The validity and reliability of the Patient Health questionnaire 9 in screening poststroke depression

Mrs. Piyapat Dajpratham

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ความตรงและความเที่ยงของแบบประเมินPatient Health Questionnaire 9 ในการคัดกรองภาวะซึมเศร้าของผู้ป่วยโรคหลอดเลือดสมอง

นางปิยะภัทร เดชพระธรรม

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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By	Mrs. Piyapat Dajpratham
Field of Study	Health Development
Thesis Advisor	Associate Professor Jariya Boonhong
Thesis Co Advisor	Dr Krit Pongpirul, Ph.D.

Accepted by the Faculty of Medicine, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

..... Dean of the Faculty of Medicine
(Professor SUTTIPONG WACHARASINDHU, M.D.)

THESIS COMMITTEE

..... Chairman
(Professor PICHET SAMPATANUKUL, M.D.)

..... Thesis Advisor
(Associate Professor Jariya Boonhong)

..... Thesis Co-Advisor
(Dr Krit Pongpirul, Ph.D.)

..... Examiner
(Assistant Professor Chulalak Komoltri, Ph.D.)

..... External Examiner
(Associate Professor Vilai Kuptniratsaikul, M.D.)

ปิยะภัทร เดชพระธรรม : ความตรงและความเที่ยงของแบบประเมินPatient Health Questionnaire 9 ในการคัดกรองภาวะซึมเศร้าของผู้ป่วยโรคหลอดเลือดสมอง. (The validity and reliability of the Patient Health questionnaire 9 in screening poststroke depression) อ.ที่ปรึกษาหลัก : รศ.จริยา บุญหงษ์, อ.ที่ปรึกษาร่วม : อ. ดร.กฤษณ์ พงศ์พิรุฬห์

บทนำ : ในช่วง 5 ปีแรกของการเกิดโรคหลอดเลือดสมอง ผู้ป่วยร้อยละ 30 จะเกิดภาวะซึมเศร้าได้ การวินิจฉัยและให้การรักษาอย่างทันเวลาจะส่งผลให้การฟื้นตัวของระบบประสาทสั่งการดีขึ้นอีกทั้งเพิ่มความสามารถของผู้ป่วย แบบประเมิน PHQ-9 ถือเป็นหนึ่งในแบบประเมินที่ดีที่สุดสำหรับการประเมินภาวะซึมเศร้าภายหลังโรคหลอดเลือดสมอง เนื่องจากในประเทศไทยยังไม่มีเครื่องมือที่คัดกรองภาวะนี้ได้อย่างจำเพาะ การนำแบบประเมินนี้มาหาความตรง และความเที่ยงในผู้ป่วยโรคหลอดเลือดสมองจึงเป็นสิ่งจำเป็นทางคลินิก

วัตถุประสงค์ : เพื่อศึกษาความตรงเชิงเกณฑ์และความเที่ยงของแบบประเมิน PHQ-9 ฉบับภาษาไทยในการคัดกรองภาวะซึมเศร้าภายหลังโรคหลอดเลือดสมองโดยเปรียบเทียบกับการสัมภาษณ์โดยจิตแพทย์ซึ่งถือเป็นมาตรฐานทองคำ

วัสดุและวิธีการ : ผู้ป่วยอายุตั้งแต่ 45 ปีที่เป็นโรคหลอดเลือดสมองครั้งแรกตั้งแต่ 2 สัปดาห์จนถึง 2 ปี ได้รับการประเมินด้วยแบบประเมิน PHQ-9 จากผู้วิจัยและ ได้รับการสัมภาษณ์จากจิตแพทย์ตามเกณฑ์ DSM-5 สำหรับการวินิจฉัยโรค major depressive disorder ทำการวิเคราะห์ด้วยการหาความตรงเชิงเกณฑ์ ความเที่ยง และความโค้ง ROC

ผลการศึกษา : ผู้ป่วยโรคหลอดเลือดสมอง 115 คนอายุเฉลี่ย 64+10 ปี คะแนนเฉลี่ยจากแบบประเมิน PHQ-9 เท่ากับ 5.2 + 4.8 ตามเกณฑ์การวินิจฉัยโรค DSM-5 พบผู้ป่วย 23 ราย (ร้อยละ 20) มีภาวะซึมเศร้า แบบประเมิน PHQ-9 มีความเที่ยงในระดับที่น่าพอใจ (ค่า Cronbach alpha เท่ากับ 0.78) ส่วนความตรงนั้นหากใช้ระดับคะแนน 10 ตามที่แบบประเมินแนะนำจะมีค่าความไวต่ำ (0.52) แต่ความจำเพาะสูง (0.94) ความน่าจะเป็นที่น่าจะมีภาวะซึมเศร้า (9.6) หากหาคะแนนจุดตัดคะแนนเทียบกับมาตฐานทองคำพบว่าคะแนนมากกว่าหรือเท่ากับ 6 จะมีค่าความไว 0.87, ความจำเพาะ 0.75, ค่าทำนายผลบวก 0.46, ค่าทำนายผลลบ 0.95, ความน่าจะเป็นที่จะมีภาวะซึมเศร้า 3.5 ค่าพื้นที่ใต้โค้ง ROC เท่ากับ 0.87 (95%CI=0.78,0.96).

สรุป : แบบประเมิน PHQ-9 มีคุณสมบัติทางจิตวิทยาสำหรับการคัดกรองภาวะซึมเศร้าภายหลังโรคหลอดเลือดสมองอยู่ในเกณฑ์ที่ยอมรับได้ โดยมีค่าจุดตัดคะแนนมากกว่าหรือเท่ากับ 6

สาขาวิชา	การพัฒนาสุขภาพ	ลายมือชื่อนิสิต .....
ปีการศึกษา	2561	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

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KEYWORD: depression, diagnosis, Patient Health Questionnaire-9, reliability, stroke, validity, screening

Piyapat Dajpratham : The validity and reliability of the Patient Health questionnaire 9 in screening poststroke depression. Advisor: Assoc. Prof. Jariya Boonhong Co-advisor: Krit Pongpirul, Ph.D.

Background: Poststroke depression occurred about 30% during the first five years after stroke. Timely diagnosis and management could facilitate motor recovery and improve independence. The Patient Health Questionnaire 9 (PHQ-9) is one of the best screening tools for poststroke depression. Since specific screening tool has not yet presented in Thailand, the validity and reliability of the PHQ-9 in stroke patients is clinically essential.

Objectives: To study the criterion validity and reliability of the PHQ-9 (Thai version) in screening poststroke depression by comparing to the psychiatric interview as the gold standard.

Material and Methods: First ever stroke patients age 45 years old and above who had duration of stroke from 2 weeks to 2 years were administered with PHQ-9. The gold standard was a psychiatric interview for major depressive disorder. The criterion validity and reliability analyses, and receiver operating characteristic curve analysis were performed.

Results: One hundred and fifteen stroke patients; with mean age 64+10 years old participated. The mean PHQ-9 score elicited was 5.2 + 4.8. According to the DSM-5 criteria; 23 of them (20%) were diagnosed as depressive disorder. The PHQ-9 had satisfactory internal consistency (Cronbach's alpha = 0.78). The categorical algorithm of the PHQ-9 had low sensitivity (0.52) but very high specificity (0.94) and positive likelihood ratio (9.6). Used as a continuous measure, the optimal cut-off score of PHQ-9 >/= 6 revealed a sensitivity of 0.87, specificity of 0.75, positive predictive value (PPV) of 0.46, negative predictive value (NPV) of 0.95, and positive likelihood ratio of 3.5. The area under the curve (AUC) in this study was 0.87 (95%CI=0.78,0.96).

Conclusion: The PHQ-9 has acceptable psychometric properties for screening for poststroke depression with a recommended cut-off score of six or greater.

Field of Study:	Health Development	Student's Signature .....
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		Co-advisor's Signature .....

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Piyapat Dajpratham

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Chapter 1

Introduction

After stroke or cerebrovascular disease, the common clinical presentation is hemiplegia or hemiparesis [1]. The motor and functional recovery would occur afterwards, however, the magnitude of recovery is individualized depending on demographic, severity of stroke, treatment and training factors. Approximately two thirds of stroke survivors have residual neurological deficits that impair function and 50% of them are left with disabilities making them dependent on others for their activities of daily living [2]. As a result, returning to their social roles in both family and work is rather difficult. The loss of job as well as income can certainly occur as a consequence and that might lessen the self-esteem. A negative impact on the emotional state after stroke has been varied including depression, mania, anxiety, bipolar disorder, psychotic symptoms, apathy, and catastrophic reaction.

Depression is the most common psychological problem after stroke. The pool frequency was 31% of stroke survivors at any time up to five years after stroke. However, it remains unrecognized and undertreated [3]. Poststroke depression (PSD) is associated with decreased participation in rehabilitation program resulting in less functional improvement [4]. When the patients were discharged, they tended to have physical inactivity and social isolation [5]. And this may lead to more depression, cognitive impairment, increased caregiver distress [6], and increased mortality during 2-5 years after stroke [7]. The study about an impact of poststroke depression on healthcare use by veterans with acute stroke reported that stroke patients with PSD

had significantly more hospitalizations, outpatient visits, and longer length of stays compared with those stroke patients without PSD [8].

It's rather complicated to make a diagnosis of depression after stroke because there are a few symptoms of stroke patients confusing with the symptoms of depression [9]. For example, swallowing impairment after stroke can cause weight loss while the stroke patient might have anorexia from depression. The clinician would pay more attention to the swallowing impairment than asking for other constitutional symptoms. In addition, the weakness after stroke is similar to the reduction of physical movement and having fatigue after movement is similar to fatigue in the DSM 5 criteria for diagnosis of major depressive disorder. These symptoms could possibly confuse the clinicians and lead them to underdiagnose as well as undertreat the poststroke depression.

Screening of mood disorders after stroke is recommended in many stroke and stroke rehabilitation guideline [10, 11]. In the situation of Thailand, psychiatrists are rather in a shortage so there should be an appropriate screening tool to assist primary care physicians and other specialists in detecting poststroke depression. At present, a number of screening tools for depression have been translated into Thai language and used in general population [12]. The screening tool selected for this study is Patient Health Questionnaire 9 (PHQ-9). It had been extensively studied in general population and poststroke patients. Moreover, it was reported as one of the good screening tools for poststroke depression (PSD) in term of highest sensitivity [13]. PHQ-9 has been translated into Thai language and validated in primary care patients [14]. The cutoff score of Thai PHQ-9 in primary care patients and of the original version were different [15]. The cutoff score for major depression of the original version and

Thai version were 10 and 9 respectively. For PSD, Williams et al [16]. reported cut off score 10 with sensitivity 91% and specificity 89%. However, PHQ-9 has not been validated for poststroke depression among Thai stroke patients. Because Thailand and the western countries have different health care system, culture, attitude, way of thinking, and family support. Therefore, this study aims to look at the validity and reliability of the Patient Health Questionnaire 9 (PHQ-9) in screening poststroke depression.

Research Question

1. What is the validity and reliability of the Patient Health Questionnaire-9 (Thai version) in diagnosis of depression among stroke patients?

Objectives

1. To study the criterion validity of the Thai version of the Patient Health Questionnaire-9 in diagnosis of poststroke depression.
2. To study the reliability of the Thai version of the Patient Health Questionnaire-9 in diagnosis of poststroke depression.

Conceptual framework

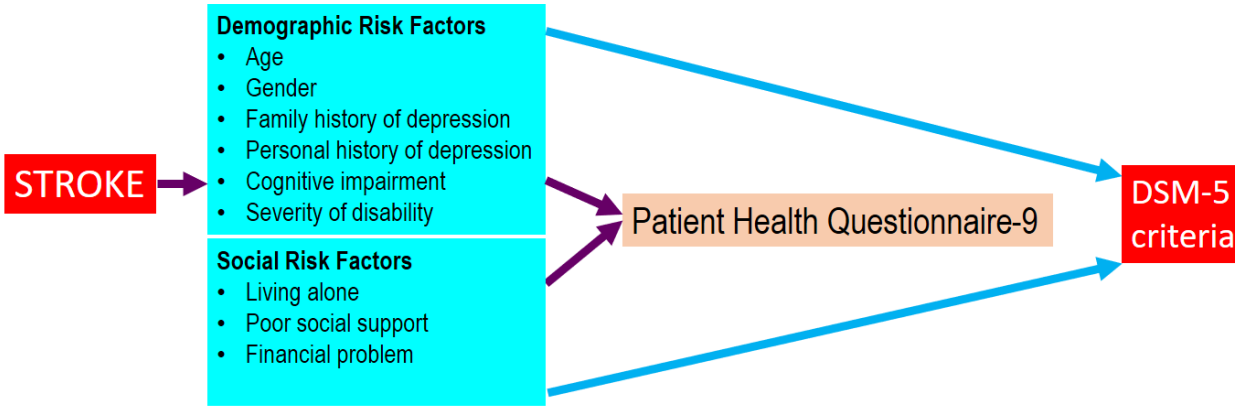

Figure 1 Conceptual framework

Keywords

Depression, Diagnosis, Patient Health Questionnaire-9, Reliability, Screening, Validity

Operational Definitions

Stroke patient [17] means a patient with rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin.

Poststroke depression means depressed mood after stroke and cannot be ascribed to any other mental illness.

Chapter 2

Literature Review

Stroke

The World Health Organization (WHO) definition of stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin [17]. It is a leading cause of disability worldwide. From the Thai Epidemiologic Stroke Study conducted between 2004-2006, the crude prevalence of stroke in Thailand was 1.88% [18]. When we consider the burden of stroke in Thailand by using disability adjusted life year loss, among non-communicable disease stroke ranked the second after ischemic heart disease from 1990-2010 [19]. The common physical impairment was hemiplegia/hemiparesis which affected 80-85% of acute stroke patients [1]. Approximately two thirds of stroke survivors have residual neurological deficits that impair function and approximately 50% are left with disabilities making them dependent on others for activities of daily living [2]. Apart from functional disability, neuropsychiatric disorders after stroke are very common including depression, anxiety disorder, apathy, cognitive disorder, mania, psychosis, pathological affective display, and catastrophic reaction. Depression is the most common psychological problem after stroke and has been identified as a significant poststroke comorbidity for the past 2 decades [10]. The pool frequency was 31% of stroke survivors at any time up to five years after stroke [3].

Poststroke Depression

Etiology

The pathogenesis of PSD is currently unclear. The different factors including neurobiological, behavioral, and social factors interact in a complex way. Behavioral

and social factors have been proved to be related to all kinds of depression. However, neurological changes after stroke might be special for PSD which is different from other subtypes of depression. Neurobiological changes after stroke are complicated with interaction among different factors. The neurobiological hypotheses are including neuroanatomical, neuronal biochemical, and neurogenesis hypothesis as follows [20].

- Neuroanatomical hypothesis: The large infarction size was found associated with PSD. In addition, cerebral pathology in various locations has been hypothesized as causes of PSD. The frontal subcortical circuit and limbic-cortical-striatal-pallidal-thalamic circuits were proved to be the key network that putatively modulates emotional behavior in nonstroke subjects. Until now, the lesion location hypothesis of PSD was still conflicting. Various locations of either right or left hemisphere has been reported an association of PSD. Although a recent systematic review of observational studies reported no association of stroke location and depression risk, the hypothesis of lesion location remains an interest.
- Neuronal biochemical hypothesis: The emotional behaviors are regulated by different neurotransmitter especially monoamines. After stroke, the biochemical factors such as glutamate, inflammatory cytokines and glucocorticoid have resulted in the dysfunction and dysregulation of the amine neurotransmitters. The resultant physiological dysfunction may lead to PSD.
- Neurogenesis hypothesis: This hypothesis emphasizes the critical role of new neurons of hippocampus in the mood control and pharmaceutical effect of

antidepressants. The patients or animal models with depression had decreased neurogenesis and hippocampal volume, whereas antidepressants could enhance the neurogenesis of hippocampus.

Risk factors

Demographic risk factors which have often been identified were female gender and old age [21]. Up until now, there has been varying patterns of relationship reported. Robinson suggested that demographic factors might not act as independent predictors, but as mediators for other risk factors [22]. Reid found that patients' depression status before the stroke is a significant predictor of PSD. Several premorbid health conditions, such as a history of stroke or cardiovascular disease, are well established risk factors for PSD [23]. After stroke, the lesion location and lateralization of lesion have been examined if they could predict PSD. However, the recent systematic review reported no relationship between lesion location of stroke and occurrence of PSD [24]. The most consistent association after stroke were severe stroke, early physical disability, and later disability [25]. Psychosocial risk factors, such as amount of social support perceived by the patients might affect depressive symptoms in the early phase and might also predict PSD in later period when reintegration to everyday life is relevant [26]. Astrom found that living alone was a factor predicting immediate major depression and few social contacts outside the immediate family contributed most to depression after 1 year [27]. In addition, poor financial status has been reported as an association factor of PSD among Thai stroke patients [28].

Frequency of Poststroke Depression

Framingham Study reported that significantly more stroke survivors suffered from depression compared with controls who were matched for age and gender [29]. Incidence and prevalence of PSD have been variously reported. The differences among studies came from timing of studies post stroke, clinical setting of stroke patients, the diagnostic tools used, and the cutoff scores among those tools. Hackett and Pickles conducted the most recent meta-analysis of 61 cohort studies including 25,488 patients. They found that 31% of patients developed depression in any settings at any time point up to 5 years following stroke [3]. The cumulative percent of patients who developed one or more depressions within the first 5 years following stroke ranged from 39-52% [30]. Robinson et al. conducted a pooled analysis of the frequency of PSD in different clinical settings and classified depression as major or minor. He reported the mean prevalence of depression among inpatients in acute or rehabilitation hospitals were 19.3% and 18.5% for major and minor depression, respectively; among individuals in community settings mean prevalence for major and minor depression were 14.1% and 9.1% [22]. Onset of poststroke depression appears to be more common in the first few weeks as opposed to months later and that depression is likely to persist the first few years after stroke [31]. The prevalence of depression for the first 2 years after stroke remained high (between 30 and 40%). However, the untreated poststroke major depression has a natural course of about 1-2 years, with associated improvement in activity of daily living scores, whereas the prognosis for poststroke dysthymic depression is frequently unfavorable and often persists for greater than 2 years [32].

In Thailand, the prevalence of poststroke depression have been variously reported. Tantibhaedhyangkul et al. [28] used the Center for Epidemiologic Studies Depression scale (CES-D) to assess poststroke depression among the first ever stroke patients in rehabilitation phase. The prevalence of PSD was 38%. Masskulpan, et al. [33] also studied the prevalence of PSD in rehabilitation phase and found 37.8% by using the Hospital Anxiety Depression scale. Kulkantrakorn and Jirapramukpitak [34] administered Clinical Interview Schedule-Revised to ischemic stroke patients 1 year after onset and reported the cumulative incidence of depression in clinical setting as 12%. Nidhinandana et al. [35] used Geriatric Depression Scale in stroke patients attending an outpatient clinic and the prevalence was 46.5%. For the community setting, Sathirapanya, et al [36] used Geriatric Depression scale and the prevalence of PSD was 72.5%. These studies did not report the timing and severity of disability poststroke which are the important factors affecting prevalence of depression. However, very long after stroke, there might not be a cause from stroke per se contributing to poststroke depression.

Diagnosis of Poststroke Depression

Diagnosis of poststroke depression is complex due to the frequent presence of other symptoms which are associated with cognitive impairment such as agnosia and change in memory. In addition, some symptoms of stroke or of depression may overlap and be indistinguishable from each other. Common symptoms to both entities include sleep disorders, difficulty concentration and loss of appetite. These similarities may lead to overestimation of depression in stroke patients. In contrary,

many symptoms are not identified as the results of depression. In these cases, those symptoms are mistaken as the consequences of stroke or elderly and this may lead to an underestimation of the diagnosis [9]. The phenomenology of depressive disorders in patients with stroke is very similar to the phenomenology described in the symptom criterion of Diagnostic and Statistical Manual (DSM) [9] major depressive disorder among patients without brain injury [9]. Cummings et al examined DSM depressive symptoms among 50 patients with poststroke depression and 79 depressive patients without brain injury. The factor analysis of 10 depressive symptoms performed in each group and demonstrated no significant differences for either psychological or physiological symptoms of depression [37]. Thus, based on the standard utility of depressive symptoms, DSM criteria are considered the gold standard for poststroke depression diagnosis [38]. Symptom profiles of depression among patients with and without stroke were not different [39]. Noticeably, da Rocha, et al [40] found that stroke patients did not have more somatic complaints than depressed patients who had not suffered a stroke. Moreover, they reported that the PSD patients showed mild typical depressive symptoms such as depressed mood, loss of pleasure and lack of interest. Moreover, the pattern of PSD symptoms is less severe than that of major depressive disorder (MDD). In general, the evaluated symptoms were more accentuated in MDD. Several studies reported that the DSM-IV symptom criterion for MDD is valid in psychiatric patients as well as in stroke patients with MDD [39, 41]. Five or more symptoms have to be present in the case of Major depressive disorder and at least two but fewer than five symptoms have to be present in minor depression. Now, DSM-IV has been updated to DSM-5 and the

diagnostic criteria for depressive disorders in both versions are similar [42]. DSM IV criteria for major depressive episode is as follows (table 1)

Table 1 DSM IV criteria for major depressive episode

DSM IV criteria for major depressive episode
1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood
2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains
4) insomnia or hypersomnia nearly every day
5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6) fatigue or loss of energy nearly every day
7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Remarks

A. **Five (or more) of the above symptoms have been present during the same 2-week period and represent a change from previous functioning. However, at least one of the symptoms is either depressed mood or loss of interest or pleasure. These symptoms do not include symptoms that are clearly due to a general medical condition, or mood incongruent delusions or hallucinations**

B. **The symptoms do not meet criteria for a Mixed Episode.**

C. **The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.**

D. **The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).**

E. **The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.**

The gold standard for diagnosis depression is based on the Diagnostic and Statistical Manual of Mental Disorders classification and the Manual of International Statistical Classification of Diseases and Related Health Problems criteria for depressive symptoms. The type of symptoms, their severity, and their duration are applied to DSM-5 [43] diagnostic criteria for “depressive disorder due to another medical condition with major depressive-like episode”. To diagnose patients with less severe depressive disorders, the research criteria from DSM-IV for minor depression (which is similar to the criteria for depressive episode with insufficient

symptoms in DSM-5) was suggested [43]. This is a subsyndromal form of major depression that requires at least 2 but less than 5 symptoms of major depression as well as the other duration and functional impairment diagnostic criteria. The duration of symptoms must be at least 2 weeks and at least 1 of the symptoms is either depressed mood or loss of interest or pleasure. Spalletta et al [42] compared the frequency of specific depressive symptoms among 50 patients with major depression, 62 with minor depression, and 88 nondepressed patients. Symptoms were elicited using the SCID–Psychiatrist version. Results showed that the 3 groups differed significantly in the frequency of every symptom. However, after correction for multiple comparisons, symptoms of self-blame and guilt failed to distinguish the 3 groups, although all other symptoms did distinguish all 3 groups. Further, patients with minor depression had significantly higher frequency of depressed mood, loss of energy, insomnia, and psychomotor disturbance, compared with nondepressed patients with stroke. Paradiso et al [41,42] examined the specificity of psychiatric disorders during 2 years among 205 patients following acute stroke. Patients were categorized by the presence or absence of depressed mood. The gold standard for major depression, according to DSM-IV criteria which is the same as DSM-5 criteria, was the existence of 5 or more symptoms that were significantly more frequent in depressed, compared with nondepressed patients. Using this gold standard, the sensitivity of standard DSM-IV criteria was 100% during the acute stroke period as well as at 3-, 6-, 12-, and 24-month follow-up. The specificity was 98%, 97%, 95%, and 96%, respectively.

Screening Tools

There are many different depression screening tools used in clinical practice. Several psychiatric rating scales and mood rating scales were validated in PSD, for example, the Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-9, Beck Depression Inventory (BDI), and Center for Epidemiologic Studies Depression Scale (CES-D). Because of the various screening tools, it has become difficult for the clinician to distinguish which one is the easiest to administer and most accurate for diagnosing depression symptoms in patients with stroke. A meta-analysis [13] suggested 3 scales namely the CES-D, the Hamilton Depression Rating Scale (HAM-D), and the PHQ-9 as the best options for screening PSD. When considering a screening tool, feasibility in clinical practice is very important. The PHQ-9 is suggested easy to score and takes less time to administer [44].

The Patient Health Questionnaire 9 (PHQ-9) [15] is a self-administered questionnaire. It is composed of 9-item scale that assesses the 9 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) depression symptom criteria (table 1). The criterion validity was determined by comparing it with the mental health professional validation interview. The interview questions were based on the structure interview for DSM-III-R (SCID) and diagnostic questions from the Primary Care Evaluation of Mental Disorders (PRIME-MD). The construct validity was assessed using the 20 item Short-Form General Health Survey, self-reported sick days and clinic visits, and symptom related difficulty. Nowadays, the PHQ-9 is used all over the world and has been translated into many languages, for example German, French, Spanish, Italian, Arabic, Bengali, Turkish, Flemish and Dutch [45, 46]. The PHQ-9 responses were rated as frequency of occurrence 4 levels during the previous 2 weeks as 0=not at all, 1=several days, 2=more than half of the days and 3=nearly

every day. There are two different methods of scoring PHQ-9 to screen for depression, including an algorithm based on DSM-IV criteria and a cut off based on summed-item scores. The algorithm based diagnosis of MDD can be considered if $\geq$ 5 of the symptom criteria have been present at least level 2 (more than half the days) with the exception of the suicidal ideation item, which counts as one of the five symptoms if it is rated as level 1 (several days) or above. The algorithm based diagnosis also requires that at least one of the symptoms scored as at least level 2 is either loss of interest or pleasure or depressed mood in the past 2 weeks [15]. This algorithm based diagnosis had high specificity as 94%, but sensitivity was rather low as 77%. This indicates that the PHQ-9 was a reliable tool if the user wants to avoid overdiagnosis. On the other hand, the chance of missing patients with MDD in an unselected primary care sample is substantial because the overall sensitivity is low [47]. In contrast, the summed-item score based diagnosis simply adds up the scores from each of the item to give a total score ranging from 0 (no depressive symptoms) to 27 (all symptoms occurring daily). A PHQ-9 score ≥10 had a sensitivity of 88% and a specificity of 88% for major depression. PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively [48]. Comparing the algorithm based and summed-item score based diagnosis, the sensitivity of the algorithm based diagnosis is less than the summed-item score based while the specificity of the algorithm based diagnosis is higher than the summed-item score based diagnosis [49]. Hence, the PHQ-9 summed-item score based diagnosis has been recommended as a method of screening for major depressive disorder [15, 48, 49]. It was one of the instruments endorsed by the National Institute for Health and Clinical Excellence for use in primary care in measuring baseline

depression severity and responsiveness to treatment [47, 50]. The PHQ-9 takes 2-5 minutes to complete and has demonstrated mood disorders with 89.5% sensitivity and 77.5% specificity in adolescents, 61% sensitivity and 94% specificity in adults and 74-100% sensitivity and 53-98% specificity in patients older than 65 years old [50].

Table 2 Criteria for diagnosis major depression based on DSM-5 criteria

The symptoms *need* to have at least one symptom.	**Symptoms *consisted of* a 5 symptoms.**
1. Depressed mood both the self and other people notice. 2. Interest or pleasure in activities is greatly reduced.	1. Weight loss is more or less (body weight changes more than 5 % per month) or with anorexia or appetite disorders. 2. Do not sleep or go to sleep. 3. What's slow, slow motion? Or restless restlessness. 4. Fatigue or lack of strength 5. Feeling self-worth less or overly guilty 6. Concentration or mind reading decreases. 7. Think about dying or thinking, dying or trying to commit suicide, or plan to commit suicide.

Diagnosis is made when the patient had the above symptoms five or more symptoms. One of the symptoms needs to be 1 or 2 of at least one symptom (left column). Those symptoms must last for two weeks, almost every day and have virtually all day. The symptoms have impact on work and social participation.

From the initial validation study, a score of 10 has been recommended as the cut-off score for diagnosing this condition [15]. Moriatry et al. conducted a meta-analysis of thirty-six studies and reported the pooled sensitivity for cutoff point 10 was 78% and pooled specificity was 87% [51]. Both these values were less than the initial study by Kroenke et al [15] because the studies included in the meta-analysis were from different settings. Therefore, single cutoff score might be inappropriate for all settings. Manea, et al. [52] conducted a meta-analysis in order to find the optimal cut-off score for diagnosing depression with the PHQ-9. They reported that PHQ-9 had acceptable diagnostic properties for detecting major depressive disorder for cut off score between 8-11. There were several validity studies reporting the various cutoff score of the PHQ-9 as a screening measure for depressive episode among various population and settings. For example, cutoff score 8 points in Ethiopian pregnant women (sensitivity of 80.8% and specificity of 79.5%) [46], 9 points in chronic care patients in a public health facility (sensitivity of 51% and specificity of 94%) [53], 10 points in Chinese patients with multiple somatic symptoms (sensitivity of 77% and specificity of 76%) [54], 11 points in adolescents in Chile (sensitivity of 86.2% and specificity of 82.9%) [45], 12 points in medical trainees in Oman (sensitivity of 80.6% and specificity of 94%) [55].

For poststroke depression (PSD), all of the criterion validity studies utilized various structured interviews as their gold or reference standard (table 3). None of the studies have employed the psychiatric interview. Interestingly, Pettersson et al. [48] performed a systematic review to explore the diagnostic accuracy of the structured interviews as index tests. The structured interviews in their study were the Structured Clinical Interview for DSM-IV (SCID), the Composite International Diagnostic Interview (CIDI), the Mini International Neuropsychiatric Interview (MINI), the Primary Care Evaluation of mental Disorders (PRIME-MD) and the Diagnostic Interview Schedule (DIS). They found only the Structured Clinical Interview for DSM-IV (SCID) and the Mini International Neuropsychiatric Interview (MINI) had sufficient accuracy for depression diagnosis. They defined diagnostic accuracy for the structured interviews as having at least 80% of both sensitivity and specificity. Therefore, some structured interviews currently in use are not accurate enough to be the reference standard for diagnosis of depression. The psychiatric diagnosis is solely accepted as the gold standard. The summed-item based diagnosis score of the PHQ-9 was applied to determine poststroke depression. The cutoff score from 8 to 10 were classified as having depression with various diagnostic accuracy according to the reference standard (table 3).

Table 3 The validity of the PHQ-9 compared with various reference standard among poststroke depression

Authors	The reference standard	PHQ-9 cut off score Summed item	Sensitivity (95%CI)	Specificity (95%CI)	Area under the curve (95%CI)
Willams LS, et al. 2005 [16]	structured clinical interview (SCID) for the Diagnostic and Statistical Manual Disorders (DSM-IV)	10	0.90 (0.85-0.96)	0.88 (0.84-0.92)	0.96 (--)
de Man-van Ginkel, et al. 2012 [57]	the Composite International Diagnostic Interview (CIDI) for the Diagnostic and Statistical Manual Disorders (DSM-IV)	10	0.80 (0.62-0.98)	0.78(0.72-0.85)	0.87 (0.80, 0.90)
Turner A, et al. 2012 [44]	Structured Diagnostic Interview for the Diagnostic and Statistical manual of Mental Disorders, 4th edition MDE module	8	0.77 (0.49-0.95)	0.75 (0.62-0.85)	0.82 (0.71, 0.90)
Prisnie JC, et al. 2016 [58]	Structured clinical interview (SCID) for the Diagnostic and Statistical Manual Disorders (DSM-IV)	10	0.81 (0.48-0.97)	0.93 (0.86-0.97)	0.866 (--)
Wang EY, et al. 2018 [59]	Computerized version of the National Institute of Mental Health Diagnostic Interview Schedule (C-DIS)	10	0.51 (0.34-0.68)	0.87 (0.79-0.92)	0.82 (0.74, 0.90)

In the situation of Thailand, psychiatrists are in a shortage, the screening tools should be utilized to enhance depression detection. As poststroke depression was the dominant mood disorder after stroke, many guidelines have recommended

screening for poststroke depression. Therefore, clinicians have to select an appropriate screening tool and consider the appropriate cutoff score. Several depression screening tools have been translated into Thai language and some of them have been used for screening depression among stroke patients of different onset and settings. None of them have been validated in stroke patients. Moreover, those scales have been developed for the western population, the cutoff scores proposed might not be appropriate for the Thai population as culture, way of thinking and attitudes towards disease are different. Among the screening tools for poststroke depression, the PHQ-9 was reported as one of the good screening tools for screening PSD in term of highest sensitivity [13] and appropriate for clinical utility. In Thailand, the PHQ-9 was translated into Thai language in 2007 [14]. The criterion validity was compared with the Mini International Neuropsychiatric Interview (MINI) which served as a gold-standard for diagnosing depression. The concurrent validity was also compared with the Hamilton Depression Rating scale for assessing symptom severity. The cutoff score of 9 and above was reported as major depression in general population. Later in 2017, Lee and Dajpratham studied the criterion validity of Thai version of the PHQ-9 among the elderly. They used MINI as the reference standard and reported the cutoff score for major depression in Thai elderly as 10 and above [59] with the sensitivity of 90% and specificity of 89%. However, there have been no study validating PHQ-9 with the reference standard among poststroke depression.

In this study, the author would like to study the validity and reliability of Thai PHQ-9 in detecting depression among stroke patients by comparing them with the psychiatric diagnosis given by a psychiatrist.

Chapter 3
Research Methodology

Research design

Cross-sectional diagnostic study

Setting

This prospective study was conducted from November 2017 to December 2018 in the Department of Rehabilitation Medicine, Faculty of Medicine Siriraj Hospital.

Population and samples

Population: stroke patients attending Department of Rehabilitation Medicine, Faculty of Medicine Siriraj Hospital at either inpatient or outpatient services during November 2017-December 2018.

Samples: stroke patients according to the inclusion and exclusion criteria below

Inclusion criteria

1. Age ≥ 45 years old
2. Having first time diagnosis of either ischemic or hemorrhagic stroke
3. Having stable medical and neurological conditions
4. Duration of stroke from 2 weeks to 2 years
5. Being able to communicate and understand Thai language

Exclusion criteria

1. Cognitive impairment measured by the Thai Mental State Examination (TMSE) < 24
2. Having previous diagnosis as dementia, psychiatric disorders, and other neurological diseases.

Sample size calculation

From the study of Williams et al. [16]

PHQ-9 was used for screening major depression after stroke with sensitivity of 91% and specificity of 79%

$$\frac{N = Z_{1-\alpha}^{2} \_ P(1-P)}{d^2}$$

Confidence level [(1-α)x100] providing α =0.05

Rate of proportion: sensitivity of the test

Allowable error [d=0.1]

According to the above formula, sensitivity of the test was estimated as 90±10%. Therefore 35 cases of depression are needed. In addition, specificity of the test was estimated as 80±10%, 72 cases of non-depression are needed. Based on the prevalence of PSD which is 30%, total stroke cases needed to enroll are 117. However, the sum of cases and non-cases of PSD is 107. Therefore, this study needs sample size of 117 stroke patients,

Outcome measurement

1. The Thai PHQ-9 [14] had satisfactory internal consistency (cronbach's alpha = 0.79) and showed moderate convergent validity with the HAM-D (r = 0.56; P < 0.001). There are two different methods of scoring PHQ-9 to screen for depression, including an algorithm based on DSM-IV criteria and a cut off based on summed-item scores. The algorithm based diagnosis of MDD can be considered if ≥ 5 of the symptom criteria have been present at least level 2 (more than half the days) with the exception of the suicidal ideation item, which counts as one of the five symptoms if it is rated as level 1 (several days) or above. The algorithm based diagnosis also requires that at least one of the symptoms scored as at least level 2 is either loss of interest or pleasure or depressed mood in the past 2 weeks [15]. The algorithm based diagnosis from the original version suggested cut-off score 10 for diagnosis of major depression. With this cut-off score, the Thai PHQ-9 had low sensitivity (0.53) but very high specificity (0.98) and positive likelihood ratio (27.37). When used as a continuous measure for diagnosis of major depression, the optimal cut-off score ≥ 9 of the Thai PHQ-9 revealed a sensitivity of 0.84, specificity of 0.77, positive predictive value (PPV) of 0.21, negative predictive value (NPV) of 0.99, and positive likelihood ratio of 3.71. The area under the curve (AUC) in this study was 0.89 (SD = 0.05, 95% CI 0.85 to 0.92).
2. The DSM-5 criteria for major depressive episode was used as a reference standard [43]. The psychiatric interview was performed to an individual

patient. The major depressive episode could occur in the following conditions.

- Major depressive disorder (MDD)
- Depressive disorder due to another medical condition with MDD
- MDD episode in bipolar disorder

3. The Thai Mental State Examination (TMSE) was developed in 1993 as the first neuropsychiatric test for the standard mental status examination for Thai people. The total score of TMSE was 30 points. The cut-off point for the diagnosis of normal healthy Thai elderly for TMSE was 24 points [60].
4. The Barthel index (BI) [61] is the most commonly used functional outcome measure in stroke rehabilitation settings. It assesses 10 functional tasks of daily living (activities of daily living-ADL), scoring the individual depending on independence in each task. Score ranges from 0-20. The higher score, the more independence in ADL function.
5. The Modified Rankin Scale (MRS) is a clinician-reported measure of global disability and has been widely applied for evaluating recovery from stroke [62, 63]. It is an ordinal scale with 7 categories ranging from zero (no symptoms) to six (death). The MRS assesses ability to ambulate and complete activities of daily living, from no limitations (0) to fatal stroke (6); a score of 4 or 5 denotes a patient who is unable to ambulate or complete activities of daily living without assistance from a caregiver or assistive device. Numerous studies demonstrate the construct validity of the MRS by its relationships to physiological indicators such as stroke type, lesion size, perfusion and neurological impairment. Convergent validity

between the MRS and other disability scales is well documented. MRS > 3 was defined as poor outcome [64].

Study procedures

1. This research was approved from the institutional Review Board of Faculty of Medicine Siriraj Hospital. The COA number was 623/2017.
2. This research was approved from the institutional Review Board of Faculty of Medicine, Chulalongkorn university. The COA number was 298/2018.
3. After IRB approval, the recruitment process began according to the inclusion and exclusion criteria.
4. The Thai Mental State Examination (TMSE) was administered in order to screen for cognitive impairment in an individual.
5. One of the authors (PD) got access to the patients' medical records and filled out the information related to stroke such as comorbid illnesses and types of stroke from the imaging studies.
6. The interview process performed by one the researcher in a quiet and private area. The following questionnaires were administered.
    - Case record form
    - Barthel index (BI)
    - Modified Rankin Scale (MRS)
    - Thai Patient-Health Questionnaire-9 (Thai PHQ-9)
7. In the same day, a psychiatrist interviewed each patient in the private area and gave diagnosis according to the DSM-5 criteria. Both a researcher and a psychiatrist were blind to each other's result.

Statistical analysis

1. Demographic data, MRS, and BI were analyzed by descriptive statistics. The quantitative data such as age and total BI were analyzed by independent sample T test, meanwhile, the duration of stroke and PHQ-9 score were analyzed by Mann-Whitney U test. The qualitative data such as gender, education levels, risk factors, pathology of stroke, side of weakness, and MRS scale were analyzed by Chi-square or Fisher's Exact test.
2. The comparison of each item in functional score and depression score between normal and depression groups were analyzed by the independent sample T test.
3. All analyses were significant at p value less than 0.05.
4. The reliability was analyzed by Cronbach's alpha and the value were as follows [65]
    - $\alpha \geq 0.9$ means excellent
    - $0.9 > \alpha \geq 0.8$ means good
    - $0.8 > \alpha \geq 0.7$ means acceptable
    - $0.7 > \alpha \geq 0.6$ means questionable
    - $0.6 > \alpha \geq 0.5$ means poor
    - $0.5 > \alpha$ means unacceptable
5. The psychiatric diagnosis as bivariate response was used as a gold standard to calculate sensitivity and specificity for both the algorithm based and summed item based diagnosis of PHQ-9.

6. The sensitivity, specificity, positive and negative predictive value as well as the positive and negative likelihood ratio were calculated for each PHQ-9 cutoff score.
7. The ROC analyses combine instrument sensitivity and specificity into one measure (referred to as area under the curve, or AUC) for all possible cutoff score. The AUC can be used to evaluate the diagnostic ability of a test to discriminate the true disease status of a patient. AUC values range from ≤0.5 (no discriminatory ability) to 1.0 (perfect discrimination). Yang and Berdine [66] suggested the range of AUC values and interpretation as follows
    - AUC = 0.5 means No discrimination, e.g., randomly flip a coin
    - 0.6 ≥ AUC > 0.5 means poor discrimination
    - 0.7 ≥ AUC > 0.6 means acceptable discrimination
    - 0.8 ≥ AUC > 0.7 means good discrimination
    - 0.9 ≥ AUC > 0.8 means excellent discrimination
    - AUC > 0.9 means outstanding discrimination
8. PASW statistics version 18.0 (SPSS Inc, an IBM company, Chicago, IL) and MedCalc online version were used.

Chapter 4
Result

There were 190 stroke patients recruited to the study. Seventy-five of them were excluded because 21 had recurrent stroke, 17 had cognitive impairment, 17 had

aphasia, 10 were younger than 45 years old, and 10 had stroke duration longer than 2 years. (Fig 2) One hundred and fifteen stroke patients; 63 males (54.8%) and 53 females (45.2%), with mean age 64±10 years old (45,88) enrolled to the study. The majority of them graduated primary school followed by secondary school and high school respectively. Comorbid illness found in descending order were hypertension, dyslipidemia, diabetes mellitus, and heart disease. The median duration of stroke was 59 days. Most of them (81.7%) suffered from ischemic stroke. Left side weakness was dominant (61%). Most of the patients (65.2%) were recruited from inpatient rehabilitation.

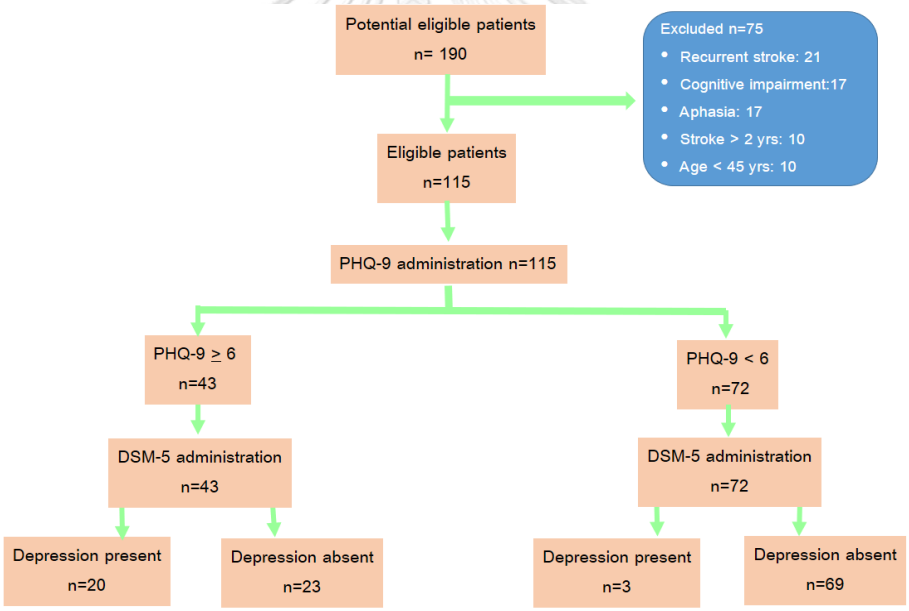

Figure 2 Study flow chart

All of them were administered the index test which was PHQ-9 and the reference standard which was DSM-5 criteria for major depressive disorder on the same day. The mean PHQ-9 score elicited from all the patients was 5.2 ± 4.8. Prevalence of poststroke depression was 20% (95%CI=13.7, 28.2). According to the

DSM-5 criteria; 8 of them (6.9%) were diagnosed as major depressive disorder, 15 of them (13.1%) were diagnosed as other depressive disorder and 92 of them (80%) were normal. In the other depressive disorder group, 12 patients (10.5%) had adjustment disorder with depressed mood and 2 patients (1.7%) had depressive disorder not otherwise specified and 1 patient (0.9%) had other specified depressive disorder. (table 4)

Table 4 The prevalence of poststroke depression according to the DSM-5 criteria

Psychological status	Frequency N (%)
Poststroke depression	**23 (20)**
• Major depressive disorder	8 (6.9)
• Adjustment disorder with depress mood	12 (10.5)
• Depressive disorder not otherwise specified	2 (1.7)
• Other specified depressive disorder	1 (0.9)
Normal	**92 (80)**

According to the demographic characteristics between patient with and without PSD group, female was dominant in the PSD group. However, this difference was not found statistically significant. Other factors such as age, educational level, risk factors, median duration after stroke, pathology of stroke, side of weakness, and setting of the patients showed no significant difference between 2 groups. The Modified Rankin Scale (MRS) and the mean PHQ-9 score were found different between 2 groups. The MRS 0-3 were defined as no disability meanwhile MRS > 3 was defined as disability. More stroke patients in the PSD group were disable than in

the without PSD group. In addition, median PHQ-9 score of the PSD group were significantly higher than of the without PSD group (table 5).

Table 5 The baseline characteristic of the stroke patients

Variables	Without PSD (92) N(%)	With PSD (23) N (%)	p value
Demographic-related			
Age*	64.7 ± 9.5	64.6 ± 12.2	0.960
Gender			0.092
• Male	54 (58.7)	9 (39.1)	
• Female	38 (41.3)	14 (60.9)	
Education level			0.430
• Primary school	42 (45.7)	13 (56.6)	
• Secondary school	26 (28.3)	5 (21.7)	
• Bachelor degree and higher	24 (26.0)	5 (21.7)	
Comorbid illness			
• Hypertension	77 (83.7)	21 (91.3)	0.518
• Dyslipidemia	53 (57.6)	17 (73.9)	0.152
• Diabetes mellitus	37 (40.2)	12 (52.2)	0.300
• Smoking	21 (22.8)	4 (17.4)	0.572
• Heart disease	19 (20.7)	6 (26.1)	0.572
Median Duration of stroke (days)**	57.5 (26, 167.5)	60 (25.5, 137.5)	0.527
Pathology of stroke			0.561
• Infarction	74 (80.4)	20 (87.0)	
• Hemorrhage	18 (19.6)	3 (13.0)	
Side of weakness			0.339
• left	54 (58.7)	16 (69.6)	
• Right	38 (41.3)	7 (30.4)	
Setting			0.793
• Inpatient	60 (65.2)	15 (65.2)	
• Outpatient	32 (34.8)	8 (34.8)	
Disability-related			
Modified Rankin Scale			0.036***
• 1	7 (7.6)	2 (8.7)	
• 2	16 (17.4)	0 (0.0)	
• 3	18 (19.6)	3 (13.0)	
• 4	50 (54.3)	15 (65.2)	
• 5	1 (1.1)	3 (13.0)	
Barthel Index *	13.3 ± 4.9	11.0 ± 5.8	0.055
Depression-related			

Median PHQ-9 score**	4.0 (0.5, 5.75)	10.0 (7.0, 15.0)	<0.001***

*mean + SD, ** median (IQR 25,75), ***significant at p value < 0.05

Regarding the function between 2 groups measured with Barthel Index, the significant difference was found in the grooming, and bladder function. Most of the patients in the without PSD group had independent grooming and bladder function. In contrary, most of the patients in the PSD group had dependent grooming and bladder function. However, other function measured with the Barthel Index showed no statistically significant difference. (table 6)

Table 6 The comparison of function between stroke patients with and without depression

Function	Normal	PSD	P value
Feeding			0.219
● Independent	78 (84.8)	17 (73.9)	
● dependent	14 (15.2)	6 (26.1)	
Grooming			0.003*
● independent	83 (90.2)	15 (65.2)	
● dependent	9 (9.8)	8 (34.8)	
Dressing			0.284
● Independent	35 (38.0)	6 (26.1)	
● dependent	57 (62.0)	17 (73.9)	
Bathing			0.083
● Independent	38 (41.3)	5 (21.7)	
● dependent	54 (58.7)	18 (78.3)	
Toileting			0.065
● Independent	44 (47.8)	6 (26.1)	
● dependent	48 (52.2)	17 (73.9)	
Mobility			0.358
● Independent	29 (31.5)	5 (21.7)	
● dependent	63 (68.5)	18 (78.3)	
Transfer			0.068
● Independent	39 (42.4)	5 (21.7)	
● dependent	53 (57.6)	18 (78.3)	
Stair			0.521

• Independent • dependent	16 (17.4) 76 (82.6)	2 (8.7) 21 (91.3)	
Bladder • Independent • dependent	77 (83.7) 15 (16.3)	15 (65.2) 8 (34.8)	0.048*
Bowel • Independent • dependent	84 (91.3) 8 (8.7)	19 (82.6) 4 (17.4)	0.222

*significant at p value <0.05

Reliability and item analysis

Cronbach's alpha for the total score was 0.78. The mean score for all PHQ-9 items are shown in Table 3. Individual items of the PHQ-9 were scored on a scale of 0 to 3 for symptom severity. The item that was endorsed most frequently was item 3 trouble falling or staying asleep, or sleeping too much. The item that was endorsed the least was item 9 thoughts that you would be better off dead or of hurting yourself. All items, if deleted, would consistently decrease the total scale alpha. The least item-total correlation was item 5 poor appetite or over eating (table 7**).**

Table 7 Mean score, standard deviation and internal consistency of the PHQ-9 score

PHQ-9 items	**mean**	Std. Deviation	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
1. Little interest or pleasure in doing things เบื่อๆทำอะไรก็ไม่เพลิดเพลิน	0.72	0.881	0.612	0.708
2.Feeling down, depressed, or hopeless ไม่สบายใจ ซึมเศร้าหรือท้อแท้	0.64	0.926	0.516	0.723

3.Trouble falling or staying asleep, or sleeping too much หลับยากหรือหลับๆตื่นๆหรือหลับมากไป	1.11	1.256	0.404	0.749
4.Feeling tired or having little energy เหนื่อยง่าย หรือไม่ค่อยมีแรง	0.68	0.984	0.321	0.755
5.Poor appetite or overeating เบื่ออาหารหรือกินมากเกินไป	0.47	0.955	0.199	0.773
6.Feeling bad about yourself – or that you are a failure รู้สึกไม่ดีกับตัวเอง– คิดว่าตัวเองล้มเหลว หรือเป็นคนทำให้ตัวเองหรือครอบครัวผิดหวัง	0.71	1.015	0.612	0.704
7.Trouble concentrating on things สมาธิไม่ดี เช่น ดูโทรทัศน์ ฟังวิทยุหรือทำงาน ที่ต้องใช้ความตั้งใจ	0.27	0.641	0.345	0.749
8.Moving or speaking so slowly that other people could have noticed พูดหรือทำอะไรช้าจนคนอื่นมองเห็นหรือกระสับกระส่าย จนท่านอยู่ไม่นิ่งเหมือนเคย	0.35	0.731	0.555	0.722
9.Thoughts that you would be better off dead or of hurting yourself พูดหรือทำอะไรช้าจนคนอื่นมองเห็นหรือกระสับกระส่าย จนท่านอยู่ไม่นิ่งเหมือนเคย	0.25	0.662	0.525	0.729

Validity analysis

The performance of the PHQ-9 against the diagnosis of major depressive disorder by the DSM-5 criteria for major depressive disorder as a criterion standard was examined. According to the DSM-5 criteria, 23 patients (20%) met the diagnosis of any depression poststroke. The median PHQ-9 score for the depression group was 10 (IQR25,75: 7, 15) whereas the median score of the no depression group was 4 (IQR25,75: 0.5, 5.75). These median PHQ-9 score showed significantly different between 2 groups.

The validity of the index test PHQ-9 as a diagnostic tool, using categorical algorithm, revealed a sensitivity of 34.8%, specificity of 97.8%, a positive predictive value (PPV) of 80%, and a negative predictive value (NPV) of 85.7%, and a positive

likelihood ratio of 16.0 (table 8). When using the summed item based diagnosis, the sensitivity, specificity, PPV, NPV, and likelihood ratio of different PHQ-9 thresholds in diagnosing PSD showed in table 8. At the cutoff score of 6 or greater showed the highest Youden's index. This cutoff score showed sensitivity of 87.0 % (95% CI=66.4, 97.2), specificity of 75.0% (95% CI=64.9, 83.4), the positive predictive value of 46.5% (95% CI=37.1, 56.2), the negative predictive value of 95.8% (95% CI=88.8, 98.5), the positive likelihood ratio of 3.5 (95% CI=2.4, 5.1), and the negative likelihood ratio of 0.2 (95%CI=0.1, 0.5) (table 8). The ROC curve illustrates that the PHQ-9 performed well in identifying patients with PSD (figure 3). The area under the curve (AUC) in our study was 0.87 (95%CI=0.78, 0.96) which demonstrated excellent discrimination.

Table 8 The performance of different PHQ-9 cut-off scores in detecting any depression

Score	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Positive predictive value (%) (95%CI)	Negative predictive value (%) (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)	Youden's index
≥10	34.8 (16.4, 57.3)	97.8 (92.4, 99.7)	80.0 (47.6, 94.6)	85.7 (81.6, 89.0)	16.0 (3.6, 70.3)	85.7 (81.6, 89.0)	----------
≥5	91.3 (71.9, 98.9)	65.2 (54.6, 74.8)	39.6 (32.6, 47.2)	96.8 (88.8, 99.1)	2.62 (1.9, 3.6)	0.13 (0.04, 0.5)	
≥6	87.0 (66.4, 97.2)	75.0 (64.9, 83.4)	46.5 (37.1, 56.2)	95.8 (88.8, 98.5)	3.5 (2.4, 5.1)	0.2 (0.1, 0.5)	0.620
≥7	78.3 (56.3, 92.5)	81.5 (72.1, 88.8)	51.4 (39.6, 63.1)	93.8 (87.3, 97.0)	4.2 (2.6, 6.8)	0.3 (0.1, 0.6)	0.598
≥8	65.2 (42.7, 83.6)	83.7 (74.5, 90.6)	50.0 (36.6, 63.4)	90.6 (84.5, 94.4)	4.0 (2.3, 6.9)	0.42 (0.2, 0.7)	0.489
≥9	56.5 (34.5, 76.8)	90.2 (82.2, 95.4)	59.1 (41.4, 74.7)	89.3 (83.8, 93.0)	5.8 (2.8, 11.8)	0.5 (0.3, 0.8)	0.467
≥10	52.2 (30.59, 73.2)	94.6 (87.7, 98.2)	70.6 (48.4, 85.9)	88.8 (83.7, 92.4)	9.6 (3.7, 24.5)	0.5 (0.3, 0.8)	0.467

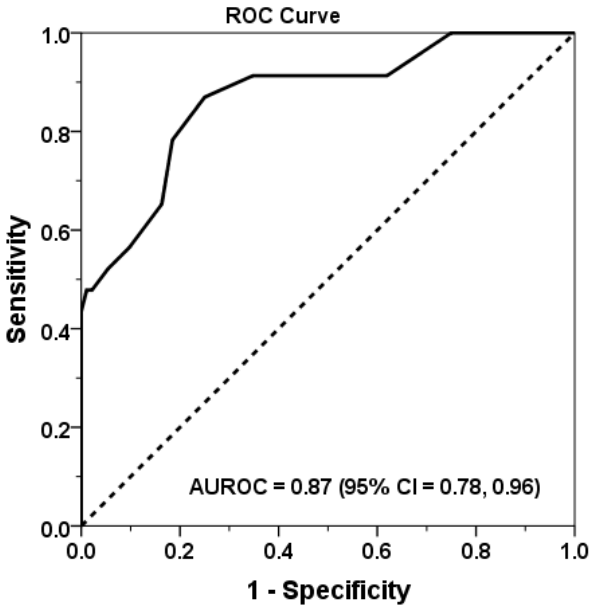

Figure 3 The Receiver Operating Characteristic (ROC) versus DSM-5 criteria for major depressive disorder among stroke patients.

When consider the criterion validity of PHQ-9 against the diagnosis of DSM-5 criteria by a psychiatrist, the cutoff score of 12 had the highest Youden's Index. This cutoff score showed sensitivity of 50.0% (95%CI=15.7, 84.3), specificity of 92.5% (95%CI=85.8, 96.7), the positive predictive value of 33.3% (95% CI=16.0, 56.7), the negative predictive value of 96.1% (95% CI=92.5, 98.0), the positive likelihood ratio of 6.7 (95% CI=2.6, 17.5), and the negative likelihood ratio of 0.5 (95%CI=0.3, 1.1) (table 9). The ROC curve illustrates that the PHQ-9 performed well in identifying patients with PSD (figure 4). The area under the curve (AUC) in our study was 0.71 (95%CI=0.0.51, 0.91) which demonstrated good discrimination.

Table 9 The performance of different PHQ-9 cut-off scores in detecting major depression

Score	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Positive predictive value (%) (95%CI)	Negative predictive value(%) (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)	Youden 's index
≥10	50.0 (15.7, 84.3)	87.8 (80.1, 93.4)	23.5 (11.5, 42.1)	95.9 (92.1, 97.9)	4.1 (1.7, 9.7)	0.6 (0.3, 1.1)	0.379
≥11	50.0 (15.7, 84.3)	91.6 (84.6, 96.1)	30.8 (14.9, 53.1)	96.1 (92.4, 98.0)	5.9 (2.3, 15.1)	0.6 (0.3, 1.1)	0.416
≥12	50.0 (15.7, 84.3)	92.5 (85.8, 96.7)	33.3 (16.1, 56.7)	89.3 (83.8, 93.0)	6.7 (2.6, 17.5)	0.5 (0.3, 1.0)	0.425
≥13	37.5 (8.5, 75.5)	93.4 (86.9, 97.3)	30.0 (11.9, 57.4)	88.8 (83.7, 92.4)	5.7 (1.8, 18.0)	0.7 (0.4, 1.2)	0.310

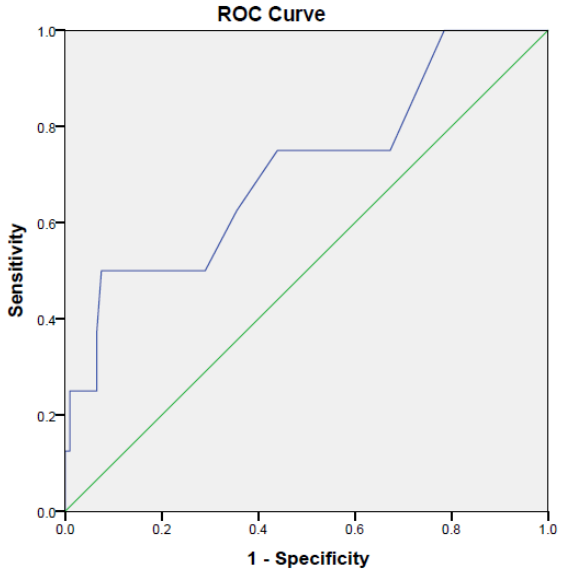

Figure 4 The Receiver Operating Characteristic (ROC) versus DSM-5 criteria for major depressive disorder among stroke patients.

Chapter 5
Discussion

This study was the first study in Thailand to determine the validity of a depression screening questionnaire among stroke patients. The depression screening questionnaire selected to use in this study was the PHQ-9 which has been reported as one of the good screening tools for PSD [13]. Its good clinical utility has also been reported by considering the practical use such as less time to administer, no cost of use and no training requirement. The psychiatric interview performed by a psychiatrist was utilized as a reference standard and this was a strength of the study. None of the previous validation studies of the PHQ-9 among PSD had employed psychiatric interviews as the reference standard (table 3). In this study, the validity of the PHQ-9 in screening PSD was good in discriminatory power (AUC=0.87) when compared to the psychiatric interview according to the DSM-5 criteria as a gold standard. In addition, the internal consistency was acceptable (cronbach's alpha=0.78).

According to the DSM-5 criteria, PSD was found in 23 patients (20%) and that was less than the previous studies. Hackett and Pickles [3] reported in a meta-analysis that 31% of stroke patients developed depression in any setting at any time point up to 5 years following stroke. Robinson et al. [22] conducted a pool analysis and reported a mean prevalence of major and minor depression as 19.3% and 18.5% among hospitalized patients in acute or rehabilitation hospitals. The low prevalence in this study probably from the inclusion criteria that only stroke patients aged more than 45 years old were recruited. From the previous research findings, younger stroke

survivors were more likely depressed than older survivors [67, 68, 69]. However, the finding of this study was in line with the study of Fuentes et al. which recruited the stroke patients of the same age group as this study and they also found low prevalence of depression only 9.9% in their study [69].

Moving on to the demographic characteristics of the stroke patients with and without PSD, the female gender was dominant in the depression group. The prospective cohort study by Wang et al. [70] found that the PSD risk factors in the acute phase of stroke differed from those in the chronic phase. In particular, they found that female gender was an independent risk factor for PSD in the acute phase. Therefore, the relationship between gender and PSD development was not established. The impact of age was as mentioned above, namely, that younger stroke survivors tend to feel more depressed than older survivors [67, 68]. In the current study, the participants with and without PSD were of about the same age, so there was no difference between the two groups. As to education level and PSD, there is conflicting evidence regarding their relationship [71]. Chatterjee et al [68] and Schepers et al [72] found no association between the level of education and PSD. In contrast, Nys et al.[73] and Sienkiewicz-Jarosz et al [74] reported that participants who developed depression had significantly low levels of education. Most of the participants in the present study graduated primary school, and no significant difference was found between the groups. Regarding the prestroke risk factors and PSD development [71], there have been no conclusions on the specific risk factors or the number of vascular risk factors. As to the stroke subtypes, only Schepers et al [72] examined the association of the stroke subtypes with the risk for PSD; however, they reported no association between the subtypes and PSD. The side and location of stroke have also

been the subject of many studies, but the results have been conflicting. In 2015, Wei et al [24] conducted a systematic review and suggested that the risk of depression was associated with right-hemisphere stroke when depression was assessed 1–6 months after stroke. In 2017, Zhang et al [75] performed a meta-analysis and concluded that patients with left hemisphere stroke may be more susceptible to PSD 1–6 months after stroke (OR, 1.50; 95% CI, 1.21–1.87).

Regarding the disability assessment, the Modified Rankin Scale (MRS) and the Barthel index (BI) are the most common clinimetrical instruments for measuring disability after stroke. The MRS has six ordinal levels of disability and patients were classified the disability level according to the definition. The BI was designed to assess 10 functions in daily life and score each function according to the level of dependence. The summed score of 10 functions was then used in comparison. Therefore, MRS could more easily detect disability and better revealed significantly different than the BI. From table 5 MRS could reveal the significant difference of dependent stroke patients (MRS4-5) between the depression and normal groups whilst BI showed no significant difference. Regarding the functional comparison between stroke patients with and without PSD, more of stroke patients without PSD was independent on grooming function and bladder control. Practically, feeding and grooming functions are both rather simple and utilize the same body mechanics. In this study, the reason that feeding function did not appear significantly different between groups might be from other types of feeding problem such as dysphagia problem. Those stroke patients with dysphagia had to rely on the nasogastric tube feeding and were rated on Barthel index as dependent feeding function despite adequate upper limb function to complete feeding function by themselves. The

other function was bladder control, Sakakibara et al[76]. conducted a review on bladder dysfunction among different groups of patients and found that frequency of bladder dysfunction in patients with depression was significantly higher than that in age-matched controls (around 10%) but lower (up to 25.9%) than that in stroke (up to 55%). This might reflect that stroke patients with depression would have more bladder dysfunction than whom without depression. Their finding was congruent to this study as the PSD group had more bladder dysfunction than the without PSD group.

The internal consistency of the PHQ-9 administered among stroke patients in this study was 0.78 which was considered acceptable. The level of internal consistency was different from the original version. The original studies performed in primary care and obstetrics and gynecology showed internal consistency of 0.89 and 0.86 respectively [15]. In addition, Turner et al, employed PHQ-9 for screening PSD and found internal consistency of 0.82 [44]. For the Thai version of PHQ-9, the validity studies among the Thai population reported the internal consistency of 0.79 [14]. Later Lee and Dajpratham employed it in the Thai elderly and the internal consistency was 0.76 [56]. From this study, the internal consistency was 0.78 and quite congruent to the studies using the Thai version of PHQ-9.

The PHQ-9 can be used as a screening tool since the AUC showed the good level of discriminatory power (AUC=0.87). The result of our study was in line with other studies using PHQ-9 for screening PSD. These studies also reported the good discriminatory power of the PHQ-9 as AUC > 0.8 (table 6). For the validity of PHQ-9, the algorithm-based diagnosis for detecting PSD in our study showed that it provided a high specificity. However, its sensitivity was poor (34.8%), rendering this

algorithm less useful for screening purpose than the cutoff score. On the other hand, its high positive likelihood ratio (LR+) of 16 may make it suitable method for diagnostic purpose. The diagnostic accuracy was in line with the meta-analysis of Manea et al [49]. In 2015, Manea et al [49] conducted a diagnosis meta-analysis of the PHQ-9 algorithm scoring method as a screening for depression and found that the sensitivity was low as 53% (95%CI= 42, 65) whilst the specificity was high as 94% (95%CI= 91, 96). The summed-item score based diagnosis with the gold standard were performed in many studies and the different cutoff scores with different diagnostic accuracy have been reported. For example, the PHQ-9 has already been validated among the Thai population and the cutoff score of 9 was reported for diagnosis of major depression with sensitivity of 84.0% and specificity of 77.0% [14]. Likewise, the validity of the PHQ-9 screening for depression in patients with type-2 diabetes mellitus in non-communicable diseases clinics in Malawi found a cutoff score of 6 in detecting depression with sensitivity of 93.23% and specificity of 77.89% [77]. Among patients with multiple sclerosis, PHQ-9 was used as a screening tool for major depressive disorder (MDD) and found a cutoff score of 11 with sensitivity of 95% and specificity of 88.3% [78]. For patients with PSD, Prisnie [58] reported a cutoff score 13 for diagnosis of PSD with sensitivity of 81.8% and specificity of 97.1%. Compared with our study, the summed score of PHQ-9 was validated with the DSM-5 criteria interviewed by the psychiatrist and revealed the cutoff score of 6. This score yielded the highest Youden's index and showed sensitivity of 87.0 % (95% CI=66.4, 97.2), specificity of 75.0% (95% CI=64.9, 83.4) for diagnosis of depression. However, the cutoff score of 6 in this study is lower than other studies because this cutoff score is for any depression, not major depression. The advantage of this low cutoff

score is early detection and can alert clinician to perform regular follow up. Considering diagnosis of major depression according to DSM-5 criteria, the ROC analyses revealed that PHQ-9 had good discrimination. The cutoff score for major depression was 12 and greater but the sensitivity was too low to be a screening tool for major depression.

The strength of our study was using a psychiatric interview according to the DSM-5 criteria as a gold standard. As yet none of the previous validation studies among patients with PSD have used a psychiatric interview as a gold standard. However, there were some limitations of our study. Firstly, as we used the prevalence of poststroke depression from the study of Hackett et al [3] which was 30% in the sample size calculation but the prevalence of any depression and major depression in this study were 20% and 7% respectively. The low prevalence results in low sensitivity, high specificity, low positive predictive value and high negative predictive value [79]. The cutoff score for poststroke depression might change in case of higher prevalence. Secondly, the participants recruited aged 45 years old and above which would not be able to generalize to the younger ones. Thirdly, only participants who could communicate were recruited. We realized that stroke patients who cannot communicate would likely be more depressed. However, the mood assessment scale for the non-communicable ones are different. Fourthly, as our study was conducted in the Department of Rehabilitation Medicine of a tertiary hospital, stroke patients whom were admitted mostly had moderate disability. Therefore, the generalizability was limited.

Caution should be exercised that, although the PHQ-9 is a valid and useful screening tool for PSD, NPV of all the cutoff score levels are higher than PPV. As for

the study of a meta-analysis of diagnostic validity studies of poststroke major depression [13], PHQ-9 had good rule out clinical utility but poor rule in clinical utility. In clinical practice this means that the positive screening results should be followed by a thorough clinical assessment, diagnostic interview or repeat screen.

In summary the Thai version of the PHQ-9 had good validity and acceptable reliability for screening PSD with a recommended cutoff score six or greater. Due to the low PPV in our study, further clinical assessment is recommended if a test result is positive. Because the categorical algorithm of the PHQ-9 revealed low sensitivity, it is less suitable for screening purpose.

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VITA

NAME	Piyapat Dajpratham
DATE OF BIRTH	12 July 1968
PLACE OF BIRTH	Bangkok, Thailand
INSTITUTIONS ATTENDED	1992: Medical Degree, Faculty of Medicine Siriraj Hospital, Mahidol University 1997: Diplomat Thai board of Physical Medicine and Rehabilitation, The Royal College of Thai Physiatrist. 1998-1999: Clinical Fellow in Neurorehabilitation & Geriatric Rehabilitation, Royal Melbourne Hospital, Northwestern Health Care Network, University of Melbourne, Australia
HOME ADDRESS	24/28 Chuancheun Regent Village, Sathorn-Rachapreuk Road, Bangramard, Taling-Chan, Bangkok 10170
PUBLICATION	1. Tantibhaedhyangkul P, Kuptniratsaikul V, Tosayanonda O. The study of the prevalence and the correlation factors of depression in stroke patients. J Thai Rehabil 1997;7:64-71 2. Harnphadunkit K. Senanarong V. Tantibhaedhyangkul P. Rapidly Reversible Generalised Weakness and Slow Nerve Conduction Velocity: a case report Siriraj Hosp Gaz. Aug 1998;50Z8X:781-4 3. Tantibhaedhyangkul P, Kuptniratsaikul V, Tosayanonda O. Grip and quadriceps strength: normative value in the Thai population. Siriraj Hosp Gaz 2001; 53(4):224-30 4. Yanyong I, Patcharawiwatpong P. stress in the

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