ORIGINAL RESEARCH

Prevalence and Course of Depression During the First Year After Mild to Moderate Stroke

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BACKGROUND: This study examined the prevalence and longitudinal course of depression during the first year after mild to moderate stroke.

METHODS AND RESULTS: We identified patients with mild to moderate ischemic stroke or intracerebral hemorrhage (National Institutes of Health Stroke Scale score <16) and at least 1 depression assessment at 3, 6, or 12 months after stroke (n=648, 542, and 533, respectively) from the Brain Attack Surveillance in Corpus Christi project (2014–2016). Latent transition analysis was used to examine temporal profiles of depressive symptoms assessed by the 8-item Patient Health Questionnaire between 3 and 12 months after stroke. Mean age was 65.6 years, 49.4% were women, and 56.7% were Mexican Americans. The prevalence of depression after stroke was 35.3% at 3 months, decreased to 24.9% at 6 months, and remained stable at 25.7% at 12 months. Approximately half of the participants classified as having depression at 3 or 6 months showed clinical improvement at the next assessment. Subgroups with distinct patterns of depressive symptoms were identified, including mild/no symptoms, predominant sleep disturbance and fatigue symptoms, affective symptoms, and severe/all symptoms. A majority of participants with mild/no symptoms retained this symptom pattern over time. The probability of transitioning to mild/no symptoms was higher before 6 months compared with the later period, and severe symptoms were more likely to persist after 6 months compared with the earlier period.

CONCLUSIONS: The observed dynamics of depressive symptoms suggest that depression after stroke tends to persist after 6 months among patients with mild to moderate stroke and should be continually monitored and appropriately managed.

Key Words: depression ■ epidemiology ■ stroke

Poststroke depression is of significant clinical and public health importance. Approximately one third of patients with stroke experience depression,[1,2] which is associated with worse functional outcomes and reduced quality of life,[2,3] adversely affects stroke prognosis and further increases the disease burden of stroke.[4] The 2018 guidelines from the American Heart Association/American Stroke Association recommend routine screening for depression among patients with acute ischemic stroke.[5] Although the class of this recommendation is strong, significant knowledge gaps remain in when and how to screen for depression

among survivors of stroke,[4–7] which is attributable at least in part to complexities of the course of depressive symptoms after stroke.

Neurovascular, biological, psychological, and social factors come into play at different stages after stroke[4,8,9] and introduce substantial heterogeneities. In the acute stage, pathophysiological changes from stroke may disrupt mood regulation through reduced cerebral perfusion, inflammation, dysfunctions of the hypothalamic-pituitary-adrenal axis and the prefrontal-subcortical circuits, and changes in neuroplasticity and neurotransmission.[8,10] In the postacute stage, residual

Nonstandard Abbreviations and Acronyms

NIHSS	National Institutes of Health Stroke Scale
PHQ-8	8-Item Patient Health Questionnaire

disability from stroke-related cognitive and functional deficits may increase social isolation, influence the employment trajectory, and have a prolonged impact on individuals' quality of life.[11] Meanwhile, stroke is a life-threatening event that may invoke psychological reactions, including catastrophizing, emotional distress, and low self-efficacy. The overlap between depressive symptomatology and stroke sequelae imposes additional challenges in diagnosis and screening.[6,7,12] As patients go through the stroke recovery process, some symptoms may decline as the influence of certain etiologic factors decreases, and some symptoms may increase as other etiologic factors become more predominant.

Existing evidence on the longitudinal course of depressive symptoms during the first year after stroke is limited and mainly focused on changes in symptom severity.[13–17] Little is known about variations in symptom profiles over time that may provide information for targeted screening, prevention, and management. The objective of this study was to examine the prevalence of depression and changes in depressive symptom severity and profiles during the first year after mild to moderate stroke.

METHODS

Study Participants

We obtained data from the Brain Attack Surveillance in Corpus Christi project, an ongoing bi-ethnic, population-based stroke surveillance study in southern

Texas.[18] Anonymized raw data may be available based on an appropriate request and existing institutional review board approvals and data-sharing agreements. Possible ischemic stroke and intracerebral hemorrhage cases were ascertained using active surveillance of hospital admission logs and passive surveillance of hospital discharge diagnosis codes based on the *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) (430–438) and then validated by stroke fellowship trained physicians.[19] Identified patients with stroke were invited to participate in a baseline interview shortly after stroke onset and outcome interviews at 3, 6, and 12 months after stroke. If a participant was unable to complete the interviews, a proxy interview was completed by an informant, but did not include a depression assessment. Details of the Brain Attack Surveillance in Corpus Christi project were described in previous publications.[18–20]

The present study focused on patients with mild to moderate stroke (National Institutes of Health Stroke Scale [NIHSS] score <16) because a depression assessment was only available for patients with in-person interviews who were primarily mild to moderate cases and not fully representative of those with greater cognitive and language deficits. The study sample consisted of 707 participants drawn from the 2014 to 2016 Brain Attack Surveillance in Corpus Christi project who had mild to moderate stroke and at least 1 depression assessment in the outcome interview(s) at 3, 6, or 12 months (Figure 1). Reasons for eligible patients' nonparticipation in the baseline interview included refusal (n=211) and loss of contact (n=89). Of 707 participants, 17 (2.4%) died during the first year after stroke, and 4 (0.6%) died within 6 months after stroke. The main reason for exclusion among participants was missing the outcome measure as a result of having a proxy interview. The completion rate of depression assessments among participants with in-person interviews was ≈98%. The sample size was 648 at 3 months, 542 at 6 months, and 533 at 12 months. Five hundred and six of 648 participants at 3 months (78.1%) completed the depression assessment at 6 months, 452 of 542 participants at 6 months (83.4%) completed the depression assessment at 12 months, and 486 of 648 participants at 3 months (75.0%) completed the depression assessment at 12 months (Figure 1).

The Brain Attack Surveillance in Corpus Christi project was approved by the institutional review boards at the University of Michigan and the local hospital systems. Patients or their surrogate provided written informed consent.

Measure of Depressive Symptoms

Frequency of depressive symptoms during the past 2 weeks was assessed among participants with
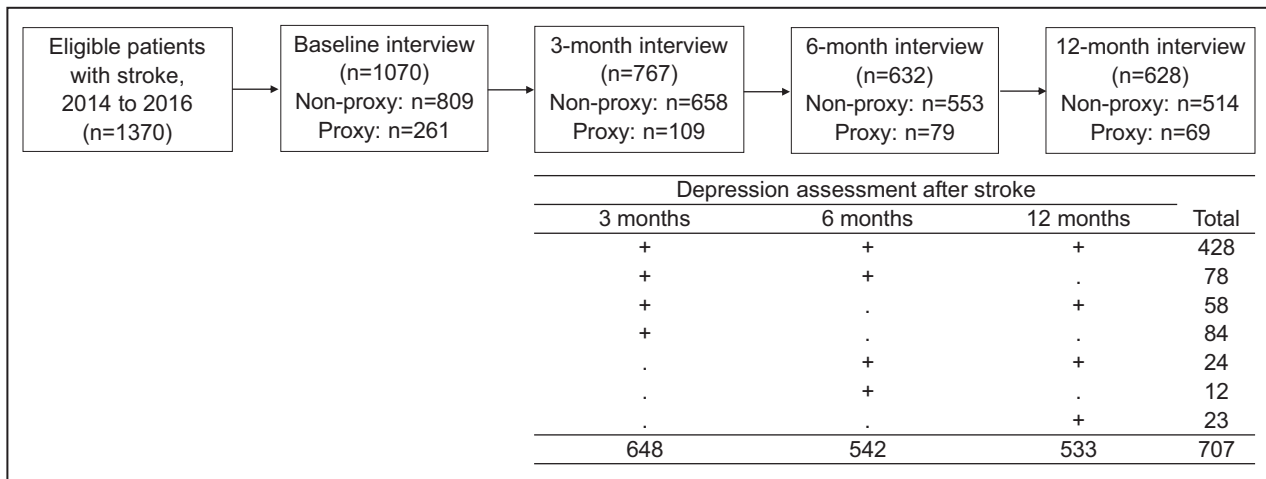
Figure 1. Study flow diagram and depression assessments.
Non-proxy indicates participants with nonproxy outcome interviews. Proxy indicates participants with proxy outcome interviews. + indicates data were available. · indicates data were not available.

nonproxy interviews using the 8-item Patient Health Questionnaire (PHQ-8), which is a commonly used measure of depression in population-based epidemiological studies.[21] The PHQ-8 differs from the 9-item Patient Health Questionnaire,[22] a depression assessment tool based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* that has been validated in patients with stroke and racially/ethnically diverse patients,[23,24] in the last item on suicidal ideation.[25] The total score ranges from 0 to 24, with a score of ≥10 classified as depression.[21] Clinically relevant changes in depressive symptoms are defined as a change score of ≥5 (clinical improvement, ≤−5; clinical worsening, ≥5), with a change score of ≤4 reflecting no clinically relevant change.[26] We generated a binary variable for each symptom by defining symptom presence as occurring "nearly every day" according to the frequency of the diagnostic criteria for major depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.[25]

Measures of Sample Characteristics

Sample characteristics were measured by sociodemographics (age, sex, race/ethnicity, education), clinical stroke characteristics (stroke type, stroke severity as measured by the NIHSS[27,28]), and prestroke characteristics (self-reported history of depression diagnosis and medication use, disability as measured by the modified Rankin Scale,[29] cognitive function as measured by the Informant Questionnaire on Cognitive Decline in the Elderly[30]) ascertained from baseline interviews or medical records. Poststroke outcomes were ascertained from outcome interviews, including neurological outcomes as measured by the NIHSS, functional outcomes as measured by a combined measure of

activities of daily living and instrumental activities of daily living,[31] cognitive outcomes as measured by the Modified Mini-Mental State Examination,[32] and quality of life assessed by the short-form Stroke Specific Quality of Life Scale.[33,34]

Statistical Analysis

We examined sample characteristics by time after stroke and further examined attrition from 3 to 6 months by comparing 3-month outcomes between participants with and without a depression assessment at 6 months.

We used cross-tabulations to estimate prevalence of individual depressive symptoms and depression classified by the cutoff of 10 at 3, 6, and 12 months after stroke, respectively; and the change in depression classification from 3 to 6 months, from 6 to 12 months, and from 3 to 12 months among those with data available from 2 time points. We also estimated the prevalence of clinical improvement, no clinically relevant change, and clinical worsening from 3 to 6 months, from 6 to 12 months, and from 3 to 12 months by depression classification, respectively.

We used latent transition analysis to identify unobserved homogeneous subgroups (latent statuses) with distinct patterns of depressive symptoms and described stage-sequential changes in the patterns across subgroups over time.[35] Specifically, we estimated item-response probabilities conditional on latent status membership and time to identify distinct subgroups of participants who manifested depressive symptoms in a particular pattern. We then estimated the prevalence of latent status membership to identify the distribution of participants across these subgroups. Lastly, we estimated transition probabilities

among latent statuses to examine changes between subgroups across time. We fit latent transition models with different numbers of latent statuses and compared them by interpretability of latent statuses and model fit statistics, including the likelihood-ratio G^2 statistic, Akaike's information criterion, and Bayesian information criterion.[36]

Statistical analyses were completed with Stata version 14.2 (StataCorp LP) and SAS version 9.4 (SAS Institute Inc.). The SAS LTA procedure was used for latent transition analysis, which estimates parameters by maximum likelihood using the expectation-maximization algorithm and handles missing data by the full-information maximum likelihood under the assumption of missing at random.[36,37]

RESULTS

Among 707 participants with at least 1 depression assessment, mean age was 65.6 years (standard deviation [SD], 11.2), 49.4% were women, 56.7% were Mexican Americans, 27.6% did not have high school education, and the mean NIHSS score was 3.5 (SD, 3.4). Characteristics of the study sample at 3, 6, and 12 months after stroke are presented in Table 1. Participants at 3 months did not differ by PHQ-8 data availability at 6 months in 3-month outcomes, including depressive symptoms, quality of life, neurological outcomes, cognitive function, and functional diability.

The prevalence of individual depressive symptoms that had occurred nearly every day consistently

Table 1. Characteristics of the Study Sample at 3, 6, and 12 Months After Mild to Moderate Stroke, Brain Attack Surveillance in Corpus Christi Project, 2014 to 2016

	Time of Assessment After Stroke		
	3 mo (n=648)	6 mo (n=542)	12 mo (n=533)
Age, y	65.8±11.2	65.7±11.0	65.5±11.0
Sex			
Male	320 (49.4)	279 (51.5)	273 (51.2)
Female	328 (50.6)	263 (48.5)	260 (48.8)
Race/ethnicity			
Non-Hispanic White	240 (37.0)	196 (36.2)	194 (36.4)
Mexican American	364 (56.2)	309 (57.0)	305 (57.2)
American Alaskan, Asian Pacific or Black	44 (6.8)	37 (6.8)	34 (6.4)
Education*			
Less than high school	174 (27.1)	152 (28.3)	150 (28.3)
High school	195 (30.3)	161 (29.9)	160 (30.2)
More than high school	274 (42.6)	225 (41.8)	220 (41.5)
Stroke type			
Ischemic	595 (91.8)	496 (91.5)	484 (90.8)
Intracerebral hemorrhage	53 (8.2)	46 (8.5)	49 (9.2)
Stroke severity	3.5±3.3	3.5±3.5	3.5±3.4
Prestroke disability†			
No symptoms/disability	280 (45.0)	239 (45.9)	239 (46.2)
Slight/moderate disability	296 (47.6)	243 (46.6)	244 (47.2)
Moderately severe/severe disability	46 (7.4)	39 (7.5)	34 (6.6)
Prestroke cognitive function‡			
Normal	314 (59.6)	271 (61.6)	262 (60.9)
Cognitive impairment no dementia	164 (31.1)	132 (30.0)	127 (29.5)
Dementia	49 (9.3)	37 (8.4)	41 (9.5)
Prestroke depression§			
No history	371 (61.3)	317 (63.2)	311 (63.3)
History of depression	103 (17.0)	82 (16.3)	82 (16.7)
On medication for depression	131 (21.7)	103 (20.5)	98 (20.0)

Data are provided as mean±SD or number (percentage).
*Number of missing values was 5 at 3 months, 4 at 6 months, and 3 at 12 months for education.
†Number of missing values was 26 at 3 months, 21 at 6 months, and 16 at 12 months for prestroke disability.
‡Number of missing values was 121 at 3 months, 102 at 6 months, and 103 at 12 months for prestroke cognitive function.
§Number of missing values was 43 at 3 months, 40 at 6 months, and 42 at 12 months for prestroke depression.

decreased after 3 months (Figure 2). The most prevalent symptoms were fatigue and sleep disturbance, with the prevalence at 3 months of 43.2% and 35.5%, respectively.

The prevalence of depression after stroke was 35.3% at 3 months, decreased to 24.9% at 6 months, and remained stable at 25.7% at 12 months. Among participants with data available from 2 time points, the percentage recovering from having depression to no depression was 50.5% from 3 to 6 months, 40.2% from 6 to 12 months, and 46.5% from 3 to 12 months; and the percentage developing depression from having no depression was 9.9% from 3 to 6 months, 13.3% from 6 to 12 months, and 10.8% from 3 to 12 months (Figure 3). Consistently, approximately half of the participants classified as having depression had clinical improvement from one time point to the other, and the percentage of participants getting clinically worse increased after 6 months regardless of depression status (Figure 4).

We identified 4 latent statuses or subgroups and labeled them based on item-response probabilities as follows: (1) severe/all symptom group, characterized by high probabilities of experiencing all symptoms nearly every day; (2) mild/no symptom group, characterized by low probabilities of having any symptom nearly every day; (3) affective symptom group, characterized by high probabilities of having depressed mood and low self-esteem nearly every day; and (4) predominant sleep disturbance and fatigue symptom group (hereinafter referred to as the sleep–fatigue symptom group), characterized by high probabilities of experiencing sleep disturbance and fatigue nearly every day but low probabilities for other symptoms (Figure 5). From 3 to 6 months, the prevalence of the mild/no symptom group increased from 42.8% to 65.3% as the prevalence of the sleep–fatigue symptom group and severe/all symptom group decreased (sleep–fatigue symptom group from 34.9% to 18.1%, severe/all symptom group from 16.7% to 10.1%), whereas the prevalence of all 4 subgroups remained relatively stable from 6 to 12 months (Figure 6). In terms of transitions between subgroups across time, the majority of the mild/no symptom group retained this pattern over time, and there were more transitions to the mild/no symptom group from the other 3 subgroups from 3 to 6 months than from 6 to 12 months (Table 2). After 6 months, however, the severe/all symptom group had a higher probability of retaining the pattern (Table 2).
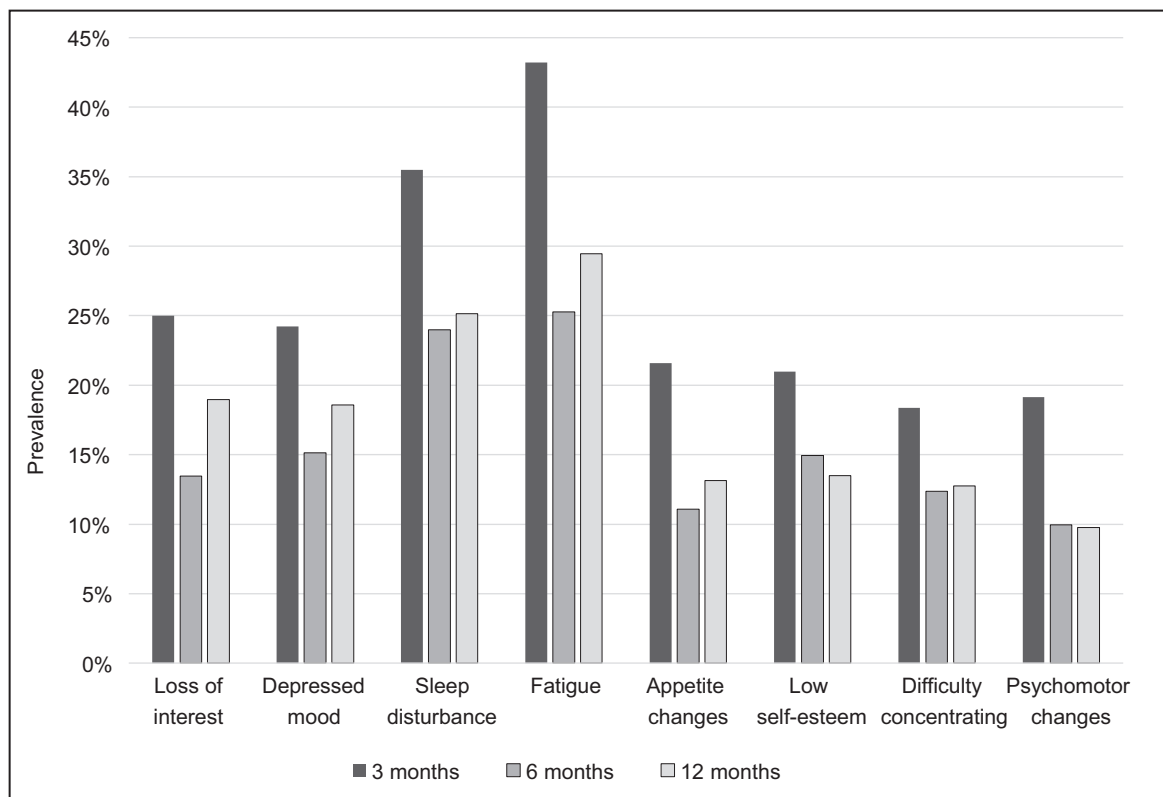

Figure 2. Prevalence of individual depressive symptoms at 3, 6, and 12 months after mild to moderate stroke.
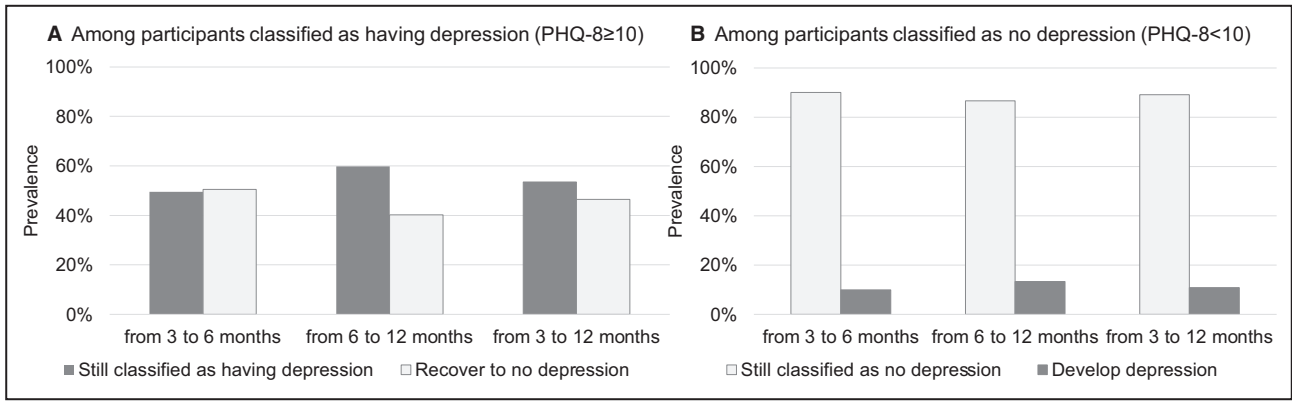
Figure 3. Changes in depression status during the first year after mild to moderate stroke (A) among participants classified as having depression (PHQ-8 ≥10) and (B) among participants classified as no depression (PHQ-8 <10).
PHQ-8 indicates the 8-item Patient Health Questionnaire.

DISCUSSION

This population-based study of patients with mild to moderate stroke provides evidence about the prevalence, dynamic patterns, and heterogeneous manifestations of depressive symptoms during the first year following stroke. We found that approximately one third of the study sample had depression at 3 months after stroke, and half of them recovered to no depression at 12 months, with more dynamic recovery from 3 to 6 months and more persistent patterns after 6 months. The observed symptom dynamics and heterogeneity suggest that the evolution of depression in patients with stroke should be continually monitored and appropriately managed, and intervention strategies may vary by stages after stroke and patterns of symptom manifestations.

We found that more patients transitioned to the mild/no symptom group between 3 and 6 months than between 6 and 12 months, and symptoms tended to be more persistent and even exacerbated in the later

period, which resulted in the decreasing overall prevalence of depression from 3 to 6 months and the stable prevalence between 6 and 12 months. Depressive symptom patterns may evolve in response to stroke recovery. Reduction in reported frequency of depressive symptoms from 3 to 6 months may be related to changes in neuroplasticity and functional limitations[8] or a decrease in stroke sequelae such as emotional lability that overlaps with depression symptoms.[4] Depressive symptoms should be closely monitored in the early stage as they change actively. Furthermore, the finding that at least 10% of patients with no depression at 3 or 6 months develop depression at 12 months suggests that screening may need to be continued for at least the first year after stroke.

We found that the majority of the mild/no symptom group retained this pattern over time. Participants in the severe/all symptom group were likely to have met the diagnostic criteria for major depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[25] given their high probabilities of reporting
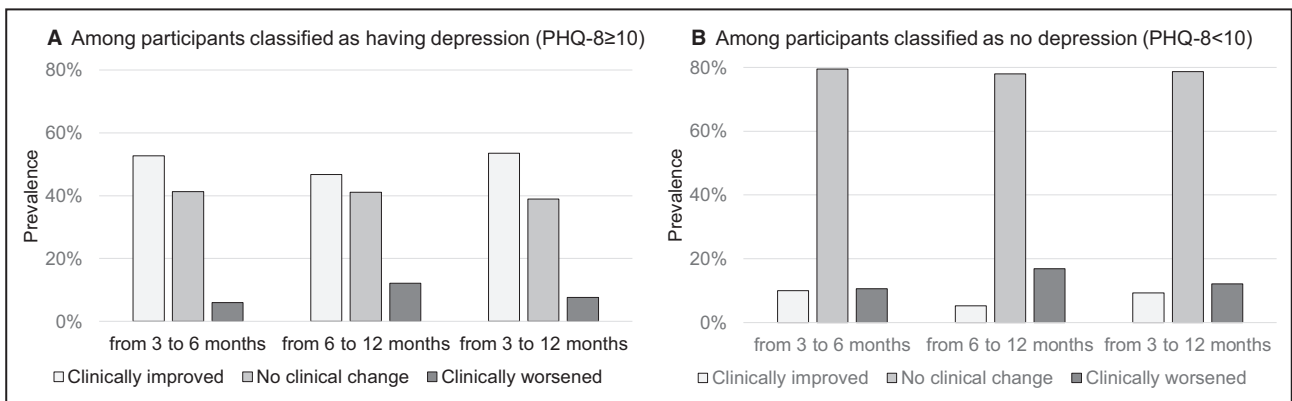

Figure 4. Clinically relevant changes in depressive symptom severity during the first year after mild to moderate stroke (A) among participants classified as having depression (PHQ-8 ≥10) and (B) among participants classified as no depression (PHQ-8 <10).
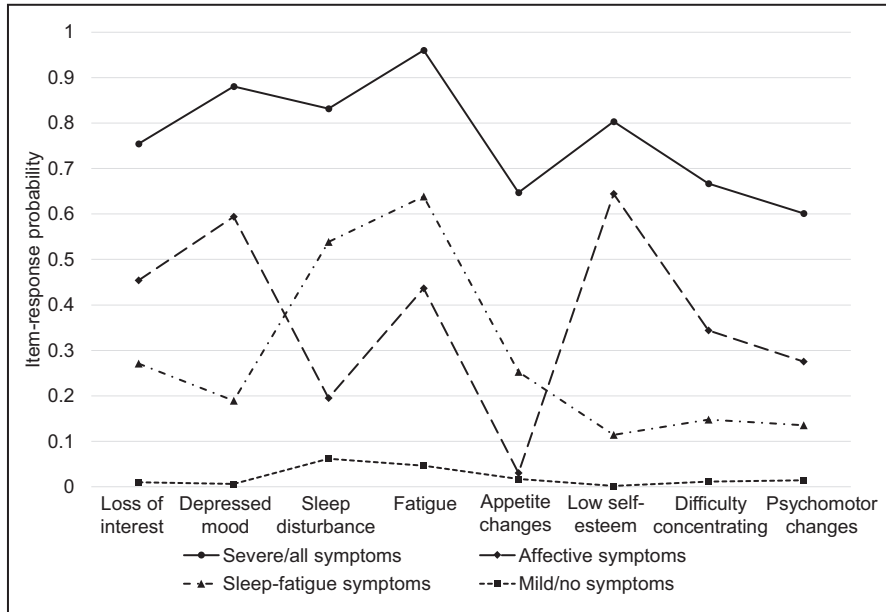PHQ-8 indicates the 8-item Patient Health Questionnaire.

Figure 5. Item-response probabilities by latent status of depressive symptoms at 3, 6, and 12 months after mild to moderate stroke.

all symptoms nearly every day, including depressed mood and loss of interest. The prevalence of the severe/all symptom group was 16.7% at 3 months, close to the prevalence of major depressive disorder defined by the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition/Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* in samples

with similar assessment timing and inclusion/exclusion criteria.[38–40] The prevalence decreased after 3 months but remained persistent around 10% afterward, which is much higher than the prevalence of major depressive disorder in the general older adult population.[41] These patients, identified by screening, may need further psychiatric evaluation and treatment. Participants
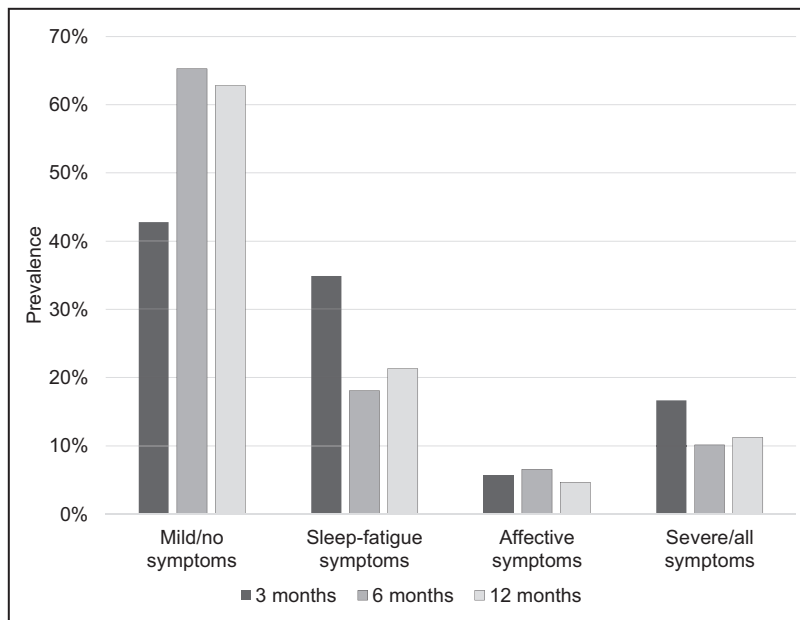

Figure 6. Prevalence of latent statuses of depressive symptoms at 3, 6, and 12 months after mild to moderate stroke.

Table 2. Transition Probabilities Across Latent Statuses of Depressive Symptoms at 3, 6, and 12 Months After Mild to Moderate Stroke, Brain Attack Surveillance in Corpus Christi Project, 2014 to 2016

	Latent Status of Depressive Symptoms After Stroke			
	Mild/no symptoms	Sleep–fatigue symptoms	Affective symptoms	Severe/all symptoms
Transitions from 3 mo (rows) to 6 mo (columns)				
Mild/no symptoms	0.96*	0.03	0.00	0.01
Sleep–fatigue symptoms	0.57	0.38*	0.00	0.05
Affective symptoms	0.27	0.00	0.66*	0.07
Severe/all symptoms	0.18	0.21	0.17	0.44*
Transitions from 6 mo (rows) to 12 mo (columns)				
Mild/no symptoms	0.85*	0.11	0.00	0.04
Sleep–fatigue symptoms	0.24	0.67*	0.00	0.09
Affective symptoms	0.24	0.00	0.65*	0.12
Severe/all symptoms	0.13	0.21	0.04	0.61*

*indicates the probability of remaining in the same symptom group from one time point to the other. The sample sizes were 648, 542, and 533 at 3, 6, and 12 months after stroke, respectively.

who fall in the middle of the symptom severity spectrum, including the sleep–fatigue symptom group and affective symptom group, should be monitored for symptom progression and targeted for preventive interventions as subthreshold depressive symptoms are associated with significantly increased risk for major depressive disorder.[42]

Participants in the sleep–fatigue symptom group are likely to be classified as no depression because of their low probabilities of reporting depressed mood and loss of interest, but may be at higher risk for depression compared with the mild/no symptom group. Evidence from a meta-analysis showed a 2-fold risk of developing depression among people with insomnia compared with those without sleep disturbance.[43] Our findings showed that the probability of transitioning to the severe/all symptom group almost doubled from 6 to 12 months compared with that from 3 to 6 months. Future studies with longer follow-up should investigate the longitudinal associations of sleep disturbance and fatigue symptoms with poststroke depression, the effect of screening and treatment for sleep disorders on reducing risk of depression among patients with stroke, and the effect of managing depression on reducing the occurrence of sleep disturbance and fatigue.

Participants in the affective symptom group had notably high probabilities of experiencing depressed mood and low self-esteem, which are symptoms highly predictive of poststroke depression.[44–46] Prevention strategies in this subgroup, such as psychological treatment in the early stage, may reduce their risk of depression.[47] However, patients with subthreshold symptoms may not be readily identified by current depression screening scales that dichotomize patients based on overall symptom severity. Comprehensive risk assessment and evaluation that

include and go beyond depressive symptoms may be needed to guide preventive interventions for poststroke depression.

The study has several limitations. First, our findings should be interpreted with consideration of the generalizability of the study. Because depression assessment by the PHQ-8 was only available among participants with in-person interviews, we restricted the study sample to patients with mild to moderate stroke, and therefore the results may not be generalizable to patients with significant cognitive or language deficits that require more complicated assessment of depression. Second, the cutoff scores used for defining clinically relevant changes were derived from a sample of adults aged ≥60 years from primary care settings. To the best of our knowledge, there has been no such validation study in survivors of stroke. Third, the NIHSS scores were abstracted from the medical chart. These were sometimes documented by nonneurologists and are likely to have been underestimated. The scores were not used in the analytical process, but only for sample selection in the present study. Because only a small proportion of participants had scores close to the commonly used cutoff for classifying moderate versus severe stroke, the influence of potential misclassification on the findings should be minimal. The predominance of mild strokes is also likely to reflect the true high prevalence of mild strokes among all stroke cases, which we were able to capture given the population-based nature of the study and the performance of surveillance in a community free from tertiary care referral bias. This provided sufficient statistical power to examine symptom patterns and transitions in this subpopulation. Fourth, the study sample was drawn from a biethnic population,

with the majority being nonimmigrant Mexican Americans. Mexican Americans have worse stroke outcomes than non-Hispanic Whites in general,[48–50] and therefore the results may not be generalizable to other racial/ethnic populations. Fifth, although the SAS LTA procedure used in the analysis handles missing data using full-information maximum likelihood under the assumption of missing at random, there is also a possibility that the probability of missing depression assessment is dependent on the PHQ-8 scores. We did not model the probability of missing not at random in the present study. Sixth, we did not investigate predictors and influential factors of the dynamics in the present study, such as antidepressant use. Because only a small proportion of patients with mental health disorders seek treatment and may represent the more severe cases, the descriptive evidence about the course of depression in this less severe subpopulation should be valid. Future research should identify modifiable risk factors for the development and persistence of poststroke depression, examine potential differences across sociodemographic subgroups, and further investigate the natural history of depression in patients with severe stroke.

CONCLUSIONS

The prevalence of depression was persistently high during the first year following mild to moderate stroke despite a decline after 3 months. The course of poststroke depressive symptoms was dynamic and heterogeneous, which suggests that tailored intervention strategies may be considered. Future research including clinical trials could investigate intervention strategies based on presenting symptoms to provide further guidance for poststroke depression screening and management.

ARTICLE INFORMATION

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Disclosures

None.

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