

Depression may not be a risk factor for mortality in stroke patients with nonsurgical treatment

A retrospective case-controlled study

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Abstract

Patients with depression have more comorbidities than those without depression. The cost of depression-associated comorbidities accounts for the largest portion of the growing cost of depression treatment. Patients with depression have a higher risk of stroke with poor prognoses than those without depression; however, previous studies evaluating the relationship between depression and stroke prognosis have not accounted for surgical treatment or other risk factors. Therefore, we investigated whether depression is a risk factor for mortality in stroke patients with nonsurgical treatment after adjusting for other risk factors.

We retrospectively analyzed the data of patients with major depressive disorder (MDD) and age and sex-matched controls without MDD during 1999 to 2005. We then identified patients who developed stroke in both groups and analyzed risk factors for death in these stroke patients who received nonsurgical treatments during a follow-up period from 2006 to 2012.

Patients with MDD had higher Charlson Comorbidity Index Scores (CCISs) and exhibited higher frequencies of comorbidities such as diabetes mellitus, hypertension, hyperlipidemia, and coronary heart disease than controls without MDD, and most of MDD patients had very low or high socioeconomic status (SES) and lived in urban settings. Most stroke patients with MDD who received nonsurgical treatment were female, had very low or high SES, and lived in urban settings; in addition, stroke patients with MDD who received nonsurgical treatment had higher CCISs and frequencies of hyperlipidemia and coronary heart disease than those without MDD who received nonsurgical treatment. However, depression was not a risk factor for death in stroke patients with nonsurgical treatment.

Hemorrhagic stroke, age, sex, and CCISs were risk factors for death in stroke patients with nonsurgical treatment, but depression did not affect the mortality rate in these patients.

Abbreviations: CAS = carotid artery stenting, CCIS = Charlson Comorbidity Index Score, CEA = carotid artery endarterectomy, CI = confidence interval, DM = diabetes mellitus, EC = enrollee category, EC-IC = extracranial-to-intracranial, HR = hazard ratio, ICD = International Statistical Classification of Diseases, MDD = major depressive disorder, NHIRD = National Health Insurance Research Database, SES = socioeconomic status, SSRI = selective serotonin reuptake inhibitor.

Keywords: comorbidity, major depressive disorder, nonsurgical treatment, stroke, Taiwan

Editor: Mirko Manchia.

Data were provided by the Health and Welfare Data Science Center in Taiwan and were analyzed in the Center for Medical Informatics and Statistics of Kaohsiung Medical University.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2019) 98:22(e15753)

Received: 22 October 2018 / Received in final form: 25 April 2019 / Accepted: 26 April 2019

<http://dx.doi.org/10.1097/MD.0000000000015753>

1. Introduction

Major depression is a mental disorder that causes disability. It is one of the most debilitating disorders in the European Union.^[1] In the United States of America (USA), the expenditure for depression showed a 30% increase from 1996 to 2006,^[2] and the economic burden for patients with depression increased by approximately 20% from 2005 to 2010^[3]; the expenditure associated with depression-related comorbidities comprises the largest proportion of the growing cost for depression management.^[3] The cost of post-stroke care in the United States is approximately 4850 dollars per patient each month.^[4] Notably, depression increases the cost of stroke hospitalization, and the increased cost may be related to depression-associated comorbidities.^[5] In fact, higher mortality has been observed in post-stroke patients with depression than in those without depression.^[6] Thus, depression combined with stroke warrants more attention.

Patients with depression are known to have a higher risk of stroke, with a poor prognosis.^[7] Accumulating evidence indicates that surgical interventions affect stroke prognosis. A study conducted in the United States found that acute ischemic stroke patients who underwent hemicraniectomies had significantly lower mortality rates than those without surgery.^[8] In addition,

compared with conservative treatment, decompressive hemicraniectomy considerably decreases mortality in patients with malignant middle brain infarctions.^[9] Moreover, an early carotid endarterectomy can prevent recurrence in some stroke patients.^[10–12] Notably, depressed stroke patients may receive surgical or nonsurgical treatment for stroke. However, most studies examining the association of depression with stroke prognosis have not accounted for the effects of surgical treatment. Accordingly, we investigated the effect of depression on mortality in stroke patients who received nonsurgical treatment in this study.

Risk factors associated with poor prognoses of stroke include age >65 years and diabetes mellitus (DM).^[13] In addition, stroke patients with Charlson Comorbidity Index scores (CCISs) >6 have an increased risk of mortality.^[14] Moreover, major depressive disorder (MDD) has been demonstrated to increase cardiovascular mortality in elderly people in a study conducted in Singapore.^[15] Additionally, age, sex, DM, and hemorrhagic stroke are risk factors for mortality in bipolar patients with stroke.^[16] In this study, we also investigated whether these risk factors are present in stroke patients with depression and without surgical treatment.

2. Methods

2.1. Subjects

This retrospective cohort study analyzed the data in the National Health Insurance Research Database (NHIRD) published by the Taiwanese government. Almost all (99%) Taiwanese citizens are registered in the National Health Insurance Program. This study was approved by the institutional review board of the Kaohsiung Municipal Kai-Syuan Psychiatric Hospital (KSPH-2015–17).

First, we divided the subjects into a control cohort and a patient cohort. The latter included subjects with MDD from 1999 to 2005, who were diagnosed by psychiatrists according to the International Statistical Classification of Diseases (ICD) codes ICD-9-CM 296.2X and 296.3X.^[17] Only patients who were stroke-free in the period were included in our study. Subjects who had stroke between 1999 and 2005 or depression from 1999 to 2012 based on the NHIRD data were excluded from the control group. Subjects in the control group were matched with those in the patient group in a ratio of 4:1 based on age and sex (Fig. 1). In total, 72,896 and 18,224 subjects were respectively assigned to the control and patient groups using the Statistical Analysis System software (SAS Institute Inc, SAS Campus Drive, Cary, NC), and the codes are shown in Table 1.

We then identified subjects who developed stroke in both groups between 2006 and 2012. Stroke was diagnosed with ICD-9-CM codes 430 to 438 and was divided into 2 types: ischemic (ICD-9-CM codes 430–432) and hemorrhagic (ICD-9-CM codes 433–438) strokes.^[18] Subsequently, stroke patients with surgical treatments were excluded from the study. Subjects whose medical records signified a stroke diagnosis but did not indicate surgical treatment for stroke were categorized as nonsurgical treatment patients. Different types of surgical treatments for stroke are shown in Table 1. Finally, we followed up stroke patients without surgical treatment from 2006 to 2012, and 7-year survival rates and all-cause mortality rates were compared using a Cox proportional-hazards model with age, sex, DM, CCISs, types of stroke, and levels of urbanization as confounding factors.

Enrollee category (EC), which indicates a patient's socioeconomic status (SES), was divided into 4 groups.^[19] EC1 and EC2 referred to a high SES; EC3 represented a moderate SES; and EC4 was defined as a low SES. CCISs were used to evaluate comorbidities.^[20] Hypertension, DM, hyperlipidemia, EC, and urbanization level have all been recognized as risk factors for stroke. Age, sex, DM, CCISs, types of stroke, and urbanization level have been demonstrated as risk factors for mortality.^[16] These factors were thus investigated in this study.

2.2. Data analysis

We examined differences in dichotomous or categorical variables between the patient and control groups using either chi-squared tests or *t*-tests. A Cox proportional-hazards regression was used to calculate survival rates and mortality rates after adjusting for sex, stroke types, EC, urbanization level, and comorbidities. Hazard ratios (HRs) with respective confidence intervals were determined. The significance level was set at $\alpha=0.05$.

2.3. Patient and public involvement

We analyzed medical records of patients in the NHIRD database in this study; therefore, patients were not directly involved in the recruitment or conduction of the study. Furthermore, no randomized controlled trials were performed. Results of the study will be sent to the NHIRD in Taiwan.

3. Results

This study first analyzed the data obtained from 18,224 depression patients and 72,896 controls between 1999 and 2005. We found that MDD patients had more physical illnesses, including coronary artery disease, and tended to live in urban areas compared with the matched controls. Additionally, patients with MDD were more frequently in the bottom or top ECs (indicating low or high SES, respectively) than those without MDD (Table 2). A total of 2265 MDD patients had stroke and received nonsurgical treatments, and 712 controls had stroke and received nonsurgical treatments between 2006 and 2012 (Table 3). Compared with stroke patients without MDD who received nonsurgical treatments, depressed stroke patients with nonsurgical treatment were more often female, had higher CCISs, and were more frequent in the top and bottom ECs; in addition, significantly more depressed stroke patients with nonsurgical treatment had coronary heart disease and lived in urban areas.

Based on HRs, neither depression (HR=1.16) nor urbanization level (suburban, HR=0.867; rural, HR=1.199) was a risk factor for death in Taiwanese stroke patients with nonsurgical treatment. However, age (≥ 65 vs. < 65 , HR=4.35), male (HR=1.26), DM (HR=1.29), CCISs (≥ 2 vs. < 2 , HR=1.35), and hemorrhagic stroke (HR=2.48) were risk factors for death in stroke patients with nonsurgical treatments (Table 4).

4. Discussion

Patients with depression are known to have a higher risk of stroke. The mechanisms underlying the association of depression with stroke include immune system dysfunction and brain structural changes.^[21] Several abnormal findings in the immune system, such as increased pro-inflammatory cytokines and glucocorticoids, decreased brain serotonin synthesis, formation

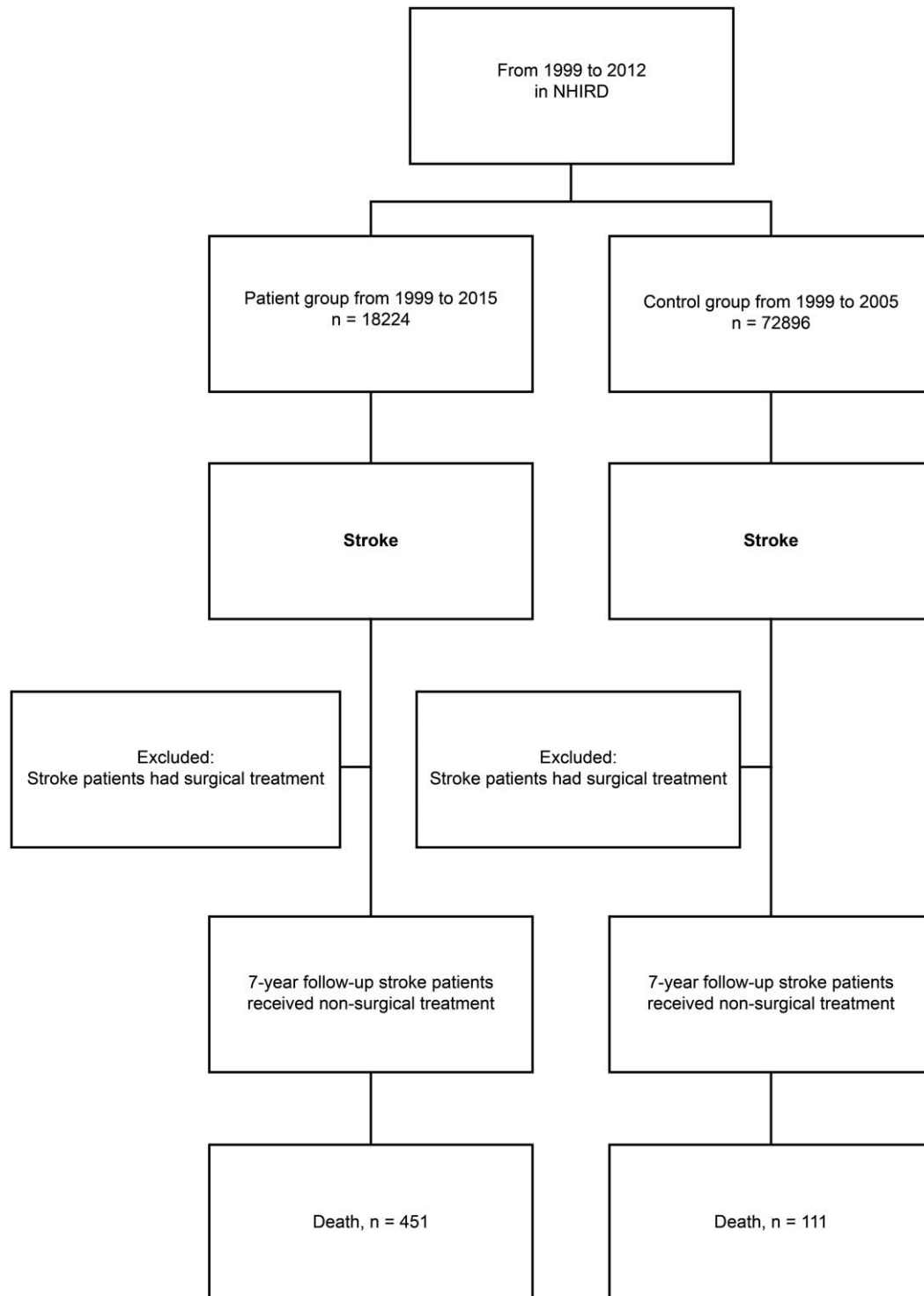


Figure 1. Flowchart of the process of patient selection from the National Health Insurance Research Database (NHIRD) and patient follow-up. NHIRD = National Health Insurance Research Database.

of quinolinic acid, and increased cell death, have been observed in the brain in depression patients.^[22] Serotonin, which effects T-cell activation and neutrophil recruitment,^[23] plays an important role in immunomodulatory functions and depression. Cytokine secretion by monocytes or macrophages and suppression of interleukin-1 β and tumor necrosis factor- α are believed to be

related to altered serotonin levels.^[23] Functional magnetic resonance imaging has revealed the altered anterior cingulate, ventromedial frontal regions, and amygdala in young depression patients.^[24] Post-stroke depression may be related to the changed frontal brain areas and basal ganglia.^[25] Refractory depression patients have the altered insula, caudate, periventricular grey

Table 1
International Statistical Classification of Diseases-9-CM procedure code of surgical treatment for stroke.

| Surgical treatment for stroke | ICD-9-CM procedure code |
|---|---|
| Craniectomy or craniotomy | (ICD-9-CM: 01.xx) |
| CEA | (ICD-9-CM: 38.12) |
| CAS | (ICD-9-CM: 00.61, 00.63, 00.64) |
| EC-IC bypass | (ICD-9-CM: 39.28) |
| Coiling | (ICD-9-CM: 39.52, 39.72, 39.79) |
| Clipping | (ICD-9-CM: 39.51) |
| Radiosurgery | (ICD-9-CM: 92.30, 92.31, 92.32, 92.33, 92.39) |
| Embolization of carotid-cavernous fistula | (ICD-9-CM: 39.53) |

CAS = carotid artery stenting, CEA = carotid artery endarterectomy, EC-IC bypass = extracranial-to-intracranial bypass, ICD = International Statistical Classification of Diseases.

matter, and habenula compared with controls.^[26] Therefore, abnormalities in the brain are related to depression.

Studies have shown that depressed patients have poor stroke prognoses.^[27] In our study, we observed that depressed patients had more comorbidities than those without depression. Notably, depression prevalence is not associated with an increased initiation of antidiabetic medication^[28] but is correlated with an increased risk of DM^[29]; in addition, antidepressant use is also associated with an increased risk of DM.^[29] We speculate that

patients with depression may have had low motivation to receive treatment, thus leading to poor prognoses.

Our results suggest sex differences in the prevalence of depressed stroke patients with nonsurgical treatment. Major depression is more prevalent in female patients than in male patients^[30]; the global annual prevalence of major depression is about 3.2% in men and 5.5% in women.^[31,32] However, stroke is more prevalent in men than in women.^[33] We found that depressed stroke female patients received nonsurgical treatment more frequently than did control patients (Table 3). Therefore, stroke is more prevalent in men than in women, but women have both stroke and depression more frequently. Some studies have shown that female stroke patients have higher fatality rates within 30 days of stroke^[34,35]; however, no difference has been observed in outcomes between males and females 60 days or 6 months after stroke.^[36] Based on these findings and our data, we speculate that female stroke patients have poor prognoses in the month following stroke, while male stroke patients have a higher mortality rate in years post stroke. We found that male stroke patients with nonsurgical treatment had a higher mortality rate than female stroke patients in the 7-year follow-up study (Table 4), and the findings are consistent with those in other studies, which indicate that male stroke patients had higher mortality rates than female stroke patients.^[37,38] In addition, clinicians and health care providers should pay attention to depressive symptoms in patients with stroke, especially in

Table 2
Personal history and demographic characteristics of patients with and without major depression.

| | Patients with depression | | Matched controls (1:4) | | P value |
|------------------------|--------------------------|-------|------------------------|-------|---------|
| | n = 18,224 | % | n = 72,896 | % | |
| | Mean | | Mean | | |
| Age (years, SD) | 40.9, 15.9 | | 40.9, 15.9 | | .9999 |
| Sex | | | | | |
| Male | 6516 | 35.8% | 26,064 | 35.8% | 1.0000 |
| Female | 11,708 | 64.2% | 46,832 | 64.2% | |
| Hypertension | | | | | |
| Yes | 4426 | 24.3% | 1585 | 2.2% | <.0001* |
| No | 13,798 | 75.7% | 71,311 | 97.8% | |
| CCIS | | | | | |
| 0 | 6269 | 34.4% | 68,886 | 94.5% | <.0001* |
| 1 | 4848 | 26.6% | 2127 | 2.9% | |
| ≥2 | 7107 | 39.0% | 1883 | 2.6% | |
| Diabetes | | | | | |
| Yes | 2715 | 14.9% | 919 | 1.3% | <.0001* |
| No | 15,509 | 85.1% | 71,977 | 98.7% | |
| Hyperlipidemia | | | | | |
| Yes | 3600 | 19.8% | 1198 | 1.6% | <.0001* |
| No | 14,624 | 80.2% | 71,698 | 98.4% | |
| Level of urbanization | | | | | |
| Urban | 13,108 | 71.9% | 49,362 | 67.7% | <.0001* |
| Suburban | 3973 | 21.8% | 18,581 | 25.5% | |
| Rural | 1143 | 6.3% | 4953 | 6.8% | |
| Coronary heart disease | | | | | |
| Yes | 3060 | 16.8% | 826 | 1.1% | <.0001* |
| No | 15,164 | 83.2% | 72,070 | 98.9% | |
| Enrollee category | | | | | |
| EC1 | 1953 | 10.7% | 6799 | 9.3% | <.0001* |
| EC2 | 8085 | 44.4% | 35,175 | 48.3% | |
| EC3 | 5984 | 32.8% | 24,752 | 34.0% | |
| EC4 | 2202 | 12.1% | 6170 | 8.5% | |

CCIS = Charlson Comorbidity Index Score, EC = enrollee category, SD = standard deviation.

* P value < .05.

Table 3**Characteristics of stroke patients with and without depression who received nonsurgical treatment.**

| | Depressive stroke patients | | Matched controls with stroke | | P value |
|------------------------------------|----------------------------|-------|------------------------------|-------|---------|
| | n = 2265 | % | n = 712 | % | |
| | (Mean) | | (Mean) | | |
| Age (years, SD) | 55.6, 14.7 | | 56.4, 13.3 | | .2008 |
| Sex | | | | | |
| Male | 1413 | 62.4% | 547 | 76.8% | <.0001* |
| Female | 852 | 37.6% | 165 | 23.2% | |
| Hypertension | | | | | |
| Yes | 1237 | 54.6% | 367 | 51.5% | .1519 |
| No | 1028 | 45.4% | 345 | 48.5% | |
| CCIS | | | | | |
| 0 | 346 | 15.3% | 230 | 32.3% | <.0001* |
| 1 | 455 | 20.1% | 171 | 24.0% | |
| 2 | 1464 | 64.6% | 311 | 43.7% | |
| Diabetes | | | | | |
| Yes | 750 | 33.1% | 209 | 29.4% | .0612 |
| No | 1515 | 66.9% | 503 | 70.6% | |
| Hyperlipidemia | | | | | |
| Yes | 847 | 37.4% | 212 | 29.8% | .0002* |
| No | 1418 | 62.6% | 500 | 70.2% | |
| Coronary heart disease | | | | | |
| Yes | 819 | 36.2% | 196 | 27.5% | <.0001* |
| No | 1446 | 63.8% | 516 | 72.5% | |
| Hemorrhagic stroke (ICD9: 430–432) | | | | | |
| Yes | 246 | 10.9% | 68 | 9.6% | .3208 |
| No | 2019 | 89.1% | 644 | 90.4% | |
| Ischemic stroke (ICD9: 433–438) | | | | | |
| Yes | 2019 | 89.1% | 644 | 90.4% | .3208 |
| No | 246 | 10.9% | 68 | 9.6% | |
| Enrollee category | | | | | |
| EC1 | 234 | 10.3% | 56 | 7.9% | <.0001* |
| EC2 | 663 | 29.3% | 228 | 32.0% | |
| EC3 | 891 | 39.3% | 328 | 46.1% | |
| EC4 | 477 | 21.1% | 100 | 14.0% | |
| Urbanization level | | | | | |
| Urban | 1554 | 68.6% | 430 | 60.4% | <.0001* |
| Suburban | 501 | 22.1% | 213 | 29.9% | |
| Rural | 210 | 9.3% | 69 | 9.7% | |

CCIS = Charlson Comorbidity Index Score, EC = enrollee category, ICD = International Statistical Classification of Diseases, SD = standard deviation.

* P value < .05.

patients who should be treated with surgery but refuse to undergo surgery.

The stroke patients who received nonsurgical treatment may not have been appropriate surgical candidates, or they may have

refused to receive aggressive treatment. Patients with severe strokes had poor prognoses after surgery. Conversely, better prognoses correlate with Glasgow scores higher than 8 and age less than 50 years in patients receiving decompressive craniec-

Table 4**Potential risk factors for death in stroke patients who received nonsurgical treatment from 2006 to 2012 (n = 2977).**

| | Adjusted HR | 95% CI | | P value |
|---|-------------|--------|-------|---------|
| Age (age ≥65 years = 1 vs. 0–64 years = 0) | 4.350 | 3.644 | 5.193 | <.0001* |
| * Depression (depression = 1, non-depression = 0) | 1.168 | 0.945 | 1.444 | .1518 |
| Diabetes | 1.298 | 1.082 | 1.556 | .0049* |
| Urbanization level (urban as reference) | | | | |
| Suburban | 0.867 | 0.708 | 1.062 | .1676 |
| Rural | 1.199 | 0.927 | 1.549 | .1666 |
| CCIS (≥2 = 1 vs. <2 = 0) | 1.352 | 1.098 | 1.665 | .0045* |
| Sex (female = 0, male = 1) | 1.268 | 1.070 | 1.503 | .0060* |
| Hemorrhagic stroke (ischemic as reference) | 2.482 | 2.008 | 3.069 | <.0001* |

CCIS = Charlson Comorbidity Index Score, CI = confidence interval, HR = hazard ratio.

* Deceased depressive stroke patients with nonsurgical treatment n = 451 (19.91%) and deceased nondepressive stroke patients with nonsurgical treatment, n = 111 (15.59%).

tomy treatment for brain injury.^[39] Furthermore, receiving a decompressive craniectomy within 2 days after stroke improves the survival rate, but operations delayed more than 2 days after stroke do not lead to a better prognosis.^[40]

Additionally, depressed stroke patients had higher CCISs than control patients (Table 3). Depressed female patients with higher CCISs may not have been suited for surgery. The higher CCISs may be due to the use of selective serotonin reuptake inhibitors (SSRIs) because they reportedly increase stroke severity in patients with hemorrhagic stroke^[35] and are believed to affect the prognosis of stroke^[41–43]; however, we did not analyze SSRI use in this study.

Surprisingly, depression was not found to be a risk factor for death in stroke patients who underwent nonsurgical treatment in this study (Table 4). We found that patients with major depression more frequently lived in urban areas and had a high SES (Table 2). Patients with both depression and stroke in urban areas or with a high SES potentially have more medical resources available, thus leading to better prognoses.^[44] Moreover, exclusion of surgical treatment for stroke may have affected the prognosis, and further investigation is needed to substantiate this hypothesis. The differences in CCISs, hyperlipidemia, coronary heart disease, EC level, and urbanization levels among patients with nonsurgical treatment (Table 3) may be related to the characteristics of patients with major depression in Taiwan (Table 2).

The current study revealed that patients with depression tend to live in urban areas in Taiwan (Table 2). In contrast, in other countries, patients with depression tend to live in rural areas.^[45,46] The discrepancy may be due to cultural differences. In Taiwan, it is not common to receive psychiatric assessments,^[47] especially in rural areas. Lack of urbanization has been reported as a risk factor for poor stroke prognosis because of fewer stroke units, neurologists, and rehabilitation facilities.^[48] However, we did not find that lack of urbanization was a risk factor for poor stroke prognosis in Taiwan, probably because Taiwanese patients in urban or rural areas all have access to neurologists without referral requirements or high treatment costs due to the national health insurance program.

Moreover, a country's income level can affect stroke prognoses^[49]; high-income countries have fewer mortalities and have more resources to allocate for stroke prevention and treatment. Every country has different characteristics of major depression, which also affect the prognoses of patients with depression and stroke. Therefore, governments should implement policies for public health regarding major depression and stroke that are tailored to the requirements of their respective countries. For example, when urbanization is a risk factor for mortality in the country, the government may need to make more medical services available for patients in rural areas or provide better economic support for treatment.

This study has some limitations. Stroke prognoses are also affected by stroke severity scores,^[50] hospital arrival times,^[44] and other risk factors including smoking,^[51] diet,^[52] obesity,^[53] and exercise.^[54] These additional factors could not be evaluated in this study because these data were not included in the NHIRD.^[55] Further studies are needed to evaluate these risk factors for stroke prognoses.

Author contributions

Concept: Hsing-Jung Li.

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Analysis of data: Kuan-Yi Tsai.

Interpretation of data: Hung-Chi Wu.

Conceptualization: Hsing-Jung Li.

Data curation: Chao-Chan Kuo.

Formal analysis: Kuan-Yi Tsai.

Methodology: Ying-Chun Li.

Validation: Hung-Chi Wu.

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