Increased Risk of Stroke in the Year After a Hip Fracture
A Population-Based Follow-Up Study

Jiunn-Horng Kang, MD; Shiu-Dong Chung, MD; Sudha Xirasagar, MBBS, PhD; Fu-Shan Jaw, PhD; Herng-Ching Lin, PhD

Background and Purpose—Stroke is a documented risk factor for hip fracture. However, no documented studies are available on the risk of stroke among patients with hip fracture. This study investigated the frequency and risk of stroke after hip fracture using a nationwide population-based study.

Methods—The study cohort included 2101 patients hospitalized with a principal diagnosis of hip fracture from 2001 to 2004. The comparison cohort consisted of 6303 randomly selected subjects matched on sex, age, and year of index healthcare use as controls. We tracked patients for a 1-year period from their index healthcare encounter to identify those who had a stroke. Stratified Cox proportional hazard regression was performed to evaluate the association of hip fracture with subsequent stroke during 1-year follow-up.

Results—Of a total of 8404 patients, 86 (4.1%) from the study group and 170 (2.7%) from the comparison group had strokes during the follow-up period (P<0.001). The stratified Cox proportional analysis shows that the 1-year crude hazard of stroke among patients with hip fracture was 1.55 times (95% CI, 1.19 to 2.03; P=0.001) that of the comparison group. Furthermore, after adjusting for the major cardiovascular risk factors, the increased stroke risk of patients with hip fracture persisted at about the same level as in the unadjusted analysis (hazard ratio, 1.53; 95% CI, 1.17 to 2.01; P=0.002).

Conclusion—Hip fracture is associated with increased risk of stroke in the next year. (Stroke. 2011;42:00-00.)

Key Words: cardiovascular risks ■ hip fracture ■ stroke

Hip fracture is a devastating event that causes major morbidity and mortality, particularly in elderly populations.1,2 Although the incidence of hip fracture varies by geography and ethnicity, its increasing incidence is a worldwide problem, which adds considerably to the public health burden and economic costs.3,4 Several risk factors are associated with the occurrence of hip fracture, including osteoporosis, physical conditions, comorbidities, concurrent pharmacological effects, and environmental factors.5 High mortality among patients after hip fractures has been demonstrated in previous studies.6–8 Acute and short-term mortality is predominantly a result of infections, cardiovascular comorbidities, and postoperative complications.7,9

Stroke is a recognized risk factor for hip fracture.10–12 In addition to significantly decreased balance, decreased reaction time could result in falls among patients with stroke. Accelerating osteoporosis in the stroke-affected limbs predisposes patients with stroke to fractures.10 Stroke in itself is also a major cause of disability and death.13 The association between cardiovascular disease and hip fracture has attracted attention in recent years.14,15 Several factors are thought to concurrently affect the vascular system and regulation of bone formation.16,17 We hypothesize that patients with hip fractures may experience several unfavorable physiological changes that predispose them to stroke. However, to date, studies regarding the risk of stroke among patients with hip fracture are lacking. We investigated the frequency of stroke during a 1-year follow-up period after a hip fracture and computed the relative risk compared with the general population using nationwide population-based data.

Methods

Database

The data source was the “Longitudinal Health Insurance Database (LHID2000),” derived from medical claims data available with the Bureau of National Health Insurance, provided to researchers for longitudinal studies of medical service use. Taiwan launched its National Health Insurance (NHI) program in 1995 to provide

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From the Institution of Biomedical Engineering (J.-H.K., F.-S.J.), College of Engineering and College of Medicine, National Taiwan University, Taipei, Taiwan; the Department of Physical Medicine and Rehabilitation (J.-H.K.), Taipei Medical University Hospital, Taipei, Taiwan; the School of Medicine (J.-H.K.), Taipei Medical University, Taipei, Taiwan; the Department of Urology (S.-D.C.), National Taiwan University Hospital, Taipei, Taiwan; the Division of Urology (S.-D.C.), Department of Surgery, Far Eastern Memorial Hospital, Taipei, Taiwan; the Department of Health Services Policy and Management (S.X.), University of South Carolina, Columbia, SC; and the School of Health Care Administration (H.-C.L.), Taipei Medical University, Taipei, Taiwan.

Correspondence to Herng-Ching Lin, PhD, School of Health Care Administration, College of Medicine, Taipei Medical University, 250 Wu-Hsing Street, Taipei 110, Taiwan. E-mail henry111111@tmu.edu.tw

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affordable health care for all residents of Taiwan. As of 2007, 22.60 million of 22.96 million Taiwanese (98.4%) were covered under the NHI program. The LHID2000, prepared by the Taiwan National Health Research Institutes, contains insured population registration files and medical claims for 1,000,000 randomly selected NHI enrollees from the 2000 Registry of NHI Beneficiaries. The representativeness of the LHID2000 relative to the population of NHI enrollees on sex distribution is validated by the Taiwan National Health Research Institutes. The LHID2000 has been released to enrollees from the 2000 Registry of NHI Beneficiaries. The representative enrollees on sex distribution is validated by the Taiwan National Health Research Institutes.20

This study was exempt from full review by the Institutional Review Board because the data set consists of deidentified secondary data released without restrictions for research purposes.

Study Sample
This was a prospective case–control study. We identified 2455 patients who were hospitalized with a principal diagnosis of hip fracture (International Classification of Diseases, 9th Revision, Clinical Modification codes 820 to 821) from January 1, 2001, to December 31, 2004 from the LHID2000. Their first hospitalization for hip fracture served as the index healthcare use for hip fracture. We excluded patients aged <18 years (n = 159), patients diagnosed with stroke (International Classification of Diseases, 9th Revision, Clinical Modification codes 430 to 438) before their index healthcare use (n = 133), and patients with an underlying disorder predisposing the patient to pathological fractures such as cancer or bone disease (n = 62). Ultimately, 2101 adult patients with hip fracture were included in the study cohort.

We selected the comparison cohort from the remaining NHI beneficiaries registered in the LHID2000. Like with the study cohort, we excluded patients aged <18 years. We also excluded patients diagnosed with a fracture, cancer, or bone disease during the period 1996 to 2005. Then, we randomly selected 6303 subjects (3 comparison patients for every patient with hip fracture) matched on sex, age (<40, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years), and year of the study patient’s index healthcare use for hip fracture. For comparison patients, their first use of health care in this year served as their index healthcare use regardless of inpatient or ambulatory setting. Patients diagnosed with stroke before their index healthcare use were excluded.

All patients, hip fracture and comparison patients, were tracked (n = 8404) for a 1-year period from their index healthcare use to identify patients who experienced a stroke. During the follow-up period, 131 sampled patients died from nonstroke causes, 73 from the study cohort and 58 from the comparison cohort.

Statistical Analysis
We used SAS programs for analysis (SAS System for Windows, Version 8.2; SAS Institute Inc, Cary, NC). We used the SAS proc surveyselect program for selecting comparison patients. We used Pearson $\chi^2$ tests to compare hip fracture versus comparison patients on geographical location of the patient’s residence (northern, central, eastern, and southern Taiwan), monthly income, and selected comorbid medical disorders at baseline (hypertension, diabetes, heart disease (including coronary heart disease, atrial fibrillation and heart failure, and hyperlipidemia), all risk factors for stroke. These disorders were captured in the study data set if such a diagnosis appeared either in an inpatient claim or in ≥2 ambulatory care claims coded 6 months before and after the index healthcare use.

We used the Kaplan-Meier method and log-rank test to estimate survival curves and to compare the 1-year stroke-free survival rate among patients with hip fracture versus the comparison group. In addition, stratified Cox proportional hazard regression (stratified by age, sex, and the year of index healthcare use) was performed to evaluate the association of hip fracture with a subsequent stroke within 1 year, censoring cases that died from nonstroke causes during that time. We computed hazard ratios (HRs) and 95% CIs to estimate the risk of stroke using a significance level of 0.05.

Results
Table 1 shows the distribution of the hip fracture and comparison patients by demographic characteristics and co-morbid medical disorders at baseline. Of 8404 sampled patients, the mean age was 63.8 years for all patients (SD, 20.2) and 63.9 years and 63.8 years, respectively, for hip fracture and comparison patients ($P = 0.244$). Over half (54.5%) were aged >70 years. After being matched for age and sex, the patients with hip fracture had a higher prevalence of diabetes than the comparison group ($P < 0.001$). Both groups were similar in hypertension, hyperlipidemia, and heart disease prevalence at baseline.

Table 2 presents the distribution of strokes during 1-year follow-up among hip fracture versus comparison patients. Of the total 8404 patients, 256 (3.1%) had a stroke, 86 among patients with hip fracture (4.1%) and 170 (2.7%) among comparison patients. The Figure presents the stroke-free survival curves obtained by the Kaplan-Meier method and shows that patients with hip fracture had significantly lower 1-year stroke-free survival than comparison patients (log-rank test: 12.353; $P < 0.001$).

Among patients who had a stroke during follow-up, the median period between index healthcare use and stroke onset was 155 days for all patients and 170 and 154 days, respectively, for hip fracture and comparison patients, respectively ($P = 0.452$). There was no significant difference in the type of stroke between the 2 cohorts ($P = 0.473$).

Table 2 also shows the crude HRs for stroke. Stratified Cox proportional hazard analysis showed that the hip fracture group had a crude HR of 1.55 relative to the comparison group (95% CI, 1.19 to 2.03; $P < 0.001$).

Table 3 presents the covariate-adjusted stroke HRs. After adjusting for patients’ geographic location, monthly income, and presence of hypertension, diabetes, heart disease, and hyperlipidemia at baseline, patients with hip fracture were more likely to have a stroke relative to the comparison group (HR, 1.53; 95% CI, 1.17 to 2.01; $P = 0.002$).

Discussion
Although high mortality associated with hip fracture is well recognized (11% to 23% at 6 months and 22% to 29% at 1 year postfracture), the role of comorbidities/complications in mortality remains unclear. Stroke is a leading cause of disability and mortality worldwide. Patients with hip fracture and comorbid stroke are disadvantaged in recovering their functional status and on their survival probability. Our study finds that patients with hip fracture face a higher risk of stroke in the next year. To our knowledge, this is the first longitudinal population-based study to explore the frequency and risk of stroke among patients with hip fracture. Our study suggests that physicians should be proactive to prevent strokes given the subsequent higher risk of stroke among patients with hip fracture.

The mechanisms mediating stroke occurrence among patients with hip fracture is little studied and largely unclear. Several factors may be involved. First, physical inactivity, psychological distress, and pain are common after a hip fracture. Disruption or deterioration of pre-existing cardiovascular risk could be triggered in such circumstances.
Second, embolic phenomena arising out of deep vein thrombosis, fat embolization, and pulmonary embolization are not uncommon in patients with hip fracture during the acute and postoperative periods. Recent studies found that systemic migration of emboli to the brain through intracardiac or extracardiac right to left shunts resulting in stroke is more common than thought earlier. In addition, systemic hypercoagulative status is a documented complication after surgery for proximal femoral fracture, which could trigger a stroke. Third, the hospitalization and surgery required for hip fracture treatment are inevitably associated with unfavorable physiological changes during anesthesia and surgical procedures, which could predispose these patients to cerebro- and cardiovascular events.

Table 1. Demographic Characteristics and Comorbid Medical Disorders at Baseline Among Hip Fracture and Comparison Patients in Taiwan, 2001–2004 (n=8404)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Hip Fracture (N=2101)</th>
<th>Comparison Patients (N=6303)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>Column Percent</td>
<td>Total No.</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1183</td>
<td>56.3</td>
<td>3,495</td>
</tr>
<tr>
<td>Female</td>
<td>918</td>
<td>43.7</td>
<td>2,754</td>
</tr>
<tr>
<td>Age, mean (SD); monthly income, mean (SD)</td>
<td>76.7 (7.2); NT $12,821 (12,985)</td>
<td>77.4 (8.8); NT $13,211 (12,698)</td>
<td>0.518; 0.212</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>366</td>
<td>17.4</td>
<td>1,098</td>
</tr>
<tr>
<td>40–49</td>
<td>142</td>
<td>6.8</td>
<td>426</td>
</tr>
<tr>
<td>50–59</td>
<td>160</td>
<td>7.6</td>
<td>480</td>
</tr>
<tr>
<td>60–69</td>
<td>287</td>
<td>13.7</td>
<td>861</td>
</tr>
<tr>
<td>70–79</td>
<td>684</td>
<td>32.5</td>
<td>2,052</td>
</tr>
<tr>
<td>&gt;79</td>
<td>462</td>
<td>22.0</td>
<td>1,386</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49</td>
<td>2.3</td>
<td>190</td>
</tr>
<tr>
<td>No</td>
<td>2,052</td>
<td>97.7</td>
<td>6,113</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>511</td>
<td>24.3</td>
<td>1,605</td>
</tr>
<tr>
<td>No</td>
<td>1,590</td>
<td>75.7</td>
<td>4,698</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>310</td>
<td>14.7</td>
<td>566</td>
</tr>
<tr>
<td>No</td>
<td>1,791</td>
<td>85.3</td>
<td>5,737</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>191</td>
<td>9.1</td>
<td>543</td>
</tr>
<tr>
<td>No</td>
<td>1,190</td>
<td>90.9</td>
<td>5,760</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>843</td>
<td>40.1</td>
<td>2,765</td>
</tr>
<tr>
<td>Central</td>
<td>532</td>
<td>25.3</td>
<td>1,511</td>
</tr>
<tr>
<td>Southern</td>
<td>656</td>
<td>34.2</td>
<td>1,866</td>
</tr>
<tr>
<td>Eastern</td>
<td>70</td>
<td>3.4</td>
<td>161</td>
</tr>
</tbody>
</table>

$1 US=$33 NT in 2005.

Table 2. Crude and Covariate-Adjusted HRs for Stroke Among the Sampled Patients During the 1-Year Follow-Up Starting From the Index Healthcare Use

<table>
<thead>
<tr>
<th>Presence of Stroke</th>
<th>Total Sample (N=8404)</th>
<th>Patients With Hip Fracture (N=2101)</th>
<th>Comparison Patients (N=6303)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
<td>No.</td>
</tr>
<tr>
<td>One-year follow-up period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>256</td>
<td>3.1</td>
<td>86</td>
</tr>
<tr>
<td>No</td>
<td>8,148</td>
<td>96.9</td>
<td>2,015</td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>—</td>
<td></td>
<td>1.55* (1.19–2.03)</td>
</tr>
</tbody>
</table>

*P<0.001.
with matched control subjects. Patients with diabetes are at higher risk for falls, possibly due to diabetic neuromuscular dysfunction and impaired vision due to retinopathy and cataract. Impaired bone quality rather than impaired bone density may compound the risk of fractures among diabetic patients. Recurrent hypoglycemia, vitamin D deficiency, and thiazolidinedione therapy are all reported to increase fracture risk in diabetic patients. Appropriate screening for bone density, intervention for osteoporosis, and appropriate fall prevention strategies should be considered for integration into routine care protocols for diabetic patients. Interestingly, Van Diepen et al found that heart failure is also associated with a higher risk for hip fracture in a large population-based study.

Elevated aldosterone levels in patients with heart failure may induce secondary hyperparathyroidism. Vitamin D levels are lower in patients with heart failure than in matched control subjects. All of these factors are associated with osteoporosis and, consequently, increased fracture risk.

The incidence of hip fracture increases with an aging population typical of modern societies. To minimize morbidity and mortality among patients with hip fracture, a multidisciplinary approach, including medical, orthopedic, and rehabilitative specialty collaboration, is suggested to improve outcomes. The clinical goal of postoperative care, chiefly early mobilization, muscle strengthening, gait training, and pain management, is to achieve maximum functional status and prevent subsequent falls and fractures. Our study suggests that the postoperative management should be expanded to address any level of cardiovascular risk, both short-term and long-term cardiovascular risks. Controlling cardiovascular risks, enhancing physical activity, and minimizing psychological stress may decrease the risk of stroke after hip fracture. Interestingly, recent data suggest that bisphosphonate, a common antosteoporotic agent, could concurrently retard atherosclerosis. Specific preventive interventions against adverse cardiovascular events in patients with hip fracture need to be explored further.

A strength of our study is the minimal selection bias due to the use of a representative sample drawn from population-based data providing important epidemiological data regarding this issue. However, several limitations of our study should be noted. First, a widespread skepticism prevails regarding the validity of diagnostic coding in medical claims. Taiwan’s NHI is 1 of the largest single-payer health insurance systems in the world. To maximize diagnostic coding accuracy in medical claims, the NHI has extensive and systematic processes of quality assurance including routine crosschecking of stratified random samples of claims using comprehensive chart reviews by clinical specialists. Additionally, epidemiological studies conducted with the LHID have yielded results that are consistent with population-based surveys for several conditions. Therefore, the reliability of diagnostic coding in medical claims is considered acceptable for epidemiological studies.

Second, potentially important confounding variables are not captured in claims data such as family history, cigarette smoking, alcohol consumption, physical activity, and dietary habits. Third, we did not account for pharmaceuticals. Medications such as nonsteroidal anti-inflammatory drugs are usually prescribed for management of pain in hip fracture cases. Long-term use of nonsteroidal anti-inflammatory drugs is associated with an increased risk of stroke. Fourth, our study population largely consists of ethnic Han Chinese, and therefore our results may not generalize to all populations. Ethnic differences in both stroke and hip fracture are documented. Therefore, our findings should be evaluated against other ethnic groups. Fifth, we assigned the first episode of healthcare use as the patient’s index healthcare use regardless of inpatient or ambulatory setting. This design may select a
healthier set of control subjects and therefore underestimate the risk of stroke among other hospitalized control subjects. Our study design, however, is consistent with our objective of assessing the overall relative risk of stroke among patients with hip fracture relative to the general population. Selection of control subjects from among hospitalized patients would provide the excess stroke risk among patients with hip fracture relative to other significant ill patients. Although useful in itself, it was not a study objective and therefore not studied. Finally, the type of hip fracture, anesthesia, and surgery is not accounted for in our study. Some authors suggest that the type of fracture and surgery affects the outcome.9,41 Further studies are needed to explore the risk of stroke among hip fracture subtypes.

In conclusion, patients with hip fracture are at increased risk of a subsequent stroke within the next year. The mechanisms involved need further study. Aggressive monitoring and modification of cardiovascular risk factors may help to reduce adverse cardiovascular events in this population.

Acknowledgments

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, Taiwan, and managed by the National Health Research Institutes. The interpretations and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or the National Health Research Institutes.

Disclosures

None.

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일반 인구 집단에서의 추적 관찰 연구

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(Stroke. 2011;42:336-341.)

Key Words: cardiovascular risks ■ hip fracture ■ stroke

배경과 목적
뇌졸중은 고관절 골절(hip fracture)의 주요한 위험인자이다. 그러나 고관절 골절 환자에서의 뇌졸중 위험에 대하여서는 아직 발표된 연구가 없다. 본 연구는 전국적인 인구 기반 연구를 이용하여, 고관절 골절 이후 뇌졸중의 반도 및 위험도에 대하여 분석한 것이다.

방법
본 연구 코호트는 2001~2004년에 고관절 골절로 입원한 환자 2,101명을 대상으로 하였다. 이들에 대하여 성별, 연령 및 건강 검진년도를 기준으로 하여 6,303명의 무작위 추출 대조군을 선정하였다. 고관절 골절 이후 1년간의 추적 관찰 기간 동안 발생하는 뇌졸중과 고관절 골절의 연관성을 분석하기 위하여, 중화 록스 비례 위험 회귀 분석(stratified Cox proportional hazard regression)을 실시하였다.

결과
총 8,404명의 환자 중, 추적 관찰 기간 동안 86명(4.1%)의 고관절 골절 환자 및 170명(2.7%)의 대조군 환자에서 뇌졸중이 발생하였다. 중화 록스 비례 위험 분석을 통하여, 고관절 골절 환자의 1년 뇌졸중 위험도는 대조군에 비하여 1.55배(95% CI, 1.19~2.03; P=0.001) 높았다. 또한 주요 심혈관적 위험인자들 보정한 후, 고관절 골절 환자들의 뇌졸중 위험도 증가는 보정하지 않은 분석과 비슷하였다(위험비[hazard ratio], 1.53; 95% CI, 1.17~2.01; P=0.002).

결론
고관절 골절은 이후 1년간 뇌졸중 위험 증가와 연관되어 있다.