Association Between Stroke and Patients With Pelvic Inflammatory Disease
A Nationwide Population-Based Study in Taiwan

Po-Chih Chen, MD; Teng-chu Tseng, MD; Jui-Yang Hsieh, MD; Hui-Wen Lin, PhD

Background and Purpose—The aim of this study is to estimate the risk of stroke in a 3-year period after pelvic inflammatory disease (PID) using a nationwide population-based study.

Methods—Our study cohort consisted of all patients with a diagnosis of PID (N=64,515) between 2004 and 2005 with a control cohort (1:2) of age-matched controls (N=129,030). Each patient was tracked from hospitalization until the end of 2006. Cox regressions were performed to compute the 3-year stroke-free survival rates after adjusting for possible confounding factors.

Results—we found that women with PID were more likely to have strokes than the control population. After adjusting for potential confounding factors, the adjusted hazard ratio of stroke was 1.63 (95% CI, 1.45–1.85) for PID patients as compared to the general population cohort. Sensitivity analysis using a bootstrap approach further ensured the validity of the results of our study.

Conclusions—we concluded that patients with PID have an association with stroke. Further research is necessary to investigate the pathophysiology between PID and stroke.

Key Words: epidemiology ■ pelvic inflammatory disease ■ risk factors ■ sensitivity analysis ■ stroke

Pelvic inflammatory disease (PID) is a common cause of morbidity for women younger than age 45 years. Untreated or delayed treatment of PID may cause impaired fertility, an increased chance of ectopic pregnancy, and chronic pelvic pain.1

Atherosclerosis increases cardiovascular morbidity and mortality and has been associated with various infectious or inflammatory diseases.2,3 A variety of mechanisms, such as immune reaction, endothelial dysfunction, or oxidized low-density lipoprotein,3–5 may cause atherosclerosis. The aim of this study was to estimate the risk of stroke among patients with PID during a 3-year follow-up period after diagnosis and to compare the results with those of a cohort of control patients.

Materials and Methods

Study Population

The source of data in this study was a longitudinal dataset compiled by the Longitudinal Health Insurance Database 2005. The Longitudinal Health Insurance Database 2005 comprises ambulatory care, inpatient care, and claimed medical expenses related to the demographic factors of 1,000,000 beneficiaries sampled randomly from among the 25,68 million enrollees in Taiwan.

The study comprised all patients who had visited ambulatory care centers for treatment of PID (International Classification of Diseases 9 clinical modification codes 614, 615, and 616) between January 1, 2004 and December 31, 2005. Patients who were younger than age 18 years, older than age 60 years, or had a diagnosis of any type of stroke before the study were excluded from the cohort. In addition, to ensure the validity of the PID diagnosis, only those patients who had at least 2 consensus diagnoses of PID were selected. After all exclusions, the study cohort included 64,515 PID patients. In the comparison cohort, patients who had a stroke diagnosed before 2004 or PID between 2004 and 2006 were excluded. The remaining 129,030 subjects (2 for every patient in the study cohort) were randomly stratified and matched to those in the study cohort in terms of age (18–30, 31–40, 41–50, and 51–60 years) and entry year. Each patient was followed-up from their entry day to December 31, 2006, to determine whether they had any type of stroke develop (International Classification of Diseases 9 clinical modification codes 430–438).

Statistical Analysis

Pearson χ2 tests were used to compare differences in baseline variables. The stroke-free survival function was evaluated using Cox regression models to examine differences in the risk of stroke between the 2 cohorts after adjusting for potential confounding factors such as age, coronary heart disease, diabetes mellitus, hypertension, hyperlipidemia, endometriosis, monthly income, and level of urbanization.
Sensitivity analysis was performed using a bootstrap approach.6,7 The bootstrap approach is a method for deriving robust estimates of standard errors and CI for estimates such as the hazard ratio (HR). It is most useful as an alternative to parametric estimates when the assumptions of those methods are in doubt, or when parametric inference is impossible or requires complicated formulas for the calculation of CI.6 Additionally, our data were reanalyzed excluding patients who had used oral contraceptives for >28 days in the Cox model to demonstrate that the association of PID with stroke was not caused by contraceptive use.

**Results**

Table 1 shows that the 64 515 patients with PID were more likely to have comorbidities of coronary heart disease (P<0.001), diabetes mellitus (P<0.001), hyperlipidemia (P<0.001), and endometriosis (P<0.001) than those in the comparison cohort. Of the 193 545 patients, 1090 experienced stroke during the 3-year follow-up period, including 456 among PID patients and 634 from the comparison cohort. In the Cox regression analysis, after adjusting for potential confounding factors including age, coronary heart disease, diabetes mellitus, hypertension, hyperlipidemia, endometriosis, monthly income, and level of urbanization, the adjusted HR of stroke was 1.63 (95% CI, 1.45–1.85) for PID patients compared to the comparison cohort. PID patients were divided into ischemic and hemorrhagic groups and were further analyzed. Analysis determined that the adjusted HR of ischemic stroke was 1.72 (95% CI, 1.51–1.95) for PID patients compared to patients in the comparison cohort. No significant relationship was found for the occurrence of hemorrhagic stroke (P=0.891) between the 2 groups. The Figure displays stroke-free survival curves based on the Cox models for PID patients and the comparison cohort after adjusting for potential confounding factors.

We performed sensitivity analyses using a bootstrap approach (Table 2) to ensure the validity of the results. Statistically similar results were found in analyses that excluded strokes occurring within the first 6 months of the follow-up. This was performed to ensure capture of the incident rather than to show the prevalence of strokes. Of the 64 515 PID patients, 358 experienced stroke. The adjusted HR of strokes was 1.44 (95% CI, 1.25–1.67). Patients using contraceptives were also excluded. Of the 62 484 PID patients, 447 experienced strokes. The HR (HR, 1.64; 95% CI, 1.43–1.84) of strokes in patients with PID were statistically similar to those in the primary analysis (HR, 1.63; 95% CI, 1.43–1.83). Moreover, covariance with age, coronary heart disease, diabetes mellitus, hypertension, and hyperlipidemia
was associated with strokes. This was especially true for hypertension (HR, 2.6; 95% CI, 2.23–3.04; not shown in Tables).

**Discussion**

This study discovered a possible relationship between PID and stroke. The actual mechanisms causing this relationship between PID and stroke are multifactorial and not fully understood. Chronic infection and atherosclerosis have been associated with cytokines, endothelial dysfunction, oxidized low-density lipoprotein, or elevated C-reactive protein.8–10 Interleukins and other cytokines markedly increase in PID patients.8 Increased cytokines may cause further endothelial dysfunction and atherosclerosis.2,9 Infectious diseases trigger endothelial dysfunction. 10 Low-density lipoprotein transforms to oxidized low-density lipoprotein with infection11 and promotes activation of macrophage and T lymphocytes, resulting in the formation of foam cells.4,5 Elevated C-reactive protein is associated with inflammatory processes and atherosclerosis.9,10 In addition, C-reactive protein binds to oxidized low-density lipoprotein, thereby further increasing the possibility of atherosclerosis developing.

The major limitations to our study are the surveillance bias and the inability to get detailed personal information. Because most symptoms of PID are mild to moderate, patients who are aware of their symptoms and seek medical help also may be aware of a mild neurological focal deficit. Details of personal history not recorded in this database include the body mass index and whether the person was a smoker. Our study may provide evidence connecting PID to subsequent stroke, but further studies are needed to confirm this association.

**Disclosures**

None.

**References**


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**Table 2. Sensitivity Analysis: Bootstrap Hazard Ratio Point Estimates for Stroke in Pelvic Inflammatory Disease Patients and the Empirical 95% Confidence Interval**

<table>
<thead>
<tr>
<th>PID</th>
<th>Presence of Stroke</th>
<th>Age (y), Mean (SD) Yes/No</th>
<th>Bootstrap Hazard Ratio*</th>
<th>Empirical 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PID Presence of Stroke Yes/No</td>
<td>456/64 059</td>
<td>45.45 (10.10)/35.93 (9.96)</td>
<td>1.63</td>
<td>1.43–1.83</td>
</tr>
<tr>
<td>At least 6 mo of follow-up (to ensure capture of the incident rather than the prevalence of stroke)</td>
<td>358/64 157</td>
<td>45.67 (9.93)/35.94 (9.97)</td>
<td>1.44</td>
<td>1.25–1.67</td>
</tr>
<tr>
<td>Exclusion of patients treated with contraceptives</td>
<td>447/62 037</td>
<td>45.60 (10.04)/36.04 (9.98)</td>
<td>1.64</td>
<td>1.43–1.84</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; PID, pelvic inflammatory disease; SD, standard deviation.

*Adjustments are made for potential confounding factors.
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