sertãozinho already presented higher proportions (NIHSS > 10: 48.3 and 47.1%, respectively), compared to the cities of Joinville (17.6%) and Canoas (28.3%) ($p < 0.001$).

There were registered 105 HS cases, and the corresponding detailed data are given in Table 5. The incidence per 100,000 inhabitants, adjusted for the Brazilian population, was 7 (95% CI: 3–14) in Sertãozinho; 8 (95% CI: 6–11) in Joinville; 8 (95% CI: 5–11) in Canoas, and 13 (95% CI: 8–20) in Sobral, without a significant difference between sexes. Regarding the functional status of patients affected by HS, there was no significant difference among analyzed cities 30 days after the event. At 90 days of follow-up, Sertãozinho showed a significant proportion of independent patients (62.5%; $p < 0.001$); however, due to the small number of cases ($n = 5$), such a result should be considered sparingly. The cities that presented the highest lethality rates for HS in 30 and 90 days post-event were Canoas (40% and 65%, respectively) and Sobral (50% and 59%), surpassing the reference center – Joinville (16% and 23%), both showing significant differences ($p = 0.022$ and 0.005). More severe cases (NIHSS> 10) were also found mostly ($p = 0.008$) in Canoas (78.1%) and Sobral (70%).

A total of 43 cases of SAH were registered in the four cities, with Sertãozinho standing out, where 13% of events corresponded to this type of stroke ($p = 0.004$). It has not been found that there are significant differences regarding sex, functional status, and lethality in 30 days for SAH. More details on SAH and HS are given in Table 5.

The Kaplan–Meier curve (Figure 3) shows the cumulative 90-day survival of patients of all types of stroke, clarifying the significant differences among studied cities (Log-rank $p < 0.001$). The result reinforces that Joinville, the reference center, has the best survival rate, while Sobral, the representative of the Northeast macro-region, shows the worst epidemiological situation.

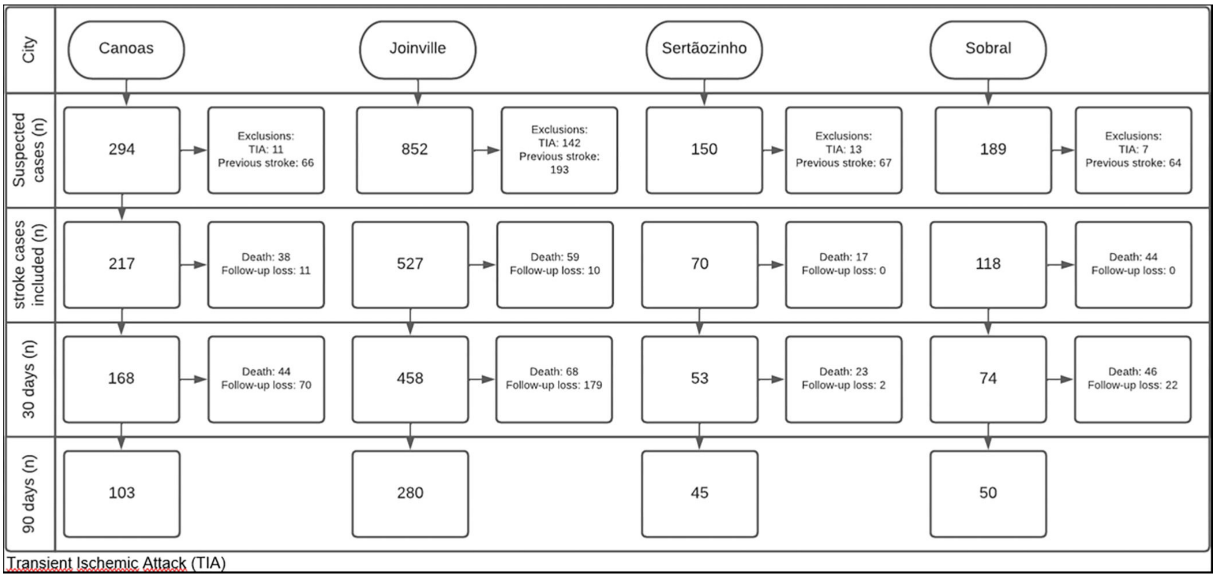

FIGURE 1
Flowchart of the study follow-up.

Discussion

For the first time, an observational study was able to analyze the incidence and lethality of stroke in medium-sized cities in three Brazilian macro-regions, prospectively and simultaneously, in addition to follow-up of the patients for 90 days to evaluate their post-event functional status. The rate of loss of patient follow-ups was similar to other studies (22).

The demographic and socioeconomic characteristics of the population studied are in line with the findings described in several international studies, in which hospitals in low- and middle-income countries treated patients diagnosed with stroke who were, on average, younger and less educated when compared with high-income countries (23). A trend toward stabilization in the general population or an increase in stroke incidence rates in middle-aged people has been observed more recently in European countries, the United States, Brazil, and China (24).

In this study, a significant variation was observed in the proportion of stroke types among the participating cities, with Joinville having the highest case proportion related to IS (87.7%, $p = 0.006$); Sobral for HS (16.9%, $p = 0.011$); and Sertãozinho for SAH (12.9%, $p = 0.004$), as well as there were significant variations on IS subtypes. Béjot et al. (2016) analyzed contemporary European population-based records and identified huge discrepancies regarding the distribution of stroke types (IS: 55–90%, HS: 10–25%, and SAH: 0.5–5%), and also among the ischemic subtypes (25). Those differences can occur due to ethnic/racial background, variations in the prevalence of cardiovascular risk factors, and socioeconomic and environmental status (26).

Incidence rates per 100,000 inhabitants, adjusted for the world population, found in the cities of Canoas (63), Joinville (106), Sertãozinho (72), and Sobral (96) are in line with the rates described for low- and medium-income countries (60–93), as pointed out in the publication of the "Global Burden of Disease Study 2017" (27).

In China, a North-South gradient was identified, demonstrating a wide variation in stroke within the same country. According to the authors, their results may be related to the differences in socioeconomic conditions, knowledge of the population about the disease, and quality of primary prevention across regions (28). In Brazil, the demographic and epidemiological changes that occurred in the past 50 years have not been experienced uniformly across states, resulting in subnational health disparities and corresponding burdens on health systems (6). In general, there was a decline in transmitted diseases due to the improvements in the public health system in Brazil – SUS, financed by the government and active in prevention and health care. On the contrary, there is an increase in the burden of non-transmittable diseases, in addition to the growth of the elderly population (25, 29).

Previously, there was a little variation in functional status from 3 months to 10 years after stroke (30). In Brazil, there are little comprehensive data on functional status post-stroke (31). The proportion observed in this study of dependent patients (mRS> 2) in 90 days (ischemic: 17.8%, hemorrhagic: 22.9%) was lower than that found in studies carried out in Sweden (ischemic: 33.9%, hemorrhagic: 30.3%) and Iran (ischemic:

TABLE 1 Baseline demographic and socioeconomic data of patients, risk factors, and access to stroke assistance in four Brazilian cities.

	Canoas ($N = 217$) *n* (%)	Joinville ($N = 527$) *n* (%)	Sertãozinho ($N = 70$) *n* (%)	Sobral ($N = 118$) *n* (%)	*p*
Age, y–mean age (SD)	64.4 (13.4)	65.2 (14.3)	64.8 (15.4)	66.1 (16.5)	0.785
<45	16 (34.7)	43 (8.2)	6 (8.6)	14 (11.9)	0.848
<55	48 (22.1)	116 (22.0)	16 (22.8)	29 (24.6)	0.964
Men	109 (50.2)	283 (53.7)	37 (52.8)	60 (50.8)	0.829
Skin color*					
Black	14 (6.5)	14 (2.7)	6 (8.6)	20 (17.1)	<0.001
Brown	32 (14.7)	18 (3.4)	24 (34.3)	64 (54.7)	<0.001
Indigenous	4 (1.8)	0	0	2 (1.7)	0.013
White	165 (76.0)	493 (93.7)	39 (55.7)	31 (26.5)	<0.001
Yellow	2 (0.9)	1 (0.2)	1 (1.4)	0	0.254
Years of education[y]					
<4 or illiterate	111 (51.4)	322 (61.1)	47 (68.1)	90(78,9)	<0.001
4–8	72 (33.3)	77 (14.6)	6 (8.7)	9 (7.9)	<0.001
8–11	29 (13.4)	95 (18.0)	12 (17.4)	13 (11.4)	0.209
>11	4 (1.9)	33 (6.3)	4 (5.8)	2 (1.8)	0.026
Social class					
A	2 (0.9)	7 (1.3)	0	0	0.464
B1	4 (1.8)	13 (2.5)	5 (7.1)	4 (3.4)	0.113
B2	59 (27.2)	115 (21.8)	22 (31.4)	12 (10.2)	0.001
C1	63 (29.0)	170 (32.3)	18 (25.7)	13 (11.0)	<0.001
C2	61 (28.1)	129 (24.5)	11 (15.7)	30 (25.4)	0.219
D	27 (12.4)	92 (17.5)	13 (18.6)	55 (46.6)	<0.001
E	1 (0.5)	2 (0.4)	1 (1.4)	4 (3.4)	0.012
Alcohol use	35 (16.1)	35 (6.7)	22 (31.4)	16(13.6)	<0.001
Physical activity–Low	210 (96.8)	483 (91.7)	50 (71.4)	103 (87.3)	<0.001
Physiological factors					
High BMI (> 23)[z]	178 (82.0)	407 (77.2)	47(67.1)	84 (71.2)	<0.001
High fasting glucose (≥ 5.6 mmol/L)[§]	89 (90.8)	470 (91.4)	15 (100)	2 (100)	0.646
High systolic pressure (≥140 mmHg)	175 (85.4)	477 (90.5)	57 (89.1)	88(91.7)	0.461
High total cholesterol (≥6.2 mmol/L)[¶]	31 (21.2)	50 (10.9)	0	0	0.001
Previous atrial fibrillation	1 (0.5)	45 (8.5)	4 (5.7)	0	<0.001
Previous myocardial infarction	14 (6.4)	38 (7.2)	5 (7.1)	3 (2.5)	0.314
Tobacco smoke					
Smoking	124 (57.1)	266 (50.5)	34 (48.6)	58 (49.1)	0.324
Secondhand smoke**	76 (35.0)	153 (29.0)	35 (50.0)	30 (25.4)	0.001
Symptom-to-door time (Hours)[yy]	04:48	06:25	05:59	05:14	
SAMU	69 (31.9)	291 (55.7)	23 (32.9)	58 (49.2)	<0.001
Hospital type[zz]					
Public	179 (83.6)	415 (78.9)	0 (0.0)	0	<0.001
Private	0	111 (21.1)	4 (6.9)	0	<0.001
Mixed (Public/Private)	35 (16.4)	0	54 (93.1)	56 (100.0)	<0.001

SD, standard deviation; SAMU, emergency mobile care service; BMI, body mass index. Data unavailable: *Skin color: Joinville (n = 1; 0.2%) and Canoas (n = 1; 0.8%). [†] Years of education: Canoas (n = 1; 0.5%) and Sertãozinho (n = 1.4%). [z] BMI: Canoas (n = 1; 0.5%), Joinville (n = 3; 0.6%), and Sertãozinho (n = 10; 14.1%). [§] Glucose: Canoas (n = 119; 54.8%), Joinville (n = 13; 2.5%), Sertãozinho (n = 55; 78.6%), and Sobral (n = 116; 98.3%). [¶] Cholesterol: Canoas (n = 71; 32.7), Joinville (n = 67; 12.7%), Sertãozinho (n = 70; 100.0%), and Sobral (n = 118; 100.0%). [**] Secondhand smoke: Joinville (n = 2; 0.4%). [yy] Symptom-to-door time: Canoas (n = 1; 0.4%) and Sertãozinho (n = 4; 5.7%). [zz] Hospital type: Canoas (n = 3; 2.2%), Joinville (n = 1; 0.7%), Sertãozinho (n = 70; 51.1%), and Sobral (n = 62; 52.5%).

TABLE 2 Stroke incidence rates per 100,000 inhabitants according to age and sex in four Brazilian cities.

Age strata	Canoas		Joinville		Sertãozinho		Sobral	
(years)	N/N at risk	Rate (95% CI)	N/N at risk	Rate (95% CI)	N/N at risk	Rate (95% CI)	N/N at risk	Rate (95% CI)
Men								
<35	0/95,634	0 (0.1–4.4)	5/168,548	3 (1–7)	0/33,974	0 (0.1–4.4)	4/65,714	6.09 (1.7–15.6)
35–44	4/25,070	16 (4.3–40.9)	10/44,334	22.6 (10.8–41.6)	3/9,419	31.9 (2.6–76.7)	4/13,401	29.9 (8.1–76.4)
45–54	12/21,155	56.7 (29.3-99.1)	40/35,918	111.4 (79.6–151.7)	4/7,588	52,7 (21.4–153.8)	8/9,580	83.5 (36.1–164.5)
55–64	44/17,067	257.8 (187.3–346.1)	79/20,926	377.5 (298.9–470.5)	10/5,366	186.4 (198.8–530.2)	12/5,356	224.1 (115.8–391.4)
65–74	34/8,849	384.2 (266.1–536.9)	80/8,946	894.3 (709.1–1,113)	7/2,585	270.8 (108.9–557.9)	15/2,950	508.5 (284.6–838.6)
75–79	10/2,131	469,3 (193.1–801.7)	31/2,283	1,357.9 (922.6–1,927.4)	3/653	459.4 (94.7–1,342.6)	6/925	648.7 (238–1,411.8)
≥ 80	16/1,858	861.1 (451.9–1,331.6)	33/1,980	1,666.7 (1,147.3–2,340.7)	9/645	1,395.3 (251.7–1,809.1)	9/906	993.4 (454.2–1,885.7)
Total	120/171,764	69.1 (56.9–82.3)	278/282,935	98.3 (87.1–110.6)	36/60,230	59.8 (47.4–90.4)	58/98,832	58.7 (44.6–75.9)
Age-adjusted to Brazil		58.5 (47.6–68.9)		114.6 (101.5–128.9)		55.4 (43.7–83.2)		72.67 (55.2–93.9)
Age-adjusted to World		86.1 (50.5–73.1)		172.8 (109–138.4)		91.6 (45.3–86.3)		105 (58.4–99.5)
Women								
< 35	3/93,754	3.2 (0.1–4.4)	11/162,098	3.2 (0.7–9.4)	2/45,639	6.79 (0–2.3)	0/64,336	4.38 (0.5–15.8)
35–44	9/26,272	34.3 (15.7–65)	17/45,367	37.5 (21.8–60)	1/8,902	11.2 (2.7–81.2)	6/14,489	41.4 (15.2–90.1)
45–54	20/23,679	84.5 (51.6–130.4)	33/37,449	88.1 (60.7–123.8)	6/7,689	78 (21.1–151.8)	7/10,705	65.4 (26.3–134.7)
5–64	15/19,810	75.7 (42.4–124.9)	40/23,019	173.8 (124.1–236.6)	11/5,581	197.1 (11.1–157.1)	7/6,536	107.1 (43.1–220.7)
65–74	26/11,817	220 (143.7–322.4)	68/11,248	295.4 (229.4–374.5)	6/3,061	196 (71.9–426.6)	16/4,048	395.3 (225.9–641.9)
75–79	11/3,278	385.6 (233.5–716.6)	32/3,522	284.5 (194.6–401.6)	4/873	458.1 (252.2–1,495.9)	7/1,379	507.6 (204.1–1,045.9)
≥ 80	13/4,191	310.2 (272.9–708)	48/4,006	1,198.2 (883.5–1,588.6)	4/1,119	357.5 (490.7–1,758.9)	17/1,445	1,176.5 (685.3–1,883.6)
Total	97/182,801	53,1(47.5–70.1)	249/28,6709	86.9 (76.4–98.3)	34/72,864	46,7 (33.4–66.8)	60/102,938	58.3 (44.5–75)
Age-adjusted to Brazil		47.8(43–63.5)		77.1 (70.3–90.5)		56,3 (42.2–84.3)		77.1 (58.9–99.3)
Age-adjusted to World		49,8 (42.4–62.7)		90,6 (69.5–89.5)		58,9 (41.9–83.6)		87,9 (58.2–98.2)
All								
< 35	3/189,388	1.6 (0.3–4.7)	16/330,646	4.8 (2.7–7.8)	2/66,669	3 (0.4–10.8)	4/130,050	3.1 (0.8–7.9)
35–44	13/51,342	25.3 (12.9–43.3)	27/89,701	30.1 (19.8–43.8)	4/18,321	21.8 (5.9–55.8)	10/27,890	35.9 (17.2–66)
45–54	32/44,834	71.4 (48.8–100.8)	73/73,367	99.5 (78–125.1)	10/15,277	65.5 (31.4–120.5)	15/20,285	73.9 (41.4–121.9)
55–64	59/36,877	160 (121.8–206.4)	119/43,945	270.8 (224.3–324.1)	21/10,947	191.8 (118.7–293.2)	19/11,892	159.8 (96.2–249.5)
65–74	60/20,666	290.3 (221.5–373.7)	148/20,194	336.8 (284.7–395.6)	13/5,646	230.3 (122.6–393.8)	31/6,998	443 (301–628.8)
75–79	21/5,409	388.2 (269.5–638)	63/5,805	312 (239.7–399.2)	7/1,526	458.7 (269.7–1,119.6)	13/2,304	564.2 (300.4–964.8)
≥ 80	29/6,049	479.4 (403–804.7)	81/5,986	1,353.2 (1,074.6–1,681.9)	13/1,764	737 (518.4–1,472.9)	26/2,351	1,105.9 (722.4–1,620.4)
Total	217/354,565	61.25 (55.5–72.4)	527/569,644	92.5 (84.8–100.7)	70/120,150	58.3 (49.8–79.3)	118/20,1770	58.5 (48.4–70.1)
Age-adjusted to Brazil		54.9 (49.3–64.3)		85 (77.9–92.5)		58.7 (49.1–78.2)		77 (63.7–92.2)
Age-adjusted to World		63.4 (54–70.4)		105.8 (85.2–101.2)		71.8 (55.7–88.8)		95.8 (70.4–101.9)

CI, confidence interval.

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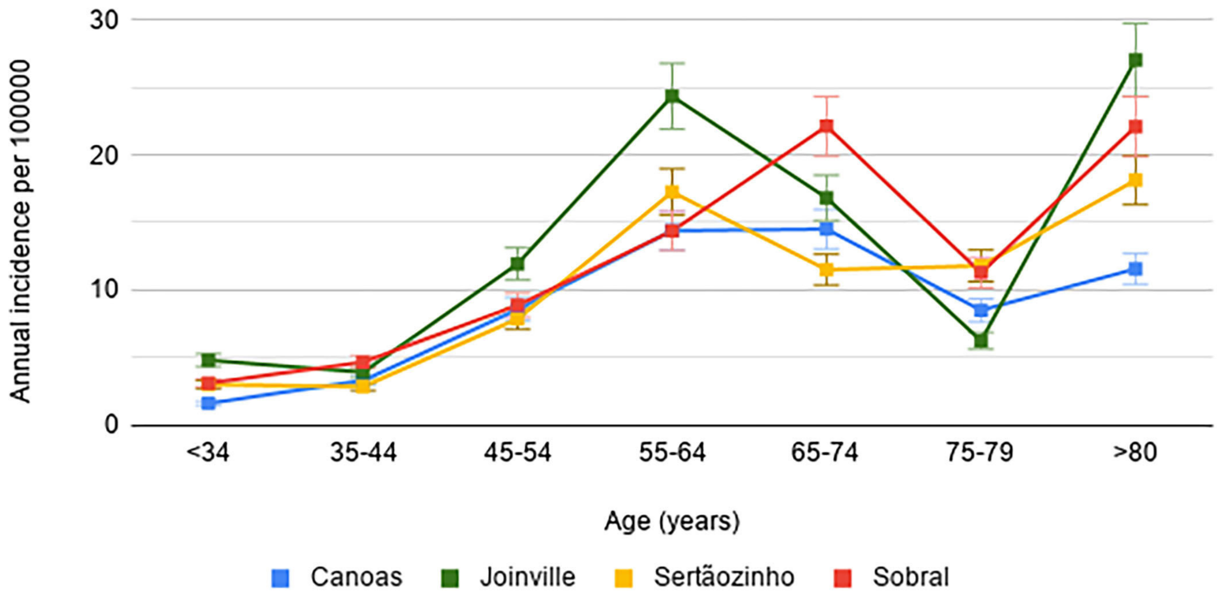

FIGURE 2
Stroke incidence rates (95% CI) adjusted for the world population in four Brazilian cities.

TABLE 3 Relative incidence rates of stroke by age strata.

Age, years	IRR (95% CI)		
	Joinville vs Canoas	Joinville vs. Sertãozinho	Joinville vs. Sobral
All < 35	3.0 (1.0–13.1)	1.6 (0.4–10.4)	1.6 (0.5–5.5)
All < 45	1.5 (0.9–2.9)	1.4 (0.6–3.7)	1.5 (0.6–2.2)
All < 55	1.4 (1.0–2.0)*	1.5 (0.9–2.6)	1.4 (0.9–2.2)
55–64	1.7 (1.2–2.3)*	1.4 (0.9–2.3)	1.7 (1.1–2.8)*
65–74	2.5 (1.0–3.4)*	3.2 (1.8–5.8)*	1.6 (1.1–2.5)*
75–79	2.5 (1.6–4.2)*	1.8 (0.9–3.9)	1.9 (1.1–3.6)*
≥ 80	2.3 (1.6–3.5)*	1.5 (0.9–2.6)	1.2 (0.8–1.9)

IRR, incidence rate ratio; CI, confidence interval. *p < 0.05.

28.4%, hemorrhagic: 33.3%) (32, 33). It is well-known today that there is a major impact on the life quality of patients who have survived stroke due to the resulting disabilities, in addition to the emotional and economic factors imposed on them and their families, which means that functional dependence also carries a significant financial burden on health systems (34).

In Brazil, stroke has been the main cause of death for more than 30 years. Although mortality has decreased, it is still occupying the second position, with more than 100,000 deaths per year (35, 36). In this study, the most severe cases were observed in Sobral, in the Northeast macro-region, which also has the highest lethality rate. Factors such as geographical location, race/ethnicity, and the interactions between these various factors, need to be considered (37). Among the studied cities, patients from Sobral presented lower educational levels and the worst socioeconomic conditions, reflected in its lower Human Development Index (HDI). A range of evidence suggests that socioeconomic deprivation is not only associated with the occurrence of stroke and its risk factors but also increases the severity, mortality, and incidence of the event at younger ages (38–40). The higher age-standardized burden of stroke may also be related to poorer acute healthcare for stroke (41).

Stroke care in low- and middle-income countries is patchy, fragmented, and often results in poor patient outcomes (42). Individuals presenting with acute stroke may be severely affected by healthcare coverage, including the availability of ambulance services, stroke units, reperfusion therapy, or rehabilitation in different health settings (3). Despite the advances in the treatment of stroke in recent years, access to diagnosis and treatment remains heterogeneous in Brazil (7). The strategic allocation of financial resources for healthcare, according to disease priorities in each state or macro-region, remains a great challenge (6). Joinville, a reference center in stroke assistance that has a public hospital with an acute and integral stroke unit (U-stroke), despite having a higher incidence when compared to the other cities in the study, had patients with a better degree of functional independence and a lower lethality rate. The interstroke study showed that patient admission to a hospital with a U-stroke is associated with increased chances of survival as well as survival without severe disability. This suggests that stroke units indeed can provide benefits in low- and middle-income countries as observed in high-income countries (23).

TABLE 4 Ischemic stroke cases and outcomes in one and 3 months after event.

	Canoas		Joinville		Sertãozinho		Sobral		*p*
	N (%)	Mean age (SD)	*N* (%)	Mean age (SD)	*N* (%)	Mean age (SD)	*N* (%)	Mean age (SD)	
IS proportion	180 (82.9)	63.7 (13.3)	460 (87.3)	64.8 (14.3)	52 (74.3)	64.9 (14.3)	92 (78.0)	66.0 (16.6)	0.006
OCSP									
LACS	16 (8.9)	64.0 (11.3)	116 (26.0)	64.3 (13.8)	14 (26.9)	62.9 (9.7)	36 (40.9)	66.8 (15.1)	<0.001
PACS	118 (65.6)	64.8 (13.2)	222 (49.7)	64.9 (14.8)	11 (21.2)	63.3 (13.6)	32 (36.4)	59.4 (16.8)	<0.001
TACS	23 (12.8)	64.2 (13.3)	42 (9.4)	62.4 (14.6)	19 (36.5)	65.3 (17.1)	20 (22.7)	74.4 (13.7)	<0.001
POCS	23 (12.8)	57.4 (13.8)	67 (15.0)	65.1 (12.7)	8 (15.4)	69.7 (15.9)	0	-	0.002
TACS vs. non-TACS	0.1	0.1	0.6	0.3					
TOAST									
Atherotrombotic	23 (12.8)	66.3 (14.0)	76 (16.5)	65.9 (14.2)	6 (11.5)	65.2 (15.8)	15 (16.5)	69.3 (18.9)	0.557
Lacunar	21 (11.7)	66.8 (10.8)	88 (19.1)	66.4 (13.8)	4 (7.7)	56.7 (6.2)	25 (27.5)	62.8 (16.2)	0.002
Cardioembolic	19 (10.6)	68.0 (11.1)	109 (23.7)	64.0 (14.1)	7 (13.5)	73.3 (12.9)	9 (9.9)	60.8 (15.4)	<0.001
Undetermined	117 (65.0)	61.9 (13.6)	187 (40.7)	64.0 (14.7)	35 (67.3)	64.0 (14.5)	42 (46.2)	67.8 (16.4)	<0.001
NIHSS									
Minor (0–3)	90 (50.0)	61.8 (14.0)	234 (50.9)	65.5 (14.4)	12 (23.5)	67.0 (15.8)	21 (23.6)	64.9 (15.5)	<0.001
Moderate (4–10)	39 (21.7)	68.0 (11.4)	145 (31.5)	64.4 (14.0)	15 (29.4)	65.3 (13.4)	25 (28.1)	63.1 (17.6)	0.104
Severe (>10)	51 (28.3)	63.6 (12.7)	81 (17.6)	63.5 (14.6)	24 (47.1)	63.8 (14.8)	43 (48.3)	68.9 (15.5)	<0.001
mRankin—30 days									
Independency (0–2)	120 (70.2)	63.6 (13.3)	318 (70.5)	65.2 (14.3)	24 (46.2)	64.2 (14.1)	43 (46.7)	63.1 (18.1)	0.003
Dependency (3–5)	29 (17.0)	64.1 (14.5)	89 (19.7)	65.3 (14.0)	16 (30.8)	65.7 (12.3)	15 (16.3)	70.2 (13.9)	0.117
Lethality (6)	22 (12.9)	65.2 (11.9)	44 (9.8)	60.1 (15.5)	12 (23.1)	65.5 (17.8)	34 (37.0)	68.0 (15.5)	<0.001
mRankin—90 days									
Independency (0–2)	71 (59.2)	64.7 (12.6)	192 (64.0)	65.2 (14.5)	24 (47.1)	64.5 (14.1)	29 (39.2)	65.0 (16.4)	0.055
Dependency (3–5)	24 (20.0)	61.3 (13.2)	55 (18.3)	65.8 (15.0)	9 (17.6)	61.7 (12.5)	9 (12.2)	61.3 (21.6)	0.909
Lethality (6)	25 (20.8)	63.2 (12.4)	53 (17.7)	60,7 (15.4)	18 (35.3)	67.3 (15.9)	36 (48.6)	68.9 (15.8)	<0.001

SD, standard deviation; IS, ischemic stroke; OCSP, Oxfordshire Community Stroke Project classification; LACS, lacunar syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; TACS, total anterior circulation syndrome; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale.

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TABLE 5 Hemorrhagic stroke and subarachnoid hemorrhage cases and outcomes in 1 and 3 months after event.

	Canoas		Joinville		Sertãozinho		Sobral		*p*
	N (%)	Mean age (SD)	*N* (%)	Mean age (SD)	*N* (%)	Mean age (SD)	*N* (%)	Mean age (SD)	
HS proportion	32 (14.7)	68.0 (13.4)	44 (8.3)	67.1 (12.0)	9 (12.9)	70.0 (21.1)	20 (16.9)	65.3 (17.1)	<0.001
NIHSS									
Minor (0–3)	5 (15.6)	61.8 (14.0)	11 (25.0)	65.5 (14.4)	1 (11.1)	67.0 (15.8)	2 (10)	64.9 (15.5)	0.436
Moderate (4–10)	2 (6.3)	68.0 (11.4)	15 (34.1)	64.4 (14.0)	3 (33.3)	65.3 (13.4)	4 (20.0)	63.1 (17.6)	0.032
Severe (>10)	25 (78.1)	63.6 (12.7)	18 (40.9)	63.5 (14.6)	5 (55.6)	63.8 (14.8)	14 (70.0)	68.9 (15.5)	0.008
Rankin—30 days									
Independency (0–2)	7 (23.3)	77.1 (9.5)	19 (43.2)	68.5 (13.7)	5 (55.6)	79.0 (17.4)	6 (30.0)	74.3 (7.6)	0.100
Dependency (3–5)	11 (36.7)	65.0 (18.8)	18 (40.9)	67.3 (11.4)	2 (22.2)	59.0 (38.2)	4 (20.0)	59.2 (12.1)	0.766
Lethality (6)	12 (40.0)	67.3 (7.2)	7 (15.9)	62.8 (8.6)	2 (22.2)	59.0 (1.4)	10 (50.0)	62.4 (21.3)	0.022
Rankin 90 days									
Independency (0–2)	3 (13.0)	84.0 (9.6)	11 (35.5)	62.1 (14.8)	5 (62.5)	73.6 (26.8)	2 (11.8)	76.5 (0.7)	<0.001
Dependency (3–5)	5 (21.7)	60.0 (25.8)	13 (41.9)	70.0 (11.4)	1 (12.5)	86.0 (0.0)	5 (29.4)	63.6 (13.1)	0.040
Lethality (6)	15 (65.2)	69.0 (7.6)	7 (22.6)	62.8 (8.6)	2 (25.0)	59.0 (1.4)	10 (58.8)	62.4 (21.3)	0.005
SAH proportion	5 (2.3)	68.4 (15.7)	23 (4.4)	68.7 (17.4)	9 (12.9)	58.9 (15.3)	6 (5.1)	69.5 (15.6)	0.004
NIHSS									
Minor (0–3)	1 (20.0)	79.0 (0.0)	7 (30.4)	69.7 (17.5)	3 (33.3)	60.7 (25.0)	3 (50.0)	60.0 (15.4)	0.743
Moderate (4–10)	0 (0.0)	0 (0.0)	4 (17.4)	60.7 (12.3)	2 (22.2)	64.5 (0.7)	2 (33.3)	84.0 (7.1)	0.551
Severe (>10)	4 (80.0)	65.7 (16.8)	12 (52.2)	70.7 (19.2)	4 (44.5)	54.7 (12.7)	1 (16.7)	69.0 (0.0)	0.204
Rankin—30 days									
Independency (0–2)	1 (20.0)	79.0 (0.0)	10 (45.5)	63.3 (20.5)	5 (55.6)	62.0 (17.8)	5 (83.3)	69.6 (17.4)	0.190
Dependency (3–5)	0 (0.0)	0 (0.0)	4 (18.2)	77.0 (2.9)	1 (11.1)	36.0 (0.0)	1 (16.7)	69.0 (0.0)	0.751
Lethality (6)	4 (80.0)	65.7 (16.8)	8 (36.4)	72.0 (17.6)	3 (33.3)	61.3 (3.1)	0 (0.0)	0 (0.0)	0.054
Rankin—90 days									
Independency (0–2)	0 (0.0)	0 (0.0)	7 (41.2)	61.6 (21.7)	5 (55.6)	62.0 (17.8)	4 (80.0)	71.0 (19.8)	0.101
Dependency (3–5)	0 (0.0)	0 (0.0)	2 (11.8)	73.5 (10.6)	1 (11.1)	36.0 (0.0)	1 (20.0)	69.0 (0.0)	0.830
Lethality (6)	4 (100.0)	65.7 (16.8)	8 (47.1)	72.0 (17.6)	3 (33.3)	61.3 (3.1)	0 (0.0)	0 (0.0)	0.023

SD, standard deviation; HS, hemorrhagic stroke; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage.

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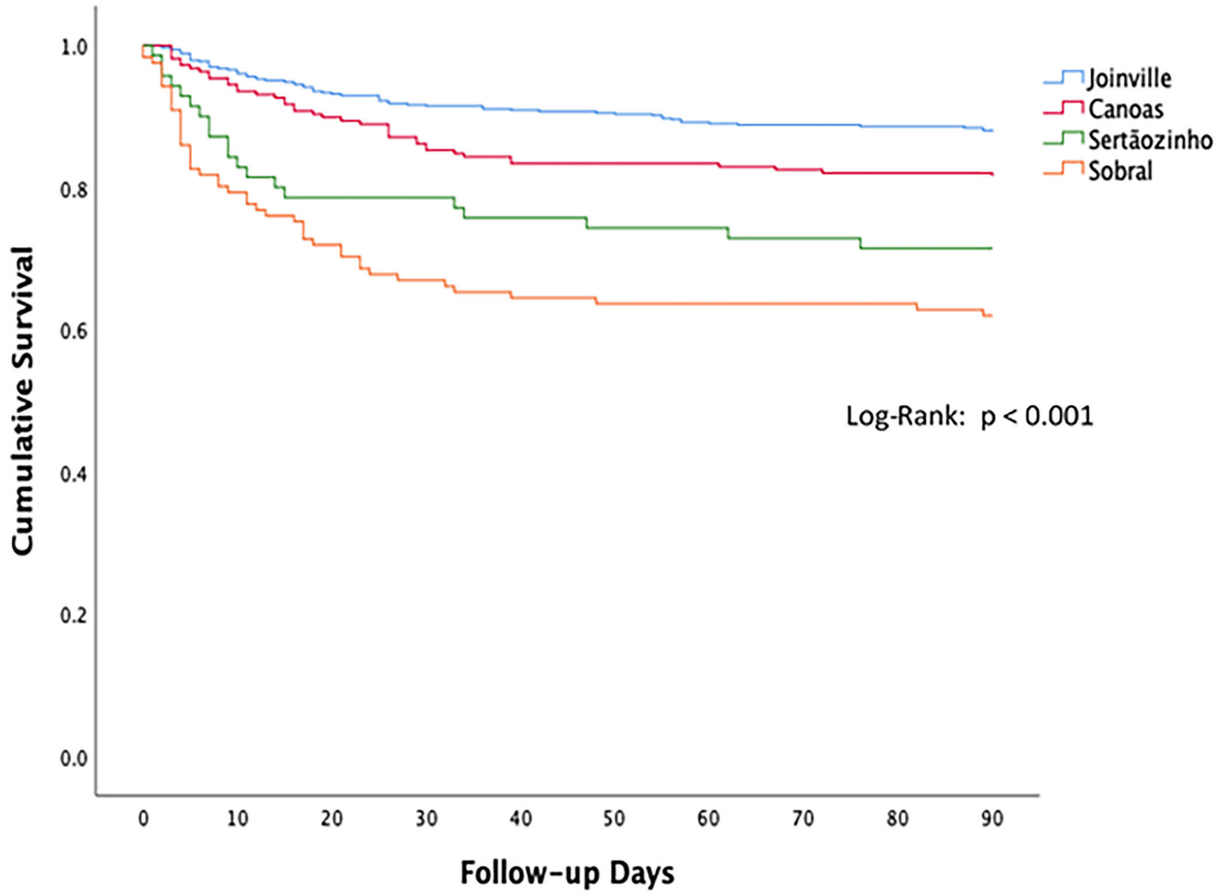

FIGURE 3
Kaplan–Meier curve showing 90-day cumulative survival after stroke in four Brazilian cities.

Improving stroke services is critical for reducing the global stroke burden (43).

The study strengths are related to the prospective capture of all cases, following the three-step criteria proposed by WHO for population-based epidemiological studies on stroke (10). The studied cities belong to three different macro-regions of a middle-income country with large territorial extensions. Furthermore, the study included cities located outside of the stroke reference centers in the country, allowing a better recognition of the impact of the disease in locations with scarce epidemiological data.

On the contrary, the main weakness of this study is related to the absence of equivalent data from the North and Midwest regions, thus not reflecting a comprehensive picture of the country. In addition, difficulties encountered in one or more participating cities may have impacted the results, such as data from private services; lack of complementary diagnostic tests, essential for the research purpose; short hospital stay, due to overcrowding; and lack of specialized stroke treatment units. Another example of difficulty was the temporary unavailability of CT, resulting in high rates of undetermined subtype of IS, due to incomplete investigation. Moreover, it can be assumed that there may have been underreported mild cases seen outside hospitals. Comparisons among cities regarding time to needle were not possible, despite its importance and possible influence on the results presented, since such data were not collected in all participating centers. It is also important to highlight that we had a significant loss of patient follow-up (approximately 30% after 90 days of the event), due to difficulties faced by the teams in each city. Unfortunately, these facts reflect the weaknesses of the Brazilian health system itself.

It is concluded that the observed differences in the incidence and impact of stroke, among cities in different Brazilian macro-regions, are alarming, with particular prominence for the representative city of the Northeast region, where lethality was significantly higher when compared to the stroke reference center located in the South region. This epidemiological reality reflects the need for a better allocation of resources and more effective strategies for healthcare. Therefore, future studies focused on the identification and measurement of differences in access to the diagnosis and treatment of stroke are necessary to discover and possibly remedy the weak points of health assistance in the most deprived Brazilian regions.

Data availability statement

Primary data will be made available upon reasonable request.

Ethics statement

This study was approved by the Brazilian Research Ethics Commission, under opinion 759670, from April 29th, 2014. The local ethics committees from each of the participating cities also approved the study. The cities involved were Campo Grande - Federal University of Mato Grosso do Sul, Canoas - Hospital de Clínicas de Porto Alegre, Joinville - University of the Joinville Region, Sertãzinho - Hospital das Clínicas, Faculty of Medicine, University of São Paulo and Sobral - Vale do Acaraú State University. Written informed consent was obtained from all study participants or their legal representatives.

Author contributions

NC, VN, PF, and LFe contributed to study design. VN, GWo, HP, LFu, RM-F, and GWe contributed to data collection. ES contributed to data analysis, data interpretation, and writing. NC, PF, LFe, and SM contributed to data interpretation and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

The reviewer CS declared a shared affiliation with the author RM-F to the handling editor at the time of review.

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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.2022.966785/full#supplementary-material

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Stroke systems of care in the Philippines: Addressing gaps and developing strategies

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In the Philippines, the mortality from stroke during the last 10 years remains high. This paper aims to describe the gaps in stroke care and the development of stroke systems of care in the Philippines. Gaps in stroke systems of care include low number of neurologist, inadequate CT scan machines, lack of stroke training among health workers, lack of stroke protocols and pathways, poor community stroke awareness, low government insurance coverage with high out of pocket medical expenses, lack of infrastructure for EMS, inadequate acute stroke ready hospitals, stroke units and rehabilitation facilities. Although there are government programs for primary stroke prevention, the strategies are inadequate to address the stroke pandemic. The Stroke Society of the Philippines has worked with the government for nationwide and regional stroke training of health care workers, community stroke awareness, setting up acute stroke ready hospitals and acute stroke units in different areas of the country and adapting stroke protocols and pathways. Stroke registries are now utilized for quality improvement. Thrombolysis rate has improved from 1.4% in 2014–2016 to 11% in 2021 based on RES-Q database. Because of government subsidy, thrombolysis in the government hospitals is higher at 7.4% (range 4.4–16.9) compared to 4.8% (range 0–10.1) rate in private hospitals. Mechanical thrombectomy rate remained low at 0.4% of all acute ischemic stroke patients because of the cost. With limited resources, infrastructures for emergency medical service is lacking. The innovations done by other LMIC can be done in the Philippines including the use of technology to reach out to geographically isolated areas and use of mobile stroke units. Non neurologist can be trained to help treat stroke patients. Upgrading of the Philhealth insurance to cover for reperfusion therapies, adequate stroke infrastructures and network, and increase in community stroke awareness are areas for improvement in the Philippine stroke systems of care.

KEYWORDS

stroke care, lower middle income country, Philippines, developing countries, stroke

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Introduction

Eighty six percent (86%) of global stroke death and 89% of stroke related DALYs occur in low and lower-middle income countries (LMIC) (1). Delivery of quality and evidenced-based care for optimal patient outcomes is limited and poor in LMIC compared to high-income countries (2). There is inadequacy of resources and many challenges in setting up stroke services in LMIC. However, the researches on prevention and treatment of stroke have focused primarily on the needs of high-income countries.

The Philippines has a population of 109 million and only 5.7% are above age 65 years old (3). Despite the young population, stroke remains a fatal disease and the second cause of death (3). Even with the advances in science and introduction of government health programs, the mortality remains high. With paucity of good epidemiologic data, the real burden of disease is still not known. While the annual stroke mortality in the country is reported, the number of stroke survivors with the disability has not been evaluated.

Stroke, together with cardiovascular diseases is the biggest pandemic. Many Filipinos suffer from stroke that are preventable and treatable with cost-effective interventions. Despite the increasing stroke prevalence, prevention and treatment including emergency care are inadequately funded and poorly prioritized. The implementation of primary and secondary stroke prevention is difficult without sufficient government funding. There are no standardized acute stroke management. With limited resources, the reperfusion therapies are not accessible to the majority of Filipino stroke victims.

Strategies to improve stroke systems of care require coordinated efforts from the government, the healthcare workers and community. Mortality will remain high without improvement in infrastructures, access to essential medicines, community education and stroke training among health workers. In low resource areas, greater resources should be allocated for stroke prevention.

This paper aims to describe the gaps in stroke care and the development of stroke systems of care in the Philippines.

Methodology

A search was conducted for recently published studies on stroke epidemiology and stroke care in the Philippines. The search for studies published since January 2000 on stroke in the Philippines was conducted using Medline (2000–September 2022), HERDIN Plus and Google scholar. The search identified any citations containing the words "stroke" or "cerebrovascular" as title words and "Philippines" anywhere in the abstract or citation. The search was limited to English language manuscripts. Abstracts from the searches were screened and papers of stroke epidemiology and care were selected. Additional papers were identified from the reference lists of previously published studies and reviews. The Stroke Society of the Philippines website was accessed for stroke activities in improving stroke awareness and care.

Results

Stroke mortality

The mortality from stroke during the last 10 years remains high with an average of 63,804 deaths per year (Figure 1) (4). In 2021, despite the COVID pandemic, the recorded annual Philippine stroke death was 68,180 (5), increased from 64,381 in 2020 (4). These data taken from death certificates may not be accurate with under reporting as 34% of Filipinos die without medical attendance (4). About 50% of the population do not have access to primary care facilities within 30 min (6). Uncontrolled risk factors, poor stroke awareness, delay of hospital access, high out-of-pocket medical expenses, overcrowding of public hospitals, inadequate CT scan machines and lack of stroke training among health workers could have contributed to the high stroke mortality rate (7).

Gaps in stroke system of care in the Philippines

The overall stroke system of care can be assessed at least partly by different factors such as the number of neurologists providing stroke care, the density of imaging facilities in the country, the rate of thrombolysis and the availability of stroke units (8). Furthermore, the stroke continuum of care highlights the importance of stroke rehabilitation in improving outcomes (9). Unfortunately, the current state of the Philippines' stroke system of care is lacking in all of these areas.

In 2021, there is one neurologist providing healthcare needs for every 218,000 Filipinos which is very low compared to the recommended ratio of 106 neurologists per 100,000 population (10). There is also unequal distribution of neurologist with as much as 67% of neurologists are concentrated in the highly urbanized centers in the country (10).

One essential component of stroke diagnosis and management is brain imaging. In the Philippines, the reported density of computed tomography (CT) scan and magnetic resonance imaging (MRI) are 1.09 per million population and 0.30 per million population, respectively (7). There is also a big disparity between the public and private sector as the former has fewer number of machines available for stroke diagnosis (11).

In the Philippines, the use of recombinant tissue plasminogen activator (rTPA) for eligible acute ischemic stroke patients within the 3–4.5 h time window was approved in 1999. However, the utilization of this important drug remains

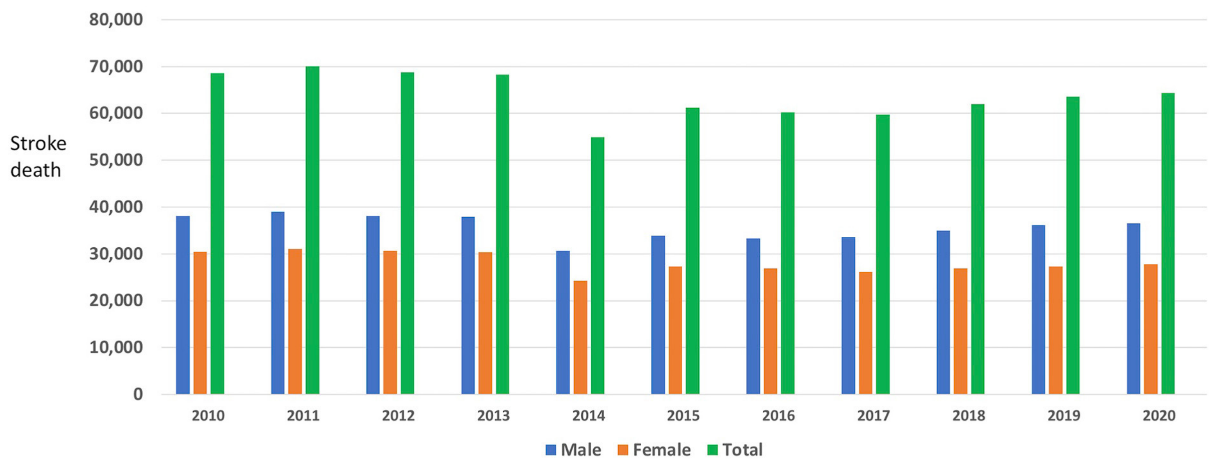

FIGURE 1
Philippine stroke mortality 2010–2020 (4, 5).

low. In 2016, the department of health (DOH) implemented the Stroke Medicine Access Program (SMAP) which provided more than 1,000 free vials of rTPA to selected government hospitals across the country (12). However, due to gaps in the implementation of SMAP such as lack of healthcare workforce training and facilities for stroke diagnosis and care, the program was put on hold (13). Just recently, alteplase was included in the Philippine National Formulary (PNF) as an essential medicine for stroke care and as such may be reimbursed to the country's national health insurance system, the Philippine Health Insurance Corporation (PhilHealth) (14). Navarro et al. reported a thrombolytic rate of 1.4% from year 2014 to 2016 (15) which is within the lower bracket of 1.3%–9% intravenous rTPA use among other Asian countries (16).

Admitting acute stroke patients in the stroke units (SU) yield better care and improved stroke outcomes (17). Through the efforts of the Stroke Society of the Philippines (SSP), the number of SUs increased from merely two in 1999 to 47 in 2021, However, it is still low compared to the ideal number as recommended by the World Stroke Organization. Majority of SUs are located in urbanized centers and access to care of stroke patients from remote areas is difficult (18).

Rehabilitation after stroke remains as the primary means of which maximal recovery of function may be achieved (9). However, access to stroke rehabilitation services and facilities remains inadequate as there are only 452 rehabilitation centers to serve 148 stroke cases per 100,000 population (19, 20) in the country. Similar to access to neurologists, patients have poor access to post stroke care physiatrists and rehabilitation specialists as they are concentrated in highly urbanized areas. Only 15.8% of hospitals in the Philippines have rehabilitation centers (21). Gonzales-Suarez et al. in their 2015 audit study of hospitalized stroke patients reported that only 54.1% was referred to rehabilitation services despite that the data was collated only in hospitals with rehabilitation centers. This suggests that there is a significant low utilization of stroke rehabilitation services even in centers where it is available. Other than poor access to services and facilities, cost of rehabilitation also poses as a limiting factor. The current PhilHealth packages for stroke cover only medical expenses while rehabilitation costs are borne out of pocket and private health insurance covers only a limited amount of the rehabilitation expenses (22).

Strategies in improving stroke care

There is inequality in stroke care which differs greatly across rural and urban locations. Addressing the stroke care gaps needs government reforms and policies. Figure 2 shows the initial steps done by the government and the Stroke Society of the Philippines (20). There are a lot of challenges and limitations. The impact will be assessed in the next few years.

National stroke policy

In 2020, the Philippine government through the Department of Health (DOH) approved the Stroke National policy through the creation and implementation of the Administrative Order No. 2020-0059 (23). This mandates the timely and quality stroke care to be delivered to all Filipinos in all health facilities. This will facilitate the standardization of stroke protocol and pathways for diagnosis and treatment. With the national stroke policy, the department of health shall facilitate the referral pathways and utilize health care provider networks to ensure timely referral of patients to ASRH. The government will facilitate

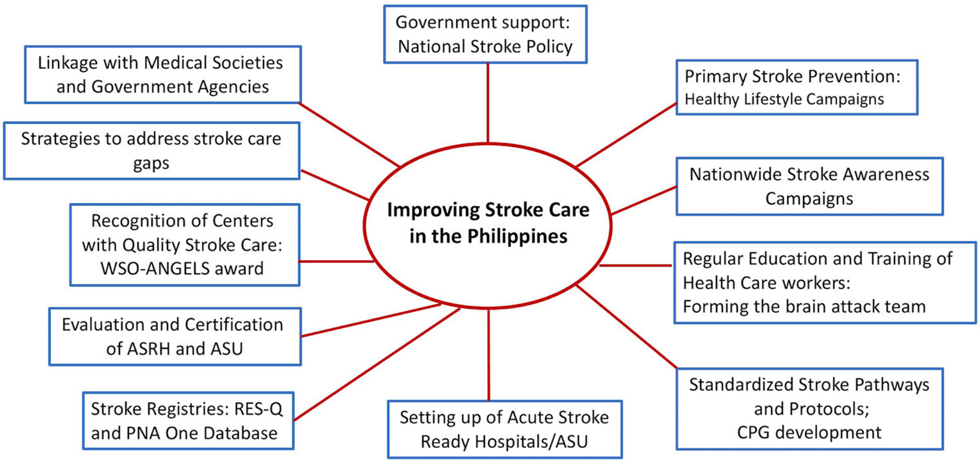

FIGURE 2
Improving stroke care in the Philippines (20).

capacity building and formation of interdisciplinary teams. Access to essential medicine like rTPA will also be ensured by the government and its attached agencies (23).

Primary stroke prevention campaigns

In 2011, the DOH implemented the National Policy on Strengthening the Prevention and Control of Chronic Lifestyle Related Non-Communicable Diseases (24). The aim was to adopt a nationwide, integrated and comprehensive program on prevention and control of lifestyle diseases. It targeted the reduction of risk factors like smoking, hypertension and diabetes with a goal of 2% reduction of NCD mortality per year (24). Looking at the 5-year stroke mortalities, the reduction has not yet been achieved.

The government passage of Sin Tax Reform Law in 2012, raised the excise taxes on tobacco products and effectively reduced tobacco use among smokers from 29.7% in 2009 to 23.8% in 2015 based on the results of the Global Adult Tobacco Survey (GATS) (25). In 2018, an excise tax on sugar sweetened beverages was launched (26) which could be one of the reasons for reduction of diabetes prevalence among age 20–79 from 9.7% in 2011 to 7.1% in 2021 (27).

In 2013, the DOH launched its Go4Health program, a nationwide healthy lifestyle movement that aims to inform and encourage Filipinos to practice a healthy lifestyle by making a personal commitment to avoid the four risk factors - unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol and to promote and establish a sustainable environment for healthy lifestyle (28). Several community healthy lifestyle campaigns were also done by the different medical societies (29, 30).

Stroke awareness campaigns

There is low stroke awareness in many regions of the country. In a community survey by Roxas et al. (31), only 34.4% were knowledgeable on stroke and respondents even misconstrued the disease with heart attack. The SSP held regular lay fora, television and radio campaigns on stroke awareness (32). The creation of stroke infomercial for health care facilities, movie houses and public places was also done (33–36). In addition, regular social media stroke campaigns on YouTube, Facebook and Instagram were also intensified (37–41).

Stroke education

In 2015, the Stroke Society of the Philippines in collaboration with the WSO, embarked on a nationwide 5-year stroke training on Cardinal Principles of Stroke Treatment (CPOST). The aim of the training was to help organize stroke teams, develop stroke ready hospitals and acute stroke units (42). This was one of the first steps to organize and standardize stroke education and training among physicians and nurses in the different regions of the country. Thrombolysis simulation and case-based neuroimaging workshops were the highlights of the training (42).

In 2020, amidst the surging COVID pandemic, the Stroke Society of the Philippines continued to push its advocacy of improving stroke care throughout the Philippines by hybrid method. The project Bringing evidenced-based stroke treatment to Philippine hospitals (BEST-PH) continued to provide the needed training for health care facilities to become Acute Stroke Ready Hospitals (ASRH) (43). Focusing on the developing stroke policy frameworks and formation of interdisciplinary stroke teams, the project facilitated the education and training of health care workers on the safe stroke protocols, care algorithms and treatment guidelines. In addition, the BEST-Ph project was able to provide the groundwork for the formation of a Telestroke network in the different hospitals (43).

The ANGELS initiatives not only facilitated stroke training but provided standardized evidenced-based stroke protocols, checklists, thrombolysis mechanics, monitoring and after stroke care procedures (44). The SSP is in the process of developing the Philippine Clinical Practice Guidelines on acute stroke care and management.

Setting up of acute stroke ready hospitals and certification

After the stroke education and training, there was an increase in the number of acute stroke ready hospitals (ASRH) and acute stroke units (ASU) in the different areas of the country. There are 53 ASRH and 47 ASU in the country (35). The stroke society is currently evaluating and beginning the process of certification so that the ASRH and ASU meet the highest standard of care.

Some hospitals with limited beds and where stroke units do not exist, patients with stroke are admitted to the general wards, staffed by a coordinated multidisciplinary team with training in stroke care.

Improvement in thrombolysis rate

In 2014–2016, the thrombolysis rate (Figure 3) was low at 1.4% of all acute ischemic strokes. Through various stroke training and education in the different areas of the country by the stroke society, the thrombolysis rate increased to 11% in 2021 based on RES-Q database (45). The Res-Q database is participated by 27 ASRH hospitals but not all stroke cases are encoded as only a minimum of 30 representative cases per quarter are encoded. There was a slight decrease in the thrombolysis rate during the COVID pandemic in 2020. The PNA Stroke Database (45) is participated by 11 Neurology training institutions and encodes all stroke cases seen at the training hospitals. There is a higher thrombolysis rate in the public hospitals (Table 1) since the medicine rTPA is subsidized by the government. The initial cost of one vial of rTPA was 1,200 USD but in 2020, the cost was reduced to 600 USD through a government executive order regulating prices of drugs and medicines to improve access to health care (4).

Of all the acute ischemic strokes patients, 50%–60% in the RES-Q database and 71% in the PNA Database arrive at the ER beyond 3 h from the time of stroke (Figure 4) (44, 45).

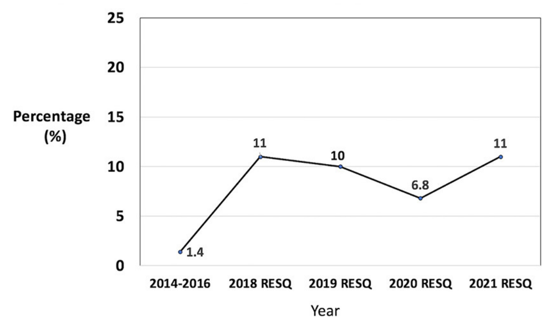

FIGURE 3
Thrombolysis rate (%), 2014–2021 (15, 45).

TABLE 1 Average thrombolysis rates in different hospitals, PNA stroke database, 2021.

% Thrombolysis	Government hospitals	Private hospitals
PNA stroke database, 2021–2022 (4)	7.4% (range 4.4–16.9)	4.8% (range 0–10.1)

Mechanical thrombectomy

The Philippines, together with Bangladesh, Mongolia, Nepal and Pakistan is one of the countries with limited EVT and IVT despite the high stroke burden (46). The high cost of EVT, lack of adequate stroke infrastructures, inadequate number of neuro-interventionists to perform the procedure, lack of unified territory -wide triage systems and inadequate awareness and education of both physicians and patients about this therapy are the identified impediments to thrombectomy (46). A retrospective study of a single center in Manila reported 31 thrombectomy cases among 924 ischemic stroke patients from 2018 to 2021 with discharge MRS 0–2 in 23%, 48% with MRS 3–5 and 29% mortality (47).

In the PNA Stroke Database, the annual thrombectomy rate of three comprehensive stroke centers in Manila is 0.4 and 0.2% for combined intravenous rTPA and endovascular therapy (4).

Missed opportunities for improvement in stroke outcome

Figure 4, shows the percentage of delayed arrival to hospitals, with missed opportunities for IV thrombolysis. More than 50% of acute stroke patients have a delayed ER arrival time (44, 45). The reasons include poor stroke awareness,

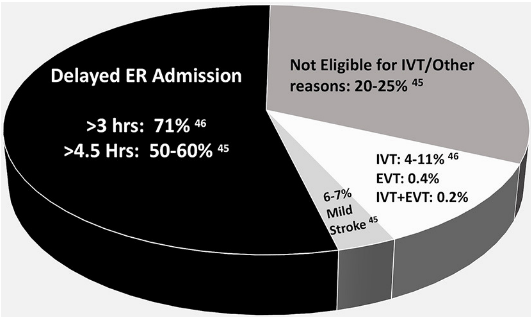

FIGURE 4
Patients thrombolyzed and not thrombolyzed among all acute ischemic strokes.

transportation problems and traffic, transfer from a primary hospital with minimal stroke care and incomplete facilities, overcrowding of public hospitals, lack of organized stroke network and lack of EMS (7).

Stroke registry

An interoperable national stroke registry across public and private facilities is vital in improving stroke care. The Philippine Neurological Association One Database – Stroke (PNA1DB-Stroke; clinicaltrials.gov NCT04972058) started data collection on 1 June 2021 (45). This project is supported by the Philippine Neurological Association. This multi-center observational study includes all patients diagnosed with TIA or stroke, ≥18 years old, who are admitted in the country's 11 accredited adult neurology residency training institutions. Based on 2017–2019 census, ∼10,000 cases each year may be included. As of 21 August 2022, 3,721 cases (mean age 58.1 ± 14.1 years, 42% women) have been registered, comprised of ∼4% TIA, 58% ischemic stroke, 33% intracerebral hemorrhage, 5% subarachnoid hemorrhage and 0.1% cerebral venous thrombosis cases. Collective data spanning three years will be extracted, summarized and analyzed every year. Real-world data will be extremely valuable in identifying areas for improvement in stroke care by monitoring trends over the years and benchmarking against management guidelines. Findings are expected to guide public health policies and resource allocations. While situations in participating sites may not be fully representative of all hospitals in the country, the PNA1DB-Stroke may become a model that may be implemented in other designated stroke-ready hospitals.

Twenty seven (27) ASRH in the Philippine have joined the RES-Q database (45), a global registry to help physicians monitor and improve stroke care quality. Every hospital and country gets feedback for improvement. Acute stroke ready hospitals in the country have been given Angels award confirming compliance to the standard quality stroke care.

Discussion

The National Stroke Policy will not resolve all issues as resources are needed. Emergency medical services (EMS) is a critical component and is needed to improve stroke outcome. In the Philippines, there is no EMS but limited number of ambulances to transport patients without protocols for field triage, standards of care or communication to receiving facilities. Legislations for the establishment of pre hospital emergency medical services including capacity building will facilitate time sensitive stroke treatment.

Technology can help bridge the gap in health care delivery in geographically isolated areas. Stroke education, training, stroke assessment, treatment and rehabilitation can be done online. Managing patients with acute ischemic stroke (AIS) using the guidance of telemedicine consultation is safe and reliable (48).

In rural and remote settings, mobile stroke units (MSU) may be adapted to local needs. In Thailand where the city has the worst traffic, the MSU decreased the alarm to needle time (49).

Telecommunication approaches between MSU and the stroke center can provide real time remote specialist advise. Stroke network with hub and spoke model can be adapted.

To address the limited number of neurologists, non-neurologists can be trained to do thrombolysis. In Thailand, to cope with the limited number of neurologists, they established stroke network project which assists the non-neurologists in the treatment of AIS with rtPA. Non-neurologists was able to thrombolyze AIS patients safely and effectively (50). Similar to Malaysia, non-neurologist hospitals may be able to provide thrombolysis service to AIS patients safely and effectively (51). In the Philippines, the neurologist can train the non-neurologists and form a stroke network, guiding the health care workers via telemedicine platform on acute stroke treatment. Although the thrombolysis rate has improved from 1.4 to 11%, this can still improve if the 50%−60% of acute ischemic stroke patients with delayed ER admission can be transported faster with EMS or organized stroke network.

The gap between LMIC and HIC is even more pronounced with endovascular treatment options for acute stroke. For the provision of mechanical thrombectomy, the center requires highly specialized staff, facilities and technical resources. In the Philippines, because of out of pocket expenses, admission to the comprehensive stroke centers are limited to those in the high economic strata. Similar to coronary artery stenting and bypass, the Philhealth insurance should provide funding for catastrophic illness like stroke with large vessel occlusion needing mechanical thrombectomy.

To address the limited number of rehabilitation facilities, home or community-based tele-rehabilitation may be used. In

Nigeria, a video home based telerehabilitation was developed and found to be feasible, acceptable and useful among mild to moderate stroke survivors (52).

In low resource areas, greater resources should be allocated for stroke prevention. Primary stroke prevention reduces prevalence and incidence preventing need for a tertiary care, saving enormous expenses. This requires both community-based and government-based approaches to prevention. It is important to recognize the gravity of stroke pandemic so that urgent measures and strategies are done for prevention and treatment.

Conclusion

Strategies to address stroke care gaps included community awareness, training of neurologists and nurses on acute stroke care, standardization of stroke protocols, setting up of ASRH and ASU and stroke registries. However, there is still a need to increase community stroke awareness, upgrading in Philippine health insurance, development of adequate stroke infrastructures and network which will greatly improve stroke outcomes.

Limitations

The data were taken from limited number of published studies on stroke in the Philippines. Data from stroke registries may not reflect the real situation in the country as majority of the ASRH participating in the stroke database are in the urban areas where health care is better.

Author contributions

MC, JN, RG, and AB took the lead in preparing the draft manuscript for publication. All authors participated in the data gathering and provided input in developing the manuscript and approved the final version submitted.

Conflict of interest

The 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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Characteristics of stroke service implementation in Armenia

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Background: Acute stroke care service in Armenia was established in 2019 after the implementation of the National Stroke Program (NSP). This study aimed to provide an up-to-date account of the current image and clinical characteristics of acute stroke service implementation at a tertiary hospital in Armenia by analyzing the quality of care and identifying the areas that need improvement.

Methods: We analyzed patient data from a single hospital in 1 year after the establishment of acute stroke care service (February 2021–January 2022). We selected patients who were within 0–24 h from symptom onset at admission and included patients who benefited from reperfusion therapies (intravenous thrombolysis (IVT) and/or endovascular thrombectomy (EVT)). A favorable outcome was defined as a drop in the National Institutes of Health Stroke Scale (NIHSS) by more than four points at discharge and a modified Rankin score (mRS) of 0–2 at 90 days.

Results: Of the total 385 patients, 155 underwent reperfusion therapies, 91% of patients (141/155) arrived by ambulance, 79.2% (122/155) had neurological improvement at discharge, and 60.6% (94/155) had an mRS of 0–2 at 3 months. Less than 5% of patients had early direct access to the rehabilitation center.

Conclusion: Our study demonstrated that the implementation of NSP with organized protocol-driven inpatient care led to significant advancement in acute stroke service performance. We believe that our report will serve as a model for achieving advanced and structured stroke care in a resource-limited context and contribute to the future development of the healthcare system in our country.

KEYWORDS

stroke service, Armenia, quality indicator, thrombolysis (tPA), performance measure

1. Introduction

Stroke is the leading cause of acquired physical disability in adults worldwide and the second leading cause of mortality in middle- to high-income countries (1). Moreover, it is a major and challenging healthcare problem, with over 12.2 million new cases each year and over 143 million years of healthy life lost annually due to stroke-related death and disability (2). Current strategies to reduce mortality and disability caused by stroke are based on organized stroke unit care with the implementation of evidence-based clinical guidelines. Patients with stroke who receive organized inpatient care in a dedicated stroke unit are more likely to be alive, independent, and living without disability 1 year after the stroke (3). However, stroke systems of care and the availability of resources for acute stroke care vary considerably across geographic regions, which leads to uneven levels of and, at times, suboptimal care (4).

In a low-resource setting, many barriers to access to appropriate stroke care services are identified, such as inadequate awareness of stroke signs, lack of state-funded medical transportation, non-availability of brain imaging, stroke units and rehabilitation services, low access to health insurance, insufficient training of specialists, and lack of community support in post-discharge care. As a result, morbidity and mortality rates of acute stroke are higher in low- and middle-income countries (LMICs), contributing to 75% of the total death burden (5).

Despite these challenges, there are many efficient models of stroke care available in LMICs, the most frequent ones of which are multidisciplinary team care led by a stroke neurologist, specialist-led care by the general neurologist, physician-led care, stroke telemedicine, and task sharing involving community health workers (6).

Armenia is a country with limited financial resources, resulting in disparities in healthcare coverage among the population. The epidemiology of stroke in the country is neither well-investigated nor controlled, and most of the available data on stroke burden is based on hospital-admitted cases**.** Though access to the emergency ambulance and primary care service is available to the whole population, there still exists a huge proportion of undiagnosed and non-treated stroke cases like in other developing countries. The reasons for these cases include both, the lack of awareness of stroke symptoms and the seriousness of the situation and possible complications, as well as limited access to urgent medical transportation, inappropriate management and treatment practices by specialists, heterogeneous structure of stroke care services, high cost or non-availability of neuroimaging, and the lack of targeted public and medical staff education (7–9).

Armenia has a population of ∼3 million, of which 1.092 million live in Yerevan. (10) Acute stroke care service in Armenia was established in 2019 after the implementation of the National Stroke Program (NSP). The program, funded by the Ministry of Health, is regulated by the experts of the Armenian Stroke Council (ASC) and addresses the hyper-acute and acute management of ischemic stroke. This makes time-sensitive stroke treatment modalities [intravenous thrombolysis (IVT) and/or endovascular thrombectomy (EVT)] accessible to patients.

The Armenian Stroke Council was founded the same year as a collaborative international scientific advisory and educational organization to update the existing stroke service model and to develop accreditation guidelines and procedures for future stroke centers. Members of ASC are experts in the subject of stroke and work in different parts of the world (11). Armenian protocols of stroke unit certification and acute stroke care were formed by the ASC by adapting international guidelines and the American Heart Association/American Stroke Association (AHA/ASA) recommendations to the local needs and characteristics (12). The basic model of stroke care service was based on the reorganization of an existing hospital infrastructure by training health professionals to implement protocol-driven care and multidisciplinary approaches.

Currently, there are four-stroke centers in Armenia, three of which are located in the capital. Thus, there is a huge disparity in access to evidence-based stroke care between capital and rural areas. Moreover, NSP does not cover acute stroke cases with contraindications to reperfusion therapies or cases of hemorrhagic or subacute ischemic stroke. This means that these patients have to pay partially out of their pocket for their inpatient service ("co-payment method"). For this group of patients, there is neither routine control of protocol-based disease management nor regular monitoring of the quality of care.

This study aimed to provide an up-to-date account of the current image and clinical characteristics of acute stroke service implementation at a tertiary hospital in Armenia by analyzing the quality of care and identifying the areas needing improvement.

2. Material and methods

A single hospital-based retrospective study design was used to analyze the medical records of patients with ischemic stroke admitted within 0–24 h from symptom onset in 1 year after the opening of acute stroke service in our hospital (February 2021–January 2022). According to the national certification criteria defined by the Ministry of Health, our center is considered a comprehensive stroke center, offering advanced neurosurgical and endovascular procedures for different cerebrovascular pathologies and stroke-related complications. Designed by German architects, the structure of our center is considered to be the most accurate, taking into account the routes between the departments and the rapid transfer system for the patient. We have advanced neuroimaging capabilities available 24 h/7 days, including magnetic resonance imaging (MRI)/angiography 1.5 and 3T, computed tomography (CT)/angiography/perfusion, and conventional digital subtraction angiography. Before 2021, all patients with stroke or other cerebrovascular pathologies were treated in the intensive care unit or general neurology/neurosurgery ward, depending on the clinical state and hemodynamic stability. Dedicated stroke unit care staffed by a multidisciplinary team, including a trained neurologist onsite 24 h/7 days and neuro-intervention staff on call, was established in 2021 after the implementation of NSP. As mentioned earlier, the program addresses time-specific treatment modalities of ischemic stroke, enabling evidence-based protocol-driven care for reperfusion therapy candidates.

To assess the structure and quality of organized stroke unit care, we used the Joint Commission standardized performance measures as a quality indicator in ischemic stroke care (13). We selected patients with hyper-acute or acute ischemic stroke who benefited from reperfusion therapies (IVT and/or EVT). The diagnosis of hyper-acute or acute ischemic stroke was confirmed by neurological examination at admission and neuroimaging results. The mode of imaging (CT angiography/CT perfusion/MRI or all) was selected on an individual basis for every patient by the neurologist in charge. The decision for IVT or EVT was made by following the adapted national guidelines evaluating the risk–benefit ratio for every individual case and after the final agreement of the patient or their family members. Post-procedural care for all patients included non-invasive monitoring and control of vital signs in the stroke unit, assessment of swallowing function by a stroke nurse or speech therapist, assessment of NIHSS score by a neurologist, a follow-up CT at 24 h, etiological workup with a screening of cervical arteries, and echocardiography.

We collected data including baseline demographic and clinical characteristics, patient arrival method (the proportion of pre-notified cases in case of ambulance arrival), the modality of neuroimaging and reperfusion therapy, length of hospital stay (LOHS), in-hospital complication and mortality rate, discharge destination, as well as standardized quality measures including documentation of time of last known well time prior to hospital arrival (LKWT), NIHSS score before recanalization therapy and at discharge, door-to-needle (DTN), door-to-imaging (DIT), and door-to skin puncture (DTP) time, Thrombolysis in Cerebral Infarction (TICI) grade, onset-to-treatment time (OTT), rehabilitation and swallowing assessment within 48 h, administration of antithrombotic therapy by hospital day 2, and stroke education provided during the hospital stay or at discharge. Data were collected by stroke team physicians and clinical residents using prospective registration in the hospital computer system.

Clinical outcome evaluation (modified Rankin score (mRS) at 90 days) was assessed by a standardized telephone interview or during outpatient visits by stroke team neurologists. A favorable outcome was defined as a drop of the NIHSS by more than four points at discharge and an mRS of 0–2 at 90 days. The goal set for the door-to-needle time was defined as <60 min for more than 50% of all IVT cases (14). The analyses were performed using IBM-SPSS statistics.

3. Results

Between February 2021 and January 2022, 385 patients were presented to the emergency department of the Astghik Medical Center (AMC) with a suspicion of acute stroke in the first 0–24 h of symptom onset. Of 385 patients, 155 corresponded to the selection criteria of NSP and benefited from reperfusion therapies (IVT, IVT+EVT, and EVT). The median age of the patients was 71. The majority arrived by ambulance (91%), with prenotification of the hospital prior to arrival (89.7%). All patients had documentation of LKWT and NIHSS scores before recanalization therapy. The median DTN time was 60 min, and the median DTP time was 105 min. A total of 98 out of 155 patients (63.6%) had a DTN time of <60 min.

In the EVT group, the proportion of patients with TICI grade 2b or higher was 54 out of 67 patients (85.7%). A total of 143 out of 155 patients (92.3%) had antithrombotic therapy by the end of hospital day 2, and 137 out of 155 patients (87.3%) had an assessment for rehabilitation and swallowing. Stroke education to patients and caregivers was provided in 139 cases (89.6%). Only six patients were directly discharged to the rehabilitation center (3.9%). Furthermore, 122 out of 155 patients (79.2%) had neurological improvement at discharge, and 94 out of 155 patients (60.6%) had mRS of 0–2 at 3 months. In four cases (2.6%), data regarding mRS at 3 months were missing.

Table 1 presents the baseline characteristics of patients and the stroke service performance.

4. Discussion

Our hospital is the only JCI-accredited clinic in Armenia, and to our knowledge, this is the first report of stroke service quality assessment in our country using performance measures based on Joint Commission standards of care.

A performance measure, as defined by the American Agency for Healthcare Research and Quality, is a mechanism for assessing the degree to which a provider competently and safely delivers the appropriate clinical services to the patient within the optimal period (14, 15). Researchers in both advanced and developing countries have attempted to measure the quality of care by quality indicators adapted to the level of local health service capacity (16). Adherence to these quality indicators is associated with the reduction of death and disability after stroke, thus leading to better stroke care (17).

Our results are encouraging and mostly meet international standards in terms of acute reperfusion therapy management. However, the lack of trained personnel, corresponding infrastructure, quality control, and targeted continuous medical education lead to a heterogeneous structure of stroke service resulting in inappropriate management at different stages of care.

As time is critical for improving stroke outcomes, ASC and local health authorities used major efforts to train emergency staff for appropriate prehospital management.

TABLE 1 Baseline characteristics of patients and stroke service.

Study group characteristics	n = 155	%
Age (Median, IQR)	**71 (64–79)**	
Gender	Female *n* = 74 Male *n* = 81	47.7% 52.3%
Arrival method	*by ambulance, n* = 141 *by own transport, n* = 12 *from another clinic, n* = 2	91% 7.7% 1.3%
Stroke provenance city	***Capital Yerevan, n = 119*** ***Other cities/regions, n = 36***	**76.8%** **23.2%**
Presence of comorbidities	***n* = 139**	**89.7%**
Hypertension	***n* = 110**	**71%**
Diabetes type 2	***n* = 24**	**15.5%**
Cardiac diseases*	***n* = 128**	**82.3%**
IVT	*n* = 88	56.8%
IVT+EVT	*n* = 29	18.7%
EVT	*n* = 38	24.5%
Pre-notification of the hospital before arrival	*n* = 139	89.7 %
Non-prenotified cases	*n* = 16	10.3%
Neuroimaging prior to IVT/EVT	MRI *n* = 25 CT angiography *n* = 105 CT perfusion *n* = 5 MRI+CT angiography *n* = 19	16.2% 67.7% 3.2% 12.2%
LOHS (Median, IQR)		*8 (5–11)*
In-hospital mortality rate	*n* = 14	9%
IVT/EVT-related complication rate ** Symptomatic hemorrhagic transformation	*n* = 11 *n* = 7	7.1% 4.5%
Discharge destination	*Discharge: to home, n* = 134 *to the rehabilitation center, n* = 6	87% 3.9%
NIHSS coverage prior to IVT/EVT	*n* = 155	100%
NIHSS admission (Median, IQR)		11 (7–15)
NIHSS discharge (Median, IQR)		3 (2–6)
DTN time, min.(Median, IQR)		60 (50–80)
DTP time, min.(Median, IQR)		105 (80–120)
DIT, min.(Median, IQR)		16 (10–25)
DTN time <60 min	*n* = 98	63.6%
OTT, min. (Median, IQR)		150 (110–200)
Documentation of LKWT prior to hospital arrival	*n* = 155	100%
Post-EVT TICI grade 2b or higher	*n* = 54	85.7%
Antithrombotic therapy by end of hospital day 2	*n* = 143	92.3%
Stroke Education performance	*n* = 139	89.6%
mRS 5–6 at 3 months	*n* = 23	14.8%
mRS 0–2 at 3 months	*n* = 94	60.6%
Neurological improvement at discharge	*n* = 122	79.2 %
Rehabilitation and swallowing were assessed within 48 h	*n* = 137	87.3%

IVT, intravenous thrombolysis; EVT, endovascular thrombectomy; MRI, magnetic resonance imaging; NSP, National Stroke Program; CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; DTN time, door-to-needle time; DIT, door-to-imaging time; OTT, onset-to-treatment time: mRS, modified Rankin score; TICI grade, Thrombolysis in Cerebral Infarction grade; DTP time, door-to skin puncture time; NECT, non-contrast-enhanced computed tomography; LKWT, last known well time; LOHS, length of hospital stay; JCI, Joint Commission International.

*cardiomyopathy, heart failure, ischemic heart disease, cardiac arrhythmias, and valvular heart disease.

**symptomatic brain hemorrhage, major extracranial hemorrhage, orolingual angioedema, and post-puncture femoral hematoma.

A recent meta-analysis by Chowdhury et al. showed that prehospital and in-hospital stroke workflow optimizations significantly improve reperfusion rates and time metrics related to stroke treatment. Intervention protocols in prehospital care aim to improve emergency medical system (EMS) response to a stroke by using an EMS stroke survey and/or EMS education, to allow better identification of potential reperfusion therapy candidates. In those cases, activation of a prenotification system to a stroke team enables high-priority triage, allocation of resources, and preparation of the in-hospital pathway (18).

Moreover, in-hospital system interventions are associated with significantly reduced mortality and sICH at 90 days (19).

Currently, there is no national standardized stroke recognition and assessment scale for ambulance physicians in Armenia. Stroke educational programs and training were organized in recent years for ambulance physicians and nurses, but none was provided to emergency call handlers.

A system of prenotification of the stroke service before arrival was established by NSP of a direct phone call from the ambulance physician to the stroke neurologist, enabling better triage and direct instructions regarding prehospital management. Though the majority of patients (91%) arrived at the hospital by ambulance and with prenotification before arrival, there is no available report of the proportion of patients taken to non-stroke-ready hospitals during the first 24 h from symptom onset.

All patients had a clear LKWT documented in their medical history. In about half of the cases, this measure was not appropriately determined by ambulance physicians, possibly due to a lack of corresponding training. NIHSS score was performed and documented for all patients who benefited from reperfusion therapies at admission, at 1 h and 24 h after the therapeutic procedure, and at discharge. Patients who did not undergo revascularization procedures had no NIHSS score recorded in their medical history.

NECT or MRI is recommended within 25 min of the patient's arrival at the emergency department to facilitate the timely administration of intravenous thrombolytic therapy. The goal for DTN time should be established within 60 min for more than 50% of stroke cases (20).

To reduce treatment delays and to optimize in-hospital stroke workflow efficiency, stroke centers must prioritize the implementation of multi-level system interventions, such as prenotification by EMS, direct-to-imaging procedures, bedside IVT administration, education and training, and monitoring and feedback (18).

Our data show that 122 patients (78.7 %) had neuroimaging performance in 25 min, and 63.6 % of patients had DTN time within 60 min. None of our patients had direct access to CT or MRI imaging. IVT was performed in the stroke emergency room. Monitoring and analysis of treatment delays were performed if DNT was longer than 60 min. The reasons for delays were mainly associated with the severity of symptoms and non-stable hemodynamic signs. Our study showed that only five patients out of 155 had CT perfusion, thus highlighting the insufficient use of perfusion imaging in stroke care.

The majority of patients (87.3%) had swallowing and rehabilitation assessment within 48 h of the hospital arrival by a speech and physical therapist. Stroke education was provided for 138 patients and their caregivers (89.6%), addressing all of the following: activation of the emergency medical system, need for follow-up after discharge, medications prescribed at discharge, risk factors for stroke, and warning signs and symptoms of a stroke. Educational materials were provided regarding poststroke care and the prevention of complications. Future studies are needed to evaluate the role of early swallowing and rehabilitation assessment, as well as stroke education, on patient outcomes.

The findings from this study indicate that post-hospital care remains underdeveloped for stroke survivors. Less than 5% of patients were directly discharged to the rehabilitation center. No social or community support was provided in the home setting. No report was found regarding post-discharge occupational therapy. Less than 20% of patients had physical or speech therapy in the outpatient setting.

However, patient outcome based on mRS is encouraging: 60.6% of patients had mRS of 0–2 at 3 months. We believe that the improvement of the poststroke care system in the future will increase this percentage. Moreover, future studies are warranted to evaluate the association of the residual functional deficit with the quality of life and activities of daily living.

We definitely need to expand our access to rehabilitation techniques and develop comprehensive facilities (self-rehabilitation and social reintegration strategies) to support our patient's post-discharge care. The other task must be tight cooperation with patients' primary care physicians to establish an effective framework of patient control and secondary prevention. Third, we suggest specialized neuroradiology training to improve the application of perfusion imaging in our hospital.

Overall, to improve curative and rehabilitative services in separate clinics and enhance the stroke care system in the whole country, it is essential to establish a national stroke registry. We believe that, for better results, the national stroke register should be adapted to address all dimensions of high healthcare quality defined by the World Health Organization (effectiveness, efficiency, accessibility, acceptability, equitability, and safety) (21, 22). Today, the need for a national stroke registry is recognized by healthcare authorities, and steps are being undertaken to arrange the implementation in the future.

4.1. Limitations of the study

The limitations of our research include the single-center design, lack of a control group, and relatively small sample size. We only addressed patients who benefited from NSP: we did not include patients with acute hemorrhagic or subacute ischemic stroke. No monitoring was performed for patients with acute ischemic stroke who had contraindications to reperfusion therapies. We hope that in near future, NSP will address these groups of patients, enabling evidence-based and protocol-driven care to all stroke survivors.

5. Conclusion

Implementation of an evidence-based stroke system of care in a country with a population of approximately 3 million was in acute demand for many years. Our study demonstrated that despite many challenges, the implementation of NSP with organized protocol-driven inpatient care led to significant advancement in acute stroke service performance. Our results are encouraging and mostly meet international standards in terms of reperfusion therapy management. However, many areas in the stroke care system remain underdeveloped and may negatively affect the outcome of the patients. We believe that our report will serve as a model for achieving advanced and structured stroke care in a resource-limited context and contribute to the future development of the healthcare system in our country.

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

GS wrote the first draft of the manuscript and is responsible for design, structure, and the final version of the manuscript. MO, SB, AA, MH, and HaM did data collection, data entry, and analysis. SE was responsible for statistical analysis. YM provided critical edits. HoM provided guidance in drafting and is responsible for the final version of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The 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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Pre- and in-hospital delays in the use of thrombolytic therapy for patients with acute ischemic stroke in rural and urban Egypt

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Background: Reducing pre- and in-hospital delays plays an important role in increasing the rate of intravenous thrombolysis (IVT) in patients with acute ischemic stroke. In Egypt, the IVT rate has increased steadily but is still far away from an ideal rate.

Aim: The study aimed to investigate the factors associated with pre- and in-hospital delays of IVT among patients with acute ischemic stroke coming from urban and rural communities.

Methods: This prospective, multicenter, observational cohort study was conducted from January 2018 to January 2019. Patients with acute ischemic stroke, who did not receive IVT, were included in the study. Patients were recruited from three large university stroke centers in Egypt, Assiut (south of Egypt), Tanta (north of Egypt), both serving urban and rural patients, and the University Hospital in Cairo (capital city), only serving an urban community. All participants underwent the National Institutes of Health Stroke Scale and full neurological assessment, urgent laboratory investigations, and computed tomography or magnetic resonance imaging to confirm the stroke diagnosis. The patients were subjected to a structured questionnaire that was designed to determine the parameters and time metrics for the pre- and in-hospital delays among patients from rural and urban regions.

Results: A total of 618 patients were included in the study, of which 364 patients (58.9%) lived in rural regions and 254 (41.1%) in urban regions. General demographic characteristics were similar between both groups. Approximately 73.3% of patients who arrived within the therapeutic time window were urban patients. The time from symptom onset till hospital arrival (onset to door time, ODT) was significantly longer among rural patients (738 ± 690 min) than urban patients (360 ± 342 min). Delayed onset to alarm time (OAT), initial misdiagnosis, and presentation to non-stroke-ready hospitals were the most common causes of pre-hospital delay and were significantly higher in rural patients. For patients arriving within the time window, the most common causes of in-hospital delays were prolonged laboratory investigations and imaging duration.

Conclusion: The limited availability of stroke-ready hospitals in rural Egypt leads to delays in stroke management, with subsequent treatment inequality of rural patients with acute stroke.

KEYWORDS

pre-hospital, in-hospital, delays, thrombolytic therapy, urban, rural, Egypt

Introduction

Within the Middle East region, Egypt has the highest incidence of stroke (1). Epidemiological studies identified a prevalence of 963 per 100,000 Egyptians. The mean and median incidence rates were 187/100,000 and 181/100,000, respectively (2–6). Presentation of patients with acute ischemic stroke within the thrombolysis time window of 4.5 h after symptom onset is required to gain access to intravenous thrombolysis (IVT) treatment following standard stroke imaging assessment (7).

In 2016, IVT for acute ischemic stroke became government-covered and free of charge for treatment-eligible Egyptian patients with stroke (8). To deliver treatment, the number of stroke-ready hospitals has increased significantly in recent years, with currently 43 stroke units delivering the service (8). Despite the availability of IVT and increased numbers of stroke units in Egypt, nearly 94.2% of eligible patients with acute ischemic stroke (AIS) do not receive IVT (9). Patients living in rural communities are more at risk of arriving at the hospital too late for treatment. Moreover, a relevant number of patients presenting within the therapeutic treatment window do not receive IVT due to in-hospital delays. Thus far, the evidence available for IVT treatment delays of patients with AIS comes from stroke units serving urban areas only, and studies analyzing the factors responsible for pre- and in-hospital delays in Egyptian stroke centers are limited (9, 10). The aim of this study is to investigate the factors lying behind pre- and in-hospital delays in patients with stroke coming from both rural and urban communities in Egypt.

Materials and methods

Study design

From 1 January 2018 to 1 January 2019, we conducted a prospective, multicenter, open-label cohort study in three comprehensive stroke centers in Egypt. We compared stroke management of patients coming from rural to those coming from urban areas. Patients were recruited from the tertiary university hospitals of three different geographical regions in Egypt, which were Assiut University hospital, the largest tertiary stroke center in the south of Egypt, Tanta University hospital, in the north of Egypt, and Cairo University hospital (the capital of Egypt). Assuit and Tanta hospitals both serve rural and urban communities, while Cairo only serves an urban community (Figure 1). The Egyptian government classification system, which classifies all Egyptian regions into Governorates, districts (Markaz) (urban), and villages or satellites (rural), was used to allocate participants to the rural or urban groups (11). The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Assuit University, Egypt, and followed the principles described in the Declaration of Helsinki.

Patients' selection and stroke pathways

Consecutive patients with AIS presenting to the three comprehensive stroke centers participating in the study were recruited. To investigate the reasons for not receiving IVT, patients could only participate if they had not received IVT even though suffering from an IVT-eligible AIS. Rural patients with stroke came directly to these hospitals or were referred from other healthcare facilities, where IVT was not available. The enrolled patients fulfilled the following inclusion criteria: diagnosis of acute ischemic stroke, aged 18 years or older, not treated with IVT although eligible, and sought medical advice within the IVT time window either in places where IVT was not available or missed treatment because of in-hospital delay. Patients were excluded from participation if they suffered from a transient ischemic attack or had contraindications to IVT in their history (12).

Data collection

All patients were subjected to detailed history taking, neurological assessment, initial NIHSS assessment, computed tomography (CT) imaging, or magnetic resonance imaging (MRI) of the brain. Urgent laboratory investigations were performed for all patients in the emergency department (ED) (Figure 2). All information led to the patient's diagnosis. Information about the first diagnosis and the number of patients with correct acute stroke diagnoses was documented. Demographic data were collected for all participants and

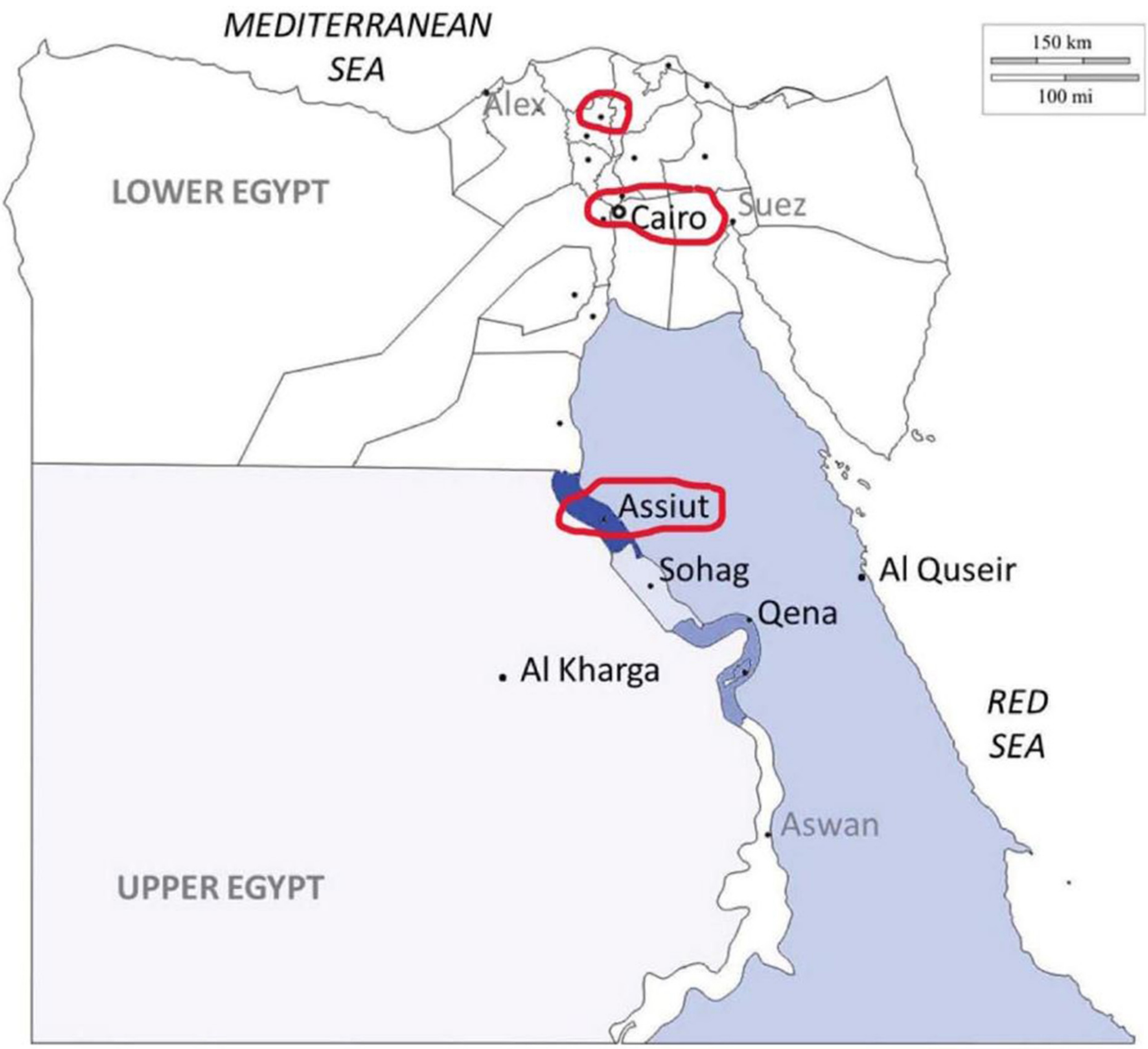

FIGURE 1
Egypt map showing the distribution of catchment areas.

included age, gender, risk factors, previous medical history, and living distance to the next hospital, where IVT was available (13).

For all participants, the following management times were documented for later analysis: time of symptom onset, onset to alarm time (OAT), time of public ambulance response (in Egypt, the emergency medical service is run by the government and access to ambulances in an emergency is free to all Egyptians), time spent in referral from hospitals, where IVT was not available to the study participating centers, onset to door time (ODT), which is time from symptom-onset hospital door in minutes, time spent from hospital door to neurological examination, time spent in imaging (calculated from the time of sending the patient to imaging till imaging results), time spent till laboratory results, and time spent from arrival to the hospital to decision of management. In addition, we documented the type and the pathway of emergency patients, or their relatives used and the means of transport to the hospital.

As a safety outcome, the ability of physicians, ER doctors, EMS, or relatives to recognize the patient's symptoms as the stroke was calculated. The help-seeking behaviors of patients or their relatives and the most common diagnosis the patients had by initial assessment were investigated.

All data were collected by a structured questionnaire (Supplementary material).

Statistical analysis

We analyzed the possibility of rural and urban variations in the pre- and in-hospital delays. Data obtained from this

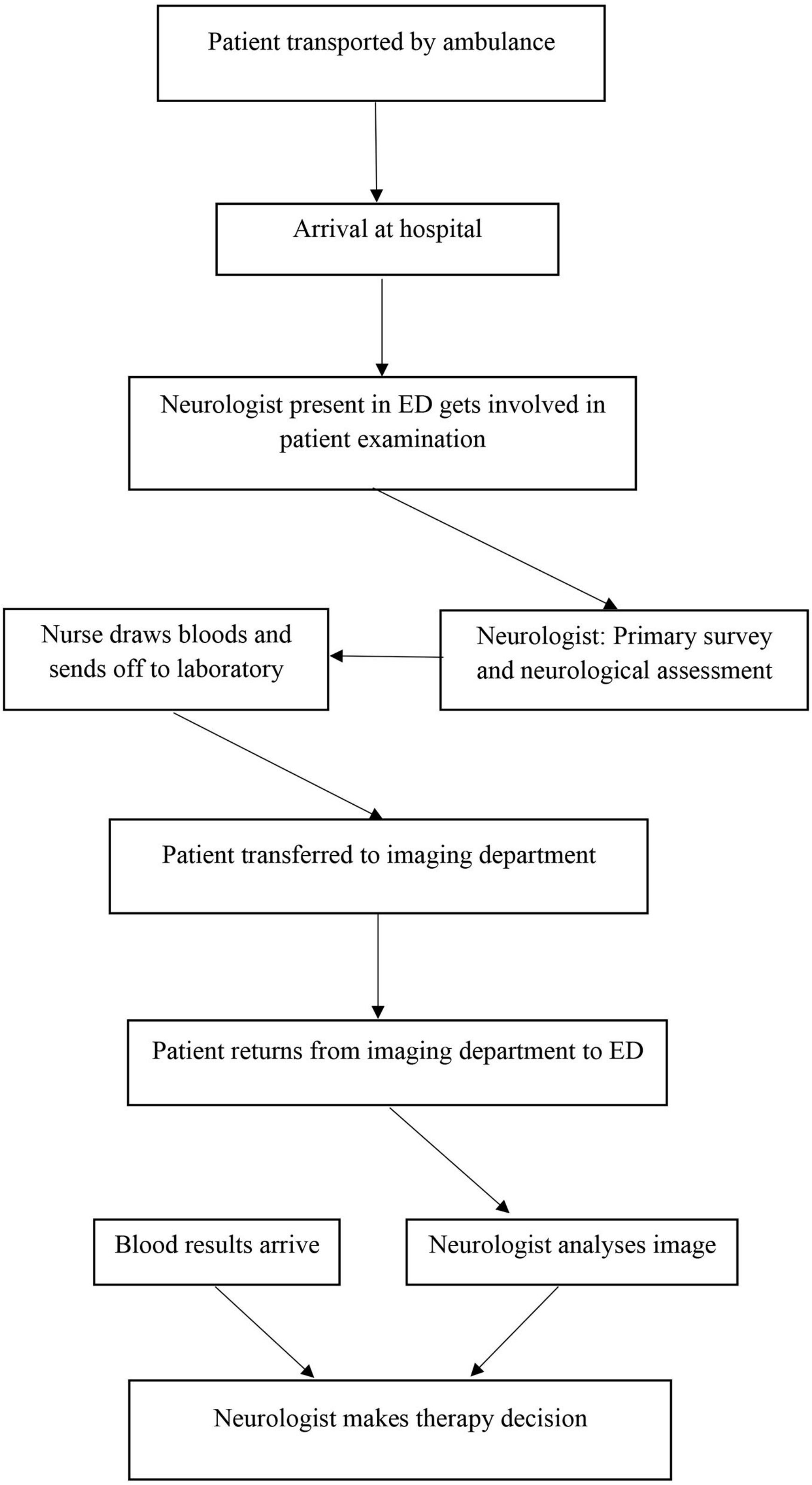

FIGURE 2
In-hospital workflow in the studied hospitals.

study were fed into an IBM-compatible computer. Descriptive statistics (mean (SD), numbers and percentages) were calculated using the Software Package for Social Sciences (SPSS, Inc, Chicago, Illinois) for Windows, version 25. Frequencies were noted and associations were determined using the Pearson chi-square test (X^2 test). Also, results were analyzed using an independent-samples *t*-test that did not assume equal variances. The significance level was set at $p < 0.05$.

Results

Demographics

Of the total of 618 patients, 351 (56.8%) men and 267 (43.2%) women, were included in the study between January 2018 and January 2019. A total of 364 patients (58.9%) came from rural regions and 254 (41.1%) from urban regions. The mean age for patients living in the rural regions was 63.57 ± 11.51, and the mean for urban was 63.48 ± 11.96 (Table 1). Hypertension, dyslipidemia, DM, AF, valvular heart diseases, and smoking were the most common stroke risk factors among rural patients. DM, hypertension, dyslipidemia, smoking, AF, and valvular heart diseases were the most common risk factors among urban patients. There was no statistical difference in the risk factor distribution among people living in urban and rural regions.

Pre-hospital time metrics and management pathways

The onset to alarm time was significantly longer among rural (234 ± 192 min) than urban patients with stroke (172.2 ± 135.6 min, $p < 0.05$). In addition, 85% of urban patients were living within 50 km of hospitals, where IVT was available in comparison to 21.2% only of our rural patients. Notably, 53.3% of rural patients live within 50–100 km and 25.5% live more than 100 km away from hospitals where IVT was available. This inequality contributed markedly to the pre-hospital delays among rural patients.

People in rural regions showed a higher tendency to contact emergency medical services than people living in urban regions. They also showed a higher tendency to seek medical advice from non-neurologists than the urban population (Table 2). In patients coming from rural areas, stroke diagnosis was significantly more often missed by the first treating physicians or examiners (68.7%) (Table 3). The time of ambulance response (from alarm to arrival at the patient's site) to the notification was also significantly longer among rural regions (31.88 ± 5.98 min in comparison to 26.86 ± 8.05 in urban regions).

In-hospital time metrics and management pathways

Notably, 81.9% of patients coming from rural regions were first treated by non-stroke-ready hospitals and needed referral to an IVT-capable center (Table 1). The time needed to refer a patient from the hospital where IVT was not available to the hospital where IVT was available did not differ between rural and urban regions (537 ± 684 min in rural and 534 ± 414 min in urban patients) (Figure 3). In patients, who arrived at one of the three stroke centers within their IVT treatment window, the time from symptom onset to the stroke center door was significantly longer for patients coming from rural areas (mean 216 ± 18 min) compared to patients coming from urban areas (mean 180 ± 30 min). This inequity was similar for patients who arrived at the stroke hospitals outside the IVT time window. The patients coming from rural areas needed (804 ± 708 min) from symptom onset to the stroke center door, which was significantly longer than for those who came from urban areas (mean 522 ± 408 min) (Table 4, Figure 3). Notably, 73.3% of patients arriving at the hospital within the IVT time window came from urban regions. Approximately 63.6% of urban and 59% of rural patients arriving at the hospital where IVT was available within the time window were men; however, there was no statistically significant difference in sex (Table 4). Among patients presenting to hospitals within the therapeutic time window, 86.4% of the rural patients presented within 3.5–4 h from stroke onset, which left only a narrow therapeutic time window (Table 4). Time spent in imaging for rural patients with stroke was 64.7 ± 12.3 min, which is lower than for urban patients with stroke 75.1 ± 24.5 min. 29.8 % of urban patients with stroke had MRI imaging for their stroke diagnosis in comparison to 11.4% only of rural patients with stroke. Surprisingly, patients with stroke who were eligible for thrombolysis but did not receive it had a door to stroke unit management of 100.1 ± 23.5 min if coming from urban regions, which was significantly higher than for rural patients with stroke (88.4 ± 13.8 min; Table 4).

Discussion

Acute stroke management and IVT utilization showed progress in Egypt. Despite that, IVT is still far away from the aimed rate (9, 10). In this study, we studied the main causes of delayed presentation to hospitals and in-hospital obstacles to the administration of IVT among urban and rural Egyptian patients with stroke.

The current study has shown that 47.6% of urban patients arrived within the therapeutic time window in comparison to 12% only of rural patients. Our results were in line with another report that showed pre-hospital delay is more common among rural patients; however, no definite proportion of rural

TABLE 1 General demographics of the study population.

	Rural (*n* = 364, 58.9%)	Urban (*n* = 254, 41.1%)	*p*-value
Male (*n*, %)	208 (57.1%)	143 (56.3%)	0.86
Female (*n*, %)	156 (42.9%)	111 (43.7%)	
Age (y) (Mean ± SD)	64 ±12	63 ± 12	0.92
NIHSS at admission (Mean ± SD)	9 ± 4	9 ± 4	0.49
mRS at admission (Mean ± SD)	3 ± 0.9	3 ± 0.9	0,18
Distance to hospital:			
<10 km	0	52 (20.5%)	
10–50 km	77 (21.2%)	166 (65.4%)	
51–100	194 (53.3%)	36 (14.2%)	
>100 km	93 (25.5 %)	0	
Risk factors distribution (*n*, %)			0.11
No risk factors	5 (1.4%)	3 (1.2%)	
Diabetes mellitus	73 (20 %)	77 (30.3%)	
Hypertension	104 (28.6%)	61 (24.0%)	
Ischemic heart disease	19 (5.2%)	10 (3.9%)	
Atrial fibrillation and valvular heart disease	38 (10.4%)	18 (7.1%)	
Dyslipidemia	81 (22.3%)	58 (22.9%)	
Smoking	37 (10.2%)	21 (8.3%)	
Vasculitis	7 (1.9 %)	6 (2.4%)	
Onset to alarm time (OAT) (in minutes) (Mean ± SD)	234 ± 192	172.2 ±135.6	< 0.05
Time of ambulance response (in minutes) (Mean ± SD)	31.88 ± 5.98	26.86 ± 8.05	< 0.05
Number of Patients referred from non-stroke ready hospitals	298 (81.9%)	40 (15.7%)	< 0.05
Time spent (in minutes) for referral from non-stroke ready hospital to stroke ready hospital (Mean ± SD)	537 ± 684	534 ± 414	0.97

Data described as numbers and percentages or mean ± standard deviation according to need. Q square and independent *t*-tests were used.

TABLE 2 Type of help-seeking behaviors among the study population.

Different types of contact for help (*n*, %)	Rural (*n* = 364, 58.9%)	Urban (*n* = 254, 41.1%)	*p*-value
Ambulance	97 (26.6 %)	51 (20.1%)	< 0.05
General practitioner	64 (17.6 %)	31 (12.2%)	
Internal medicine physicians	59 (16.2 %)	39 (15.4%)	
Neurologists	30 (8.2 %)	50 (19.7%)	
Relatives, friends, neighbors	60 (16.5 %)	44 (17.3%)	
ENT (Ear, Nose, Throat physicians)	18 (4.9 %)	16 (6.3%)	
Ophthalmologists	13 (3.6 %)	4 (1.6%)	
Other medical specialties	18 (4.9 %)	17 (6.7%)	
Traditional healers	5 (1.4 %)	2 (0.8%)	

Patients contacted physicians in their private clinics, hospital outpatient clinics, and emergency rooms.

TABLE 3 Accuracy of stroke diagnosis variations among rural and urban regions.

Initial diagnosis of the patients (*n*, %)	Rural (*n* = 364, 58.9%)	Urban (*n* = 254, 41.1%)	*p*-value
Recognize incident as stroke	114 (31.3 %)	111 (43.7%)	< 0.05
Recognize the incident as non-stroke related	250 (68.7%)	143 (56.3%)	
Functional disorder	15 (4.1%)	12 (4.7%)	
Cardiovascular disorder	35 (9.6%)	9 (3.5%)	
Diabetic coma	34 (9.3 %)	12 (4.7%)	
ENT disorder	26 (7.1%)	22 (8.7%)	
Ophthalmic disorder	16 (4.4%)	7 (2.8%)	
GIT	2 (0.5%)	4 (1.6%)	
No diagnosis	53 (14.6%)	27 (10.6%)	
Coma of unclear cause	28 (7.7%)	32 (12.6%)	
Other diagnosis	41 (11.3%)	18 (7.1%)	

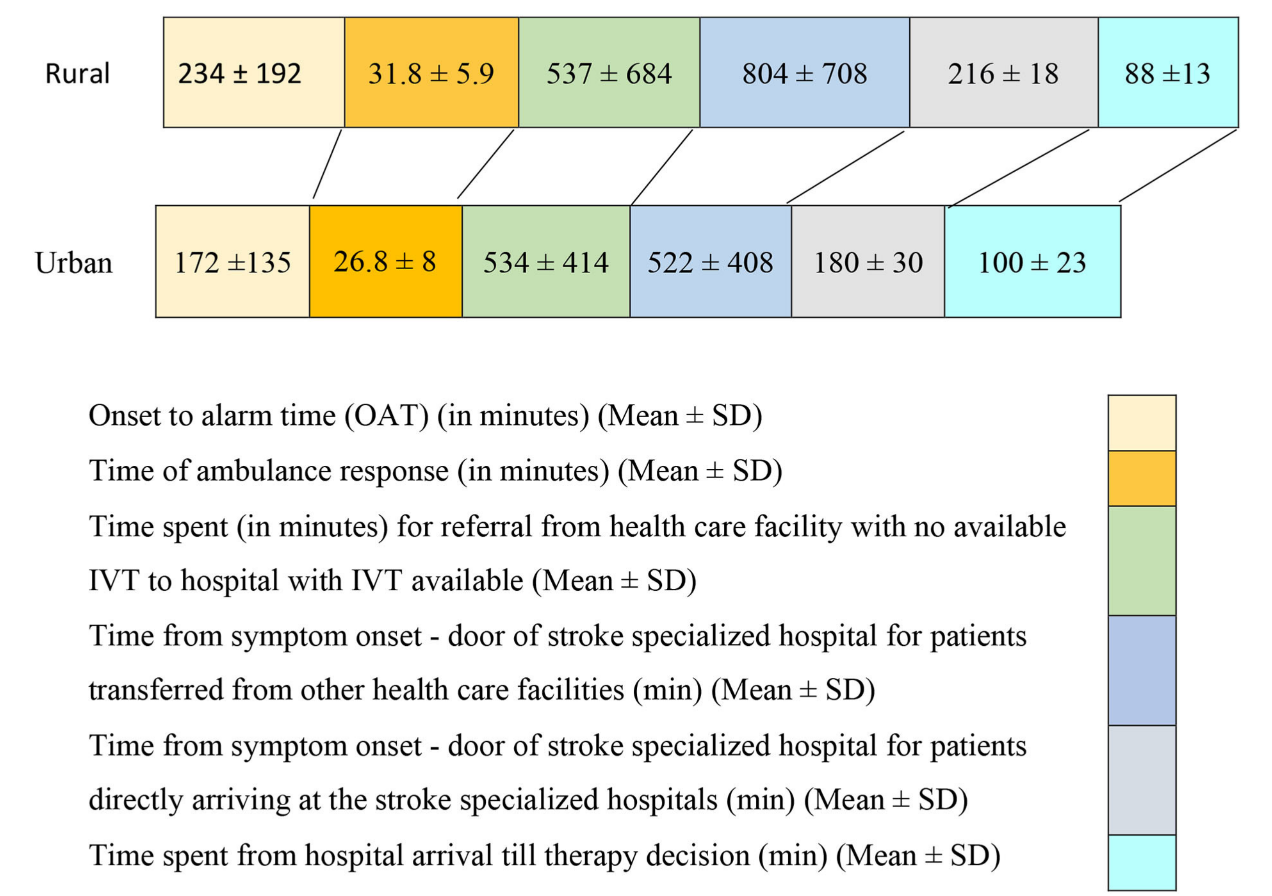

FIGURE 3
Time metrics variations among rural and urban patients.

patients with stroke presenting outside the time window in comparison to urban patients was reported (9). Another study showed a proportion as low as 26.4% of urban patients arriving at the hospital within the time window. These results were lower than our results, which may be attributed to the conduction of this study in 2015 when IVT was not

TABLE 4 General demographic characteristics of patients arrived within 4.5 h after symptom onset.

	Rural (n = 44, 12%)	Urban (n = 121, 47.6 %)	p-value
Number patients arrived within time window (%)			<0.05
Within 2 h of stroke onset	1 (2.3%)	14 (11.6 %)	
Within 2.5 h of stroke onset	5 (11.4%)	16 (13.2%)	
Within 3 h of stroke onset	16 (36.4 %)	47 (38.8%)	
Within 3.5 h of stroke onset	22 (50 %)	38 (31.4%)	
Within 4 h of stroke onset		6 (5%)	
Male (n, %)	26 (59%)	77 (63.6%)	0.09
Females (n, %)	18 (41%)	44 (36.4%)	
Time from symptom onset - door of stroke specialized hospital for patients arrived outside IVT time window (min) (Mean ± SD)	804 ± 708	522 ± 408	<0.05
Time from symptom onset - door of stroke specialized hospital for patients arrived within IVT time window (min) (Mean ± SD)	216 ± 18	180 ± 30	
Time from hospital arrival- meeting neurologist (min) (Mean ± SD)	12.7 ± 2.7	12.6 ± 2.8	0.86
Time spent for laboratory investigations in minutes (Mean ± SD)	97.9 ± 59.3	121.3 ± 74.1	0.06
Time spent for imaging in minutes (Mean ± SD)	64.6 ± 12.2	75.12 ± 24.45	< 0.05
Type of first imaging (n, %)			< 0.05
CT	41 (93.2%)	89 (73.6%)	
MRI	3 (6.8%)	32 (26.4%	
Time spent from hospital arrival till therapy decision (min) (Mean ± SD)	88.4 ±13	100.08 ± 23	< 0.05

Data described as numbers and percentages or mean ± standard deviation according to need. Q square and independent t-tests were used.

widely available in Egypt and not sponsored by the Egyptian government (10).

A recent study examining the main causes of pre-hospital delays in EDs found that living in rural areas is one of the main causes of delayed presentation (14). Similar results were obtained in a cohort analysis conducted in the southwest of Germany. Compared to rural patients, patients living in urban areas were more likely to present themselves within the time window (15). This rural–urban gap also exists in high-income countries (16, 17).

The ODT was 804 ± 708 min among our rural patients who arrived outside the time window, which was significantly higher than for urban patients (522 ± 408 min). The reported data from Egypt regarding ODT showed marked heterogeneity; one study showed that ODT was 162 min (18). This significant difference is attributed to a difference in study participant selection criteria, which excluded patients with acute stroke presenting later than 24 h after symptom onset. Our results were shorter than another Egyptian study (19), which reported that was 1,956 ± 1,968 min. Our results were similar to the reports from other countries with ODT among rural patients ranging from 300 to 1,800 min (20–23). The ODT for patients who arrived within the therapeutic time window was 216 ± 18 min among rural patients, which was also significantly higher than for people living in urban regions (180 ± 30 min). This means that even when rural patients arrived within the therapeutic time window, they have limited chance to take the thrombolytic therapy due to narrow in-hospital time.

This delay in ODT could be attributed to multiple factors. A major factor is a delay in help seeking. Onset to alarm times was nearly 4 h among rural patients, which was significantly higher than the 3 h patients from urban areas needed to call. This onset to alarm times was longer than the results described in the literature (20, 24). This delay in onset to alarm times could be explained by the low level of stroke awareness among the Egyptian population (25). Patients with stroke in rural regions tended to alarm ambulances (26.6% of patients), general practitioners (GPs) or internal medicine doctors, relatives, neighbors, neurologists, and other medical specialties. While urban patients alarmed ambulances (20.1%), neurologists, relatives, neighbors, internal medicine doctors, GPs, and other specialties. A recent Egyptian study (10) identified that nearly 20% of urban patients in Egypt used ambulances to reach the hospital. Similar to our study patients tended to alarm neurologists, internists, GPs, and other specialties. Also, data coming from the Netherlands showed that patients alerted relatives or friends, GPs, and ambulances (26). The pre-hospital delay in our study may be attributed to the fact that more than half of our patients were referred from non-stroke-ready hospitals, private hospitals, or community clinics. The majority of referred patients (88%) were rural patients, which likely is caused by a major deficit of stroke-ready hospitals in rural Egypt. Pre-hospital delays of rural patients are not a unique phenomenon in low-middle-income countries, but also reported in high-income countries, for example, in the United States, data from the national stroke registry has consistently related the arrival to a rural hospital as one of the factors to the failure of IVT (27). Ambulance response time to patients with stroke was significantly longer in rural regions compared to urban regions. This delayed response time does not meet the established American Heart Association/American Stroke Association guidelines for being at the scene within <15 min (28). Despite this delay, it is not far from the time recorded in other high-income countries like the United States (29). Pre-hospital delays in rural Egyptian areas can also be explained by the presence of the Egyptian ambulance system solely focused on urban regions. Misdiagnosis of stroke symptoms is another factor adding to delays. In our study, most patients were not identified as suspected strokes (rural patients 69%, urban patients 56%). This can be explained by false referrals of the patients to non-stroke specialists. Another reason might be that patients themselves directly went to seek help from non-stroke specialists in private hospitals after misjudging their symptoms. This percentage was much higher than those recorded by other Egyptian authors (10), who reported that the stroke misdiagnosis by the first examination was 18.2%. In our study, only 8.2% of rural patients and 19.7% of urban patients were initially examined by neurologists compared to 44.2% in other studies (10). Our results were lower than another Egyptian study (19), which found that 82.8% of patients with stroke were initially misdiagnosed by the first examiners. Surprisingly, the door to decision of therapy among urban patients was significantly longer than among rural patients (100 ± 23.4 min) vs. (88.40 ± 13.79 min), respectively. This difference could be explained by 26.4% of urban patients with stroke who had brain MRI to diagnose their stroke in comparison to only 6.8% of rural patients, which represents an important factor for in-hospital delays in urban patients. Our results were similar to Abraham and collaborators (30), who found that the door to decision in tertiary care centers in India was 94.17 ± 54.5 min.

Delays in laboratory investigations and imaging durations were the most common causes of in-hospital delays in our study. Laboratory investigations done routinely in patients with stroke prior to treatment were based on the high number of patients affected by the hepatitis C virus (31).

An earlier Egyptian study found that the unavailability of the IVT drug, lack of physician experience, and imaging delays were the most common causes of in-hospital delay (10). Their study was performed before IVT was widely available and covered by the government. Our results were far away from the standards of international recommendations for door to decision of management times, especially in rural areas, and this is a call for health authorities to invest in health education and acute stroke management program.

Our study has several limitations. We did not investigate the patient's education, level of stroke awareness, and economic level as the possible causes of the pre-hospital delays. We did not investigate the time lost in administrative issues as a possible cause of in-hospital delays. The demographic data analysis shows a much greater proportion of male participants so these results might vary among women with acute stroke.

Conclusion

Increasing population awareness about early stroke identification and the value of early arrival to stroke-ready hospitals, and training EMS personnel about bypassing non-stroke-ready hospitals to the nearest ready one, could reduce pre-hospital delays. The establishment of more stroke-ready hospitals and training of more physicians on acute stroke management in rural Egypt would reduce the burden on the urban hospitals and improve stroke systems of care among rural patients.

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 Ethical Committee of Faculty of Medicine, Assuit University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AN: conceptualization, methodology, and writing the manuscript. SW: supervision and writing and reviewing. KM, AG, and AD: data collection. GS: conceptualization and data collection. KF: supervision and project administration. FA-A: conceptualization and writing the manuscript and reviewing. All authors have read and approved the manuscript.

Conflict of interest

The 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1070523/full#supplementary-material

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National stroke management plan in Uruguay: Challenges and opportunities

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Stroke accounts for 5.5% of the national Global Burden of Disease (GBD) and ∼2,000 deaths per year in Uruguay. To respond to this medical emergency, the Ministry of Public Health (MPH) of Uruguay devised the National Stroke Plan (NSP). Scientific associations, universities, scholars, and patient organizations, both at the national and international levels, took part in the process, which ended with the generation of the national stroke management guidelines, including measures based on the best evidence available. This was accompanied by presidential regulatory decrees and several ordinances that set the foundations of the legal framework for their implementation as of 2020. Forty-two Stroke Ready Centers (SRC) and seven Comprehensive Stroke Centers (CSC) were strategically established and interlinked to ensure compliance with international accessibility recommendations, offering, in turn, the required training for their healthcare teams. A pre-hospital care protocol was also created for all countrywide mobile units. For NSP assessment, stroke was included as a "Care Goal (objective)" for the whole health system, providing the involved healthcare organizations with a financial incentive for compliance with the basic objectives related to the treatment of hyper acute stroke. The NSP came into force during the COVID-19 pandemic and, considering the special circumstances imposed, it made it possible to maintain hyper acute medical care and increase population access to recanalization treatment, particularly mechanical thrombectomy. The purpose of this article is to share our experience in the development of the NSP by describing some preliminary outcomes.

KEYWORDS
stroke, public health, Uruguay, care system, thrombolysis

Introduction

Stroke accounts for ∼5.5 % of the GBD (1) of Uruguay. It causes around 2,000 deaths per year and is the first leading cause of disability in the country (2). Due to the importance of this condition, in 2020, the MPH of Uruguay established stroke as a top priority and, through the development of a specific plan, it formalized some actions having an impact on the prevention, diagnosis, treatment, and rehabilitation with a clear view to reducing the burden of disease in the population of Uruguay. In this article, we will describe the characteristics of the National Stroke Plan (NSP) of Uruguay: planning, execution, and assessment thereof. As there are different approaches to address stroke from the perspectives of health systems at a global level, we share our experience and some initial outcomes of the NSP to contribute to the development of strategies aimed at reducing morbimortality arising from this condition in Latin America (3).

Impact of stroke in Uruguay

The average annual incidence of stroke in Uruguay is 125.14/100,000 inhabitants and has remained stable with no significant changes from 2016 to 2020. According to an epidemiological study carried out in the town of Rivera, 73.4 % of the strokes were ischemic (4). There is a slight predominance in female subjects with 51.74 %. The average mortality rate from 2012 to 2020 was 52.9/100.00 inhabitants (in 2019, 1905 deaths were recorded, and in 2020, 1790 were recorded (I61–I64 International Classification of Diseases v10 ICD-10) with a decreasing trend in recent years (Figure 1) (5). The mean age was 72.8 years, and the median age was 75 years (6).

Characteristics of the health system of Uruguay

Uruguay is a country located in South America, with a total surface of 176,220 km² and coasts on Río de la Plata and the Atlantic Ocean. According to the last 2011 census (7): its population is 3,390,077 with an annual growth rate of 1.9 %. It has a birth rate of 13.62 % and a mortality rate of 9.48 %, which has led to population aging, with 14.1 % of the population aged >65. Life expectancy is 76.01 years.

The National Integrated Health System (SNIS, *Sistema Nacional Integrado de Salud*) is composed of public and private health care providers who offer universal coverage with explicit guarantees [Comprehensive Health Care Plan (PIAS, *Plan Integral de Atención de Salud*)] whose funding comes from the National Health Fund (FONASA, *Fondo Nacional de Salud*) using a mixed mechanism of capitation and payment by results (health care goals). Furthermore, the system receives contributions from the national income. The high-cost and high-complexity coverage is implemented through a Public Fund (National Resource Fund). In Uruguay, government expenditure on health accounts for 6.93 % of the GDP. Leadership and governance of the health system come under the Ministry of Public Health, jointly with other dependent bodies.

National stroke management plan in Uruguay

As agreed in the Ministerial Meeting of Gramado in 2018, where it was decided to carry forward a strong campaign to reduce the high impact of stroke in Latin America (8), a specific department responsible for devising the NSP was established within the MPH of Uruguay. The School of Medicine of the University of the Republic (UdelaR, *Universidad de la República*), the Medical Association of Uruguay, the National Academy of Medicine, scientific associations, and patient organizations were consulted. National and international experts from different fields were also consulted, including experts from the World Stroke Organization (WSO) and Global Stroke Alliance (GSA). After the different planning, development, writing, and correction stages, the first version of the National Stroke Protocol was published in Uruguay, in 2020 (9). It focused on three main verticals: prevention, stroke treatment (general management, reperfusion, stroke unit), and rehabilitation, including a specific protocol for pre-hospital management with a focus on baseline medical actions and key interventions of renowned efficacy to improve care provision times, such as pre-notification to the receiving hospital (10).

The measures included in the guidelines were assessed in relation to their budgetary financial impact by the Health Economy unit of the MoH, and the National Resource Fund. Presidential regulatory decrees and several ordinances were passed, which set the foundations of the legal framework for the NSP.

Prevention

With the implementation of the NSP, massive campaigns related to prevention, risk factors, and early detection of stroke symptoms were launched on social and mass media. The Spanish acronym "ACV" was associated with the motto in Spanish "*actuemos con velocidad*" (let's act fast), following the model of other campaigns in Spanish for rapid detection of symptoms and activation of pre-hospital emergency services. In 2021, front-of-package food labeling started for products with excessive saturated fat, salt, sugars, and trans fatty acids, which was included by the WHO as a priority measure for the control of non-communicable diseases. Press and media coverage on

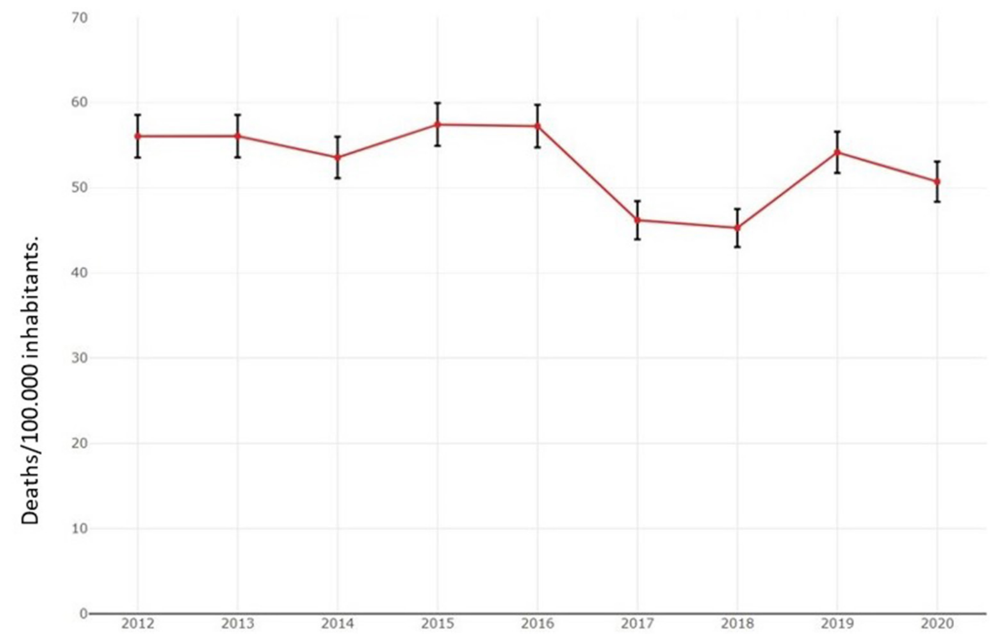

FIGURE 1
Mortality progress due to stroke in Uruguay from 2012 to 2020.

the issue were undertaken across the country for 2 years. Furthermore, guidelines for the inclusion of these issues in the school curricula were established, and the implementation of the Hearts Program of the PAHO in Uruguay is currently being sought.

Treatment

Stroke as a health system goal

The "National Health Objectives 2030" of Uruguay established non-communicable diseases, including stroke, as a priority. In such a sense, one of the first measures was to position stroke as a "health care goal" within the whole Integrated Health System. Healthcare goals imply that healthcare providers are offered a financial incentive in return for compliance with the basic indices related to acute stroke treatment. In the first stage, healthcare providers must submit the "roadmap" (stroke code) followed by patients with stroke to the MPH. They need to establish how coordination with pre-hospital healthcare will be achieved, the organization of "stroke teams" in each institution, 24/7 coverage of CT technicians for rapid execution of scans, the existence of strict protocols for application of thrombolysis and thrombectomy procedures in each case, and the existence of stroke units, among others. On a quarterly basis, the "health care goals" become more complicated, accounting for the ratio of thrombolyzed patients, door-to-scan and door-to-needle times, and the disability measured as per the Rankin scale during follow-up. The quality of secondary prevention should also be considered. At present, we can affirm that 100% of healthcare providers in Uruguay, either public or private, have established their roadmaps in relation to stroke care. Preliminary outcomes show that since the onset of NSP, the average thrombolysis ratio has increased from 9 to 11%, as well as thrombectomy procedures, which have increased by 30%, compared to previously published national data (11). Some sites, such as Hospital de Clínicas (Public University Hospital) have shown substantial development, exceeding a 20% thrombolysis ratio in 2020 and 2021, and being awarded the Angel's Award Diamond Status of the WSO.

Stroke centers in Uruguay

Forty-two Stroke Ready Centers (SRC) and seven Comprehensive Stroke Centers (CSC) were recognized country-wide. Geographic distribution enables compliance with the international recommendation of, at least, one stroke unit per 100,00 inhabitants, and of one angiography suite per 1,000,000 inhabitants. Medical coverage relating to stroke is universal and free, establishing that the patient is provided with care in the closest stroke center, irrespective of the healthcare provider servicing the patient. At each center, a multidisciplinary "stroke team" was identified and created. Thrombolytic drugs are covered by the National Therapeutic Forum, ensuring universal coverage throughout the health system. Uruguay has a wide coverage of the pre-hospital system, assisted by medical staff, and with adequate distribution of tomography equipment. For the creation of the CSC, international experts offered their support, ensuring the existence of seven state-of-the-art angiography machines to perform thrombectomy procedures. Two were established in the North of Uruguay, and five in the South, where most of the population resides. A committee of experts validated the competencies of Uruguayan neuro-interventional surgeons, trained abroad at reference centers. Funding for thrombectomy procedures was established through the National Resource Fund (NRF), with a two million US dollar fund for the 1st year.

Uruguay complies with the certification of Stroke Centers of the WSO and the Iberoamerican Cerebrovascular Diseases Society (SIECV, *Sociedad Iberoamericana de Enfermedad Cerebrovascular*). A local Accreditation Committee was established, which promoted international certification of stroke centers with quality standards, having already achieved certification of local centers. The International Accreditation Committee recently visited several centers in the country. Hospital de Clínicas of Uruguay was certified as a CSC. Within this context, the integration of Uruguay into the international registries such as Safe Implementation of Treatments in Stroke (SITS) and Registry of Stroke Care Quality (RES-Q) was promoted.

Medical education

The NSP was massively fostered, as well as its recommendations for hyperacute and prehospital management. Moreover, stroke training courses with different complexity levels were offered countrywide, following the Angel's Initiative model (with the endorsement of the European Stroke Organization - ESO) for all the interdisciplinary teams. Including both in-person and virtual training workshops, more than 1,500 healthcare providers were present. An augmented reality system was used for the resolution of case studies and *in situ* simulations were made in the different centers. The teaching staff was composed of experts from the School of Medicine, the MPH, scientific associations such as the Neurology Association, and international expert guests. Uruguay also joined the Mission Thrombectomy Campaign leadership of the WSO and GSA. Through this initiative, neuro-interventional surgeons who work in reference centers worldwide, came to Uruguay to carry out on-call shifts and procedures together with Uruguayan specialists, as well as to participate in case discussions, seminars, and academic activities.

Rehabilitation

A national survey of neurological rehabilitation centers was established, as well as a guide of available geo-referenced resources for patients and their families and caregivers, who also have access to a care guide after a stroke (12). The Uruguayan government made important investments in rehabilitation centers at two public sites (Hospital de Clínicas and Banco de Seguros del Estado).

Conclusions

Uruguay has demonstrated a strong commitment to addressing stroke by implementing the NSP which organized and optimized the health system resources for better and earlier treatment of stroke. The NSP was accompanied by an extensive prevention and community dissemination campaign as well as training of the healthcare staff. A significant regulatory framework was also established and the inclusion of healthcare goals enables quality control in establishing a continuous improvement process. From its initial stages, the NSP has shown signs of improvement in terms of access to recanalization therapies, in compliance with the main objective of public health, enabling universal access to stroke prevention, treatment, and rehabilitation, a highly-prevalent condition in the country having a deep individual, social and family impact on the health system and the Uruguayan society as a whole.

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.

Author contributions

IA: original idea, general coordination, review and co-writing of the entire article. AS: review of stroke care systems in the world, contribution to the introduction. AG: writing the section on establishing stroke centers. CC: writing on medical education. MM: contribution of statistical data. BT and SY: wrote about rehabilitation. RD and TM: wrote about certifying stroke centers. All authors contributed equally to the original idea of the article and its conclusions.

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Conflict of interest

The 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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Delivering acute stroke care in a middle-income country. The Mexican model: "ResISSSTE Cerebro"

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Introduction: Founded in 2019, the "ResISSSTE Cerebro" program is the first and only stroke network within the Mexican public health system. One advanced stroke center (ASC) and seven essential stroke centers (ESC) provide acute stroke (AS) care through a modified hub-and-spoke model. This study describes the workflow, metrics, and outcomes in AS obtained during the program's third year of operation.

Materials and methods: Participants were adult beneficiaries of the ISSSTE health system in Mexico City with acute focal neurological deficit within 24 h of symptom onset. Initial evaluation could occur at any facility, but the stroke team at the ASC took all decisions regarding treatment and transfers of patients. Registered variables included demographics, stroke risk factors, AS treatment workflow time points, and clinical outcome measures.

Results: We analyzed data from 236 patients, 104 (44.3%) men with a median age of 71 years. Sixty percent of the patients were initially evaluated at the ESC, and 122 (85.9%) were transferred to the ASC. The median transfer time was 123 min. The most common risk factor was hypertension (73.6%). Stroke subtypes were ischemic (86.0%) and hemorrhagic (14.0%). Median times for onset-to-door, door-to-imaging, door-to-needle, and door-to-groin were: 135.5, 37.0, 76.0, and 151.5 min, respectively. The rate of intravenous thrombolysis was 35%. Large vessel occlusion was present in 63 patients, from whom 44% received endovascular therapy; 71.4% achieved early clinical improvement (median NIHSS reduction of 11 points). Treatment-associated morbimortality was 3.4%.

Conclusion: With the implementation of a modified hub-and-spoke model, this study shows that delivery of AS care in low- and middle-income countries is feasible and achieves good clinical outcomes.

KEYWORDS

acute ischemic stroke, stroke centers, hub-and-spoke, low- and middle-income countries, public health

1. Introduction

In Mexico, as in most low- and middle-income countries (LMICs), there is an enormous need for strategies to improve access to acute stroke (AS) care (1, 2). Intravenous thrombolysis (IVT) rate in Mexican hospitals is <10% (3), being the main reasons for its low utilization rate: patients arriving outside the therapeutic window (4), lack of knowledge regarding stroke symptoms and treatment in the Mexican population (5) and the documented fact that a significant proportion of patients undergo medical evaluations in facilities unable to provide adequate treatment before reaching an acute reperfusion capable center (3). Also, despite endovascular treatment (EVT) being the current standard of care for patients with acute large vessel occlusion (LVO), the access rate to EVT in Mexico is unknown, but a case series has shown it to be a feasible intervention with efficacy comparable to centers in high-income countries (6). Nevertheless, the widespread use of EVT in the country faces several barriers that still need to be overcome, mainly the high costs and the lack of public funding (7).

Regrettably, the number of new stroke cases and deaths in Mexico increased by 70.7 and 75.3%, respectively, from 1990 to 2019. And although the age-standardized mortality and the disability-adjusted life years rates were reduced −41.6 and −38.1%, respectively, in the same period, the burden of stroke continues to be a significant healthcare issue for the country (8).

To address this high burden of disease, in 2019, the "*Instituto de Seguridad y Servicios Sociales de Los Trabajadores del Estado*" (ISSSTE), which provides healthcare for the employees of the Mexican government and to their first-degree relatives, approved the creation of a pilot program; "ResISSSTE Cerebro," a publicly funded program that provides AS care for the beneficiaries of the ISSSTE healthcare system in Mexico City. Before the program's implementation, data from the epidemiology department of the ISSSTE puts AS treatment rate at <10% (Unpublished data).

In this study, we report the results from the third year of operation of the "ResISSSTE Cerebro" program, including the population's characteristics, treatment, performance metrics, and early clinical outcomes.

2. Materials and methods

2.1. The "ResISSSTE Cerebro" program

The "ResISSSTE Cerebro" program includes seven urban healthcare facilities located in Mexico City and one in each of the neighboring states of Morelos and Hidalgo. According to the World Stroke Organization global stroke services guidelines and action plan (9), seven facilities are cataloged as essential stroke centers (ESC). Thus they offer access to non-contrast computed tomography (NCCT), clinical evaluation, and potentially IVT (according to IVT criteria cited below). At ESC, there is no personnel with expertise in AS treatment. The eighth facility is an advanced stroke center (ASC) capable of providing advanced stroke services on a 24/7 basis, including multidisciplinary stroke expertise, multimodal imaging, and acute reperfusion therapies for ischemic stroke.

Since its approval in 2019, the program has operated as a modified hub-and-spoke model. It receives funding from the Mexican government through the ISSSTE healthcare system and has access to ambulance services available 24/7. It also includes a stroke telemedicine network to facilitate the evaluation and care of potential patients.

As mentioned above, the program's functioning is mainly based on the hub-and-spoke model but with certain adequations to the Mexican Healthcare system. For example, most hub-and-spoke models function by offering daytime AS treatment at local centers, and the patients in need of treatment out-of-hours and on weekends are treated at hub hospitals. But, in the "ResISSSTE Cerebro" program, all centers provide AS treatment regardless of time or day, with the only difference being that advanced modalities of treatment (EVT and IVT guided by perfusion imaging up to 9 h after the onset of symptoms) are available only at the ASC. Similarly, the drip-and-ship model, as initially conceived, assumes that all centers within a network can diagnose LVO, thus allowing emergency medical services (EMS) to move patients to the closest hospital and only transfer to a thrombectomy-ready hospital for those patients with confirmed LVO. The drip-and-ship model was only partially implemented in our program due to constrained access to ambulances and human and technological infrastructure to perform advanced imaging in stroke patients at the ESC. Our model also accommodates that most of the patients in Mexico arrive at a hospital by their means (for example, the family car or public transportation), with few coming by EMS; therefore, prenotification is uncommon. Consequently, by concentrating the human and technological resources in a single center, the "ResISSSTE Cerebro" program can deliver advanced AS treatment 24/7 while preserving the capability of ESC to provide telemedicine supervised IVT also 24/7.

The stroke telemedicine network utilizes an instant messaging app that includes all the emergency room staff of all shifts grouped by each ESC. Each group, in turn, has all the stroke team members located at the ASC. Emergency room physicians are in charge of all initial evaluations and are responsible for alerting the stroke team and carrying out their instructions regarding treatment. At the same time, they order the NCCT and arrange for a possible transfer to the ASC. The ESC prenotifies all transfers to ASC. The protocol is known by all the staff at the emergency rooms of the ESC, and a print or electronic copy is available for consultation at the office of the head of the emergency department. Figure 1 depicts the pathway for patients initially arriving at ESC, and Figure 2 is that of patients coming directly to the ASC. All the ESCs are staffed 24/7 with emergency physicians, residents (emergency medicine is a 3-year residency program in Mexico), and radiologists. At the ASC, the staff comprises emergency physicians and emergency medicine residents, radiologists, neuroradiologists, clinical neurologists and clinical neurology residents, neurosurgeons and neurosurgery residents, and interventional neurologists and interventional neurology residents.

2.1.1. Improvement and maintenance of the program

The program has implemented continuing medical education activities at the ESC. These activities include lectures and seminars for emergency department personnel, clinical rotations at the ASC for emergency medicine, written

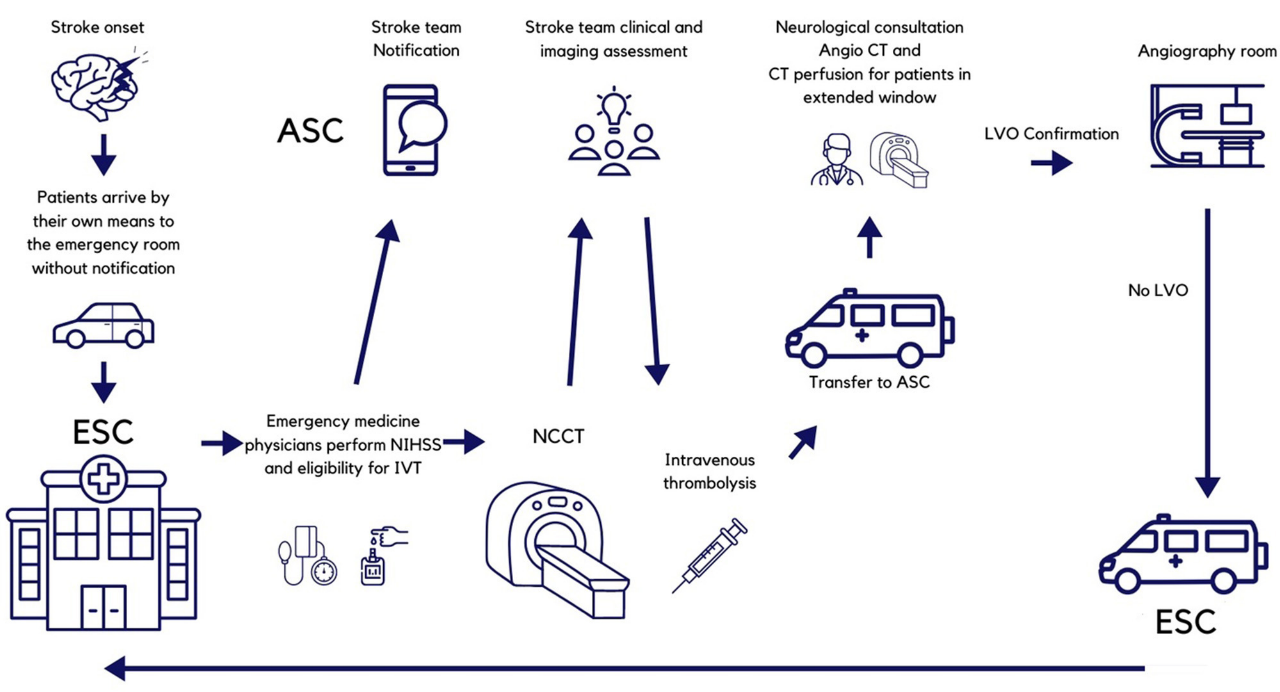

FIGURE 1
Pathway for patients initially arriving to Essential Stroke Centers. NIHSS, National Institutes of Health Stroke Scale; ASC, Advanced Stroke Center; IVT, intravenous thrombolysis; CT, computed tomography; LVO, large vessel occlusion.

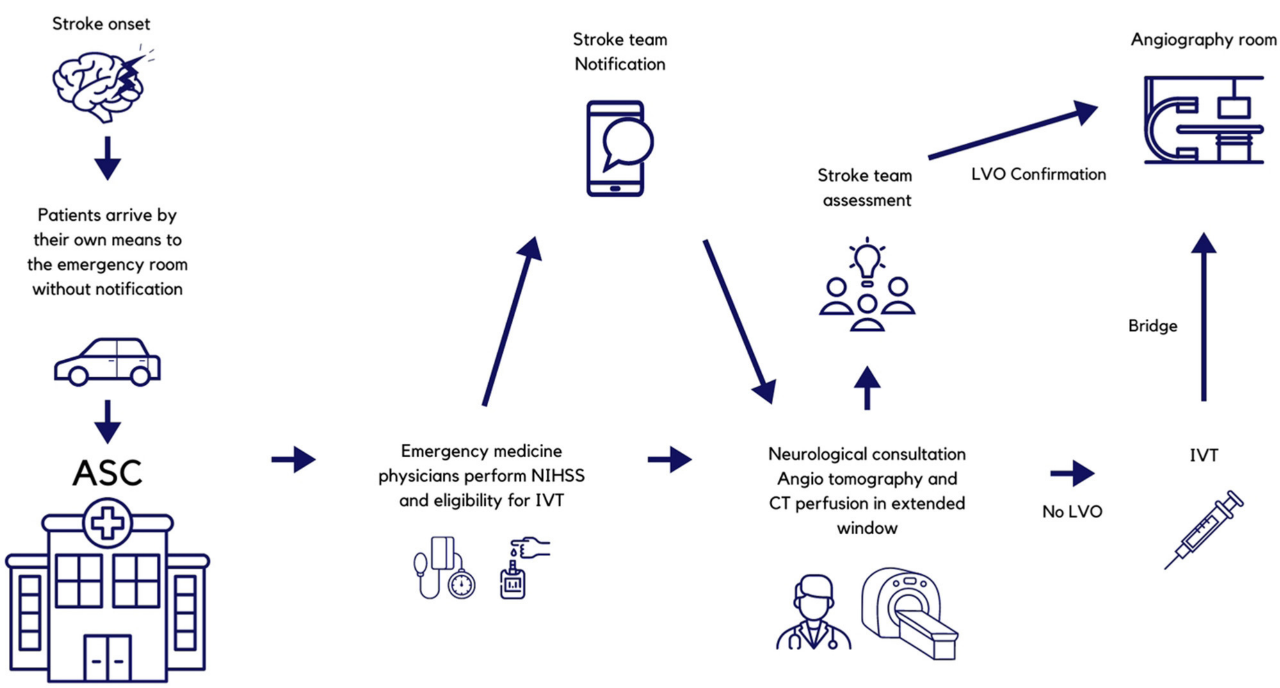

FIGURE 2
Pathway for patients arriving directly to the Advanced Stroke Center. NIHSS, National Institutes of Health Stroke Scale; ESC, Essential Stroke Center; ASC, Advanced Stroke Center; IVT, intravenous thrombolysis; CT, computed tomography; LVO, large vessel occlusion.

protocols for managing data, patient transfer, neuroimaging protocols, and flow charts. At the ASC, improvement measures included written protocols for collecting data, neuroimaging protocols, and flow diagrams for the separate treatment windows of treatment for acute ischemic stroke up to 24 h from symptom onset.

The program also takes notice of the increasing importance of routine monitoring of the quality of stroke care (10). Consequently, the ASC participates in the RES-Q initiative of the ESO East Project (European Stroke Organization-Enhancing and Accelerating Stroke Treatment) and registers all the patients treated, and conducts annual reviews of the gathered data (11). Additionally, in March 2021, an interventional neurology residency program was initiated. Its first class is expected to graduate in February 2023. One example of the continuing medical education implemented is the change in the use of tenecteplase. Since the recruitment period for the preset study predates the publication of the Norwegian tenecteplase stroke trial results, the dose for IV tenecteplase was set at 0.4mg/kg according to local practices.

Nevertheless, since the NORTEST trial publication (12) the "ResISSSTE Cerebro" program protocol has been modified, and the current dose is set at 0.25 mg/kg. Additionally, although tenecteplase is available at all the network centers, the protocol establishes that Alteplase is always the drug of choice, with tenecteplase reserved for rare occasions when Alteplase is unavailable. The low usage of tenecteplase in the present study supports the practice. Additionally, it is worth mentioning that as a result of all the strategies for improvement and maintenance, the main center was certified by the World Stroke Organization as an ASC in August 2022.

2.2. Selection of the acute reperfusion intervention

Patients 18 years or older arriving within the 4.5 h time window are eligible for IVT at the ESC after the evaluation of the NCCT by the stroke team at the ASC *via* telemedicine. Patients evaluated outside the 4.5-h time window are transferred to the ASC, undergoing brain computed tomography perfusion imaging combined with head and neck computed tomography angiography. Based on the results of advanced neuroimaging, extended window IVT (up to 9.0 h from symptoms onset) is offered according to the EXTEND—IA criteria using RAPID—AI software or EVT (up to 24 h) using DEFUSE −3 or DAWN criteria. Wake-up stroke and stroke of unknown onset are offered treatment based on the EXTEND and ECASS4—EXTEND trial for up to 9.0 h IVT is administered at standard doses, 0.9 mg/kg for Alteplase, a single bolus of 0.4 mg/kg for Tenecteplase, and 0.25 mg/kg single bolus of Tenecteplase when subsequent EVT was planned.

The EVT technique was at the discretion of the attending neuro-interventionalist and consisted of direct aspiration, stent retrievers, or a combination.

2.3. Data and outcomes

Data was prospectively registered from March 1st, 2021, to February 28th, 2022. Stroke severity was determined by the National Institutes of Health Stroke Severity scale (NIHSS) with minor symptoms defined as NIHSS 0 −5 and severe stroke if NIHSS > 25 points. Successful recanalization was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b−3. Early neurological improvement (ENI) was defined as a reduction of ≥4 on the National Institutes of Health Stroke Scale (NIHSS), compared with the baseline score or an NIHSS of 0 or 1 at 24 h after treatment; European Cooperative Acute Stroke Study (ECASS) II criteria were used to define any intracranial hemorrhage and symptomatic intracranial hemorrhage (sICH) after t-PA administration. The compound measure of adding mortality and morbidity is reported as morbimortality.

2.3.1. Workflow times definitions

We utilized standardized definitions for workflow times except for the door-to-evaluation time, which was not included because, for most of the patients evaluated initially at the ESC, the time to the medical evaluation was registered irregularly. Instead, we used door-to-imaging (DTI) time (measured from arrival at the hospital to the arrival at the imaging suite) as an estimate of the time that passed until the assessment of the patient since the initial evaluation forcibly had to be complete before the transfer to radiology. Onset-to-door (OTD) was measured from the onset of symptoms to the arrival at the hospital regardless of if it was an ESC or the ASC. The time from arrival at the hospital to the starting of IVT is reported as door-to-needle (DTN), whereas the time from the onset of symptoms and arrival at the ASC to groin puncture is reported as onset-to-groin (OTG) and door-to-groin (DTG), respectively. Finally, the transfer time (TT) was measured from the stroke team notification to the patient's arrival at the ASC.

2.4. Statistical analysis

Categorical variables are presented as frequency and percentages, continuous variables as mean ± standard deviation or median (second–third quartiles) according to the Kolmogorov–Smirnov test result.

As appropriate, comparisons were conducted using a chi-squared test, Fisher's exact test, Student T-test, and Mann–Whitney-U-test. The p-value was considered significant at <0.05. All analyses were computed with Stata version 15.0, StataCorp (Texas, USA).

2.5. Ethical considerations

The institutional review board of the ISSSTE, Centro Médico Nacional "20 de Noviembre," reviewed and approved the protocol (reference 582.2019). The same committee waived the signing of the informed consent form per local regulations. Only de-identified data were registered and stored.

3. Results

3.1. Baseline characteristics of the patients

Data from 235 patients were available for the analysis; 104 (44.3) were men with a median age of 71 (60–78) years. One hundred and forty-two (60.4%) patients received their initial

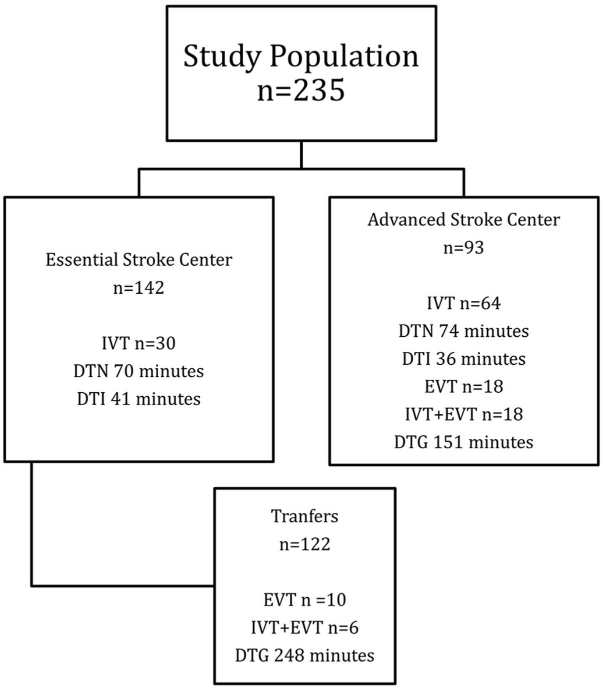

FIGURE 3
Flow chart of study population. IVT, intravenous thrombolysis; DTN, door-to-needle; DTI, door-to-imaging; EVT, endovascular therapy; DTG, door-to-groin.

evaluation at one of the seven ESC of the stroke network, and 122 (85.9%) of them were transferred to the ASC for further assessment with a median transfer time (TT) of 123 min. Figure 3 depicts the flow chart of the study population. Ninety-three (39.6%) patients arrived directly at the ASC for urgent care. Vascular risk factors identified in order of frequency were hypertension 173 (73.6%), diabetes mellitus 81 (34.5%), obesity 40 (17.0%), cancer 20 (8.5%), valvular heart disease 14 (6.0%) and smoking 13 (5.5%). After clinical and imaging evaluation, 63 (26.8%) patients were identified with a stroke mimic. Subtypes of stroke were as follows: ischemic stroke 139 (80.8%), hemorrhagic stroke including intracerebral hemorrhage and subarachnoid hemorrhage 24 (14.0%), and nine transient ischemic attacks (5.2%). The median baseline NIHSS was 10 (4–18). Eighty-seven (61.3%) patients and 41 (44.1%) patients arrived within the 4.5 h therapeutic window to the ESC and ASC, respectively. As shown in Table 1, for baseline characteristics, overall, there were no differences between patients whose care took place in an ESC compared to the ASC except for previous disability ($p = 0.044$), frequency of any cancer, and valvular heart disease ($p < 0.001$), baseline NIHSS ($p = 0.028$) and therapeutic window arrival ($p = 0.044$).

3.2. Time points for acute stroke treatment

Performance time points achieved were as follows:

OTD median time 135.5 (90–270) min.
DTI median time 37 (26–52) min.
DTN median time 76 (40–133) min, and
DTG median time of 151.5 (118–225) min.

Table 2 shows comparisons in the time points for acute stroke treatment workflow between ASC and ESC patients. Forty-nine (35.3%) patients received IVT at either center. Thrombolysis was achieved within the first hour of arrival to the emergency department in 15 (30.6%) patients (Table 3).

3.3. Efficacy and safety of intravenous thrombolysis

After IVT, 35 patients (71.4%) showed ENI with a median NIHSS reduction of 11 points (4–16). Hemorrhage after intravenous thrombolysis presented in eight patients, but only two were symptomatic. Unfortunately, both cases produced the patient's death, and one additional death occurred with a mortality rate of 6.1%. All the patients that developed hemorrhage received Alteplase. Three patients received tenecteplase (6.1%).

3.4. Endovascular treatment

The ASC performed 28 endovascular procedures. The median OTG time was 500 min (353–792), and the median DTG time was 151.5 min (118–225). Seven (25%) patients were treated within the 6-h window. One patient arrived at the ASC beyond the 24-h windows but was still eligible for EVT. According to the study design, all other patients received treatment in the 6-to-24 h therapeutic window per protocol.

4. Discussion

The present study constitutes the first description of an AS treatment program in Mexico; its results show adequate performance in standardized workflow metrics in AS treatment and good immediate clinical outcomes.

When there is a need to decide whether to treat *in situ* or transfer a patient AIS, two main issues are essential: (1) prolonged transfer times will result in delays in IVT administration which are associated with significant morbidity and mortality, and (2) patients carrying LVO (∼10%−46% of the cases), will significantly benefit from EVT (1, 13). Therefore, it is critical to consider the regional infrastructure available along with the location of ESC and ASC concerning the patient's geographical location (14). In this respect, Bekelis et al. consider bypassing primary stroke centers making sense if the center is located within 90 min from the patient's location. But they also did not find any differences between patients treated with a hub-and-spoke model and those treated directly in ASC in several outcomes, including inpatient case-fatality, discharge to a specialized facility, and length of stay (13).

In other studies, the hub-and-spoke model has been associated with better outcomes, highlighting that rapid inter-facility transfer is a pivotal key to the efficacy of such a model (15). Milne et al. (14) demonstrated that ESC near an ASC retained their

TABLE 1 Baseline characteristics of the patients.

	All $n = 235$	ESC $n = 142$	ASC $n = 93$	p-value
Male	104 (44.3)	67 (47.2)	37 (39.8)	0.264
Age—median (2nd–3rd quartiles)	71 (60–78)	70.5 (60–79)	72 (62–78)	0.273
Previous stroke	30 (12.9)	20 (14.1)	10 (11.0)	0.479
Modified Rankin Scale				
0	168 (72.1)	111 (78.7)	57 (62.0)	0.042
1	27 (11.6)	12 (8.5)	15 (16.3)	
2	9 (3.9)	4 (2.8)	5 (5.4)	
3	16 (6.9)	9 (6.4)	7 (7.6)	
Risks factors				
Hypertension	173 (73.6)	104 (73.2)	69 (74.2)	0.871
Diabetes	81 (34.6)	56 (39.4)	25 (27.2)	0.054
Obesity	40 (17.1)	26 (18.3)	14 (14.2)	0.539
Cancer	20 (8.6)	2 (1.4)	18 (19.6)	<0.001
Valvular heart disease	14 (6.0)	2 (1.4)	12 (13.0)	<0.001
Smoking	13 (5.6)	10 (7.0)	3 (3.3)	0.257
Type of stroke				
Ischemic	139 (59.1)	93 (65.5)	46 (49.5)	0.096
Hemorrhagic	24 (10.2)	14 (9.9)	10 (10.8)	
Transient ischemic attack	9 (3.8)	4 (2.8)	5 (5.4)	
Large vessel occlusion	63 (26.8)	63 (26.8)	0	–
NIHSS—median (2nd–3rd quartiles)	10 (4–18)	11 (4–18)	8 (1–17)	0.028
Time of arrival				
<4.5 h	128 (54.5)	87 (61.3)	41 (44.1)	0.044
4.5–6.0 h	18 (7.7)	10 (7.0)	8 (8.6)	
6–16 h	22 (9.4)	9 (6.3)	13 (14.0)	
16–24 h	2 (0.9)	1 (0.7)	1 (1.1)	
>24 h	1 (0.4)	0	1 (1.1)	

All values n (%) unless otherwise specified.
NIHSS, National Institutes of Health Stroke Scale; ESC, Essential Stroke Center; ASC, Advanced Stroke Center.

significance through the drip and ship approach if they could administer IVT within 30 min. Prior experiences in LMIC of successful development and implementation of stroke units have been reported in the private setting of Panamá, but it was a single-center program (16). Considering all these factors, our local infrastructure, capabilities, and the geographical distribution of the healthcare facilities, we decided to adopt the hub-and-spoke model. The results for the third year since the implementation of the program show higher transfer times compared to similar programs [123 vs. 104 min in the study by Prabhakaran et al. (15)].

According to national epidemiological data, the ISSSTE healthcare system covers only a tiny proportion of the Mexican population (11.3%) (17). Regardless, in our population of beneficiaries, we observed similar demographics, risk factors, and proportion of stroke subtypes than reported in previous studies performed in Mexico (18). Regarding AS treatment rates before the introduction of the extended time window, IVT and EVT range from 0.5 to 7.6% (4, 18–22). In light of these figures, the results of the present study show a substantial improvement in rates of IVT and EVT (35.3%), something unprecedented for the country. Moreover, the "ResISSSTE Cerebro" program differs from previous efforts in Mexico due to its multicenter nature, usage of telemedicine, and public origin of the funding source; these differences allow for bypassing common barriers to treatment of AIS, such as low availability of stroke expertise, thrombolytics, angiography suites, and endovascular devices, and uncoordinated transfer protocols. Lastly, its most crucial facilitator is the availability of public funding to support the interventions.

We also significantly improved in time metrics. OTD diminished from 11 h to 135.5 min. Our program's arrival times were lower, with 54.5 and 62.1% arriving within the 4.5- and 6.0-h windows, respectively. Previous studies had reported 17%–23% of patients coming in <3.0 h (21, 22), 17.4% coming in <4.5 h (17), and 39%–42% within 6 h from symptoms onset (19, 22).

TABLE 2 Time points for acute stroke treatment workflow.

	ESC	ASC	*p*-value	Transferred	*p*-value
OTD time	127.5 (90–195)	182.5 (93–354)	0.0813		
DTI time	41 (23–81)	58 (26–52)	0.0582	30.5 (40–92)	<0.001
DTN time	70 (40–134)	97 (45–97)	0.5067	67.5 (47–76)	0.1568

All values median (2nd—3rd quartiles). All values in minutes unless otherwise specified.
ESC, Essential Stroke Center; ASC, Advanced Stroke Center; OTD, onset-to-door; DTI, door-to-imaging; DTN, door-to-needle.

TABLE 3 Comparison of overall and within the first hour intravenous thrombolysis rates by treatment center.

	All	ESC	ASC	*p*-value
IVT	49 (35.3)	30 (61.2)	19 (38.8)	0.558
1st hour IVT	15 (30.6)	9 (30.0)	6 (31.6)	0.452

All values n (%).
ESC, Essential Stroke Center; ASC, Comprehensive Stroke Center; IVT, intravenous thrombolysis.

Remarkably, there were no differences in patients' arrival time between ESC and ASC. Also, the ESC administered most of the IVT; this situation is optimal because it allows for complex cases to be treated in the ASC (23).

Besides OTD, the present study's most important finding is that there were no differences in DTN times between the ESC and the ASC, demonstrating that the program can provide timely care decisions regardless of the physical infrastructure or geographical location of the stroke team. Still, we detected a non-significant (∼30 min) delay in IVT for patients arriving at the ASC without prenotification.

The good performance in time measures after IVT also translated into excellent early efficacy outcomes, with 71.4% of the patients achieving ENI, as evidenced by their post-IVT NIHSS scores. Concerning safety, the rate of symptomatic intracerebral hemorrhage and in-hospital deaths was lower than those previously reported for public healthcare facilities in Mexico (19). Interestingly, transferred patients from ESC had a shorter DTN when compared to patients that arrived directly at the ASC. Similarly, DTG in the RACECAT trial (24) was higher in the thrombectomy-capable center than in the local stroke center, 71 (49–97) vs. 43 (32–59) min, respectively. The time differences, although not statistically significant, underline the importance of specific processes, such as the prenotification system and the stroke team's activation, and give us the cue to develop further and implement strategies to improve the program. Some methods we could implement to reduce performance time measures include critical components of the Helsinki model, such as those successfully implemented in other parts of the world (25). For example, the direct transfer of patients from triage onto the CT table on the ambulance stretcher; and the delivery in the CT room immediately after imaging. Others, such as ambulance prenotifications, will continue to be a challenge in Mexico due to the general population's low usage of EMS.

Despite all the positive findings, the present study has some limitations, mainly the data that was not registered; these data included door-to-evaluation time, transfer selection criteria, mechanism of stroke, time to start secondary prevention strategies, and long-term clinical outcomes. We have also previously identified long transfer times as a significant cause for delays in DTG and DTI times at the ASC (26). The prolonged transfer times are explained majorly by two factors: the use of ambulances at ESC for pre-scheduled transfers without a backup ambulance for emergency transfers and the fact that Mexico City is the world's most traffic-congested city. To tackle the first issue, we strongly required the ISSSTE board to designate at least one ambulance per ESC exclusive to the "ResISSSTE Cerebro" program; however, funding and logistic matters still prevent such improvement to our program.

Additionally, the generalizability of our findings is restricted to the beneficiaries of the ISSSTE living in the urban setting of Mexico City. In other cities of the country or different LMICs, the scarcity of resources, lack of organized communication among facilities, and restricted access to technology make the widespread implementation of our program non-viable at the present moment.

Regardless, the present study serves as an initial experience that provides evidence that implementing programs aimed to reduce the burden of stroke in LMICs is possible and has a high chance of success, provided that adequate funding is available. In the design of the "ResISSSTE Cerebro" program, we incorporated multiple strategies proven to increase rates of AIS treatment (27), such as education programs, enabling access to stroke expertise and technology, and timely communication in a stroke network.

5. Conclusion

The "ResISSSTE Cerebro" program is a successful AS treatment model capable of achieving high rates of IVT and EVT for the treatment of AIS within its third year of operation. Also, workflow metrics were within international standards and, for IVT, did not differ between ESC and ASC. The previous results translated into ENI for most patients without increases in morbimortality. We are confident that in LMICs, implementing programs like "ResISSSTE Cerebro" can lead to the successful delivery of AS care.

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 Institutional Review Board of the ISSSTE, Centro

Médico Nacional XX de Noviembre. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

DB-D design and conceptualization of the study, significant role in acquiring data, analyzed the data, and drafted the manuscript for intellectual content. EC-P analyzed the data and drafted the manuscript for intellectual content. BM-G and CS-M had a substantial role in the acquisition of data, analyzed the data, and drafted the manuscript for intellectual content. JM-R the study's conceptualization, analyzed the data, and drafted the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Assessment of stroke knowledge and awareness among primary healthcare providers: A cross-sectional survey from the Kezhou quality improvement in acute stroke care project

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Objective: Acute stroke care is a highly complex type of emergency medical service (EMS) involving patient-centered care in a highly unpredictable and stressful environment with the help of several busy providers. The ability of primary healthcare providers (PHPs) to identify stroke onset early and further manage referrals to higher-level hospitals becomes critical.

Methods: We conducted a cross-sectional survey about stroke knowledge and awareness among PHPs in China from September 2021 to December 2021. A total of 289 PHPs were divided into two groups, the stroke treatment window (STW) Aware group vs. the STW Unaware group according to their knowledge on the time window for acute ischemic stroke (AIS) management. Logistic regression analysis was performed to explore the predictors associated with knowledge of the time window for acute stroke management.

Results: Of 289 PHPs surveyed during the study period, 115 (39.7%) participants were aware of the time window for stroke management and were in the STW Aware group, while 174 (60.2%) were in the STW Unaware group. Forty percent of PHPs in the STW Aware group were familiar with the secondary stroke prevention goal of <140/90 mmHg, compared with 27.01% in the Unaware group ($P < 0.05$). PHPs were not sufficiently aware of loss of consciousness also a symptom of stroke in two groups (75.7 vs. 62.6%, $P < 0.05$). A higher proportion of PHPs in the STW Aware group believed that thrombolysis was an effective treatment for AIS (96.5 vs. 79.9%, $P < 0.01$). Endovascular therapy is indicated for AIS was perceived by a higher proportion of PHPs in the STW Aware group than that in the Unaware group (62.6 vs. 6.9%, $P < 0.01$). Eighty percent of PHPs in the STW Aware group reported attending training on stroke management compared with 58.1% in the Unaware group ($P < 0.01$). Logistic regression results showed that the predictors of stroke knowledge and awareness among PHPs included sex (OR: 2.3, 95% CI, 1.2–4.6), received training (OR: 2.9, 95% CI, 1.60–5.1), and times of training per year (OR: 0.70, 95% CI, 0.6–0.9).

Conclusions: PHPs present with a mild to moderate level of stroke management knowledge in northwest China. Strategies to help increase stroke knowledge and awareness among PHPs should be considered in order to help improve the stroke related health service system.

KEYWORDS

primary healthcare providers, stroke, awareness, emergency medical services, quality improvement, training strategies

Introduction

Stroke is the leading cause of death and disability in the general population, and the burden of stroke is increasing globally (1). According to the Global Burden of Disease (GBD) 2019, it is the major contributor of disability-adjusted life years (DALYs) (2). Furthermore, as the global population ages, the incidence, prevalence, and DALYs of stroke are expected to increase. Stroke has also become the leading cause of DALYs in China, with 45.9 million DALYs in 2019 (3). Over the past three decades, the crude death rate from stroke in China has been increasing rapidly, rising faster than any other country. In the coming years, China faces increasing challenges in reducing the morbidity, mortality and disease burden of stroke (3).

Early reperfusion therapy, including intravenous thrombolysis (IVT) and endovascular therapy (EVT), is the most effective evidence-based treatment for acute ischemic stroke (AIS). Despite strong guideline recommendations, however, only 10% to 20% of patients with AIS in China reach the hospital within 3 h (3, 4). Between 2019 and 2020, only 5.64% of patients were treated with IVT and 1.45% with EVT. These rates are much lower than in developed countries (4). The time from onset to reperfusion therapy affects mortality and favorable outcomes and should be considered a major goal in the management of patients with AIS (5). Emergency stroke care is highly complex and involves patient-centered care in a highly non-predictable and stressful setting with several busy providers, such as nurses, emergency physicians, radiologists, and neurointerventionists, coordinating with each other and requiring a high degree of functional operability. The American Heart Association (AHA) created what it called the 8Ds of Stroke Care, known as the Stroke Survival Chain, which are the primary steps family members, emergency and hospital staffs take in diagnosing and treating a stroke (6). Detecting stroke symptoms is the first link in the stroke survival chain. However, there is a lack of public awareness of stroke symptoms and the need for emergency medical care (7). In some countries, stroke patients prefer to seek general practitioners rather than emergency medical services (EMS), especially in many low- and middle-income countries (8).

Primary care providers (PHPs), who work in primary care facilities at the community level, are the foundation of China's tertiary care system after the 2009 health care reform (9). PHPs consist of physicians, nurses, lab technicians, imaging technicians, etc. There are two physician pathways representing becoming a general practitioner in China (10). The 3+2 pathway for assistant practitioners requires 3 years of college and 2 years of clinical training. Assistant practitioners perform protocol-limited clinical assignments under the direction and supervision of a national registered practitioner. This physician pathway is primarily in underdeveloped areas of China. The 5+3 pathway includes 5 years of bachelor's degree training in clinical medicine and 3 years of standardized residency training. PHPs provide diagnosis, initial treatment, and transfer of acute or chronic medical care to secondary or tertiary hospitals (11). When a stroke occurs, stroke patients generally consult their PHPs in rural areas of northwestern China (12). Therefore, the ability of PHPs to identify stroke onset early and further manage referrals to superior hospitals *via* EMS to stroke centers became essential (11). The present cross-sectional survey aims to further assess stroke knowledge and awareness among PHPs from the Kezhou Quality Improvement in Acute Stroke Care Project (KQI-ASC Project), in Kezhou, Northwest China, which may be used to provide appropriate training for PHPs in stroke management and as a reference for improving the stroke related health service system.

Materials and methods

Design and participants

Kezhou is located in Northwest China, with a total population of 0.622 million in 2020. It has 4 counties and 36 townships[1]. There is one tertiary general hospital, four secondary general hospitals, 37 primary healthcare service centers, and about 1,500 registered PHPs[2]. PHPs include physician, nurse, and others, such as laboratory technologist and imaging technologist. This was a cross-sectional study conducted among the PHPs in Kezhou from September 2021 to December 2021. All participants aged 18 and above were invited to participate in this study. The demographic characteristics of PHPs were showed in Table 1. The study was approved by the Institutional Review Board of the Affiliated Kezhou People's Hospital of Nanjing Medical University with the following IRB No: 2021-06-19. All participants provided their written consent prior to participation in the interview.

Specific questionnaire design

The questionnaire comprised three sections, including the demographic characteristics, the knowledge about risk factors, symptoms and acute management of stroke, and training on acute stroke management. The first section of this questionnaire collected the demographic data, including sex, age, education, current profession, and professional title. The second section was about the knowledge of risk factors, symptoms and acute management of stroke, including 9 questions. Risk factors for stroke included hypertension, high cholesterol levels, diabetes mellitus, obesity, smoking, and alcohol consumption. There were seven common symptoms of stroke onset, including weakness on one side of the body, facial weakness, speech impairment, impairment of balance, headache, visual impairment, and loss of consciousness. We also inquired about the F.A.S.T. Stroke Assessment (13). Among the items related to acute stroke management knowledge, the recommended targets for the lowering of blood pressure, glucose, best period for stroke treatment, whether thrombolytic or endovascular therapy indicated for acute ischemic stroke and pre-hospital managements in stroke

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TABLE 1 Demographic characteristics of primary healthcare providers.

Items	All (n = 289)	STW Aware group (n = 115)	STW Unaware group (n = 174)	χ^2	*P*-value
Sex, *n* (%)				4.9	0.03
Male	66 (22.8)	34 (29.6)	32 (18.4)		
Female	223 (77.2)	81 (70.4)	142 (81.6)		
Age, *n* (%)				1.6	0.7
<20 years old	3 (1.0)	1 (0.9)	2 (1.2)		
20–40 years old	228 (78.9)	93 (80.9)	135 (77.6)		
41–60 years old	56 (19.4)	21 (18.3)	35 (20.1)		
>60 years old	2 (0.7)	0 (0)	2 (1.2)		
Education, *n* (%)				0.9	0.7
Secondary school	42 (14.5)	17 (14.8)	25 (14.4)		
Junior college	150 (51.9)	63 (54.8)	87 (50.0)		
Undergraduate	97 (33.6)	35 (30.4)	62 (35.6)		
Current profession, *n* (%)				1.4	0.5
Physician	136 (47.1)	58 (50.4)	78 (44.8)		
Nurse	136 (47.1)	52 (45.2)	84 (48.3)		
Others	17 (5.8)	5 (4.4)	12 (6.9)		
Professional title, *n* (%)				0.8	0.7
Senior	206 (71.3)	83 (72.2)	123 (70.7)		
Mid-level	59 (20.4)	21 (18.3)	38 (21.8)		
Junior	24 (8.3)	11 (9.6)	13 (7.5)		

STW, stroke treatment window.

patients were in accordance with published guidelines (14, 15). The third section investigated whether PHPs had received training, the frequency of training, and education strategies for stroke management.

All items in the questionnaire were discussed through both focus groups and panel reviews. The survey was administered anonymously by certified investigators following a formal protocol. We also pretested the survey with 50 PHPs in two hospitals and revised the questionnaire according to the feedback. The Cronbach's alpha of the total scale in this research was 0.82 and examined for testing the internal consistency reliability.

The questionnaires were distributed to all participants online *via* the Wenjuanxing platform (https://www.wjx.cn/) in four WeChat groups (the most widely used instant messaging software in China). These WeChat groups consist of some of primary care providers in Kezhou. The four WeChat groups had a total of about 720 primary care providers, with about 48% participating in the platform. Three hundred primary care providers responded to the survey, a response rate of 41.7%. We totally collected 300 questionnaires, 289 of which were used for research. Reasons for non-response included: incomplete demographic information (n = 6); and out of contact with participants (n = 5).

Questionnaire data grouping

The purpose of this study was to make a statistical inference by analyzing the current difference in PHPs knowledge between aware and unaware groups according to the participants' perceptions about the stroke treatment window (STW). According to the time window for acute stroke treatment recommended by the Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders, the optimal treatment time for acute ischemic stroke treatment is less than 4.5 h (15). Of 289 PHPs surveyed during the study period, 115 (39.7%) participants were aware of the time window for stroke management and were in the STW Aware group, while 174 (60.2%) were in the STW Unaware group.

Statistical analysis

SPSS version 27 for Windows (IBM, Armonk, New York, USA) was used for data analyses. The data were presented as percentages (relative frequencies) for categorical data. Frequencies of categorical variables were compared using Pearson χ^2-test when appropriate. To investigate factors associated with knowledge of the time window for acute stroke management, we used a

TABLE 2 The knowledge and awareness among primary healthcare providers regarding risk factors of stroke.

Items	All ($n = 289$)	STW Aware group ($n = 115$)	STW Unaware group ($n = 174$)	χ^2	*P*-value
Risk factor for stroke, *n* (%)					
Hypertension	259 (89.6)	102 (88.7)	157 (90.2)	0.2	0.4
High cholesterol levels	219 (75.8)	85 (73.9)	134 (77.0)	0.5	0.3
Diabetes mellitus	212 (73.4)	81 (70.4)	131 (75.3)	0.8	0.2
Obesity	211 (73.0)	80 (69.6)	131 (75.3)	0.9	0.2
Smoking	272 (94.1)	110 (95.7)	162 (93.1)	0.7	0.3
Alcohol consumption	216 (74.7)	92 (80.0)	124 (71.3)	1.5	0.1
Target of <140/90 mmHg for secondary prevention of stroke, n (%)				4.8	0.03
Yes	93 (32.2)	46 (40.0)	47 (27.0)		
No	196 (67.8)	69 (60.0)	127 (73.0)		
Target of <7.0 mmol/L for fasting blood glucose control, *n* (%)				3.3	0.1
Yes	137 (47.4)	47 (40.9)	90 (51.7)		
No	152 (52.6)	68 (59.1)	84 (48.3)		

STW, stroke treatment window.

TABLE 3 The knowledge and awareness among primary healthcare providers regarding symptoms of stroke.

Items	All ($n = 289$)	STW Aware group ($n = 115$)	STW Unaware group ($n = 174$)	χ^2	*P*-value
Stroke symptoms, *n* (%)					
Weakness on one body side	231 (79.9)	94 (81.7)	137 (78.7)	0.5	0.3
Face weakness	236 (81.7)	97 (84.4)	139 (79.9)	0.8	0.2
Speech impairment	233 (80.6)	95 (82.6)	138 (79.3)	0.5	0.3
Impairment of balance	217 (75.1)	88 (76.5)	129 (74.1)	0.3	0.4
Headache	198 (68.5)	83 (72.2)	115 (66.1)	1.0	0.2
Visual impairment	216 (74.7)	86 (74.8)	130 (74.7)	−0.1	0.5
Loss of consciousness	196 (67.8)	87 (75.7)	109 (62.6)	2.2	0.01
F.A.S.T. stroke assessment, *n* (%)					
Yes	236 (81.7)	97 (84.4)	139 (79.9)	0.9	0.3
No	53 (18.3)	18 (15.7)	35 (20.1)		

STW, stroke treatment window.

binary logistic regression model. The degree of association between independent variables with the dependent variable was estimated by odds ratio (OR) with 95% confidence interval (CI). Statistical tests were two-tailed with a significance level of 5%.

Results

Demographic characteristics of primary healthcare providers

Of the 289 participants in the study, 39.7% were aware of the time window for stroke management. More than half of the PHPs were female ($N = 223$, 77.2%), while 22.8% were male. There was significant difference with respect to sex ($P = 0.03$) between the STW Aware and Unaware groups. The percentage of participants with the age range from 20 to 40 years old was 78.9% ($N = 228$). In terms of education level, 33.6% had undergraduate degree, 51.9% had junior college and 14.5% had at least less than secondary school. Forty-seven percent of the participants were physician, 47.1% were nurse and 5.9% were others, such as laboratory technologist and imaging technologist. Among the professional title of participants, 71.3% were senior, 20.4% were mid-level, and 8.3% were junior. However, the age, education level, current profession and professional title displayed no difference between the two groups (Table 1).

The knowledge of risk factors, symptoms, and acute management of stroke

When comparing the proportion of PHPs who knew the risk factors of stroke well in both groups, it showed no significant

TABLE 4 The knowledge and awareness among primary healthcare providers regarding stroke treatment and the response when stroke was suspected.

Items	All ($n = 289$)	STW Aware group ($n = 115$)	STW Unaware group ($n = 174$)	χ^2	*P*-value
Best period for stroke treatment is < 4.5 h, *n* (%)				284.8	<0.01
Yes	115 (39.8)	115 (100)	0 (0)		
No	174 (60.2)	0 (0)	174 (100)		
Thrombolytic therapy is indicated for acute ischemic stroke, *n* (%)				15.0	<0.01
Yes	250 (86.5)	111 (96.5)	139 (79.9)		
No	39 (13.5)	4 (3.5)	35 (20.1)		
Endovascular therapy is indicated for acute ischemic stroke, *n* (%)				101.6	<0.01
Yes	84 (29.1)	72 (62.6)	12 (6.9)		
No	305 (70.9)	43 (37.4)	162 (93.1)		
Pre-hospital management for patients with acute stroke, *n* (%)					
Observation of circulatory/respiratory problems	273 (94.5)	110 (95.6)	163 (93.7)	0.5	0.5
Observation of the heart	241 (83.4)	99 (86.1)	142 (81.6)	1.0	0.3
Securing the airways	266 (92.0)	110 (95.7)	156 (89.7)	3.4	0.1
Establishing intravenous access	264 (91.3)	106 (92.2)	158 (90.8)	0.2	0.7
Oxygen inhalation	256 (88.6)	105 (91.3)	151 (86.8)	1.4	0.2
Assess for hypoglycemia	214 (74.1)	92 (80.0)	122 (70.1)	3.5	0.1
Transferring the patient to a nearby stroke center	244 (84.4)	101 (87.8)	143 (82.2)	1.7	0.2

STW, stroke treatment window.

differences. The proportion of accurate perceptions about the target of <140/90 mmHg for secondary prevention of stroke was significantly higher in the STW Aware group than that in the Unaware group (40 vs. 27.0%, $P < 0.05$). While the proportion of accurate perceptions about the target of <7.0 mmol/L for fasting blood glucose control showed no significantly difference between two groups (Table 2). The proportion of PHPs who were able to recognize seven symptoms of stroke shown no difference between the STW Aware group and Unaware group, expect the symptom of loss of consciousness (75.7 vs. 62.6%, $P < 0.05$). The proportion of accurate perceptions about the F.A.S.T. Stroke Assessment also shown no difference between two groups (Table 3). A higher proportion of PHPs in the STW Aware group believed that intravenous thrombolysis was an effective treatment for acute ischemic stroke (96.5 vs. 79.9%, $P < 0.01$). The recommendations that endovascular therapy is indicated for acute ischemic stroke was perceived by a higher proportion of PHPs in the STW Aware group than that in the Unaware group (62.6 vs. 6.9%, $P < 0.01$). However, the knowledge of pre-hospital management showed no significant difference between the STW Aware group and the Unaware group (Table 4).

Training on stroke management

Among all subjects, 80% of PHPs in the STW Aware group reported attending training on stroke management compared with 58.1% in the Unaware group ($P < 0.01$). In both groups, most participants received 1–2 trainings per year at their local hospital, whereas in the STW Aware group, more PHPs received more than two trainings per year ($P < 0.01$). There were no significant differences in educational strategies for stroke management between the two groups (Table 5).

Predictors of stroke knowledge and awareness among primary healthcare providers

Multiple logistic regression was performed to examine the predictors of stroke knowledge and awareness among PHPs (Table 6). The results showed that the predictors included sex (OR: 2.3, 95% CI, 1.2–4.6), received training on stroke management (OR: 2.9, 95% CI, 1.6–5.1), and times of training on stroke management per year in local hospital (OR: 0.7, 95% CI, 0.6–0.9).

Discussion

Acute stroke care is an emergency that is conceptualized as a stroke survival chain occurring between stroke onset and appropriate disposition of the acute stroke patient receiving reperfusion therapy, and includes the eight steps of acute stroke recognition, diagnosis, and treatment (6, 16). Delays in any step can lead to delays in overall treatment and may even make the patient ineligible for certain reperfusion therapies (16). Especially

TABLE 5 The knowledge and awareness among primary healthcare providers regarding training of stroke management.

Items	All (*n* = 289)	STW Aware group (*n* = 115)	STW Unaware group (*n* = 174)	χ^2	*P*-value
Received training on stroke management, *n* (%)				14.1	<0.01
Yes	193 (67.8)	92 (80.0)	101 (58.1)		
No	96 (33.2)	23 (20.0)	73 (42.0)		
Times of training on stroke management per year in local hospital, *n* (%)				28.5	<0.01
1–2	188 (65.1)	61 (53.0)	127 (73.0)		
3–4	48 (16.6)	17 (14.8)	31 (17.8)		
5–6	32 (11.1)	25 (21.7)	7 (4.0)		
7–8	9 (3.1)	5 (4.4)	4 (2.3)		
9–10	1 (0.4)	0 (0)	1 (0.6)		
>10	11 (3.8)	7 (6.1)	4 (2.3)		
Education strategies for stroke management, *n* (%)				3.7	0.3
Lectures or courses	149 (51.6)	64 (55.7)	85 (48.9)		
Video-based education	83 (28.7)	34 (29.6)	49 (28.2)		
Stroke resources shared on the web or social media	35 (12.1)	9 (7.8)	26 (14.9)		
Stroke simulation training	22 (7.6)	8 (7.0)	14 (8.0)		

STW, stroke treatment window.

TABLE 6 Predictors of stroke knowledge and awareness among primary healthcare providers.

Predictors	*P*-value	Odds ratio	95% confidence interval
Sex	0.02	2.3	1.2–4.6
Received training on stroke management	<0.01	2.9	1.6–5.1
Times of training on stroke management per year in local hospital	<0.01	0.7	0.6–0.9

in geographic areas with limited stroke centers, PHPs can be reconceptualized as the backbone of the stroke survival chain in some low- and middle-income countries or regions (16, 17). In the present cross-sectional survey about assessment of stroke knowledge and awareness among PHPs from the KQI-ASC Project, we found that only 115 (39.7%) participants aware that the optimal time window for IVT in acute stroke is less than 4.5 h. Gender of PHPs, stroke management training received, and number of stroke management presentations given at local hospitals per year were the predictors of stroke knowledge and awareness among PHPs.

Geographic level, hospital level, and healthcare provider level play a role in timely access to advanced healthcare services, including emergency stroke care services, to prevent unnecessary mortality and morbidity (17–20). In a report by Yang et al., only 49.1% of 997 community healthcare practitioners were aware of the time window for stroke management in 9 community health centers in Guangdong province, southern China, which was higher than what we found in Kezhou, northwest China, probably because Guangdong was a developed coastal region of China with a higher level of stroke care among PHPs than other areas in China (11). In the United States, there are also regional and hospital-level variabilities in stroke care. Zachrison et al. described the ability of community emergency departments (EDs) to diagnose and treat acute stroke and found that of 154 participating EDs in 30 states, 65 reported having written protocols for managing acute stroke (17). Khettar et al. conducted a cross-sectional study by administering an electronic standardized self-assessment questionnaire to community pharmacists in the Rhône-Alpes region of France and showed that 104 participants presented moderate levels of stroke management knowledge (20). Thus, even in a high-functioning pre-hospital stroke care system, optimizing the assessment and treatment of stroke patients in primary healthcare practitioners is necessary to strengthen the entire stroke survivorship chain (16).

Lack of awareness of stroke risk factors, symptoms, and insufficient attention to thrombolytic therapy in PHPs may lead to pre-hospital delays. We revealed that 40% of PHPs in the STW Aware group were familiar with the secondary stroke prevention goal of <140/90 mmHg, compared with 27% in the Unaware group. In addition, our findings showed that PHPs were not sufficiently aware of stroke symptoms, with only 62.6% of PHPs knowing that loss of consciousness is also a symptom of stroke, which is consistent with previous findings (11). We also indicated that 79.9% of PHPs had the knowledge that AIS was amenable to intravenous thrombolysis within 4.5 h, but only 6.9% of PHPs knew that AIS was also amenable to endovascular treatment in the STW Unaware group, and these proportions were lower than in the STW Aware group. Therefore, training of PHPs in acute stroke management becomes urgent. In our study, only 58.1% of PHPs reported attending training on stroke management in the STW Unaware group and most of them received less than two trainings per year. This was similar to what has been found by Yang et al., where only 23.5% of community healthcare providers in the unawareness group reported participation in training on cerebrovascular disease management (11). Multiple logistic regression analysis also revealed an association between female gender, received training, times of training and the knowledge and awareness on stroke management.

One of the most important goals in improving the quality of treatment for AIS is to reduce door-to-needle time (DTN) and door-to-penetration (DTP) time. The AHA recommends a DTN time of less than 60 min and a DTP time of less than 90 min (19). Various training programs have been designed to improve the knowledge of first responders in order to improve the quality of emergency care for stroke patients in China and other countries and to promote the further development of the emergency training system (21–24). A pre-hospital EMSs training program consisting of three courses combining video learning, group discussions and quizzes was implemented in Shanghai, China. The results showed that the average DNT after the training was 53 min compared to 84.0 min before the training, demonstrating a significant reduction (21). Rababah et al. designed a randomized post-test study that consisted of a one-session stroke education program offered to 189 healthcare providers (physicians, registered nurses, and paramedics) in acute care settings, and the educational program implemented had a positive effect on improving healthcare providers' knowledge of stroke (22). However, some studies suggest that future assessments need to consider more sustained and multisite efforts supported by implementation science methods, rather than just DTN or DTP time, such as the patient's outcomes (23). Therefore, we developed a simulation-based education curriculum to train PHPs in stroke management according to Kern's six-step approach (25), and the Kirkpatrick model was used to guide the evaluation of intervention effects (26). Because only 33.6% of PHPs in our sample had undergraduate degree, a curriculum on pre-hospital and in-hospital management of stroke was designed to accommodate the needs of primary care providers, following the Chinese guideline (15).

The present study has several limitations. First, this is a cross-sectional survey and there is selection bias in our sample of PHPs who participated in the KQI-ASC Project in northwest China. These PHPs have high participation and are likely to be high performers and may not be representative of all PHPs. Consequently, the results may not be generalizable to other settings. Second, our data are self-reported and therefore depend on the knowledge of the respondents and may be influenced by social desirability bias (17). Finally, essential conditions for an effective stroke survival chain include a low threshold for detection, rapid onsite assessment of cardinal symptoms, and immediate transport by ambulance of patients considered for thrombolysis (27). Only a fraction of stroke patients is willing to seek PHPs rather than EMS (8). Therefore, further investigation of stroke knowledge and awareness among other providers of stroke EMS is warranted (28).

In conclusion, PHPs present with a mild to moderate level of stroke management knowledge in northwest China. PHPs in Kezhou need to improve their ability to deal with acute stroke onset in a timely and effective manner and provide effective treatment within a favorable "stroke treatment window". To help improve the stroke related health services system, continuing education strategies that contribute to increased stroke knowledge and awareness among PHPs should be considered.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of the Affiliated Kezhou People's Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

G-BD and Y-FW drafted the manuscript. QS, H-JH, and X-MW added the survey data. QS and Y-FW revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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Current status and future aspects in the Japan Stroke Data Bank

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The Japanese National Plan for the Promotion of Measures Against Cerebrovascular and Cardiovascular Diseases was formulated on October 27, 2020. One purpose of this plan was to promote research on cerebrovascular and cardiovascular diseases. Therefore, it is necessary to clarify the actual status of stroke treatment in Japan and operate a national stroke database with high public interest completely and accurately. The Japan Stroke Data Bank (JSDB; https://strokedatabank.ncvc.go.jp/en/) was established by the Ministry of Health, Labor and Welfare Scientific Research in Shimane University (Shimane, Japan) in 1999 and was transferred to the National Cerebral and Cardiovascular Center (Osaka, Japan) as a part of the Cardiovascular Disease Registry in 2015. More than 200,000 of stroke cases have been registered using individual forms from more than 100 nationwide stroke centers over ∼20 years. Since there are few large-scale stroke registries with nationwide coverage in Asia, including Japan, compared with those in Europe and North America, the role of the JSDB in the plan will be important in the future. To construct a high-quality stroke registry, we aimed to (1) collect detailed data through individual questionnaires for each participating stroke center, (2) link to external databases (e.g., insurance claims and public death registries), (3) improve the quality of treatment at participating hospitals through benchmarking, and (4) obtain stable funding through sustained support from government and academic societies. We also describe the history of the JSDB and changes in the trend of real-world stroke treatment in Japan based on the results of analysis of data in the JSDB.

KEYWORDS

Japan Stroke Data Bank, cerebrovascular disease, cardiovascular disease, stroke registry, acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage

1. Introduction

Stroke is the fourth leading cause of death and requires the most nursing care in Japan (∼30% of all diseases) (1). Since the annual medical cost of stroke is estimated at ∼1.7 trillion yen and the cost of nursing care at ∼1.9 trillion yen (2), the effect of stroke on the society and economy of Japan is extremely high. Thus, in December 2018, the Cerebrovascular and Cardiovascular Disease Control Act was established, which was the first legislative measures to stroke and cardiovascular disease in Japan (3). The Japanese National Plan for Promotion of Measures Against Cerebrovascular and Cardiovascular Diseases was also formulated on October 27, 2020 (4). The plan included preventive measures and dissemination of accurate information for cerebrovascular and cardiovascular diseases, and development of service systems on medicine, health and welfare. One of the objectives of the plan was to promote research on cerebrovascular and cardiovascular diseases.

Therefore, it was necessary to establish and maintain a comprehensive and accurate nationwide database and serve the public interest by promoting rational and economical stroke countermeasures.

The Japan Stroke Data Bank (JSDB), a Japanese stroke registry started from 1999, has been collecting clinical data using individual patient data, including patients' characteristics, examination, treatment, and stroke outcomes, from many hospitals in Japan (5). As of July 2021, 132 hospitals participated in the JSDB, and approximately 240,000 patients with acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and transient ischemic attack (TIA) have been registered (Figure 1) (6). The JSDB can provide information for the construction of a nationwide database in the future. In this review, we report about the history and recent results analyzed by the JSDB.

FIGURE 1
Distribution of hospitals participating to the Japan Stroke Data Bank. The hospitals were shown in white map with red points, and the map were proceeded by the authors using GSI map (6) https://maps.gsi.go.jp/vector/#4/35.354185/131.992306/&ls=vblank&disp=1&d=l.

2. History of the JSDB

The prototype of the JSDB was a research project started in 1999 by Shotai Kobayashi (currently Professor Emeritus, Shimane University) to construct a database of patients with acute stroke (including TIA) under a Grant-in-Aid for Scientific Research. The project management was transferred from Shimane University (Shimane, Japan) to the National Cerebral and Cardiovascular Center (Osaka, Japan) in 2015.

In 2016, a 5-year plan to overcome stroke and cardiovascular diseases was published in collaboration with the Japan Stroke Association and Japan Cardiovascular Society. The plan listed the promotion of registration projects as a part of its major goals, which emphasized the need for a nationwide stroke patient registry system. Thus, research groups were organized under the auspices of the Japan Agency for Medical Research and Development (FY2015, FY2016, granted for Kazuo Minematsu) to develop a system. The group validated domestic and international stroke registry studies, for example "European Registers of Stroke" and "Get With the Guidelines-Stroke," to propose an optimal medical information collection system for Japan (7–9). Consequently, several points were identified. First, there are few large and well-disseminated registry studies in Asia, including Japan, compared with those in Europe. Second, more patients were registered using opt-out methods or were not required to give informed consent. Third, no stroke registry was identified in Japan with support from academic societies and patient advocacy groups then, in addition to public research funds such as the International Stroke Registry. Fourth, cooperation with other databases using personal IDs also progressed in Europe. Therefore, a stroke registry meeting the following four goals needed to be established: (1) collecting detailed data through individual questionnaires for stroke centers, (2) linking to external databases (e.g., insurance claims and public death registries), (3) improving the quality of treatment at participating hospitals through benchmarking, and (4) obtaining stable funding through sustained support from governments and academic societies. The JSDB, one of the stroke registries in Japan, aims to achieve these four goals.

Abbreviations: AIS, acute ischemic stroke; DPC, Diagnosis Procedure Combination; eGFR, estimated glomerular filtration rate; ICH, intracerebral hemorrhage; JSDB, Japan Stroke Data Bank; mRS, median modified Rankin Scale; NIH, National Institutes of Health; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack; WFNS, World Federation of Neurosurgical Surgeons.

3. Location of the JSDB

The JSBD, similar to many stroke registries, uses individual questionnaires to collect data. The use of individual questionnaires allows setting of items according to a specific purpose and ensures collection of detailed information; however, it is labor intensive, particularly in inputting and cleaning data. For this reason, many countries are attempting to manage registries to obtain accurate data while reducing the burden on participants by using web system or a dedicated web application (7). As an example of stroke registries using individual questionnaires in Asia, the China National Stroke Registry is a government-led hospital-based registry that enrolls more than 10,000 patients annually with detailed individual data collection and 2-year follow-up (10).

In Japan, there are regional stroke registries that collect individual data, such as the Akita Stroke Registry, Fukuoka Stroke Registry, and Takashima Stroke Registry (11–13). However, other than the JSDB, no other stroke registries are known to collect data using individual questionnaires across Japan. As a nationwide stroke registry in Japan, the J-ASPECT Study is currently active and has successfully obtained a large amount of data in a short period using Diagnosis Procedure Combination (DPC) data (14). DPC is developed as a measurement tool for transparency in the content of acute inpatient care, with the aim of standardizing, evaluating and improving the quality of medical care in Japan (15). DPC

FIGURE 2
Cumulative number of registered patients and outcome books. Created based on Figure 1, Page 2 in (17) © 2021 Nakayama Shoten.

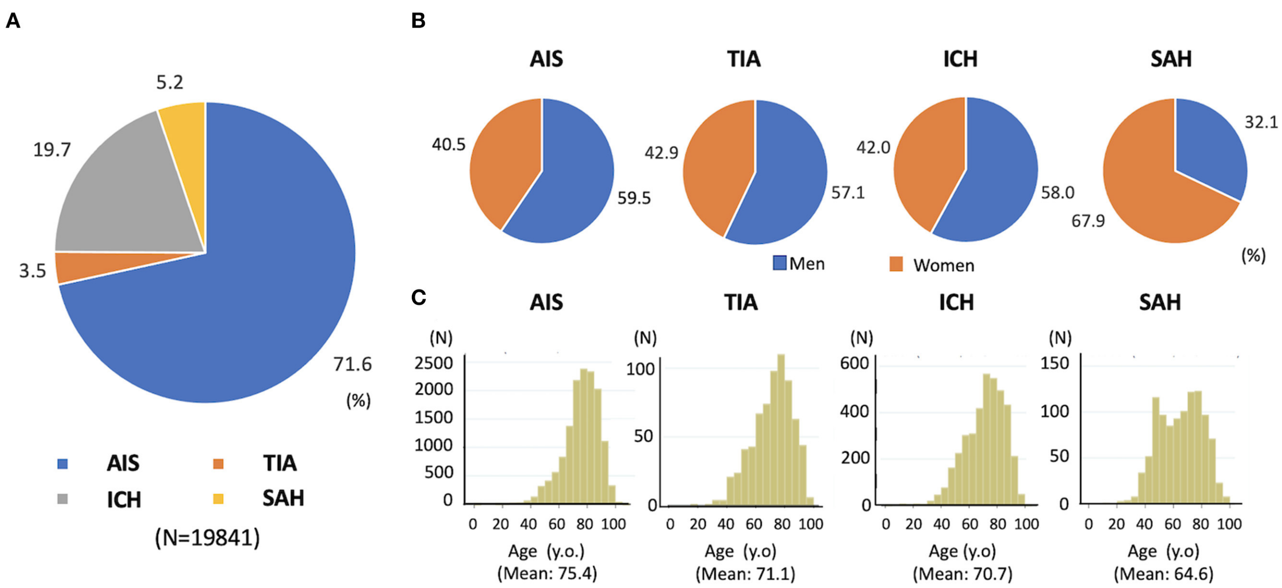

FIGURE 3
Distribution of stroke subtype, sex and age in 19841 patients registered in JSDB during 2020 year. **(A)** Stroke subtypes, **(B)** sex, and **(C)** age. AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; JSDB, Japan Stroke Data Bank; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack. The data was cited with modification from annual report of JSDB in 2021. (Available from reference 5, in Japanese).

data are extracted from external sources, enabling collection of a large amount of patient information using existing large-scale data. Moreover, once the extraction method is established, information can be collected continuously with less effort in terms of complete coverage and continuity. Meanwhile, the JSDB aims to build a database that will aggregate individual data from all over Japan and enable comprehensive and more detailed analysis by adding information not included in the DPC.

4. Management system of the JSDB

The Department of Cerebrovascular and Cardiovascular Disease Information (currently the Department of Medical and Health Information Management) serves as the secretariat under the management of a steering committee comprising a group of stroke medical researchers from across Japan. We have started to modify the management system to obtain stable funding through

TABLE 1 Secular changes in favorable outcomes at discharge.

Outcome	Odds ratio (95% CI)[a]			
	Crude	Model 1[b]	Model 2[c]	Model 3[d]
Women				
Total ischemic stroke	0.994 (0.995–1.003)	1.020 (1.015–1.024)	1.003 (0.998–1.009)	0.997 (0.991–1.003)
Cardioembolism	1.009 (1.002–1.017)	1.037 (1.029–1.045)	1.023 (1.012–1.034)	1.008 (0.997–1.019)
Large-artery atherosclerosis	1.010 (1.003–1.018)	1.028 (1.020–1.036)	1.004 (0.994–1.014)	1.002 (0.992–1.013)
Small-vessel occlusion	0.997 (0.989–1.005)	1.014 (1.005–1.022)	0.986 (0.975–0.997)	0.985 (0.974–0.995)
Intracerebral hemorrhage	0.984 (0.976–0.992)	0.994 (0.986–1.003)	0.980 (0.968–0.992)	NA
Subarachnoid hemorrhage	1.000 (0.990–1.010)	1.011 (1.000–1.022)	1.002 (0.989–1.016)	NA
Men				
Total ischemic stroke	1.002 (0.999–1.005)	1.015 (1.011–1.018)	0.995 (0.991–1.000)	0.990 (0.985–0.994)
Cardioembolism	1.006 (1.000–1.013)	1.023 (1.016–1.029)	1.007 (0.998–1.016)	0.993 (0.984–1.002)
Large-artery atherosclerosis	1.009 (1.003–1.015)	1.020 (1.014–1.026)	1.001 (0.993–1.008)	0.998 (0.991–1.006)
Small-vessel occlusion	0.997 (0.991–1.004)	1.009 (1.002–1.016)	0.982 (0.973–0.991)	0.980 (0.971–0.989)
Intracerebral hemorrhage	0.983 (0.976–0.990)	0.989 (0.982–0.996)	0.971 (0.961–0.982)	NA
Subarachnoid hemorrhage	0.996 (0.982–1.009)	1.002 (0.988–1.017)	0.989 (0.970–1.008)	NA

Abbreviations: NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; WFNS, World Federation of Neurological Surgeons.
[a]Odds ratio (95% CI) per 1 year.
[b]Model 1 is adjusted by age.
[c]Model 2 is adjusted by age, NIHSS score (WFNS grade for subarachnoid hemorrhage), and history of stroke.
[d]Model 3 is adjusted by age, NIHSS score (WFNS grade for subarachnoid hemorrhage), history of stroke, and reperfusion therapy.
The table is cited from Table 2 in (20) [Toyoda, et al. JAMA Neurol. (2022) 79:61–69].

sustained support from the government and academic societies. In detail, we prepared a research protocol that complied with current research ethics policies. We do not obtain written consent from the patients; however, we provide an opt-out opportunity for patients who do not wish to use their information because it is important to ensure complete coverage to achieve high academic and social importance. Next, we adopted a web-based collection system using a multipurpose clinical data repository system (16). In the past, data were collected using standalone PCs and sent periodically, but this system allows the secretariat to manage the system, review data, and clean data as needed. The survey items are updated as appropriate according to current stroke trends. Data are collected at the National Cerebral and Cardiovascular Center of the Department of Medical and Health Information Management. In the future, a low-labor, low-cost, highly comprehensive, and accurate information collection system needs to be established for each hospital. We would also like to link the JSDB with existing large-scale databases in the future.

5. Publications from the JSDB

The collected data, including baseline characteristics, examination, treatment, and stroke outcome, were published regularly. The JSDB data were published in Japanese as five volumes set at intervals of approximately 5 years from 2003 by Nakayama Shoten Co., Ltd., (Figure 2) (17). In these series, researchers from the participating hospitals reported the results of analyzed data on major issues related to acute stroke. In addition, the collected data were analyzed at the National Cardiovascular Disease Information Center every year, targeting data from patients registered within the previous year. The results were sent to the participating hospitals once a year as an annual report and made publicly available on the web in Japanese (5). Figure 3 showed a part of annual report in patients registered in 2020. If others want to use the collected data for academic purposes, such as reprinting or citations in academic papers, the source can be cited clearly. For example, the annual report of the JSDB has been cited in papers on malignancy-related strokes and post-stroke discharge destinations (18, 19). In addition to academic purposes, researchers can request the data by applying to the secretariat and specifying the purpose and intended use of the report without payment. Permission is granted if the use is considered highly public, such as for stroke awareness activities in the mass media. We aim to continue and expand the scale of patient information collection, enhance academic activities, provide feedback to participating hospitals, and provide information to public institutions, academic societies, and public interest groups, further promoting information disclosure and returning research results to society.

6. Recent reports published by the JSDB

Several reports have recently been published using JSDB-collected data. For example, changes in stroke severity and outcomes within 7 days after stroke onset, including ischemic and hemorrhagic stroke, for the past 20 years from January 2000 to December 2019 in the JSDB have been reported (20). Briefly, 183,082 patients (135,268 patients with AIS, 36,014 patients with ICH, and 11,800 with SAH) were examined. Women accounted for 39.8, 42.7, and 67.2% of cases with a median age of 74 (66–82), 70 (59–79), and 64 (53–75) years in AIS, ICH, and SAH, respectively. The National Institutes of Health (NIH) Stroke Scale score on admission was a median of 5 [2–13]/3 [2–8] (women/men, respectively) for AIS patients and 12 [4–24]/11 [4–22] for ICH patients. The median value of the World Federation of Neurosurgical Surgeons (WFNS) score in SAH was 2 [1–5]/2 [1–4]. In AIS patients, 8.6/8.9% of patients received reperfusion therapy. The median modified Rankin Scale (mRS) score at discharge was 3 [1–4]/2 [1–4] in AIS patients, 4 [2–5]/4 [2–5] in ICH patients, and 3 [0–5]/2 [0–5] in SAH patients. The rate of in-hospital death was 6.1/3.6% for AIS, 13.9/14.9% for ICH, and 22.1/20.9% for SAH.

This study demonstrated that the median onset age increased in all the three types of stroke, and the NIH Stroke Scale score in AIS and ICH and the WFNS score in SAH decreased during the past 20 years on multivariable analysis. Moreover, although the rate of the favorable outcome (mRS 0–2 at discharge) of AIS patients increased over time after adjustment for age in both sexes, it decreased after adjusting for reperfusion therapy, especially in men, which may reflect the efficacy of reperfusion therapy (Table 1). In contrast, the rate of the favorable outcome of ICH and SAH patients did not increase over time in the multivariable analysis, suggesting the lack of a powerful therapy equivalent to reperfusion therapy in AIS or the widespread use of anticoagulant agents prior to stroke onset. Thus, the long study duration and large population in the JSDB helped to clarify the trend of stroke outcomes in Japan.

The other study in JSDB has shown that the effect impact of renal dysfunction on stroke onset and outcomes differed according to the clinical pathology (21). In detail, 10,392 AIS patients whose results of serums creatinine level or dipstick proteinuria on admission were available were examined. Among patients with AIS, lower estimated glomerular filtration rate (eGFR) levels were associated with a higher rate in cardioembolic stroke and lower in small vessel occlusion linearly (21). As for unfavorable outcome (mRS 3–6 at discharge), lower eGFR <40 mL/min/1.73 m^2 was significantly associated in both small vessel occlusion and cardioembolic stroke. In addition, since higher eGFR was also significantly associated with unfavorable outcomes in cardioembolic stroke, eGFR had U-shaped association to the outcomes in cardioembolic stroke (21). Moreover, proteinuria (dipstick proteinuria $\geq$1) was associated with unfavorable outcome in patients with both stroke subtypes on multivariable analysis (Odds-ratio 3.18 [95% confidence interval: 2.03–4.98] in cardioembolic stroke and 2.08 [1.08–3.98] in small vessel occlusion, respectively). Chronic kidney disease is known to enhance endothelial dysfunction, various atherosclerotic change including calcification and alternations in coagulation systems resulted in a prothrombotic state, which lead to increased risk of any AIS and to an associated worse outcome. This study demonstrates that renal impairment was associated with difference in distributions and outcomes between cardioembolic stroke and small vessel occlusion and may have a predictive value for outcome after specific AIS subtypes.

We are also actively disseminating information worldwide by publishing papers using data from this project, such as the association between habitual alcohol consumption and stroke severity and the creation of a score for the indication of treatment for ruptured cerebral aneurysms (22, 23).

7. Conclusion

Although the promotion of registration projects in the Second 5-Year Plan to Conquer Stroke and Cardiovascular Disease is important for future stroke and cardiovascular disease countermeasures, basic all-inclusive registry data on stroke in Japan are currently lacking. Over the past 20 years, the JSDB has gradually developed and has the possibility of fulfilling its role as a large-scale depository of clinical statistics in Japan. The JSDB is expected to play a role in the registration system and serve as a cornerstone of stroke care in Japan.

Author contributions

Study concept and design: SW and SY. Supervision: KM, YI, MK, and KT. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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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An economic evaluation of a primary care-based technology-enabled intervention for stroke secondary prevention and management in rural China: a study protocol

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Introduction: Secondary prevention of stroke is a leading challenge globally and only a few strategies have been tested to be effective in supporting stroke survivors. The system-integrated and technology-enabled model of care (SINEMA) intervention, a primary care-based and technology-enabled model of care, has been proven effective in strengthening the secondary prevention of stroke in rural China. The aim of this protocol is to outline the methods for the cost-effectiveness evaluation of the SINEMA intervention to better understand its potential economic benefits.

Methods: The economic evaluation will be a nested study based on the SINEMA trial; a cluster-randomized controlled trial implemented in 50 villages in rural China. The effectiveness of the intervention will be estimated using quality-adjusted life years for the cost-utility analysis and reduction in systolic blood pressure for the cost-effectiveness analysis. Health resource and service use and program costs will be identified, measured, and valued at the individual level based on medication use, hospital visits, and inpatients' records. The economic evaluation will be conducted from the perspective of the healthcare system.

Conclusion: The economic evaluation will be used to establish the value of the SINEMA intervention in the Chinese rural setting, which has great potential to be adapted and implemented in other resource-limited settings.

KEYWORDS
stroke, economic evaluation, cost-utility analysis, cost-effectiveness analysis, secondary stroke prevention

Introduction

Stroke is one of the rising public health challenges worldwide. In 2019, there were ∼12 million incident cases of stroke, of which 32.8% were in China (1). Although the stroke incidence rate is increasing, the stroke mortality rate has been decreasing over the past few decades, resulting in a huge number of stroke survivors globally (2). As these stroke survivors need continuous health management and risk control, the spending on post-stroke care causes an economic burden (3). The financial burden of stroke in rural areas is extremely severe (4, 5). As in many undeveloped areas, primary care lacks the capacity to provide guideline-based essential care to stroke patients, and community-based management for secondary prevention of stroke is far from adequate (6). Therefore, it is necessary to emphasize the prevention of recurrent strokes in the rural setting.

The system-integrated and technology-enabled model of care (SINEMA) study was designed to empower both stroke survivors and primary healthcare providers for secondary stroke prevention by training and incorporating both provider-facing and patient-facing mHealth technologies. The effectiveness of the SINEMA model has been evaluated and proven through a two-arm cluster-randomized controlled trial conducted in 50 rural villages of Hebei province in northern China (7). During the 1-year intervention, a statistically significant greater reduction in systolic blood pressure (SBP) was observed in the intervention arm compared with the control arm. Improvement in a few secondary outcomes including a 35–55% relative reduction in stroke recurrence, hospitalization, disability, and death has also been reported, which indicates the great potential benefits of the SINEMA intervention on secondary stroke prevention (8).

Despite indicating the effectiveness of the intervention, cost-effectiveness is another important factor to be considered. Previous economic evaluation studies of mHealth-based stroke prevention were reported to be cost effective. For example, the TEXT-ME trial conducted in Australia, a text message-based intervention for patients with cardiovascular diseases, reported that the intervention could gain 1,143 more QALYs and save a direct medical cost of Aus$10.56 million over a lifetime horizon for a hypothetical cohort of 50,000 patients with cardiovascular diseases in Australia (9). However, previous economic evaluations were mainly conducted in developed countries, and the cost-effectiveness of an integrated mobile health intervention on secondary stroke prevention in a resource-constrained setting like rural China remains unclear. Therefore, the economic evaluation of the SINEMA intervention is necessary. This protocol describes the methods for the economic evaluation of the SINEMA program based in a rural Chinese setting.

Aim and objectives

This protocol describes the methods for the economic evaluation of the SINEMA program, which is nested in the SINEMA trial (8). This study aims to provide an economic evaluation of the SINEMA program to identify, measure, and value key resource and outcome impacts from the SINEMA intervention model compared with usual care for stroke secondary prevention in rural China. A within-trial economic evaluation will be conducted to calculate the within-trial incremental cost-effectiveness ratio to determine the value of the SINEMA intervention model.

Materials and methods

Study design

The economic evaluation is a nested study based on the SINEMA trial, a cluster-randomized controlled trial implemented in 50 villages in rural China. A detailed description of the SINEMA program and intervention design can be found in previous publications (7, 10–12). The economic evaluation will involve a within-trial cost-effectiveness analysis and cost-utility analysis with a 12-month time horizon equal to the follow-up period of the trial. We will calculate the incremental cost-effectiveness ratio in terms of the incremental cost per 1 mmHg change in systolic blood pressure, which is the primary outcome of the trial. In addition, we will also conduct a cost-utility analysis to calculate the incremental cost per quality-adjusted life year (QALY). The SINEMA intervention is deemed as cost-effective if the incremental cost per QALY is no greater than the cost-effective threshold. Following previous research (13), we will adopt the conventional approach by considering the benchmark as 1.5 times of gross domestic product per capita.

Participants and study settings

Study participants in the economic evaluation will be the same as those recruited in the SINEMA trial. Participants were eligible if they were adults (older than 18 years), had a history of stroke diagnosed at a county or higher level hospital, were in a clinically stable condition with at least basic communication ability, and were expected to be available for the 12-month follow-up. Individuals who were unable to get out of bed had severe life-threatening diseases or had an expected life span shorter than 6 months were excluded. All participants were recruited in 50 villages from five townships in a rural county in Hebei Province, China. The county is a provincial-level impoverished county lying on the "stroke belt," with a stroke burden double the national average level (10). Participants were recruited between 23 June 2017 and 21 July 2017 and followed until 27 July 2018.

Intervention and control

The SINEMA intervention involved provider-side components and patient-facing components and was supported by a digital health system. In brief, village doctors, as primary healthcare providers, received training based on the train-the-trainer to train model. They were also equipped with the SINEMA app, they conducted monthly follow-up visits to patients. Additionally, financial incentives were also provided to encourage their ongoing commitment to deliver quality healthcare services. Stroke patients received monthly follow-up visits delivered by village doctors at the village clinics or their own homes if they had difficulty visiting the clinics. During each visit, they were provided with suggestions about medication use and physical activities. Participants who had access to their own or shared cell phones received one voice message, at no cost to them, for delivering health education information regarding medication adherence and physical activities.

For villages allocated to the control arm, village doctors continued their standard practices, which included practicing general clinical care and performing the "Basic Public Health Services" (BPHS). BPHS was announced when a new healthcare reform plan started in China in 2009, aiming at assisting community health organizations in delivering a set package of basic health services across the country (14). Patients in the control villages received the usual care. In the context of rural China, the usual care involved patients seeking care in village clinics, township healthcare centers, or county hospitals, as necessary. People with hypertension and diabetes may also receive quarterly follow-up visits by village doctors as covered by the Basic Public Health Services (10).

Identification, measurement, and valuation of effectiveness

The intervention effectiveness will be measured by comparing the systolic blood pressure reduction and the QALYs between the intervention and control arm over the 12-month follow-up period.

Measurement of systolic blood pressure as the primary outcome

Blood pressure (BP) was measured as the primary outcome in the SINEMA trial at baseline and 1-year later, following the sample measurement protocol and approach among all participants. Blood pressure was measured on the right upper arm with participants seated and after 5 min of rest, with an electronic BP monitor (Omron HEM-7052). Two measurements were taken, and the mean value was calculated. If the difference between the two systolic BP measures was larger than 10 mmHg, a third measurement was conducted, and the mean value of the last two readings was calculated.

Health state utility

Health state utility (HSU) estimations will be derived from self-reported health-related quality of life (HRQoL) which was measured using the Chinese version of the EQ-5D-5L, a broadly used generic multi-attribute health utility instrument (15) at baseline and 1-year follow-up. For assessing HRQoL, study data collectors who were staff from the Center of Disease Prevention and Control in the nearby county read out the questionnaire and items for participants and collected the data. After answering the questions for EQ-5D, participants were asked to point out the health score by fingers on a paper version of the EQ-Visual Analog Scale, and then, the data collectors entered the responded values into the online survey platform. An HSU was calculated for each respondent by using the Chinese version of population-based preference weights (16), which ranged from −0.391 to 1, with 1 representing the value of full health, 0 representing deaths, and −0.391 representing the worst state.

Stroke recurrence, hospitalization, disability, and all-cause mortality were measured by using questionnaires at one-year follow-up. Medical and deaths records were also extracted from four major hospitals in the region. These data provide information about the status and trajectory of stroke during the trial period.

Identification, measurement, and valuation of resource use and costs

The aim of the economic evaluation is to inform decision-makers about the costs and cost-effectiveness of introducing the SINEMA intervention to stroke patients in rural regions. As such, the economic evaluation will mainly be performed from the health sector perspective, reflecting the cost and values of the healthcare system.

The resources used to support the SINEMA program include as follows: (1) the cost used to support SINEMA program delivery and (2) the health resources used to support the healthcare service delivery to stroke patients. Table 1 describes the detailed measurement and valuation of costs. The research costs, including the investigator's time and data collection, were not included in the analysis. The costs of designing the SINEMA intervention and the digital health system and other "one-off" costs were excluded, but the operation and maintenance costs of the digital health system were included in the analysis.

Resources used to support program delivery

Program costs are captured based on a detailed inventory of all resources that are used to support the design and delivery of the SINEMA program. This consists of the administrative cost of headcounts of local project manager and printing materials, the cash support that compensates for the time and efforts of the village doctors, township physicians, and county physicians in delivering the SINEMA intervention over the trial period, and the resources used for maintaining the digital component of the SINEMA intervention (including daily voice messages to patients, the mobile application server, and labor cost related to system maintenance).

Resources used for healthcare services

Medical costs are measured mainly by estimating the direct medical cost with individual-level data, including both inpatient costs and outpatient costs for medications. Inpatient costs during the trial period among all participants were retrospectively collected from the urban and rural resident basic medical insurance system from four major key hospitals in the region. A list of medical conditions, including cardiovascular or cerebrovascular events, or other cardiometabolic-related health conditions, is generated by researchers. All relevant inpatient records that matched the conditions will be included in the analysis and total costs will be used in the analysis. Outpatient costs were estimated by the number of hospital visits and medication use. Medication costs

TABLE 1 Resource use information collected and measured for cost.

Cost component	Measurement	Quantity	Valuation	potential collected resource
Intervention related cost				
Part-time project manager	Time spent coordinating the project	Number of project managers	Cost of employment converted to the annual equivalent cost	Research team to record
Materials for handbooks and handouts	Inventory on printing materials	Number of materials delivered	Replacement value converted to annual equivalent cost	Research team to record
County physicians	Time spent in training village doctors and providing consultations	Number of training sessions organized	Cost of employment converted to the annual equivalent cost	Research team to record
Township manager	Time spent in coordinating and delivering consultations	Number of townships participated	Cost of employment converted to annual equivalent cost	Research team to record
Village doctors	Time spent in delivering SINEMA follow-up visits	Number of villages participated and fidelity in adhering to the intervention protocol	Cost of employment converted to annual equivalent cost	Research team to record
Voice messages	Inventory on sending voice message via third-party platform	Number of voice message delivered	Replacement value converted to annual equivalent cost	Research team to record
Maintaining the digital health system	Inventory on server cost and cost related to human resources in maintaining the program	Duration of time supporting the program	Replacement value converted to annual equivalent cost	Research team to record
Developing digital health system	Time spent in designing the program	Number of staff involved	Cost of employment converted to annual equivalent cost	Research team to record
Medical costs (for both intervention and control arm)				
Inpatient cost	Time, human resources, facilities used for inpatient care	Mean days of stay and frequency of hospitalization within trial period	Mean cost replacement value recorded in social medical scheme	Reimbursement system
Outpatient cost	Time spent in delivering care	Number of follow-up visits	Replacement value converted to annual equivalent cost	(Estimated)
Medication cost	Self-reported medication use	Number of medications used and adherence rate	Replacement value converted to annual equivalent cost based on local medication price list	Follow-up survey

will be valued based on the general essential medication list and the standard unit cost for each type of medication as the “zero markups” regulation requires no additional costs on medications in the primary care settings (14).

Data analysis

The data analyses will be performed using STATA software (StataCorp. 2019. State Statistical Software: Release 16. College Station, TX: StataCorp. LLC). For the within-trial cost-effectiveness analysis, two incremental cost-effectiveness ratios (ICERs) will be calculated to evaluate the incremental cost per QALY and the incremental cost per 1 mmHg reduction in systolic blood pressure.

The ICER formula is given below:

$$ICER = \frac{Cost_{SINEMA} - Cost_{Usual\ care}}{Effect_{SINEMA} - Effect_{Usual\ care}}$$

Multivariable or multilevel models (with levels defined as villages considering the cluster design) will be employed to explore factors associated with health resource use, cost, and effectiveness. Generalized linear regression modeling of costs with gamma distributions and log linked for multivariable analyses that adjust for age, gender, stroke type, and length of stay will be performed.

Several sensitivity analyses will be considered to quantify the level of decision uncertainty. Deterministic sensitivity analyses will be performed on chosen variables to identify key determinants for the results, as presented in Table 2. We will generate cost-effectiveness scatterplots to explore the uncertainties around incremental costs and effectiveness. A cost-effectiveness acceptability curve (CEAC) will be created to explore the probabilities of the SINEMA intervention being cost-effective at a range of cost-effectiveness thresholds.

Discussion

This manuscript details the study protocol of the economic evaluation that aims to assess the cost-effectiveness of the SINEMA intervention among stroke patients in rural China. As one of

TABLE 2 Sensitive analysis of key indicators.

	Base case	Range
Effectiveness		
SBP outcomes	Mean value in change with fully adjustment model	95% confidence interval for non-adjusted and fully adjusted
QALY outcomes	Mean value in change with fully adjustment model	95% confidence interval for non-adjusted and fully adjusted
Cost		
Compensation for village doctors	Recorded headcount cost	Fidelity rate of follow-up visits ranging from lowest value to 100%
Missing information of inpatient care for those who were hospitalized in other healthcare facilities.	Median inpatient cost for same or similar diagnosis	25%, 75% percentile of inpatient cost for those who were hospitalized with same or similar diagnosis.
Missing information of outpatient cost which is not covered by health insurance.	Mean outpatient cost for same or similar diagnosis	25%, 75% percentile of outpatient cost for those who were hospitalized with same or similar diagnosis.
Missing information on medication cost of daily doses.	Mean cost for the conventional drugs	25%, 75% percentile of medication cost for those who took same or similar drugs.
Development cost of the digital health system	None	Development costs of the SINEMA model when the cost was shared by years of follow-up

a few studies that evaluate the economic value of community-based technology-enabled intervention for stroke prevention and management, this study employs a within-trial evaluation to analyze the incremental cost-effectiveness ratios. If proven cost-effective, the findings from this study will provide robust evidence to policymakers in low- and middle-income countries for adopting and scaling up similar interventions.

Economic evaluation is a crucial component for evaluating the impact of a community-based intervention for disease prevention. Despite the proven effectiveness of the SINEMA intervention, the economic value of the SINEMA intervention will further inform decision-makers on the allocation of scarce resources for stroke prevention and control. Although effective strategies for community-based interventions have been increasingly examined through trials (17–19), only a few studies seek to answer the economic value of the intervention. For instance, the COBRA-BPS trial aimed to assess the effectiveness of community-based interventions for improving blood pressure control in Bangladesh, Pakistan, and Sri Lanka, and the COBIN study targeted lifestyle intervention for blood pressure control in Nepal estimated the long-term economic value through budget impact and cost-effectiveness analysis from the health system perspective (20, 21). However, these assumptions may introduce certain biases which may overestimate the benefit of the intervention (22, 23). Different from these studies, our study performed a within-trial economic evaluation method with individual granularity by using first-hand data collected from the trial. In addition, existing reviews also called for research to consider the uniqueness of measuring the cost and benefit of digital health solutions compared with traditional human-delivered interventions (24). Thus, our study may shed light on the field by detailing our methodology for evaluating the cost-effectiveness of a community-based technology-enabled intervention.

Our study design has several unique features. First, the study measures a multifaceted intervention with digital health components. Digital health interventions have a high potential to deliver interventions to a large-scale population, thus, it holds the promise of improving chronic disease management. Second, compared to human-delivered intervention, the development cost for digital health intervention is relatively high; however, the operation and marginal cost for the implementation could be limited to none if it is scaled to a large population (25). In our protocol, we followed previous studies' methods to evaluate the operational cost of the SINEMA model in our design (11). We also include the development cost in our sensitivity analysis.

As for data collection, due to the constrained funding support, the SINEMA trial observed and measured the cost and effectiveness of the intervention over a 12-month period. Although such follow-up duration was reasonable to measure a high number of stroke cases, the data collected from the trial period hardly provided information about the long-term benefits and impact of the intervention. Instead, we will use data from other trials and cohort studies that were conducted in similar settings to estimate the long-term natural transition of stroke patients in rural China (26, 27). This approach enables us to estimate the long-term economic impact of the SINEMA intervention.

The main limitation of this design lies in the field of cost measurement. First, although we measured key direct health costs at the individual level, we are only able to quantify the inpatient costs and medication costs for participants from the health insurance data. Due to the limited data access, we cannot measure the cost of inpatient care if the patients seek healthcare services beyond the major four hospitals in the study regions, which is likely to happen as there is no referral system that restricts service-seeking behaviors in rural China (27). Therefore, we tend to underestimate the inpatient costs if there are relatively more inpatients in the control group. Second, the analysis may underestimate some of the labor costs. For instance, the village doctors may provide blood pressure assessments during clinic visits for free, and the payment scheme may not be set by the number of services provided at the clinic visits. These visits were not paid, thus were not included in the financial analysis.

Conclusion

This article details the study protocol of the economic evaluation of the SINEMA intervention. If proven cost-effective, the SINEMA intervention has a high potential to be adapted and implemented in other settings to benefit more people with stroke.

Ethics statement

The studies involving human participants were reviewed and approved by Duke University, Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

EG and BY drafted the manuscript. EG, JB, BO, LS, and LLY performed the study design. XC, BY, LLY, and YL contributed to the manuscript revision. LS supervised the study design and data analysis plan. All authors approved the final version for publication.

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Conflict of interest

The 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.

The reviewer WW declared a shared parent affiliation with the author ZL to the handling editor at the time of review.

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Women and stroke: disparities in clinical presentation, severity, and short- and long-term outcomes

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Objectives: There are limited data from the Middle East on sex-related differences in short- and long-term stroke outcomes. We present 8 years of experience based on the Qatar stroke database.

Setting: The Qatar stroke database prospectively collects data on all stroke patients admitted to Hamad General Hospital. For this study, we compared female and male acute ischemic stroke patients on their characteristics at admission, short-term outcomes [modified Rankin Scale (mRS) score], and long-term outcomes [incidence of major adverse cardiovascular events (MACEs)].

Participants: A total of 7,300 patients [F: 1,406 (19.3%), M: 5,894 (80.7%); mean age 55.1 ± 13.3 (F: 61.6 ± 15.1, M: 53.5 ± 12.3; $p < 0.001$)] were admitted with acute ischemic stroke.

Results: Significantly fewer women presented within 4.5 h of onset (F: 29% vs. M: 32.8%; $p = 0.01$). Although women were more likely to experience severe stroke (NIHSS >10; F: 19.9% vs. M: 14.5%; $p < 0.001$), fewer were treated with thrombolysis (F: 9.8% vs. M: 12.1%; $p = 0.02$). Women experienced more medical complications (F: 11.7% vs. M: 7.4%; $p < 0.001$) and tended to have a more prolonged length of stay in the hospital (F: 6.4 ± 7.6 days vs. M: 5.5 ± 6.8 days; $p < 0.001$).

Primary and secondary outcome measures: Good outcomes at 90 days (mRS score of 0–2) were less frequent in women (F: 53.3% vs. M: 71.2%; $p < 0.001$). Fewer female patients were taking antiplatelets (F: 78% vs. M: 84.8%; $p < 0.001$) or statins (F: 81.2% vs. M: 85.7%; $p < 0.001$). Significantly more female patients experienced a MACE (F: 12.6% vs. M: 6.5%; $p < 0.001$).

Conclusion: Older age at presentation contributes to poor outcomes following acute stroke in women. Other contributing factors include delays in admission to the hospital, lower rates of thrombolysis, and lower rates of provision of preventative treatments.

KEYWORDS
ischemic stroke, women, disparities, outcome, major adverse cardiovascular events

Highlights

- The strengths of this study include the large sample size and minimal loss to follow-up. Moreover, there are few studies on the long-term risk of major adverse cardiovascular events (MACEs) in women.
- The analytical approach employed was able to significantly reduce residual confounding.
- The single-center nature of the study setting may reduce the generalizability of the findings.
- The data were collected prospectively for entry in the Qatar stroke database, but the analysis was retrospective and therefore did not have prespecified objectives; this might have resulted in low accuracy of the comorbidity profile.
- We may have missed clinical events occurring in patients who did not go to the hospital or who may have received treatment outside the country.

Introduction

Outcomes following acute stroke may vary depending on the gender of the patient (1, 2). Stroke is more common in women, among whom it is the fourth leading cause of death, as compared to the fifth leading cause in men (3, 4). The death rate following stroke is higher in women (women: 6.2%; men: 4.4%), resulting in 55,000 more excess deaths among women annually (3, 4). Stroke rates are especially high in women in the older age category (>80 years of age) (5). In women, stroke is the most common presentation of cardiovascular disease, whereas the leading manifestation in men is coronary artery disease (6). There is evidence that modifiable risk factors for stroke may affect men and women differently. For example, the effect of diabetes on stroke risk is greater in women compared to men (7). This is especially evident in the case of type 1 diabetes (7–9). Similarly, recent evidence suggests that hypertension may have a stronger association with stroke in women compared to men (8, 10, 11). There is also an association between increased body mass index (BMI), or obesity, and stroke, and this association also appears to be more prominent in women (8). Atrial fibrillation, an important risk factor for stroke, is more frequent in women (7), and the risk of stroke is particularly high in women older than 65 years of age (12). Additionally, there are several important female-specific risk factors that also contribute to the risk of stroke in women (13–15).

Women are less likely to receive appropriate treatment for acute stroke (1, 2). Several factors may contribute to the provision of suboptimal treatment for women. First, the diagnosis of acute stroke is often missed in women. In a recent cross-sectional analysis of misdiagnosis of acute stroke, women had 25% lower odds of the correct diagnosis being made (16, 17). A higher frequency of atypical stroke symptoms in women may contribute to the misdiagnosis of stroke (18). We have previously shown that stroke mimics are more common in women (19). This may also contribute to higher rates of misdiagnosis and delays in treatment. A recent meta-analysis showed that thrombolysis was offered less frequently to women, and that results indicating lower rates of treatment with rt-PA occurred most frequently in reports from Europe and the USA (20). Women are also more likely to have severe symptoms, another factor that contributes to poor outcomes following acute stroke (21).

Most of the sex- and gender-related research on stroke diagnosis, treatment, and outcomes has been published in Europe and North America (1, 2). The effects of gender and sex on outcomes of stroke have not been thoroughly studied in populations in the Middle East or Southeast Asia. Regarding Qatar specifically, we have previously published work on the topics of ethnic variation (22), stroke risk factors (23), clinical presentation (24), thrombolysis in acute stroke management (25), and short-term (26) and long-term (27) outcomes of stroke in the population of Qatar. We have also shown that post-stroke depression tends to be more common in women in Qatar (28). We now present our experience based on analysis of a large database of prospectively collected data on 7,300 patients; using these data, we studied the risk factors, presenting symptoms, administration of reperfusion treatment, course of disease during hospital stay, and short- and long-term prognosis in male and female patients admitted to the hospital following acute stroke.

Methods

All patients with acute ischemic stroke (AIS) who were admitted to the Hamad General Hospital (HGH) between January 2014 and January 2022 were included in the study. Clinical information was entered prospectively in a database, as reported in previously published work (22–24). The hospital has a dedicated stroke ward, admits more than 95% of stroke patients in Qatar, and is the only center where AIS treatment with intravenous thrombolysis and mechanical thrombectomy is offered. The clinical information collected on all patients admitted to the HGH included prehospital Modified Rankin Scale (mRS) score, vascular risk factors, mode of transportation, symptom severity, time to CT, and "door-to-needle" time in cases where thrombolysis was offered. Clinical evaluation included the severity of stroke as measured by the National Institute of Health Stroke Score (NIHSS). Treatment at admission and discharge was recorded for all patients. We also documented any medical complications that developed during admission, including aspiration pneumonia, bedsores, bladder infections, and any systemic sepsis. All patients were assessed on the mRS at discharge and at 90 days following acute stroke. In the current study, we also reviewed the state-wide Cerner medical records of the patients to document any vascular complications following discharge.

We evaluated differences between men and women in terms of mode of transportation to the hospital, time from onset to presentation to the emergency department, severity of stroke symptoms, type of stroke, and whether the patient was treated with thrombolysis and thrombectomy. In addition, we monitored the rate of complications, length of stay in the hospital, and changes in treatment of risk factors at the time of discharge. The primary short-term outcome measure in the present study was a comparison of mRS scores at 90 days between female and male patients. An mRS score of 0–2 was considered a good outcome, and an mRS score of 3–6 was defined as a poor outcome. For analysis of long-term outcome, we compared the rate of major adverse cardiovascular

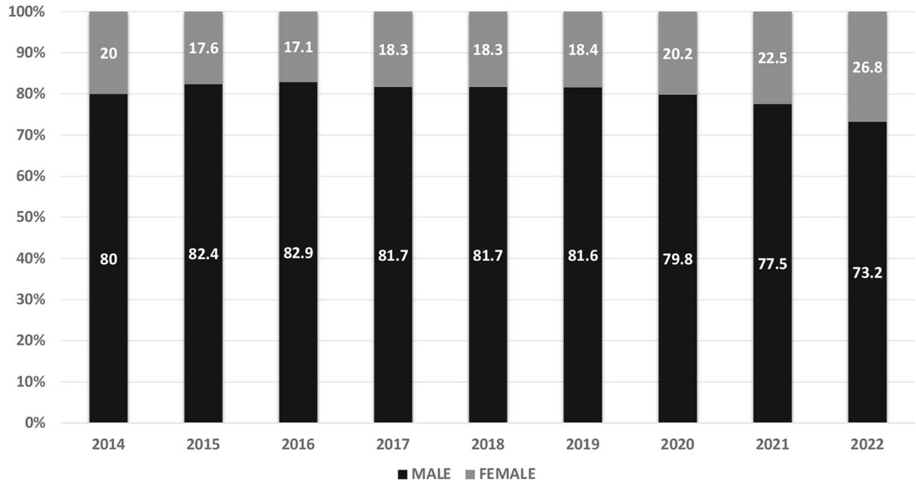

FIGURE 1
Proportion of male vs. female patients admitted annually in each year during the study.

events (MACEs) among men and women at 1 year. The occurrence of MACEs (defined as cardiovascular mortality; all-cause mortality; fatal or non-fatal myocardial infarction; recurrent stroke; and revascularization procedures, i.e., coronary artery bypass graft or percutaneous coronary intervention) during follow-up after the index event was also compared.

The study was approved by the Institutional Review Board, Hamad Medical Corporation at the Medical Research Center (MRC-01-20-1135) and the Institutional Review Board of Weill Cornell Medicine—Qatar (1932095-1/22-00016).

Informed consent: This was a registry study; hence, consent was not applicable.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting, or planned dissemination of our research.

Statistical methods

Descriptive statistics were used to characterize the study sample. Descriptive results (including graphical illustrations) for all quantitative variables (e.g., age) are presented in the form: mean, standard deviation (SD) for all interval variables; frequencies with percentages are reported for categorical variables. Inferential statistics, such as the results of Student's *t*-tests, were used to evaluate the statistical significance of mean differences between female and male ischemic stroke patients for all interval variables; chi-square tests were conducted to examine the association between sex and categorical variables among ischemic stroke patients. A multivariate binomial logistic regression analysis was conducted to examine the factors that were more common among women in comparison to men after adjusting for significant independent variables, such as age, NIHSS score, systolic blood pressure, diabetes, HTN, prior stroke, smoking, obesity, length of stay, poor outcome at 90 days, and etiology of stroke (TOAST classification). This analysis was conducted using the equation logit $E(Y) = b_0 + b_1x_1 + b_2x_2 + \ldots\ldots + b_nx_n$, where Y is the Bernoulli distributed outcome variable of sex (male $= 0$ and female $= 1$), x_i ($i = 1$ to n) represents the independent variables, and b_i ($i = 1$ to n) represents the linear parameters. A forest plot based on the same multivariate regression analysis was constructed to illustrate significant predictors of sex. A p-value of 0.05 (two-tailed) was considered to represent the threshold for statistical significance. The analysis was conducted using the SPSS 28.0 statistical software package.

Results

Demographics

During the study period (January 2014 to January 2022), 14,768 patients were admitted to the HGH stroke program. The proportions of men and women among the patients admitted in each year are shown in Figure 1. After exclusion of 1,549 patients with ICH, 1,413 patients with TIAs, 204 patients with cerebral venous thrombosis, and 4,302 patients with stroke mimics, data from 7,300 patients with a final diagnosis of acute ischemic stroke [women: 1,406 (19.3%), men: 5,894 (80.7%); mean age: 55.1 ± 13.3 (women: 61.6 ± 15.1, men: 53.5 ± 12.3; $p < 0.001$)] were available for analysis. The larger number of male patients reflects the demographics in Qatar, where there is a predominance of young expatriate male workers. Most women are either local Qatari nationals or long-stay expatriates. As shown in Table 1, hypertension, diabetes, obesity, atrial fibrillation, and prior stroke were significantly more common in women, while smoking was more common in men. Levels of triglycerides and LDL cholesterol at admission were significantly higher in men.

TABLE 1 Baseline characteristics and risk factors in the female and male population of ischemic stroke patients.

Variable	Overall ($n = 7,300$)	Women ($n = 1,406$, 19.3%)	Men ($n = 5,894$, 80.7%)	P-value
Age (mean, years)	55.1 ± 13.3	61.6 ± 15.1	53.5 ± 12.3	<0.001
Age category				
<46 years	1,807 (24.8)	223 (15.9)	1,584 (26.9)	<0.001
46–55 years	2,104 (28.8)	229 (16.3)	1,875 (31.8)	
56–65 years	1,863 (25.5)	354 (25.2)	1,509 (25.6)	
>65 years	1,526 (20.9)	600 (42.7)	926 (15.7)	
Hypertension	5,324 (72.9)	1,074 (76.4)	4,250 (72.1)	<0.001
Diabetes	4,133 (56.6)	880 (62.6)	3,253 (55.2)	<0.001
Dyslipidemia	3,500 (47.9)	705 (50.1)	2,795 (47.4)	0.07
Prior stroke	872 (11.9)	227 (16.1)	645 (10.9)	<0.001
Atrial fibrillation on admission	613 (8.4)	213 (15.1)	400 (6.8)	<0.001
Coronary artery disease	890 (12.2)	173 (12.3)	717 (12.2)	0.89
Active smoking	2,074 (28.4)	49 (3.5)	2,025 (34.4)	<0.001
Obesity (body mass index ≥30 kg/m^2)	1,848 (25.3)	577 (41.0)	1,271 (21.6)	<0.001
Prior antiplatelet use	1,523 (20.9)	405 (28.8)	1,118 (19.0)	<0.001
Prior anticoagulant use	359 (4.9)	106 (7.5)	253 (4.3)	<0.001
Prior anti-hypertensive use	2,394 (32.8)	685 (48.7)	1,709 (29.0)	<0.001
Anti-diabetic medication use	1,882 (25.8)	503 (35.8)	1,379 (23.4)	<0.001
Prior statin use	1,629 (22.3)	467 (33.2)	1,162 (19.7)	<0.001
RBS on admission (mmol/L)	9.6 ± 4.9	9.9 ± 5.0	9.5 ± 4.9	0.009
HbA1c%	7.5 ± 2.4	7.6 ± 2.4	7.5 ± 2.4	0.14
Serum cholesterol (mmol/L)	4.9 ± 1.6	4.8 ± 1.8	4.9 ± 1.5	0.20
Serum triglyceride (mmol/L)	1.8 ± 1.2	1.7 ± 1.4	1.8 ± 1.1	0.002
Serum HDL (mmol/L)	1.0 ± 0.3	1.2 ± 0.3	0.9 ± 0.3	<0.001
Serum LDL (mmol/L)	3.1 ± 1.1	2.9 ± 1.1	3.1 ± 1.1	<0.001
Systolic blood pressure (mmHg)	156.8 ± 30.4	152.2 ± 30.3	157.9 ± 30.4	<0.001
Diastolic blood pressure (mmHg)	90.6 ± 19.3	82.9 ± 18.0	92.4 ± 19.2	<0.001
Body mass index on admission (kg/m^2)	27.7 ± 5.1	29.7 ± 6.7	27.2 ± 4.5	<0.001
Antiplatelets at discharge	6,097 (83.5)	1,096 (78.0)	5,001 (84.8)	<0.001
Anticoagulants at discharge	543 (7.4)	147 (10.5)	396 (6.7)	<0.001
Anti-hypertensive at discharge	4,707 (64.5)	920 (65.4)	3,787 (64.3)	0.41
Antidiabetics at discharge	2,843 (38.9)	601 (42.7)	2,242 (38.0)	<0.001
Statin at discharge	6,191 (84.8)	1,141 (81.2)	5,050 (85.7)	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein; RBS, random blood sugar.

Women were significantly more likely to be taking antithrombotic, anti-hypertensive, anti-diabetes, and statin medications. This is likely because of the older average age and higher rates of vascular risk factors among women. While atrial fibrillation may have contributed to the occurrence of stroke, <50% of female patients were taking anticoagulants at the time of stroke. The data showed that a larger proportion of female patients were in the age group older than 65 years compared to male patients ($p = 0.001$; Table 1).

Mode of transportation to the hospital, course in hospital, and acute stroke treatment

Most patients arrived at the hospital via activation of the ambulance service (67.5%). Use of the ambulance service was, however, significantly lower among women (women: 64.3% vs. men: 68.2%; $p = 0.001$). Women were more likely to present to the hospital later after the onset of symptoms. Nearly 32% of patients

TABLE 2 Comparison of admission and in-hospital parameters between female and male ischemic stroke patients.

Variable	Overall (n = 7,300)	Women (n = 1,406, 19.3%)	Men (n = 5,894, 80.7%)	P-value
Mode of arrival				
Ambulance service	4,926 (67.5)	904 (64.3)	4,022 (68.2)	<0.001
Non-medical transport	1,952 (26.7)	404 (28.7)	1,548 (26.3)	
Already in hospital	152 (2.1)	52 (3.7)	100 (1.7)	
From another hospital	270 (3.7)	46 (3.3)	224 (3.8)	
NIHSS on admission	5.5 ± 5.9	6.1 ± 6.6	5.3 ± 5.7	<0.001
NIHSS severity				
Mild (NIHHS 0–4)	4,452 (61.0)	816 (58.0)	3,636 (61.7)	<0.001
Moderate (NIHSS 5–10)	1,715 (23.5)	310 (22.0)	1,405 (23.8)	
Severe (NIHSS >10)	1,133 (15.5)	280 (19.9)	853 (14.5)	
Arrival time from onset				
<4.5 h	2,340 (32.1)	409 (29.1)	1,931 (32.8)	0.011
<24 h	1,703 (23.3)	319 (22.7)	1,384 (23.5)	
>24 h	2,471 (33.8)	515 (36.6)	1,956 (33.2)	
Wake-up stroke	265 (3.6)	46 (3.3)	219 (3.7)	
Unsure of onset timing	521 (7.1)	117 (8.3)	404 (6.9)	
IV thrombolysis	849 (11.6)	138 (9.8)	711 (12.1)	<0.02
Thrombectomy	312 (4.3)	62 (4.4)	250 (4.2)	0.78
Reasons for no thrombolysis				
Out of window	4,649 (72.1)	920 (72.6)	3,729 (71.9)	0.02
Low NIHSS/improved	978 (15.2)	166 (13.1)	812 (15.7)	
High NIHSS/established or large infarct	331 (5.1)	61 (4.8)	270 (5.2)	
Wake-up stroke/unsure of onset/missed/ late/declined	130 (2.0)	30 (2.4)	100 (1.9)	
Contraindications/other reasons	363 (5.6)	90 (7.1)	273 (5.3)	
Post-thrombolysis bleed	54 (6.3)	7 (5.0)	47 (6.6)	0.49
Length of stay	5.7 ± 6.9	6.4 ± 7.6	5.5 ± 6.8	<0.001
Complications during admission	599 (8.2)	165 (11.7)	434 (7.4)	<0.001
Aspiration pneumonia	292 (4.0)	60 (4.3)	232 (3.9)	0.57
Urosepsis	187 (2.6)	68 (4.8)	119 (2.0)	<0.001
Bedsores	36 (0.5)	16 (1.1)	20 (0.3)	<0.001
Sepsis	209 (2.9)	62 (4.4)	147 (2.5)	<0.001
Deep venous thrombosis	6 (0.1)	1 (0.1)	5 (0.1)	0.87
TOAST classification				
Small vessel disease	3,460 (47.4)	621 (44.2)	2,839 (48.2)	<0.001
Large vessel disease	1,541 (21.1)	261 (18.6)	1,280 (21.7)	
Cardioembolism	1,412 (19.3)	352 (25.0)	1,060 (18.0)	
Stroke of other determined etiology	553 (7.6)	100 (7.1)	453 (7.7)	
Stroke of undetermined etiology	334 (4.6)	72 (5.1)	262 (4.4)	

NIHSS, National Institute of Health Stroke Scale; IV, intravenous; TOAST, trial of Org 10,172 in acute stroke treatment.

presented to the hospital within 4.5 h of onset (women: 29% vs. men: 32.8%; $p = 0.01$). Significantly more women presented to the hospital more than 24 h after the onset of symptoms (women: 36.6% vs. men: 33.2%; $p = 0.01$). Women were also more likely to

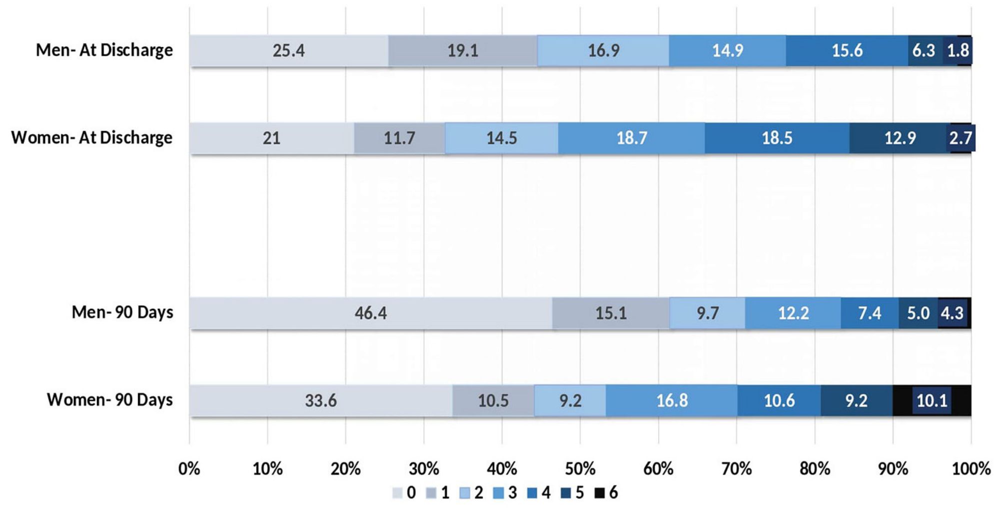

FIGURE 2
Modified Rankin Scale scores at discharge and at 90 days for women and men.

report that they were unsure about the time of onset (women: 8.3% vs. men: 6.9%; $p < 0.01$). Female patients had significantly lower systolic blood pressure (women: 152.2 ± 30.3 vs. men: 157.9 ± 30.4; $p < 0.001$) and diastolic blood pressure (women: 82.9 ± 16.7 vs. men: 92.4 ± 19.2; $p < 0.001$) at admission. Severe stroke (NIHSS > 10) was significantly more common among women than among men (19.9% vs. 14.5%; $p < 0.001$). Intravenous thrombolysis with rt-PA was, however, less likely to be offered to women compared to men (women: 9.8% vs. men: 12.1%; $p = 0.02$). Door-to-needle time among patients offered this treatment was significantly longer for women compared to men (women: 65.9 ± 35.5 min vs. men: 58.9 ± 34.4 min; $p = 0.03$). Thrombectomy was carried out in 4.3% of patients, and there was no difference in rate between women and men. Decompressive hemicraniectomy was carried out in a small number of patients (1.3%), and was significantly less common in women (women: 1.5% vs. men: 0.8%; $p = 0.04$). There was no difference in the rate of post-rt-PA cerebral hemorrhage (women: 5.0% vs. men: 6.6%; $p = 0.49$). The frequencies of various reasons for not offering rt-PA are shown in Table 2; rates of post-rt-PA symptomatic hemorrhage are also shown in Table 2.

Medical complications were significantly more common in women compared to men (women: 11.7% vs. men: 7.4%; $p < 0.001$), as shown in Table 2. Although the rate of aspiration pneumonia was similar in both sexes, other complications (including urosepsis, bedsores, and systemic sepsis) were significantly more common among female patients. Women also tended to have a significantly more prolonged length of stay in the hospital (women: 6.4 ± 7.6 vs. men: 5.5 ± 6.8; $p < 0.001$). Fewer female patients were taking antiplatelet medications at discharge (women: 78% vs. men: 84.8%; $p < 0.001$), but more female patients were discharged on anticoagulant medications (women: 10.5% vs. men: 6.7%; $p < 0.001$). The number of patients discharged on anti-hypertensive medications was similar for both sexes (women: 65.4% vs. men: 64.3%; $p = 0.41$). More female patients were discharged on antidiabetic medications (women: 42.7% vs. men: 38.0%; $p < 0.001$). The use of statins, however, was less frequent in women (women: 81.2% vs. men: 85.7%; $p < 0.001$). Significantly fewer female patients received long-term rehabilitation care (women: 16.8% vs. men: 23.5%; $p < 0.001$). The proportion of patients falling into each final TOAST classification, representing the etiology of stroke diagnosis, is shown in Table 2. There were significantly more women with a diagnosis of cardioembolic stroke (women: 25% vs. men: 18%; $p < 0.001$).

Short-term outcomes at 90-day follow-up and MACEs at 1-year follow-up in ischemic stroke patients

Short-term outcomes were measured in the form of mRS scores at discharge and at 90 days. As shown in Figure 2, an mRS score of 0–2, implying a good outcome, was observed in 47.2% of female patients and 61.3% of male patients at discharge ($p < 0.001$). At 90-day follow-up, there were still significantly fewer female patients with a good outcome (women: 53.3% vs. men: 71.2%; $p < 0.001$). Among female patients, prognosis was related to age at the time of presentation. A poor prognosis at 90 days was most likely among female patients over the age of 65 (women: 62.9% vs. men: 29.9%; $p = 0.001$; Table 3). Additionally, significantly more deaths occurred among women, both during the hospital stay (women: 2.7% vs. men: 1.8%; $p = 0.02$) and during the 90 days following discharge (women: 10.1% vs. men: 4.3%; $p < 0.001$), as shown in Table 3.

For assessment of outcomes at 1-year follow-up, we analyzed the occurrence of MACEs in the two groups. As shown in Table 3, significantly more female patients experienced at least one MACE during the year following discharge from the

TABLE 3 Differences between female and male ischemic stroke patients in terms of short-term and 1-year outcomes.

Outcome measure	Overall (n = 7,300)	Women (n = 1,406, 19.3%)	Men (n = 5,894, 80.7%)	P-value
mRS score at 90 days				
0	2,470 (43.8)	382 (33.6)	2,088 (46.4)	<0.001
1	799 (14.2)	119 (10.5)	680 (15.1)	
2	541 (9.6)	104 (9.2)	437 (9.7)	
3	739 (13.1)	191 (16.8)	548 (12.2)	
4	451 (8.0)	120 (10.6)	331 (7.4)	
5	328 (5.8)	105 (9.2)	223 (5.0)	
6	308 (5.5)	115 (10.1)	193 (4.3)	
mRS category at discharge				
Good (mRS 0–2)	4,279 (58.6)	664 (47.2)	3,615 (61.3)	<0.001
Poor (mRS 3–6)	3,021 (41.4)	742 (52.8)	2,279 (38.7)	
mRS category at 90 days (n = 5,636, 77.2%)				
Good (mRS 0–2)	3,810 (67.6)	605 (53.3)	3,205 (71.2)	<0.001
Poor (mRS 3–6)	1,826 (32.4)	531 (46.7)	1,295 (28.8)	
Poor outcome (mRS 3–6) at 90 days (n = 1,826)				
Age <46 years	312 (17.1)	42 (7.9)	270 (20.8)	<0.001
Age 46–55 years	382 (20.9)	45 (8.5)	337 (26.0)	
Age 56–65 years	450 (24.6)	110 (20.7)	340 (26.3)	
Age >65 years	682 (37.3)	334 (62.9)	348 (26.9)	
Mortality rate at discharge	144 (2.0)	38 (2.7)	106 (1.8)	0.03
Mortality rate at 90 days	308 (5.5)	115 (10.1)	193 (4.3)	<0.001
1-year outcomes				
Recurrent stroke (ischemic or hemorrhagic)	132 (2.3)	28 (2.4)	104 (2.3)	0.85
Post-stroke MI (fatal or non-fatal)	44 (0.8)	9 (0.8)	35 (0.8)	0.99
All-cause mortality	372 (6.5)	139 (11.7)	233 (5.1)	<0.001
Post-stroke cardiac arrest	94 (1.7)	37 (3.2)	57 (1.3)	<0.001
Post-stroke cardiac revascularization (CABG or PCI)	44 (0.8)	7 (0.6)	37 (0.8)	0.46
Major cardiac adverse event (MACE)	561 (7.7)	177 (12.6)	384 (6.5)	<0.001
Total MACEs over 5 years				
0 events	6,739 (92.3)	1,229 (87.4)	5,510 (93.5)	<0.001
1 event	439 (6.0)	134 (9.5)	305 (5.2)	
2 events	119 (1.6)	43 (3.1)	76 (1.3)	
3 events	3 (0.1)	0	3 (0.1)	

mRS, Modified Rankin Scale; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MACE, major adverse cardiovascular event.

hospital (women: 12.6% vs. men: 6.5%; p < 0.001). The rate of recurrent stroke was similar among both sexes, but women were more likely than men to undergo cardiac arrest and to die. Women were also more likely to experience recurrent events compared to men. The higher incidence of events during follow-up may be related to the older age, higher incidence of vascular risk factors, and more frequent co-morbidities evident in women.

TABLE 4 Multivariate binomial logistic regression of factors associated with sex among ischemic stroke patients.

Variable	Adjusted odds ratio	95.0% CI		*P*-value
		Lower	Upper	
Age				
<46 years	1.00	–	–	<0.001
46–55 years	0.99	0.79	1.26	0.96
56–65 years	1.72	1.37	2.17	<0.001
>65 years	3.43	2.73	4.31	<0.001
Systolic blood pressure (mmHg)	0.99	0.993	0.998	0.002
Diabetes	0.94	0.80	1.09	0.42
Hypertension	0.87	0.72	1.04	0.13
Prior stroke	0.95	0.77	1.18	0.65
Smoking status	0.08	0.06	0.11	<0.001
Obesity (kg/m^2)	2.46	2.10	2.87	<0.001
Length of stay	1.00	0.99	1.01	0.69
Poor outcome at 90 days (mRS score 3–6)	1.49	1.27	1.76	<0.001
TOAST classification				
Small vessel disease		–	–	0.03
Large vessel disease	0.88	0.72	1.08	0.22
Cardioembolism	1.15	0.95	1.39	0.14
Stroke of other determined etiology	0.90	0.67	1.21	0.49
Stroke of undetermined etiology	1.41	0.99	2.00	0.05

Variables entered into the model: age category; SBP on admission; diabetes status on admission; hypertension status on admission; prior stroke history; active smoker status; obesity (BMI ≥ 30); length of hospital stay; poor prognosis at 90 days; and TOAST classification of ischemic stroke.

Multivariate analysis

We performed a multivariate logistic regression analysis to identify factors associated with women in comparison to men among ischemic stroke patients.

The rate of obesity was 2.5 times greater in female patients compared to male patients (adjusted OR: 2.5, 95% CI: 2.1–2.9). Similarly, a TOAST classification of ischemic stroke of unknown etiology was observed 1.5 times more frequently in female patients compared to male patients (adjusted OR: 1.4, 95% CI: 1.02–2.0). The rates of other diagnoses (small vessel disease, large vessel disease, cardioembolism, and stroke of other determined etiology) did not differ significantly between the sexes.

After adjusting for associated factors in the multivariate logistic regression, including age, NIHSS on admission, DM on admission, HTN on admission, prior stroke history, active smoker status, obesity, LOS, complications during admission, and TOAST classification, the likelihood of a poor outcome (mRS score 3–6) at 90 days was found to be greater among women than among men (adjusted OR: 1.61, 95% CI: 1.30–1.92). The details are shown in Tables 4, 5 and in Figure 3.

Discussion

This is the largest study using prospectively collected data on the role of sex in terms of evaluation, management and prognosis, and long-term outcomes for ischemic stroke patients in the Middle East. The patients represented multiple ethnicities, but were predominantly Arabic or from Southeast Asia. The significantly higher average age among women reflected the disproportionately high number of young male expatriate workers in Qatar compared to women, as we have previously reported (22–26). We have previously shown that stroke occurs at a younger age among expatriate subjects and that this is likely to be related to undiagnosed or poorly controlled risk factors. We have also previously shown that a higher incidence of lacunar stroke occurs among patients with a low NIHSS score, which is also related to poorly controlled hypertension and diabetes (22–26).

The present research revealed that, despite presenting with more severe stroke, women reported to the hospital later, underutilized the ambulance service, and were significantly less likely to receive intravenous thrombolysis treatment. In addition, the time to treatment (door-to-needle time) was also significantly delayed in women compared to men. The significantly higher rate of medical complications among women while in hospital can be explained by the older age of this group, the higher incidence of diabetes and obesity, and the likelihood of more severe stroke at presentation. These are all likely contributors to lower rates of recovery at discharge and at 90-day follow-up. Despite greater severity of stroke, fewer women than men were admitted for rehabilitation. Our research also showed that the incidence of MACEs during the 1-year follow-up period was significantly higher among women. This may in part be explained by their older age

TABLE 5 Multivariate binomial logistic regression analysis of factors associated with poor outcome (mRS score 3–6) at 90 days in ischemic stroke patients.

Variable	Adjusted odds ratio	95.0% CI		*P*-value
		Lower	Upper	
Age (years)	1.05	1.04	1.05	<0.001
Female sex	1.7	1.39	1.99	<0.001
NIHSS on admission	1.2	1.18	1.21	<0.001
Systolic blood pressure (mmHg)	1.00	1.000	1.005	0.09
Diabetes	1.28	1.09	1.49	0.002
Hypertension	1.22	1.02	1.47	0.03
Prior stroke	1.62	1.32	1.99	<0.001
Smoking status	0.96	0.81	1.14	0.65
Obesity (kg/m^2)	0.92	0.78	1.09	0.34
Length of hospital stay	1.14	1.12	1.16	<0.001
TOAST classification				
Small vessel disease				0.001
Large vessel disease	1.22	1.02	1.48	0.03
Cardioembolism	1.01	0.83	1.24	0.91
Stroke of other determined etiology	0.68	0.49	0.92	0.01
Stroke of undetermined etiology	1.44	1.01	2.05	0.04

NIHSS, National Institute of Health Stroke Scale.
Variables entered into the model: age (years); sex (female = 1); NIHSS on admission; SBP on admission; diabetes status on admission; hypertension status on admission; prior stroke history; active smoker status; obesity (BMI ≥30); length of hospital stay; and TOAST classification of ischemic stroke.

and the more frequent presence of diabetes. However, significantly fewer women were receiving antithrombotic, antidiabetic, or statin medications at the time of discharge, even though the incidence of diabetes was higher in women. These are important observations and require further analysis in the context of previously published literature on women and stroke. Special attention is required for women in order to improve awareness of the early signs of stroke, achieve rapid admission to the hospital, increase provision of reperfusion treatment, improve provision of care to prevent acute stroke-associated medical complications, and provide aggressive post-stroke care to improve prognosis and decrease the incidence of MACEs during follow-up.

Stroke is more common in women compared to men throughout life (1), and is especially prominent as a cause of death in the elderly (29). Elderly women are more likely to live alone and to have a higher degree of disability, making it more difficult for them to reach the hospital in good time (29). Treatable risk factors, including hypertension, diabetes, and atrial fibrillation, are also more common in the elderly and (as was evident from our study) may be undertreated. In our study, 50% of female patients with atrial fibrillation were not taking anticoagulation medication, and this likely accounted for the higher rate of cardioembolic stroke. We also observed that the use of statins was significantly lower in female patients at the time of discharge, despite this group having a significantly higher incidence of diabetes. Undertreatment of diabetes (30) and lower rates of statin use (31) in women have previously been noted. The use of antithrombotic medications was also significantly lower in women, an observation that has previously been noted (21). Our study shows that there focused attention needs to be placed on better management of vascular risk factors before and after stroke. Given the high rates of MACEs observed in women, this is especially critical following discharge after admission for acute stroke.

Women are significantly delayed in their arrival at the hospital and are less likely to receive rt-PA (32). In our study, fewer female patients presented within the 4.5-h time window, and women were less likely to use the ambulance service, which contribution to delay in their evaluation. The longer door-to-needle time observed in our study may also be a contributing factor in the fact that fewer female patients make a good recovery (33). Furthermore, women experience significantly higher rates of medical complications during hospitalization. Medical complications, especially aspiration pneumonia and sepsis, are important causes of increased mortality in stroke patients (34) and have been underreported in recent reviews on stroke in women (1, 2). Older age at presentation and greater neurological deficits at presentation are also important risk factors for medical complications in acute stroke patients. The combination of these factors likely contributed to the longer hospital stays and higher rate of mortality observed in women in our study. In our study, these higher rates of poor recovery and mortality in women persisted even after correction for the age difference in our multivariate analysis.

Our study showed a significantly lower rate of good recovery in women compared to men. Multiple factors likely contributed to this difference, as discussed above in detail. Women had a 50% lower rate of recovery even after correction for age, risk factors,

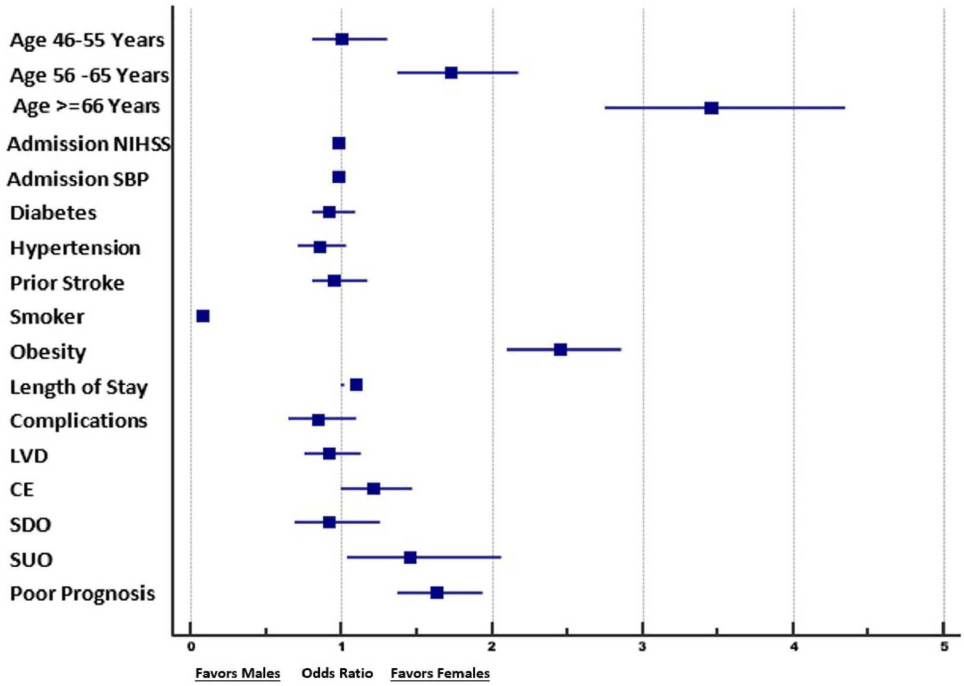

FIGURE 3
Forest plot of the results of the logistic regression analysis, showing the factors associated with female patients vs. male patients. NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; LVD, large vessel disease; CE, cardioembolic stroke; SDO, stroke of determined origin; SUO, stroke of undetermined origin.

and occurrence of complications in the hospital. However, a meta-analysis published recently has suggested that baseline differences in age, vascular risk factors, and stroke etiology can explain most of the sex-related difference in mortality (2, 35). In our population, the higher door-to-needle time for women may also be related in part to local social and ethnic practices. Traditionally, treatment-related decisions are made by male members of the family. It is not uncommon to wait for a male family member (for example, the patient's husband or brother) to arrive at the hospital before treatment can be initiated.

Few studies have been conducted on the long-term risk of MACE in women (1–4). We have previously shown that depression is more common in women following a stroke in our population (28), and depression has been found to be associated with slower post-stroke recovery (28). There are additional significant factors that may also contribute to the fact that fewer women make a good recovery and that MACEs occur at higher rates in women. Women are more likely to experience mobility issues (36), cannot tolerate pain well (1, 2), and are more likely than men to be single or widowed (1, 2). In a recent study conducted in London, in which patients were followed for more than 10 years following acute stroke, women were older and had significantly poorer outcomes in terms of activities of daily living (37). Despite their older age at presentation, women were less likely to experience recurrent strokes and had a lower rate of death during follow-up (37). In our study, we observed a higher rate of MACE in women during 1-year post-stroke follow-up. This may in part be related to lower rates of preventive treatment at the time of discharge. Despite the higher incidence of diabetes in women, we noticed that the use of antidiabetic medications and statins was lower in women than in men.

Our study shows that attention to some of the factors identified may lead to better outcomes in female patients. Vascular risk factors, especially diabetes, hypertension, obesity, and atrial fibrillation, were more common in women, and yet at the time of discharge, women were less likely to be offered statins and antithrombotic medications. Women were also less likely to receive rehabilitation treatment and had higher all-cause mortality during follow-up. Attention to strategies that may improve early admission to hospital, higher rates of thrombolysis, reduction in medical complications, and improved management of vascular risk factors may contribute to improving the care of female patients who suffer from acute stroke. The results are similar to those of a recent report from China on 9,038 patients, among whom stroke occurred at an older age and the outcomes were worse in women (38). The unfavorable outcome remained after correction for age, risk factors, and onset-to-door time (38). Lower acceleration of biological age for ischemic stroke in women may in part explain the older age at presentation (39).

There are limitations to our study. This was a single-center study and therefore may not reflect stroke practices across the entire Middle East. The data were collected prospectively for entry into the Qatar stroke database, but the analysis was retrospective and therefore did not have prespecified objectives. The male patients included were younger and the majority were expatriates, while the women were older and a larger proportion represented the Qatari and Arab population. The older age is likely responsible for the higher percentage of women who made a slower recovery, but does not explain why fewer patients were offered thrombolysis acutely or the lower rates of treatment with preventative therapies. For analysis of MACE incidence, we used electronic medical records. We may have missed clinical events occurring in patients who did not go to the hospital or who may have received treatment outside the country. Finally, the population of Qatar is skewed, with a larger proportion of younger expatriate men. This may account for the higher percentage of women in the older segment of the patient population.

In summary, we present a large study from the Middle East on sex differences in the management of acute stroke. Our study shows that, compared to men, women are significantly older at presentation, experience longer delays in coming to the hospital, and are less likely to receive thrombolysis. We also showed that women are more likely to suffer in-hospital complications and make a slower recovery. Despite higher rates of disease burden and vascular risk factors, fewer women are discharged on antithrombotic, statin, or antidiabetic medications.

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.

Ethics statement

The study was approved by the Institutional Review Board, Hamad Medical Corporation at the Medical Research Center (MRC-01-20-1135) and the Institutional Review Board of Weill Cornell Medicine-Qatar (1932095-1/22-00016). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HN, NA, and AS: conceptualization, design, and drafting of the manuscript. HN, MA, BK, AN, NA, and AS: acquisition, analysis, and interpretation of data and technical and administrative support. SK, SA, and AS: critical review. RS, ST, and NA: statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The 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.

Publisher's note

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The effect of telerehabilitation on balance in stroke patients: is it more effective than the traditional rehabilitation model? A meta-analysis of randomized controlled trials published during the COVID-19 pandemic

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Objective: Telerehabilitation and telemedicine have gradually gained popularity. In 2019, the outbreak of COVID-19 started in Wuhan and then spread across the world. To date, most countries have opted to coexist with the virus. However, patients, especially those who have suffered a stroke, should take measures to avoid being infected with any disease as much as possible since any infectious disease can lead to adverse events for them. Telerehabilitation can be beneficial to stroke patients as they are less likely to be infected by the virus. In recent years, several studies on telerehabilitation have been conducted globally. This meta-analysis aimed to investigate the effects of telerehabilitation on the balance ability of stroke patients, compare the efficacy of conventional rehabilitation with telerehabilitation, explore the characteristics of telerehabilitation and conventional rehabilitation, and provide recommendations for rehabilitation programs in the context of the global pandemic.

Methods: We searched Pubmed, Embase, the Web of Science, and The Cochrane Library databases from 1 January 2020 to 31 December 2022 for randomized controlled trials published in English that evaluated the improvement of balance function in stroke patients after telerehabilitation and compared the differences between telerehabilitation (TR) and conventional rehabilitation (CR). The random-effects model was utilized to calculate mean differences (MDs) with 95% confidence intervals (CIs) to estimate intervention effects. Statistical heterogeneity was assessed according to the I^2 values. The risk of bias was measured using the Cochrane risk-of-bias assessment tool.

Results: We included nine studies in the system evaluation, all of which were included in the pooled analysis. All outcomes in the experimental and control groups improved over time. The comparison between groups concluded that people who received the telerehabilitation intervention had a significant improvement in the Berg Balance Scale (MD = 2.80; 95% CI 0.61, 4.98, $P < 0.05$, I2 = 51.90%) and the Fugl-Meyer Assessment (MD = 8.12; 95% CI 6.35, 9.88, $P < 0.05$, I2 = 0) compared to controls. The Timed Up and Go test (MD = −4.59; 95% CI −5.93, −.25, $P < 0.05$, $I^2 = 0$) and Tinetti Performance-Oriented Mobility Assessment—Balance (MD = 2.50; 95% CI 0.39, 4.61, $P < 0.05$) scored better in the control group than in the experimental group. There were no significant differences in other outcomes between the two groups.

Conclusion: Studies on changes in medical conditions during the COVID-19 pandemic also demonstrated that, for stroke patients, telerehabilitation achieves similar effects as the conventional rehabilitation model and can act as a continuation of the conventional rehabilitation model. Owing to the different equipment and intervention programs of telerehabilitation, its curative effect on the static balance and reactive balance of stroke patients may be different. Currently, telerehabilitation may be more conducive to the rehabilitation of patients' static balance abilities, while conventional rehabilitation is more effective for the rehabilitation of patients' reactive balance. Therefore, further studies are needed for investigating the difference in efficacy between varied devices and telerehabilitation programs. Further research is needed on static and reactive balance. In addition, such research should have a large body of literature and a large sample size to support more definitive findings based on the context of the COVID-19 pandemic.

Systematic review registration: CRD42023389456.

KEYWORDS

COVID-19, stroke, telerehabilitation, meta-analysis, balance, rehabilitation, telemedicine

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV2). The rapid spread of COVID-19 has led to major challenges to the world since it was first detected in Wuhan, China, at the end of 2019 (1, 2). By 12 January 2023, the number of confirmed cases related to COVID-19 had exceeded 660 million, including a staggering 6.69 million deaths (3). As of the writing of this article, the associated diagnoses and deaths were higher as the world's most populous country, China, has opened up. The morbidity and mortality of COVID-19 are much higher than those of common influenza, and the infection can cause persistent symptoms such as headache, fatigue, and dyspnea, which is called long COVID-19 (4–6). Every infection with COVID-19 causes great harm to the human body, and infection with COVID-19 is more likely to lead to adverse events for stroke patients or other people who are already affected by some type of disease. Given that COVID-19 is a highly contagious disease, medical facilities can be a source of infection, and new methods to avoid face-to-face contact between medical staff and patients are urgently needed (7). In the current situation, telemedicine has become one of the important options for providing medical services that can reduce the possibility of patients being infected with the virus by reducing face-to-face contact (8, 9). Telerehabilitation is the delivery of rehabilitation services to patients at a distance through information and communication technologies (10, 11). Remote communication between patients and physical therapists or rehabilitation professionals can occur through a variety of media, such as phone calls, text messages, Internet apps, Internet-based video conferencing, or virtual reality programs (12, 13), which enables rehabilitation services to be delivered over the Internet, effectively reducing patient visits to hospitals, costs, and the likelihood of infection. Balance is a complex function that encompasses dynamic balance and static balance (14). It is a major determinant of community ambulation and gait performance following strokes (15). The main obstacle to independence in daily living for stroke patients is the impairment of balance caused by the stroke (16). Approximately 75% of individuals with stroke in China have motor dysfunction, and 40% of them have a severe disability (17). Stroke survivors often have deficits in motor control, resulting in decreased balance (18, 19). Good motor control enables the body to maintain an upright posture to maintain balance; poor posture control will adversely affect the body's balance (20). Decreased static and dynamic balance is a major risk factor for falls in stroke patients (21, 22) and limits their ability to perform activities of daily living (23). They often lose their balance due to balance disorder, which leads to serious injury (24, 25). Therefore, one of the main goals of stroke rehabilitation is to restore the patient's functional balance (26), and the restoration of postural control is a prerequisite for the patient to perform activities of daily living independently (27). Given the importance of balance in the prognosis of stroke survivors and because we consider that the meta-analysis should be more fine-grained in the area of stroke rehabilitation to yield greater clinical significance, we chose to conduct the study from the perspective of balance in stroke patients rather than assessing the various aspects of change in stroke patients as a result of telerehabilitation. Despite the importance of balance function in stroke patients, previous studies remain incomplete and limited by traditional rehabilitation programs (28), making it important to investigate the effects of telerehabilitation on balance function in stroke patients. In recent years, several randomized controlled trials (RCTs) have been conducted to compare the effects of telerehabilitation with conventional rehabilitation in patients after stroke (29). These studies have shown that telerehabilitation is equal to (9, 30) or superior to conventional rehabilitation in terms of improving balance function in stroke patients (31–33). Although there have been some studies on telerehabilitation before, the COVID-19 pandemic has greatly changed all aspects of people's lives worldwide and impacted the conventional diagnosis and treatment model. As a result, stroke survivors have limited opportunities to obtain outpatient rehabilitation treatment (33); therefore, the application and effect of telerehabilitation in patients after a stroke may be different from the past. Moreover, a lot of innovative findings have been published in recent years, and discoveries in related fields are updated. Besides, previous meta-analyses have not concluded whether telerehabilitation is superior to conventional rehabilitation (29). This study aimed to explore the benefits of telerehabilitation in the rehabilitation of balance function after stroke during the COVID-19 pandemic using a meta-analysis framework, to research the characteristics of the outcomes brought by the two types of rehabilitation, and understand which modality, telerehabilitation or conventional rehabilitation, is more beneficial for patients to finally provide a reference for the rehabilitation mode of patients during the pandemic. Moreover, the defects and deficiencies of related research were discussed in this study to provide a reference for further research.

Methods

This meta-analysis followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary material 1) (34, 35). This review was registered with Prospero with the unique identifier CRD4202 3389456.

Search strategy

We searched Pubmed, Embase, the Web of Science, The Cochrane Library, and the Joanna Briggs Institute databases for articles from 1 January 2020 to 31 December 2022. The framework of Population, Intervention, Comparator, and Outcome (PICO) was used to search for eligible studies with the search terms stroke (P), telerehabilitation (I), and postural balance (O). The detailed search strategy can be found in Supplementary material 2. In addition, we adapted the terminology to suit the requirements of each database. References to systematic reviews with similar research questions were also manually searched.

Criteria for considering studies for this meta-analysis

The inclusion criteria were as follows: (1) the study was conducted in English; (2) the efficacy of telerehabilitation after stroke was evaluated using varied modes; (3) an RCT design was used; and (4) the literature was published between 1 January 2020 and 31 December 2022. Studies that were not randomized or designed with one arm were excluded, as were studies that examined the technical components of telerehabilitation systems. According to the above criteria, the literature was imported into Endnote and Excel and evaluated by four reviewers in two stages: first the title and abstract, and then the full text. If two reviewers did not agree, the other reviewer resolved the disagreement.

Data extraction and management

To extract prespecified data, two independent reviewers used prefabricated Excel sheets, including the study title, first author information, year of publication, participants, experimental group, control group, intervention and control protocol, follow-up, and the results of outcomes. We used Engauge Digitizer 11.1 (45) to extract data from figures when quantitative data were not reported in text or Supplementary material. For missing data, we emailed the author requesting availability and indicated that we would acknowledge him accordingly. Data were extracted as the mean (SD) of change before and after treatment and then compared between groups. When these values were not given in the included studies, they were calculated using the equations in the new edition of the Cochrane Handbook for Systematic Reviews of Interventions (46).

Risk of bias assessment for the included studies

The Cochrane collaborative tool (47) was utilized by two researchers independently for estimating the risk of bias in the included studies. High risk of bias, low risk of bias, and unclear risk of bias were used to classify the included studies, which addressed the following sources of bias: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and outcome assessors); (3) loss bias (incomplete result data); (4) reporting bias (selective reporting); and (5) other sources of bias. Discrepancies were resolved by discussion or consultation with a third investigator.

Statistical analysis and outcome interpretation

All data analyses and graphical displays were performed using the STATA17.0 software. Post-intervention means and standard deviations were entered into STATA by one author and checked by another author. The values of the post-intervention outcomes were combined. The mean difference (MD) and 95% confidence

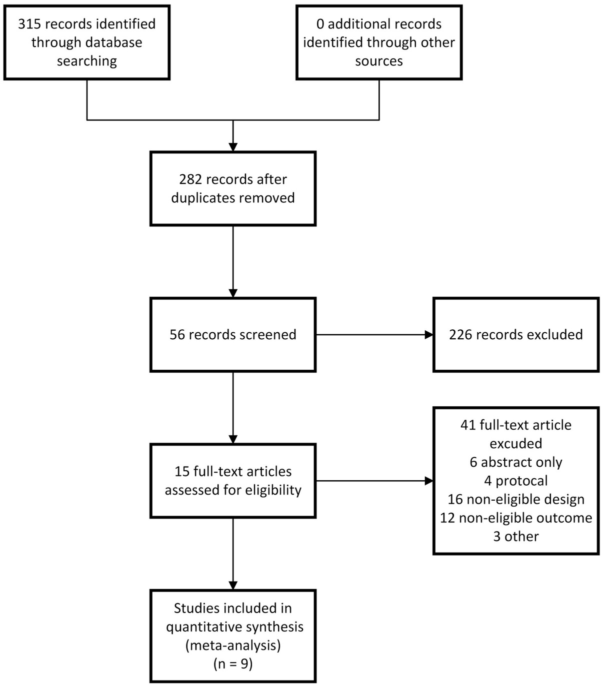

FIGURE 1
A flow diagram of the literature search and study selection procedure.

interval (CI) for all outcomes were calculated using a random effects model (48). Subsequently, the *P*-values were statistically tested. Heterogeneity was assessed visually by forest plots and I^2 statistics. The sensitivity analysis was conducted for the most important outcome.

Results

Results of the research

A total of 315 unique records were initially retrieved in our literature search, leaving 282 records after removing duplicates, which were reduced to 56 records after title and abstract screening. After careful full-text screening, nine RCTs (328 patients) (9, 30–33, 49–52) were identified to comply with the request of our systematic review and were included in the meta-analysis. Each study was published in English between 1 January 2020 and 31 December 2022. The flowchart of the search strategy and the study selection process is presented in Figure 1. Detailed search strategies are provided in Supplementary material 1.

Characteristics of the included studies

The demographic characteristics, intervention modalities, outcomes, and main results of the included studies are provided in Table 1. The studies were published between 1 January 2020 and 31 December 2022. Overall, 328 patients were treated and evaluated, and the number of patients ranged from 17 to 61. All patients had a subacute or chronic stroke. Telerehabilitation interventions were varied (Nintendo Wii, Microsoft Kinect, or customized devices). Among them, Shih-Ching Chen et al. (30), together with Melisa Junata et al., used Microsoft Kinect (33), Elena Marques-Sule et al. utilized Nintendo Wii (32), and the intervention devices used in the remaining studies were customized. A control group was set up in all studies, except for Wu et al. (31), who added telephone follow-up with the conventional means of rehabilitation as the control group. In the other studies, there were only conventional forms of rehabilitation in the control group. All studies measured post-intervention outcomes in terms of time, and post-intervention scores were compared between groups in this review. The types of outcomes varied among the studies. The primary outcomes (Table 2) of the balance function were as follows: BBS, a 14-item balance scale that evaluates balance in different postures (53); TUG, expressed in terms of time, is a test that commonly evaluates the functional movement required for sitting, standing, and walking (54); S-TIS 2.0, a tool that evaluates dynamic sitting balance and trunk control in stroke patients (38); S-PASS, a 12-item scale (40) that assesses the ability to balance in three positions (lying down, sitting, and standing); S-FIST, a clinical functional assessment of sitting balance in adults with stroke (39); TIS, a scale that assesses static and dynamic sitting balance and trunk coordination (55); FMA, an assessment test that evaluates measures of limb movement, balance, sensation, joint range of motion, and pain (56); POMA, a 16-item scale (9 balance-related items and 7 gait-related items) (32); and ABC, a scale that estimates individual confidence in a sense of balance (57). A funnel plot was constructed for the most reported outcome in the included studies.

Methodology quality

The methodological quality of each study is shown in Figure 2, and all studies assessed using the Cochrane Collaboration risk-of-bias tool are shown in Figure 3. All of the studies were RCTs with clear random sequence generation and allocation except for one of the trials (30), which only reported that the patients were randomly assigned but did not specify the method of randomization or how the groups were assigned to avoid selection bias. One study (49) indicated that it was difficult to blind caregivers, therapists, and patients due to the nature of the intervention. Two studies (9, 31) did not report blinding, while the remaining studies reported well-developed blinding. Most studies had fewer data on incomplete outcomes, except for two studies (31, 49). Four studies (9, 30, 31, 49) had possible reporting bias since the study protocols were not available. In addition, they reported more outcomes, which may be associated with overreporting and a higher risk of bias. In terms of other biases, only one study (32) provided a detailed description of the aspects, including financial support, while all other studies were unclear.

Intervention effect

Comparison 1: Berg balance scale. Telerehabilitation vs. conventional rehabilitation

The Berg Balance Scale (BBS) is a tool globally known to evaluate balance and has been reported to be reliable and valid in

TABLE 1 Characters of study's include in this meta-analysis, k = 9.

Reference	Patients (exp/ctrl)	Experimental	Control	Dosage	Outcomes	Key findings
Chen et al. (30)	30 (15/15)	Telerehabilitation based on a Kinect camera-based interactive telerehabilitation system, including three commercially available video games, focusing on participants' balance, weight bearing, strength, weight shifting, and walking	CT, including sitting to standing movements, balance exercises, standing, overground walking, and facilitation or strengthening of the paretic limb. Therapists adjust the conventional physiotherapy according to the functional status of each participant	40 min/d, 3 d/w, 4 m	BBS, TUG	No significant differences were found
Salgueiro et al. (51)	49 (20/29)	APP plus CT. Users have been able to voluntarily access the exercises guide (description, photo and video) and to confirm its performance. Participants were asked to perform 10 repetitions of each of the 32 exercises proposed in the program and were encouraged to perform as many exercises as possible, respecting their perception of tiredness, taking as many breaks as they found necessary	CT, which consisted of face-to-face session of therapeutic techniques such as muscle stretching to reduce hipertonicity or spasticity, passive and functional mobilization of body segments affected by stroke, practice of sitting and standing posture and gait, task and aerobic training as cycling or treadmill training. The techniques used were chosen at the discretion of the physiotherapist in charge following the clinical practice guidelines. The intervention was totally adapted and personalized to the needs and capacities of the patient. Participants maintained their usual dose of treatment during participation in this study	20 min/d, 5 d/w, 3 m	BBS, S-TIS2.0, S-PASS, S-FIST	No significant differences were found
Salgueiro et al. (52)	30 (15/15)	Home-based core-stability exercises plus CT. The core stability training conducted during hospitalization was continued. All the training was made by experienced neurophysiotherapists and was monitored and talked through the APP	CT, including therapeutic techniques such as muscle stretching, passive and functional mobilization of the affected body segments, balance exercises and gait training	1 h/d, 2 d/w, 12 w	BBS, S-TIS2.0, S-PASS, S-FIST	Improvement in S-TIS2.0
Lee et al. (9)	17 (9/8)	40-min, non-face-to-face, dance-therapy plus CT. Dance classes begin with a warm-up while sitting, which transition into chair and/or standing choreography; which follows by dance-skill practice	CT, receiving conventional physical therapy for the duration the experimental group receives therapy (the dance program in addition to existing conventional physical therapy)	40 m/d, 2 d/w, 3 w	BBS, TUG, TIS	No significant differences were found
Junata et al. (33)	30 (16/14)	A Kinect-based Rapid Movement Training. Assessments for pre- and post-training included "lean-and-release" assessment and clinical score measures of balance confidence, balance, motor functioning, and independent mobility. The Kinect-based rapid movement training platform system prompted the RMT group participants with a limb (arm or leg) and a direction cue on a screen and tracked the 3D trajectory and timing of their movements. Participants were encouraged to perform arms and legs movement in 22 different directions as quickly and as far as possible. The 22 directions were randomized and were repeated four times	CT, the exercises include balance and functional weight-shifting training: sitting-to-standing (using a stool), lateral stepping (walk 3 m back and forth), forward and backward stepping (5 times right leg steps first and 5 times left leg steps first), forward walking for five meters (walk 3 m back and forth, turn right at one end and turn left at one end), stepping up and down (5 times right leg steps first and 5 times left leg steps first), and throwing and catching plastic ball (using a soft volleyball) or small bean bag	1 h/d, 3 d/w, 7 w	BBS, TUG, FMA, ABC	Improvement in BBS, TUG, FMA

(Continued)

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TABLE 1 (Continued)

Reference	Patients (exp/ctrl)	Experimental	Control	Dosage	Outcomes	Key findings
Jarbandhan et al. (50)	30 (20/10)	Home-based, semi-supervised physiotherapy program, the home-based physiotherapy program included stair climbing, sit-to-stand exercise and walking. The physiotherapist provide weekly telephone encouragements and instructions	CT,none is given if no physiotherapy is requested by the patient	70 min/d, 3 d/w, 8 w	BBS	No significant differences were found
Wu et al. (31)	61 (30/31)	TCMeeting V6.0 plus CT. The system consists of a computer, a projector, a camera, and a data storage system. The patient installs the system on a computer at home, and the rehabilitation engineer and rehabilitation nurse perform a personalized remote rehabilitation instruction twice a week. The rehabilitation process is divided into two phases, including health education, physical strength training, balance training, breathing training, walking training and other training for patients	CT plus telephone follow-up.During the hospitalization, the patients in the control group received routine early rehabilitation guidance and routine nursing measures. The main contents were the normal limb position, bed position transfer, and joint activity maintenance training. After discharge, Patients in the control group received only routine rehabilitation and nursing measures, including dietary guidance, medication guidance, and rehabilitation guidance, which were conducted by telephone follow-up once a week. Patients can go to the rehabilitation clinic to get rehabilitation instructions as needed	0.5 h/d, 2 d/w, 12 w	BBS, TUG, FMA	Improvement in BBS,TUG,FMA
Marques-Sule et al. (32)	29 (15/14)	Wii Fit VR plus CT. Participants of VRWiiG received, in addition to conventional PT, a virtual rehabilitation program using Nintendo Wii with the Wii Remote and Wii Balance Board. The Wii Balance Board is a lightweight board that calculates the weight and pressure that is exerted on it, detecting the displacements of the pressure center, thus allowing to train balance. Each session was divided into (1) lower limb balance training (15 minutes) and (2) upper limb training (15 minutes). Each game was performed as 2 sets with a 1-minute rest interval between each game, although time for the games and the intervals were adapted to the patient's capacity	CT, including 7 different techniques based on stroke guidelines: (1) warm-up (stationary bicycle, 15 minutes); (2) mobility and strengthening lower limb exercises in supine position (3 series,15 repetitions); (3) active-assisted/passive lower and upper limb kinesiotherapy (3 series, 15 repetitions); (4) upper limb strengthening exercises using weights and elastic bands (3 series, 15 repetitions); (5) balance, stability, and coordination exercises (3 series, 15 repetitions); (6) walking reeducation exercises with emphasis inweight transfer, swing phase, step and stride length, and training with obstacles (10 minutes); (7) cool-down stretching and mobilizations of lower and upper limbs adapted to characteristics of each participant (10 min), in the university rehabilitation clinic	0.5 h/d, 2 d/w, 4 w	BBS, TUG, POMA	Improvement in BBS,TUG and POMA
Chen et al. (49)	52 (26/26)	Home-based telerehabilitation. Patients assigned to the TR group participated in rehabilitation training at home with the Telemedicine Rehabilitation System (TRS) under the therapists' guidance. The TRS consists of a therapist end, a network data system and a patient end. Therapists supervise the patients to conduct occupational therapy (OT)/physical therapy (PT) and electromyography-triggered neuromuscular stimulation (ETNS) by live video conferencing via TRS	CT, including occupational therapy (OT) and physical therapy (PT) and electromyography-triggered neuromuscular stimulation (ETNS), training in the outpatient rehabilitation department, and the training was conducted face-to-face with the rehabilitation therapists	160 min/d, 5 d/w, 2 w	FMA	Improvement in FMA

BBS, Berg Balance Scale; TUG, Timed Up and Go Test; FMA, Fugl-Meyer Assessment; TIS, Trunk Impairment Scale; S-TIS2.0, The Spanish-version of the Trunk Impairment Scale 2.0; S-PASS, Spanish-version of Postural Assessment for Stroke Patients; S-FIST, Spanish-version of Function in Sitting Test; ABC, Activities specific Balance Confidence Scale; POMA, Tinetti performance-oriented mobility assessment.

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TABLE 2 Outcomes.

Assessment scale	Reference
(1) Berg balance scale (BBS)	Downs (36)
(2) The timed up and go (TUG)	Browne and Nair (37)
(3) The Spanish version of the trunk impairment scale 2.0 (S-TIS 2.0)	Cabanas-Valdés et al. (38)
(4) The Spanish version of the function in sitting test (S-FIST)	Cabanas-Valdés et al. (39)
(5) The Spanish version of the postural assessment scale for stroke patients(S-PASS)	Benaim et al. (40)
(6) Fugl-Meyer assessment (FMA)	Gladstone et al. (41)
(7) Activities specific balance confidence scale (ABC)	Powell and Myers (42)
(8) Tinetti performance-oriented mobility assessment (POMA)	Tinetti (43)
(9) Trunk impairment scale (TIS)	Verheyden et al. (44)

cases of stroke (58, 59). The internal reliability of BBS in the elderly and stroke patients was 0.98 and 0.97, respectively (60). It consists of a series of 14 functional balance tasks to evaluate balance in different postures, including maintaining a quiet posture, sitting, transferring weight and stretching, turning in place, standing on one leg, and maintaining a tandem posture (30, 53). Each task is scored on a 5-point scale (from 0 to 4). The value 0 indicates an inability to perform the task, and the value 4 indicates the ability to complete the task according to a predetermined standard. The maximum score is 56 points. As provided in Figure 4, eight studies containing 275 patients reporting BBS were analyzed. The analysis was performed using MD with a random effects model and a confidence interval (CI) of 95%. The analysis showed a significant difference between TR and CR (MD = 2.80; 95% CI 0.61, 4.98, I2 = 51.90%). The heterogeneity of the meta-analysis was significantly reduced by sensitivity analysis after excluding the study by Melisa Junata et al. (33) from the meta-analysis. There was still a significant difference between TR and CR (MD = 3.89; 95% CI 1.89, 5.88, I2 = 16.26%), and the funnel plot is provided in Figure 5.

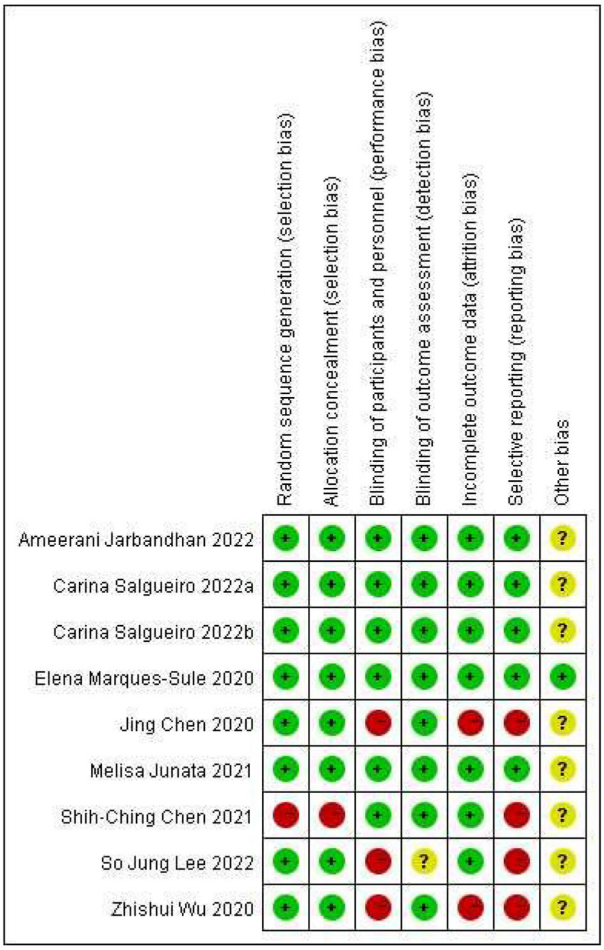

FIGURE 2
Risk-of-bias summary of all items for each included study.

Comparison 2: timed up and go test. Telerehabilitation vs. conventional treatment

The Timed Up and Go (TUG) test is commonly used to examine functional mobility, balance, and fall risk (33, 44, 53, 61). A cone is placed 3 m from the front of the chair, and participants are asked to stand up, walk 3 m to the cone, walk around the cone, walk back, and sit down (30). The score showed excellent intra-rater, inter-rater, and retest reliability in patients with chronic stroke (62). As shown in Figure 6, a total of five studies with 167 participants were included in the meta-analysis. The analysis was performed using mean difference (MD). There was a significant difference between TR and CR for the Timed Up and Go test (MD = −4.59; 95% CI −5.93, −3.25, $I^2 = 0$).

Comparison 3: the spanish version of the trunk impairment scale 2.0. Telerehabilitation vs. conventional rehabilitation

The S-TIS 2.0 is a clinical test that assesses movement disorders and is a reliable scale for evaluating dynamic sitting balance and trunk coordination in stroke survivors (38). As shown in Figure 7A, two studies containing 79 participants were included in the meta-analysis. Here, the analysis was also performed using MD with a random effects model, and the analysis showed no significant difference between TR and CR (MD = 1.37; 95% CI −1.85, 4.60, $I^2 = 65.61\%$).

Comparison 4: Spanish version of postural assessment for stroke patients. Telerehabilitation vs. conventional rehabilitation

The PASS is suitable for evaluating the postural abilities of stroke patients in the 1st months after stroke in a neurological and rehabilitation context. Among the different postural scales dedicated to stroke patients, the PASS has undergone one of the most complete validation phases (40). As shown in Figure 7B, two studies with a total of 79 participants were included in the meta-analysis. The analysis was also performed using MD with a random effects model, and the results showed no significant difference between TR and CR (MD = −0.12; 95% CI −3.56, 3.32, $I^2 = 1.88\%$).

Comparison 5: Spanish version of function in sitting test. Telerehabilitation vs. conventional rehabilitation

This scale consists of 14 test items corresponding to daily functional activities. Performance is scored by the therapist using a set of scoring criteria for all items. It can be used for a variety of purposes, such as evaluating functional sitting ability, describing sitting balance dysfunction, selecting the most appropriate treatment, and tracking changes in sitting balance over time (39). As shown in Figure 7C, there were also two studies with 79 participants that were included in the meta-analysis. The analysis was also performed using MD with a random effects model. No significant difference was found between TR and CR (MD = 2.24; 95% CI −0.96, 5.44, $I^2 = 0$).

Comparison 6: trunk impairment scale. Telerehabilitation vs. conventional rehabilitation

The Trunk Impairment Scale (TIS) for patients after stroke was designed to measure ADL (activities of daily living)-related selective trunk movements rather than the participation of the trunk in gross transfer movements (44). The TIS has no ceiling effect in subacute and chronic stroke patients and already appeared to be strongly related to measures of gait, balance, and functional ability in a cross-sectional study (55, 63). As shown in Figure 8A, a total of 17 patients in one study reported TIS, with no significant difference between TR and CR (MD = −2.14; 95% CI −6.91, 2.63).

Comparison 7: Tinetti performance-oriented mobility assessment—Balance (POMA-Balance). Telerehabilitation vs. conventional rehabilitation

The Tinetti Performance-Oriented Mobility Assessment (POMA) is a balance tool that was originally developed for use in the institutionalized, older adult population and contains both a balance and a gait component (43). The balance component of the test assesses the patient's ability to maintain postural control while sitting statically, while rising from a chair, during the period immediately after standing, while standing with eyes open and eyes closed, while turning 360°, and during perturbation. The gait component assesses symmetry, initiation, continuity, path, the base of support, and postural sway during gait (64). The POMA measures reactive balance by asking the patient to react to a perturbation and has items such as base of support and trunk sway, which are measured during gait and are aspects of balance that are not measured by the BBS. It also evaluates step length, floor clearance, the base of support, and path deviation during gait, which is not captured in the TUG. The POMA may be a more useful measure than the BBS or TUG in patients who have dynamic balance deficits during walking or have difficulty with reactive balance (65). As shown in Figure 8B, a total of 29 patients in one study reported POMA and the balance section in it. We found a significant difference in the balance section of POMA between TR and CR (MD = 2.50; 95% CI 0.39, 4.61).

Comparison 8: activities-specific balance confidence scale. Telerehabilitation vs. conventional rehabilitation

The 16-item ABC scale was used to evaluate older adults' fear of falling as a response to their confidence in their balance. As shown in Figure 8C, 30 patients in one study reported ABC with no significant difference found between TR and CR (MD = 3.97; 95% CI −9.31, 17.25).

Comparison 9: Fugl-Meyer assessment of motor recovery after stroke. Telerehabilitation vs. conventional rehabilitation

The FMA evaluates limb movement, balance, sensation, joint mobility, and pain (31) and is evaluated sequentially from the flaccid phase, the stagnation period, the combined movement period, the partial separation period, and the separation movement period based on the theory of Brunnstrom limb function recovery.

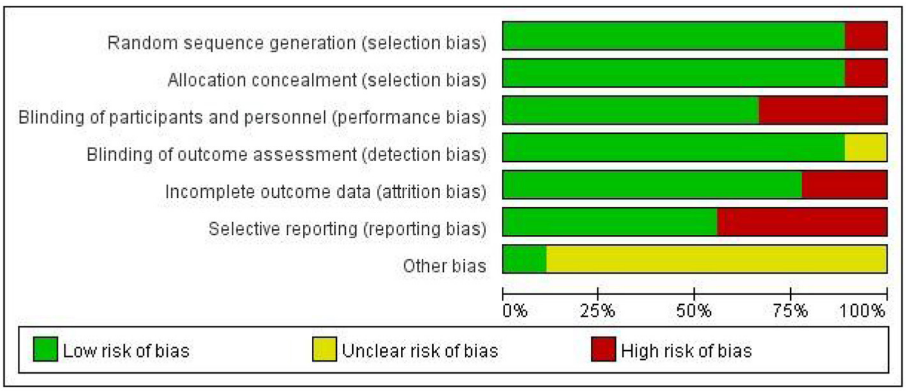

FIGURE 3
Risk-of-bias graph of all items shown as a percentage across all included studies.

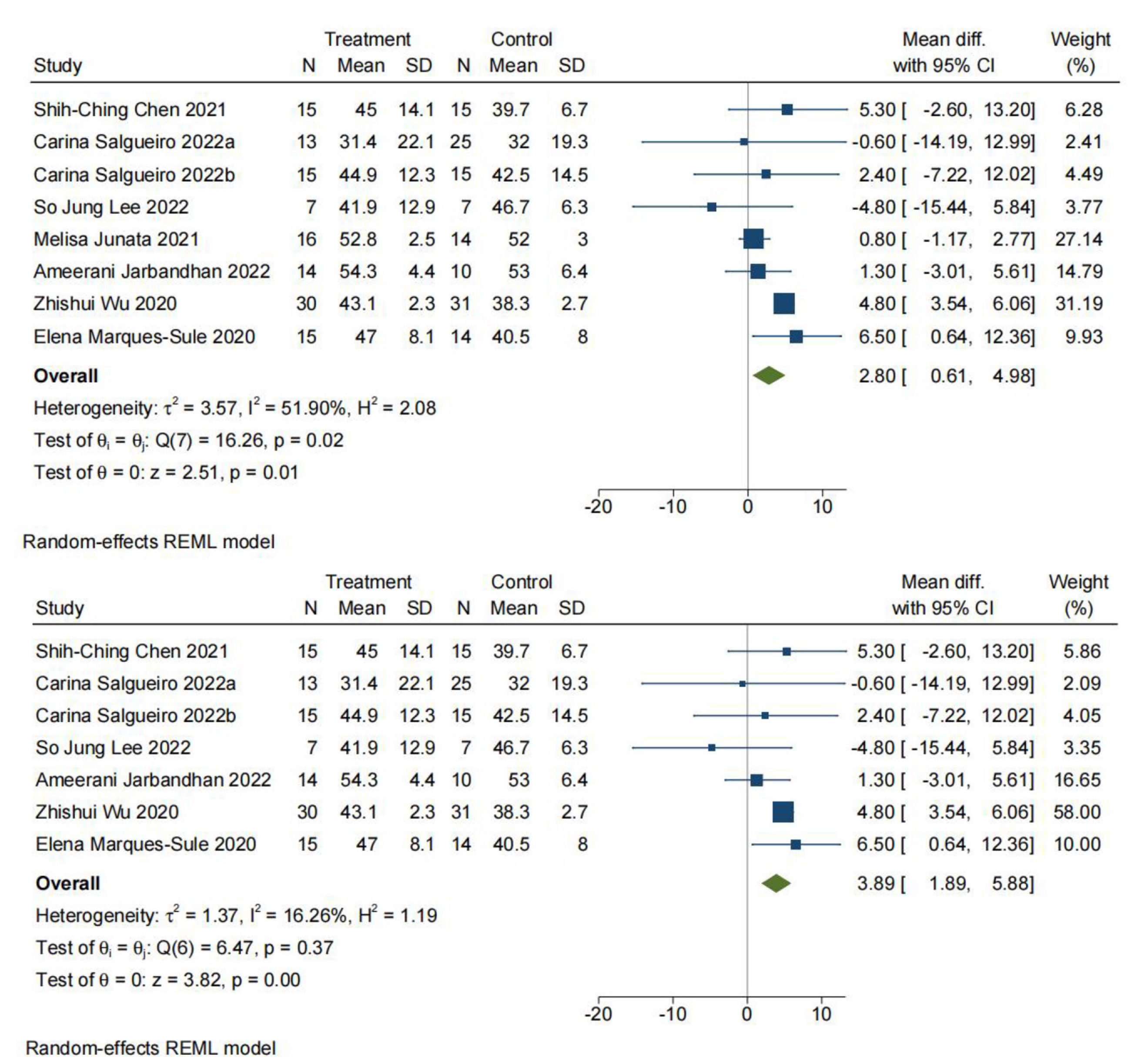

FIGURE 4
Comparison 1. Berg Balance Scale (BBS). Telerehabilitation vs. conventional rehabilitation. SD: standard deviation; 95% CI: 95% confidence interval.

Each project is divided into three levels, with 0 points (not completed), 1 point (partially completed), and 2 points (fully completed). The total score for the upper extremity is 66 points, and the total score for the lower extremity is 34 points out of 100 points (31). As shown in Figure 9, 143 patients from three studies were included in the meta-analysis, which showed a significant difference between TR and CR (MD = 8.12; 95% CI 6.35, 9.88, $I^2 = 0$).

Discussion

The purpose of this systematic review was to analyze and synthesize the evidence on the effectiveness of telerehabilitation interventions for patients after stroke compared to conventional face-to-face rehabilitation modalities against the background of the COVID-19 pandemic, as well as to assess which modality is more effective, telerehabilitation vs. conventional rehabilitation, to provide recommendations on the choice of rehabilitation modalities for patients after stroke during the pandemic. SARS-CoV-2 is a global pandemic that began in 2019, and the pandemic of SARS-CoV-2 was continuing until the writing of this manuscript, with mutations of the virus continuing and multiple new subtypes of the virus emerging. Each infection with a new coronavirus can be extremely damaging to the body. During the COVID-19 pandemic, patients, especially stroke patients, had limited access to outpatient rehabilitation. Telerehabilitation or the use of computer-assisted training systems can be used for stroke rehabilitation during the COVID-19 pandemic by minimizing face-to-face interactions and the risk of infection (33). We evaluated BBS, TUG, S-TIS 2.0, S-PASS, S-FIST, ABC, POMA—Balance, TIS, and FMA as outcome indicators for stroke patients, each partially reflecting the ability of patients after stroke to balance and the corresponding improvement after they have been rehabilitated.

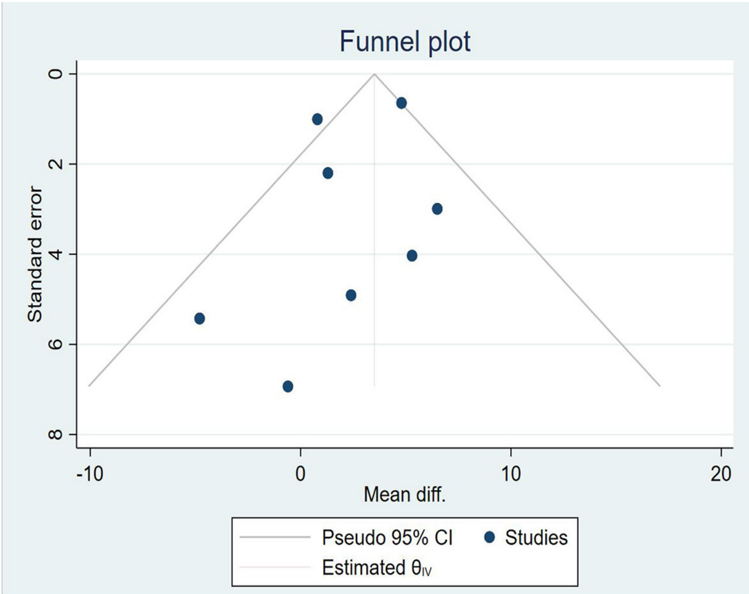

FIGURE 5
Funnel plot.

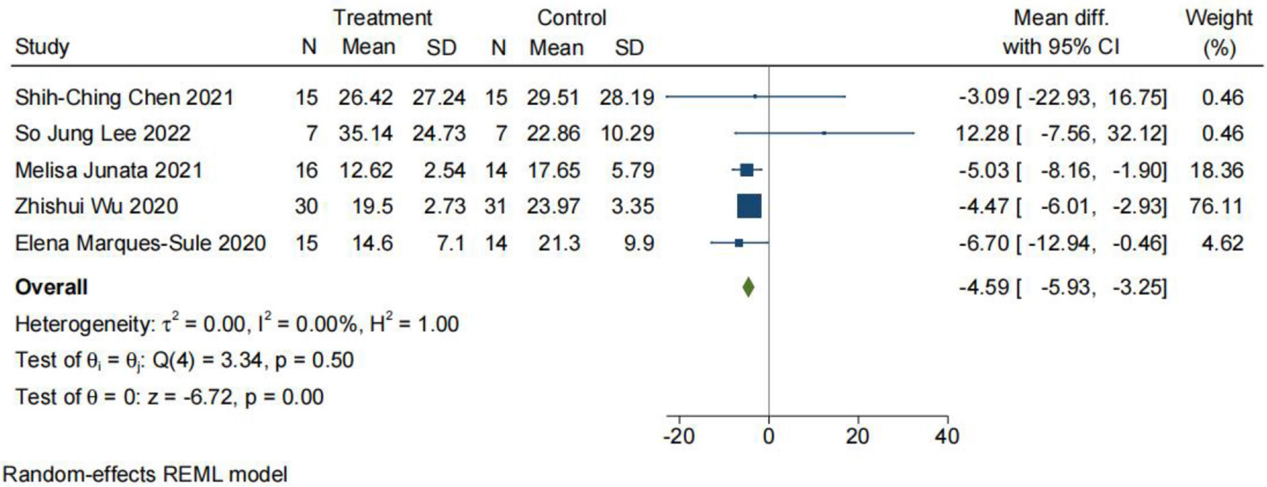

FIGURE 6
Comparison 2. Timed Up and Go (TUG) test. Telerehabilitation vs. conventional rehabilitation. SD, standard deviation; 95% CI, 95% confidence interval.

Generally, the intervention effects of the TR and CR groups were equivalent in all studies, among which BBS and FMA supported better efficacy of telerehabilitation; however, TUG and POMA—Balance supported better efficacy of the conventional rehabilitation model, with no statistical difference between the two groups in other outcomes. To the best of our knowledge, our study is the first to investigate the efficacy of telerehabilitation vs. conventional rehabilitation using data from studies conducted during the COVID-19 pandemic, and the results have been able to demonstrate that TR interventions possess the same efficacy as CR, in line with the results of previous studies (66). The coronavirus has already spread worldwide. Globally, nearly 2.8 million new cases and over 13,000 deaths were reported in the week of 9–15 January 2023. From 19 December 2022 to 15 January 2023, nearly 13 million cases and almost 53,000 new deaths were reported globally (67). The severity of the virus rampage may even be more serious since these are only the reported figures. To date, SARS-CoV-2 has a high mutation rate and continues to mutate at a rapid rate (67). In the long term, the COVID-19 pandemic will continue for a long time. Furthermore, the coronavirus may remain with humans like the influenza virus. Since stroke survivors are vulnerable, each infection may cause great harm before they fully recover. Therefore, stroke patients need to reduce any possible exposure to the virus. Telerehabilitation also plays an increasingly important role. In

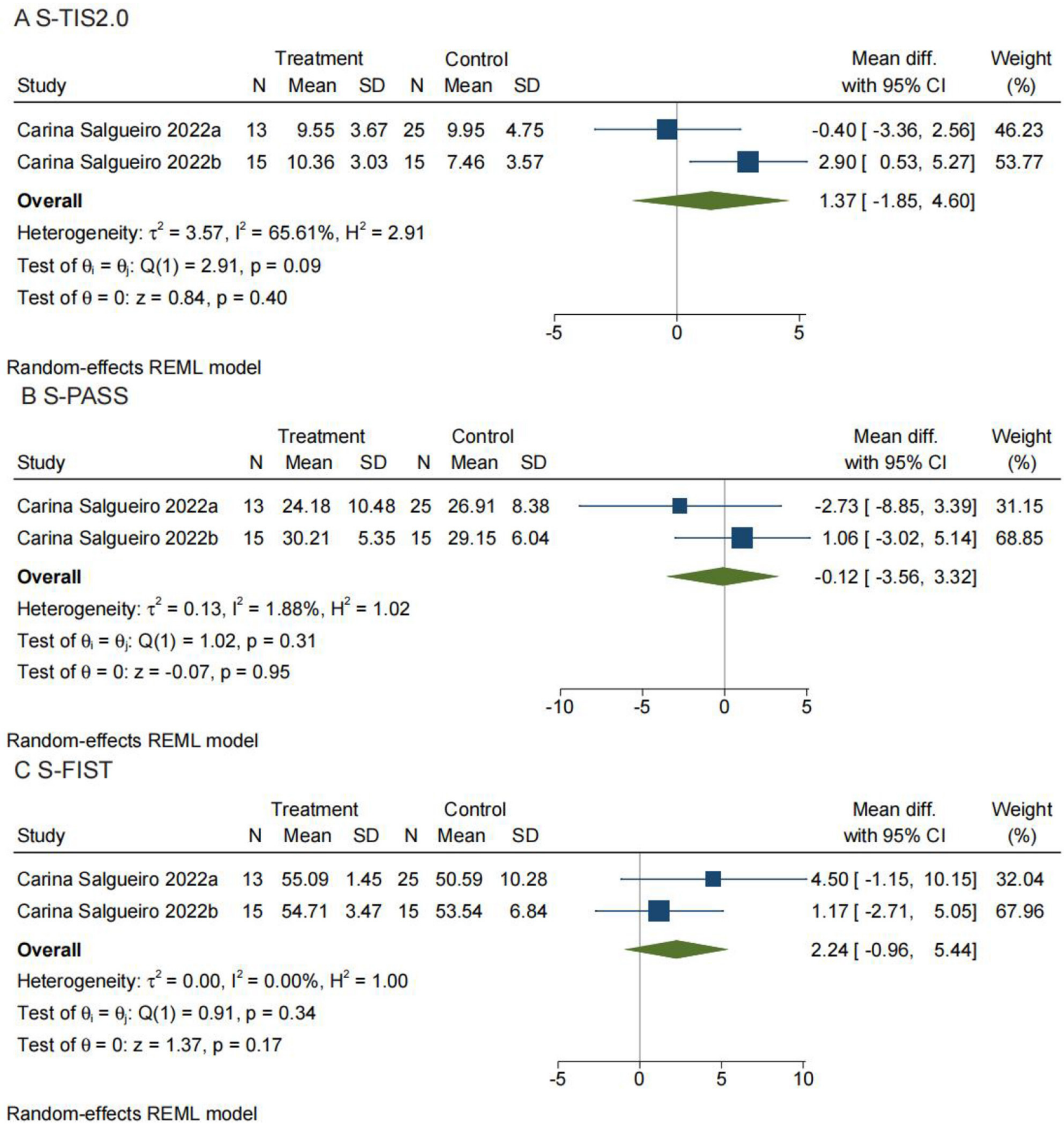

FIGURE 7
Comparisons 3, 4, and 5: **(A)** The Spanish version of the Trunk Impairment Scale 2.0 (S-TIS 2.0). Telerehabilitation vs. conventional rehabilitation. **(B)** The Spanish version of the Postural Assessment for Stroke Patients (S-PASS). Telerehabilitation vs. conventional rehabilitation. **(C)** The Spanish version of the Function in Sitting Test (S-FIST). Telerehabilitation vs. conventional rehabilitation. SD, standard deviation; 95% CI,95% confidence interval.

addition, it is important to conduct a meta-analysis utilizing data from studies published during the pandemic since patient care and access to health care have changed significantly. Additionally, it has been demonstrated that TR applies to all neurological disorders (66), and recent studies on neurological diseases also support this notion (68, 69).

With low heterogeneity, the greater improvement of BBS and FMA in the TR group compared to the CR group suggested that TR is more effective in promoting poststroke rehabilitation to some extent. The BBS and FMA scales have more content than other scales for assessing balance in sitting and standing positions and in some specific positions. Based on the content and characteristics of the BBS and FMA scales (24, 25), we suggest that telerehabilitation may be more useful for the rehabilitation of balance in sitting, standing, and specific static postures after stroke, while the rehabilitation of balance in locomotion and reactive

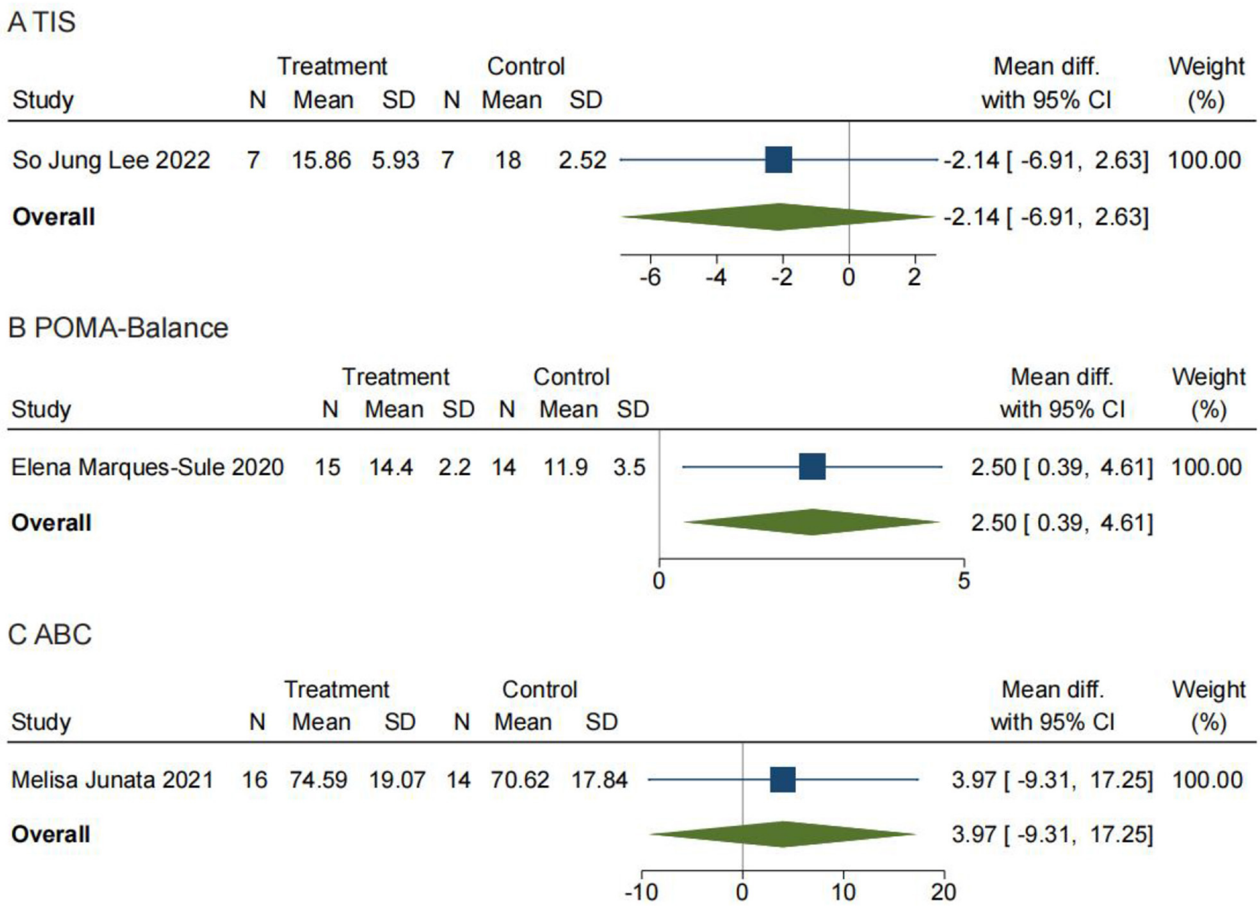

FIGURE 8
Comparisons 6, 7, and 8: **(A)** Trunk Impairment Scale (TIS). Telerehabilitation vs. conventional rehabilitation. **(B)** Tinetti performance-oriented mobility assessment—balance (POMA—Balance). Telerehabilitation vs. conventional rehabilitation. **(C)** Activities-specific balance confidence scale (ABC). Telerehabilitation vs. conventional rehabilitation. SD, standard deviation; 95% CI: 95% confidence interval.

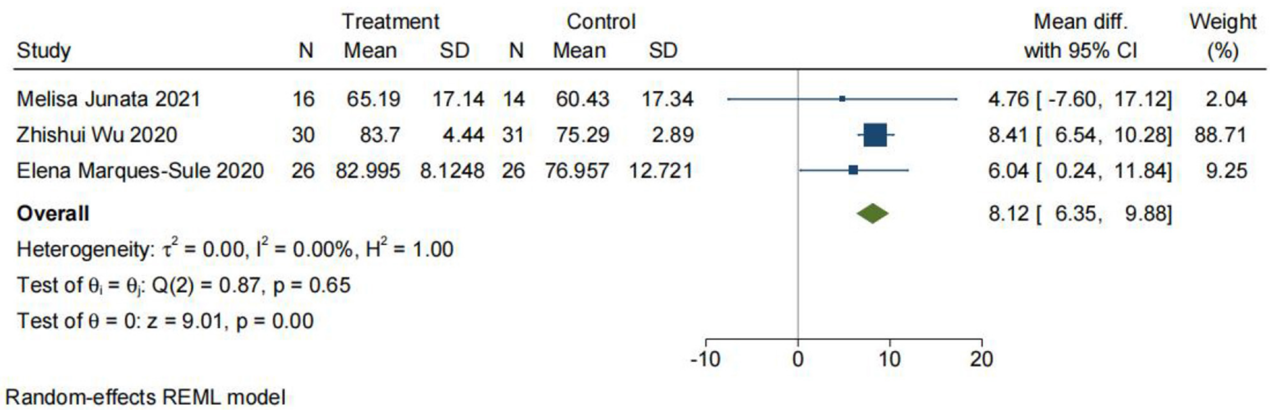

FIGURE 9
Comparison 9: Fugl-Meyer Assessment of Motor Recovery After Stroke (FMA). Telerehabilitation vs. conventional rehabilitation. SD: standard deviation; 95% CI: 95% confidence interval.

balance is similar or more effective in the conventional modality as the TUG and POMA—Balance results from our meta-analysis support this view.

Moreover, we found that different intervention devices and their corresponding intervention modalities may have a significant impact on the results of TR intervention in patients after stroke.

In two papers with the highest heterogeneity in this study (32, 33), one demonstrated an intervention based on Kinect with accompanying telerehabilitation and interactive body motion detection technology, while the other was based on Wii Fit with telerehabilitation and interactive body movement detection technology. The rest of the intervention devices and rehabilitation modalities in the TR group were customized on their own. We did not find any literature on different intervention devices and their intervention modalities during the meta-analysis. However, we may conduct corresponding research in the near future.

Finally, the question of how the effectiveness of telerehabilitation compares to that of conventional rehabilitation, which is more effective and which should be used, is no longer a question of which treatment is more appropriate for a particular disease group but rather what treatment is available to that group in the pandemic context. Since patients may not receive rehabilitation in the conventional model at all under the risk of pandemic infection and in the context of a lockdown brought about by the possible emergence of new variants of the virus (8), TR may become the only way for some patients to receive treatment and maintain their connection to society in a pandemic situation. With the further development of Internet technology and 5G, the advantages and adaptability of telerehabilitation have been increasingly reflected. In the meantime, telerehabilitation spares more healthcare expenses and allows more people to be treated while opening up a wider medical market, which is the call of the entire medical community as well as society as a whole. We have been able to demonstrate that TR can achieve similar rehabilitation results as CR. In the future, we will attempt to explore ways to achieve a better level of rehabilitation for patients through TR, which will be a focus of our study and will be beneficial to the majority of patients.

Strengths and limitations

The strength of this study is that we carefully screened the databases to include the most relevant randomized controlled trials in an attempt to provide a strong basis for decision-making and program planning for telerehabilitation. Additionally, during our investigation, we searched for studies that are currently lacking, such as different modalities of telerehabilitation interventions that may lead to different intervention effectiveness. Besides, our study incorporated the context of the COVID-19 pandemic as people's lives after the emergence of COVID-19 have been significantly different from those before the pandemic. We also propose that the efficacy of telerehabilitation vs. conventional modalities of rehabilitation may differ across patients in terms of physical function, which is worthwhile to conduct a correspondingly detailed study. This study also has inevitable drawbacks that need to be pointed out. First, the number of included studies was small, and the lack of sample size limited further findings. In addition, only one set of data was available for some outcome measures, which may have affected our statistical analysis. Additionally, our outcome indicators are all scales. Although the scales we analyzed are all the most used scales in clinical and research practice, it is undeniable that recall bias will inevitably occur in the assessment process of scales. Avoiding such deviations completely is very difficult (7). In terms of source, five of the nine studies were conducted in China and three in Spain, both of which had serious infections during the initial outbreak of COVID-19. However, the pandemic has become a global problem, and shortly, there will be no great differences in the distribution of the pandemic worldwide. During the literature search, we also identified from the literature sources that there may be significant regional differences in the application of telerehabilitation, and therefore, there is a need to promote telerehabilitation globally, especially outside of East Asia and Europe.

Conclusion

Telemedicine and telerehabilitation are currently gradually becoming hot topics, especially in the current COVID-19 pandemic. Admittedly, the public does not yet consider that telerehabilitation can replace the conventional modality of rehabilitation, but telerehabilitation has the potential to serve as a complement to the conventional rehabilitation modality. It can contribute to reducing the cost of rehabilitation and saving medical resources while minimizing social pressures on health care as well as extending the duration of patients' rehabilitation. Studies during the COVID-19 pandemic have demonstrated that, for stroke patients, telerehabilitation has similar efficacy to the conventional modality of rehabilitation while possibly having better efficacy in terms of static balance. However, the conventional rehabilitation modality is superior in terms of reactive balance. It is probably associated with the equipment that is used for the different interventions as well as the rehabilitation program. Meanwhile, this study revealed that more research on telerehabilitation for stroke patients and patients with other diseases is still needed and that different intervention devices and rehabilitation protocols will have to be investigated and compared. The overall quantity and quality of research still need to be improved sustainedly. Finally, it is particularly important to promote telerehabilitation worldwide, which could also contribute to the development of telerehabilitation and lead to a better prognosis for patients while providing more comprehensive and credible evidence for the study of the field.

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.

Author contributions

Execution: ZS, ZG, WW, and YaoL. Aanalysis: WW, MZ, WC, HX, and NM. Design, writing and editing of the final version of the manuscript, and contributed to the article and approved the submitted version: All authors.

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Conflict of interest

The 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1156473/full#supplementary-material

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Improving door-to-reperfusion time in acute ischemic stroke during the COVID-19 pandemic: experience from a public comprehensive stroke center in Brazil

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Background: The global COVID-19 pandemic has had a devastating effect on global health, resulting in a strain on healthcare services worldwide. The faster a patient with acute ischemic stroke (AIS) receives reperfusion treatment, the greater the odds of a good functional outcome. To maintain the time-dependent processes in acute stroke care, strategies to reorganize infrastructure and optimize human and medical resources were needed.

Methods: Data from AIS patients who received thrombolytic therapy were prospectively assessed in the emergency department (ED) of Hospital de Clínicas de Porto Alegre from 2019 to 2021. Treatment times for each stage were measured, and the reasons for a delay in receiving thrombolytic therapy were evaluated.

Results: A total of 256 patients received thrombolytic therapy during this period. Patients who arrived by the emergency medical service (EMS) had a lower median door-to-needle time (DNT). In the multivariable analysis, the independent predictors of DNT >60 min were previous atrial fibrillation (OR 7) and receiving thrombolysis in the ED (OR 9). The majority of patients had more than one reason for treatment delay. The main reasons were as follows: delay in starting the CT scan, delay in the decision-making process after the CT scan, and delay in reducing blood pressure. Several actions were implemented during the study period. The most important factor that contributed to a decrease in DNT was starting the bolus and continuous infusion of tPA on the CT scan table (decreased the median DNT from 74 to 52, DNT $\leq$ 60 min in 67% of patients treated at radiology service vs. 24% of patients treated in the ED). The DNT decreased from 78 min to 66 min in 2020 and 57 min in 2021 (p = 0.01).

Conclusion: Acute stroke care continued to be a priority despite the COVID-19 pandemic. The implementation of a thrombolytic bolus and the start of continuous infusion on the CT scan table was the main factor that contributed to the reduction of DNT. Continuous monitoring of service times is essential for improving the quality of the stroke center and achieving better functional outcomes for patients.

KEYWORDS

stroke, thrombolysis, COVID-19, quality of care, door to needle time

Introduction

Stroke is the second leading cause of death and the main cause of disability in Brazil and worldwide (1, 2). Since the proven benefit of thrombolysis for reperfusion in acute ischemic stroke (AIS) in 1995 (3), hospitals have implemented protocols, workflows, and training for physicians and nurses in all stages of the process, allowing for rapid assessment and treatment. Intravenous thrombolysis (IVT) with a recombinant tissue plasminogen activator (rtPA) has proven benefits up to 4.5 h from symptoms onset (4), but its effectiveness decreases over time.

Therefore, stroke teams worldwide have been making efforts to initiate reperfusion treatment as soon as possible after the patient arrives in the emergency department (ED). Several studies have attempted to identify the reasons for treatment delay and create strategies to reduce the time between arrival at the ED and the start of intravenous thrombolysis (door-to-needle time, DNT) (5–8). It has been well-demonstrated that the DNT can be much lower than the goal of <60 min, and there is currently a recommendation that at least 50% of treatments should be performed in <45 min (9).

In-hospital treatment delay may occur during any stage of acute stroke treatment, including patient triage, medical assessment, neuroimaging, blood sample collection and analysis, obtaining consent, treatment of high blood pressure, and the decision-making process (6, 10, 11). The implementation of protocols with a well-trained team and the division of duties in each stage may reduce treatment delay. Monitoring treatment times supports identifying the reasons for the delay and allows for structuring the service for better patient outcomes (12, 13).

The global COVID-19 pandemic has had a major impact on all aspects of emergency stroke healthcare, including the pre-hospital care system and in-hospital workflow. There has been a significant reduction in the number of stroke admissions and stroke patients treated with reperfusion therapy worldwide (14–17). Brazil recorded its first COVID-19 patient on 26 February 2020 and experienced rapid spread of the infection. Stroke team members had to make substantial adaptations to current stroke care protocols in emergency rooms due to the institution of infection control measures. Some centers have reported increased door-to-needle times during the COVID-19 pandemic, while others have noted no change (14, 17, 18).

The aim of this study is to assess rates of IVT treatment, evaluate the reasons for the delay in each stage of IVT treatment in a public stroke center, and propose and implement strategies to reduce treatment times based on the results obtained.

Methods

Hospital structure

Hospital de Clínicas de Porto Alegre (HCPA) is a public university hospital located in Southern Brazil that has had a well-structured acute stroke unit (ASU) in the ED since 2006 (19) and a comprehensive stroke unit (CSU) since 2012. It was the first hospital in Brazil to be licensed as a stroke center in 2012 by the Ministry of Health. Since 2013, after the implementation of the National Stroke Policy, the number of stroke centers in the region has increased from 2 to 16. This also included engagement with emergency mobile care service, the well-organized public pre-hospital Emergency Medical System (EMS). As a result of the aforementioned strategies, the overall number of thrombolysed patients has increased in the entire region, avoiding the burden on a single-stroke center. Since then, the number of thrombolysed patients in this hospital has remained stable between 70 and 80 patients per year.

The stroke center is staffed by a trained multidisciplinary stroke team, which includes four stroke neurologists who provide supervision and support to neurology residents. This occurs on-site during the day and by telemedicine during the night. Neurology residents provide on-site coverage during the day and on-call coverage from 6 p.m. to 8 a.m. The stroke team is available 24 h a day, 7 days a week, on a rotating schedule to support all stroke cases from arrival in the ED to the hospital discharge. Additionally, patients are followed up by the stroke team at the stroke outpatient clinic.

The hospital maintains a prospective data registry for all consecutive stroke patients to monitor the quality of stroke care. The diagnosis of AIS was confirmed by a computed tomography (CT) scan on admission. Acute stroke treatment protocols of the Brazilian Stroke Society/Brazilian Academy of Neurology (20, 21) were followed, which are in accordance with the American Stroke Association Guidelines (9).

Patient workflow and treatment protocols

The in-hospital workflow for stroke patients begins upon their arrival at the ED. At this moment, the stopwatch is started. The use of the stopwatch has been part of the stroke protocol since the hospital was recognized as a stroke center. Patients can arrive in two different ways: approximately 70% of the patients are brought by EMS (SAMU), while the remaining patients arrive by their own means (family vehicle, taxi, or bus). SAMU is trained in pre-hospital stroke care and operates within a network that allocates AIS patients among the three public stroke centers in the city of Porto Alegre since 2008 and among the 16 stroke centers licensed by the Ministry of Health since 2013.

SAMU notifies the destination hospital in advance that an IVT candidate is being transported. The patient is evaluated by a triage nurse, who then immediately directs the SAMU team to the ASU in the ED. The administrative receptionist opens the patient's file to allow access to the patient's medical records, and until this process is completed (which takes up to 10 min), no tests can be ordered. When patients arrive by their own means, they wait for triage and risk classification with other patients. Once a possible AIS is identified by the triage nurse, the patient is immediately transported to the ASU.

At the ASU, nurses and physicians simultaneously begin the patient's assessment and call the neurologist over the phone. Blood pressure and capillary glycemia are measured, and two venous accesses are punctured. Since 2018, all the supplies and medication needed to evaluate and treat patients with AIS (including blood sample tubes, blood pressure-lowering agents, and rtPA) have been stored in a stroke box located in the ASU.

All neurologists and residents are certified in the use of the National Institute of Health Stroke Scale (NIHSS). Acute stroke patients are assessed by neurology residents in the ED, where the severity of the neurological deficit on admission is evaluated using the NIHSS. The patient is monitored and taken, along with the stroke box, to the neuroimaging acquisition room, which is 225 m and 4 min 15 s from the ED. The elevator is still used on this route as the radiology service is on the second floor. Whenever the stroke neurologist is in the hospital, cases are discussed face-to-face with residents, and the images are assessed on a PACS workstation. Otherwise, all relevant clinical information and DICOM images are shared in real-time with the entire stroke team *via* a smartphone application (Join© App, Allm Inc. Tokyo, Japan), which is locally validated for use as a telemedicine device for stroke treatment assessment (22). After the neuroimaging acquisition, the patient returns to the ASU, and the stroke neurologist reviews the clinical and imaging data in the Join© App, deciding on reperfusion therapy with IVT or conservative treatment.

The times for treatment were collected from the medical records, including the time of arrival at the ED, time of risk classification (time of triage), time of the neurologist's call, time of the neurologist's arrival, time of the tPA bolus (registered by the nurse in the ED or on the smartphone application when the tPA bolus and infusion started on the CT scan table), and the CT scan time, which is collected in the first image. Reasons for treatment delay were collected from the medical records, stroke database, and Join© App.

Barriers identified prior to this study

Some factors that may possibly delay the patient's treatment were previously identified. (1) The neurology resident is on call from 6 p.m. to 8 a.m. and needs to go to the hospital to assess the patient. (2) The time required to open the patient's medical record delays the performance of laboratory tests and neuroimaging. (3) Blood sample collection is delayed whenever the lab collector is not available, resulting in a delay in neuroimaging acquisition; (4) The distance between the ED and the radiology service delays the neuroimaging acquisition and transportation back to the ED delays the start of IVT, when applicable; (5) Acquisition of CT angiography before transporting the patient back to the ED and acquisition of brain magnetic resonance imaging (MRI) for patients with unknown onset of symptoms also delay the initiation of treatment—MRI is not always available, and even the rapid protocol takes longer than CT scan. (6) The carrier to take the patient to radiology service was not always available; however, this issue was resolved in 2017 with the decision that the nursing staff and the emergency physician (or the neurologist) are allowed to take the patient to radiology, without having to wait for the carrier.

Influence of the COVID-19 pandemic on the acute stroke care pathway

Many stroke centers around the world have reported a decrease in the number of stroke admissions, intravenous thrombolysis, and mechanical thrombectomy volumes compared to the pre-COVID-19 era. The turning of health staff and hospital resources toward the COVID-19 emergency inevitably led to an important impairment in stroke care worldwide (16, 18, 23). Since the onset of the COVID-19 pandemic, Brazil has adopted unprecedented measures such as social isolation and nationwide lockdown at great economic cost.

Acute stroke protocols, including the adequate screening of symptoms and signs of COVID-19 infection, pathways for acute stroke treatments, and isolation of patients in protected areas, were adjusted according to the Brazilian guideline indications for the management of acute stroke care during the COVID-19 pandemic (18, 23). All stroke patients were tested for COVID-19 infection. Patients with unknown COVID-19 status were evaluated with appropriate personal protective equipment in the ED.

Study design

We conducted a prospective study in a public university hospital, Hospital de Clínicas de Porto Alegre (HCPA), over a 3-year period (January 2019 to December 2021). During 2019, we evaluated the reasons for the delay, and in 2019 and 2020, we implemented strategies to improve the door-to-reperfusion time. In 2020, the study was affected and therefore changed due to the coronavirus pandemic. Therefore, in 2020 and 2021, we evaluated the effects of the pandemic on the volume of stroke patients, thrombolysis rates, and reperfusion time. We included all consecutive patients with AIS who arrived at the ED and received IVT in the study. We excluded patients who had a stroke in the hospital and patients who received thrombectomy without IVT.

The main objective was to identify specific factors associated with delay in hospital treatment through prospective monitoring of all treatment times, from the patient's arrival in the ED to the start of IVT treatment. Table 1 shows the maximum expected times for each stage. Times above these targets were considered reasons for

TABLE 1 Recommended time targets for stroke care.

Times	Maximum expected time
Door-to-triage time	5 min
Triage-to-neurologist call (time from triage to the emergency physician call to the neurologist)	15 min
Neurologist call-to-neurologist evaluation	15 min
Door-to-CT	20 min
CT-to-needle time	20 min
Door-to-needle time (DNT)	60 min

Powers (9); Ruff (17).

the delay. DNT medians were analyzed according to the patient's clinical variables, means of transport to the hospital, and in-hospital procedures. We compared patients with DNT of ≤60 min with those with more than 60 min. We also described changes to the stroke protocol to improve treatment times during the study and the repercussion of the COVID-19 pandemic on acute stroke care.

Statistical analysis

Categorical variables were presented as proportions and comparisons were made using the $\chi 2$ or Fisher exact tests. Continuous variables were shown as a median and interquartile range (IQR) of 25–75%, and the Mann–Whitney U-test was used for comparisons. Comparisons were made according to DTN (≤60 min vs. >60 min). A p-value below 0.05 was considered to be statistically significant. In addition, multiple logistic regression analysis was performed to evaluate the independent factors in the stroke treatment related to DNT delay. In this study, we included the regression model variables based on results from other studies and on clinical observation and variables that had a p-value of <0.10 in univariate tests. All data were analyzed using SPSS for Windows version 20 (SPSS Inc, Chicago, IL). Informed consent was obtained from all patients or family members. The study protocol was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre.

Results

Between January 2019 and December 2020, 1,739 patients with suspected AIS were evaluated in the ED. Of these, 567 AIS cases were confirmed in 2019 and 753 in 2020, with 143 patients receiving IVT (82 in 2019 and 61 in 2020). In 2021, there were 1,038 suspected AIS cases, 789 confirmed AIS cases, and 113 patients received thrombolytic therapy. Data from 2021 were used for comparison with the main study period, which was 2019 and 2020. The median age was 69 years (ranging from 29 to 99 years), where 49% were men, and 69% of them arrived through SAMU.

Table 2 shows the median DNT according to baseline patient characteristics in 2019 and 2020. Patients with unknown onset of symptoms had slightly longer DNT time but without statistical significance. Patients who underwent an MRI on admission had a higher median DTN time compared to those who had a CT scan (96 min [IQR 85–113] vs. 70 min [55–92], $p = 0.61$). Patients with a previous stroke had a longer median DNT (84 [IQR 64–110] vs. 69 [56–87], $p = 0.05$), while patients who arrived through EMS had a shorter DNT (70 [IQR 57–87] vs. 80 [55–111], $p = 0.012$). Patients who received IVT bolus on the CT scan table had a shorter DNT compared to those treated at the ASU (52 min [IQR 39–71] vs. 74 min [IQR 62–94], $p < 0.0001$).

Table 3 shows the proportion of patients with DNT ≤60 min in the univariate analysis based on baseline characteristics. Patients with diabetes were more likely to be treated within ≤60 min (46 vs. 26%). However, patients with AF were treated later, with only 9% receiving treatment within ≤60 min compared to 28% receiving treatment after >60 min ($p = 0.01$). Patients treated on the CT scan table were more likely to receive IVT within ≤60 min when compared to patients treated in the ED (67 vs. 24%, $p = 0.0001$). Among the 143 thrombolysed patients, only 9 were assessed through brain MRI at admission, and only one was treated in ≤60 min. Of the 44 patients treated with IVT in ≤60 min, 66% of them arrived by EMS. There was no significant difference in the proportion of patients treated with DNT ≤60 min between patients who arrived within 0 to 60, 61 to 120, 121 to 180, or >180 min from the symptom onset (33, 26, 36, and 35%, respectively, $p = 0.68$).

Most patients experienced multiple reasons for treatment delay (Table 4). The most common reason was the delay in starting the IVT after the CT scan, with a CT-to-needle time of >20 min in 90% of the patients. The second most frequent reason for the delay was the patient's return to the emergency room for treatment (77%), followed by the delay in starting the CT scan in radiology service (65%) and performing CT angiography before IVT (46%). Only 8% of patients had no delay in IVT, considering the benchmarks in Table 1. Table 5 shows the main reasons for delay in each patient, defined as the major cause of delay. The main reason was the delay to start the CT scan (22%), which specifically refers to the delay in the radiology service initiating the CT scan, followed by the delay in starting IVT after the CT scan (19%) and the delay in decreasing blood pressure (11%). The delay in triage, in the emergency department, image acquisition in the radiology service, as well as in stabilizing the patient, correspond to the pre-imaging delay, increasing the door-to-CT time. Conversely, delays in the laboratory and delays in the definition and initiation of IVT treatment after the image correspond to the post-imaging delay.

In the multivariate analysis to evaluate independent factors for treatment delay, including age, gender, baseline NIHSS score, AF, arrival by EMS, and the use of MRI in the initial evaluation and treatment in the ED, only AF (OR, 6.8; 95% CI, 1.8 to 26.2) and thrombolysis in the ED (OR, 8.9; 95% CI, 2.9 to 27.5) were independent factors for treatment delay.

Actions implemented to decrease the DNT

Specific actions shown in Table 6 were implemented to decrease DNT in addition to the actions that occur every year as stroke campaigns to inform the population and training for the pre-hospital team, emergency staff, neurologists, and radiology team.

TABLE 2 Median door-to-needle time according to the baseline characteristics.

	No (%)	Median DNT [IQR]	Min-Max	*p*
Age ≥ 70				0.29
No	72 (50)	74 [60–94]	31–165	
Yes	71 (50)	69 [52–92]	23–145	
Male sex				0.61
No	73 (51)	69 [56–93]	23–145	
Yes	70 (49)	74 [59–93]	31–165	
Baseline NIHSS ≥15				0.09
No	106 (74)	69 [55–90]	23–165	
Yes	37 (26)	81 [62–105]	31–140	
Mechanical thrombectomy				0.89
No	132 (92)	72 [55–83]	23–165	
Yes	11 (8)	73 [63–87]	43–114	
Hypertension				0.59
No	26 (18)	70 [50–93]	33–165	
Yes	117 (82)	73 [59–93]	23–158	
Diabetes				0.15
No	97 (68)	73 [61–93]	31–165	
Yes	46 (32)	68 [49–94]	23–158	
Ischemic heart disease				0.61
No	120 (86)	72 [56–93]	23–165	
Yes	20 (14)	71 [54–91]	38–107	
Atrial fibrillation				0.10
No	111 (78)	68 [54–91]	23–165	
Yes	31 (22)	78 [67–98]	31–128	
Previous stroke				0.05
No	107 (75)	69 [56–87]	31–165	
Yes	35 (25)	84 [64–110]	23–158	
Magnetic resonance in acute stroke				0.61
No	134 (94)	70 [55–92]	23–165	
Yes	9 (6)	96 [85–113]	56–134	
Time of arrival				0.45
7:00 am to 6:59 pm	92 (64)	69.5 [53–93]	23–165	
7:00 pm to 10:59 pm	38 (27)	73 [64–91]	31–132	
11:00 pm to 6:59 am	13 (9)	80 [62–109]	48–158	
Arrival by EMS				0.01
No EMS	45 (32)	80 [55–111]	38–165	
EMS (SAMU)	98 (68)	70 [57–87]	23–140	
Local of thrombolysis				<0.0001
At the acute stroke unit (ED)	119 (83)	74 [62–94]	37–163	
At the CT scan room	24 (17)	52 [39–71]	23–108	

EMS, emergency medical service; MRI, magnetic resonance imaging.

TABLE 3 Proportion of patients with DNT ≤60 min according to the baseline characteristics.

	N	DNT > 60 min	DNT ≤ 60 min	*p*
		99 (69%)	44 (31%)	
Age ≥ 70	71	44 (48%)	24 (55%)	0.44
Male sex	70	50 (51%)	20 (46%)	0.58
Baseline NIHSS ≥ 15	37	29 (29%)	8 (18%)	0.16
Mechanical thrombectomy	11	10 (10%)	1 (2%)	0.17
Risk factor				
Diabetes	46	26 (26)	20 (46)	**0.02**
Ischemic heart disease	20	13 (14)	7 (16)	0.71
Atrial fibrillation	31	27 (28)	4 (9)	**0.01**
Previous stroke	35	27 (28)	8 (18)	0.23
Time of arrival				
7:00 am to 6:59 pm	92	58 (60)	34 (77)	**0.09**
7:00 pm to 10:59 pm	38	31 (31)	7 (16)	
11:00 pm to 6:59 am	13	10 (10)	3 (7)	
Arrival by EMS	98	69 (70)	29 (66)	0.65
MRI in acute phase	9	8 (8)	1 (2)	0.28
Thrombolysis on CT scan	24	28 (24)	16 (67)	**<0.0001**

EMS, emergency medical service; MRI, magnetic resonance imaging.

The main action was to start IVT bolus and continuous infusion on the CT scan table (Figure 1).

Figure 2 shows the times in each stage of treatment in 2019 and 2020. The door-to-CT scan time of ≤25 min was not different in 2019 compared to 2020 (50 vs. 54%, $p = 0.63$). However, CT-to-needle time decreased from 49 to 39 min ($p = 0.02$), and DNT decreased from 78 to 66 min ($p = 0.02$), respectively. The proportion of patients with DNT ≤60 min increased significantly (21% in 2019 compared to 44.3% in 2020).

TABLE 4 All reasons for the door-to-needle time delay*.

Reasons for the DNT delay	Benchmark	*N* (%)
Delay to start the treatment (CT-to-treatment delay)	20 min	129 (90)
Thrombolysis in the emergency room	60 min	91 (77)
Delay to start CT scan	20 min	93 (65)
Perform CTA before IVT	-	66 (46)
Delay in triage	5 min	45 (32)
Delay in reducing blood pressure	-	27 (19)
Lack of information (patient alone)	-	27 (19)
Delay in neurology evaluation	15 min	27 (19)
Delay in emergency physician evaluation	15 min	21 (15)
Unstable patient	-	12 (8)
Perform MRI for thrombolysis selection	-	10 (7)
Delay in the laboratory (anticoagulated patients)	30 min	7 (5)
Delay in the consent form	-	9 (8)
Delay in uploading images in the application	-	5 (4)
Wrong diagnosis in triage	-	5 (4)
Difficult venous access	-	5 (4)
Delay to collect blood exams	-	5 (4)
Delay in triage due to COVID	5 min	2 (1)
Any delay	-	12 (8)

*Each patient can have more than one reason for delay.

TABLE 5 Main reasons for the delay in door-to-needle time for each patient*.

Reasons for the DNT delay	*N* (%)
Delay to start CT scan	31 (22)
Delay to start the treatment after CT scan	27 (19)
Delay in reducing blood pressure	15 (11)
Delay in the emergency department	11 (8)
Unstable patient	12 (8)
Perform MRI for thrombolysis selection	10 (7)
Delay in the laboratory (anticoagulated patients)	7 (5)
Perform CTA before IVT	6 (4)
Wrong diagnosis in triage	3 (2)
Delay in triage	3 (2)
Difficult venous access	3 (2)
Delay in the consent form	2 (1)
Delay in uploading images in the application	1 (<1)
No delay	12 (8)

*One main reason per patient.

TABLE 6 Actions implemented to decrease the DNT during 2019–2020.

Action	Date	Result
Collection of blood tests by nursing staff when the first *abocath* is punctured	January 2019	Decreased the delay in the blood sample collection
Urgent registry of a patient at the emergency arrival	June 2019	Decreased the delay in requesting the exams
Training of the neurology residents to prepare the rtPA in the radiology service	September 2019	The residents started to initiate the thrombolytic treatment in the CT scan table
Training of the neurology residents to a faster blood pressure control	September 2019	Faster BP control
Pack of urgent exams in the electronic system (including CT, CTA, and laboratory exams)	December 2019	Faster transfer of the CT scan

Effects of the COVID-19 pandemic

The COVID-19 pandemic was an atypical situation that had an impact on stroke care in 2020. The proportion of patients arriving from SAMU decreased from 74% in 2019 to 61% in 2020 ($p = 0.08$). Breaking expectations, the DNT was lower after the start of the pandemic (75 min before vs. 63 min after in 2020, $p = 0.018$), maintaining the decrease that had been occurring since the implementation of the actions (57 min in 2021, 59% of treated patients).

In January, 83 patients with acute stroke arrived at the ED, followed by 66 in February, 80 in March, and 44 in April (a reduction of approximately 50% in the first month after the pandemic reached Brazil). Since then, the numbers have recovered, with 1,002 patients with suspected stroke evaluated in 2020 and 1,038 in 2021. More patients arrived out of the 4.5 h window for IVT (35% from January to March and 20% from April to December 2020). The IVT eligibility (IVT treated/all AIS ratio) decreased from 14.5% in 2019 to 8.8% in 2020, rising again to 14.3% in 2021. Patients with AIS treated with IVT after the pandemic were younger (65 years [IQR 59–68] in 2020 vs. 71 years [67–73] in 2019, $p = 0.011$). Figure 3 shows the volume of patients with suspected stroke and DNT in each year from 2019 to 2021, demonstrating that despite the pandemic, it was possible to reduce the metrics for acute stroke care.

Discussion

Detecting the reasons for the delay in treatment and implementing actions to reduce treatment times are essential to improve patients' functional outcomes (24), reducing disability and stroke mortality even in the most severe cases of large vessel occlusions (25). The study demonstrated the main reasons for the delay in acute stroke treatment in a public university hospital, including during the COVID-19 pandemic, which is a high-volume stroke center. Despite many years of experience, education,

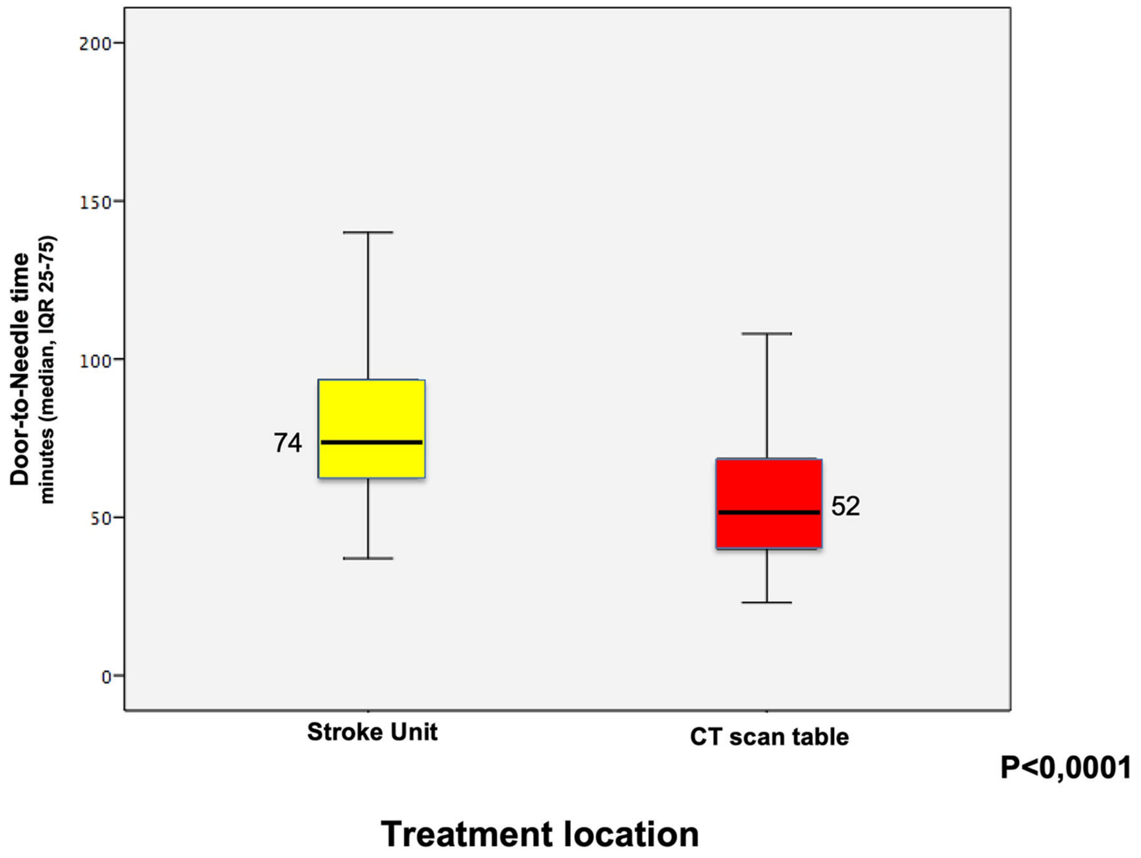

FIGURE 1
Median times (IQR 25–75) according to the local of thrombolysis.

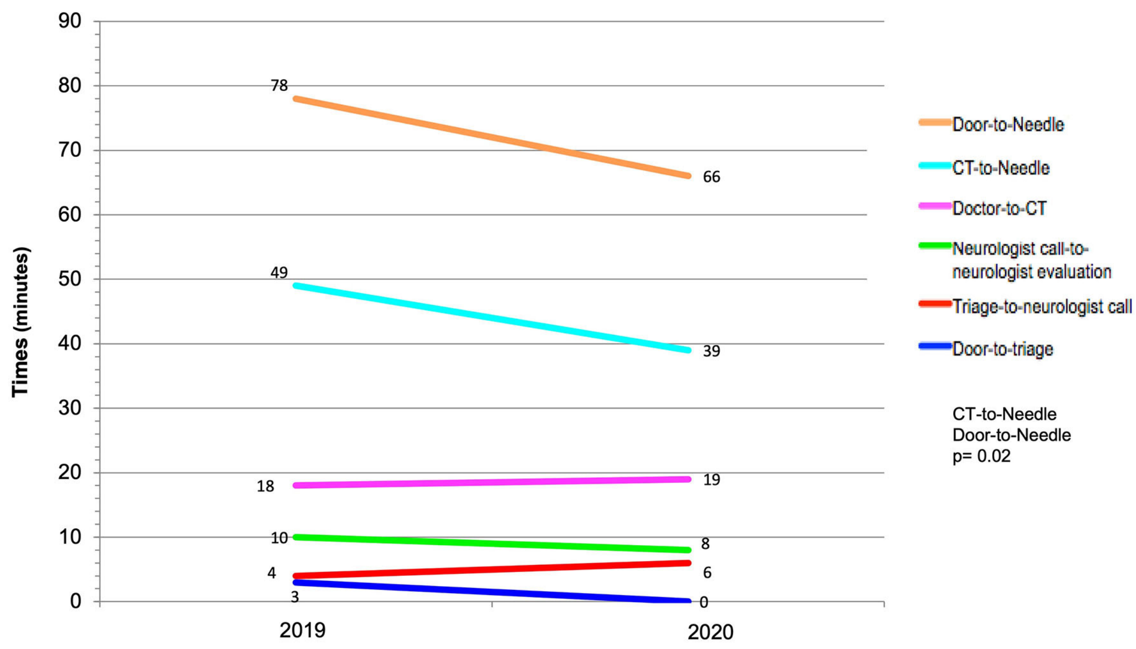

FIGURE 2
Median time for different quality indicators in acute ischemic stroke care during 2019–2020.

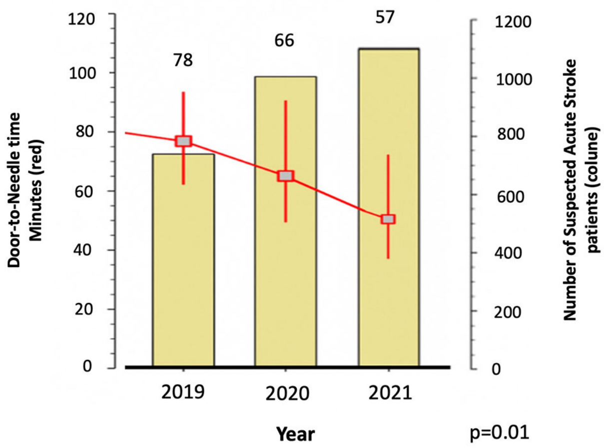

FIGURE 3
Number of suspected acute stroke patients assisted in the emergency room and door-to-needle-time in each year from 2019 (pre-COVID-19 pandemic) and 2020–2021 (during the COVID-19 pandemic).

frequent training of staff, continuous monitoring of data, and review of service times, this study showed that there are still barriers to overcome in order to reduce treatment times and improve quality.

In general, the median door-to-CT time was 25 min, still within the international standard (9). A door-to-CT time >20 min is considered above our institutional goal to improve treatment times. The median DNT was 73 min despite constant efforts to reduce this time. Although the recommended time of ≤60 min is a challenge in most centers, several studies have shown that a median DNT of 20–35 min is possible (6, 8, 11, 26, 27).

The need to perform a brain MRI in AIS of unknown onset symptoms delays treatment by 25 min. Although without statistically significant difference, probably due to the small number of cases, only one of the nine patients selected by MRI was treated in <60 min (28). Without this exam, however, these patients would not have received reperfusion therapy with IVT. MRI better visualizes the ischemic area in the acute phase compared to CT scan (29), but it is less available, requires more time to perform, and, in the case of this public hospital, the radiology technician is on-call at night, which delays the MRI and consequently the treatment. For these reasons, as a head CT scan is still the gold standard for assessing acute stroke, it is the first option at HCPA.

Patients with a previous history of stroke had a 15-min increase in DNT possibly due to uncertainties about the treatment of a patient with previous functional impairment. Approximately 69% of patients arrived through SAMU. As previously demonstrated in the literature, patients arriving by EMS have a greater chance of receiving IVT and have a lower DNT (6, 8, 10, 11). In our study, patients who arrived by SAMU had an almost 2-fold chance to receive IVT in ≤60 min (66% arrived by SAMU vs. 34% from other transportation).

The incorporation of a stopwatch into the stroke protocol has been a standard practice since the hospital was designated as a stroke center. The use of a stopwatch in acute stroke care plays a crucial role in ensuring timely treatment and improving patient outcomes. By accurately measuring the time intervals involved in acute stroke management, a stopwatch provides valuable feedback that enables healthcare professionals to promptly identify and address potential delays. This real-time feedback serves as a powerful tool in identifying areas for improvement. Furthermore, the presence of a visible timekeeping device serves as a constant reminder of the urgency of stroke care, promoting a culture of time sensitivity and adherence to evidence-based guidelines (9, 30–33).

Some factors previously identified in the hospital as barriers that delayed patient care were modified during this study. A critical factor was the distance between the ED and the radiology service and, in addition, the waiting time for the elevator to arrive because the CT scan is located on the second floor. Part of this problem was reduced by IVT infusion on the CT scan table, which was frequently performed in this study. Patients who received treatment on the CT scan table had a median DNT of 52 [IQR 39–71], which is 22 min lower than patients who returned to start IVT at the ASU. Of patients treated on the CT scan table, 67% had a DNT ≤60 min compared to 24% of those treated in the ED. Other studies demonstrate that the IVT treatment on the CT scan table is one of the most important factors in reducing the time to treatment (6, 8, 10, 11).

Diabetic patients received IVT in <60 min more often than non-diabetics. One possible explanation for this finding is that patients with diabetes may have more severe strokes, which would require prompt initiation of treatment. It is also possible that healthcare providers may more closely monitor and manage diabetic patients, leading to faster identification, and treatment of stroke symptoms. In general, this is an interesting observation that requires further investigation. Some studies show that patients with higher NIHSS tend to have a shorter DNT (34). In our study, patients with NIHSS ≥ 15 had a tendency to have a higher median DNT (81 vs. 69) but without statistical significance ($p = 0.095$). In the multivariate analysis, the independent factors for treatment delay were previous AF (OR 7.0) and IVT in the ED (OR 9.0). Patients with previous AF frequently have more severe strokes and need to be assessed for the use of anticoagulants, and some of them need to wait for the INR result in the case of vitamin K antagonist use. Additionally, AF patients may have a higher risk of bleeding complications during thrombolysis treatment, which can also impact the decision-making process and delay the treatment. Regarding IVT in the ED, probably the time to move the patient out of the CT scan room, return to the ED, and place the patient on a bed in the stroke unit is an important delay factor, which can be reduced by treating patients on the CT scan table.

In the evaluation of all stages of the protocol until the start of IVT, the most frequent delay factor in treatment (considering that each patient could have more than one reason for delay) was the time between the CT scan and the start of IVT treatment. Several factors may be associated with treatment delay after a CT scan without contrast: the need to perform CT angiography (35, 36), delay in lowering blood pressure (27), difficult cases and decision-making delay, lack of information about the patient, and the need to wait for a family member, and delayed waiting for INR results in anticoagulated patients due to lack of point-of-care INR testing in the hospital. Approximately 90% of patients had a CT-to-treatment >20 min. The second most frequent reason was IVT in the ED, followed by a delay in performing the CT scan and CT angiography.

Removing the treatment site as a treatment delay cause since the treatment on the CT scan table was implemented during the study, we consider the single most important reason for the delay in treatment in each patient was (1) the delay to perform the CT scan in 22% of cases, followed by (2) a delay in starting treatment after CT scan due to delay in the decision-making process in 19%, and (3) a delay in reducing blood pressure in 11% (Table 5). All these reasons have been described as causes of treatment delay in the international literature (6, 8, 10, 11, 26–29, 34). Only 8% of patients showed no delay in any of the stages, demonstrating that there are still many opportunities to reduce treatment times.

Several actions implemented during the study period certainly contributed to the reduction of DNT between the evaluated period, from 78 to 66 min, with a reduction of the CT-To-needle time from 49 to 39 min. The main factor to decrease the DNT was performing IVT bolus and starting the continuous infusion on the CT scan table, especially in patients who started the bolus on the CT scan table before the CT angiography acquisition. Despite the door-to-CT being the main isolated cause of delay, the median time was 25 min and remained between 2019 and 2020.

Despite all attempts to decrease stroke care times, some centers have enormous success leading to media DNT between 20 and 30 min; however, in most centers, it is still difficult to reach DNT $\leq$ 60 min. The quality program of the American Stroke Association (Get with the Guidelines) demonstrates that the program helps to progressively decrease these times, but are still not ideal, with the majority of American hospitals presenting a median DNT of >60 min (37).

The COVID-19 pandemic, as in other parts of the world, brought an initial drop in the number of stroke patients arriving at the hospital. In addition, there was a significant drop in eligibility for thrombolysis and in the number of patients treated (reduction from 35% of patients arriving within 4.5 h before the pandemic to 20% after). The initial decrease in cases was followed by an increase in the number of stroke patients. It is possible that the increase in stroke admissions at our center during the pandemic was due to the fact that our center is a reference for a population with a higher prevalence of stroke risk factors, including hypertension, and diabetes. Additionally, the implementation of policies and protocols to ensure timely and appropriate care for stroke patients during the pandemic may have contributed to this increase.

Acute stroke protocols have been adjusted according to national indications for protection against COVID-19 infection. As all stroke patients were tested for COVID-19 infection and evaluated with appropriate personal protective equipment, it was not necessary to wait for COVID test results to proceed with acute stroke reperfusion treatment. Many patients received IV thrombolysis bolus and started continuous infusion of tPA in the radiology department before returning to the ED. DNT continued to decline in 2021, even during the pandemic, with the implementation of the new measures despite the greater number of patients arriving with AIS in this period.

Our study has limitations. The study was conducted at a single hospital, which may limit the generalizability of the findings to other healthcare settings. The study covered the period from 2019 to 2021, which was affected by the COVID-19 pandemic. The improvement in DNT observed in 2020 compared to 2019 could be attributed to the less satisfactory DNT in the previous year. Additionally, the study focused on treatment times and did not assess long-term functional outcomes. Therefore, the impact of treatment times on patient outcomes was not evaluated.

Conclusion

The monthly volumes for IVT and stroke hospitalizations reduced at the beginning of the COVID-19 pandemic in our center, but the delivery of acute stroke care remained a priority. Continuing education and staff training help to reduce IVT times for stroke patients despite all necessary safety measures during acute stroke care due to the risk of coronavirus infection. In this study, the main reason for treatment delay was the delay in performing CT scan, followed by the decision-making process delay. The implementation of the IVT bolus and the start of continuous infusion on the CT scan table was the main factor in reducing DNT during the COVID-19 pandemic. Monitoring data in a public hospital in a middle-income country allows us to identify the main reasons for treatment delay and to plan specific actions. New measures to be implemented soon will help to reduce even more the treatment times: CT scan in the ED and the use of point-of-care INR testing for anticoagulated patients.

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 Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

SM designed the study, analyzed the data, and wrote the first draft and the final version of the document. MK collected the data, wrote and reviewed the first draft, and approved the final version. AS and LC wrote the first draft of the document. TS wrote the final version of the document. All others collected the data and reviewed the final version of the document.

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Conflict of interest

The 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.

Publisher's note

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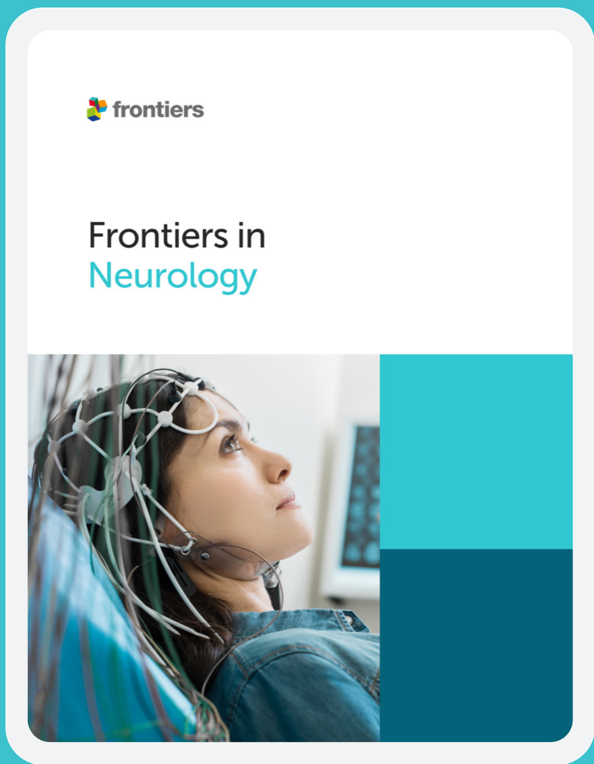

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