Rheumatic mitral valve disease is associated with worse outcomes in stroke: a Thailand National Database Study

Running title: Prognosis of stroke patients with rheumatic mitral valve disease

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Abstract

Background and purpose: Rheumatic valvular heart disease is associated with increased risk of cerebrovascular events, although there are limited data on the prognosis of patients with rheumatic mitral valve disease (RMVD) following stroke.

Methods: We examined the association between RMVD and both serious and common cardiovascular and non-cardiovascular (respiratory and infective) complications in a cohort of hospitalised stroke patients based in Thailand. Factors associated with in-hospital mortality were also explored. Data were obtained from a National Insurance Database. All hospitalised strokes between 1st October 2004 and 31st January 2013 were included in the current study. Characteristics and outcomes were compared for RMVD and non-RMVD patients. Logistic regression, propensity score matching, and multivariate models were employed to assess study outcomes.

Results: In total, 594,681 patients (mean (SD) age=64(14.5) years) with a diagnosis of stroke (ischemic = 306,154; hemorrhagic= 195,392; undetermined = 93,135) were included in this study, of whom 5461 had RMVD. Results from primary analyses showed that following ischemic stroke, and controlling for potential confounding covariates, RMVD was associated (P<0.001) with increased odds for cardiac arrest (OR(95%CI)=2.13(1.68-2.70)), shock (2.13(1.64-2.77)), arrhythmias (1.70(1.21-2.39)), respiratory failure (2.09(1.87-2.33)), pneumonia (2.00(1.81-2.20)), and sepsis (1.39(1.19-1.63)). In hemorrhagic stroke patients, RMVD was associated with increased odds (fully adjusted model) for respiratory failure (1.26(1.01-1.57)), and in patients with undetermined stroke, RMVD was associated with increased odds (fully adjusted analyses) for shock (3.00(1.46-6.14)), respiratory failure (2.70(1.91-3.79)), and pneumonia (2.42(1.88-3.11)).

Conclusions: RMVD is associated with development of cardiac arrest, shock, arrhythmias, respiratory failure, pneumonia, and sepsis following acute stroke.

Introduction

Rheumatic valvular heart disease is the most common form of acquired heart disease in children and young adults in many parts of the world. In a 2005 summary report commissioned by the World Health Organisation, the overall global burden of this disease was estimated to be 15.6 million prevalent cases with 282,000 new cases and 233,000 deaths per year[1]. These extrapolated figures are based on limited data and likely underestimate the true burden of this condition in endemic regions such as sub-Saharan Africa, south-central Asia, the Pacific, and indigenous populations of Australia and New Zealand[2-4]. The populations in these areas are also likely to have significant exposure to risk factors for cerebrovascular disease such as smoking, regular use of alcohol, and poor nutrition, as well higher prevalence of hypertension, hypercholesterolemia and diabetes[5-7]. This may explain why many of these regions also have high incidence and mortality rates for stroke[8].

Mitral valve disease is the most prevalent early valvular manifestation of rheumatic heart disease. Associated left atrial dilation increases the likelihood for development of atrial fibrillation, with stasis of blood flow elevating the risk for arterial thromboembolism[9]. By virtue of their common underlying socioeconomic risk factors, rheumatic mitral valve disease (RMVD) and stroke are inextricably linked in many developing countries worldwide. Nevertheless, there are currently limited data on prognostic implications of RMVD following stroke, although advancing age, female gender, and history of cerebrovascular events, chronic ischemic heart disease, and congestive heart failure have previously been identified as independent predictors of death in RMVD patients[10-13].

We aimed to examine the effect of RMVD on a comprehensive range of serious and common cardiovascular and non-cardiovascular (respiratory and infective) complications in a large cohort of hospitalised stroke patients. We also aimed to explore factors associated with

in-hospital mortality in this cohort whilst controlling for patient characteristics, history of comorbid conditions, and post stroke complications.

Methods

Study participants and design

So as to optimally address our research objective, we employed an observational epidemiological approach using routine consecutive admission data representative of all hospital admissions. This approach overcomes selection bias which is the major limitation of clinical studies including trials. Study participants comprised a prospectively identified cohort of 594,681 participants (mean (SD) age = 64 (14.5) years) admitted to provincial and large community hospitals in Thailand between 1st October 2004 and 31st January 2013 who received a diagnosis of stroke. We selected this time period as stroke management in Thailand has become more in line with current international practice since 2004. Data were obtained from the Universal Coverage Health Security Insurance Scheme Database in Thailand. The Thai population is covered by three insurance schemes. The Civil Servant Benefit System covers government employees and their dependants (~7% of the population), and 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 remainder of the population[14].

In Thailand, diagnosis of stroke is made during individuals' inpatient hospital stay by attending clinical teams based on clinical features and investigation findings including brain imaging (since 2009 all patients with suspected stroke received a head CT scan). All hospitalised patients were clinically managed in accordance with Thai National Clinical Practice Guidelines. This includes ECG monitoring for at least 24-hours following hospital admission. Demographic and clinical data were obtained from insurance reimbursement

forms using International Classification of Disease (ICD-10) codes on an annual basis. Stroke types were categorised as hemorrhagic (I61, I62), ischemic (I63) or stroke of undetermined pathology (I64). Diagnoses of RMVD and other comorbid conditions were identified from ICD coding (ICD-10) on reimbursement forms (stroke (I61-I64), RMVD (I05), hypertension (I10), ischaemic heart disease (I25), atrial fibrillation and flutter (I48), heart failure (I50), anaemia (D50,D53,D56,D58,D59), type II diabetes mellitus (E11), dyslipidaemia (E78), chronic kidney disease (N18), and HIV (Z21)). Our study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee in Human Research, Khon Kaen University, Khon Kaen, Thailand.

Outcome measures

Serious and common cardiovascular and non-cardiovascular post-stroke complications were examined as primary outcomes in this study. In hospital mortality following stroke was also examined. Data were collected for each patient on age, gender, and previous history of major chronic disease (stroke, heart failure, primary hypertension, dyslipidaemia, atrial fibrillation and flutter, chronic kidney disease, COPD, chronic ischemic heart disease, type II diabetes mellitus, and HIV). Data on post stroke cardiovascular complications (cardiac arrest, myocardial infarction, shock, and arrhythmias), respiratory failure, and infective complications (pneumonia, and sepsis) were recorded also, as were length of hospital stay and mortality status at discharge.

Statistical methods

Analyses were performed using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA) for descriptive statistics and regression models and Stata version 14 (StatCorp, USA) for propensity score matched models. Descriptive statistics were calculated separately

for study participants with and without RMVD. Continuous variables were presented as mean values (± SD), and for categorical variables the number and percentage were given. Characteristic data and stroke outcomes were compared between patients with and without RMVD using independent samples t-tests for continuous variables and chi-squared tests for categorical variables.

The effect of RMVD on the development of complications following stroke (cardiac arrest, acute myocardial infarction, shock, arrhythmias, respiratory failure, infective endocarditis, pneumonia, and sepsis) was examined using logistic regression for each stroke subtype (ischemic, haemorrhagic, or undetermined). The reference category for these regression models was 'patients with no RMVD', and patient complications were the dependent variables.

For all complications we examined unadjusted outcomes (model A), and outcomes adjusted for age, gender, and previous history of major chronic disease (stroke, heart failure, chronic kidney disease, COPD, cancer, chronic ischemic heart disease, diabetes, and HIV) (model B). For cardiovascular complications (cardiac arrest, acute myocardial infarction, shock, arrhythmias), the influence of additional covariates relevant to cardiovascular function in hospitalised patients were examined by submitting them in isolation to model B. Adjustment was made for presence of existing primary hypertension, dyslipidaemia, and atrial fibrillation and flutter (models C, D, and E respectively). For the complication of respiratory failure, additional adjustment was made for presence of post stroke pneumonia which can be closely linked to respiratory failure in the critically ill (model C).

The association of rheumatic mitral valve disease with complications following stroke was further examined using propensity score matching analysis. This approach matches RMVD patients with unaffected patients that are comparable for all observed covariates, thereby minimising bias due to confounding. Propensity scoring was carried out using full

Mahalanobis matching in Stata using the psmatch2 command, using logistic regression to estimate the propensity scores. Matching was then carried out on a 1:1 basis. The explanatory factors in the matching were age, gender, and previous history of major chronic disease (stroke, heart failure, chronic kidney disease, COPD, cancer, chronic ischemic heart disease, diabetes, and HIV).

Factors associated with in-hospital mortality following stroke were examined using multivariate logistic regression analysis with in-hospital mortality as the dependent variable. Covariates were entered using forward selection with a cut-off of 10% significance level from patient demographic and pre-existing comorbidity data (model A). A further multivariate model (B; generated as described above) examined additional adjustment for the post-stroke complications.

Results

From 594,681 study participants with diagnosis of stroke (ischemic = 306,154; hemorrhagic= 195,392; undetermined subtype = 93,135), 5461 had pre-existing RMVD. Table 1 shows sample characteristics for participants with and without RMVD. Participants with RMVD were significantly younger, more likely to be female, and had lower prevalence of pre-existing hypertension, dyslipidaemia, and type II diabetes ($P<0.001$). The proportion of participants with pre-existing heart failure, atrial fibrillation and flutter, ischemic heart disease, and anaemia was significantly higher in those with RMVD, as was the incidence of ischemic stroke (whereas incidence of hemorrhagic and undetermined stroke subtypes were lower) ($P<0.001$).

Table 2 shows the proportion of study participants suffering serious post stroke complications (stratified by presence or absence of RMVD). Rate of in-hospital mortality was lower in participants with RMVD (10.4% vs. 11.8%; $P<0.001$). Participants with RMVD had

higher incidences of respiratory failure, pneumonia, sepsis, acute myocardial infarction, arrhythmias, cardiac arrest, and shock (when compared with those without RMVD; $P<0.001$). Median (IQR) length of hospital stay was longer in participants with RMVD than those without (4(5) vs. 3(4) days respectively; $P<0.001$).

Table 3 shows odds ratios and corresponding 95% CIs from binary logistic regression analyses examining the association of RMVD with serious complications following stroke (where no mitral valve disease was the reference category). For patients diagnosed with ischemic stroke, and when controlling for age, gender, and previous history of major chronic disease (stroke, heart failure, chronic kidney disease, COPD, chronic ischemic heart disease, type II diabetes, and HIV) (model B), presence of RMVD was associated ($P<0.003$) with increased odds for developing cardiac arrest, shock, arrhythmias, respiratory failure, pneumonia, and sepsis. Associations remained significant (with the exception of arrhythmias) following additional covariate adjustment (primary hypertension, dyslipidaemia, and atrial fibrillation and flutter for cardiovascular complications (models C-E respectively); and post-stroke pneumonia for respiratory failure (model C)).

For hemorrhagic stroke, presence of RMVD was associated with increased odds for respiratory failure (Model C OR (95% CI) = 1.26 (1.01-1.57) $P=0.04$). For undetermined stroke subtype, presence of RMVD was associated with increased odds ($P<0.001$) for post-stroke shock (OR = 3.00 (1.46-6.14)), respiratory failure (OR = 2.70 (1.91-3.79)), and pneumonia (OR = 2.42 (1.88-3.11)) (model B). These associations remained significant following additional covariate adjustment (primary hypertension, dyslipidaemia, and atrial fibrillation and flutter for shock (models C-E); and post-stroke pneumonia for respiratory failure (model C)).

Propensity score matched results (supplementary Table I; please see http://stroke.ahajournals.org) were comparable with those from logistic regression analyses.

In patients diagnosed with ischaemic stroke, presence of RMVD was associated with increased odds for developing cardiac arrest, shock, respiratory failure, pneumonia, and sepsis (P<0.002). Following haemorrhagic stroke, RMVD was associated with increased odds for respiratory failure (OR=2.48(1.72-3.58)), and sepsis (OR=2.55(1.39-4.69)). In patients with undetermined stroke subtype, presence of RMVD was associated with increased odds for respiratory failure (OR=5.50(2.43-12.40)) and pneumonia (OR=3.03(1.64-5.61)).

Multivariate analysis showed that factors associated (P<0.001) with in-hospital mortality following ischemic stroke were increasing age, female gender, history of stroke, heart failure, chronic kidney disease, chronic ischemic heart disease, HIV, and development of post-stroke myocardial infarction, shock, arrhythmias, respiratory failure, pneumonia, and sepsis (Supplementary Table II; please see http://stroke.ahajournals.org). Associations were consistent across stroke subtype. Similar findings were seen for hemorrhagic stroke although female gender was not associated with in hospital mortality in this group. For undetermined stroke subtype, type II diabetes was additionally associated with in hospital mortality whereas history of previous stroke was not.

Discussion

We present the largest population-based study to investigate prognosis after stroke in patients with RMVD. Strengths of our analyses include prospective identification of study participants, and a representative study population drawn from the community. We used specific ICD codes for ischemic and hemorrhagic stroke rather than the broader and more general ICD codes (I60-69) used in other population based studies. This allowed a more detailed sub-analysis of prognosis based on underlying stroke type. In addition, by validating population-based insurance data of all participants with hospital admission data, we have

been able to take detailed co-morbidity information into account during analyses in a way that has not previously been possible in this setting.

The group of stroke patients with RMVD were substantially younger and largely female (70.1%), similar to previous studies of rheumatic heart disease patients[15-17]. Participants without RMVD were more likely to suffer from hypertension, dyslipidaemia, and type II diabetes mellitus. This is consistent with the morbidity profile of older individuals from Asia[18]. Lower rate of in-hospital mortality for patients with RMVD compared with non RMVD patients may be explained by differences in age and comorbid characteristics given the increased odds for in hospital mortality with RMVD following robust covariate adjustment.

RMVD patients were significantly more likely (compared to patients without RMVD) to present with a diagnosis of ischemic stroke. These patients had more cardiovascular co-morbidities such as heart failure, atrial fibrillation and flutter, ischemic heart disease, and anaemia. It is unclear what proportion of this association with ischemic stroke is due to the pathophysiology of RMVD and what proportion is due to shared underlying socioeconomic / cardiovascular risk factors such as poor diet, smoking, and excessive alcohol consumption in the lower socio-economic regions where RMVD is more common[2-4].

When comparing stroke patients with RMVD to those without RMVD, a number of complications (respiratory failure, pneumonia, sepsis, acute myocardial infarction, arrhythmias, cardiac arrest, shock) were more common in the presence of RMVD. In order to better understand potential mediators of these associations, further adjustments were made to our models by including additional covariates relevant to respiratory and cardiovascular function in isolation. Associations remained consistent for complication outcomes across all stroke subtypes with the exception of RMVD associated arrhythmias in ischemic stroke

patients following adjustment for atrial fibrillation and flutter. This may relate to over adjustment bias.

In adjusted analyses RMVD patients had significantly greater odds for in-hospital mortality compared to those without. This could be linked to reduced cardiovascular reserve to compensate for the physiological stress following stroke in the presence of RMVD. When assessing factors associated with mortality in stroke patients, the clinical impact of pre-existing comorbid conditions on mortality risk becomes apparent. Increased mortality risk in the presence of comorbidities likely relates to a myriad of pathological processes (such as dyslipidaemia, chronic inflammation, endothelial dysfunction, hypertension, volume overload, impaired left ventricular function, microvascular disease, and immune compromise)[19-22].

Whereas age-adjusted stroke incidence rates in high-income countries have decreased by 42% since the 1970s, the stroke incidence rates in low to middle income countries have more than doubled during this period (52 per 100 000 and 117 per 100 000 person-years, respectively; $p<0.0001$) with little sign of slowing[23]. As a result, the incidence of stroke in low- to middle-income countries has now exceeded that of high-income countries. Furthermore, these low- to middle-income countries often have younger stroke sufferers and higher stroke-related mortality[24-25].

The prevalence of rheumatic valvular heart disease, which is highest in children in resource poor nations[26], is likely to be underestimated in these regions due to reliance on clinical screening criteria that lack the sensitivity to detect all cases of the condition[15]. Rheumatic fever following group A streptococcus infection is the predominant cause for rheumatic valvular heart disease. Progressive damage to the heart and its valves is associated with clinical complications such as asymptomatic irreversible ventricular dysfunction, pulmonary hypertension, atrial fibrillation and flutter, and stroke, which are major causes of

long-term morbidity[27]. In terms of global public health, if we are to limit the burden of these adverse outcomes, preventative strategies should focus on improving diagnosis and management of rheumatic fever and resultant valvular heart disease. Emphasis should be placed on reinforcing current control strategies such as recognition and treatment of streptococcal pharyngitis for primary prevention of rheumatic fever and long-term antistreptococcal prophylaxis for secondary prevention [27], and improving general living conditions.

We acknowledge some limitations. We did not have information on the severity of mitral value disease or the clinical severity of the stroke, nor did we have information on medication use and therefore cannot account for potential effects of pre stroke cardiovascular medication (e.g. antihypertensive use) on stroke severity. Furthermore, no information was available around left ventricular function in patients with or without RMVD that may have confounded some of the relationships that we have reported. It was not possible to examine data from patients who suffered mild strokes not admitted to hospital or very severe strokes resulting in death prior to admission. Nevertheless, truncation of distribution would be likely to attenuate the associations.

Despite robust adjustment for a wide range of pre-existing comorbidities, our outcomes may be limited by residual confounding. It is possible that worse prognosis following stroke in RMVD patients could be attributable to other factors that were not adjusted for in our analyses such as biological covariables which were unavailable. Inclusion of these data however is likely more relevant for examination of outcomes over the longer term such as incident cardiovascular disease and stroke recurrence[28-29]. Our propensity score matched results were markedly similar to those obtained from logistic regression. Consistency of outcome data further reduces the likelihood that outcomes may be related to unmeasured confounding covariates.

Participant data were collected during acute hospital admission and we therefore have limited follow up information. Mortality from stroke however is particularly prominent in the short term (0-30 days post event)[30], and thus examination of short-term outcomes has the potential to significantly affect overall stroke mortality. We were unable to comprehensively control for socioeconomic factors that may underlie RMVD such as habitual diet, smoking, and excessive alcohol consumption. However, the main focus of the current work is to quantify the prognostic impact of RMVD on stroke outcome.

Conclusions

We have conducted the largest study to date that reports on the impact of valvular heart disease on complications following stroke. Certain concomitant comorbidities and post-stroke complications are more common in RMVD stroke patients. These patients are at greater risk for in-hospital mortality, and their prognosis is significantly worsened by the presence of a number of post-stroke complications which presents unique challenges for patient management. The worldwide prevalence of RMVD is increasing and will continue to rise in western countries given the likely future trends in valvular heart disease epidemiology[31]. There is an urgent need for further work on how to better understand and manage potentially reversible causes of morbidity and mortality in these patients.

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Contributorship: PKM conceived the study. ST co-ordinated the data acquisition and obtained ethical approval. ABC and JHBS cleaned the data. PKM and ADW formulated analysis plan. ADW analysed the data. ADW and GSM drafted the paper. All authors contributed in writing of the paper. PKM is the guarantor.

Table 1: Patient characteristics

Characteristic	Mitral valve disease	No mitral valve disease	*P**
N	5461	589220	
Age†, years	55 (13.9)	64 (14.5)	<0.001
Gender			
Male	1632 (29.9)	325535 (55.2)	
Female	3829 (70.1)	263685 (44.8)	<0.001
Hypertension	816 (14.9)	264373 (44.9)	<0.001
Dyslipidaemia	531 (9.7)	116967 (19.9)	<0.001
Type II diabetes mellitus	337 (6.2)	99030 (16.8)	<0.001
Heart failure	439 (8.0)	8416 (1.4)	<0.001
Atrial fibrillation and flutter	3267 (59.8)	33718 (5.7)	<0.001
Ischemic heart disease	171 (3.1)	15996 (2.7)	0.03
Anaemia	351 (6.4)	31692 (5.4)	<0.001
Previous stroke	39 (0.7)	3919 (0.7)	0.36
Stroke type			
Ischemic	3965 (72.6)	302189 (51.3)	
Haemorrhagic	703 (12.9)	194689 (33.0)	
Undetermined	793 (14.5)	92342 (15.7)	<0.001

*Characteristic data were compared between patients with and without mitral valve disease using chi squared analyses for categorical variables (gender, comorbidities, and stroke type) and independent samples t-test for continuous variables (age).

†Age presented as mean (SD). All other data presented as n (%).

Table 2: Comparison of outcomes following stroke

Outcome	Mitral valve disease, n (%)	No mitral valve disease, n (%)	*P*[a]
N	5461	589220	
In-hospital mortality	566 (10.4)	69490 (11.8)	0.001
Serious complications			
Respiratory failure	527 (9.7)	42001 (7.1)	<0.001
Pneumonia	686 (12.6)	56060 (9.5)	<0.001
Sepsis	225 (4.1)	18926 (3.2)	<0.001
Acute MI	59 (1.1)	3356 (0.6)	<0.001
Arrhythmias	44 (0.8)	2541 (0.4)	<0.001
Cardiac arrest	95 (1.7)	6117 (1.0)	<0.001
Shock	84 (1.5)	4436 (0.8)	<0.001
Length of stay > 4 days	4 (5)	3 (4)	<0.001

MI – myocardial infarction. Data are presented as median (IQR) for continuous data (length of stay) and number (%) for categorical data (in-hospital mortality, and complications).

*Outcome data were compared between patients with and without mitral valve disease using chi squared analyses.

Table 3: Association of mitral valve disease with development of complications following stroke (with no mitral valve disease as the reference category)

Ischemic stroke, n=306,154										
Cardiovascular complications	Model A*		Model B†		Model C‡		Model D‡		Model E‡	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Cardiac arrest	2.30 (1.82-2.90)	<0.001	2.13 (1.68-2.70)	<0.001	2.03 (1.60-2.58)	<0.001	1.92 (1.51-2.44)	<0.001	1.40 (1.09-1.79)	0.01
Myocardial infarction	1.52 (1.12-2.05)	<0.001	1.34 (0.99-1.83)	0.06	1.30 (0.95-1.77)	0.1	1.30 (0.95-1.76)	0.1	1.02 (0.75-1.40)	0.89
Shock	2.47 (1.92-3.19)	<0.001	2.13 (1.64-2.77)	<0.001	1.92 (1.48-2.50)	<0.001	1.95 (1.50-2.53)	<0.001	1.32 (1.01-1.72)	0.05
Arrhythmias	1.58 (1.13-2.21)	<0.001	1.70 (1.21-2.39)	0.003	1.65 (1.17-2.32)	0.004	1.65 (1.17-2.32)	0.004	1.15 (0.81-1.63)	0.43
Respiratory Complications										
Respiratory failure	1.86 (1.67-2.07)	<0.001	2.09 (1.87-2.33)	<0.001	1.73 (1.53-1.94)	<0.001	-	-	-	-
Pneumonia	1.55 (1.41-1.70)	<0.001	2.00 (1.81-2.20)	<0.001	-	-	-	-	-	-
Sepsis	1.27 (1.09-1.48)	0.003	1.39 (1.19-1.63)	<0.001	-	-	-	-	-	-
Hemorrhagic stroke, n=195,392										
Complications	Model A*		Model B†		Model C‡		Model D‡		Model E‡	
Cardiovascular	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*

Cardiac arrest	1.29 (0.77-2.15)	0.33	1.19 (0.71-2.00)	0.50	1.22 (0.73-2.05)	0.45	1.16 (0.69-1.95)	0.57	0.87 (0.51-1.47)	0.59
Myocardial infarction	3.57 (1.90-6.69)	<0.001	1.87 (0.97-3.59)	0.06	1.88 (0.97-3.63)	0.06	1.88 (0.98-3.62)	0.06	1.21 (0.62-2.36)	0.58
Shock	1.80 (1.06-3.07)	0.03	1.45 (0.85-2.49)	0.18	1.32 (0.77-2.27)	0.31	1.42 (0.83-2.42)	0.20	0.91 (0.53-1.58)	0.74
Arrhythmias	2.70 (1.12-6.54)	0.03	2.03 (0.83-4.99)	0.12	2.15 (0.87-5.28)	0.10	2.03 (0.83-4.98)	0.12	0.92 (0.37-2.30)	0.86
Respiratory										
Respiratory failure	1.24 (1.01-1.53)	0.05	1.26 (1.01-1.57)	0.04	1.26 (1.01-1.57)	0.04	-	-	-	-
Infective										
Pneumonia	1.04 (0.83-1.30)	0.75	1.04 (0.83-1.30)	0.72	-	-	-	-	-	-
Sepsis	1.48 (1.06-20.6)	0.02	1.36 (0.98-1.91)	0.07	-	-	-	-	-	-
Undetermined, n=93,135										
Complications	Model A*		Model B†		Model C‡		Model D‡		Model E‡	
Cardiovascular	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Cardiac arrest	1.76 (0.78-3.95)	0.17	1.67 (0.74-3.79)	0.23	1.61 (0.71-3.66)	0.25	1.61 (0.71-3.65)	0.26	1.29 (0.56-2.99)	0.55
Myocardial infarction	1.65 (0.68-4.01)	0.27	1.50 (0.61-3.70)	0.38	1.50 (0.61-3.69)	0.38	1.49 (0.60-3.66)	0.39	1.19 (0.48-2.97)	0.71
Shock	2.79 (1.38-5.65)	0.004	3.00 (1.46-6.14)	0.003	2.71 (1.32-5.55)	0.007	2.87 (1.40-5.87)	0.004	2.30 (1.09-4.83)	0.03
Arrhythmias	1.40 (0.52-3.76)	0.50	1.43 (0.53-3.88)	0.48	1.43 (0.53-3.89)	0.48	1.40 (0.52-3.79)	0.51	0.92 (0.33-2.53)	0.87
Respiratory										

Respiratory failure	2.34 (0.68-3.26)	<0.001	2.70 (1.91-3.79)	<0.001	2.18 (1.53-3.11)	<0.001	-	-	-	-
Infective										
Pneumonia	1.72 (1.35-2.20)	<0.001	2.42 (1.88-3.11)	<0.001	-	-	-	-	-	-
Sepsis	1.35 (0.84-2.16)	0.21	1.58 (0.99-2.55)	0.06	-	-	-	-	-	-

*Unadjusted.

†Adjusted for age, gender, year of hospital admission, and previous history of major chronic disease (stroke, heart failure, chronic kidney disease, COPD, chronic ischemic heart disease, type II diabetes mellitus, and HIV).

‡For cardiovascular complications, model C = model B with additional adjustment for primary hypertension; model D = model B with additional adjustment for dyslipidaemia; model E = model B with additional adjustment for atrial fibrillation and flutter.

For the complication of respiratory failure, model C was additionally adjusted for post stroke pneumonia (no model D-E).

For infective complications, there no additional covariate adjustments were made (no model C-E).

‘Patients with no rheumatic mitral valve disease’ was the reference category and patient complications were dependent variables in regression models.

SUPPLEMENTAL MATERIAL

Supplementary Table I: Propensity scoring results

Ischemic stroke	Adjusted using propensity scoring (n=7930)	
Complications	OR (95% CI)	*P*
Cardiac arrest	2.08 (1.39-3.10)	<0.001
Myocardial infarction	1.47 (0.92-2.34)	0.10
Shock	3.92 (2.26-6.80)	<0.001
Arrhythmias	1.03 (0.64-1.65)	0.90
Respiratory failure	2.94 (2.41-3.59)	<0.001
Pneumonia	1.90 (1.50-2.41)	<0.001
Sepsis	1.46 (1.15-1.85)	0.002
Hemorrhagic stroke	OR (95% CI)	*P*
Cardiac arrest	1.51 (0.67-3.39)	0.32
Myocardial infarction	0.91 (0.38-2.15)	0.83
Shock	2.36 (0.90-6.18)	0.080
Arrhythmias	1.67 (0.40-7.02)	0.48
Respiratory failure	2.48 (1.72-3.58)	<0.001
Pneumonia	1.33 (0.83-2.14)	0.23
Sepsis	2.55 (1.39-4.69)	0.003
Undetermined stroke	OR (95% CI)	*P*
Cardiac arrest	2.01 (0.50-8.06)	0.33
Myocardial infarction	2.51 (0.49-12.97)	0.27
Shock	Not estimatable	
Arrhythmias	1 (0.25-4.01)	1.00
Respiratory failure	5.50 (2.43-12.40)	<0.001
Pneumonia	3.03 (1.64-5.61)	<0.001
Sepsis	2.28 (0.99-5.27)	0.06

* Adjusted for age, gender, year of hospital admission, and previous history of major chronic disease (stroke, heart failure, chronic kidney disease, COPD, chronic ischemic heart disease, diabetes, HIV, primary hypertension, dyslipidaemia, and atrial fibrillation).

Supplementary Table II: Multivariate regression analyses to examine factors associated with in-hospital mortality following stroke

Ischemic stroke, n=306,154	Model A*			Model B†	
Covariates	OR (95% CI)	*P*	Covariates	OR (95% CI)	*P*
Rheumatic mitral valve disease	1.19 (1.06-1.34)	<0.001	Age	1.01 (1.01-1.01)	<0.001
Age	1.02 (1.02-1.02)	<0.001	Gender	1.28 (1.23-1.32)	<0.001
Gender	1.30 (1.26-1.34)	<0.001	Previous stroke	3.81 (3.01-4.83)	<0.001
Previous stroke	4.18(3.41-5.12)	<0.001	Heart failure	2.05 (1.90-2.22)	<0.001
Heart failure	3.76 (3.53-4.00)	<0.001	Chronic kidney disease	1.15 (1.07-1.24)	<0.001
Chronic kidney disease	1.52 (1.43-1.62)	<0.001	Chronic ischemic heart disease	1.49 (1.39-1.60)	<0.001
COPD	1.60 (1.48-1.62)	<0.001	HIV	3.00 (2.28-3.97)	<0.001
Chronic ischemic heart disease	151 (1.42-1.61)	<0.001	Type II diabetes mellitus	1.11 (1.07-1.16)	<0.001
HIV	2.89 (2.23-3.75)	<0.001	Dyslipidaemia	0.45 (0.43-0.47)	<0.001
Type II diabetes	1.24 (1.19-1.28)	<0.001	Myocardial infarction	4.21 (3.78-4.68)	<0.001
Hypertension	0.94 (0.91-0.97)	<0.001	Shock	4.99 (4.47-5.56)	<0.001
Dyslipidaemia	0.40 (0.39-0.42)	<0.001	Arrhythmias	1.84 (1.57-2.14)	<0.001
Alcohol	1.40 (1.23-1.60)	<0.001	Respiratory failure	5.89 (5.65-6.13)	<0.001
			Pneumonia	3.12 (3.00-3.24)	<0.001
			Sepsis	8.18 (7.80-8.58)	<0.001
Hemorrhagic stroke, n=195,392	Model A*			Model B†	

Covariates	OR (95% CI)	*P*	Covariates	OR (95% CI)	*P*
Age	1.01 (1.01-1.01)	<0.001	Age	1.00 (1.00-1.01)	<0.001
Previous stroke	1.15 (1.06-1.25)	<0.001	Previous stroke	1.10 (1.00-1.20)	<0.001
Heart failure	2.07 (1.87-2.29)	<0.001	Heart failure	1.67 (1.50-1.86)	<0.001
Chronic kidney disease	1.40 (1.31-1.49)	<0.001	Chronic kidney disease	1.23 (1.15-1.32)	<0.001
			Chronic ischaemic heart disease	1.29 (1.18-1.42)	<0.001
Chronic ischaemic heart disease	1.31 (1.20-1.43)	<0.001	HIV	1.71 (1.29-2.28)	<0.001
HIV	1.80 (1.36-2.38)	<0.001	Type II diabetes mellitus	1.09 (1.05-1.13)	<0.001
Type II diabetes mellitus	1.16 (1.12-1.21)	<0.001	Hypertension	1.07 (1.04-1.09)	<0.001
Hypertension	1.09 (1.07-1.12)	<0.001	Dyslipidaemia	0.37 (0.35-0.39)	<0.001
Dyslipidaemia	0.36 (0.34-0.37)	<0.001	Myocardial infarction	2.65 (2.29-3.08)	<0.001
Alcohol	1.11 (1.04-1.19)	<0.001	Shock	2.96 (2.71-3.24)	<0.001
			Arrhythmias	1.46 (1.20-1.76)	<0.001
			Respiratory failure	2.66 (2.59-2.74)	<0.001
			Pneumonia	1.05 (1.01-1.08)	0.007
			Sepsis	3.88 (3.68-4.09)	<0.001
Undetermined, n=93,135	Model A*			Model B†	
Covariates	OR (95% CI)	*P*	Covariates	OR (95% CI)	*P*
Rheumatic mitral valve disease	1.67 (1.21-2.30)	0.001	Age	1.01 (1.01-1.01)	<0.001

Age	1.02 (1.02-1.02)	<0.001	Gender	1.15 (1.06-1.24)	0.002
Gender	1.15 (1.07-1.24)	0.001	Heart failure	1.73 (1.39-2.16)	<0.001
Heart failure	2.48 (2.03--3.02)	<0.001	Chronic kidney disease	1.36 (1.13-1.65)	0.001
Chronic kidney disease	1.64 (1.38-1.95)	<0.001	Chronic ischemic heart disease	1.33 (1.09-1.62)	0.005
COPD	1.34 (1.08-1.65)	0.005	HIV	3.80 (1.57-9.18)	0.002
			Dyslipidaemia	0.39 (0.34-0.46)	<0.001
Chronic ischemic heart disease	1.42 (1.18-1.70)	0.001	Alcohol	2.02 (1.46-2.78)	<0.001
HIV	4.19 (1.81-9.71)	0.001	Myocardial infarction	3.14 (2.25-4.39)	<0.001
Dyslipidaemia	0.39 (0.33-0.45)	0.001	Shock	3.85 (2.86-5.17)	<0.001
Alcohol	2.28 (1.68-3.08)	0.001	Arrhythmias	2.56 (1.74-3.76)	<0.001
			Respiratory failure	7.34 (6.50-8.29)	<0.001
			Pneumonia	3.15 (2.84-3.48)	<0.001
			Sepsis	8.43 (7.41-9.58)	<0.001

*Covariates were entered into this multivariate model using forward selection with a cut-off of 10% significance level from patient demographic and pre-existing comorbidity data (age, gender, and previous history of major chronic disease (stroke, heart failure, primary hypertension, dyslipidaemia, alcohol abuse, chronic kidney disease, COPD, chronic ischemic heart disease, type II diabetes, and HIV).

†Additional post stroke complication data were entered into this model using forward selection with a cut-off of 10% significance level.