A 3-year follow-up study on the risk of stroke among patients with conjunctival haemorrhage

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ABSTRACT.

Purpose: **To the best of our knowledge, no large population-based studies on the relationship between conjunctival haemorrhage and stroke have been conducted to date. Using a nationwide population-based data set, this study investigated the relationship between conjunctival haemorrhage and the subsequent risk of stroke within a 3-year period following diagnosis.**

Methods: **We analysed data sourced from the Taiwan Longitudinal Health Insurance Database 2000. The study cohort consisted of 17 349 patients with conjunctival haemorrhage and 86 745 comparison subjects. Each patient was individually tracked for a 3-year period from their index date to identify all those who had subsequently received a diagnosis of stroke.**

Results: **The incidence rate of stroke was 2.44 (95% CI = 2.31–2.55) per 100 person-years in patients with conjunctival haemorrhage and 1.63 (95% CI = 1.59–1.68) per 100 person-years in comparison patients. After adjusting for patients' monthly income and geographic location, as well as for hypertension, atrial fibrillation, diabetes, hyperlipidaemia and coronary heart disease, stratified Cox proportional hazards regressions revealed a statistically significant hazard ratio for stroke in patients with conjunctival haemorrhage (HR = 1.33; 95% CI = 1.24–1.42, p < 0.001).**

Conclusions: **In this study, patients with conjunctival haemorrhage were found to be at a significant risk of stroke during a 3-year follow-up period after diagnosis.**

Key words: cerebrovascular disease – conjunctival haemorrhage – epidemiology – stroke

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Introduction

Haemorrhage can occur in any ocular tissue (Mimura et al. 2009, 2010). When a haemorrhage occurs under the conjunctiva, this is known as a conjunctival or subconjunctival haemorrhage. Conjunctival haemorrhages are diagnosed clinically (Pitts et al. 1992) and most commonly present as a spontaneous events without aetiological factors, especially in the elderly or arteriosclerotic, but also in healthy subjects (Fukuyama et al. 1990; Mimura et al. 2009). Although it has been speculated that patients with more severe haemorrhaging tend to have higher systolic blood pressure, the morphology (size and shape) of the lesion has not been found to have any influence on or association with hypertension (Mimura et al. 2010). Despite the lack of evidence in prior studies for an association between lesion morphology and hypertension, the literature continues to suggest that all patients suffering from conjunctival haemorrhages have their blood pressure checked (Kannel et al. 1971; Wilson 1986; Izzo et al. 2000; Chobanian et al. 2003; Bodack 2007; Mimura et al. 2009).

Stroke is the most common cause of serious disability in adults. Systemic risk factors associated with stroke include hypertension, diabetes mellitus, cardiovascular diseases and old age (Elkind & Sacco 1998; Goldstein et al. 2001). Many of these conditions are also associated with the development of conjunctival haemorrhage. Signs of retinal microvascular have been proposed to predict stroke and stroke-related death, regardless of the typical risk factors (Mitchell et al. 2005; Wong & Mitchell 2007; Baker et al. 2008, 2010). Thus, investigating whether conjunctival haemorrhage is a statistically reliable predictor for future stroke is clinically relevant. To the best of our knowledge, no large population-based studies on the relationship between conjunctival haemorrhage and stroke have been conducted to date. Therefore, using a nationwide population-based data set from Taiwan, this study investigated the relationship between conjunctival haemorrhage and the subsequent risk of stroke during a 3-year follow-up period following diagnosis with conjunctival haemorrhage.

Methods

Database

Our analysis was based on data sourced from the Longitudinal Health Insurance Database 2000 (LHID 2000). Taiwan initiated its National Health Insurance (NHI) programme in 1995, with 22.60 million of Taiwan's 22.96 million citizens enrolled in 2007. The LHID 2000 includes all the original claims data for one million beneficiaries, randomly sampled from the year 2000 registry of NHI beneficiaries (n = 23.72 million). The Taiwan National Health Research Institute reported that there were no statistically significant differences in gender distribution between the sampled beneficiaries in the LHID 2000 and all beneficiaries under the NHI programme. The LHID 2000 allows researchers to accurately assess the medical histories of these 1 million beneficiaries since the initiation of the NHI programme.

Because the LHID 2000 consists of anonymous secondary data that are routinely released to the public for research purposes, this study was exempt from full review by the Taipei Medical University Institutional Review Board.

Study population

Our 3-year follow-up study included a study group and a comparison group. When selecting the study group, we identified 36 649 patients who had received a diagnosis of conjunctival haemorrhage (ICD-9-CM code 372.72) during ambulatory care visits between January 2002 and December 2006. Of these, we excluded 5939 patients who had received a diagnosis of conjunctival haemorrhage diagnosis prior to 2002 to increase the possibility of only including new conjunctival haemorrhage cases. We also excluded 11 534 patients younger than 40 years of age.

For each patient in the study group, we selected up to five comparison patients from the remaining beneficiaries in the LHID 2000. The total comparison group comprised 86 745 patients. They were frequency-matched with conjunctival haemorrhage patients with regard to age group (40–59, 60–69, 70–79 and >79), sex, urbanization level of the patient's residence (five levels, with 1 referring to the most urbanized and 5 referring to the least) and index year. We included urbanization level as matching criteria to help control for error variables, namely unmeasured neighbourhood socioeconomic characteristics. Our method of stratifying urbanization level was in accordance with prior research (Lin et al. 2008).

For the study group, we assigned each patient's first ambulatory care visit for the treatment of conjunctival haemorrhage as their index date. We excluded 1827 patients who had been diagnosed with any type of stroke (ICD-9-CM codes 430–438) between the initiation of NHI in 1995 and the patient's index date. The final study group included 17 349 patients with conjunctival haemorrhage who were 40 years of age or older. For the comparison group, we again assigned the first ambulatory care visit occurring during the study period as the index date and ensured that no comparison patients had ever received a diagnosis of either stroke or conjunctival haemorrhage between the initiation of NHI in 1995 and their index date.

The LHID 2000 did not allow us to trace patients' use of medical services prior to the start of the NHI in 1995. Therefore, some of the patients in the study group may have possibly had a pre-1995 stroke diagnosis, and some of the patients in the comparison group may have had a pre-1995 stroke or conjunctival haemorrhage diagnosis. However, we did select only patients and comparison patients who had not received these respective diagnoses between 1995 and 2002.

Each patient from both groups was individually tracked for a 3-year period from their index date to identify all those who had received a diagnosis of stroke. Although the stroke diagnoses in this study relied completely on the claims data reported by physicians and hospitals rather than standardized individual procedures, almost all Taiwanese hospitals that admit stroke patients are equipped with CT and/or MRI equipment to confirm their diagnoses. Therefore, it is likely that stroke diagnosis has a high validity in the LHID 2000.

In the regression model, we excluded all the subjects who died from nonstroke causes during the 3-year follow-up period. A total of 3331 patients died from nonstroke causes: 729 were from the study group, and 2602 were from the comparison group.

Statistical analysis

Statistical analyses were performed with the SAS statistical package (SAS System for Windows, Version 8.2; Cary, NC, USA). We used Pearson's chi-square tests to compare categorical variables between patients with conjunctival haemorrhage and comparison patients. We used the Kaplan–Meier method and the log-rank test to calculate 3-year stroke-free survival rates and to examine differences in the risk of stroke between the two groups. Stratified Cox proportional hazards regressions (stratified by sex, age group, urbanization level, index year and propensity score) were performed to assess the relationship between conjunctival haemorrhage and the risk of stroke, after adjusting for monthly income (0, NT$1–NT15 840, NT15 841–NT25 000, ≥NT25 001), geographic location in which the patient resided (northern, central, eastern and southern Taiwan) and several medical comorbidities measured at baseline [hypertension, diabetes, hyperlipidaemia, atrial fibrillation and coronary heart disease (CHD)].

Medical comorbidities were defined on the basis of data obtained before the index date. We only included comorbidities if they had either occurred in an inpatient setting or appeared in two or more ambulatory care visits.

In this study, we initially calculated a propensity score for each patient to balance the demographic and treatment characteristics of the study and comparison group. As patients with conjunctival haemorrhage were more likely to have hypertension, diabetes, hyperlipidaemia, atrial fibrillation and CHD than comparison patients, we entered these comorbidities along with geographic region and monthly income into a multivariable logistic regression model as predictors to calculate the expected probability of having conjunctival haemorrhage for each patient. Patients were subsequently stratified based on propensity score deciles to ensure that, within each stratum, comparisons were made for patients with a similar expected probability of having conjunctival haemorrhage and, to a large extent, a similar distribution of confounders. Two-tailed p-values of 0.05 or less were considered statistically significant.

Results

Of the total 104 094 subjects in both groups, the mean age (±SD) was 49.4 (±18.6) years. Over 55% were women. Table 1 presents the results of Pearson's chi-square tests for examining the difference in the distributions of sociodemographic characteristics and medical comorbidities between patients with and without conjunctival haemorrhage. After matching for age, sex, urbanization level and index year, we found that patients with conjunctival haemorrhage had a higher prevalence of comorbidities in the form of hypertension, diabetes, hyperlipidaemia, atrial fibrillation and CHD than comparison patients (all $p < 0.001$).

The incidence of stroke during the 3-year follow-up period for patients with and without conjunctival haemorrhage is presented in Table 2. It shows that of the total 104 094 subjects, 5515 (5.3%) had strokes during the 3-year follow-up period. Of the patients with conjunctival haemorrhage, 1272 (7.3%) had a stroke, in comparison with 4251 (4.9%) of the comparison patients. The incidence rate of stroke was 2.44 (95% CI = 2.31–2.55) per 100 person-years in patients with conjunctival haemorrhage and 1.63 (95% CI = 1.59–1.68) per 100 person-years in comparison patients. The log-rank test revealed that patients with conjunctival haemorrhage had significantly lower 3-year stroke-free survival rates than comparison patients (χ^2 value = 173.45; $p < 0.001$). The results of the Kaplan–Meier survival analysis are presented in Fig. 1.

Table 1. Demographic characteristics and comorbid medical disorders for patients with conjunctival haemorrhage and comparison group patients at baseline, Taiwan, 2002–2006 (n = 104 094).

	Patients with conjunctival haemorrhage n = 17 349		Comparison patients n = 86 745		
Variable	Total no.	Column %	Total no.	Column %	p-value
Gender					
Male	7759	44.7	38 795	44.7	1.000
Female	9590	55.3	47 950	55.3	
Age (years)					
40–59	6824	39.3	34 120	39.3	1.000
60–69	5056	29.1	25 280	29.1	
70–79	3447	19.9	17 235	19.9	
≥80	2022	11.7	10 110	11.7	
Urbanization level					
1	5896	34.0	29 480	34.0	1.000
2	5030	29.0	25 150	29.0	
3	2862	16.5	14 310	16.5	
4	2139	12.3	10 695	12.3	
5	1422	8.2	7110	8.2	
Hypertension	6310	36.4	27 758	32.4	<0.001
Diabetes	2717	15.7	11 017	12.7	<0.001
Coronary heart disease	2432	14.0	9542	11.0	<0.001
Hyperlipidaemia	3740	21.6	15 614	18.0	<0.001
Atrial fibrillation	214	1.2	694	0.8	<0.001
Monthly income					
NT$0–15 840	4664	26.9	23 595	27.2	0.687
NT$15 841–25 000	7779	44.8	38 688	44.6	
≥NT$25 001	4906	28.3	24 462	28.2	
Geographic region					
Northern	8648	49.8	43 112	49.7	0.668
Central	3900	22.5	19 257	22.2	
Southern	4541	26.2	23 074	26.6	
Eastern	260	1.5	1302	1.5	

Table 2. Crude and adjusted hazard ratios for stroke among the sample patients during the 3-year follow-up period starting from the index date (n = 104 094).

	Total sample	Comparison patients n = 86 745	Patients with conjunctival haemorrhage n = 17 349
Presence of stroke	N (%)	N (%)	N (%)
Three-year follow-up period			
Yes	5517 (5.3)	4251 (4.9)	1272 (7.3)
Incidence rate per 100 person-years (95% confidence interval)	1.77 (1.72–1.81)	1.63 (1.59–1.68)	2.44 (2.31–2.55)
Crude HR (95% CI)[†]	–	1.00	1.54 (1.44–1.64)***

*** $p < 0.001$.

[†] Hazard ratio was calculated using stratified Cox proportional regression (stratified on sex, age group, urbanization level, the year of index date and propensity score).

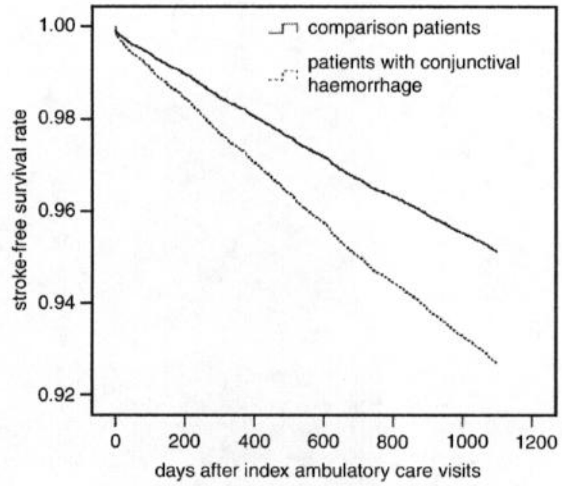

Fig. 1. Stroke-free survival rates for patients with conjunctival haemorrhage and comparison patients in Taiwan.

Table 2 also shows the hazard ratio (HR) and corresponding 95% confidence interval (95% CI) of stroke between patients with and without conjunctival haemorrhage. The hazard ratio of stroke during the 3-year follow-up period for patients with conjunctival haemorrhage was 1.54 (95% CI = 1.44–1.64) times that of comparison patients.

Table 3 presents the adjusted HR and corresponding 95% CI for stroke. After adjusting for patient monthly income, geographic location, hypertension, atrial fibrillation, diabetes, hyperlipidaemia and CHD, the stratified Cox proportional hazards regression (stratified on sex, age group, urbanization level, index year and propensity score) revealed that the hazard ratio of stroke for patients with conjunctival haemorrhage was 1.33 (95% CI = 1.24–1.42, $p < 0.001$).

We further analysed the difference in stroke subtype (subarachnoid haemorrhage, intracerebral haemorrhage, ischaemic stroke and unspecified strokes) between patients with and without conjunctival haemorrhage. We found no difference in the distribution of stroke subtype between these two groups.

Table 3. Adjusted hazard ratio for stroke during the 3-year follow-up period starting from the index date (n = 104 094).

	Stroke occurrence		
Variables	Hazard ratio	95% CI	p-value
Group			
Conjunctival haemorrhage	1.33	1.24–1.42	<0.001
Comparison	1.00		
Hypertension	4.97	4.51–5.49	<0.001
Diabetes	1.41	1.31–1.51	<0.001
Coronary heart disease	2.34	2.15–2.55	<0.001
Hyperlipidaemia	1.58	1.47–1.71	<0.001
Atrial fibrillation	4.42	3.51–5.56	<0.001
Monthly income			
NT$0–15 840	1.00		
NT$15 841–25 000	2.23	1.95–2.55	<0.001
≥NT$25 001	2.05	1.69–2.49	<0.001
Geographic region			
Northern	1.00		
Central	0.99	0.92–1.07	0.804
Southern	0.98	0.91–1.05	0.499
Eastern	0.61	0.50–0.76	<0.001

Hazard ratio was calculated using stratified Cox proportional regression (stratified on sex, age group, urbanization level, the year of index date and propensity score).

Discussion

To the best of our knowledge, no study has attempted to examine the relationship between conjunctival haemorrhage and stroke to date. This study found that the risk of stroke was increased during the 3-year follow-up period following diagnosis with conjunctival haemorrhage. We also found that in addition to hypertension, other related medical comorbidities including diabetes mellitus, hyperlipidaemia, atrial fibrillation and CHD were more prevalent among patients with conjunctival haemorrhage than comparison patients. Nevertheless, as these medical comorbidities (hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation and CHD) had been adjusted for in the regression model, these findings suggest that patients with a diagnosis of conjunctival haemorrhage were at a significantly increased risk of stroke during the 3-year follow-up period.

Hypertension is a major risk factor for the development of retinal vein occlusion, retinal artery occlusion and ischaemic optic neuropathy (Wong & Mitchell 2007; Ho et al. 2009). Microvascular changes occur in the course of hypertension, and such changes may be related to both conjunctival haemorrhage and stroke (Wong & Mitchell 2007). By comparing 78 patients with subconjunctival haemorrhage to 78 controls with unrelated ophthalmic conditions, Pitts et al. (1992) confirmed that blood pressure is higher in those patients with conjunctival haemorrhage. In another study conducted by Mimura et al. (2009), it was reported that most cases of conjunctival bleeding could be explained by uncontrolled hypertension in older patients. Furthermore, Mimura et al. surveyed the underlying disease related to subconjunctival haemorrhage. They found that the number of patients with conjunctival haemorrhage increased noticeably among those aged 50 and above. Diseases such as diabetes mellitus and hyperlipidaemia, as well as complications with anticoagulant therapy, also increase with age. In contrast, the role of trauma in developing conjunctival haemorrhage was greater for younger patients (< 40 years old) than older patients (40 years or older). For this reason, we not only excluded trauma from our study patients (according to ICD coding), but also selected subjects who were at least 40 years old. We still found that conjunctival haemorrhage was an independent risk factor for subsequent stroke.

However, our study faced several limitations. First, we used the patient's recorded ICD-9-CM diagnosis code 372.72 (conjunctival haemorrhage) as our diagnostic criteria. This identification method may be less precise than a diagnosis acquired via a standardized clinical examination. Further, our use of ICD-9-CM coding system precluded our ability to ascertain the severity of conjunctival haemorrhage. This is the major limitation of our study compared with other population-based studies, which have used a standard dry eye examination to diagnose conjunctival haemorrhage. However, the NHI Bureau of Taiwan interviews patients at random and assesses medical charts every year, to ensure that standards are being maintained with regard to diagnostic validity and quality of care. Hospitals constantly face scrutiny and risk heavy penalties if discrepancies or evidence of malpractice is found. Therefore, we assured that every patient with a recorded diagnosis of conjunctival haemorrhage had received a thorough slit-lamp biomicroscopic examination in the clinic.

Second, we were unable to rule out the possibility that some of the comparison patients in this study may have also been suffering from conjunctival haemorrhage but were overlooked as they did not seek treatment. However, if such a bias exists in the data, the results of our analysis would be biased towards the null.

Conclusions

Our study indicated that hypertension, diabetes, hyperlipidaemia, atrial fibrillation and CHD were associated with conjunctival haemorrhage. These medical conditions may be medically controlled if patients receive early intervention and regular follow-ups at the clinic. After appropriately adjusting for confounding factors, our results suggested that patients suffering from conjunctival haemorrhage were at a significantly increased risk of stroke during the first 3 years following their diagnosis. Ophthalmologists should warn their patients suffering from conjunctival haemorrhage about the possibility of their increased risk of stroke.

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