FACTORS ASSOCIATED WITH DISTRESS, DEPRESSIVE AND ANXIETY SYMPTOMS IN CAREGIVERS OF ISCHEMIC STROKE PATIENTS

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Abstract

Objectives To delineate the features of ischemic stroke patients and their caregivers that may predict distress, depression, and anxiety symptoms in the caregivers.

Methods The Hospital Anxiety and Depression Score (HADS), Zarit Burden Interview (22 item-ZBI), and Perceived Stress Scale (PSS-10) were used to assess caregivers' burden, stress, depressive, and anxiety symptoms. We performed partial least square-structural equation modeling (PLS-SEM) in order to delineate a multi-step mediation model.

Results In this study, 97 stroke patients and their caregivers were included. Multiple regression analysis revealed that ZBI-personal strain and stroke of other determined etiology explained 15.0 percent of the variance in the HADS depression score ($p=0.001$). We discovered that the caregiver's underlying disease and the National Institute Stroke Score (NIHSS) of the patients explained 13.6 percent of the variance in the total ZBI score of the caregivers ($p=0.001$). The total ZBI score, the presence of lacunar circulation infarction in the patients, and the caregiver's underlying disease explained 40.9 percent of the variance in the total PSS score of the caregivers ($p <0.001$). Moreover, PLS analysis showed that the NIHSS and the caregiver's underlying disease had significant indirect effects on the HADS score which were mediated by the ZBI score.

Conclusions A large part of the variance in stress and depressive scores in caregivers of ischemic stroke patients is determined by the patient's disability, dependency, cognition, and stroke phenotypes, as well as the caregiver's health status and burden. Screening for the aforementioned factors in ischemic stroke caregivers is critical.

Keywords: depression, anxiety, stress, ischemic stroke, psychiatry, mental disorders

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1.Introduction

As the silver wave hits Thailand and the rest of the world, health-care providers must be more vigilant about diseases and their consequences. (1, 2) One of those ageing-related conditions is ischemic stroke which shows a prevalence that is expected to double by 2050 compared to 2010. (3) As a result of improved acute ischemic stroke care, the increase in prevalence leads to an increase in disability-adjusted life years. (1, 2)

Stroke has a wide range of consequences that affect not only the survivors but also their families. (6-8) A year after the stroke, half of the stroke survivors are still disabled and require medical attention. (9) The majority of family members who stepped up to become informal caregivers, while being untrained and unpaid, are usually female spouses and the patients' daughters. (10)

Family changes, confinement, changes in personal plans, loss of autonomy, and uncertainty about the future are among the most reported strains stroke patients' caregivers have to face. (3) Reaction to the abovementioned strains is not only determined by the severity of the strain but also by the coping strategies of the caregivers. (4) Passive and palliative coping styles are more associated with negative outcomes than positive coping styles. (4)

The stressors that caregivers face may put them at risk of mental distress. Many caregivers do not seek treatment despite suffering from stress, depressive and anxiety symptoms which may evolve into anxiety and substance abuse disorders, and suicide. (5) Factors that predispose caregivers to depression and anxiety are female sex, being spouse, Caucasian ethnicity, severity of disability, level of dependency, care time of $\geq$13 hours a day,

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self-funded financial source, care burden, and task difficulty. (6-10), although there are some discrepancies, for example, being spouse. (11)

A more comprehensive assessment of the caregivers should include not only evaluation of the burden but also depressive and anxiety symptoms (4) which may be assessed using the Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ-9), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), and Hamilton Anxiety Rating Scales (HARS). (7, 9, 10, 12, 13). A meta-analysis published in 2017 showed a prevalence of 40.2% and 21.4% for depression and anxiety among caregiver of stroke survivor, respectively. (11) Nevertheless, most studies included in this meta-analysis were conducted in Western countries.

Hence, we performed a study in Thailand to delineate the caregivers and patients (ischemic stroke) features that may predict distress, depressive and anxiety symptoms.

2.Methods

2.1 Study methodology

This is a cross-sectional descriptive study. Participants completed self-reported questionnaire including demographics, Thai-Hospital Anxiety and Depression Score (Thai HADS), Zarit Burden Interview (Thai ZBI-22 items) and Perceived stress scale (Thai PSS-10). Patients' clinical data, including clinical diagnosis, cognitive assessment, disability and dependency assessment, were retrieved from electronic medical records. Ethical approval was granted from Institutional Review Board, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Study was listed as IRB No. 532/63.

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2.2 Study population

The target population comprised dyads of caregivers and their ischemic stroke patients who were previously admitted and currently doing follow-up visits at the stroke clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Dyads who were present at the follow up visit between October 1, 2020 to March 31, 2021 were invited to participate in the study. Participants were eligible if the caregivers were of age between 18-70 years old, fluent in Thai, cared for ischemic stroke patients diagnosed using ICD-10 criteria (I63 or I69.3), had been providing care for at least 4 weeks and provided care for more than 8 hours a day. Informed consent was provided by the dyads to acquire data from questionnaires and electronic medical records. Participants were excluded if the caregiving was compensated for with money or if the patients were residents of nursing home or long-term care facilities.

2.3 Sample size

The sample size was estimated prior to starting the study. Using a power of 0.8, probability of alpha error of 0.05, and 4 predictors, a total of 85 participants is required.

2.4 Instruments

2.4.1 Stress and burden

The 14-item Perceived Stress Scale (PSS) was used to measure the levels of distress. (14) The rating scale was translated into Thai and showed a Cronbach's alpha value of 0.85.(15) The Zarit Burden Interview (ZBI) was developed to assess perceived burden in caregiving.(16) The

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dimensions of the ZBI have been studied in Asian population and revealed aspects that correlate with patients' disease severity are personal strain, role strain, and worry about caregiving performance.(17) The 22-items ZBI was also translated into Thai and showed a Cronbach's alpha of 0.86. (18)

2.4.2 Depressive and anxiety symptoms

The Hospital Anxiety and Depression Score (HADS) was developed for screening of individuals who are at risk of developing the depressive or anxiety symptoms. (19) Its use has been generalized with good validity to somatic, psychiatric, primary care or even general population. (19, 20) Using a cut-off of 8 for either condition, HADS has the sensitivity and specificity at approximately 0.8 for each disorder. (20) The scale has been translated into Thai and shows a Cronbach's alpha of 0.82 and 0.85 for depression and anxiety, respectively.(21)

2.4.3 Classification of ischemic stroke

In this study, the Oxfordshire Stroke Project Classification (OSPC) and Trial of ORG 10172 in Acute Stroke Treatment classification (TOAST classification) were utilized to classify patients based on phenotype and causation, respectively. OSPC divides stroke into 4 groups which are total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI), and lacunar infarcts (LACI). (22) Each subtype differs in area of brain affected, outcome from thrombolysis, risk of recurrent stroke, disability, functional outcome, and mortality rate. (22) The TOAST classification was employed to provide data

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regarding etiologies comprising of large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. (23)

2.4.5 Disability and dependency

We used the Barthel Index (BI) to evaluate the dependency of the stroke victims and the modified Rankin Scale (mRS) and the National Institute Stroke Scale (NIHSS) to assess severity of disabilities and neurological dysfunctions. As there is no specific tool that covers all the aspects of disability and dependency, it has been proposed that the combination of BI, mRS, and NIHSS is accurate to evaluate the basic activities of daily living, global disability, and neurological impairment. (24) Cut-off scores, although not in a complete unanimity, of favorable outcome are ≥ 95 for BI and ≤ 2 for mRS. (25)

2.4.6 Cognitive assessment

The Thai Mental Status Examination (TMSE) and Montreal Cognitive Assessment-Thai (MoCA) were utilized to detect cognitive impairments and dementia.(26-28)

2.4.7. Statistical analysis

Intercorrelations between variables were assessed using Pearson's product moment correlation coefficients. Multiple regression analysis was used to identify the most important biomarkers that predict rating scale scores while controlling for demographic data (e.g. age and education). We used an automated stepwise method with a 0.05 p-to-entry and a 0.06 p-to-remove. R^2 changes, multivariate normality (Cook's distance and leverage), homoscedasticity (using the

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White and modified Breusch-Pagan tests), and multi-collinearity were all examined (using tolerance and variance inflation factor). All regression analysis results were bootstrapped (5.000 samples), and the latter results are displayed if the results are not concordant. All tests were two-tailed, and significance was set at p=0.05. All statistical analyses were performed using IBM SPSS windows version 25, 2017. We employed Smart Partial Least Squares (SmartPLS) path analysis to check multi-step mediated paths between explanatory variables (patients NIHSS and stroke phenotype; and patients' ZBI scores and socio-demographic data) and dependent variables (patients' PSS and HADS scores). The final outcome variable is the HADS score with all other variable as direct or indirect explanatory variables. We performed compete SmartPLS analysis with 5.000 bootstrap samples only when the inner/outer models met the following quality criteria: a) Confirmatory Tetrad analysis confirms that the latent vectors are not mis-specified as reflective models; b) the overall fit of the pathway model is adequate with SRMR <0.08; c) the outer model latent vector loadings are > 0.666 at p< 0.001; and d) the latent vectors show adequate construct validity, namely average variance extracted (AVE) > 0.5, Cronbach's alpha > 0.7, rho A > 0.8, and composite reliability > 0.7. Subsequently, we ran a complete PLS path analysis on 5.000 bootstrap samples, calculating path coefficients (with p values), outer model loadings, and specific indirect and total effects. To test the model's predictive performance, we used blindfolding and PLSpredict with 10-fold cross-validation.(29) Compositional invariance was assessed using Predicted-Oriented Segmentation analysis, Multi-Group Analysis, and Measurement Invariance Assessment.

3.Results

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3.1. Characteristics of ischemic stroke survivors and caregivers

Ninety-seven dyads of ischemic stroke survivors and caregivers completed the questionnaires and were included in the analysis. Dyads' characteristics are displayed in ***Table 1*** (see Supplementary Digital Content). The majority of caregivers were in their middle adulthood and were of age (mean, [SD]) 46.2 [14.6] years. Daughters (27.8%) and wives (25.8%) commonly took the role of caregivers, reflecting the fact that two-thirds of them are female (66.0%). They provided care despite being employed (77.3%) and a small part of them was health-care personnel (12.4%). Moreover, around one-third (34%) was affected by medical conditions including hypertension, dyslipidemia, diabetes. In addition, around three-fourths (77.3%) of them were unassisted despite the mean [SD] number of household member is 4.1 (1.8).

Table 1. Descriptive Statistic of Demographics, Patient's Factors, and Caregiver's Factors

Factors			Participants, No. (%)
Overall			97 (100)
Patient	Age (mean [SD], years)		63.3[12.7]
	Gender	Female	45 (46.3)
	Ethnicity	Thai	81 (83.5)
	Education	12 years and above	45 (46.4)
	Financial coverage	Universal Coverage	38 (39.2)
		Social Security	11 (11.3)
		Government Officer Benefits	44 (45.4)
	Oxford classification	TACI	7 (7.2)
		PACI	18 (18.6)
		LACI	61 (62.9)
		POCI	11 (11.3)
	TOAST classification	LAA	32 (33.0)
		Cardioembolism	9 (9.3)
		Small vessel occlusion	43 (44.3)
		Stroke of other determined etiology	4 (4.1)
		Stroke of undetermined etiology	9 (9.3)
	Aphasia	Present	5 (5.2)
	NIHSS (mean [SD])		1.56 [2.7]
	TMSE (mean [SD])		26.3 [3.8]
	MoCA (mean [SD])		21.2 [6.3]
	mRS (mean [SD])		1.28 [1.3]

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	BIS (mean [SD])		91.37 [17.6]
Caregivers	Age (mean [SD], years)		46.2 [14.6]
	Gender	Female	66 (66.0)
	Ethnicity	Thai	84 (86.6)
	Education	Bachelor's degree and above	56 (57.7)
	Prior health-care training		12 (12.4)
	Occupation	Employed	75 (77.3)
	Underlying disease	Present	33 (34.0)
	Relations to patient	Wife	25 (25.8)
		Husband	11 (11.3)
		Daughter	27 (27.8)
		Son	12 (12.4)
		Other relatives	22 (22.7)
	Duration of caregiving (mean [SD], months)		13.27 [13.6]
	Hours of caregiving per day (mean [SD])		13.85 [8.4]
	Assistance in caregiving		22 (22.7)
	Number of assistants in caregiving (mean [SD])		1.32 (0.7)
	Number of household member (mean [SD])		4.1 (1.8)
	Household income (mean [SD])		55 026 (67 431)
Outcomes	HADS-Depression (mean [SD])		3.2 [3.0]
	HADS-Anxiety (mean [SD])		4.3 [3.3]
	PSS-10 (mean [SD])		9.9 [6.3]
	ZBI-22-Overall (mean [SD])		15.7 [11.1]
	ZBI-22-Personal strain (mean [SD])		3.5 [3.6]
	ZBI-22-Role strain (mean [SD])		9.9 [7.8]
	ZBI-22-Worries about caregiving performance (mean [SD])		1.4 [1.3]

Abbreviations: SD: standard deviations, TACI: Total anterior circulation infarction, PACI: Partial anterior circulation infarction, LACI: Lacunar circulation infarction, POCI: Posterior circulation infarction, LAA: Large artery atherosclerosis, NIHSS: National Institute Stroke Scale,TMSE: Thai Mental Status Examination, MoCA: Montreal Cognitive Assessment ,mRS: modified Rankin Scale ,BIS: Barthel Index ,HADS: Hospital Anxiety and Depression Score , PSS-10

: Perceived Stress Scale-10 item, ZBI-22: Zarit Burden Interview-22 item

Most ischemic stroke survivors were middle to late adulthood men (53.7%) with a mean [SD] age of 63.3 [12.7] years. Approximately half of them suffered either LACI (62.9%) per Oxford classification or small vessel occlusion (44.3%) per TOAST classification, with a severity comparable to minor stroke in accordance with NIHSS, as their mean [SD] scores are

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1.56 [2.7]. Their neurocognitive test scores raised suspicion of MCI, but not dementia; as their mean [SD] of MoCA and TMSE are 21.2 [6.3] and 26.3 [3.8], respeectively. The dyads' mean [SD] monthly household incomes were 55 026 (67 431) baht which was almost twice that of the average in Bangkok. Substantial number of dyads' medical care are not self-funded (95.8%).

3.2. Burden, Perceived Stress, Depressive and Anxiety Symptoms

The mean [SD] scores of depressive and anxiety symptoms among familial caregivers, as measured by HADS, were 3.25 [3.09] and 4.32 [3.38], respectively. Using a cut-off score of HADS≥8 in either subscales, 7.2% and 17.5% of caregivers demonstrated clinically relevant depressive and anxiety symptoms, respectively. The mean [SD] scores of the caregiver's perceived stress and burden, assessed using PSS-10 and ZBI-22, were 9.92 [6.37] and 15.73 [11.169], respectively.

3.3. Predictors of Depressive and Anxiety Symptoms

The correlation analysis matrix of the outcome variables (HADS subscales, PSS-10, and ZBI-22) in ***Table 2*** shows that total anterior circulation infarcts and stroke of other determined etiology were correlated with HADS depression (see Supplementary Digital Content). Assistance in caregiving was correlated with HADS anxiety. The presence of aphasia and NIHSS were related to ZBI. In addition, stroke of other determined etiology was related to the PSS. Moreover, caregiver's career in health care was correlated with HADS depression and anxiety and PSS. The caregiver's underlying disease was related to all four outcomes.

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Table 2 Intercorrelation analysis matrix

	HADS-D	HADS-A	ZBI	PSS	TACI	SOD	Aphas.	NIHSS	Cg's HC career	Cg's UD	Asst. in cg.
HADS-D	1										
HADS-A	0.676	1									
ZBI	0.233	0.259	1								
PSS	0.172	0.112	0.572	1							
TACI	-0.244	0.022	0.045	0.017	1						
SOD	0.258	0.075	-0.076	-0.217	-0.058	1					
Aphas.	0.063	0.163	0.279	0.084	0.115	-0.048	1				
NIHSS	0.109	0.150	0.242	-0.041	0.096	0.045	0.388	1			
Cg's HC career	-0.195	-0.230	-0.051	-0.124	0.016	-0.078	-0.088	-0.015	1		
Cg's UD	0.191	0.217	0.321	0.336	0.052	-0.039	0.325	0.087	-0.204	1	

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Asst. in cg.	0.091	0.219	0.063	-0.008	-0.056	-0.112	0.096	0.108	0.021	-0.077	1

Abbreviations *HADS*: Hospital Anxiety and Depression Score, *HADS-D*: HADS Depression, *HADS-A*: HADS Anxiety, *ZBI*: Zarit Burden Interview, *PSS*: Perceive Stress Scale, *TACI*: Total Anterior Circulation Infarction, *SOD*: Stroke of Other Determined Etiology, *Aphas.*: Aphasia*NIHSS*: National Institute of Health Stroke Scale, *Cg*: Caregiver, HC: Health-care, *UD*: Underlying disease, *Asst*: Assistance

1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00

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The results of multiple regression analysis are displayed in ***Table 3***. We found that 40.9% of the variance in the patients' PSS score was explained by the regression on total ZBI, lacunar circulation infarcts, and caregiver's underlying disease (all positively associated). Fifteen percent of the variance in the HADS score was explained by the regression on ZBI personal strain domain score and stroke of other determined etiology (both positively associated). We found that 13.6% of the variance in the total ZBI score was explained by the regression on caregiver's underlying disease and the patients NIHSS score (both positively associated).

Table 3. Multiple regression analyses with the Perceived Stress Scale (PSS), Depressive domain on Hospital Anxiety and Depression Score (HADS-D) and Zarit Burden (ZBI) scores as dependent variables.

Dependent variables	**Explanatory variables**	**β**	**t**	**p**	**F model**	**df**	**p**	**R^2**
PSS	**Model**							
	ZBI (Total)	0.54	6.35	<0.001	20.76	3/90	<0.001	0.409
	Lacunar circulation infarction	0.24	2.96	0.004				
	Caregiver's U/D	0.17	2.01	0.047				
HADS-D	**Model**							
	ZBI persstrain	0.28	2.89	0.005	8.03	2/91	0.001	0.150
	SOD	0.28	2.87	0.005				
ZBI	**Model**							
	Caregiver's U/D	0.28	2.89	0.005	7.14	2/91	0.001	0.136
	NIHSS	0.22	2.21	0.030				

Abbreviations: HADSdep: HADS depression, ZBIpersstrain: ZBI personal strain; ZBI (Total): Total score of ZBI, Cg's UD: Caregiver's underlying disease, the National Institute Stroke Scale (NIHSS)

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Figure 1 shows the results of the PLS-SEM analysis. The construct reliabilities of the ZBI latent vector is satisfactory, with AVE = 0.888, Cronbach = 0.954, rho A = 0.960, and composite reliability = 0.967. At p <0.0001, the outer model loadings on the ZBI latent vector were greater than 0.856. With SRMR=0.024, the model fit was very good. The CTA showed that the outer model was not misspecified as a reflective model. The construct cross-validated redundancies of the latent vector were more than adequate. According to the results of Prediction-Oriented Segmentation analysis, Measurement Invariance Assessment, and Multi-Group Analysis, full compositional invariance was obtained. We found that 6.3% of the variance in the HADS score was explained by the ZBI latent vector, while 38.6% of the variance in the PSS score was explained by the ZBI factor, lacunar circulation infarcts and caregivers' disease. Finally, 15.2% of the variance in the ZBI factor was explained by the NIHSS and caregiver's disease. Both the NIHSS (t=1.74, p=0.041) and caregiver's disease (t=1.73, p=0.042) had significant specific indirect effect on the HADS score which were mediated by the ZBI factor. The NIHSS had also a significant indirect effect on the PSS, which was mediated via the ZBI latent vector (t=0.245, p=0.007). Moreover, caregiver's disease has a significant specific indirect effect (t=2.73, p=0.003) on the PSS score mediated by the ZBI latent vector indicating that the latter is a partial mediator.

Discussion

We found that part of the caregivers suffered from at least mild degree of depressive and anxiety symptoms, namely 7.2% and 17.5% respectively. The Depressive HADS score is influenced by the caregiver's burden as assessed with the ZBI and the patient's disability and

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caregiver's disease are indirectly associated with the depressive scores and are mediated via the burden. Our findings extent the results of previous studies showing that the dependency level and caregiving burden are associated with depression and anxiety symptoms. (10, 15). Moreover, in our study, the caregiver's distress as assessed with the PSS, was positively correlated to lacunar circulation infarcts, caregiver's disease, and burden, and was not related to depressive scores.

Stroke of other determined etiology (SOD), as assessed with TOAST criteria, was associated with caregiver's distress, depression, and anxiety symptoms. This is probably due to the fact that SOD has a rare etiology and the highest mortality rate. (23, 30) Particular cognitive appraisals (i.e., concern regarding future care) could mediate this finding.(7)

We found that the NIHSS score of the stroke patients was significantly associated with the PSS and HADS scores of their caregivers and that these effects were mediated via increases in burden as assessed with the ZBI. Survivors of ischemic stroke are left with neurological sequelae of various deficits (i.e., visual, mobility, tactile sensory, language impairment), and as such the severity of stroke, disabilities and neurological symptoms (including aphasia) correlates with the caregiver's burden. Tasks of caregiving require verbal communication between the dyad. Failure of the patient to follow caregiver's instructions and the patient's difficulty in communicating his/her needs could explain why caregivers of patients with aphasia are more burdened. Moreover, the duty of caregiving is time-consuming and could be sensed as negative life distress, which could potentially lead to a deterioration of the caregiver's mental health.(8, 31) The relationship between survivor's physical health and the caregiver's mental health is probably why caregiver with medical illnesses feel more burdened. Interestingly,

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relative caregivers who are assisted with caregiving have higher rate of anxiety symptoms. As caregiving involved stressful tasks (i.e., dealing with patient physically and emotionally), and anxiety per se is a response to perceived future threat, familiar caregiver might respond to patient's needs more effectively.(32) Caregivers recruited in our study were required to have the highest contact time with the patient, thus, delegating care to those who are unexperienced might left the primary caregivers with the fear of what could potentially go wrong.

The strengths of our study are the broad coverage of potential factors (survivor- and caregiver-wise) and the application of PLS-SEM to enhance the methodological validity. However, our study is not without limitations. Firstly, this was a cross-sectional study and therefore no causativeness between these factors and symptoms can be firmly established. Secondly, the principal instrument we applied (HADS), although validated in the Western general population, has been validated in Thai diseases individuals but not in a Thai healthy population. This might raise concern whether the reported prevalence is higher than general population or not. Many explanations could contribute to the lower prevalence of depressive and anxiety symptoms in our study compared to the previous meta-analysis.(11) Firstly, the self- and public- stigma of psychiatric conditions do still exist, and 43% of individuals tend to not disclose depressive symptoms to primary care physician.(33, 34) Secondly, the lower prevalence was potentially due to cultural differences. Moreover, the number of household members in our study was around four, which is higher than in the Western world.(35) There is some evidence that a strong relationship among family members is capable of reducing the likelihood of depression.(36) Apart from that, HADS itself is not a diagnostic tool but a screening tool that prompts a more comprehensive evaluation by clinicians. The prevalence of

both symptoms based on the HADS cannot substitute that of the clinical diagnosis of major depression and anxiety disorders according to the DSM/ICD criteria. Furthermore, characteristics of our participants might not reflect true characteristics of Thai population (i.e., household income of this study exceeded twice that of Thais' average). Thus, extrapolation of our data might best suit only population in urban areas.

Conclusions

A large part of the variance in stress and depression scores in caregivers of ischemic stroke patients is determined by the patients' disabilities, dependency, cognition, and stroke phenotypes; caregivers' health status and burden; and patients' disability, dependency, cognition, and stroke phenotypes. It is critical to screen ischemic stroke caregivers for the aforementioned factors

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