Weekly variation in healthcare quality across day and time: nationwide registry based prospective cohort study of acute stroke care

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Abstract

Background

Studies in many health systems have found evidence of poorer quality of healthcare for patients admitted on weekends or overnight (the "weekend effect"). We hypothesised that variation in quality was dependent on not just day but also time of admission and aimed to describe the pattern and magnitude of 24/7 variation in the quality of acute stroke care occurring across the entire week.

Methods

Nationwide registry based prospective cohort study. Data were from the Sentinel Stroke National Audit Programme of 74307 patients admitted with acute stroke in England and Wales. Adjusted odds for thirteen measures of acute stroke care quality were estimated by fitting multilevel multivariable regression models across 42, four hour time periods per week.

Findings

Care quality varied across the entire week, and not just between weekends and weekdays, with different quality measures showing different patterns and magnitudes of variation. Four patterns of variation were identified: a diurnal pattern (e.g. dysphagia screening), a day of the week pattern (e.g. physiotherapy assessment), an off hours pattern (e.g. door to needle time for thrombolysis) and a flow pattern where quality changed sequentially across days (stroke unit admission). The largest magnitude of variation was for door to needle time within 60 minutes (Range 35-66%, coefficient of variation 18·2). There was no evidence of a difference in 30 day survival between weekends and weekdays (adjusted OR 1·03, 0·95-1·13) but patients admitted overnight on weekdays had lower odds of survival (adjusted OR 0·90, 0·82-0·99).

Interpretation

The "weekend effect" is a simplification, and just one of several patterns of weekly variation occurring in the quality of stroke care. Weekly 24/7 variation should also be sought for in other healthcare settings and quality improvement should focus on reducing 24/7 variation in quality and not just the weekend effect.

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Research In Context

Evidence before this study

We carried out a literature search of the MEDLINE database for English language studies published prior to June 2015 describing temporal variation in healthcare quality. The primary focus was to identify studies of stroke care but we also carried out searches to identify studies in other clinical settings. The search included the following terms: "Weekend", "Weekend effect", "Off hours", "Temporal variation", " AND Stroke", "AND quality". Studies of the weekend effect were identified in a wide range of clinical settings and geographies, describing evidence of poorer outcomes for patients admitted on the weekend or overnight with MI, stroke and general emergency admissions. We identified only a small number of studies that considered variation across both time of admission and day of week, including a study of obstetric outcomes in California and a study of hospital inpatients from Australia.

Added value of this study

We found evidence that in acute stroke care, the weekend effect is just one of several patterns of variation in quality that occur in real world practice. Quality varied across the whole week and different aspects of quality showed different patterns of variation.

Implications of all the available evidence

These findings imply that in acute stroke care, the weekend effect is a simplification of the true extent of temporal variation in healthcare quality that occurs across the week. A focus just on reducing differences in care quality between weekends and weekdays will therefore not fully address the problem of variation in healthcare quality across the week. Although we only looked at stroke care, the findings from previous studies observing the weekend effect in a wide variety of clinical setting suggests that these 24/7 variations in quality might also be pervasive across acute healthcare settings, and should be sought for and be a focus of quality improvement efforts.

Introduction

It is now well recognised that the quality of healthcare that patients receive may in part be determined by when they are admitted to hospital.[1] The "weekend effect" (poorer care quality and outcomes for patients admitted at the weekend) or “off hours effect” (poorer care outside of usual working hours) have been observed in many studies across a wide variety of clinical presentations.[2,3,4] Such studies have had a major, and sometimes contentious, impact on health policy, for example by prompting moves to increase the number of doctors working in hospitals at weekends.[5] However, our understanding of why healthcare quality may be worse overnight or at the weekend is lacking in evidence and remains largely speculative[6], creating difficulty in guiding health policy and quality improvement. Moreover, previous studies have generally taken the approach of comparing weekdays with weekends, or regular and off-hours, rather than measuring care quality across both day of the week and time. This risks obscuring other patterns of temporal variation in care quality which might occur and which might have important implications for understanding and improving the quality of healthcare services.

We therefore aimed to describe the pattern and magnitude of 24/7 variation in multiple domains of care quality for people admitted to hospital with acute stroke. Globally, stroke is the second leading cause of death[7] and the third largest contributor to disease burden[8]. There is good quality evidence for acute interventions (such as intravenous thrombolysis and organised stroke unit care) effective in improving outcomes after stroke[9]: how quickly acute stroke care is delivered is therefore both important and can be measured against evidence based standards. Our hypothesis was that care quality is dependent on not just day but also time of admission.

Methods

The study was carried out using data from the Sentinel Stroke National Audit Programme (SSNAP), the national register of stroke care in England and Wales. SSNAP collects data on the clinical characteristics and care quality (measuring multiple aspects of care from the time of admission up to six months after stroke) of patients admitted to all acute admitting hospitals in England and Wales with acute ischaemic stroke or primary intracerebral haemorrhage. Data were collected prospectively and validated by clinical teams and entered into the SSNAP database using a secure web interface. The investigators used an anonymised extract of this database. SSNAP is estimated to include approximately 95% of all adults admitted to hospital in England and Wales with stroke.[10]

Care quality was measured using a pre-existing set of quality indicators reported routinely by SSNAP[10], which are derived from UK national guidelines.[9] These indicators reflect the time critical nature of acute stroke care: Receiving a brain scan within one hour or 12 hours of admission, direct admission to a stroke unit (or intensive care unit/high dependency unit) within four hours of admission, administration of intravenous thrombolysis with alteplase, door to needle time of <60minutes for patients treated with thrombolysis, dysphagia screen within 4 hours of admission, reviews by a stroke specialist physician and nurse within 24 hours of admission, and assessments by physiotherapy, occupational therapy and speech and language therapy within 72 hours. Patients with clinical exclusions for dysphagia screening or therapy assessments (e.g. being treated palliatively only) were excluded from the denominator of these specific indicators. Only patients with ischaemic stroke presenting within 4.5 hours of stroke onset were included in the denominator for thrombolysis. The outcome measure was 30-day post admission survival.

The cohort was all adult patients (aged >16 years) admitted to hospital with acute stroke (ischaemic or primary intracerebral haemorrhage) in England and Wales from April 2013-March 2014.

SSNAP has approval to collect patient data under Section 251 of the NHS Act 2006 from the Confidentiality Advisory Group of the Health Research Authority. No additional ethical approval was sought.

Statistical Analysis

Time Stratification

We carried out time stratified analyses by classifying patients according to time of admission. The time of stroke onset was used instead for patients with stroke occurring as an inpatient. Two methods for stratifying time were used. Firstly, using six, four-hour time blocks per day of week (Midnight to 03:59 , 04:00 to

07:59, 08:00 to 11:59, 12:00 to 15:59, 16:00 to 19:59 and 20:00 to 23:59), resulting in 42 time categories in total. Periods of four hours were chosen because it was the shortest time period that provided sufficient numbers of patients in each block for model fitting (≈350+). Secondly we used larger time periods corresponding to weekends/weekdays and office/off hours, in order to aid comparison with previous literature on weekend effects: Monday-Friday 0800-1959, Saturday-Sunday 0800-1959, Monday-Friday 2000-0759 and Saturday-Sunday 2000-0759.

Model fitting

The magnitude of variation in care quality between time blocks was quantified by calculating the coefficient of variation (CoV; the ratio of the standard deviation to the mean, multiplied by 100). The CoV was used because it allows the dispersion of variables with different means to be compared.

Multivariable analysis was carried out by fitting multilevel[11] logistic regression models including patient age, sex, place of stroke onset (inpatient or out of hospital), stroke type, vascular comorbidity (atrial fibrillation, heart failure, diabetes mellitus, previous stroke or TIA, hypertension), pre-stroke functional level (as measured by the modified Rankin score[12]), time from stroke onset to admission, stroke severity (National Institutes of Health stroke score, or the level of consciousness on admission) and hospital level random intercepts. Time categories were included as fixed effects. The middle ranking time period (21st) in the unadjusted analyses was used as the reference category in the models using 42 time blocks per week, and Mon-Fri 0800-1959 was used as the reference category in the models using four time blocks per week. Adjusted absolute effect sizes were calculated using marginal standardisation[13].

Sensitivity Analyses

Data were 100% complete for all baseline variables apart from NIHSS on admission, which was available for 54048 patients (73%). We carried out sensitivity analyses to explore the effect of these missing data. Firstly, models were fitted using level of consciousness on admission (which was available for 100% of patients) as a proxy for stroke severity, and the results compared to models using NIHSS. Secondly, models were fitted following multiple imputation[14] of 20 datasets. Sensitivity analyses were also carried out after excluding patients who died within 1 day of admission.

Analyses and visualisations were carried out using Stata 14 (StataCorp, College Station, TX).

Results

There were 74307 patients with acute stroke admitted to 199 hospitals. The median age of patients was 77 (IQR - Interquartile range 67-85) and 65193 (88%) had an ischaemic stroke [Figure 1]. The most frequent day of admission was Monday (16%), and admissions were less frequent on Saturdays (13%) and Sundays (13%) compared to weekdays. Discharges from hospital were less common at weekends, with only 6% and 3% of hospital discharges occurring on Saturday and Sunday respectively.

There was wide variation in both the magnitude and pattern of temporal variation in quality across the 13 quality indicators [Figure 2]. In unadjusted analyses, the greatest magnitude of variation was observed for door to needle time of < 60 minutes, which ranged from 35-66% (Coefficient of Variation 18·2). The indicators with the smallest variation were 30 day survival, which ranged from 80-90 % (CoV 3·1) and assessment by a stroke nurse (Range 77-90%, CoV 3·5).

We observed four main patterns of 24/7 variation in the heatmaps and these were similar in both the unadjusted and multivariable analyses of each indicator [Figs 3-6]. Four of the indicators showed a diurnal pattern of variation, with quality varying across time of day (dysphagia screen, brain scan within 12 hours, brain scan within 1 hour, thrombolysis). This variation was not only restricted to differences between daytimes and overnight – for example patients arriving during the morning were more likely to receive a brain scan within one hour compared to those admitted in the afternoon [Figure 3]. Six of the indicators varied across days of the week, with lower quality care for weekend admissions (stroke physician assessment and nurse assessment) [Figure 4] or for patients admitted on a Thursday or Friday (Physiotherapy, occupational therapy, communication SLT therapy and swallow SLT assessments) [Figure 5]. The third pattern was for a poorer care both overnight and at the weekend (door-to-needle time for thrombolysis). The fourth pattern was of sequential change in quality across both day and time, with quality improving sequentially across weekdays and then deteriorating at the weekend, resulting in patients on Mondays having the lowest odds of being admitted to a stroke unit within four hours [Figure 4].

There was no evidence for a difference in adjusted 30 day survival between patients admitted during the day at the weekend compared to weekdays [Figure 7 and Web Appendix] in the models using either NIHSS (aOR 1·03, 0·95-1·13) or level of consciousness (aOR 0·97, 0·91-1·04). There was weak evidence that survival was worse for patients admitted overnight on weekdays, (aOR 0·90, 0·82-0·99; absolute difference in adjusted survival -0·7%, -1·2 to -0·2). The point estimate and confidence intervals of survival for patients admitted overnight at weekends differed between models – there was evidence that survival was poorer in the models using level of consciousness (aOR 0·84, 0·77-0·93; absolute difference -1·5%, -2·3 to -0·7%) and with multiply imputed NIHSS (aOR 0·86, 0·77-0·95) but not in the model using NIHSS (aOR 0·89, 0·78-1·01). The sensitivity analyses using imputed datasets and excluding patients dying within one day of admission were otherwise similar - the only change of note in the latter sensitivity analysis was a modest reduction in effect size for brain scanning within 1 hour.

Discussion

Variations in the quality of acute stroke care were found to occur across the whole week and not just between weekends and weekdays, with individual indicators of care quality differing in the magnitude and pattern of variation. This suggests that even within a single, well defined clinical pathway such as acute stroke care, temporal variation is a complex phenomenon that probably has multiple causes. Our findings indicate that the concept of the "weekend effect" is a major simplification of the true extent and nature of temporal variation in healthcare quality and that it is just one of a number of patterns of variation in care quality that occur in real world clinical practice. Unmasking these potentially hidden sources of variation in quality through appropriate data collection and visualisation might help in identifying the factors causing variation in quality (such as staffing levels or bed capacity) and has the potential of being an important tool for quality improvement in healthcare.

There is an extensive previous literature exploring differences in care quality and outcomes between weekdays and weekends.[2,3,4,15,16] [Research in Context Panel]. Some studies have also described differences in care between daytimes and overnight[17] and between regular hours and off-hours[18]. Studies of the weekend effect in stroke care specifically have been conflicting. Some have found evidence for reduced quality of care (but no difference in mortality) for patients admitted on weekends [19], and the evidence for differences in mortality between weekend and weekday admissions is mixed.[20,21,22] These differences might be explained by differences in how stroke care services are organised[22], and there is evidence that low nurse staffing levels on stroke units are associated with higher mortality at weekends.[23]

The limitation of much of the previous literature on the "weekend effect" is that it has typically been based on comparisons of weekends versus weekdays, or regular versus off-hours, without taking into account variation that might occur across both day of the week and time of day. There are however a small number of studies that have considered how care might vary in this way. For example, administrative data has been used to model daily and diurnal patterns in mortality risk as part of a prognostic model for hospital inpatients[24] and identified weekend effects lagging into the following week.[25] Diurnal patterns have also been observed in the frequency of obstetric complications.[26] It therefore seems likely that the patterns of healthcare quality we observed in this study are not restricted to stroke care and would be found in other acute healthcare settings if they were sought for.

We identified four main patterns of temporal variation in stroke care quality and we hypothesise that they reflect differing underlying causal factors. This study is not able to identify what these causal factors are, but may generate hypotheses for future studies. Recognising characteristic patterns of variation might be useful in helping identify and tackle these underlying causes and so organise healthcare services more effectively.

The diurnal patterns we observed may be the result of reduced clinical services overnight – such as lower staffing levels or reduced access to diagnostics. However, we found that variation in quality also occurred during usual working hours, suggesting that there may be other contributory factors. For example, that patients admitted in the afternoon were less likely to get an urgent brain scan than those admitted in the morning might be due to higher demand for CT scanning at busier times of the day.

Variation in quality that relates directly to admission on, or in relation to the weekend suggests that how healthcare is organised on the weekend affects quality. Survey data show that stroke services in England and Wales are more likely to provide seven day physiotherapy than occupational therapy or speech therapy services[10] - consistent with the pattern of variation seen in this study. The data are also evidence that the provision of healthcare on weekends may also affect patients admitted on other days of the week, with patients admitted on Thursdays and Fridays experiencing the longest waits for therapy assessment.

One indicator (door to needle time) showed a strong relationship to both day of week and time of day, with reduced performance both overnight and at weekends. Achieving fast door to needle times in acute stroke requires that the entire diagnostic, decision making and treatment pathway is carried out quickly – if just one stage is slow then this may cause critical delays in the whole pathway. Interventions that require this type of rapid coordinated, systems response with on-site presence of key decision makers might be therefore show the greatest magnitude of 24/7 variation.

The pattern of care quality observed for stroke unit access seems most likely to reflect patient flow and bed capacity within stroke care services. We hypothesise that this is due to loss of spare bed capacity over the weekend as a result of reduced frequency of hospital discharges, resulting in the slowest transfers to stroke units occurring on Mondays.

Variation in survival after stroke was largely explained by differences in patient characteristics, with proportionally more unwell patients being admitted during off hours. Therefore one of the reasons for apparent temporal variation in care quality are factors which determine when and how patients present to healthcare services. It is possible therefore that the conflicting nature of the literature on the presence or not of the weekend effect reflects the ability of different studies to control for this source of confounding.[27]

Further research could help to test these hypotheses and identify the reasons for these patterns of temporal variation, identify new patterns of temporal variation and perhaps aid in developing new taxonomies of temporal variation in healthcare quality. In the meantime, these findings imply that there will not be a single solution to eradicating time based inequalities in care. Solutions are likely to require not just ensuring appropriate clinical staffing but also measures to improve the capacity and utilisation of beds, generate more efficient patient flow, improve access to diagnostic and clinical support services, and improve the overall resilience of care pathways. They also need to consider the wider healthcare system and not just the hospital in isolation, such as the availability of social care and community services at the weekends, on which patient discharges from hospital are dependent. Much of the current discourse on reducing weekend effects has occurred in the absence of a detailed understanding of why temporal variation in care quality occurs. Since solutions are likely to come at significant financial and opportunity cost[28], policy makers, healthcare managers and funders need to ensure that the reasons for temporal variation in quality are properly understood and that resources are targeted appropriately. For example, simply transferring clinicians from weekdays to weekends may not have the intended effect on quality and may lead to unintended consequences for the quality of care provided on weekdays. One potential method for gaining a better insight into variations in care quality might be to make use of the types of data visualisations we have used in this study, which is becoming increasingly feasible as electronic healthcare data increases in scope and detail.

Limitations

Overall the data were very complete and strengthened by being from a national registry of clinical (rather than administrative) data, but data were missing for one variable. Although the main analysis used a complete case analysis, we found that the study results were similar when a proxy measure was used, and when multiple imputation was used to account for missing data. Outcomes were measured using survival, which although important is a relatively limited measure of stroke outcomes. The study have been strengthened by other measures such as disability and quality of life. Nonetheless, most of the process measures used in this study have a strong empirical rationale from randomised controlled trial evidence[29,30], and longer term disability data are not currently available in SSNAP. There appeared to be little similarity in the pattern of variation between survival and the other quality measures , which might be because these interventions do not influence survival (e.g. thrombolysis reduces disability but not mortality [29]) or that associations exists at the patient level but not at the group level. The study used time sensitive care quality indicators, which are likely to be more subject to temporal variation than aspects of care where timeliness is less important. The use of these indicators was however not arbitrary, and the study used the already existing national set of acute stroke indicators. We used the relatively simple method of stratifying by time rather than fitting more complex time series models; this has the disadvantage of assuming that time changes in blocks rather than continuously. In future studies we plan to explore different methods to model the effect of day of week and time of day, and use larger datasets to reduce the time resolution to shorter time periods.

Summary

We found evidence that care quality in acute stroke care varies with time in much more complex ways than previous studies of the "weekend effect" in healthcare would suggest. Although this study is of the quality of care received by people with acute stroke, it seems unlikely that stroke is alone in displaying such patterns of temporal variation in quality. Extending this methodology to other areas of healthcare, particularly for presentations where the timeliness of care is an important determinant of outcomes (such as acute myocardial infarction or surgical emergencies) would be useful further areas of research. Finally, this study suggests that there is a need for a more sophisticated understanding of the patterns of and reasons for temporal variation in care quality and that this should become a routine part of quality improvement in healthcare.

	Characteristic
n	74307
Female (n, %)	37434 (50)
Age (Median, IQR)	77 years (67-85)
Stroke Type (n,%)	
Ischaemic	65193 (88)
ICH	8038 (11)
Undetermined	1076 (2)
Pre stroke modified Rankin Scale (n,%)	
0	42524 (57)
1	11311 (15)
2	7011 (9)
3	7801 (11)
4	4249 (6)
5	1391 (2)
NIHSS on arrival (Median, IQR)	4 (2-10)
Level of consciousness on arrival (n,%)	
0 (Alert)	61638 (83)
1 (Not alert: Responds to voice)	7482 (10)
2 (Not alert: Responds to pain)	2978 (4)
3 (Totally unresponsive)	2209 (3)
Co-Morbidity (n,%)	
Heart failure	4079 (6)
Hypertension	39918 (54)
Atrial fibrillation	15385 (11)
Diabetes mellitus	14424 (19)
Previous stroke or TIA	20292 (27)
Onset in hospital (n,%)	3969 (5)
Time from onset to admission, minutes (n,%)	
Unclear symptom onset (eg wake up stroke)	28739 (39)
<180	25441 (34)
180-359	7126 (10)
>360	13001 (18)
Day of admission (n,%)	
Sun	9515 (13)
Mon	11618 (16)
Tue	11077 (15)
Wed	11058 (15)
Thu	10882 (15)
Fri	10756 (15)
Sat	9401 (13)
Day of discharge if discharged alive (n,%)	

Sun	1955 (3)
Mon	10701 (17)
Tue	11467 (18)
Wed	11012 (18)
Thu	11061 (18)
Fri	13268 (21)
Sat	3578 (6)
30 day survival (n,%)	64597 (87)

Fig 1. Characteristics of the cohort

	Mean (SD)	Range in quality from lowest to highest time category (n, %)	Coefficient of Variation
Thrombolysis rate (%)	32·1 (3·9)	38/179 - 76/205 21-37%	12·6
Door to needle time <60 minutes (%)	49·1 (8·9)	16/46 -232/350 35-66%	18·2
Brain scan within 1 hour (%)	41·7 (2·8)	186/543 - 1403/2980 34-47%	6·6
Brain scan within 12 hours (%)	84·0 (7·3)	1815/2510 - 2837/2980 72-95%	8·7
Stroke unit admission within 4 hours (%)	56·4 (4·5)	293/607 -2026/3086 46-65	8·0
Dysphagia screen within 4 hours (%)	61·5 (5·8)	249/495 - 1911/2624 50-73%	9·4
Stroke physician within 24 hours (%)	71·8 (9·8)	266/543 - 1148/1351 49-85%	13·6
Stroke nurse within 24 hours (%)	85·4 (3·0)	394/509 - 2784/3086 77-90%	3·5
Physiotherapy assessment within 72 hours (%)	93·0 (3·9)	363/447 - 551/566 81-97%	4·2
Occupational therapy assessment within 72 hours (%)	85·8 (5·4)	293/415 - 1830/1998 71-92%	6·3
Communication SLT assessment within 72 hours (%)	77·4 (8·9)	620/1253 - 623/700 50-89%	11·5
Swallow SLT assessment within 72 hours (%)	78·3 (5·6)	749/1184 - 263/301 63-87%	7·2
30 day survival (%)	85·9 (2·6)	432/543 - 2918/3252 80-90%	3·1

Fig 2. Care quality across the 42 time categories in the week. Thrombolysis rate is of patients with ischaemic stroke presenting within 4.5 hours of stroke onset.

Fig 3. Heatmap showing variation in thrombolysis, door to needle time, brain scan within 1 hour and brain scan within 12 hours

Fig 4. Heatmap showing variation in stroke unit admission, dysphagia screen within 4 hours, stroke physician within 24 hours and stroke nurse within 24 hours

Fig 5. Heatmap showing variation in physiotherapy assessment within 72 hours, occupational therapy assessment within 72 hours, communication speech and language therapist (SLT) assessment within 72 hours, swallow SLT assessment within 72 hours

Fig 6. Heatmap showing variation in 30 day survival

	Weekday 0800-1959	Weekend 0800-1959		Weekday 2000-0759		Weekend 2000-0759	
	-	OR	95%CI	OR	95%CI	OR	95%CI
Thrombolysis	REF	0•86	0•79-0•95	0•67	0•61-0•74	0•73	0•64-0•84
Door to needle time < 60 minutes	REF	0•55	0•47-0•63	0•40	0•34-0•46	0•35	0•28-0•43
Brain scan within 1 hour	REF	0•83	0•78-0•87	0•76	0•72-0•80	0•72	0•66-0•78
Brain scan within 12 hours	REF	0•76	0•70-0•81	0•51	0•47-0•55	0•51	0•45-0•57
Stroke unit admission within 4 hours	REF	0•78	0•74-0•83	0•71	0•67-0•75	0•67	0•61-0•73
Dysphagia screen within 4 hours	REF	0•75	0•71-0•79	0•61	0•58-0•65	0•55	0•50-0•60
Stroke physician within 24 hours	REF	0•42	0•40-0•45	0•77	0•72-0•82	0•34	0•31-0•37
Specialist stroke nurse within 24 hours	REF	0•63	0•58-0•68	0•80	0•73-0•88	0•48	0•42-0•54
Physiotherapy assessment within 72 hours	REF	1•25	1•11-1•40	0•95	0•85-1•07	1•00	0•84-1•19
Occupational therapy assessment within 72 hours	REF	1•18	1•08-1•29	0•94	0•87-1•03	1•03	0•90-1•18
Communication assessment by SLT within 72 hours	REF	1•25	1•14-1•37	1•09	0•99-1•20	1•05	0•91-1•22
Swallow assessment by SLT within 72 hours	REF	1•10	1•00-1•23	1•04	0•94-1•16	0•94	0•80-1•11
30 day survival	REF	1•03	0•95-1•13	0•90	0•82-0•99	0•89	0•78-1•01

Fig 7 Adjusted odds ratio of receiving each of care quality indicator· Multivariable model including stroke severity (NIHSS), age, sex, stroke type, place of stroke onset, pre stroke level of functioning, vascular comorbidity, elapsed time from stroke onset to admission and hospital level random intercepts

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Contributions

BDB – Devised the study, carried out the analysis and wrote the manuscript

GCC – Wrote the manuscript, provided clinical insight and critical commentary

MAJ – Wrote the manuscript, provided clinical insight and critical commentary

HH – Wrote the manuscript, and provided critical commentary

LP – Carried out the analysis and wrote the manuscript

KS – Wrote the manuscript, and provided critical commentary

PJT - Wrote the manuscript, provided clinical insight and critical commentary

CDAW - Wrote the manuscript, and provided critical commentary

AGR – Wrote the manuscript, provided clinical insight and critical commentary

Competing Interests

Conflicts from each author are listed below:

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