Variations in practice patterns and outcomes after stroke across countries at different economic levels: the INTERSTROKE study

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Abstract

Background

Stroke disproportionately affects people in low and middle-income countries (LMICs). Although improvements in stroke care and outcomes have been reported in high income countries (HICs), little is known about practice and outcomes in LMICs. We aimed to compare patterns of care available and their association with patient outcomes across countries at different economic levels.

Methods

We studied the patterns and impact of practice variations (treatments used and access to services) among stroke participants in the INTERSTROKE study, an international observational study that enrolled 13,447 stroke patients from 142 clinical sites in 32 countries between January 11, 2007 and August 8, 2015. We supplemented patient data with a questionnaire about healthcare and stroke service facilities at each participating hospital. Using univariate and multivariate regression analyses to account for patient case-mix and service clustering, we estimated the association between services available, treatments given, and patient outcomes (death or dependency) at one month.

Findings

We obtained full information for 12,342 (92%) of 13,447 INTERSTROKE patients, from 108 hospitals in 28 countries; 2576 from 38 hospitals in 10 HICs and 9766 from 70 hospitals in 18 LMICs. Patients in LMICs more often (P<0.0001) had severe strokes, intracerebral haemorrhage, poorer access to services, and lower use of investigations and treatments, although only differences in patient characteristics explained the poorer clinical outcomes in LMICs. However across all countries, access to a stroke unit was associated (P<0.0001) with improved use of investigations and treatments, access to other rehabilitation services, and improved survival without severe dependency (1.29; 1.14-1.44) which was independent of

patient case-mix characteristics and other measures of care. Use of acute antiplatelet therapy was associated with improved survival (1.39; 1.12-1.72) irrespective of other patient and service characteristics.

Interpretation

Evidence based treatments, diagnostics, and availability of stroke units were less commonly available or used in LMICs. Access to stroke units and appropriate use of antiplatelet therapy were associated with improved recovery. Improved care and facilities in LMICs are essential to improve outcomes.

Funding

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Introduction

Stroke is the second commonest cause of death worldwide and one of the leading causes of disability.[1-3] Although prevention strategies can reduce this burden of disease[4,5] effective and affordable treatments are essential for reducing mortality and morbidity in those who have already suffered a stroke. Aspirin[4,5] , intravenous thrombolysis[4,5] and mechanical thrombectomy[6] for acute ischaemic stroke, and plus stroke unit care and early rehabilitation services for all stroke patients[4,5] can reduce mortality and morbidity.

The PURE study[7] recently demonstrated that after stroke clinical outcomes were substantially poorer in low- and middle-income countries (LMIC) than in high income countries (HICs). It is not clear if this reflects differences in the patient population, services available, or treatments received. In many HICs, clinical practice guidelines and national strategies now recommend the establishment of stroke units in all hospitals that care for patients with acute stroke[9-13]. This has been linked to an increased provision of evidence-based care[14-19] and improved patient outcomes[17-20]. However the greatest adoption of these practices has been in HICs where most clinical trials of stroke units have been carried out. It is not known how common stroke units are in LMICs or whether they are associated with improved outcomes.[4,5,8] Such information could inform the establishment of stroke units in LMICs.

INTERSTROKE is an international observational stroke study conducted in 32 countries at different economic levels.[21] Individuals who had had a stroke were selected using standardised criteria and were characterised in detail. This allowed us to compare the patterns of care available, and their association with patient outcomes, across a much broader range of healthcare settings than has previously been possible.

Methods

INTERSTROKE is an international case-control study of risk factors for first stroke[21], which enrolled 13,447 stroke patients from 142 clinical sites in 32 countries between January 11, 2007 and August 8, 2015.

For this analysis of practice patterns, our hypotheses were that, across all countries studied, there would be variations in access to stroke treatments and services and that, after adjusting for variations in patient case-mix, patient outcomes will be influenced by the treatments and services they can access. We proposed that outcomes would be better where; i) healthcare resources are greater, ii) guideline investigations and treatments are provided, and iii) guideline services (especially stroke units) are available at the hospital.

Data collection operated at two levels;

a) Individual stroke patient data included the following; demographic features (age, sex, level of education), risk factors, pre-stroke disability (using the modified Rankin Score[22]), comorbidity (based on the Charleston Comorbidity Index[23]), stroke characteristics (including haemorrhage or infarct classified with the Oxfordshire Community Stroke Project (OCSP) classification[24], modified Rankin Score[22] at baseline, level of consciousness at baseline) and acute management received at enrolment in the study (brain imaging, antiplatelet therapy, thrombolysis, lipid lowering therapy and blood pressure lowering therapy).

b) Data collected at the level of the service; Using a short questionnaire (see Appendix), we collected information on service features at each participating hospital: i) local and national healthcare characteristics (e.g. source of health funding, items for payment), ii) hospital characteristics and resources (e.g. tertiary or secondary level hospital, departments and beds available), iii) stroke service characteristics (presence of stroke unit, stroke unit characteristics and resources), iv) additional features (other aspects of patient care such as post-discharge rehabilitation). The survey was first circulated electronically in June 2011

with a reminder sent in early 2012. If no there was no reply by early 2012, the electronic message was resubmitted via national leads.

Outcomes

Patient outcomes were recorded at one month follow up[21] and included; death, discharge disposition after hospital (home, rehabilitation centre or nursing home), dependency using the modified Rankin score[22], and length of hospital stay. Patient details were collected from the participants or from a proxy respondent[21].

Analysis

We carried out the following analyses:

1) Description of the patient characteristics and clinical practice (investigations, treatments and services provided) at recruiting hospitals grouped by the 2011 World Bank Country Income Categories (CIC), using Chi-squared and t-tests,

We carried out statistical analyses using SPSS V.23 and SAS V.9.4. using multivariate analyses to calculate case-mix adjusted outcomes (see below) and a 2-level multivariable model using random intercepts to take into account potential clustering of clinical practice by centre. We used multivariable logistic regression models to adjust for case-mix covariates that are known to influence patient outcomes[25]; age, sex, level of education, pre-stroke disability, number of comorbidities, stroke type and classification and initial stroke severity. No significant multi-collinearity was identified. Adjustment was subsequently also made for country wealth (ranked by GDP) and clustering by centre. We then used binary logistic regression to identify variables that had the closest association with patient outcomes. Subgroup analyses stratified results by key patient and service characteristics. Availability of a stroke unit was clustered in regions and correlated with patient age, level of consciousness

and stroke severity. Therefore we also sought to confirm our findings in a propensity-matching analysis accounting for these variables. Finally we conducted exploratory sensitivity analyses of the association between patient outcomes and access to stroke units (with or without particular characteristics). These comparisons were based on;

a) Stroke unit quality criteria[26] in terms of whether six key features were present; (i) discrete ward, ii) multidisciplinary care, iii) staff specialist interest in stroke, iv) programmes of staff education and v) patient management protocols and vi) information for patients and families,

b) Staffing levels that meet basic benchmark levels for nursing, medical and therapy staff[26],

c) Stroke unit capacity (ability to manage >50% of the stroke patients in the hospital), and

d) Access to post-discharge rehabilitation.

Ethics

The study was approved by the ethics committees in all participating centres.[21] Participants, or their proxy, provided written informed consent. None of the authors reported major conflicts of interest.

Role of the funding source

The current analysis was supported by a grant from Chest, Heart and Stroke Scotland. The main INTERSTROKE study was supported by several funders (see Appendix). None of the funders had a role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

Results

Between January 11, 2007 and August 8, 2015, the INTERSTROKE study[21] enrolled 13,447 acute stroke patients from 142 centres; 34 centres (1105 participants) did not provide information on the service survey. We therefore had complete individual patient data and service information from 12,342 participants from 108 hospitals in 28 countries covering Western Europe, East and Central Europe, the Middle East, Africa, South Asia, China, South East Asia, Latin America, North America and Australia.

Table 1 outlines the characteristics of patients, investigations and treatments provided and services available. These are categorised by the 2011 World Bank Country Income Category. A total of 38 hospitals (2576 participants) were in HICs (Australia, Canada, Croatia, Denmark, Germany, Ireland, Poland, Sweden, United Arab Emirates, UK) and 70 hospitals (9766 participants) in LMICs. The latter consisted of 50 hospitals (5859 participants) in upper-middle income countries (Argentina, Brazil, Chile, China, Columbia, Ecuador, Malaysia, Peru, Russia, South Africa, Turkey), 17 hospitals (3361 participants) in lower-middle income countries (India, Nigeria, Pakistan, Philippines, Sudan), and 3 hospitals (546 participants) in low income countries (Mozambique, Uganda). LMIC hospitals (Table 1) recruited patients who were on average younger, less well educated, had fewer comorbidities, more severe strokes and more intracerebral haemorrhage (all $P<0.0001$). Although CT scanning was mandated for all INTERSTROKE patients, those from HICs were more likely to get imaging done on the day of admission. Other investigations were also more readily available (Table 1). HIC patients were more likely to receive antiplatelet therapy, intravenous thrombolysis or a carotid intervention following an ischaemic stroke, but any variations in BP lowering treatments and lipid lowering therapy were not clearly linked to World Bank CIC. Data reporting was almost complete (12266; 99.4%) for all reported variables with the

exception of thrombolysis and carotid interventions for which non-reporting was assumed to indicate that the treatment was not given.

Table 1 also summarises the services available in each site categorised by World Bank CIC. A total of 6055 patients (49%) were admitted to hospitals reporting that they had some form of stroke unit available; (95% of centres and 92% of patients in HIC; 30% of centres and 38% of patients in LMICs). However there was no clear gradient by World Bank CIC with fewest stroke units being available in upper-middle income countries. When present, stroke units in LMICs were less likely to meet all of the six key quality characteristics[26] or to report having sufficient capacity to accommodate most hospitalised stroke patients (Table 1). This was corroborated by information that, for the same number of admissions (a median of 50 stroke patient admissions per month), HIC stroke units reported having a median of 18 beds available compared with 8 beds in LMIC units.

Stroke patients from wealthier countries had better outcomes at one month. When grouped as HICs versus LMICs, the number (%) surviving and surviving without major dependency (mRS 0-3) were 2501 (98%) and 2308 (90%) respectively in HICs compared with 8580 (88%) and 7536 (78%) in LMICs. This was confirmed when outcomes were regressed against country wealth; ranked from lowest to highest country GDP (Table 2). Differences in patient characteristics appeared to explain much, but not all, of the variation by country wealth. After adjusting for baseline patient case-mix variables (age, sex, education, pre-stroke disability, stroke type, number of comorbidities, level of consciousness, and modified Rankin score at baseline) the relationship between country income and recovery was reduced but not abolished (Table 2). There was no further attenuation of the relationship after including common medications given (antiplatelet, lipid lowering and BP lowering therapy plus thrombolysis), and access to services (medical stroke specialist, stroke unit and rehabilitation

post-discharge). These results indicate that the incrementally better patient outcomes observed in wealthier countries were partly explained by patient case-mix.

We then explored the relationships between treatments given, services available and patient outcomes across all World Bank CIC settings (Table 3). For these analyses we included all treatments and services that were less common in LMIC centres (Table 1). We did not include carotid interventions as this applied to only 97 patients overall. After adjustment for patient case-mix and country wealth (GDP ranking), the appropriate provision of antiplatelet therapy (prescribed for those with cerebral infarction), and the availability of stroke unit care and post-discharge rehabilitation were each associated with a greater chance of survival without severe dependency (Table 3). The appropriate provision of antiplatelet therapy, and availability of stroke unit care and post-discharge rehabilitation were also associated with a higher odds of survival at one month (Table 3). When the analysis also took into account clustering by centre (Table 3), the availability of stroke unit care and post-discharge rehabilitation were each associated with a greater chance of survival without severe dependency (Table 3). The appropriate provision of antiplatelet therapy, and availability of post-discharge rehabilitation were associated with a higher odds of survival at one month when taking into account clustering by centre.

Using a forward binary logistic regression, including all variables listed in Table 3, we found that survival without severe dependency (mRS 0-3) was greater with access to stroke unit care and appropriate antiplatelet therapy. Significant covariates were pre-stroke disability plus the five patient variables (age, comorbidities, baseline mRS, level of consciousness and stroke classification). Survival at one month was best explained by appropriate antiplatelet therapy, access to stroke unit care, and access to post-discharge rehabilitation. Significant covariates were country GDP ranking, patient education and the five patient variables above.

Table 4 highlights the univariate and multivariate analyses exploring the association of access to a stroke unit with the provision of other stroke treatments and with patient outcomes. Admission to a hospital with a stroke unit was associated with increased odds of receiving all the other process measures plus an increased odds of survival and survival without severe dependency. However after adjusting for clustering by centre, access to a stroke unit was only associated with increased access to CT scanning and post-discharge rehabilitation and with survival without severe dependency (1.29; 1.14-1.44).

As stroke unit availability was unevenly distributed between regions we used a matched propensity analysis that excluded the five regions where availability was either universal (Western Europe, Eastern Europe, North America, Australia) or absent (Middle East). Variables that were related to patient outcomes and also closely associated with stroke unit availability were patient age and stroke severity. Therefore we compared two groups of 3,466 stroke participants with or without access to a stroke unit who were matched on; age (mean of 60 versus 60 years); reduced level of consciousness (45% versus 45%); baseline modified Rankin Scale, (mean of 3.40 versus 3.40). Admission to a hospital with a stroke unit was again associated with increased odds of survival (1.15; 1.01-1.31) and of survival without major disability (1.30; 1.17-1.44).

In view of the imbalance between HIC and LMIC in the numbers of patients with intracerebral haemorrhage, we repeated the analyses with the exclusion of intracerebral haemorrhages (supplemental Tables 1-2). On multivariate analyses patients with ischaemic stroke had an increased odds of survival without severe dependency (1.42; 1.23-1.64; $p<0.0001$) if admitted to a hospital with a stroke unit. Results were directionally consistent but non-significant for survival (1.15; 0.96-1.39; $p=0.14$).

Further subgroup analyses found a consistent association of access to stroke unit services with patient outcomes across a range of patient and service subgroups (Figure 1). The association of improved outcomes with antiplatelet drug use was seen across all subgroups (Figure 2) except for stroke type where no benefit was seen for the very small number of haemorrhage patients treated with aspirin.

Finally in sensitivity analyses we repeated the analysis in Table 4 for the outcome of survival without severe dependency (mRS 0-3) but compared stroke units with and without specific quality characteristics (as described in Table 1). The association with improved outcomes was greater in the presence (compared to absence) of quality features; the stroke unit was described as having the six key characteristics (1.32; 1.11-1.56); stroke unit staffing met basic benchmark levels (1.34; 1.11-1.62); and the stroke unit had the capacity to house at least 50% of stroke patient admissions (1.20; 1.00-1.45). The availability of post-discharge rehabilitation was not associated with additional benefit in this analysis (1.08; 0.67-1.33).

Discussion

We had anticipated that INTERSTROKE patients enrolled in LMIC hospitals would have poorer access to investigations, treatments and services than those from HIC hospitals. However, LMIC patients also had poorer clinical outcomes (survival 88% compared with 98% in HICs; survival without severe disability 78% versus 90%) which could only be partly explained by the inclusion of more severe stroke patients. Across all countries studied, the practice variables most consistently associated with improved patient outcomes were access to stroke unit care and post-discharge rehabilitation plus receiving appropriate antiplatelet therapy. This may reflect more limited access to state or insurance funded healthcare services.

The poorer stroke prognosis in LMICs has been described previously.[2,3,7] We have confirmed that stroke in poorer countries appears to be either a more severe disease (more intracerebral haemorrhage) and/or has different referral patterns (patients admitted to hospital more likely to have severe stroke). The potential role of stroke units and antiplatelet therapy in LMIC settings has not been described before but is potentially complex. Access to drugs or services could not explain differences between patient outcomes in wealthy versus less wealthy countries but they did appear to explain associations across all countries. This may reflect the observation that access to a stroke unit varied greatly within as well as between wealth categories (World Bank CICs).

Several observational studies[16,18,20,28] have reported on the association of appropriate antiplatelet therapy (early use in acute cerebral ischaemia) with improved survival and reduced disability. Also a recent meta-analysis of aspirin trials[29] confirms an important short term benefit of aspirin therapy to prevent recurrent cerebral ischaemia. However, these studies have almost all been in higher income settings[28]. Earlier access to brain imaging may serve to facilitate earlier antiplatelet use.

In the INTERSTROKE study, the apparent benefit of stroke units is comparable to that reported in RCTs[4] and appears to be due to a combination of an "intrinsic" stroke unit effect as well as stroke unit patients having better access to antiplatelet therapy, risk factor modification, and post-discharge rehabilitation. The apparent benefits were seen across a range of stroke patient groups and tended to be greater if the stroke unit was reported to be well staffed, to meet recognised service standards, and to have sufficient capacity to provide care for most stroke patients admitted to hospital. Our findings suggest that, stroke units can have a similar benefit in LMICs as has been observed in HICs.

At present few hospitals in LMICs have stroke units. Even in our study, which is likely to have included a higher proportion of better-resourced tertiary care centres (with better access to imaging and drug therapies) than in average LMIC hospitals, only 38% had stroke units. Our study suggests that establishment of simple stroke units could enhance the level and organisation of care and improve stroke outcomes in LMICs. The World Health Organisation has targeted a 25% reduction in premature mortality from cardiovascular disease globally by 2025. This is unlikely to be achieved by risk factor reduction alone but also requires investment in medical treatments and organisation of better systems of care. Investment in specialised stroke units is likely to be cost effective and should be a priority worldwide.

Limitations of this study include the observational design which cannot completely exclude the possibility of residual confounding. We carried out a large number of analyses which raises the possibility of chance findings. However, use of the 99% confidence threshold would not alter our main conclusions. Service features were described at the level of the hospital so we cannot be certain which specific patients were actually admitted to a stroke unit. Although this introduces some uncertainty it also reduces any potential bias resulting from selective admission of better prognosis patients within a hospital to the stroke unit; it is testing the impact of the stroke unit on all patients at that hospital. Interestingly the sensitivity analyses suggest improved outcomes where stroke units had greater capacity to accept most stroke patients. As only a proportion of patients were enrolled in INTERSTROKE it is possible (but unlikely) that stroke unit sites enrolled patients with a better prognosis. An additional challenge was that service characteristics tended to cluster together in hospitals, countries and regions making it difficult to separate the impact of different aspects of service delivery. In particular, the availability of post-discharge rehabilitation services was closely related to stroke units. Finally, several regions had no variation in the provision of stroke units, although exclusion of these regions from the analysis did not alter our conclusions.

The strengths of our study are that we collected standardised information from over 12,000 well-characterised acute stroke patients including an independent assessment of outcome at one month. We recruited from a large number of hospitals in diverse settings with variations in care. This was facilitated by national co-ordinators and investigators who were trained in collecting data in a standardised manner. The study investigators had a research interest in stroke epidemiology, but there was not usually a special interest in service delivery. Although we recognise that the hospitals participating in INTERSTROKE are likely to have had a higher level of resources and support than is typical of poorer resourced areas, we know of no other study that has obtained such a broad range and quality of data using such standardised and prospective methods. If the centres participating in INTERSTROKE were better equipped than the average centres in each country (especially in LMICs), the gaps between HIC and LMIC in facilities , organized care , treatments and outcomes for stroke patients may be even greater than what we report.

Several previous studies have explored the potential impact of indicators of service quality in routine hospital settings,[27,28] however, almost all have been carried out in HIC settings. The most recent review of LMICs[8] could only identify limited observational information that could not adjust for confounders. Individual case studies in India, Thailand, South Africa and Mauritania[8] suggested that stroke unit care could have a beneficial impact in those settings. Only two studies have explored the impact of antiplatelet agents in LMICs and their results were inconclusive[28].

We believe that this analysis supports the widespread provision of appropriate early antiplatelet therapy and stroke unit care within hospitals in LMIC settings. It also indicates that a certain basic standard of care and supporting resources are likely to be needed to fully realise these benefits. These include adequate staffing and the capacity to accept the majority

476 of stroke patients. Further research needs to develop and test methods of effectively
477 implementing lower-cost, regionally appropriate models of stroke unit care.

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Research in context

Evidence before this study

We searched Medline, EMBASE and PubMed from January 1, 2000 to May 24, 2017, for large stroke register studies using Medical Subject Headings including stroke OR cerebral hemorrhage OR cerebral infarction AND quality indicator OR performance indicator OR quality improvement OR quality of care OR quality of health care OR registry OR register OR audit AND outcome OR mortality OR case fatality OR survival OR disability OR function OR recovery OR discharge OR discharge destination OR return home OR complications.. We identified 20 studies but none had been done in low or middle-income country settings.

Added value of this study

This is the first large study to use standardised, prospective data collection across a range of CIC levels in over 12,000 carefully characterised acute stroke patients from 108 hospitals in 28 countries. We have found that evidence-based treatments, diagnostics, and availability of stroke units were less common in LMICs. Access to stroke units and appropriate antiplatelet therapy were consistently associated with improved recovery.

Implications of all the available evidence

This analysis supports the widespread provision of appropriate early antiplatelet therapy and stroke unit care within hospitals in LMIC settings. A certain basic standard of care and supporting resources are likely to be needed to fully achieve these benefits. Further

research needs to develop and test methods of effectively implementing lower-cost, regionally appropriate models of stroke unit care.

Contributors

This sub-project of INTERSTROKE was conceived and jointly led by PL and MJO'D in conjunction with the study secretariat comprising the key national coordinators and members of the coordinating team at PHRI. PL and MJO'D designed the study, planned analyses, and wrote the first draft of the report. PL, MT and MJM did statistical analyses. All authors contributed to the collection of data, discussion and interpretation of the data, and to the writing of the report. All authors had full access to data and reviewed and approved the drafts of the report. MJO'D and SY jointly designed and led the overall INTERSTROKE study.

Declaration of interests

GJH reports personal fees from Bayer and Medscape, outside of the submitted work. H-CD has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfi zer, Sanofi -Aventis, Schering-Plough, Servier, Solvay, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi; financial support for research projects provided by AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi -Aventis, Syngis, and Talecris; served as editor of *Aktuelle Neurologie*, *Arzneimitteltherapie*, *Kopfschmerznews*, *Stroke News*, and the Treatment Guidelines of the German Neurological Society within the past year; and served as co-editor of *Cephalalgia*, and on the editorial board of *Lancet Neurology*, *Stroke*, *European Neurology*, and *Cerebrovascular Disorders*. PL, MJO'D, SLC, HZ, DX, AA, NM, MT, MJM, PL-J, AD,

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