Severely Depressed Young Patients Have Over Five Times Increased Risk for Stroke: A 5-Year Follow-Up Study

Hsin-Chien Lee, Herng-Ching Lin, and Shang-Ying Tsai

Background: This study aims to estimate the risk of developing stroke within 5 years of discharge among young patients ages 18 to approximately 44 who were hospitalized for depressive disorders.

Methods: Our study design features a study cohort and a comparison cohort. The study cohort included patients ages 18 to approximately 44 who were hospitalized with a principal diagnosis of depressive disorder ($n = 827$), whereas the comparison cohort consisted of 4,135 patients selected randomly (five for every depressed patient) and matched with the study group in terms of gender, age, and date of discharge. Each patient was tracked for 5 years after their discharge in 1998. Cox proportional hazard regressions were performed to compute the 5-year stroke-free survival rates after adjusting for possible confounding factors.

Results: During the 5-year follow-up period, 50 depressed patients (6.05% of the study cohort) and 48 non-depressed subjects (1.16% of the comparison cohort) developed strokes. The adjusted hazard of stroke was 5.43 (95% confidence interval = 3.47–8.51, $p < .001$) times greater for depressed patients than for non-depressed subjects.

Conclusions: Our findings show young patients ages 18 to approximately 44 who were hospitalized for depressive disorders were at over five times greater risk of developing stroke within 5 years of discharge compared with non-depressed age- and gender-matched subjects.

Key Words: Depressed patients, depression, stroke

A leading cause of disability, depressive disorders were estimated to account for 4.4% of total disability-adjusted life years in the year 2000 (1). A great health burden in this population does not come from the depressive illness per se but stems from its high association with several comorbid medical conditions (2).

In recent decades, the relationship between depression and cardiovascular disease has attracted much attention. Depression is now considered to be a major risk factor for development of cardiovascular disorders (3). As regards other vascular disorders, the association between depression and stroke has likewise been observed for years (4) but has until now focused on depression as a consequence of stroke (5).

A recent report based on the Framingham Heart Study shows a 4.21 times greater risk of developing stroke among depressed participants under 65 years of age as compared with non-depressed participants (6). Still, information directly linking depressive disorder to stroke is scant and controversial (7–9). The present study aims to estimate the risk of developing stroke within 5 years of discharge among severely depressed patients ages 18–44, as compared with age- and gender-matched subjects.

Methods and Materials

Database

This study used the National Health Insurance Research Database (NHIRD). The dataset included all medical claims data from the Taiwan National Health Insurance (NHI) program, which currently enrolls approximately 97% of the country's population. Hundreds of published papers have used the NHIRD as the basis for their studies (10). Because the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Internal Review Board.

Study Sample

The study cohort consisted of severely depressed patients ages 18 to approximately 44 who were discharged during 1998. Severely depressed patients were defined as those with depressive disorders (ICD-9-Clinical Modification [CM] codes 296.2, 296.3, 300.4, and 311) severe enough to be hospitalized (11).

To ensure the validity of diagnoses and to avoid chronicity, we excluded patients hospitalized for any type of mental disorder (ICD-9-CM codes 290–319) during the previous 2-year period and those who developed any other major psychiatric disorder during the follow-up period. Patients who had previous strokes (ICD-9-CM codes 430–438) were also excluded.

Our comparison cohort was extracted from the NHIRD subdataset consisting of 1,073,891 randomly selected subjects, approximately 5% of all enrollees in the NHI program. Subjects were excluded if they had been diagnosed with any other mental disorder or previous stroke. We chose our final comparison cohort from this representative dataset by randomly selecting five patients for every depressed one, matched by age (18 to approximately 29 and 30 to approximately 44, in accordance with a prior study [7]), gender, and the date of discharge. Ultimately, there were 827 patients and 4,135 subjects in the study and comparison cohorts, respectively.

Each sampled case was tracked 5 years from the date of discharge to identify whether stroke occurred. The data were linked to Taiwan death certificate data, with cases censored if individuals died from non-stroke causes during that time. Sociodemographic variables included gender, age, monthly income, level of urbanization (five standardized levels published by the Taiwan National Health Research Institute) and geographic location of the community in which the patient resided. The reason we selected NT$15,840 as the first income level cutoff point was that this is the government-stipulated minimum wage for full-time employees in Taiwan. Details on substance use and comorbid medical disorders at the time of the index discharge were also collected.

From the Department of Psychiatry & Sleep Center (Hs-CL, S-YT), Taipei Medical University Hospital, Taipei, Taiwan; Department of Psychiatry (Hs-CL, S-YT), School of Medicine; and the School of Health Care Administration (He-CL), Taipei Medical University, Taipei, Taiwan.

Address reprint requests to Herng-Ching Lin, Ph.D., School of Health Care Administration, Taipei Medical University, 250 Wu-Hsing St., Taipei 110, Taiwan; E-mail: henry11111@tmu.edu.tw.

Received May 5, 2008; revised June 30, 2008; accepted July 6, 2008.

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2008.07.006

Statistical Analysis

The SAS statistical package (SAS System for Windows, Version 8.2; Cary, North Carolina) was used. Pearson χ^2 tests were carried out to distinguish differences between the study and comparison cohorts. The 5-year stroke-free survival rate was estimated with the Kaplan-Meier method and the log-rank test to examine the differences in the risk of developing stroke between the two cohorts. Cox proportional hazard regressions were then performed to compute the 5-year survival rate, adjusting for variables that were significantly related to stroke from the prior χ^2 analyses. Finally, we present hazard ratios (HR) along with 95% confidence intervals (95% CI) with a significance level of .05.

Results

Table 1 presents the distributions of demographic characteristics and comorbid medical disorders for the study and comparison cohorts. It shows that severely depressed patients were more likely to have certain medical comorbidities at baseline.

During the 5-year follow-up period, 50 depressed patients (6.05% of the study cohort) and 48 non-depressed subjects (1.16% of the comparison cohort) developed strokes. The log-rank test indicated that severely depressed patients had significantly lower 5-year stroke-free survival rates ($p < .001$). (Figure 1).

Table 2 presents the adjusted hazard ratios for stroke by cohort. After adjusting for sociodemographic variables, comorbid medical disorders, and substance abuse, the hazard of developing stroke during the 5-year follow-up period was 5.43 (95% CI = 3.47–8.51, $p < .001$) times greater for severely depressed patients than for subjects in the comparison cohort.

Discussion

The results of this study demonstrate that young, severely depressed patients are at more than five times greater risk of

Table 1. Demographic Characteristics and Comorbid Medical Disorders for Severely Depressed and Comparison Group Patients in Taiwan, 1998

	Depressed Patients $n = 827$		Comparison Subjects $n = 4135$		
Variable	Total No.	Column %	Total No.	Column %	*p*
Gender					1.000
Male	362	43.8	1810	43.8	
Female	465	56.2	2325	56.2	
Age (yrs)					1.000
18–29	257	31.1	1285	31.1	
approx. 30–44	570	68.9	2850	68.9	
Hypertension					.001
Yes	11	1.3	17	.4	
No	816	98.7	4118	99.6	
Diabetes					.004
Yes	15	1.8	31	.8	
No	812	98.2	4104	99.3	
Hyperlipidemia					<.001
Yes	13	1.6	15	.4	
No	814	98.4	4120	99.6	
Renal Disease					.400
Yes	2	.2	5	.1	
No	825	99.8	4130	99.9	
Substance Abuse					—
Yes	198	23.9	—	—	
No	629	76.1	4135	100	
Monthly Income					<.001
0	156	18.9	834	20.2	
NT$1–15,840	248	30.0	818	19.8	
NT$15,841–25,000	322	38.9	1668	40.3	
≥NT$25,001	101	12.2	815	19.7	
Urbanization Level					<.001
1	288	34.8	1277	30.9	
2	261	31.6	1127	27.3	
3	108	13.1	784	19.0	
4	104	12.6	537	13.0	
5	66	8.0	410	9.9	
Geographic region					<.001
Northern	508	61.4	2042	49.4	
Central	119	14.4	861	20.8	
Southern	172	20.8	1110	26.8	
Eastern	28	3.4	122	3.0	

N = 4962.
NT, New Taiwan.

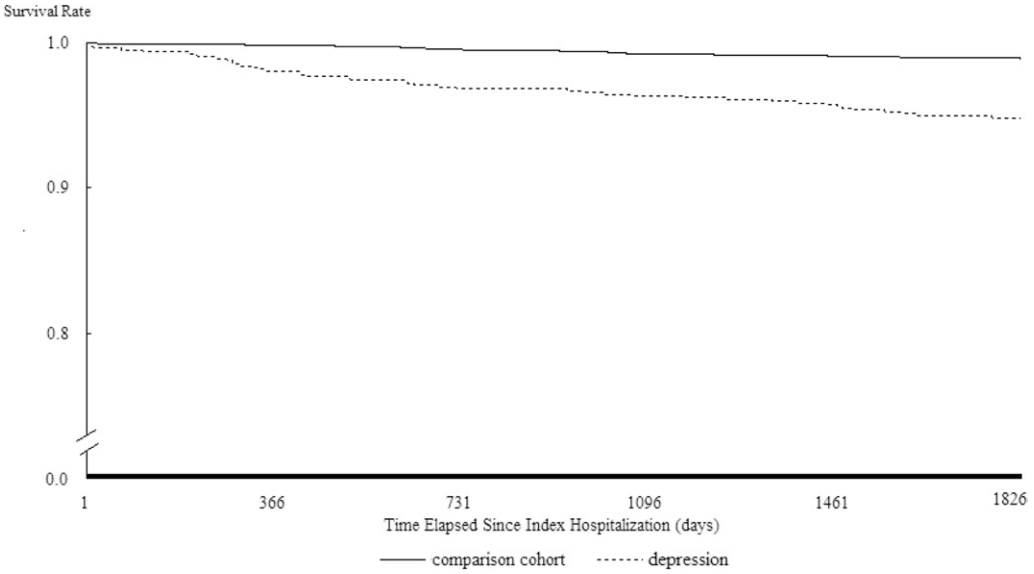

Figure 1. Stroke-free survival rates for depressive disorder and comparison group patients in Taiwan, 1998–2003.

developing stroke within 5 years of discharge, as compared with non-depressed age- and gender-matched subjects, after adjusting for other risk factors.

The association between depression and stroke has been mainly based on community-based studies of people with depressive symptoms rather than depressive disorders (12–14). In term of depressive disorders, Larson *et al.* (7) reported a two- to three-times greater risk over a 13-year follow-up period of developing stroke among community-dwelling persons with a lifetime history of depressive disorders. However, the limited number of persons with depressive disorders at baseline (n = 128) and the accuracy of stroke incidence measured by self-reporting could compromise their findings. A large-scale community-based study in the U.K. indicated that elevated stroke risk is associated with psychological distress but not episodic major depressive disorder (9). Because the psychiatric diagnosis was made on the basis of a self-administered questionnaire, it could be different from clinical depression and confounded by recall bias.

Table 2. Adjusted Hazard Ratio for Stroke During the 5-Year Follow-Up Period for Severely Depressed and Comparison Group Patients in Taiwan

	Stroke Occurrence		
Model	Hazard Ratio	95% CI	*p*
Unadjusted	5.48	3.66–8.20	<.001
Depression			
Comparison (reference group)	1.00		
Adjusted for Sociodemgraphic Variables			
Depression	5.50	3.67–8.24	<.001
Comparison (reference group)	1.00		
Adjusted for Sociodemgraphic Variables and Substance Abuse			
Depression	5.56	3.74–8.87	<.001
Comparison (reference group)	1.00		
Adjusted for Sociodemgraphic Variables, Comorbid Medical Disorders, and Substance Abuse			
Depression	5.43	3.47–8.51	<.001
Comparison (reference group)	1.00		

N = 4962. CI, confidence interval.

Our findings are consistent with results by Nilsson and Kessing (8), which found that patients with depression severe enough to be hospitalized had a 1.22 times increased risk of stroke compared with those with osteoarthritis. Given that the majority of the patients sampled were older, the authors addressed the medical need for stroke prevention only among the severely depressed elderly population. However, the great magnitude of risk observed strongly suggests this warning applies also to persons younger than 45 years old.

The increased risk of stroke among depressed persons has been considered to be mediated by unhealthy behaviors including smoking, poor diet, and lack of exercise (15). Despite the absence of such information within our dataset, previous studies suggest that the increased stroke risk among depressed persons cannot be fully explained by such unhealthy behaviors (9,14).

Researchers have proposed similar models linking depressive disorders to stroke mainly extrapolated from findings on the occurrence of cardiovascular disorders among depressed people (3). Therefore, obesity, metabolic syndrome, and incidental physiological changes such as increased platelet activation, high sympathetic tone, increased inflammatory markers, and endothelial dysfunction, although not specific to stroke, are of research interest (16). Decreased cerebrovascular reactivity associated with a higher risk of stroke has been found among patients with major depressive disorder (17,18). A common etiological basis for depression and stroke might exist.

Recently, the risk of stroke associated with antidepressant use has begun to draw increasing attention. Chen *et al.* (19) reported that the risk of stroke was 1.55 times higher in patients with current exposure to selective serotonin-reuptake inhibitors, the most commonly used antidepressant drugs, as compared with nonusers. That could potentially explain the greater risk found in this study compared with previous ones, because sampled depressed patients in this study were much more likely to take antidepressant drugs long-term after discharge compared with those whose depressive disorders were not severe enough to require hospital stay.

Our findings need to be interpreted in the context of two

inherent limitations of administrative datasets. First, depressive disorders and stroke diagnoses totally reliant upon administrative claims data might be less accurate than those made through a standardized procedure. Secondly, individual information on as dietary habits, cigarette smoking, and body mass index, which contribute to stroke, were not available in the dataset. Furthermore, differences in the use of psychotropic and other medications between the study and comparison cohorts were not taken into consideration. Likewise, the NHIRD does not contain data regarding the patient's duration of illness and number of depression episodes. Finally, subtypes of stroke were not taken into consideration for the analyses. These limitations might compromise our findings.

Given that the co-occurrence of depression and stroke places an enormous burden not only on patients and their families but also on health care systems and societies, further studies are needed to replicate these findings and to verify whether young, severely depressed patients are at increased risk of stroke for reasons inherently related to their depressive disorder or related to resultant lifestyle and treatment.

Drs. Lee, Lin, and Tsai reported no biomedical financial interests or potential conflicts of interest.

1. Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ (2004): Global burden of depressive disorders in the year 2000. *Br J Psychiatry* 184:386–392.
2. Benton T, Staab J, Evans DL (2007): Medical co-morbidity in depressive disorders. *Ann Clin Psychiatry* 19:289–303.
3. Musselman DL, Evans DL, Nemeroff CB (1998): The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Arch Gen Psychiatry* 55:580.
4. Colantonio A, Kasl SV, Ostfeld AM (1992): Depressive symptoms and other psychosocial factors as predictors of stroke in the elderly. *Am J Epidemiol* 136:884.
5. Williams LS (2005): Depression and stroke: Cause or consequence? *Semin Neurol* 25:396.
6. Salaycik KJ, Kelly-Hayes M, Beiser A, Nguyen AH, Brady SM, Kase CS, *et al.* (2007): Depressive symptoms and risk of stroke: The Framingham study. *Stroke* 38:16.
7. Larson SL, Owens PL, Ford D, Eaton W (2001): Depressive disorder, dysthymia, and risk of stroke: Thirteen-year follow-up from the Baltimore Epidemiologic Catchment Area Study. *Stroke* 32:1979.
8. Nilsson FM, Kessing LV (2004): Increased risk of developing stroke for patients with major affective disorder: A registry study. *Eur Arch Psychiatry Clin Neurosci* 254:387.
9. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT (2008): Psychological distress, major depressive disorder, and risk of stroke. *Neurology* 70:788–794.
10. Lee HC, Tsai SY, Lin HC, Chen CC (2006): The association between psychiatrist numbers and hospitalization costs for schizophrenia patients: A population-based study. *Schizophr Res* 81:283–290.
11. Olfson M, Marcus SC, Shaffer D (2006): Antidepressant drug therapy and suicide in severely depressed children and adults: A case-control study. *Arch Gen Psychiatry* 63:865–872.
12. Everson SA, Roberts RE, Goldberg DE, Kaplan GA (1998): Depressive symptoms and increased risk of stroke mortality over a 29-year period. *Arch Intern Med* 158:1133.
13. Simons LA, McCallum J, Friedlander Y, Simons J (1998): Risk factors for ischemic stroke: Dubbo study of the elderly. *Stroke* 29:1341.
14. Jonas BS, Mussolino ME (2000): Symptoms of depression as a prospective risk factor for stroke. *Psychosom Med* 62:463.
15. May M, McCarron P, Stansfeld S, Ben-Shlomo Y, Gallacher J, Yarnell J, *et al.* (2002): Does psychological distress predict the risk of ischemic stroke and transient ischemic attack? The Caerphilly study. *Stroke* 33:7.
16. Joubert J, Cumming TB, McLean AJ (2007): Diversity of risk factors for stroke: The putative roles and mechanisms of depression and air pollution. *J Neurol Sci* 262:71–76.
17. Neu P, Schlattmann P, Schilling A, Hartmann A (2004): Cerebrovascular reactivity in major depression: A pilot study. *Psychosom Med* 66:6–8.
18. de Castro AGC, Bajbouj M, Schlattmann P, Lemke H, Heuser I, Neu P (2008): Cerebrovascular reactivity in depressed patients without vascular risk factors. *J Psychiatr Res* 42:78.
19. Chen Y, Guo JJ, Li H, Wulsin L, Patel NC (2008): Risk of cerebrovascular events associated with antidepressant use in patients with depression: A population-based, nested case-control study. *Ann Pharmacother* 42: 177–184.