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Impact of HIV on inpatient mortality and complications in stroke in Thailand: a National Database Study

K. CUMMING[1], S. TIAMKAO[2,3], K. KONGBUNKIAT[2,3], A. B. CLARK[4], J. H. BETTENCOURT-SILVA[4], K. SAWANYAWISUTH[5], N. KASEMSAP[2,3], M. A. MAMAS[6,7], J. A. SEELEY[8,9] AND P. K. MYINT[1]*

[1] *Epidemiology Group, Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Aberdeen, UK;* [2] *Neurology Division, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand;* [3] *North-eastern Stroke Research Group, Khon Kaen University, Khon Kaen, Thailand;* [4] *Norwich Medical School, University of East Anglia, Norwich, UK;* [5] *Ambulatory Medicine Division, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand;* [6] *Cardiovascular Research Group, Keele University, Stoke-on-Trent, UK;* [7] *Farr Institute, University of Manchester, Manchester, UK;* [8] *Medical Research Council Uganda Virus Research Institute, Research Unit on AIDS, Entebbe, Uganda;* [9] *London School of Hygiene & Tropical Medicine, London, England, UK*

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SUMMARY

The co-existence of stroke and HIV has increased in recent years, but the impact of HIV on post-stroke outcomes is poorly understood. We examined the impact of HIV on inpatient mortality, length of acute hospital stay and complications (pneumonia, respiratory failure, sepsis and convulsions), in hospitalized strokes in Thailand. All hospitalized strokes between 1 October 2004 and 31 January 2013 were included. Data were obtained from a National Insurance Database. Characteristics and outcomes for non-HIV and HIV patients were compared and multivariate logistic and linear regression models were constructed to assess the above outcomes. Of 610 688 patients (mean age 63·4 years, 45·4% female), 0·14% (866) had HIV infection. HIV patients were younger, a higher proportion were male and had higher prevalence of anaemia ($P < 0·001$) compared to non-HIV patients. Traditional cardiovascular risk factors, hypertension and diabetes, were more common in the non-HIV group ($P < 0·001$). After adjusting for age, sex, stroke type and co-morbidities, HIV infection was significantly associated with higher odds of sepsis [odds ratio (OR) 1·75, 95% confidence interval (CI) 1·29–2·4], and inpatient mortality (OR 2·15, 95% CI 1·8–2·56) compared to patients without HIV infection. The latter did not attenuate after controlling for complications (OR 2·20, 95% CI 1·83–2·64). HIV infection is associated with increased odds of sepsis and inpatient mortality after acute stroke.

Key words: Complications, HIV, mortality, outcomes, stroke.

INTRODUCTION

The incidence of stroke in low- to middle-income countries where HIV is prevalent has increased by over 100% during the past four decades [1]. Co-existence of HIV and stroke has increased and associations between HIV and stroke have been

* Author for correspondence: Professor P. K. Myint, Epidemiology Group, Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Aberdeen, AB25 2ZD, UK. (Email: phyo.myint@abdn.ac.uk)

increasingly recognized [2, 3]. Indeed, both these conditions are leading causes of death and disability globally, and thus their increasing co-existence is of significant public health relevance [4]. An independent association between HIV and ischaemic stroke has been demonstrated and, in some cases, stroke has been the presenting manifestation of HIV [5–7].

Despite this, the impact of HIV on stroke outcome is poorly understood. In particular, the prognostic implications of HIV on stroke have never been specifically investigated. With advances in HIV treatment associated with improved survival rates, the population ageing with HIV will continue to grow with a likely increasing incidence of non-communicable conditions including stroke.

We investigated the characteristics and prognostic implications of stroke patients with co-existing HIV infection in Thailand. Serious and common complications, inpatient mortality and length of acute inpatient hospital stay (LOS) after stroke were the selected outcomes of interest.

METHODS

Data were obtained from the Universal Coverage Health Security Insurance Scheme Database in Thailand. Briefly, in Thailand, the whole population is covered by three insurance schemes: the Civil Servant Benefit System covers government employees and their dependants (~7% of the population). The Social Security scheme covers private sector employees (~13% of the population). The Universal Coverage Health Security Scheme is a basic health insurance scheme covering the rest of the population [8].

All acute hospitalized strokes in Thailand between 1 October 2004 and 31 January 2013 were studied. We selected this time period as stroke management in Thailand has become more in line with current international practice since 2004. Diagnosis of stroke was identified from ICD coding (ICD-10 codes I60-I64) on reimbursement forms. In Thailand, diagnosis of stroke is made during an individual's inpatient hospital stay by the attending clinical teams based on clinical features and investigative findings including brain imaging. Demographic and clinical data were obtained from reimbursement forms using ICD codes, on an annual basis, from 2004 until 2013. Data included age, sex, HIV status, co-morbidities, stroke type, complications of stroke occurring during hospital admission (pneumonia, sepsis, respiratory failure and convulsions; using ICD codes), admission and discharge date and inpatient mortality. Stroke types were categorized as haemorrhagic (I61, I62), ischaemic (I63) or stroke of undetermined pathology (I64).

Statistical analysis was performed using Stata v. 11.2/SE (StataCorp., USA). Statistical significance was assumed where $P < 0{\cdot}05$. Descriptive statistics were calculated separately for individuals with and without HIV infection and compared.

Post-stroke complications for stroke patients with HIV were assessed using four logistic regression models using non-HIV patients as the reference category. Model A presents an unadjusted analysis; model B adjusted for age and sex; model C adjusted for age, sex and stroke type; model D was constructed as model C with additional adjustment for the three commonest co-morbid conditions (hypertension, history of previous stroke and anaemia); and model E (mortality and LOS outcomes only) was constructed as in model D with additional adjustment for complications of stroke (pneumonia, sepsis, respiratory failure and convulsions). Models were repeated stratifying by stroke type. For LOS outcome a linear regression model was used, but in order to allow for the non-normal distribution of LOS a bootstrap using 1000 replications was used to estimate the P value and confidence interval for the mean difference in LOS between HIV and non-HIV stroke patients.

The study was approved by the Ethics Committee in Human Research, Khon Kaen University, Khon Kaen, Thailand.

RESULTS

Between 1 October 2004 and 31 January 2013, 610688 hospitalized stroke patients were identified and included in this analysis. Sample mean age was 63·4 years (±14·7 years), 45·4% ($n = 276\,178$) were female and the prevalence of HIV was 0·14% ($n = 866$). Characteristics of the study sample, according to HIV status, are presented in Table 1. On average, those with HIV were 22·2 years younger and a higher proportion were male ($P < 0{\cdot}001$). Hypertension and diabetes were almost five times more prevalent in the non-HIV group ($P < 0{\cdot}001$) but the overall number of patients with diabetes in the HIV group was very low ($n = 29$). The prevalence of anaemia in the HIV group was more than double than in the non-HIV group ($P < 0{\cdot}001$). The proportion of individuals with different types of stroke varied between the two groups ($P < 0{\cdot}001$). Haemorrhagic stroke was

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Table 1. *Sample characteristics of 610 688 hospitalized stroke patients with and without HIV infection in Thailand, 2004–2013*

Characteristic	Non-HIV	HIV	*P* value
Number (*N*)	609 802	866	
Age (years)			
Mean (±S.D.)	63·5 (14·7)	41·3 (11·3)	<0·001
Female sex, % (*n*)	45·2 (275 911)	30· 8 (267)	<0·001
Co-morbidities, % (*n*)			
Hypertension	44·2 (269 562)	9 (78)	<0·001
Diabetes	16·5 (100 319)	3·3 (29)	<0·001
Previous stroke	7·8 (47 467)	7·4 (64)	0·666
Anaemia	5·4 (32 652)	12·9 (112)	<0·001
Rheumatic heart disease	0·9 (5488)	0·3 (3)	0·085
Chronic obstructive pulmonary disease	1·9 (11 591)	0·3 (3)	0·001
Chronic ischaemic heart disease	2·7 (16 344)	0 (0)	<0·001
Chronic kidney disease	3·1 (19 188)	0·7 (6)	<0·001
Atrial fibrillation	6·1 (37 177)	0·7 (6)	<0·001
Heart failure	1·5 (8994)	0·7 (6)	0·056
Stroke type, % (*n*)			<0·001
Haemorrhagic	34·6 (211 117)	30·1 (261)	
Ischaemic	50·1 (305 621)	61·3 (531)	
Stroke of undetermined pathology	15·3 (93 061)	8·5 (74)	

Table 2. *Comparison of outcomes after stroke in 610 688 hospitalized stroke patients with and without HIV infection in Thailand, 2004–2013*

Outcome investigated	Non-HIV	HIV	*P* value
Number (*N*)	609 802	866	
Complication of stroke, % (*n*)			
Pneumonia	9·6 (58 524)	7·2 (62)	0·015
Sepsis	3·2 (19 654)	5 (43)	0·004
Respiratory failure	7·3 (44 333)	6·7 (57)	0·436
Convulsion	3·4 (20 475)	6·4 (55)	<0·001
Inpatient death	13·3 (80 977)	20·2 (175)	<0·001
Length of inpatient stay (days)			
Mean (±S.D.)	7·5 (11·5)	9 (10·6)	0·2909

marginally more common in the non-HIV group while ischaemic stroke was more common in the HIV group. The prevalence of stroke of undetermined pathology was almost double in the non-HIV group compared to that in the HIV group.

The commonest complications of stroke in this cohort were pneumonia, sepsis, respiratory failure and convulsions, and these were therefore selected as outcomes of interest (Table 2). Overall, stroke complications were more prevalent in the HIV group, apart from pneumonia ($P = 0{\cdot}009$) and there was no significant difference in rates of respiratory failure ($P = 0{\cdot}48$). The remaining complications sepsis, convulsions and inpatient death were significantly more prevalent in the HIV group ($P = 0{\cdot}004$, $P < 0{\cdot}001$, $P < 0{\cdot}001$, respectively). Mean LOS was 20% greater in the HIV group compared to the non-HIV group ($P = 0{\cdot}002$).

Odds ratios (OR) and corresponding 95% confidence interval (CI) for complications of stroke in patients with HIV are detailed in Table 3. Similarly, the analysis stratified by stroke type is presented in Table 4. After full adjustment, HIV was associated with higher odds of sepsis (OR 1·75, 95% CI 1·29–2·4) and mortality (OR 2·15, 95% CI 1·8–2·56). Additionally controlling for complications did not attenuate the poor mortality outcome (OR 2·20, 95% CI 1·83–2·64). HIV was associated with a higher

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Table 3. *Odds ratios (OR) and corresponding 95% confidence intervals (CI) [mean length of stay (LOS) differences and 95% CI for LOS outcome] for complications of hospitalized stroke in 866 patients with HIV using 609 802 non-HIV patients as the reference category in Thailand, 2004–2013*

	OR (95% CI)				
Complication	Model A	Model B	Model C	Model D	Model E
Pneumonia	0·73 (0·56–0·94)	1·14 (0·88–1·48)	1·21 (0·93–1·57)	1·01 (0·78–1·32)	
Sepsis	1·57 (1·15–2·13)	2·16 (1·59–2·95)	2·17 (1·6–2·96)	1·75 (1·29–2·4)	
Respiratory failure	0·9 (0·69–1·18)	1 (0·76–1·31)	1·16 (0·88–1·52)	1·02 (0·78–1·35)	
Convulsion	1·95 (1·48–2·57)	1·29 (0·98–1·7)	1·23 (0·94–1·62)	1·05 (0·8–1·38)	
Death	1·65 (1·4–1·95)	1·65 (1·4–1·95)	2·29 (1·92–2·73)	2·15 (1·8–2·56)	2·2 (1·83–2·64)
Mean difference in LOS (days)	1·54 (0·84–2·24)	1·55 (0·85–2·25)	2·05 (1·30–2·79)	1·64 (0·89–2·39)	1·11 (0·41–1·82)

Model A: unadjusted analysis.
Model B: analysis adjusted for age and sex.
Model C: analysis adjusted for age, sex and stroke type.
Model D: analysis adjusted for age, sex, stroke type and co-morbidities.
Model E: analysis adjusted for age, sex, stroke type, co-morbidities and complications (pneumonia, sepsis, respiratory failure or convulsion).

risk of convulsions in earlier models, in haemorrhagic and ischaemic stroke, but the associations observed did not reach statistical significance after adjustments. Overall, HIV was associated with longer LOS but only model C reached statistical significance. However, in the stratified analysis, HIV had a higher odds of longer inpatient stay in ischaemic stroke (OR 2·74, 95% CI 1·8–3·68).

DISCUSSION

Our study is the largest analysis to date of the clinical characteristics and outcomes of hospitalized strokes in patients with HIV. In line with previous reports, stroke patients with HIV were younger and a higher proportion were male, compared to those without HIV infection [2, 6, 9, 10]. Traditional stroke risk factors were more prevalent in the non-HIV group, while anaemia was more prevalent in the HIV group [11]. We demonstrate a higher rate of post-stroke complications in patients with HIV and, to the best of our knowledge, are the first group to specifically report this. HIV infection had an impact on the likelihood of developing sepsis during acute hospital stay after stroke and was associated with increased inpatient mortality.

The lower prevalence of traditional stroke risk factors in our HIV cohort supports literature suggesting that the mechanisms and risks of stroke in HIV are different from the general population. These include combination antiretroviral therapies (cARTs), chronic systemic and opportunistic infections, vasculopathies, coagulopathies and metabolic and immune dysregulation [12, 13]. As previously reported, ischaemic stroke was the commonest type of stroke in patients with HIV [2, 5, 10]. It is perhaps surprising that the prevalence of stroke of undetermined pathology was higher in the non-HIV group. In HIV, neurological complications, e.g. cerebral toxoplasmosis, are common and may mimic stroke. These alternative diagnoses, with different treatment requirements, should always be considered in HIV patients with suspected stroke.

Our HIV cohort had a higher incidence, and in some cases risk, of convulsions, sepsis, inpatient mortality and longer LOS than those patients without HIV. Convulsions were almost twice more frequent in the HIV group although the fully adjusted ORs were not statistically significant. In a much smaller sample Hoffman *et al.* observed a higher prevalence of seizures on admission in stroke in HIV, but this was not statistically significant [14]. Our findings related to increased likelihood of sepsis in HIV- compared to non-HIV-infected stroke patients (fully adjusted OR 1·75) are not surprising. This is important because acute inflammatory response and sepsis, in the acute stroke setting, are associated with poorer outcomes [15, 16]. Our finding is also in keeping with reports of co-existent and causative infection in ischaemic stroke in HIV [10, 14, 17]. It is not clear why those with haemorrhagic stroke were at highest risk of sepsis (OR 2·16). It may be because haemorrhagic strokes present with more severe neurological

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Table 4. *Odds ratios and corresponding 95% confidence intervals (CI) [mean length of stay (LOS) differences and 95% CI for LOS outcome] for complications of hospitalized stroke in 866 patients with HIV stratified by stroke type using 609 802 non-HIV patients as the reference category in Thailand, 2004–2013*

Stroke type	Pneumonia	Sepsis	Respiratory failure	Convulsion	Death	LOS
Haemorrhagic						
Model A	0·6 (0·38–0·95)	1·86 (1·14–3·05)	1·06 (0·74–1·53)	1·88 (1·13–3·12)	1·6 (1·24–2·06)	−1·03 (-2·33 to 0·27)
Model B	0·8 (0·51–1·26)	2·23 (1·36–3·65)	1·21 (0·84–1·74)	1·23 (0·74–2·04)	1·82 (1·41–2·34)	−0·81 (-2·07 to 0·46)
Model C	0·71 (0·44–1·12)	1·9 (1·15–3·14)	1·14 (0·79–1·65)	1·06 (0·64–1·77)	1·76 (1·37–2·27)	−1·28 (−2·53 to −0·03)
Model D	—	—	—	—	1·71 (1·32–2·23)	−0·88 (-2·19 to 0·43)
Ischaemic						
Model A	0·77 (0·56–1·07)	1·34 (0·89–2·01)	0·77 (0·5–1·16)	2·03 (1·45–2·84)	1·98 (1·55–2·54)	2·84 (1·90 to 3·78)
Model B	1·66 (1·19–2·31)	2·25 (1·49–3·4)	1·23 (0·81–1·88)	1·42 (1·01–1·98)	3·16 (2·46–4·05)	3·50 (2·56 to 4·44)
Model C[c]	1·3 (0·93–1·82)	1·72 (1·14–2·61)	0·98 (0·65–1·5)	1·19 (0·85–1·66)	2·72 (2·12–3·5)	2·99 (2·05 to 3·93)
Model D	—	—	—	—	2·97 (2·27–3·89)	2·74 (1·80 to 3·68)
Undetermined stoke type						
Model A	0·98 (0·36–2·67)	1·61 (0·39–6·56)	0·65 (0·09–4·66)	1 (0·24–4·06)	3·09 (1·54–6·22)	1·61 (0·09 to 3·14)
Model B	2·49 (0·9–6·87)	2·89 (0·71–11·86)	1·07 (0·15–7·75)	0·66 (0·16–2·69)	4·71 (2·34–9·51)	2·37 (0·87 to 3·86)
Model C	2·18 (0·79–6·02)	2·54 (0·62–10·44)	1·01 (0·14–7·28)	0·62 (0·15–2·53)	4·36 (2·15–8·8)	2·30 (0·83 to 3·77)
Model D	—	—	—	—	4·12 (1·96–8·66)	1·92 (0·46 to 3·38)

Model A: unadjusted analysis.
Model B: analysis adjusted for age and sex.
Model C: analysis adjusted for age, sex and co-morbidities.
Model D: analysis adjusted for age, sex, stroke type, co-morbidities and complications (pneumonia, sepsis, respiratory failure, convulsions.

deficits, requiring invasive treatment entailing a higher infection risk.

The higher risk of mortality in stroke in HIV (fully adjusted OR 2·20) has previously been found, but is not consistent with all literature [10, 11, 18]. These smaller single-centre studies may have lacked power to detect statistically significant findings. Differences in results may also reflect the increasing availability of cARTs over time, or changes in acute stroke treatment [10]. Our finding is important because since the genesis of cART, non-HIV-related conditions, including cardiovascular and cerebrovascular disease, have become the leading causes of death in people with HIV infection [19]. It is interesting that ischaemic stroke of undetermined pathology in HIV carried the highest risk of death (OR 4·12), raising the possibility of serious life-threatening causes of stroke in these cases. Unfortunately, data on the precise cause of death were not available from our dataset and so this was not accounted for in our analysis. In keeping with the higher prevalence of complications found here, and with previous literature, mean LOS was longer in HIV patients, particularly those with ischaemic stroke [11].

Overall this study shows that HIV in stroke has poorer clinical outcomes. We found that, compared to non-HIV stroke patients, HIV patients with stroke are younger and have different co-morbid conditions which may contribute to risk of stroke in HIV and subsequent clinical sequelae. Alternatively, there may be a broader spectrum of stroke severity in older non-HIV stroke patients and that HIV patients suffer more severe stroke at a younger age, with higher complication rates. Our dataset did not allow us to investigate this, but another group have reported greater stroke severity in HIV while others have found no differences [9, 10, 18]. Another explanation for our findings may be the aetiology of stroke in HIV. Reported aetiologies of stroke in HIV, e.g. vasculopathies may incur more widespread arterial involvement and hence worsen outcomes [10, 20]. To this end, our findings and those in reported literature reiterate that stroke in HIV is a complex issue.

Our study has some limitations that should be acknowledged. First, we relied on ICD coding to identify diagnosis of stroke and co-morbidity data, including HIV. Second, our data source meant that detailed clinical information, e.g. stroke severity and pre-stroke disability, which are important determinants of outcome were not available [21]. Third, we did not have data on cARTs, which may impact stroke outcome. However, cARTs have been widely available free of charge throughout Thailand since 2002 [22]. Fourth, we were not able to study mild strokes not admitted to hospital and very severe strokes resulting in death prior to admission. However, the truncation of distribution is only likely to attenuate the results.

Notwithstanding these limitations this work makes an important contribution to understanding of outcomes of stroke in HIV. The use of reimbursement forms as a dataset allowed us to capture an almost actual population service use for stroke in Thailand and to study a large nationwide, unselected population and availability of outcome data was complete.

CONCLUSIONS

In conclusion, the findings confirm that the characteristics of stroke in patients with HIV are different from those in the general population and show that the prevalence, and in some instances risk, of sepsis, convulsions, inpatient mortality, and longer LOS stroke are higher in patients with HIV. Foresight and prompt treatment of these complications, and any co-existing illnesses, could potentially help improve outcomes of stroke in people with co-existing HIV infection. Future studies should focus on fully establishing risk factors and mechanisms of stroke in HIV, and developing optimal treatment strategies for stroke in HIV.

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DECLARATION OF INTEREST

None.

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