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# SMIJ

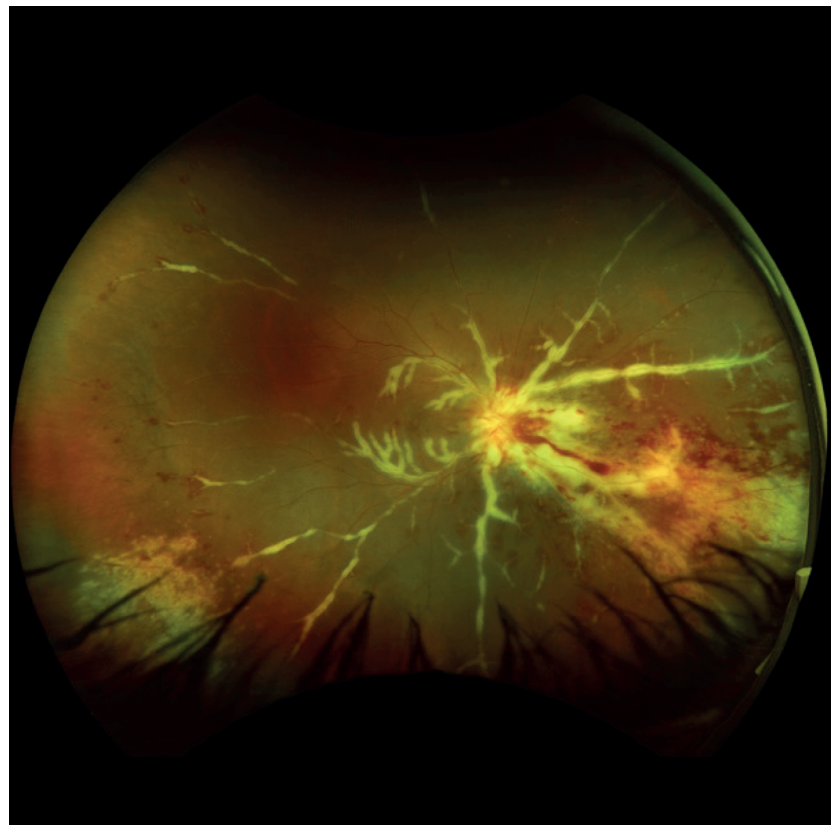
## Siriraj Medical Journal

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**MONTHLY**

*By Sutasinee Boonsopon, et al.*

**REVIEW ARTICLE**  
**ORIGINAL ARTICLE**



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# Retinal Vasculitis: Fundamentals, Diagnostics, and Management

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## ABSTRACT

Retinal vasculitis is inflammation of retinal blood vessels typically resulting from infection or immune-mediated inflammatory processes. It may present as isolated ocular inflammation or as a part of severe or potentially fatal systemic disease. Ocular complications of retinal vasculitis include cystoid macular edema, neovascularization, tractional retinal detachment, and vitreous hemorrhage, which all greatly threaten vision. Multimodal imaging and thorough systemic investigations are the main tools for making a precise diagnosis, which aids in predicting disease prognosis and visual outcome as well as preserving a patient's vision and possibly their life. This review aims to discuss the current understanding of retinal vasculitis as well as current diagnostic tools and treatments.

**Keywords:** Retinal vasculitis; retinal vascular inflammation; posterior uveitis (Siriraj Med J 2021; 73: 493-500)

## INTRODUCTION

Retinal vasculitis (RV) is a sight-threatening condition that is characterized by inflammation of the retinal blood vessels. This condition is defined by ophthalmologists as impairment of the blood-retina barrier resulting from inflammatory processes. Diagnosis of RV can be primarily made by finding sheathed retinal vessels or perivascular exudate during dilated fundus examination. However, this condition should be evaluated by and can be confirmed with fluorescein fundus angiography. RV may be idiopathic or may be a manifestation of systemic inflammatory diseases, such as Adamantiades-Behcet's disease (ABD), granulomatosis with polyangiitis (GPA), and systemic lupus erythematosus (SLE). RV can also occur as a result of infection, such as viral acute retinal necrosis, ocular toxoplasmosis, and ocular tuberculosis. It may seldomly occur in the setting of a malignant masquerade syndrome. Multimodal imaging and a

thorough systemic work up are important when trying to uncover the etiology of the inflammation as it may help to improve prognosis and visual outcome, as well as reduce secondary complications such as retinal and macular ischemia, cystoid macular edema (CME), and secondary glaucoma. These are associated with poor visual outcome.<sup>1-3</sup> This review focuses first on the fundamentals of retinal vascular inflammation, and then aims to further discuss newer diagnostic tools and treatments.

## Epidemiology

Studies have shown RV to be found in 6-15% of patients with uveitis.<sup>4,5</sup> Ethnicity may be responsible for differences in the incidence and prevalence of RV worldwide. Each specific disease related to RV was also found to have a different incidence and prevalence, such as in ABD, which was found in 20-420/100,000 population in Turkey, in 80/100,000 population in Iran,

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and in 0.64/100,000 population in the United Kingdom, and among these ABD patients, uveitis presented with or without RV in 45-90%.<sup>6</sup> The incidence of SLE also differs among regions, ranging from 0.3 to 8.7/100,000 population/year, and the prevalence ranged from 1.1 to 534.9/100,000 population. The highest incidence of SLE was found in the USA, the Caribbean, Brazil, and Sweden.<sup>7</sup> The incidence of retinal involvement in SLE was 7-26%.<sup>8</sup> Regarding infectious etiology, ocular tuberculosis (TB) is the predominant culprit in Asia. The incidence of ocular TB in Australia was 0.77/100,000, and 11% of those patients presented with RV.<sup>7</sup> In India, the reported incidence of ocular TB was as high as 9.86% among all types of uveitis.<sup>9</sup>

### Pathogenesis

The mechanisms of the development of RV are not fully understood. Type III (immune complex-mediated) hypersensitivity is generally believed to be responsible for the development of RV,<sup>3</sup> but humoral and cell-mediated immunity may also play an important role. Immunohistochemical analysis of enucleated eyes from ABD and sarcoidosis patients revealed T-helper lymphocytes comprise most of the involved cells. Major histocompatibility complex (MHC) I and II antigens and the cell adhesion molecules intercellular adhesion molecule-1 (ICAM-1), E-Selectin, vascular cell adhesion protein-1 (VCAM-1), lymphocyte function-associated antigen (LFA)-1a, and LFA-1b were found on vascular endothelial cells.<sup>1</sup> In animal models and following systemic inoculation and induction of experimental autoimmune uveitis, retinal S antigen was found to play an important role in immune-mediated uveitis and RV.<sup>10-12</sup> Many studies also reported a genetic predisposition to be related to retinal vascular inflammation. Previous reports described a condition called autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) as being related to the development of intraocular inflammation that results from mutations in calcium-dependent cysteine protease (Calpain 5).<sup>13</sup> Some mutations may associate with predisposition to specific diseases, such as three prime repair exonuclease 1 (TREX1) in SLE<sup>14</sup>, and tumor necrosis factor alpha-induced protein 3 (TNFAIP3) in ABD-like disease.<sup>15</sup>

### Classification

Retinal vascular inflammation can be classified as either occlusive or non-occlusive depending on the mechanisms of inflammation. When vascular occlusion develops, the affected area of the retina and/or macula may become ischemic. Neovascularization (NV) generally develops

when there is a significant area of retinal ischemia, and NV may eventually lead to fibrovascular traction and/or vitreous hemorrhage. RV can also be categorized by the affected retinal blood vessels into periarteriolitis, periphlebitis, or combined arteriolitis and phlebitis. Also, a pattern of small vessel leakage affecting retina where the vasculature is not clearly visible may be considered capillaritis. The usefulness of identifying the involved retinal blood vessels is to narrow the differential diagnosis in hopes of unveiling the etiology of inflammation. Causes of RV associated with different types of retinal blood vessel involvement are shown in [Table 1](#),<sup>2</sup> which can be categorized into systemic autoimmune-related RV, infectious-related RV, isolated ocular inflammation with known etiology, and idiopathic RV.<sup>1</sup> The etiologies of RV categorized by systemic disease association are shown in [Table 2](#).

### Clinical findings

The most common ocular symptom of patients with RV is blurred vision. Additional symptoms depend on several factors, including extension of involved retinal blood vessels, associated findings, and existing complications, such as vitritis, vitreous hemorrhage, CME, retinal or macular ischemia, and papillitis. Patients may also experience photopsia, floaters, metamorphopsia, and either focal or diffuse scotomas. The location of inflammation may be limited to the posterior segment of the eye as posterior uveitis, or as panocular inflammation in more severe cases. On dilated fundus examination, one may find perivascular infiltration, vascular cuffing, or vascular sheathing. In SLE (with or without antiphospholipid thrombosis), presentation with classic RV with perivascular infiltration was less common than presentation with features of occlusive vasculopathy.<sup>7</sup> Exudates that result from vascular leakage are occasionally observed. Cotton wool spots representing retinal nerve fiber layer infarction can be seen in occlusive retinal arteriolitis. Late presentations of retinal vascular occlusion include retinal telangiectasia, neovascularization, tractional retinal detachment, rubeosis iridis, neovascular glaucoma, and optic disc atrophy.<sup>16</sup>

### Diseases mimicking retinal vasculitis

Non-inflammatory conditions, such as diabetic retinopathy and Coats' disease, can sometimes be confused with RV because of extensive vascular leakage. Significant amounts of perivascular exudates along retinal blood vessels may mislead the diagnosis. Sheathing of retinal blood vessels, which can be found in RV, can also be found in other conditions, such as retinal vein or artery occlusion due to other causes.<sup>17-19</sup> The presence of inflammatory signs

**TABLE 1.** Retinal vasculitis categorized by type of retinal blood vessel involvement.

Arteriolitis	Periphelebitis	Combined arteriolitis and periphelebitis
Acute retinal necrosis	Ocular tuberculosis	Crohn's disease
Cat-scratch	Sarcoidosis	Granulomatosis with polyangiitis
Ocular syphilis	Birdshot chorioretinopathy	Relapsing polychondritis
Ocular toxoplasmosis	Pars planitis	Multiple sclerosis
Idiopathic retinal vasculitis, aneurysm and neuroretinitis		Adamantiades-Behcet's disease
Polyarteritis nodosa		
Systemic lupus erythematosus ± antiphospholipid syndrome		

**TABLE 2.** Differential diagnosis of retinal vasculitis according to etiology of inflammation.

Immune-related		Infectious	Masquerade
Systemic	Ocular		
Adamantiades-Behcet's disease	Birdshot chorioretinopathy	Acute retinal necrosis	Leukemia
HLA*-B27 related/ seronegative spondyloarthropathy	Pars planitis	Cytomegalovirus retinitis	Lymphoma
Granulomatosis with polyangiitis	Idiopathic retinal vasculitis, aneurysm and neuroretinitis	Syphilis	
Multiple sclerosis		Toxoplasmosis	
Polyarteritis nodosa		Tuberculosis	
Sarcoidosis			
Systemic lupus erythematosus			

\*HLA = human leukocyte antigen

and associated findings of uveitis, such as inflammatory cells and keratic precipitate, support an inflammatory origin.

### Multimodal imaging

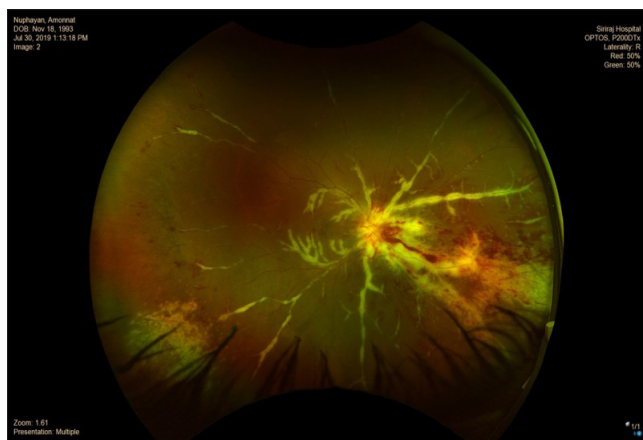
#### *Fundus photography*

Location and extension of retinal and choroidal inflammation can sometimes be documented using fundus photography, and images from each follow-up visit can be used for treatment monitoring except for the patients with subclinical RV. Ultrawide field images facilitate visualization of a wider field of peripheral retina.

**Fig 1** shows an ultrawide field image of cytomegalovirus retinitis with frosted branch angiitis.

#### *Fundus fluorescein angiography (FFA)*

FFA is the gold standard method for diagnosis of RV. It can also be used as a tool for treatment monitoring, for complication detection, and (in some instances) for evaluating disease prognosis. FFA can reveal non-perfusion areas of ischemic retina in patients with occlusive RV, and showcase damage induced in vital sections of retina crucial for fine vision (i.e. macula). Patients with a large area of retinal ischemia and/or macular



**Fig 1.** Ultrawide field image of cytomegalovirus retinitis.

A 27-year-old polymyositis patient presented with blurred vision. Fundus photo of the right eye shows a classic presentation of cytomegalovirus retinitis. Whitish fluffy retinal infiltrates, optic disc infiltrates, intraretinal hemorrhages, peripheral granular retinal infiltrates and perivascular infiltrates are presented.

ischemia generally have poor visual outcome.<sup>20</sup> FFA can also detect subclinical RV in patients thought to be otherwise clinically inactive. FFA findings in patients with RV include retinal vascular leakage/staining, optic disc leakage/staining, macular leakage, capillary drop out, vascular occlusion, and blockage.<sup>21</sup> Ultrawide field FFA images are preferred to conventional FFA method due to improved detection of peripheral retinal lesions.<sup>22-24</sup> Figs 2 & 3 show fundus photos and fundus fluorescein angiography of RV patients.

### Indocyanine green angiography (ICG)

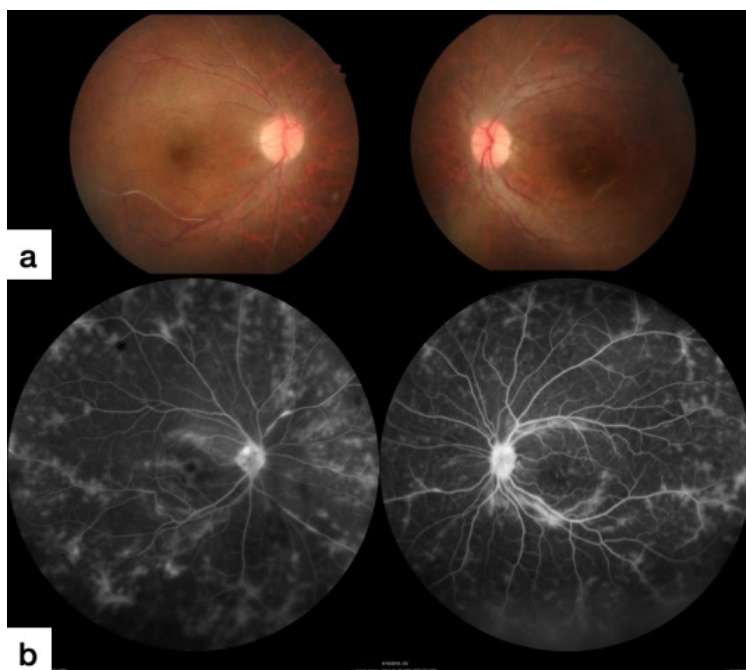
ICG is generally used to detect abnormalities in choroidal vasculature. In RV, combined FFA and ICG would be beneficial when inflammation involves both the retina and choroid, such as in Vogt-Koyanagi-Harada disease and birdshot chorioretinopathy (BSCR). Examples of choroidal abnormalities related to RV include patchy hypo-cyanescence, fuzzy choroidal vasculature, and late hyper-cyanescence of choroidal vasculature.<sup>21</sup>

### Adaptive optics (AO) imaging

AO, which was previously developed for astronomical application, is a non-invasive and feasible imaging system. AO imaging in RV may reveal blood vessel wall thickening from inflammatory cell deposition. AO can also be used for follow-up imaging, with more defined vessel lumens indicating less inflammatory cell deposition. Other advantages of AO over FFA in addition to its non-invasive nature include its ability to detect subclinical RV earlier than detected by FFA.<sup>25</sup> Current challenges associated with the use of AO imaging in this setting include media opacity, peripheral RV, and pseudophakia. Also, this is not readily available in a clinical setting.

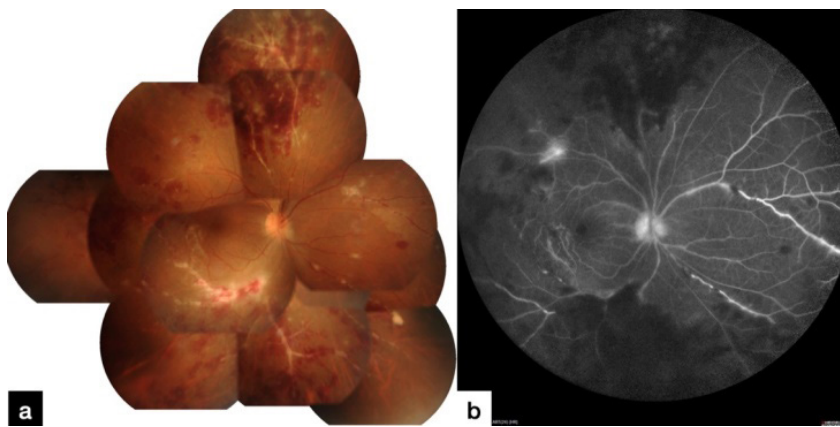
### Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA)

Structural abnormalities related to RV can be identified by OCT. Focal retinal thickening with loss of normal retinal lamination that suggested retinal damage has been reported.<sup>26</sup> Kyrieleis plaques in ocular toxoplasmosis



**Fig 2.** Fundus photo and fundus fluorescein angiography of bilateral retinal vasculitis with Behcet's disease.

Fundus photo of a 36-year-old male, Behcet's disease patient shows retinal vascular sheathing in both eyes (a). Fundus fluorescein angiogram demonstrates more obvious vascular leakage, optic disc leakage in both eyes and macular leakage in the right eye (b) compare to fundus photo.



**Fig 3.** Fundus photo and fundus fluorescein angiography of ocular tuberculosis.

A 31-year-old male patient was diagnosed with ocular tuberculosis. Interferon gamma releasing assay was 2.1, Mantoux test was 8 mm, chest radiograph showed no pulmonary infiltration. Dilated fundus examination showed retinal periphlebitis with secondary branch vein occlusion (a). Fundus fluorescein angiogram demonstrates optic disc leakage, vascular leakage, and capillary drop-out (b).

and cytomegalovirus retinitis can be observed on OCT as hyper-reflectivity of blood vessel walls.<sup>21</sup> CME is clearly identified on OCT. Enhanced-depth imaging OCT yields more detail about choroidal thickness, including suprachoroidal fluid.<sup>3</sup> Microvascular flow of the retina and choroid can be detected by OCTA. Moreover, OCTA can identify microvascular occlusion without injection of dye. Unfortunately, the stage of inflammation (active vs. inactive) cannot be determined. Another limitation of OCT and OCTA is its limited field of view.<sup>21</sup>

### Diagnostic testing

The causes of RV vary. Laboratory investigations and imaging should be based on clinical presentations. As such, the pattern of investigation should be based on each patient's clinical presentation and provisional diagnosis. A summary of common diagnostic studies in RV is shown in [Table 3](#).

### Treatment modalities

Treatment for RV is generally dependent on the etiology of underlying disease, if any. In infectious RV, specific antimicrobial therapy is indicated. In non-infectious RV, treatment aims to control inflammation to regain or at least stabilize vision and to prevent further complications.

### Systemic corticosteroids

The initial mainstay therapy for non-infectious RV, and particularly in bilateral cases, is systemic corticosteroids due to their effectiveness and rapid response. High-dose prednisolone is generally prescribed at the initial stage. Both short term and long term unwanted and widely recognized side effects of high-dose corticosteroids are at times unavoidable, however an absolute certainty when used chronically. In patients who require long-term treatment or who suffer from serious systemic

autoimmune diseases, immunomodulatory therapy (IMT) or biologics can be considered to reduce the side effects of corticosteroids and to achieve better control of inflammation.

### Regional corticosteroids

Regional steroids, such as trans-septal/sub-Tenon's/intravitreal triamcinolone acetonide (TA) injection, can be considered as an adjunctive therapy for RV with or without CME. However, since the duration of TA injection treatment is short, the use of TA injection alone is not recommended. Intravitreal dexamethasone implant is thought by many to produce a slightly more sustained effect than TA<sup>27,28</sup> but was comparable to intravitreal triamcinolone injection at 8 weeks in terms of decreasing central subfield thickness of uveitic macular edema.<sup>29,30</sup> The available fluocinolone acetonide implants convey an even longer treatment duration making them more reasonable for non-infectious RV. In these therapies, systemic side effects are often avoided, while local side effects, including complicated cataract and steroid-induced glaucoma, are often still seen.<sup>27,28,31-33</sup>

### Immunomodulatory therapy

IMT is generally required when patients become steroid-dependent, and they require long-term systemic steroids to control inflammation. Prednisolone of any duration, but particularly more than 7.5 mg/day is considered risky by many if used chronically. Studies have shown that the use of prednisone 5 mg daily for only 8 weeks in post-menopausal women was associated with the potential development of steroid-related complication, specifically decreased indices of bone formation.<sup>34</sup> Guidelines created by Jabs *et al.* recommend prescription of steroid-sparing agents when patients require chronic use of prednisolone greater than 10 mg/day.<sup>35</sup> The Ocular Immunology and Uveitis Foundation recommended to administer IMT

**TABLE 3.** Investigations related to retinal vasculitis.

Basic investigations	Specific investigations		Imaging
	Infection	Inflammation	
Complete blood count	Anti-HIV*	Antibody blood tests Antinuclear antibody ANCA <sup>†</sup>	Chest radiograph/ computerized tomography
Blood chemistries	Interferon-gamma releasing assay for tuberculosis/ T-Spot TB	Anti-cardiolipin Anti-b2 glycoprotein Lupus anticoagulant Anti-Smith antibody	Brain computerized tomography/ magnetic resonance imaging
Blood sugar	Toxoplasma serology	Anti-SSA <sup>‡</sup> /anti-SSB <sup>§</sup>	Ultrasound
Urinalysis	Treponemal/ non-treponemal testing	Complement/immune complex studies	Gallium scan
	Mantoux test	C-reactive protein	
	Polymerase chain reaction for Herpesviridae (ocular specimen)	Erythrocyte sedimentation rate	
		HLA <sup>  </sup> testing	
	CSF <sup>¶</sup> analysis Vitreous biopsy		

\*HIV = human immunodeficiency virus, <sup>†</sup>ANCA = antineutrophilic cytoplasmic antibody, <sup>‡</sup>SSA = Sjogren's syndrome A antibody, <sup>§</sup>SSB = Sjogren's syndrome B antibody, <sup>||</sup>HLA = human leukocyte antigen, <sup>¶</sup>CSF = cerebrospinal fluid

when corticosteroid therapy is required for longer than 3 months or a dose of more than 5 mg/day is required to control inflammation.<sup>36</sup> Treatment with corticosteroids alone is not recommended in certain diseases, such as ABD, GPA, and BSCR, since inflammation is generally severe and requires long-term therapy.

Favored types of IMT include antimetabolite therapy using methotrexate, azathioprine, and mycophenolate mofetil, or the interleukin-2 inhibitor cyclosporine, though the latter is seldom used as monotherapy. These are typically well tolerated and have a relatively low risk profile. Alkylating agents, such as cyclophosphamide and chlorambucil, have use, especially in more severe disease or inflammation that is recalcitrant to approaches associated with less risk, but are usually relied upon later due to their potential complications.<sup>1,37,38</sup>

### Biologics

ABD is a good example of RV that responds well to biologics. Anti-tumor necrosis factor alpha (TNF- $\alpha$ )

medications (i.e., infliximab and adalimumab) are recommended as a first-line therapy for active ABD with ocular inflammation by the American Uveitis Society.<sup>39</sup> The VISUAL I and VISUAL II clinical trials reported favorable results of adalimumab treatment in non-infectious uveitis patients.<sup>40</sup> Other biologics in addition to anti-TNF- $\alpha$  agents have been used to treat RV, including rituximab (anti-CD20), daclizumab (anti-CD25), and tocilizumab (IL-6R inhibitor).<sup>3,20,41</sup>

### Anti-vascular endothelial growth factor (anti-VEGF)

NV and CME are two main complications found in RV that often require intravitreal anti-VEGF injection, and this treatment can be used in both infectious and non-infectious RV. When anti-VEGF is considered, it is sometimes used in combination with panretinal photocoagulation (PRP) for prevention or treatment of ischemic RV.<sup>37</sup> A systematic review of 4 studies comparing intravitreal triamcinolone and intravitreal bevacizumab revealed no significant difference in visual acuity at

any time point after the treatment of uveitic macular edema. One study showed significant difference in central macular thickness with potential favorable benefit with intravitreal triamcinolone.<sup>42</sup>

### **Laser photocoagulation**

NV, tractional retinal detachment, and vitreous hemorrhage are more severe complications that are frequently found in occlusive RV. The mainstay therapy for managing these complications associated with widespread and irreversible retinal ischemia is PRP. Unlike ischemic central retinal vein occlusion, there is no consensus regarding the appropriate timing of PRP in occlusive RV. Rouvas *et al.* proposed PRP when there is retinal ischemia in more than 2 quadrants in idiopathic RV, aneurysm, and neuroretinitis (IRVAN).<sup>43</sup> Aggressive PRP may be beneficial in preventing these complications.<sup>1,37</sup>

### **Complications and prognosis**

Chronic CME, macular ischemia, secondary glaucoma, and optic disc atrophy are leading causes of permanent visual damage.<sup>2,4</sup> Occlusive RV tends to develop complications, such as epiretinal membrane, CME, and NV, that are more likely to associate with poor visual outcome.<sup>2,20</sup> Smoking may associate with vascular leakage and CME, but the precise association is unknown.<sup>44</sup>

## **CONCLUSION**

RV is a severe and vision threatening problem that is one of the presenting features of many specific diseases and can be very difficult to treat. Appropriate investigations and management should be tailored to the needs of each patient. Understanding of the presentation of RV and its possible systemic associations will improve diagnosis, treatment, and outcomes.

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### **List of abbreviations**

ABD, Adamantiades-Behcet's disease

ADNIV, autosomal dominant neovascular inflammatory

vitreoretinopathy

Anti-TNF $\alpha$ , anti-tumor necrosis factor alpha

Anti-VEGF, anti-vascular endothelial growth factor

AO, adaptive optics

BSCR, birdshot chorioretinopathy

Calpain 5, calcium-dependent cysteine protease

CME, cystoid macular edema

FFA, fundus fluorescein angiography

GPA, granulomatosis with polyangiitis

ICG, indocyanine green angiography

IMT, immunomodulatory therapy

MHC, major histocompatibility complex

NV, neovascularization

OCT, optical coherence tomography

OCTA, optical coherence tomography angiography

RV, retinal vasculitis

SLE, systemic lupus erythematosus

TA, triamcinolone acetonide

TB, tuberculosis

TNFAIP3, tumor necrosis factor alpha-induced protein 3

TREX1, three prime repair exonuclease 1

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# Antimicrobial Resistance Patterns Amid Community-Acquired Uropathogens in Outpatient Settings of a Tertiary Care Hospital in Thailand

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## ABSTRACT

**Objective:** To document the distribution of antimicrobial resistance patterns of community-acquired uropathogens. **Materials and Methods:** Outpatient microbiology data of urine culture results in Songklanagarind Hospital between January to December 2019 were reviewed.

**Results:** This study included 649 episodes of positive urine cultures in 598 patients, in which 80.7% were symptomatic cases. The elderly (median  $63 \pm \text{IQR } 26$  years) showed high prevalence of urinary tract infections in this study, for which nearly 80% of all samples were female. The three most common uropathogens identified were: *Escherichia coli* (*E. coli*) (69.6%), *Klebsiella pneumoniae* (9.5%) and *Staphylococcus saprophyticus* (4.9%). *E. coli* were highly resistant to ciprofloxacin (49.0%), cotrimoxazole (41.2%) and ceftriaxone (20.6%), but had a low level of resistance to fosfomycin (0%), and amikacin (0.4%).

**Conclusion:** The antimicrobial resistance pattern of *E. coli* was high for commonly antimicrobial agents used in outpatients; especially quinolone, cotrimoxazole and cephalosporin. However, due to low resistance levels, fosfomycin and amikacin could be considered as effective treatment options for community acquired UTIs in our study.

**Keywords:** Community; urinary tract infection; antibiotic resistance (Siriraj Med J 2021; 73: 501-509)

## INTRODUCTION

Urinary tract infections (UTIs) are amongst one of the common infectious conditions in a primary setting.<sup>1</sup> The main cause of an UTI is bacterial infection, for which 95% of UTI cases, in primary settings, prescribe antibiotics.<sup>2</sup> Frequently, the therapy for an UTI are initiated empirically before the results of urine culture and antibiotic susceptibilities are received. Consequently, drug-resistance may increase, because of frequent and inappropriate use of antibiotics.

The Trend of antibiotic resistance is increasing around the world, with misuse or overuse of antibiotics seemingly being the primary driver of this problem.<sup>3</sup>

In a previous study in Songklanagarind Hospital, 20084, *Escherichia coli* (*E. coli*) isolated from outpatients with UTIs were resistant to norfloxacin (41.2%), ceftriaxone (16.4%), and cotrimoxazole (49.3%).<sup>4</sup> However, resistance patterns are ever changing over time, and vary in different regions. Therefore, it is necessary to periodically review these changes, for enabling better decision making in antimicrobial selection.

## MATERIALS AND METHODS

### Setting

We conducted a retrospective cohort study in Songklanagarind Hospital, which is an 860-bed tertiary

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care facility, serving as a medical school with residency training and as a referral center for the South of Thailand.

### Inclusion criteria

- Patients above the age of 15 years who visited the Outpatient Department (OPD) and Emergency Department (ED) from 1 January 2019 to 31 December 2019.
- Single bacterial species with significant bacteriuria ( $\geq 10^5$  cfu/ml).
- A clean catch mid-stream urine sample.

### Exclusion criteria

- Patients with suspected healthcare issues associated with UTIs; following the adapted Friedman criteria<sup>5</sup>, were excluded.
  - (a) An indwelling urinary catheter in place at the time or within 48 hours before urine collection.
  - (b) Prior hospital admissions within 90 days.
  - (c) Regular dialysis or received intravenous chemotherapy within 30 days.
  - (d) Receiving intravenous therapy, wound care, or nursing care at home within 30 days.
  - (e) Receiving any urinary procedure within 30 days.
- Patients with follow up clinical symptoms after treatment, and repeat urine cultures.

All positive aerobic urine cultures were identified by the Hospital Information System (HIS). In total there were 1,013 samples from patients presenting with significantly positive urine cultures at the OPD and ED. From this 295 samples were excluded, due to suspected healthcare associated UTI, and 69 samples were excluded due to repeat or follow up urine cultures in the same conditions. Finally, there were 649 samples analyzed in this study.

### Definitions

Uncomplicated UTI is identified as a UTI with no relevant functional or anatomical anomalies in the urinary tract or comorbidity.<sup>6</sup> Complicated UTI is identified as a UTI with one of the following characteristics: male gender, pregnancy, diabetes mellitus, abnormal urological structure, and immunosuppression.<sup>6</sup>

Extended spectrum beta-lactamases (ESBLs) are defined as enzymes produced by certain bacteria that are able to hydrolyze extended spectrum cephalosporin.<sup>7</sup>

### Data collection:

Clinical information was extracted from medical databases; including: patient age, gender, medical condition, clinical symptoms of urinary tract infection, risk factors of complicated UTIs, the uropathogens isolate and antibiotic

susceptibility. The data was collected via Google form and entered into Microsoft Excel for analysis.

### Microbiological studies

#### Urine collection and processing

Clean-catch midstream urine specimens were processed within 2 hours after collection. In the laboratory, the sample is plated on Mac Conkey medium and Blood agar, by using a standard loop (0.001-millimeter diameter loop). The cultures plated were incubated at  $35 \pm 2$  C, for 18-24 hours. For this study, significant bacteriuria was identified as a culture of a single bacterial species with colony count  $\geq 10^5$  cfu/ml. The uropathogens isolated were identified by standard biomedical methods, and susceptibility tests were interpreted corresponding to the Clinical and Laboratory Standard Institute 2019 (CLSI).<sup>8</sup>

#### Susceptibility testing

The antibiotic discs used were for amikacin, cefotaxime, ceftazidime, cefuroxime, cotrimoxazole, imipenem, tazocin, ampicillin, cefoxitin, ceftriaxone, cephalothin, gentamicin, norfloxacin and meropenem. Extended-spectrum  $\beta$ -lactamases (ESBLs) were interpreted by using zone diameter breakpoints. The CLSI interpretation breakpoint for fosfomycin sensitivity is at least 16 mm, intermediate is between 13-15 mm and resistant is at most 14 mm. Disc diffusion is required for fosfomycin Antimicrobial Susceptibility Testing (AST), and was performed according to the CLSI recommendations.<sup>8</sup>

### Data analysis:

Descriptive statistical analysis was performed using Microsoft Excel 2010. Discrete variables were expressed as percentages and proportions. The 95% confidence interval was derived from exact binomial statistic calculation.

## RESULTS

All positive aerobic urine cultures were identified by HIS, with 1,013 samples from patients presenting with a significantly positive urine. From this 295 samples were excluded due to suspected healthcare associated UTIs; additionally, 69 samples were excluded due to repeat or follow up urine cultures. Finally, there were 649 samples analyzed in this study.

### Sample characteristics

This included; 125 (19.3%) asymptomatic bacteriuria and 524 (80.7%) symptomatic UTIs. Among the symptomatic cases, which were classified to be complicated UTI (57.4%) and uncomplicated UTI (42.6%). (Table 1)

**TABLE 1.** Demographic data of patients presenting with culture-positive urine in the study.

Variable	N (%)		
	Total N = 649	Asymptomatic bacteriuria N = 125	Symptomatic UTI N = 524
<b>Sex</b>			
Female	512 (79%)	91 (72.8%)	421 (80.3%)
Male	137 (21%)	34 (27.2%)	103 (19.7%)
<b>Age</b>			
Overall Age, Years (Median ± IQR)	63 ± 26	68 ± 22	62 ± 25
15- 30	64 (9.9%)	7 (5.6%)	64 (12.2%)
31 – 45	59 (9.1%)	10 (8%)	59 (11.3%)
46 -60	125 (19.3%)	26 (20.8%)	125 (23.9%)
>60	401 (61.8%)	82 (65.6%)	276 (52.7%)
<b>Medical conditions</b>			
Diabetes mellitus	183 (28%)	48 (38.4%)	135 (25.8%)
Hypertension	222 (34%)	48 (38.4%)	174 (33.5%)
Asthma	18 (3%)	2 (1.6%)	16 (3.1%)
COPD	9 (1%)	0 (0%)	9 (1.7%)
Ischemic heart disease	37 (6%)	6 (4.8%)	31 (5.9%)
Thyroid disease	28 (4%)	7 (5.6%)	21 (4%)
Gout	19 (3%)	6 (4.8%)	13 (2.5%)
Cerebrovascular disease	28 (4%)	5 (4%)	23 (4.4%)
Chronic kidney disease	80 (12%)	32 (25.6%)	48 (9.2%)

**Abbreviations:** N: number, UTI: urinary tract infection, IQR: interquartile range

Clinical symptoms are shown in [Table 2](#). More than half of the patients rated dysuria as the most frequent symptom, in both uncomplicated and complicated UTIs.

#### Distribution of uropathogens and antibiotic resistance patterns

[Table 3](#) shows the frequency and distribution of uropathogens in related types of UTIs, in which *E. coli* was the main causative uropathogens in each group of UTI.

[Table 4](#) shows that the resistance to antibiotic of *E. coli* urinary isolates that were highly resistant to ampicillin

(73.2%), ciprofloxacin (49.0%) and norfloxacin (49.3 %).

The resistance pattern of *E. coli*, classified and analyzed by type of UTI, are shown in [Table 5](#). (uncomplicated UTI and complicated UTI) and [Table 6](#). (asymptomatic bacteriuria).

#### Asymptomatic bacteriuria

Among *E. coli* in asymptomatic bacteriuria (N= 87), high proportions of isolates were resistant to ampicillin (75.9%), norfloxacin (70.1%). However, the study found low resistance of *E. coli* to amikacin (1.1%), carbapenem groups (0%) and fosfomycin (0%).

**TABLE 2.** Clinical symptoms of patients with uncomplicated and complicated urinary tract infection.

Symptoms of UTIs	N (%)	
	Uncomplicated UTI	Complicated UTI
<b>Common in lower part UTI</b>		
Dysuria	140 (62.78%)	154 (51.16%)
Urgency	32 (14.32%)	49 (16.28%)
Increase frequency	53 (23.77%)	67 (22.26%)
Hematuria	38 (17.04%)	36 (11.96%)
Cloudy urine	32 (14.35%)	33 (10.96%)
Abdominal pain	111 (49.78%)	22 (7.31%)
<b>Common in upper part UTI</b>		
Fever (documented >38 or subjective)	69 (30.94%)	138 (45.85%)
Flank pain	29 (13%)	25 (8.31%)

**Abbreviations:** N: number, UTI: urinary tract infection, IQR: interquartile range

**TABLE 3.** Frequency and distribution of uropathogens in related type of urinary tract infections.

No Uropathogens	Asymptomatic bacteriuria N= 125		Uncomplicated UTI N= 223		Complicated UTI N= 301		Total N= 649	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
1 <i>Escherichia coli</i>								
Non- ESBLs	66 (52.8%)	44.0 – 61.6	141 (63.2%)	57.0 – 69.5	152 (50.5%)	44.9 – 56.1	359 (55.3%)	51.5 – 59.2
ESBLs	21 (16.8%)	10.4 – 23.2	22 (9.9%)	6.3 – 13.9	50 (16.6%)	12.6 – 20.9	93 (14.3%)	11.7 – 17.1
2 <i>Klebsiella pneumoniae</i>								
Non- ESBLs	12 (9.6%)	4.8 – 15.2	16 (7.2%)	4.0 – 10.8	22 (7.3%)	4.7 – 10.3	50 (7.7%)	5.7 – 9.9
ESBLs	2 (1.6%)	0.0 – 4.0	2 (0.9%)	0.0 – 2.2	8 (2.7%)	1.0 – 4.7	12 (1.8%)	0.9 – 2.9
3 <i>Staphylococcus saprophyticus</i>	0 (0%)	NA	30 (13.5%)	9.0 – 17.9	2 (0.7%)	0.0 – 1.7	32 (4.9%)	3.4 – 6.6
4 <i>Enterococcus spp.</i>	9 (7.2%)	3.2 – 12.0	2 (0.9%)	0.0 – 2.2	16 (5.3%)	3.0 – 8.0	27 (4.2%)	2.6 – 5.7
5 <i>Proteus mirabilis</i>	3 (2.4%)	0.0 – 5.6	3 (1.3%)	0.0 – 3.1	12 (4.0%)	2.0 – 6.3	18 (2.8%)	1.5 – 4.2
6 <i>Streptococcus spp.</i>	4 (3.2%)	0.8 – 6.4	3 (1.3%)	0.0 – 3.1	10 (3.3%)	1.3 – 5.3	17 (2.6%)	1.5 – 3.9
7 <i>Staphylococcus aureus</i>	2 (1.6%)	0.0 – 4.0	1 (0.4%)	0.0 – 1.3	7 (2.3%)	0.7 – 4.3	10 (1.5%)	0.6 – 2.6
8 <i>Citrobacter spp.</i>	1 (0.8%)	0.0 – 2.4	2 (0.9%)	0.0 – 2.2	7 (2.3%)	0.7 – 4.3	10 (1.5%)	0.6 – 2.6
9. <i>Pseudomonas aeruginosa</i>	3 (2.4%)	0.0 – 5.6	0 (0%)	NA	3 (1%)	0.0 – 2.3	6 (0.9%)	0.3 – 1.7
10. Others	2 (1.6%)	0.0 – 4.0	1 (0.4%)	0.0 – 1.3	12 (4%)	2.0 – 6.3	15 (2.3%)	1.2 – 3.5

**TABLE 4.** The in vitro resistance pattern among *E. coli* urinary isolates from outpatient.

Antibiotic agent	Test (N)	Resistance N (%)	95% CI
<b>Aminoglycoside</b>			
Gentamicin	452	119 (26.3%)	22.3 – 30.5
Amikacin	452	2 (0.4%)	0.0 – 1.1
<b>Carbapenems</b>			
Imipenem	452	1 (0.2%)	0.0 – 0.7
Ertapenem	452	1 (0.2%)	0.0 – 0.7
Meropenem	421	0 (0%)	NA
<b>Cephalosporin</b>			
Cefuroxime	452	128 (28.3%)	24.1 – 32.5
Cefotaxime	452	93 (20.6%)	16.8 – 24.3
Ceftriaxone	452	93 (20.6%)	16.8 – 24.3
Ceftazidime	451	93 (20.6%)	16.9 – 24.4
<b>Cephamycin</b>			
Cefoxitin	448	15 (3.3%)	1.8 – 5.1
<b>Fluoroquinolones</b>			
Ciprofloxacin	447	219 (49.0%)	44.3 – 53.7
Norfloxacin	450	222 (49.3%)	44.7 – 54.0
<b>Folate pathway inhibitors</b>			
Cotrimoxazole	452	186 (41.2%)	36.7 – 45.8
<b>Penicillin</b>			
Ampicillin	452	331 (73.2%)	69.0 – 77.2
<b>Antipseudomonal penicillin+ beta lactamase inhibitor</b>			
Tazocin	449	2 (0.4%)	0.0 – 1.1
<b>Phosphonic acids</b>			
Fosfomycin	403	0 (0%)	NA
<b>Polymyxins</b>			
Colistin	451	0 (0%)	NA

## DISCUSSION

Out of the 649 significantly positive bacteriuria samples that were reviewed in this study, a large number of organisms were isolated from female patients in both groups. Older adults represented as a high proportion in this study (median of all age 63 years old, IQR 26 years). These findings were similar to a prior study conducted by Ho, in Singapore.<sup>9</sup> On the other hand, they were inconsistent with some studies conducted in rural areas in India, and a multicenter in Russia; wherein, younger to middle aged adults had the highest prevalence rate in

community acquired UTIs.<sup>10,11</sup> This is probably because of the difference of characteristics in our geography; in that tertiary hospitals might have more elderly patients with complex medical problems. In addition to the fact that young, adult females were frequently in the uncomplicated UTI group, which often leads to self-limiting and said group may prefer self-medication, or over the counter drug use. This could explain our low prevalence in young adult community acquired UTIs in our study.

**TABLE 5.** *E. coli* resistance to antibiotic among Uncomplicated and Complicated UTI.

Antibiotics	Uncomplicated UTI			Complicated UTI		
	Tests (N)	Resistance N (%)	95% CI	Tests (N)	Resistance N (%)	95% CI
<b>Aminoglycoside</b>						
Gentamicin	163	48 (29.4%)	22.7-36.8	202	50 (24.8%)	18.8-30.7
Amikacin	163	0 (0%)	NA	202	1 (0.5%)	0.0-1.5
<b>Carbapenems</b>						
Imipenem	163	0 (0%)	NA	202	1 (0.5%)	0.0-1.5
Ertapenem	163	0 (0%)	NA	202	1 (0.5%)	0.0-1.5
Meropenem	149	0 (0%)	NA	191	0 (0%)	0.0-1.5
<b>Cephalosporin</b>						
Cefuroxime	163	35 (21.5%)	15.3-28.2	202	64 (31.7%)	25.2-38.1
Cefotaxime	163	22 (13.5%)	8.6-19.0	202	49 (24.3%)	18.3-30.2
Ceftriaxone	163	22 (13.5%)	8.6-19.0	202	49 (24.3%)	18.3-30.2
Ceftazidime	162	22 (13.6%)	8.6-19.1	202	49 (24.3%)	18.3-30.2
<b>Cephamycin</b>						
Cefoxitin	162	5 (3.1%)	0.6-6.2	200	8 (4%)	1.5-7.0
<b>Fluoroquinolone</b>						
Ciprofloxacin	162	58 (35.8%)	28.4-43.2	201	103 (51.2%)	44.3-58.2
Norfloxacin	163	59 (36.2%)	28.8-43.6	200	102 (51%)	44.0-58.0
<b>Folate pathway inhibitors</b>						
Cotrimoxazole	163	69 (42.3%)	35.0-49.7	202	87 (43.1%)	36.1-50.0
<b>Penicillin</b>						
Ampicillin	163	123 (75.5%)	68.7-82.2	202	142 (70.3%)	63.9-76.7
<b>Antipseudomonal penicillin+ beta lactamase inhibitor</b>						
Tazocin	163	0 (0%)	NA	201	2 (1%)	0.0-2.5
<b>Phosphonic acids</b>						
Fosfomycin	147	0 (0%)	NA	179	0 (0%)	NA
<b>Polymyxins</b>						
Colistin	163	0 (0%)	NA	201	0 (0%)	NA

**Abbreviations:** N: number, UTI: urinary tract infection, 95%CI: 95% confidence interval, NA: not applicable

**TABLE 6.** *E. coli* resistance to antibiotic among asymptomatic bacteriuria.

Antibiotic agent	Test (N)	Resistance N (%)	95% CI
<b>Aminoglycoside</b>			
Gentamicin	87	21 (26.3%)	14.9-33.3
Amikacin	87	1 (1.1%)	0.0-3.4
<b>Carbapenems</b>			
Imipenem	87	0 (0%)	NA
Ertapenem	87	0 (0%)	NA
Meropenem	81	0 (0%)	NA
<b>Cephalosporin</b>			
Cefuroxime	87	29 (33.3%)	24.1-43.7
Cefotaxime	87	22 (25.3%)	16.1-34.5
Ceftriaxone	87	22 (25.3%)	16.1-34.5
Ceftazidime	87	22 (25.3%)	16.1-34.5
<b>Cephamycin</b>			
Cefoxitin	86	2 (2.3%)	0.0-5.8
<b>Fluoroquinolones</b>			
Ciprofloxacin	84	58 (69.0%)	59.5-78.6
Norfloxacin	87	61 (70.1%)	59.8-79.3
<b>Folate pathway inhibitors</b>			
Cotrimoxazole	87	30 (34.5%)	24.1-44.8
<b>Penicillin</b>			
Ampicillin	87	66 (75.9%)	66.7-85.1
<b>Antipseudomonal penicillin + beta lactamase inhibitor</b>			
Tazocin	85	0 (0%)	NA
<b>Phosphonic acids</b>			
Fosfomycin	77	0 (0%)	NA
<b>Polymyxins</b>			
Colistin	87	0 (0%)	NA

**Abbreviations:** N: number, UTI: urinary tract infection, 95%CI: 95% confidence interval, NA: not applicable

*E. coli* (69.9 %) was the main causative organism of community acquired UTIs in our study. This is in concordance to previous studies from other locations around the world<sup>4,9-10,12-16</sup>, which also showed *E. coli* as the commonest uropathogens isolated in community acquired UTI patients. Furthermore, the extend-spectrum beta-lactamase (ESBL) producing among *E. coli* was reported as 14.3% in this study, which was similar to the research in Lob et al. done in the USA and Canada 2014 (15%)<sup>12</sup>, and was lower than the prior study in Young Jun et al. conducted in Korea 2017. (23.3%).<sup>13</sup>

In 2019, the National Antimicrobial Resistant Surveillance in Thailand (NARST) 2019<sup>17</sup> reported that *E. coli* urinary isolates from outpatients were susceptible to ciprofloxacin 30.1%, cotrimoxazole 42.2%, ceftriaxone 59.7%, fosfomycin 98.8% and amikacin 98.8%, which meant that the resistance level to quinolone, cotrimoxazole and cephalosporin were higher when compared with our study. The interpretation of these information must be done with precaution because of difference in inclusion and exclusion criteria.

However, the in vitro resistance rates among *E. coli* urinary isolates in our study had changed when compared with a previous study in 2008<sup>4</sup>. The percentage of resistance was higher in norfloxacin (41.2% in 2008 and 49.3% in 2019) and ceftriaxone (16.4% in 2008 and 20.6% in 2019). On the other hand, the percentage of resistance was greatly declined in cotrimoxazole (56.7% in 2008 and 41.2% in 2019). This is attributable to a decrease in the popularity of prescribed cotrimoxazole and the fact that physicians have been prescribing new antibiotics instead. This result implies that antibiotic resistance can change over time, and the resistance of antibiotics commonly used in primary care is still high.

For uncomplicated UTIs, the prevalence of *E. coli* resistance to cotrimoxazole (42.3%) and ciprofloxacin (35.8%) was higher when compared with the study in Hongkong 2012<sup>14</sup> and Singapore 2015<sup>9</sup> (29-31.8% in cotrimoxazole and 23.4-29% in ciprofloxacin). The Infectious Diseases Society of America (IDSA) guidelines of 2010<sup>18</sup> suggest avoiding empirical specific antibiotics when local resistance among *E. coli* isolated is more than 20% in cotrimoxazole and 10% for quinolone. However, low resistance levels were detected to antibiotics; such as, fosfomycin 0%, carbapenem groups 0% and amikacin 0%, which were not easily obtained as over-the counter drugs, and are relatively expensive in cost compared to others.

For complicated UTI, *E. coli* reported resistance to ciprofloxacin at 51.2 %, and cotrimoxazole at 43.1% in our

results. These were higher when compared with a previous study conducted by Arslan in Turkey<sup>15</sup> and Klingenberg in Germany<sup>16</sup> (23.3% - 42% in cotrimoxazole, 15.6% - 38% in ciprofloxacin). In addition, the resistance rate of complicated UTIs seems to be higher when compared with uncomplicated groups; especially in quinolone and cephalosporin. So, the selection of empirical antibiotics in complicated UTI should be of more concern, due to probability of treatment failure from antibiotic resistance.

Low resistance levels were detected to antibiotics; such as, fosfomycin, carbapenem groups, and amikacin in both complicated and uncomplicated UTI in this study. The carbapenem groups were high board spectrum drugs that are not commonly used within the community, so fosfomycin and amikacin may be an effective treatment option for community acquired UTIs in our study. The major issue of aminoglycoside use concerns its toxicity such as decrease in renal function, ototoxicity. The rate of aminoglycoside-related nephrotoxicity is 8% to 14%<sup>19</sup>, which increases at higher doses, with prolonged therapy of 10 days or more, and with the co-administration of nephrotoxic agents.<sup>20</sup>

Strengths of our research include; an update to the distribution and antibiogram of community-acquired uropathogens in 2019. In addition, we classified and analyzed patients according to clinical presentation, and host risk factors (uncomplicated, complicated UTI and asymptomatic bacteriuria), for the aim of minimizing risk of bias between groups.

There were some limitations in our study, which warrant caution in interpreting the results. First, only tertiary-care hospital patients participated in the study. Consequently, our results, theoretically, may not be fully concluded to other populations receiving care in different facilities. Second, we did not perform the minimum inhibitory concentration (MIC) of potent antibiotics, for which we did not receive information of the lowest concentration of an antibiotic that inhibits visible growth.

Nevertheless, our findings demonstrate purely in-vitro antibiotic resistance, for which the efficacy may be quite different from those obtained in vivo. Thus, in addition to considering resistance patterns, the selection of empirical antibiotics should depend on other factors; such as, drug absorption and clearance, cost, and adverse events. Future prospective studies are needed to evaluate the in vivo outcomes and other risk factors of antibiotic resistance, in order to determine the most appropriate treatment for community UTIs.

**CONCLUSION**

The antimicrobial resistance patterns of uropathogens has changed overtime when compared to the previous study of 2008, with an increased resistance in commonly antimicrobial agent use; especially quinolone and cephalosporin. However, due to low resistance levels, fosfomycin and amikacin could be considered as an effective treatment option for community acquired UTIs in our study.

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**Conflicts of interest:** None to declare

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# Factors Influencing Severity and Impact of Symptoms in Patients with Upper Respiratory Tract Infection at Community Hospitals and Health-Promoting Hospitals

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## ABSTRACT

**Objective:** This study aimed to examine the factors that influence the severity and impact of symptoms in patients with an Upper Respiratory Tract Infection (URTI).

**Materials and Methods:** This study is a correlational predictive research. The sample size included 127 patients with URTI accessing care at community hospital and 5 health-promoting hospitals from February to June in 2020. Data were collected by using a questionnaire on demographic data, a questionnaire on health literacy, a questionnaire on self-care behavior in patients with URTI, the Nutrition Alert Form (NAF), the Pittsburgh Sleep Quality Index (PSQI), and the Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21). Subsequently, the data were analyzed using descriptive statistics and multiple regression analysis.

**Results:** The sample had a mean age of 45.30 years in which 73.2% were females; the average score of severity and impact of symptoms was minimal (Mean = 52.75 ± 22.85). The results from the multiple regression analysis indicated that all variables were able to co-predict the severity and impact of symptoms in patients with URTI as 25.9% ( $R^2 = .259$ ,  $F = 10.676$ ,  $p < .05$ ). Sleep quality and health literacy were the most statistically significant in predicting the severity and impact of symptoms in this sample group ( $\beta = .393$  and  $-.221$  respectively,  $p < .05$ ).

**Conclusion:** The findings suggested that nurses should encourage their patients to be aware of the importance of sleep, promoting a good sleep method and health literacy in order to make better decisions in their daily health.

**Keywords:** Upper respiratory tract infection; health literacy; nutritional status; sleep quality; severity and impact of symptoms (Siriraj Med J 2021; 73: 510-517)

## INTRODUCTION

Upper Respiratory Tract Infection (URTI), an acute infectious disease of the respiratory system, continues to be a significant public health issue and is becoming more significant each day. URTIs are mostly caused by viral and bacterial infections. On average, a common

cold occurs two to three times per year in adults and five to seven times per year in young children.<sup>1,2</sup> In addition, URTIs are both frequently encountered and inclined to increase in prevalence in elderly persons, particularly those with chronic illness, thereby leading to severe symptoms and multiple bacterial infections that spread

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and cause increased inflammation of the respiratory tract and lungs, resulting in respiratory failure and death.<sup>3</sup>

The statistics for the global population in 2017 reported that 17.1 million people had URTI and that the number was higher than 2007 by 11.5%<sup>4</sup>, whereas the mortality rate for URTI is as high as 9,100 people.<sup>5</sup> In the case of Thailand, URTIs are not classified as dangerous and does not require monitoring or pursuance according to the Communicable Diseases Act A.D. 2015. In Thailand, there are no statistical reports for this disease. At Thaimuang Chaipat Hospital, Phang-nga, Statistics of patients with URTI who received outpatient care services reveal that the number of patients is not only continually increasing with 1,901, 2,515 and 2,735 patients in 2017, 2018 and 2019, respectively, but it is also one of the top five diseases that patients sought services for at the hospital (Medical records of Thaimuang Chaipat Hospital, 2020). These statistics are also consistent with the statistics for the world population indicating the increasing numbers of patients. Therefore, URTI is a major problem that requires serious attention.

According to literature reviews, seasonal influenza is significantly correlated with clinical and economic burden and they are a cause of repeated and severe infections in persons with chronic illnesses, particularly in persons who are older than 65 years and pregnant women.<sup>3,6</sup> As a result, there are many factors related to the severity and impact of symptoms of respiratory tract infection (RTI) such as knowledge, sleep duration, exercise, BMI, etc. Furthermore, health literacy, self-care behaviors, nutritional status, and sleep quality may have significance for severity and impact of symptoms. However, to the best of my knowledge, there are no studies on these important factors.

Firstly, Health Literacy (HL) is the ability of an individual to access, understand, appraise, utilize and communicate health information to promote and maintain good health. HL correlates with health outcomes.<sup>7</sup> Furthermore, a poor HL might be an indicator of social inequality by contributing to increased likelihood of poor health, limiting proper health behaviors and practices of individuals.<sup>7,8</sup> British Columbia Health, found that people with URTI need to engage in appropriate self-care because doing so significantly contributes to alleviation of discomfort, reduction of severity and prevention of disease complications.<sup>9</sup> Moreover, malnutrition conditions can cause changes to immune system response and may increase infection risks, thereby increasing RTI risks.<sup>10</sup> Another important factor is sleep quality, for example, if deep sleep is achieved, the body and mind will be prepared for engaging in daily activities with improved

health and improved quality of life. Extensive reduction in sleep and responses to stress can contribute to increased proinflammatory cytokines.<sup>11,12</sup>

As mentioned above, literature review found that most research related to the severity and impact of symptoms of URTI were studies in children and elderly, while there were few studies in adults. In addition, no studies were finding factors that influence the severity and impact of symptoms of URTI, and the same applies to Thailand. The aforementioned factors were studied only among patients with chronic respiratory illness and lower respiratory tract infections. Moreover, the aforementioned factors can contribute to risk of developing.

## MATERIALS AND METHODS

### *Study design and setting*

This correlational predictive research aimed to study the influence of health literacy, self-care behaviors, nutritional status, and sleep quality over the severity and impact of symptoms in patients with URTI at community hospitals and health-promoting hospitals. It was certified for human research ethics by the Institutional Review Board from the Faculty of Nursing, Mahidol University (COA NO.IRB-NS 2019/536.2612) and was conducted in Thaimuang Chaipat Hospital in Phang-nga and networked health-promoting hospitals.

### *Participants*

Patients diagnosed with URTI aged 18 years and older. Samples were both male and female, and sought care services at Thaimuang Chaipat Hospital and networked health-promoting hospitals. The study lasted from February to June 2020. A total of 127 samples was obtained according to the set criteria. The samples must have shown complete perception and cognition while being able to communicate in Thai. The sample size was calculated through power analysis for research using multiple regression statistics with reliability set to  $\alpha = 0.05$  and power of test to 0.80. Because no research with similar characteristics to this research were found, the correlation size was set to medium at  $r = 0.30$ . Then the squared multiple correlation was calculated at  $p^2 = 0.09$  to produce the effect size of 0.098 and the sample size of 127 samples.

### *Research Instrumentation*

The instruments used to collect data in this research consisted of three parts as follows:

**Part 1** Mini-Cognitive Assessment Instrument Thai version was used. It is a cognitive assessment evaluation form for patients 60 years and older that was translated

into Thai by Trongsakul et al. (2014)<sup>13</sup> for assessing the cognitive impairment of elderly persons. A score of 3 or more indicated no cognitive impairments.

**Part 2** The demographic data was used to collect general data about patients covering 15 items, such as education, literacy, chronic illness, number of sicknesses by common cold or cold, medication used before meeting with a physician, influenza vaccination history, channels for receiving information and history of illnesses related to URTI.

**Part 3** The data collection questionnaires consisted of the five following questionnaires:

Set 1 A health literacy questionnaire developed by the researcher based on an instrument by the Health Education Division (2018).<sup>14</sup> This questionnaire contains 36 questions divided into 6 parts covering access to health information and services, understanding, asking of questions, decision-making, health behavior modification, and health recommendations for the individual, family and community. Scores were interpreted according to four levels: insufficient, low, fair, and adequate health literacies. A high overall score indicated adequate health literacy.

Set 2 A self-care behavior questionnaire for patients with URTI modified by the researcher based on a questionnaire by Shangyom et al. (2018).<sup>15</sup> The questionnaire contained 35 questions total covering nonpharmaceutical and pharmaceutical. Total scores were interpreted on four levels: poor, fair, good and very good self-care behaviors. A high overall score indicated very good self-care behaviors.

Set 3 The Nutrition Alert Form developed by Dr. Surat Komindr.<sup>16</sup> The evaluation form was used to evaluate risk of malnutrition and contained 8 items. Answers were multiple-choice, and total scores were interpreted according to 3 levels: no risk, risk of malnutrition and severe malnutrition. A high overall score indicated severe malnutrition.

Set 4 The Pittsburgh Sleep Quality Index that was translated into Thai by Sitasuwan et al. (2014).<sup>17</sup> The form covered self-assessment about sleep quality over the past month. Evaluation covered 2 characteristics, namely, quantitative sleep quality and qualitative sleep quality. A score less than or equal to 5 indicated good sleep quality.

Set 5 The Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21) developed by Barrett et al. (2004)<sup>18</sup> and translated by the research team contained 2 components, namely, perceived signs and symptoms and impact of symptoms or deficiencies in performing activities of daily living. The form contained 21 sub-

divided questions. Answers were in the form of Likert scales with the total score interpreted according to 4 levels. A high overall score indicated perceived symptoms at a severe level.

### Data analysis

Data were analyzed using SPSS Statistic for Windows to distribute frequencies, percentages, mean values and standard deviations of demographic data, HL, self-care behavior, nutritional status, sleep quality and severity and impact of URTI symptoms. In addition, predictive power over the severity and impact of symptoms in patients with URTI was analyzed by using an enter multiple regression analysis with statistical significance set to .05.

## RESULTS

A total of 127 adults participated in the study, their age range from 18-82 years with a mean age at  $45.30 \pm 14.531$  years. There were nearly 3 times more female samples than male samples (73.2% and 26.8%, respectively). A total of 86.6% of samples held a regular job and worked to earn income and provide family security, while a total of 69.3% of samples completed education on the primary level. Only 3.9% of samples never went to school. A total of 45.7% of samples had more than 1 comorbidity, while 78.7% of samples previously had a common cold or flu. The majority of samples (65.4%) used universal health coverage, and only 3.1% of samples paid out of pocket. Most samples had sufficient income. Furthermore, 59.8% of samples were diagnosed with common cold as shown in (Table 1).

The sample groups's mean includes five different factors, HL, Self-Care Behavior, Nutritional Status, Sleep Quality, and Severity and Impact in Patients with URTI (i) The sample group's mean HL score was fair (Mean =  $133.58 \pm 19.235$ ). Approximately 34.6% of samples had fair HL, and 32.3% had adequate HL, (ii) The sample group's average self-care behavior score was good (Mean =  $125.17 \pm 14.310$ ). Most samples (76.4%) had good self-care behavior. No samples were found to have poor self-care behavior, (iii) The sample group's mean nutritional status score indicated no risk for malnutrition (Mean =  $2.68 \pm 2.360$ ). Only 0.8% of samples had severe malnutrition. (iv) The sample group's mean sleep quality score was good (Mean =  $4.97 \pm 2.606$ ), 33.9% of samples had poor sleep quality, and (v) The sample group's mean severity and impact of URTI symptoms was mild (Mean =  $52.75 \pm 22.852$ ). Nearly half of the samples (44.9%) had mild severity and impact of symptoms. Only a minority of samples had severe symptoms (0.8%).

**TABLE 1.** Patient demographics data (N = 127).

Characteristics	n	Percentage
<b>Gender</b>		
Female	93	73.2
Male	34	26.8
<b>Age (in Years)</b>		
< 20	4	3.1
20 - 29	18	14.2
30 - 39	23	18.1
40 - 49	34	26.8
50 - 59	29	22.8
60 - 69	13	10.2
70 - 79	4	3.1
80 - 89	2	1.6
(mean = 45.30, S.D. = 14.531, min = 18, max = 82)		
<b>Occupation</b>		
Gardener	40	31.5
Employee	34	26.8
Government Officer	15	11.8
Merchant	13	10.2
Unemployed/ Maid/ Butler	11	8.7
Company Employee	8	6.3
Student	6	4.7
<b>Education</b>		
<b>Low Educated</b>		
Not educated	5	3.9
Primary School	41	32.3
<b>Moderate Educated</b>		
Junior High School	20	15.7
Senior High School	27	21.3
<b>High Educated</b>		
High Vocational Certificate/ Vocational Diploma	11	8.7
Bachelor's degree	20	15.7
Graduate	3	2.4
<b>Comorbidity (Answer more than 1 item)</b>		
<b>Respiratory System</b>		
Asthma	10	7.9
COPD	2	1.6
Others	15	11.8
<b>Vascular and Heart System</b>		
Dyslipidemia	23	18.1
Hypertension	22	17.3
Diabetes mellitus	6	4.7
Heart Disease	2	1.6
Stroke	1	0.8
Kidney Disease	1	0.8
Osteoarthritis	0	0
Migraine	6	4.7
Others	6	4.7
<b>In the past 1 year, have you had a cold or the flu?</b>		
Yes	100	78.7
<b>Times</b>		
1 - 3 times	87	68.4
4 - 7 times	11	8.7
More than 7 times	2	1.6
No	27	21.3

**TABLE 1.** Patient demographics data (N = 127). (Continue)

Characteristics	n	Percentage
<b>Used medications before visiting physician (Answer more than 1 item)</b>		
Not taking any medication	22	17.3
Taking medications before visiting physician	105	82.7
Antipyretic	89	70.1
Essential oils	25	19.7
Herbal	17	13.4
Polypharmacy	9	7.1
Vitamin C Supplementation	4	3.1
<b>Flu vaccination history</b>		
Annually	54	42.5
Not to get vaccinated annually	73	57.5
<b>Income sufficiency</b>		
Low income	14	11.0
Lower middle income	47	37.0
Upper middle income	47	37.0
High income	19	15.0

In addition, correlation analysis using the correlation coefficient formula of HL, self-care behavior, nutritional status, sleep quality, and severity and impact of symptoms in patients with URTI found that HL had a negative correlation with the severity and impact of symptoms in patients with URTI ( $r = .271$ ,  $p < .01$ ), while nutritional status and sleep quality had a positive correlation with the severity and impact of symptoms in patients with URTI ( $r_s = .255$ ,  $r_s = .406$ , respectively,  $p < .01$ ). Enter multiple

regression analysis found that all of the independent variables were able to co-predict variance in the severity and impact of symptoms in patients with URTI in the sample by 25.9% with statistical significance at .05 ( $R^2 = .259$ ,  $F = 10.676$ ,  $p < .05$ ). According to the findings, HL and sleep quality can predict the severity and impact of symptoms in this sample group with statistical significance ( $\beta = -.221$  and  $\beta = .393$  respectively,  $p < .05$ ) as shown in (Table 3).

**TABLE 2.** Severity and Impact of Symptoms in Patients with URTI (N = 127).

Severity and Impact of Symptoms Level	n	Percentage
Very mild	37	29.1
Mild	57	44.9
Moderate	32	25.2
Severe	1	.8
(mean = 52.75, S.D. = 22.852, min = 16, max = 117)		

**TABLE 3.** Multiple Regression Correlation Coefficients of Health Literacy, Self-Care Behavior, Nutritional Status, and Sleep Quality for the Severity and Impact of Symptoms in Patients with URTI (N = 127).

Variable	B	Std. Error	B	t	p - value
Constant	59.517	18.578	-	3.204	
Health Literacy	-.263	.102	-.221	-2.589	.011
Self-Care Behavior	.063	.132	.039	.474	.636
Nutritional Status	1.269	.806	.131	1.575	.118
Sleep Quality	3.443	.695	.393	4.954	< .001

$p < .05$

## DISCUSSION

This study found that only 0.8% of samples had severe symptoms and most samples had mild to very mild symptoms. This was consistent with a study conducted by Malathum et al. (2005) who found that most of the samples had mild symptoms. In addition, more than half of the samples with symptoms of a cold or influenza had disruptions to activities in daily living.<sup>19</sup> When compared to a study conducted by Denlinger et al. (2016) who assessed severity of symptoms by using the same WURSS-21 as in this study, mean scores were found to be at 61.3 points.<sup>20</sup> This score was similar to the findings in this study and showed symptom severity at a similarly mild. The reason that the samples in this study had mild symptom might have been due to the fact that most of the sample group (82.7%) used medications before visiting physician and that the medications used the most were antipyretic (70.1%), followed by essential oils (19.7%), the samples symptoms of URTI were alleviated from their actual symptoms. The finding concurs with a study by Ibrahim and Elkady (2016) finding that most elderly patients used medications (97.1%) and that the most used medications were analgesic, antipyretic and aspirin and that most (86.4%) chose medications on their own.<sup>21</sup> Furthermore, Thielmann et al. (2016) found that patients engaged in self-care behaviors by using at least two medicines together (63%), and that only a minority used only one type of medication. The medications used the most were paracetamol or antipyretic (38%), followed by, essential oils (10%).<sup>22</sup> These findings are consistent with the study, which found that headache, bodily aches and fever were the main discomforting symptoms that caused patients to decide to use medications on their own.<sup>23</sup>

According to the study into HL, it was found that most of the sample group (67%) had adequate HL, while 33% of the sample group needed to increase HL. This is because inadequate HL influences data usage, access to care services, self-care in times of sickness and disease prevention and contributes to health problems from a young age and poorer health than persons with adequate HL.<sup>24</sup> In this study, it was found that HL can co-predict the severity and impact of symptoms in patients with URTI with statistical significance ( $\beta = -.221, p < .05$ ). The findings are consistent with a study by Sun et al. (2013) finding that HL and existing knowledge are the top two factors of health behaviors. Thus, HL directly influences health behaviors, and health behaviors positively impact health status.<sup>25</sup> In addition, Bennet et al. (2009) found that 29% of elderly persons had poor health status, that

27% of elderly patients were not vaccinated for influenza and that these findings are correlated with inadequate HL and that HL and health outcomes vary according to ethnicity and education.<sup>26</sup> Thus, it is clear that HL is connected to infection and infection prevention behaviors and that inadequate or limited HL is correlated with disease prevention behaviors. In the same manner, this study found that 10.2% of samples had inadequate HL and that 22.8% of samples had low HL and that most of this group (64.3%) had a low education. When compared to the group with a high education, only 11.8% had low HL. This means that highly educated samples had better HL and made better healthcare decisions. Furthermore, no studies were conducted on HL and symptom severity in patients with URTI. However, a study conducted among patients with chronic respiratory illnesses found inadequate socioeconomic status and HL to be correlated with higher Chronic Obstructive Pulmonary Disease (COPD) severity, hopelessness and lower quality of life. In addition, inadequate HL was correlated with likelihood of a COPD-related hospitalizations and emergency department visits.<sup>27</sup> This was consistent with the findings of this study. Therefore, persons with inadequate HL were at risk of negative health outcomes as well.

Upon studying sleep quality, it was found that sleep quality can co-predict the severity and impact of symptoms in patients with URTI with statistical significance ( $\beta = .393, p < .05$ ). The findings are consistent with literature review, which found that extensive reduction in sleep and stress response contributes to proinflammatory cytokines which leads to chronic inflammation and a compromised immune system.<sup>19</sup> Upon evaluating the sleep duration per night of the sample group, it was found that the mean nightly sleep duration was 7.043 hours (1.484), which is adequate and similar to the findings by Cohen et al. (2009), In the findings of Cohen et al. (2009), the mean sleep duration of samples was 7.45 hours and that samples who slept for less than 7 hours were 2.94 times more likely to contract cold than samples who slept more than 8 hours, while samples whose sleep effectiveness was under 92% were 5.50 times more likely to contract cold than the group with sleep effectiveness more than or equal to 98%. It can be concluded, therefore, that low sleep effectiveness and short sleep duration over several weeks preceding infection are correlated with increased likelihood of contracting cold and a weakened immune system in the presence of illness.<sup>12</sup> Furthermore, a study by Prather et al. (2015) found that shorter sleep duration prior to exposure to viral infection has a correlation with increased sensitivity to cold. When comparing

samples who slept for less than five hours or 5-6 hours with samples who slept more than 7 hours, the samples were found to be more likely to develop cold.<sup>28</sup>

Meanwhile, nutritional status was unable to predict the severity of symptoms and impact in patients with URTI ( $\beta = .131$ ,  $p > .05$ ). This finding differs from the findings of Tongo and Sy (2017), which found that malnourished elderly persons were at risk of contracting severe community-acquired pneumonia.<sup>29</sup> Thus, the fact that most of the sample group (89%) had no risk of malnutrition might be why the prediction failed. The lack of risk for malnutrition is due to the fact that most samples had a sufficiently socio-economic status with medium to high education levels and sufficient income to cover expenses. Moreover, the southern region's geography has seas on both sides, and fertile soil and water, which enables them to procure nutritious foods more easily.

Although a previous study exists relating to the correlation between self-care and severity of Type 2 diabetes mellitus<sup>30</sup>, its findings differ from the present study, which found that self-care behavior had no correlation with the severity and impact of symptoms in patients with URTI with statistical significance ( $r = -.043$ ,  $p > .05$ ). It cannot predict the severity and impact of symptoms in patients with URTI ( $\beta = .039$ ,  $p > .05$ ), possibly due to the fact that most samples were working age individuals who were still able to take care of themselves for the most part (78.7%) who were sick with a common cold or flu in the past year. In addition, the data collection period overlapped with the outbreak of the Coronavirus 2019 pandemic, when news and information about behaviors to lower risk of acute respiratory illness are widely and frequently available in every communications channel, which led patients to have better self-care, and strict measures to counter the pandemic provided indirect control and supervision over the sample group's behaviors.

## RECOMMENDATION

There are two major recommendations on this study including nursing practice and research. Firstly, for the nursing practice, (i) Patients should be encouraged to recognize the importance of sleep and appropriate sleep problem management and (ii) HL should be promoted in patients which should include thinking and social interaction skills for accessing, understanding, appraising and utilizing health information. An adequate HL can help patients make better health decisions in their daily living. Secondly, for nursing research, (i) additional studies should be conducted in patients with URTI in contexts

that are different from this study such as patients who seek services in secondary or tertiary hospitals.

## CONCLUSION

This research revealed that the overall severity and impact of symptoms in most patients with URTI at Thaimuang Chaipat Hospital and health-promoting hospitals were at a mild level, which accounted for 44.9% of participants. Among 5 factors, including HL, self-care behavior, nutritional status and sleep quality, sleep quality and HL are the 2 important factors that influenced severity and impact of symptoms.

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# Depression, Social Support, and Coping Strategies in Individuals with Spinal Injury Depression with Spinal Injury Patients

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## ABSTRACT

**Objective:** To investigate the prevalence of and factors associated with depression, the social support received by, and the coping strategies used by individuals with spinal injury.

**Materials and Methods:** Individuals with spinal injury who received follow-up evaluation at the Siriraj Hospital during 2016 to 2018. The instruments used included a general information, the Zung Self-Rating Depression Scale (Thai version), the Social Provisions Scale, and the Spinal Cord Lesion-Related Coping Strategies Questionnaire (Thai version).

**Results:** Eighty-six individuals with spinal injury (age:  $43.1 \pm 15.7$  years, 66.3% male) were included, and 59.3% had some level of permanent impairment. The prevalence of depression was 55.8%. Depression was found to be negatively associated with all social support domains. Regarding coping, depression was shown to be negatively associated with the fighting spirit, but positively associated with the social reliance strategy. Multivariate analysis by multiple logistic regression showed level of impairment ( $p=0.005$ ), guidance provision ( $p=0.040$ ), fighting spirit strategy ( $p=0.031$ ), and the social reliance strategy ( $p=0.032$ ) to be independently associated with depression.

**Conclusion:** The prevalence of depression among SCI was 55.8%. The results revealed the types of social support received, and the coping strategies used by individuals with spinal injury after hospital discharge. These findings can be implemented in an intervention to reduce depression among the individuals with spinal injury such as the promotion of the guidance provision which is provided by the professionals and the arrangement of a counseling psychology workshop focusing on effective coping strategy, especially for individuals with paraplegia and tetraplegia.

**Keywords:** Spinal cord injury; depression; social support; coping strategies; SCI (Siriraj Med J 2021; 73: 518-525)

## INTRODUCTION

Psychological problems, including feelings of discouragement and hopelessness, increased stress, and onset of depression, often develop among individuals with spinal cord injury who have experienced loss of physical functions due to spinal cord injury (SCI),

and these psychological problems can adversely affect daily routines and other activities of daily living.<sup>1</sup> These psychological problems, particularly depression, are very likely to develop in individuals with spinal cord injury with severe and chronic loss that are unable to accept their loss and successfully adapt to their new reality.<sup>2</sup>

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Among SCI patients who returned to living in the community after receiving medical care, it was found that 32% had depression<sup>3</sup>, 23% had moderate depression, and 21% had severe depression. Hoffman, *et al.*<sup>4</sup> conducted a study to evaluate depression among individuals with spinal cord injury at 1 year and 5 years after their injury, and that research group found depression rates of 21% and 18%, respectively. A previous study from Thailand found that 39% of SCI patients had depression after their discharge from Siriraj Hospital.<sup>5</sup>

An important factor relating to depression is social involvement, and the relationships that they have with and the support that they receive from family, friends, and the community. A lack of social support is a risk factor for depression.<sup>6</sup> Patient satisfaction with the social interactions that they have and the social support that they receive promotes and enhances positive psychological adjustment.<sup>7</sup> A study that investigated association between social relationship and depressive behaviours among 182 SCI patients, found lower levels of depression among patients that had social relationships that made them feel valuable.<sup>8</sup>

Psychological factors, like the patterns or strategies used to cope with problems, were also found to be associated with depression among SCI patients.<sup>9</sup> If patients develop a negative perception of themselves due to feelings of being incapable of dealing with problems or of being dependent upon others, depression will eventually develop.<sup>10</sup> Elfström, *et al.*<sup>11</sup> examined the coping strategies of those with disability due to SCI and they found ineffective coping strategies (e.g., social reliance) to be significantly positively associated with depression scores. Similarly, an investigation of coping strategies among SCI patients living in different social and cultural contexts found a higher overall level of depression in settings where a greater number of patients employed the social reliance coping strategy when compared to settings where a comparatively lower proportion of patients adopted and used that same coping strategy.<sup>12</sup>

Since depression is a common consequence of SCI, enhanced understanding of this disorder in this vulnerable patient population will improve prevention, diagnosis, treatment, and outcomes. An examination of depression and its relationship with social support and coping strategies will yield additional broader insight into the psychological impact of SCI after hospital discharge and continue to receive follow-up care from Siriraj Spinal Care Unit.

Accordingly, the aim of this study was to investigate the prevalence of and factors associated with depression, the social support received by, and the coping strategies

used by individuals with spinal injury that continued to receive follow-up care from the Siriraj Spinal Unit after hospital discharge. The results of this study will be used to develop and improve mental healthcare strategies designed to enhance patient quality of life after hospital discharge and while receiving follow-up care from the Siriraj Spinal Unit.

## MATERIALS AND METHODS

### Participants

This study is a Questionnaire-based research study with a prospective data collection. The study population consisted of individuals with spinal injury who received follow-up evaluation and care at the Siriraj Spinal Unit of the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the November 2016 to December 2018 study period. Individuals with spinal injury that met all of the following criteria were included: (1) age greater than 18 years; (2) having good consciousness; and, (3) having good ability and willingness to answer the following assessment tools: the Thai version of the Zung Self-Rating Depression Scale, the Social Provisions Scale, and the Thai version of the Spinal Cord Lesion-Related Coping Strategies Questionnaire (SCI-CSQ). Patients with active psychosis or with a history or diagnosis of depression before SCI were excluded.

### Assessment instruments

The Thai version of the Zung Self-Rating Depression Scale<sup>13</sup> is a measurement of depression severity that consists of 20 items. Scoring ranges from 0 to 80. A score of equal to or less than 30 suggests no presence of emotional problems or depression, whereas a score greater than 30 suggests the presence of depression. Test-retest and split-half methods were applied for reliability testing, and the scale's reliability was found to be 0.73.<sup>13</sup>

The Social Provisions Scale, which was developed by Russell and Cutrona in 1985<sup>14</sup>, comprises 24 items. Each item is scored from 1 (do not agree at all) to 4 (absolutely agree). Scoring ranges from 24 to 96. This scale is used to measure the provision of social support for an individual in six domains, including social integration, reassurance of worth, reliable alliance, guidance, opportunity for nurturance, and attachment. The total score for each domain is calculated by summation of all item scores within each domain. A higher score indicates a higher level of social provision in that social support domain.

The Thai version of the Spinal Cord Lesion-Related Coping Strategies Questionnaire (SCI-CSQ)<sup>9</sup> consists of 12 items. Items 1, 2, 6, and 11 indicate the use of the

acceptance strategy; items 3, 5, 7, 10, and 12 suggest the use of the fighting spirit strategy; and, items 4, 8, and 9 signify the use of the social reliance strategy. The patient's response indicates the degree of agreement, as follows: *strongly disagree* = a score of 1; *disagree* = a score of 2; *agree* = a score of 3; and, *strongly agree* = a score of 4. Scoring ranges from 12 to 48. The mean score of each strategy is reported, and a higher score indicates more frequent use of that strategy.

After receiving study approval from the Siriraj Institutional Review Board (SIRB) [Si 636/2016(EC1)], written informed consent was obtained from all enrolled study participants. The following data were collected from patient medical records: age, gender, education level, income, marital status, level of impairment, injury severity, cause of injury, and time since injury. Patient level of depression and quality of life were assessed using the Thai version of Zung Self-Rating Depression Scale, the Social Provisions Scale, and the SCI-CSQ-THAI, respectively.

### Statistical analysis

SPSS Statistics software (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses. Categorical data are presented as frequency and percentage, and continuous data are presented as mean plus/minus standard deviation or median and range. Associations between depression and both social support and coping strategies among individuals with spinal injury after hospitalization were analyzed by Pearson's correlation coefficient ( $r$ ). Chi-square test or independent t-test was used to evaluate the relationship between depression and factors that included age, gender, educational level, marital status, income, cause of disease, duration of disease, severity of disability, and severity of injury. Multiple logistic regression was used for multivariate analysis, factors with a  $p$ -value < 0.10 in univariate analysis and clinical relevant were adjusted for in multivariate model. And those results are shown as adjusted odds ratio and 95% confidence interval. A  $p$ -value of less than 0.05 was considered statistically significant for the results of multivariate analysis.

## RESULTS

Eighty-six individuals with spinal injury were included. The demographic and clinical characteristics of included individuals with spinal injury are shown in Table 1. The mean  $\pm$  standard deviation age of individuals with spinal injury was  $43.1 \pm 15.7$  years (range: 18-84), and 66.3% were male. Most individuals with spinal injury (29.1%) had a bachelor's degree, and 50% were single/unmarried. The majority of individuals with spinal injury (57%)

sustained their injury in a traffic accident. Regarding level of impairment - 40.7%, 40.7%, and 18.6% of individuals with spinal injury had no impairment, paraplegia, and tetraplegia, respectively. The average duration of disease after injury was  $61.0 \pm 60.5$  months (range: 3 months to 21 years).

The prevalence of depression in this study was 55.8%, and the average depression score was  $32.4 \pm 12.6$ . Regarding social support, the mean scores of the six domains of social provision (SD) were, as follows:  $13.5 \pm 2.0$  for attachment;  $13.2 \pm 2.1$  for reliable alliance;  $13.1 \pm 2.3$  for guidance;  $12.4 \pm 2.2$  for opportunity for nurturance;  $12.5 \pm 2.0$  for social integration; and,  $12.1 \pm 2.1$  for reassurance of worth. The mean scores for the coping strategies were  $17.5 \pm 1.9$  for fighting spirit;  $12.4 \pm 1.9$  for acceptance; and,  $7.5 \pm 1.9$  for social reliance (Table 2).

Pearson's correlation coefficient ( $r$ ) was used to analyze associations between depression and both social support and coping strategies among individuals with spinal injury after hospitalization. That analysis revealed a moderately negative association between depression and all domains of social provision ( $r$  range: -0.527 to -0.644). Regarding association between depression and coping strategies, our results showed that depression are no significant correlation with the acceptance ( $r = -0.014$ ,  $p$  value 0.898) and the fighting spirit ( $r = -0.348$ ) strategies, and a positive relationship with the social reliance strategy ( $r = 0.043$ ) (Table 3).

Univariate analysis by chi-square test or independent t-test was used to evaluate the relationship between having depression and factors that included age, gender, educational level, marital status, income, cause of disease, duration of disease, severity of disability, severity of injury, social provision, and coping strategies. That analysis revealed level of impairment ( $p = 0.004$ ), severity of injury ( $p = 0.006$ ), all domains of social provision (all  $p < 0.001$ ), and the fighting spirit strategy ( $p = 0.001$ ) to be significantly associated with depression.

Multivariate analysis by multiple logistic regression showed level of impairment ( $p = 0.005$ ), the guidance provision ( $p = 0.040$ ), the fighting spirit strategy ( $p = 0.031$ ), and the social reliance strategy ( $p = 0.032$ ) to be independently associated with depression. individuals with paraplegia or tetraplegia had depression with an adjusted odds ratio of 14.7 (95% confidence interval [CI]: 2.24-95.59,  $p = 0.005$ ) compared to those with no disability. For the guidance provision, the fighting spirit strategy, and the social reliance strategy, we found that for every 1-point increase in score, the adjusted odds ratio of depression decreased 48% (95% CI: 0.28-0.97), 0.58 times (95% CI: 0.35-0.95), and 0.62 times (95% CI: 0.40-0.96), respectively (Table 4).

**TABLE 1.** Demographic and clinical characteristics of included people with spinal injury (N=86).

Characteristics	Mean $\pm$ SD or n (%)
Age (years)	43.1 $\pm$ 15.7
Male gender	57 (66.3%)
Education	
- Primary school	17 (19.8%)
- Secondary school	23 (26.7%)
- Vocational certificate	15 (17.4%)
- Undergraduate	25 (29.1%)
- Postgraduate	6 (7.0%)
Marital status	
- Single	43 (50.0%)
- Married	29 (33.7%)
- Divorced/separated/widowed	14 (16.3%)
Income (Thai baht/month)	2,500 (0-100,000)*
Cause of injury	
- Traffic accident	49 (57.0%)
- Fall	27 (31.3%)
- Violence	4 (4.7%)
- Other	6 (7.0%)
Level of impairment	
- No	35 (40.7%)
- Paraplegia	35 (40.7%)
- Tetraplegia	16 (18.6%)
Severity of injury (n=75)	
- Complete	24 (27.9%)
- Incomplete	27 (31.4%)
Time since injury (months)	36 (3-252)*

**Abbreviation:** SD, standard deviation

\* Median (range)

**TABLE 2.** Mean depression score, social support domain scores, and coping strategy scores of 86 included spinal injury patients..

Scores	Mean $\pm$ SD
Depression	32.4 $\pm$ 12.6
Social integration	12.5 $\pm$ 2.0
Reassurance of worth	12.1 $\pm$ 2.1
Reliable alliance	13.2 $\pm$ 2.1
Guidance	13.1 $\pm$ 2.3
Opportunity for nurturance	12.4 $\pm$ 2.2
Attachment	13.5 $\pm$ 2.0
Acceptance	12.4 $\pm$ 1.9
Fighting spirit	17.5 $\pm$ 1.9
Social reliance	7.5 $\pm$ 1.9

**Abbreviation:** SD, standard deviation

**TABLE 3.** Analysis for association between depression and the 6 social support domains and the 3 coping strategies.

Domains/strategies	Pearson's correlation coefficient (r)	p-value*
Social integration	-0.573	<0.001
Reassurance of worth	-0.644	<0.001
Reliable alliance	-0.565	<0.001
Guidance	-0.604	<0.001
Opportunity for nurturance	-0.527	<0.001
Attachment	-0.577	<0.001
Acceptance	-0.014	0.898
Fighting spirit	-0.348	0.001
Social reliance	0.043	0.694

A *p*-value<0.05 indicates statistical significance\*

## DISCUSSION

This study found a prevalence of depression among individuals with spinal injury after hospitalization of 55.8%. Our finding was much higher than the 21.6%<sup>18</sup>, 27%<sup>19</sup>, and 28%<sup>20</sup> rates reported by other studies. However – in contrast to the >30 point cutoff used in our study to define presence of depression using the Zung Self-Rating Depression Scale, those studies used a score of ≥50 as the cutoff. Regarding social support, most individuals with spinal injury in this study used the attachment provision, whereas most individuals with spinal injury in other studies conducted in other countries used the reliable alliance provision. These differences between and among studies may be due to sociocultural context and influences. Thai culture is rooted in kinship in which support and interdependent relationships are often found<sup>21</sup>; therefore, individuals with spinal injury may be more strongly drawn to the attachment provision than the other domains of the Social Provisions Scale.

To assess coping strategies, we used the Thai version of the Spinal Cord Lesion-Related Coping Strategies Questionnaire to measure the coping strategies of individuals with spinal injury after hospitalization.<sup>9</sup> This Thai language assessment tool is relatively short, is uncomplicated, and is easy to understand. Importantly, these features make this tool reliably useful among individuals with spinal injury with lower levels of education. Moreover, this assessment was previously used to evaluate Thai individuals with spinal injury, and the results of that

study revealed that Thai individuals with spinal injury most frequently used the fighting spirit strategy.<sup>15</sup> This strategy was also reported to be the coping strategy of choice of individuals with spinal injury included in studies conducted in other countries.<sup>16,17</sup>

Concerning the relationships between depression and both social support and coping strategies among individuals with spinal injury after hospitalization, the results of this study revealed that depression negatively associates with all domains of social provision at a moderate level. Depression increases when individuals with spinal injury perceive less social support, and it decreases when individuals with spinal injury perceive more social support. This same finding was reported by a previous study that identified lack of social support as being a risk factor for depression.<sup>6</sup> Individuals with spinal injury who received low social provision, who were withdrawn, or who had low social opportunities were likely to be at greater risk for developing depression.<sup>22</sup> Thus, patient satisfaction with the social interactions that they experience and the social support that they receive will promote positive psychological adjustment and reduce the likelihood of depression onset among individuals with spinal injury. Moreover, depression has a negative relationship with the acceptance strategy at the lowest level, and with the fighting spirit strategy at a low level. Therefore, depression is less likely to be found among individuals with spinal injury who adopt the acceptance strategy or the fighting spirit strategy.

**TABLE 4.** Univariate and multivariate analysis for factors significantly associated with depression.

Factors	No depression (n=38)	Depression (n=48)	p-value <sup>#</sup>	Adjusted odds ratio (95% CI)	p-value <sup>##</sup>
Gender			0.586		
Male	24 (63.2%)	33 (68.8%)			
Female	14 (36.8%)	15 (31.2%)			
Education			0.268		
Lower than bachelor's degree	23 (60.5%)	32 (66.6%)			
Bachelor's degree or higher	15 (39.5%)	16 (33.4%)			
Marital status			0.215		
Single	22 (57.9%)	21 (43.8%)			
Married	9 (23.7%)	20 (41.7%)			
Divorced/separated/widowed	7 (18.4%)	7 (14.6%)			
Income (Thai baht/month)	4,500 (0-100,000)	800 (0-90,000)	0.290		
Cause of injury			0.250		
Traffic accident	22 (44.9%)	27 (55.1%)			
Fall	14 (51.9%)	13 (48.1%)			
Violence	0 (0.0%)	4 (100%)			
Other	2 (33.3%)	4 (66.7%)			
Level of impairment			0.004		<b>0.005</b>
Normal	22 (57.9%)	13 (27.1%)		1.00	
Paraplegia/Tetraplegia	16 (50.0%)	16 (50.0%)		14.65 (2.25-95.59)	
Severity of injury			0.006		
Complete	10 (26.3%)	14 (29.2%)			
Incomplete	6 (15.8%)	21 (43.8%)			
Normal	22 (57.9%)	13 (27.1%)			
Time since injury (months)	45 (3-252)	36 (4-240)	0.141		
Social support domain scores					
Social integration	13.6±1.7	11.6±1.8	<0.001	0.83 (0.49-1.41)	0.490
Reassurance of worth	13.3±1.7	11.1±1.8	<0.001	0.65 (0.37-1.13)	0.128
Reliable alliance	14.2±1.7	12.3±1.9	<0.001	0.82 (0.48-1.39)	0.470
Guidance	14.5±1.8	12.1±2.2	<0.001	0.52 (0.28-0.97)	<b>0.040</b>
Opportunity for nurturance	13.5±2.1	11.5±2.0	<0.001	1.34 (0.86-2.09)	0.194
Attachment	14.6±1.5	12.7±2.0	<0.001	1.13 (0.66-1.95)	0.648
Coping strategy scores					
Acceptance	12.3±2.2	12.5±1.5	0.612	1.22 (0.79-1.89)	0.370
Fighting spirit	18.3±1.8	16.9±1.8	0.001	0.58 (0.35-0.95)	<b>0.031</b>
Social reliance	7.5±2.0	7.5±1.8	0.909	0.62 (0.40-0.96)	0.032

Data compared between depression and no depression are presented as number and percentage, median and range, or mean ± standard deviation

Factors with a  $p$ -value<0.1 in univariate analysis were included in multivariate analysis

A  $p$ -value<0.05 indicates statistical significance for the results of multivariate analysis

<sup>#</sup> $p$ -value for chi-square test or independent  $t$ -test

<sup>##</sup> $p$ -value for multiple logistic regression

**Abbreviation:** CI, confidence interval

Previous studies also found the use of effective coping strategies (e.g., acceptance and fighting spirit strategies) to be associated with lower depression scores.<sup>11,17</sup> Adoption of the acceptance strategy suggests an honest assessment by the patient, and a resulting recognition and/or tolerance for his/her new reality, and this leads to readjustment of goals and expectations. Alternatively, the fighting spirit strategy reflects a patient's desire for self-reliance, and it communicates the patient's desire to cope with the complexities of SCI on his/her own. This strategy promotes independence, helps individuals with spinal injury develop self-confidence, and enhances patient ability to deal with and overcome difficulties. These benefits all help to prevent or minimize depression among individuals with spinal injury after hospital discharge.

In contrast to the acceptance and fighting spirit coping strategies, we found the social reliance strategy to be positively associated with depression among SCI after hospital discharge. Similarly, previous study found the social reliance strategy to be positively associated with depression score<sup>11</sup>, and depression was commonly found among those who adopted and used the social reliance strategy.<sup>12</sup> Reliance on social support from others may lead to dependency that ultimately leaves individuals with spinal injury feeling that they no longer have control over their own lives. This can lead to loss of self-esteem and feelings of worthlessness, discouragement, and giving up, and these feelings - alone or in combination - can result in depression.

Concerning factors related to depression, social support, and coping strategies among individuals with spinal injury after hospitalization, our multivariate analysis revealed severity of disability, the guidance provision, the fighting spirit strategy, and the social reliance strategy to be independently associated with depression. These findings are consistent with those of previous studies that found severity of disability<sup>23</sup>, social support<sup>24,25,26</sup>, and coping strategies<sup>11,17</sup> to be factors that significantly influenced depression among individuals with spinal injury. Khazaeipour, *et al.*<sup>23</sup> found a high likelihood of the development of depression among individuals with paraplegia. This is very likely due to SCI-induced physical impairment that dramatically adversely affects functional abilities. These individuals with spinal injury often develop feelings of worthlessness, discouragement, and lack of motivation - all of which are symptoms of depression. Concerning social support, previous studies found a greater amount of social support to be associated with a lower depression score.<sup>26,25</sup> Social support that emphasizes problem management may influence a reduction in depression during the patient's adjustment to each

stage of physical impairment - especially social support provided by professionals and families because these types of support positively influence SCI patient well-being.<sup>26</sup> Concerning coping strategies, studies from Sweden<sup>11</sup> and Turkey<sup>17</sup> found that effective coping strategies associated with lower depression scores. This is consistent with the current study which found that the fighting spirit strategy, the effective coping strategy, was significantly associated with individuals with spinal injury with depression. However, the previous study in Thailand<sup>15</sup> did not find a similar relationship. This might be due to the fact that the participants in that study used the three coping strategies in similar patterns; thus, significant positive or negative relationships between depression and coping strategies were not found.

The limitation of this study is its cross-sectional design, which means that the data were collected at one point in time. However, the study participants selected the answers that they felt best described their situation and state of mind, so further elicitation to extract additional information was deemed necessary. For the more benefit of clinical application, additional studies of more variety psychological evaluation in the form of experimental comparative research are recommended.

## CONCLUSION

The prevalence of depression among SCI was a high 55.8%. The results of this study also revealed the types of social support received, and the coping strategies used by individuals with spinal injury after hospital discharge. Multivariate analysis showed level of impairment, the guidance provision, the fighting spirit strategy, and the social reliance strategy to be independently associated with depression. These findings will be helpful for developing targeted strategies that will improve follow-up care and patient quality of life.

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# Serum Theophylline Concentrations in very Preterm Neonates Receiving Intravenous Aminophylline for Apnea

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## ABSTRACT

**Objective:** To determine the percentage of neonates who achieved therapeutic theophylline level (TTL) after receiving standard IV loading/maintenance aminophylline doses. To assess factors associated with achieving therapeutic theophylline concentrations and to describe adverse effects of aminophylline.

**Materials and Methods:** This was a pilot, cross-sectional study. Preterm neonates  $\leq 34$  weeks' gestation for which aminophylline was indicated for treatment of apnea were enrolled. Standard IV aminophylline dosage is 8 mg/kg loading dose, followed by 1.5 mg/kg maintenance dose every 8 hours. Serum theophylline concentrations were measured prior to the 8th maintenance dose. Descriptive statistics, univariate and multivariate analyses were performed.

**Results:** Twenty-five neonates (52% female) were enrolled: mean (standard deviation) gestational age and birth weight were 30.4 (2) weeks and 1,277 (415) grams, respectively. Aminophylline was initiated at a median (25%tile, 75%tile) postnatal age of 4 (1, 8) days. Baseline heart rate prior to the loading dose was 153 (13) beats-per-minute. Sixty percent of neonates achieved a therapeutic theophylline level. In the univariate analysis, being male and postnatal age  $\leq 5$  days were associated with successfully achieving a TTL. After adjusting for gender, postnatal age  $\leq 5$  days was the only factor associated with achieving a TTL (adjusted odds ratio 17.7, 95% confidence interval: 1.9, 164.4). Tachycardia and feeding intolerance were observed in 44% and 24% of neonates, respectively.

**Conclusion:** Current IV aminophylline dosing conditions in Thailand achieved TTL in approximately two-thirds of neonates, suggesting therapeutic drug monitoring is beneficial for guiding dosing. A higher maintenance dose could be considered for neonates older than 5 days.

**Keywords:** Aminophylline; apnea of prematurity; therapeutic drug monitoring; serum theophylline concentration; therapeutic drug level (Siriraj Med J 2021; 73: 526-531)

## INTRODUCTION

Apnea of prematurity (AOP) is one of the most common problems in very preterm neonates. The incidence of AOP is inversely correlated with gestational age.<sup>1</sup>

Intermittent hypoxia secondary to AOP may activate pro-inflammatory cytokines and cascades, disturb bone metabolism, retinal development and cause cardiovascular instability.<sup>2</sup> Prolonged apnea and delayed resolution

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beyond 36 weeks of postmenstrual age is associated with an increased risk of neurodevelopmental disturbances.<sup>3</sup> Treatment for AOP, including respiratory support and medications, should be considered when apneic episodes become frequent and/or prolonged.<sup>4</sup> Methylxanthine therapy is considered the first-line treatment for AOP while doxapram is the second-line treatment used for refractory cases.<sup>4</sup> Caffeine citrate is the preferred choice for methylxanthine due to its once-a-day dose, broad therapeutic index and good safety profile.<sup>1</sup> Unfortunately, widespread access to Caffeine citrate is not yet available in Thailand and aminophylline remains the main methylxanthine available for treatment of AOP. Aminophylline is made up of theophylline and ethylenediamine (approximately 80% theophylline).

Theophylline-induced seizures have also been reported in neonates.<sup>5</sup> Due to its narrow therapeutic index, serum theophylline concentration (STC) measurement is commonly performed to ensure that a therapeutic drug level (TDL) between 7-12 mcg/mL is administered and to avoid any toxic reaction.<sup>6,7</sup> As routine STC is not available in many local hospitals in Thailand, we performed this pilot study to evaluate the necessity of measuring STC when following standard aminophylline IV dosing recommendations of 8 mg/kg per loading dose, then 1.5-3 mg/kg/dose every 8-12 hours.<sup>8</sup>

The objectives of this study were as follows: (1) determine STC in neonates receiving standard aminophylline IV dosing in Thailand; (2) assess factors associated with achieving TDL of theophylline; and (3) to describe adverse effects of aminophylline in neonates.

## MATERIALS AND METHODS

### Design

A single center, observational, cross-sectional study.

### Setting

The study was conducted at the Division of Neonatology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University between August 2015 and July 2016. Siriraj Hospital is a tertiary referral center with approximately 8,000 deliveries per year. Neonates were recruited for the study while in the neonatal intensive care unit (NICU) or the intermediate care unit.

### Participants and intervention

We enrolled preterm neonates less than or equal to a 34 week gestation period who were prescribed IV aminophylline for treatment of AOP. Neonates were excluded if they were receiving concomitant medications that could affect the pharmacokinetics of aminophylline

such as phenobarbital, phenytoin, erythromycin and propranolol; had received aminophylline within 7 days prior to enrollment; had acute renal insufficiency or abnormal liver function test result; had congenital anomalies with CNS involvement; were referred back to local hospital; were dead; had no informed consent obtained from their parents.

Aminophylline dosing used to treat AOP at Siriraj Hospital was an 8 mg/kg loading dose, followed by an initial maintenance dose of 1.5 mg/kg every 8 hours. The aminophylline dose was prescribed by the attending physician as per standard of care. Prior to the 8<sup>th</sup> maintenance dose, one milliliter of blood was drawn for quantification of STC. Drug concentrations were determined using the ARCHITECT ci4100 Integrated Immunoassay and Clinical Chemistry System (Abbott 2009 USA).

### Outcome measurement

The primary outcome was the percentage of neonates who achieved TDL. Meanwhile, secondary outcomes were factors associated with success in achieving TDL and the adverse effects of aminophylline, including tachycardia, feeding intolerance and abnormal neurological symptoms.

Demographic data and clinical characteristics of neonates were collected from medical records. All neonates were monitored for adverse effects and toxicity of aminophylline by bedside nurses at NICU.

### Operational definitions

Acute renal insufficiency was defined as oliguria <1 ml/kg/h within 12 hours before enrollment or serum creatinine  $\geq$ 1.6 mg/dL, 1.1 mg/dL and 1 mg/dL in preterm neonates  $\leq$ 27 weeks, 28-29 weeks and 30-32 weeks gestation, respectively.<sup>9</sup> An abnormal liver function test was defined as total bilirubin >2 mg/dL, Aspartate aminotransferase (AST) >140 IU/L, or Alanine transaminase (ALT) >50 IU/L.<sup>10</sup>

Adverse effects of aminophylline recorded were tachycardia, which is defined as a heart rate of >180 beats-per-minute within 24 hours after loading dose; feeding intolerance, defined as residual gastric content >50% of feeding volume at least once within 24 hours after loading dose, and abnormal neurological symptoms, i.e., seizure and lethargy.

### Statistical analysis

This was a pilot study of 25 neonates. The data was analyzed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including frequency and percentage, mean and standard deviation (SD), or median and 25<sup>th</sup>tile and 75<sup>th</sup>tile were used as appropriate for type

and distribution of data. A comparison of continuous data was carried out using unpaired t-test or Mann-Whitney U test depending on data distribution. Chi-square test or Fisher's exact test was used for categorical variables and those with a  $p$ -value  $<0.2$  from univariate analysis were chosen for multivariate analysis using binary logistic regression analysis. A  $p$ -value of  $<0.05$  was accepted as statistically significant.

### Ethics

The study protocol was approved by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 317/2015). A written informed consent was obtained from all parents.

## RESULTS

Between August 2015 and July 2016, 99 neonates born at less than or equal to 34 weeks' gestation were assessed for eligibility. A total of 25 neonates were enrolled (Fig 1) and the baseline characteristics of neonates are summarized in Table 1.

Median (25%tile, 75%tile) loading dose of aminophylline was 8 (8, 8.5) mg/kg and median (25%tile, 75%tile) maintenance dose was 1.5 (1.5, 1.5) mg/kg/dose every 8 hours. Mean STC was  $6.9 \pm 1.6$  mcg/mL and the percentage of neonates who achieved TDL was 60%. None of the neonates had a STC  $>12$  mcg/mL. Among the neonates

who achieved TDL, there was a higher percentage of males and had a lower postnatal age compared to those neonates who did not achieve therapeutic STC (Table 2). After adjusting for gender, a postnatal age of  $\leq 5$  days was significantly associated with achieving TDL (adjusted odds ratio 17.7; 95% confidence interval 1.9, 164.4).

Tachycardia was reported in 11 (44%) neonates and spontaneously resolved over time without any treatment. Feeding intolerance occurred in 6 (24%) neonates; and 4 neonates were placed on NPO until the results of work up for cause of apnea came back normal, after which feeding was resumed; one neonate was treated for suspected sepsis, and the remaining neonate had continuation of feeding but with less milk. None of the enrolled neonates had any abnormal neurological symptoms.

## DISCUSSION

Following the current standard IV aminophylline dosing conditions for AOP in Thailand, 60% of neonates achieved TDL of theophylline. Factors associated with achieving TDL were being male and a postnatal age of  $\leq 5$  days. After adjusting for gender, postnatal age was the only factor associated with achieving TDL. Adverse effects associated with intravenous aminophylline were tachycardia and feeding intolerance in 44% and 24% of neonates, respectively.

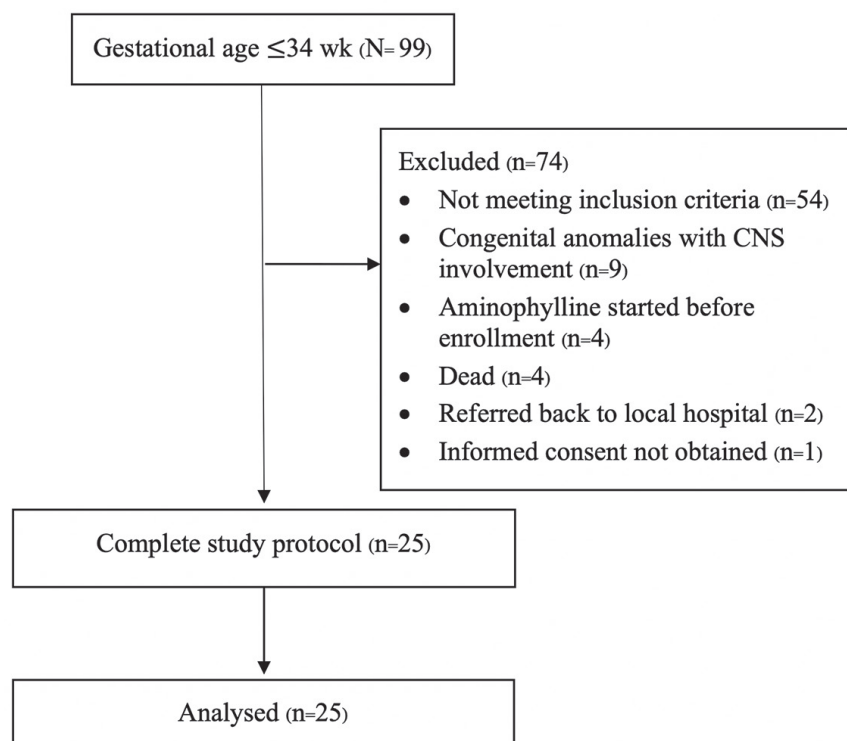


Fig 1. Diagram demonstrating the flow of participants.

**TABLE 1.** Demographic and clinical characteristics of infants (N=25).

Characteristics	N = 25
Female, n (%)	13 (52)
Gestational age, week*	30.4 ± 2
Birth weight, gram*	1278 ± 415
Weight for gestational age, n (%)	
Small for gestational age	6 (24)
Appropriate for gestational age	18 (72)
Large for gestational age	1 (4)
Apgar score <sup>†</sup>	
1 minute	8 (4.25, 8.75)
5 minute	9 (7.25, 9)
Postnatal age, day <sup>†</sup>	4 (1, 8)
Heart rate before aminophylline loading, bpm*	152.8 ± 13.1

<sup>†</sup>median (25%tile, 75%tile)

\*mean ± standard deviation

**Abbreviation:** bpm, beat-per-minute**TABLE 2.** Factors associated with achieving therapeutic drug level of theophylline and adverse effects of aminophylline.

	Achieving therapeutic drug level		p-value
	Yes (n=15)	No (n=10)	
Gestational age, week	30.8 ± 1.9	29.9 ± 2.2	0.30
Birth weight, gram	1354 ± 371.9	1161 ± 468.8	0.26
Gender, n (%)			0.04*
Female	5 (33.3)	8 (80)	
Male	10 (66.7)	2 (20)	
Small for gestational age, n (%)			0.65
Yes	3 (20)	3 (30)	
No	12 (80)	7 (70)	
Postnatal age, day <sup>†</sup>	2 (1, 4)	7.5 (5.5, 15)	0.005*
Postnatal age ≤ 5 days, n (%)	13 (86.7)	2 (20)	0.002*
Serum theophylline concentration <sup>†</sup>	7.5 (7.4, 8.1)	5.5 (5.0, 6.3)	<0.001*
Adverse effects			
Tachycardia, n (%)	7 (46.7)	4 (40)	1.0
Feeding intolerance, n (%)	6 (40)	0	0.05

<sup>†</sup> median (25%tile, 75%tile)

\*p-value &lt;0.05 indicates statistical significance

Due to the narrow therapeutic range of theophylline, it is common practice to measure STC. Adjustments of aminophylline dosage and repeated blood draws for STC is often necessary to obtain drug levels in the therapeutic range. This iatrogenic blood loss can lead to excessive blood transfusion in some cases. Several studies have assessed different aminophylline dosing regimens to ensure TDL of theophylline and to reduce the need for dosage adjustments and repeating STC. A study of infants with birth weight  $\leq 1,500$  g with postnatal age range of 1-52 days comparing the loading dose of 8 mg/kg versus 6 mg/kg of aminophylline, followed by the maintenance dose of 2 mg/kg every 8 hours, had a 79% and 74% success rate in achieving TDL respectively.<sup>6</sup> These success rates were higher than the success rate observed in our study, possibly due to a higher maintenance dose. Another study, performed in infants with gestational age less than 35 weeks, birth weight less than 2,000 g with postnatal age range of 0.4-81.2 hours, compared low loading dose (5 mg/kg) and high maintenance dose (6 mg/kg/day, divided into 3 times) vs high loading dose (8 mg/kg) and low maintenance dose (4 mg/kg/day, divided twice) and noted a TDL success rates of 86% and 68% respectively.<sup>11</sup> This indicates that our starting maintenance dose of 1.5 mg/kg every 8 hours may be suboptimal. None of the participants in our study had a STC higher than 12 mcg/mL, so we still have room within the therapeutic window to increase the maintenance dose of aminophylline. Interestingly, this previous study limited the postnatal age of participants to less than 7 days<sup>11</sup> which related to our finding that a lower postnatal age ( $\leq 5$  days) was associated with achieving TDL. Developmental changes in organs of premature neonates can have a major impact on drug distribution, metabolism and elimination. These developmental changes in pharmacokinetics have been shown to be highly dependent on postnatal age, gestational age and postmenstrual age of the neonate.<sup>7</sup> The relationship between postnatal age and achieving TDL in our study supports postnatal age as a major factor. However, we did not find any association between gestational age and achieving TDL. Bhatt, *et al*<sup>12</sup> used different equations to predict maintenance theophylline dosages for neonates younger than and older than 30 weeks' gestation and the overall success rate of achieving TDL was 74% with requirements for dosage adjustments reduced by 50%.<sup>12</sup> We found that males had a higher chance of achieving TDL of theophylline than females. However, after adjusting for postnatal age  $\leq 5$  days, gender was not significantly associated with achieving TDL. The only factor associated with achieving TDL was a postnatal age  $\leq 5$  days. However, the adjusted odds ratio

of postnatal age had a wide confidence interval, likely due to the relatively small sample size.

Pharmacodynamics in preterm neonates is also affected by developmental changes of the organs, resulting in differences in the expected efficacy or toxicity of theophylline. We observed tachycardia in 44% of participants, however, there was no association between TDL of theophylline and the occurrence of tachycardia. Feeding intolerance may be associated with STC since we observed this adverse event only in neonates who achieved TDL of theophylline. However, feeding intolerance is common in premature infants, especially during the first week of age. None of the participants had any abnormal neurological symptoms. Though these adverse effects were not severe and resolved spontaneously, we recommended that adverse effects should always be monitored and therapeutic drug monitoring is necessary to avoid aminophylline toxicity.

### Limitation of this study

Due to concerns of excessive blood loss in these preterm neonates, we only collected one time-point for the measurement of STC. Also, as this was a pilot study with a small sample size, the ability to make firm conclusions is limited.

## CONCLUSION

The current standard intravenous aminophylline dosing achieved TDL in 60% of neonates. A maintenance dose higher than 1.5 mg/kg every 8 hours could be considered, especially for neonates older than 5 days' postnatal age. Therapeutic drug monitoring should be performed where possible to ensure therapeutic levels and reduce the risk of theophylline toxicity.

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# Efficacy of Communication Skills Training of Preclinical Medical Students via Health Literacy Teaching to High School Students: A Pilot Study

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## ABSTRACT

**Objective:** Communication Skills via Health Literacy (CSvHL) was a pilot elective communication skills training (CST) course, which allowed preclinical medical students to gain communication competence through the experience of being a health educator for high school students (HSSs). The efficacy of CSvHL was explored.

**Materials and Methods:** All 10 medical students were prepared for their HSS-health-educator roles by participating in several observation sessions at an outpatient department and via communication workshops. In-field health education courses were subsequently delivered to HSSs by the medical students. Developments of the medical students' communication skills were fostered through loops of learning activities and regular feedbacks. Assessments of the pre- and post-CSvHL communication skill levels by means of an OSCE, with adapted ComON Check were evaluated by each medical student, a standardized patient, and three medical instructors.

**Results:** In general, the overall and category-specific average ComON Check scores of the whole class were significantly improved after the CSvHL course. The 3 communication defects with the lowest scores in the pre-CSvHL assessments were subsection division, summarization, and comprehension-check while counseling.

**Conclusion:** CSvHL was successfully established as a preclinical-year CST course. The improvements in the ComON Check scores reflected the transformative learning gained from the hands-on experience, individualized CST, and 360° feedback OSCE for communication skill assessment.

**Keywords:** Preclinical communication skills training (CST); early clinical exposure; health literacy; health educator; transformative learning (Siriraj Med J 2021; 73: 532-540)

## INTRODUCTION

Communication skills training (CST) is essential for medical students since productive doctor-patient communication and multidisciplinary collaboration are required for qualified medical practitioners in their daily practice.<sup>1-4</sup> However, CST is typically not specifically delivered throughout the medical curriculum. Some

institutes provide CST separately from basic clinical-skills training (e.g., history taking and counseling) during the preclinical years, whereas others expect communication competence to be indirectly gained via clinical clerkships (e.g., during ward rounds, bedside teaching, and medical report discussions) during the clinical years without any explicit CST. It has been suggested that CST in clinical

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year clerkships should be promoted via a repetitive and supportive environment, with structured training that is adaptable and tailored to medical-students.<sup>5,6</sup> However, with promising expectations, carefully-selected clinical skills and topics might be introduced and taught sooner, as part of **preclinical CST**; this early exposure has the potential to assist medical students to perform better during their later clinical years.<sup>7-9</sup>

**Health literacy** refers to the skills needed to obtain, interpret, and utilize health information<sup>10-12</sup> and comprises a wide range of biomedical knowledge and life skills. It is an appropriate foundation topic to be taught and practiced during the preclinical years. Aspects of fundamental healthcare – such as smoking cessation and diet control – can be selected to enable preclinical medical students to practice the communication skills related to patient counselling, despite lacking in-depth medical knowledge. Hess et al.<sup>13</sup> reported on a pilot project at Harvard Medical School that allowed medical students, in collaboration with the medical librarian, to deliver a short, plain-language, health-literacy presentation to adult, multi-ethnic learners. A post-intervention survey revealed that 88% of those students had improved their physician-patient communication skills, including adult learner interaction, health communication, and plain-language expression abilities. In another study by Milford et al.<sup>14</sup>, preclinical first- and second-year medical students were trained in pediatric obesity intervention strategies. They were involved with Head Start children, parents, and staff in the conduct of pediatric-obesity education programs and the setting of the related management goals for the families concerned. Pre- and post-intervention surveys found that the students had made significant improvements in confidence in their health-literacy knowledge and skills. Moreover, the sophistication of communication compositions (e.g., the pre-existing knowledge and health behaviors of parents, patients, and the community, doctor-patient interactions of empathy, and family concerns) were also acknowledged by the medical students. Hence, with such supporting evidence, involving medical students in the provision of health education for patients or communities appears to have the potential to improve quality of care, enhance medical education, and develop communication skills.<sup>8,15-20</sup>

Conducted in academic year 2018, **Communication Skills via Health Literacy (CSvHL)** was a pilot elective course for preclinical medical students. It had two major aims. The first was to develop the communication skills of preclinical medical students via direct experience gained from teaching and facilitating health education at a high school.<sup>21-27</sup> By teaching health education to high school

students (HSSs), the medical students were encouraged to identify and prepare relevant information and to practice their presentation and communication skills. Wong et al. postulated that medical students assuming the role of health educators gain high levels of trust and comfort from HSSs. More specifically, Wong and colleagues proposed that the unique position of medical students-healthcare providers who are only slightly older than HSSs – allows them to foster trust via peer relationships with HSSs rather than by adopting the more traditional authoritarian – role of a teacher.<sup>28</sup> In turn, the bonding enables the medical students to freely prepare mini-health education courses for the HSSs that incorporate an active-learning teaching style and are less stressful to deliver than with real-life patients. Moreover, essential communication skills are intensified through the preparation of the courses in that the medical students need to consider the level of the audience, the appropriate media to be utilized, and the language level to be employed. The second aim of the CSvHL course was to enhance health literacy awareness, thereby motivating the medical students to gain a comprehensive medical knowledge which could be applied in their future clinical practice.<sup>10,19</sup>

This study explored the effectiveness of the CST provided to the participating medical students by the CSvHL course.

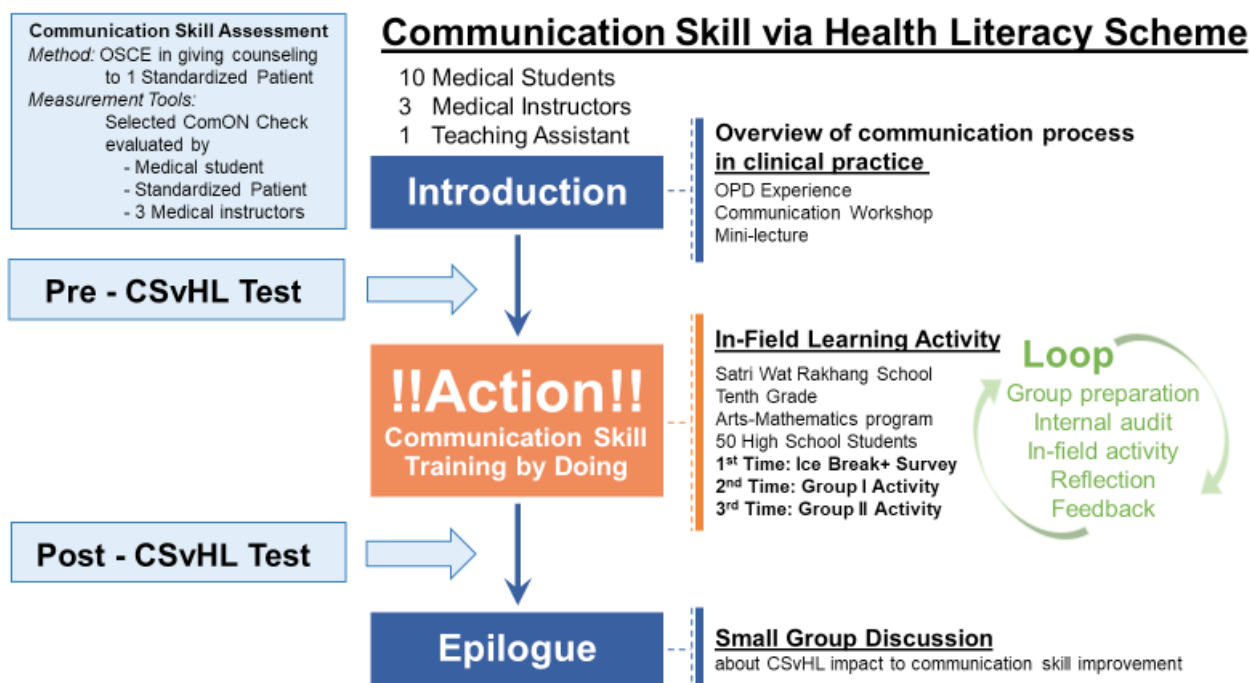
## **MATERIALS AND METHODS**

The “Communication Skill via Health Literacy (CSvHL)” course provided a health-educator experience for medical students and assessed their communication skills (Fig 1). Below are details of the participants, the curricular learning activities, and the communication skills assessments.

### **Participants**

*Medical students:* The participants comprised all ten of the 2<sup>nd</sup> and the 3<sup>rd</sup> year medical students who enrolled in the pilot CSvHL elective course in academic year 2018. They completed an informed consent form, in accordance with Siriraj Institutional Review Board protocol 580/2018 (EC1).

*Medical instructors:* Three instructors – each with 10- to 15-years’ teaching experience – assumed the roles of advisors for the medical students. They were drawn from the Radiation Oncology Division of Radiology Department (PD); the Department of Preventive and Social Medicine (TJ); and the Department of Physiology and the Health Science Education Excellence Center (YD). In addition, a 6<sup>th</sup> year medical student took on



**Fig 1. Communication Skills via Health Literacy (CSvHL) scheme.** The three phases of the CSvHL course are illustrated. To determine the communication skills improvements of the medical students, a pre-CSvHL assessment was conducted after the Introduction, while a post-CSvHL assessment was made before the Epilogue.

**Abbreviations:** OPD, outpatient department; OSCE, Objective Structured Clinical Examination.

the role of teaching assistant and curriculum developer during the externship (TP).

**High school students (HSSs):** Fifty female, 10<sup>th</sup> grade, Arts-Mathematics-program students from Satri Wat Rakhang School were included as the subjects for the in-field health education program. Informed consent was obtained as per Siriraj Institutional Review Board protocol 580/2561 (EC1). Satri Wat Rakhang School is a girls' school which is located near Siriraj Hospital. It was selected because of its accessibility.

### CSvHL curriculum

The course was divided into 3 phases: Introduction, Communication Skills Training by Doing, and Epilogue (Fig 1).

In the introductory phase, the medical students were given an overview of the communication processes utilized in clinical practice via observation sessions at the outpatient department, communication-workshop group activities, and mini-interactive lectures. Each of the aforementioned activities was 2- to 3-hours long, and they were conducted once per week for 3 consecutive weeks. The baseline communication skills of the students were assessed at the end of the phase. Verbal and nonverbal communication-skill learning points were identified for individual students, allowing the instructors to tailor the advice to be given to each student during the subsequent lessons.

As to the second phase, the medical students developed their communications skills through hands-on experience. To this end, they were assigned to 2, in-field, health education groups, with the 2<sup>nd</sup> and 3<sup>rd</sup> year students being equally distributed between the groups. To promote engagement with the HSSs, icebreaking activities were arranged to facilitate the introduction of the medical students and their subsequent surveying of the topics of interest to the HSSs. Each of the 2 education groups was then requested to devise a health education session for delivery to the HSSs that incorporated health literacy as one of its learning points. Although the learning task was required to be interactive or activity-based, no other limitation was placed on its design. The loop of presentation preparation, internal audit, and onstage HSS teaching activity lasted about 4 weeks for each education group. While one group presented its teaching activity, the members of the other group helped the medical instructor by playing the role of commentator in the internal audit and facilitator in the onstage period. Group and individual performance reflections and feedback were given for every internal audit and on-stage presentation.

In the epilogue phase, a post-CSvHL communication assessment was executed. During the following week, a group discussion about how the CSvHL course had improved the medical students' communication skills was held as the end of the course.

### Communication skills assessment and statistical analysis

As depicted in Fig 1, pre- and post-CSvHL communication skills competency was assessed by an Objective Structured Clinical Examination. Relevant materials were given to the medical students one week prior to each assessment to complement the clinical basics used in the OSCE. During a 5-minute session, each medical student was required to take a short history to probe a standardized patient's (SP's) problem before giving medical advice to the SP; 3 medical instructors observed the interaction through one-way glass. After the session, each student presented a 2-minute self-reflection of their performance before being given a 3-minute feedback by the instructors and the SP on what worked well and areas for improvement.

The simulation scenarios developed by the 3 instructors and the teaching assistant covered all scoring criteria encompassed in the communication skills assessment. Only one experienced SP, who had an MSc in psychology and was a postgraduate educator for 2 years, participated in both the pre- and post-assessments. The SP was well prepared for the scenario performance, feedback, and evaluation of the medical student.

For the pre-assessments executed after the introductory phase, pairs of students were required to advise a 1<sup>st</sup>-trimester pregnant woman who wanted to quit smoking. As to the post-assessments, they were executed one week after completing the CSvHL course. For those assessments, the medical students had to individually counsel a Type 1 diabetes mellitus patient on the choice of an appropriate insulin pump injector. The diabetic patient had a history of poor insulin-injection compliance due to a hectic lifestyle stemming from her work as a commercial designer. With both the pre- and post-assessments, the simulated patient and the 3 instructors were identical; they were blinded to the pre-assessment score before performing the post-CSvHL communication assessment.

Selected categories from ComON Check<sup>29-31</sup> namely, the starting and ending of a conversation, the structure of a conversation, general communication skills, and overall evaluation of a conversation (Fig 2) were evaluated by each medical student, the SP, and the 3 medical instructors. A paired t-test of the pre- and post-assessment scores was performed. Statistical significance was deemed to be a *p*-value of 0.05 or less.

#### How do you assess the communicative competence of the physician in this conversation?

	Strongly Disagree			Strongly Agree		
<b>A Start of the conversation</b>						
<b>A1</b> Does the physician initiate the conversation appropriately?	O	O	O	O	O	
<b>A2</b> Does the physician manage to get an idea of the patient's perspective at the beginning of, or during the consultation?	O	O	O	O	O	
<b>B Structure of conversation</b>						
<b>B1</b> Does the physician actively give structure to the conversation (set an agenda of central topics)?	O	O	O	O	O	
<b>B2</b> Does the physician set sub-sections in the course of the conversation (in detail)?	O	O	O	O	O	
<b>D End of conversation</b>						
<b>D1</b> Does the physician summarize the content of the consultation and do they close the conversation appropriately?	O	O	O	O	O	
<b>E General communication skills</b>						
<b>E1</b> Does the physician use clear and appropriate words during the conversation?	O	O	O	O	O	
<b>E2</b> Does the physician use appropriate non-verbal communication during the consultation?	O	O	O	O	O	
<b>E3</b> Does the physician adjust his pace during the consultation and does he make appropriate pauses?	O	O	O	O	O	
<b>E4</b> Does the physician offer the patient the chance to ask questions during the consultation?	O	O	O	O	O	
<b>E5</b> Does the physician check whether the patient has understood the consultation?	O	O	O	O	O	
<b>F Overall Evaluation</b>						
<b>F1</b> How do you assess the communication skills of the physician in this conversation?	O	O	O	O	O	

Fig 2. Adapted ComON Check.

Radziej et al. (2017). How to assess communication skills? Development of the rating scale ComON Check-Evaluation of communication skills.<sup>11</sup>

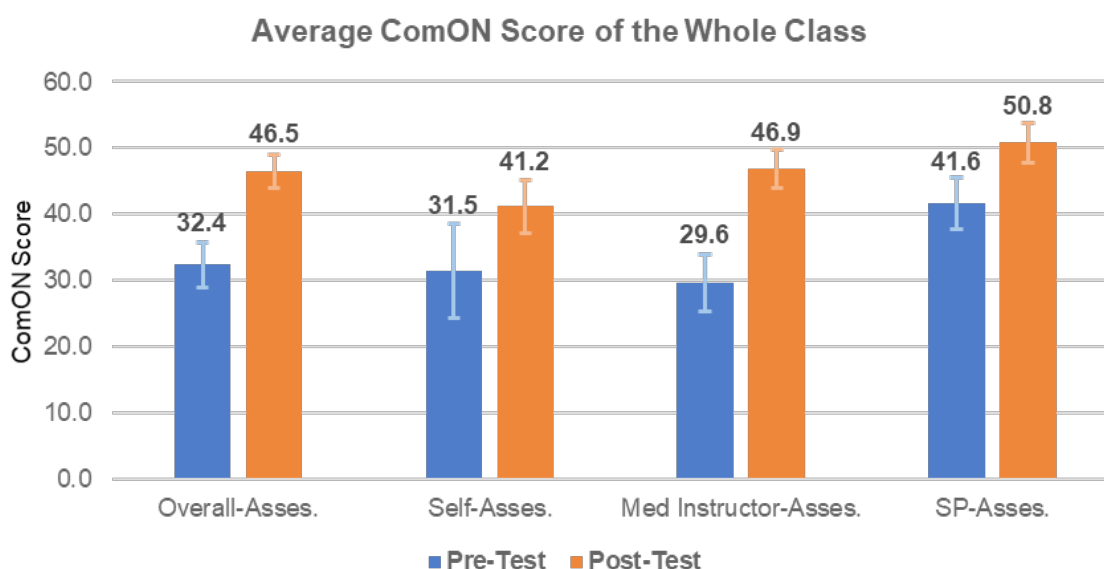
## RESULTS

In the 2 in-field learning activities, each medical student participated in one as an activity leader and the other as a facilitator.

The first group of medical students conducted an interactive lecture on weight control that was based on the educational gaming platform, Kahoot! The comprehension of the HSSs about weight control (e.g., body composition, energy expenditure, nutrition facts, and diet-control strategies) were challenged with 10 multiple-choice questions. After each question, additional discussion was held to clarify the HSSs' perceptions.

The second group of medical students examined the mythology of abnormal menstruation using a small-group discussion approach, with the HSSs divided into groups of 5-7 students each. True and false information on menstruation was drawn from social media sites (Line, Instagram, Facebook, and a popular Thai web-board) and transformed into a series of statements. Each discussion group had to decide whether to believe and share the given information via social media or to follow the suggestions of the simulated advisories. Answers were scored. Each social media statement was then reviewed at length after the activity, with the incorrect answers of the HSSs being discussed. The HSS group with the highest score received a small prize.

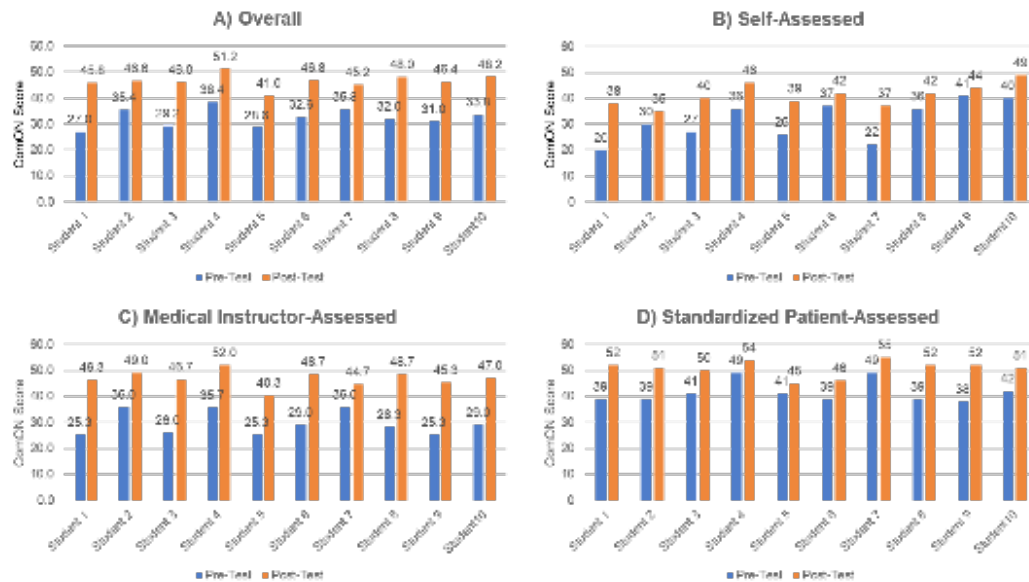
An analysis of the communication skill assessments revealed that the average ComON Check score of the whole class improved significantly (Fig 3). Compared with the overall scores, those given by the medical instructors tended to be low whereas the scores assigned by the SP tended to be high. The self-assessment scores showed the highest standard deviation. The 3 categories with the lowest scores in the pre-CSvHL assessments were B2 (setting subsections), D1 (concluding), and E5 (checking patient comprehension of a conversation). The total pre-assessment scores of 3 medical students were less than half the ComON Check score when assessed by the medical instructors. In a comparison of the ComON Check scores from the pre- and post-CSvHL assessments, most ComON Check categories assessed by the medical students, the instructors, and the SP demonstrated a significant improvement. The exceptions were A1 (appropriate initiation of a conversation), E2 (using appropriate nonverbal communication during the consultation), and E4 (offering the chance to ask questions during the consultation). The scores for these 3 items improved without statistical significance when evaluated by the medical students. Similarly, the scores assigned by the SP for both E1 (using clear and appropriate wording) and E2 went up, though with no significance. The data are presented in Fig 4 and Table 1.



**Fig 3.** Average ComON Check scores of the whole class.

**Abbreviations:** Asses, assessed; Med Instructor, medical instructor; SP, standardized patient

### Individual Medical Student ComON Score



**Fig 4.** Individual medical students' ComON Check scores.

## DISCUSSION

CSvHL was successfully established as a preclinical-year CST course. It is suggested that the significant improvements in the ComON Check scores resulted from 2 factors. The first of these is the transformative learning gained from the hands-on experience in communication in various settings. The second contributing factor is the individualized feedback and training provided by the areas of improvements individually extracted from the pre-CSvHL communication skills assessments.

From the medical students' perspectives, the learning of communication skills proved to be challenging and complex. Their lack of clinical experience limited their communication abilities and their perspectives during the communication skills training. In this pilot program, the hands-on experience of teaching the HSSs provided the medical students with the opportunity to simultaneously upskill and understand the learning process, to which the communication mechanisms homogeneously relate. By being cycled in each in-field learning activity, the communication components—learning objectives, communicator factors, and recipient factors—were critically re-evaluated, leading to a more effective teaching strategy. This was evident in the shift of the learning activity from an interactive lecture using a game-based learning platform to small group discussions, which was considered as a sign of transformative learning being experienced by the medical students.<sup>32,33</sup> In the reflection and feedback session following the first in-field activity, the interactive lecture was identified as having provided only health knowledge, being rather dull, and failing to achieve health literacy skill training

of the HSSs. Learning from the first group, the second group decided to develop a more interactive activity and facilitated the in-action health decision-making.

Moreover, with the pre-CSvHL communication skills assessment being made from 3 perspectives: the medical students, the SP, and the 3 mentors (a “360° behavior-oriented feedback” approach<sup>34,35</sup>), the potential verbal and nonverbal communication-skill learning points were identified. These points enabled the instructors to focus on the medical students' performances and give specific feedback. This approach was proved to be useful, especially during the in-field activity, as the instructor feedback enhanced the efficacy of the CST.<sup>36,37</sup> The end result was that the medical students could communicate better, as evidenced by the improved ComON Check scores.

As to the communication skills assessments using the selected ComON Check categories, the relatively low pre-CSvHL scores given by the medical instructors reflect the high expectations of medical professions, consistent with result of the prior study which lower scores were given by the experienced SP.<sup>38</sup> On the other hand, the high scores given by the SP might signify that the medical students who participated in the CSvHL course may have possessed good communication skills before their enrollment in the course. This suggests that the study may have had a selection bias.

Other than the possibility of a selection bias, the small sample size could have affected the statistical significance of the improvements in the ComON Check scores given by the medical students and SP. Moreover,

**TABLE 1.** Average ComON Check Scores  $\pm$  standard deviations.

ComON Check categories	Overall assessments				Self-assessments				Medical instructor assessments				Standardized patient assessments			
	Pre-test	Post-test	Change	P (t-test)	Pre-test	Post-test	Change	P (t-test)	Pre-test	Post-test	Change	P (t-test)	Pre-test	Post-test	Change	P (t-test)
<b>A Start of the conversation</b>																
<b>A1</b> Does the physician initiate the conversation appropriately?	3.1 $\pm$ 0.4	4.3 $\pm$ 0.5	1.2 $\pm$ 0.6	0.0002	3.3 $\pm$ 1.2	3.7 $\pm$ 0.8	0.4 $\pm$ 1.4	0.2113	2.9 $\pm$ 0.4	4.5 $\pm$ 0.4	1.6 $\pm$ 0.4	<0.0001	3.6 $\pm$ 0.5	4.5 $\pm$ 0.9	0.9 $\pm$ 1.2	0.0271
<b>A2</b> Does the physician manage to get an idea of the patient's perspective at the beginning of, or during the consultation?	3.1 $\pm$ 0.2	4.5 $\pm$ 0.3	1.4 $\pm$ 0.3	<0.0001	3.4 $\pm$ 0.8	4.1 $\pm$ 0.5	0.7 $\pm$ 0.8	0.0124	2.8 $\pm$ 0.4	4.5 $\pm$ 0.3	1.8 $\pm$ 0.5	<0.0001	3.8 $\pm$ 0.4	4.7 $\pm$ 0.6	0.9 $\pm$ 0.8	0.0050
<b>B Structure of conversation</b>																
<b>B1</b> Does the physician actively give structure to the conversation (set an agenda of central topics)?	2.8 $\pm$ 0.4	4.2 $\pm$ 0.3	1.4 $\pm$ 0.5	<0.0001	2.8 $\pm$ 0.7	3.9 $\pm$ 0.7	1.1 $\pm$ 1.0	0.0058	2.6 $\pm$ 0.5	4.1 $\pm$ 0.3	1.5 $\pm$ 0.5	<0.0001	3.5 $\pm$ 0.5	4.7 $\pm$ 0.6	1.2 $\pm$ 0.9	0.0013
<b>B2</b> Does the physician set sub-sections in the course of the conversation (in detail)?	2.8 $\pm$ 0.4	4.1 $\pm$ 0.3	1.3 $\pm$ 0.4	<0.0001	2.7 $\pm$ 0.9	3.9 $\pm$ 0.8	1.2 $\pm$ 0.9	0.0112	2.5 $\pm$ 0.4	4.1 $\pm$ 0.3	1.6 $\pm$ 0.5	<0.0001	3.7 $\pm$ 0.5	4.6 $\pm$ 0.5	0.9 $\pm$ 0.5	0.0004
<b>D End of conversation</b>																
<b>D1</b> Does the physician summarize the content of the consultation and do they close the conversation appropriately?	2.7 $\pm$ 0.5	4.2 $\pm$ 0.4	1.5 $\pm$ 0.5	<0.0001	2.2 $\pm$ 1.0	4.0 $\pm$ 1.0	1.8 $\pm$ 0.9	<0.0001	2.5 $\pm$ 0.7	4.1 $\pm$ 0.4	1.6 $\pm$ 0.7	<0.0001	3.7 $\pm$ 0.5	4.7 $\pm$ 0.5	1.0 $\pm$ 0.8	0.0019
<b>E General communication skills</b>																
<b>E1</b> Does the physician use clear and appropriate words during the conversation?	3.1 $\pm$ 0.4	4.3 $\pm$ 0.2	1.1 $\pm$ 0.3	<0.0001	2.9 $\pm$ 0.7	3.7 $\pm$ 0.5	0.8 $\pm$ 0.7	0.0054	2.9 $\pm$ 0.4	4.4 $\pm$ 0.3	1.5 $\pm$ 0.5	<0.0001	4.0 $\pm$ 0.6	4.4 $\pm$ 0.5	0.4 $\pm$ 0.7	0.0519
<b>E2</b> Does the physician use appropriate non-verbal communication during the consultation?	3.2 $\pm$ 0.4	4.1 $\pm$ 0.3	0.8 $\pm$ 0.3	<0.0001	3.2 $\pm$ 1.0	3.4 $\pm$ 0.7	0.2 $\pm$ 1.2	0.3097	2.9 $\pm$ 0.5	4.2 $\pm$ 0.4	1.3 $\pm$ 0.5	<0.0001	4.2 $\pm$ 0.4	4.3 $\pm$ 0.5	0.1 $\pm$ 0.5	0.2955
<b>E3</b> Does the physician adjust his pace during the consultation, and does he make appropriate pauses?	3.0 $\pm$ 0.4	4.2 $\pm$ 0.3	1.2 $\pm$ 0.3	<0.0001	2.8 $\pm$ 0.7	3.5 $\pm$ 0.7	0.7 $\pm$ 0.8	0.0124	2.8 $\pm$ 0.4	4.3 $\pm$ 0.4	1.5 $\pm$ 0.3	<0.0001	3.7 $\pm$ 0.8	4.5 $\pm$ 0.5	0.8 $\pm$ 0.9	0.0112
<b>E4</b> Does the physician offer the patient the chance to ask questions during the consultation?	2.9 $\pm$ 0.5	4.2 $\pm$ 0.4	1.3 $\pm$ 0.6	<0.0001	3.1 $\pm$ 1.2	3.7 $\pm$ 0.6	0.6 $\pm$ 1.0	0.0557	2.6 $\pm$ 0.6	4.1 $\pm$ 0.5	1.5 $\pm$ 0.7	<0.0001	3.6 $\pm$ 0.8	4.8 $\pm$ 0.4	1.2 $\pm$ 0.7	0.0005
<b>E5</b> Does the physician check whether the patient has understood the consultation?	2.7 $\pm$ 0.5	4.2 $\pm$ 0.5	1.5 $\pm$ 0.5	<0.0001	2.4 $\pm$ 1.2	3.8 $\pm$ 1.2	1.4 $\pm$ 0.7	<0.0001	2.4 $\pm$ 0.6	4.1 $\pm$ 0.4	1.7 $\pm$ 0.7	<0.0001	3.8 $\pm$ 0.7	4.7 $\pm$ 0.5	0.9 $\pm$ 0.7	0.0019
<b>F Overall evaluation</b>																
<b>F1</b> How do you assess the communication skills of the physician in this conversation?	3.0 $\pm$ 0.4	4.3 $\pm$ 0.3	1.4 $\pm$ 0.4	<0.0001	2.7 $\pm$ 0.9	3.9 $\pm$ 0.5	1.2 $\pm$ 1.2	0.0065	2.7 $\pm$ 0.5	4.3 $\pm$ 0.3	1.6 $\pm$ 0.5	<0.0001	4.0 $\pm$ 0.6	4.9 $\pm$ 0.3	0.9 $\pm$ 0.7	0.0019
<b>Sum ComON Check Score</b>	32.4 $\pm$ 3.4	46.5 $\pm$ 2.4	14.1 $\pm$ 2.6	<0.0001	31.5 $\pm$ 7.1	41.2 $\pm$ 4.1	9.7 $\pm$ 4.7	<0.0001	29.6 $\pm$ 4.3	46.9 $\pm$ 3.0	17.3 $\pm$ 3.8	<0.0001	41.6 $\pm$ 3.9	50.8 $\pm$ 3.0	9.2 $\pm$ 3.5	<0.0001

only the short-term outcomes of the communication skills improvement were explored, and the target group of the in-field learning activity was HSSs, not real patients. Both limitations were accepted while the study was being designed: doing so kept an appropriate teacher-per-student ratio and enabled the course to be run with a limited number of instructors.

The 3 communication defects with the lowest scores in the pre-CSvHL assessment (subsection division, summarization, and comprehension checking while counseling) should be highlighted in the counseling part of a future CST course. Including an Objective Structured Clinical Examination and seeking SP feedback are also considered crucial.<sup>9,35,39-45</sup> To achieve improvements in medical students' communication skills and, potentially, their eventual medical performance, both features should be incorporated in the CST.<sup>1,7</sup> Furthermore, the identification of the long-term outcomes-such as sustained communication-skills improvement and overall clinical proficiency-should be explored. Even though the pilot CSvHL course may be a promising vehicle for preclinical CST, a larger class may alter its efficacy by limiting the mentor-per-medical-student ratio and the in-field activities. Teacher-learner adjustment is therefore mandatory to achieve the optimal learning outcomes in any altered circumstances.

## CONCLUSION

The pilot CSvHL was proved to be successful as a preclinical-year CST course for a small class size. The improvements in the ComON Check scores reflected the transformative learning gained via hands-on experience and individualized CST. For assessment purposes, an Objective Structured Clinical Examination and 360° feedback are crucial. Teacher-learner adjustment is advised for larger CST classes to ensure that there is an appropriate mentor-per-medical-student ratio for the in-field activities.

### Practical points:

- **Communication Skills via Health Literacy (CSvHL)** provides the experience of being a health educator for high school students (HSSs).
- Transformative learning gained from the hands-on experience, individualized CST, and 360° feedback OSCE is crucial for communication skill improvement.
- The 3 communication defects in medical students from this study were subsection division, summarization, and comprehension-check while counseling.

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# Percutaneous Radiofrequency Ablation Treatment of Hepatocellular Carcinoma in Caudate Lobe Using Expandable Electrodes

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## ABSTRACT

**Objective:** To evaluate the outcome of radiofrequency (RF) ablation using expandable electrodes in the treatment of hepatocellular carcinoma (HCC) located in the caudate lobe.

**Materials and Methods:** Between January 2011 and April 2017, 29 consecutive patients with HCC at the caudate lobe were treated with RF ablation using expandable electrodes. The electrodes were placed on the targeted tumor under combined ultrasound and computed tomography (CT) guidance for each tumor in all the patients. Out of the 29 cases, 19 (65.5%) were accessed via the left hepatic lobe. The technical success, primary efficacy, local tumor progression, secondary efficacy, overall survival, and complications were evaluated. Univariate analysis was performed of the various prognostic factors for technical success, primary efficacy, and local tumor progression.

**Results:** The technical success rate was 86.2%, primary efficacy was 89.7%, and secondary efficacy was 82.8%. The local tumor progression (LTP) rate was 12.3% at one year and 31.5% at two years. The median time of LTP was 6.9 months. The overall survival rate was 85.8% at one year and 57.1% at two years. Ten patients died during the follow-up period (mean 22.5 months; with a range of 3.6–53.2 months). A minor complication of asymptomatic biloma was found in one patient (3.5%). Small-sized tumors ( $\leq 2$  cm) and Spiegel's lobe location had significantly better treatment outcomes ( $p = 0.007$  and  $0.045$ , respectively).

**Conclusion:** Radiofrequency ablation using expandable electrodes is feasible and safe in treating HCCs located in the caudate lobe, especially for small-sized tumors ( $\leq 2$  cm).

**Keywords:** Caudate lobe; Expandable electrodes; Hepatocellular carcinoma; Radiofrequency ablation (Siriraj Med J 2021; 73: 541-548)

## INTRODUCTION

Treatment of hepatocellular carcinoma (HCC) in the caudate lobe, to date, is challenging due to the deep location; proximity to the IVC and main portal vein; the unique anatomy of the caudate lobe, including the arterial feeder, the portal venous supply, and the draining vein

(directly to the IVC), and the complex biliary drainage, either by surgical resection, or through percutaneous ablation, or via transarterial treatment.<sup>1-4</sup>

With regard to the surgical resection of HCC in the caudate lobe, Tanaka et al.'s study in 20 patients showed a relatively poor prognosis compared to procedures

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performed at other locations, owing to the intraoperative blood loss, longer duration of operation, higher chances of post-operative complications, and more frequent intrahepatic recurrent rate, and a significantly poor survival rate.<sup>3</sup>

There are a limited number of studies on percutaneous RF ablation of HCC in the caudate lobe. Seror et al. studied 10 cases that underwent percutaneous RF ablation in the caudate lobe, with 8 cases being HCC. All the procedures were performed using single straight needle electrode. The results showed that percutaneous RF ablation had a high technical success rate (about 90%), without major complications. However, the local recurrence rate was relatively high, compared to other locations, possibly due to the heat sink effect from the adjacent large vessels, which made it hard to achieve an adequate ablation margin.<sup>5</sup>

In Yamakado et al.'s study, percutaneous RF ablation was performed in 6 cases of HCC in the caudate lobe, also, using a single straight needle electrode.<sup>6</sup> The difference was in the use of CT scan as imaging guidance in all the cases. The results showed not only a higher technical success rate of 100%, but also had the ability to achieve local tumor control in all the cases, with a mean follow-up period of 10 months.

Nishigaki et al.'s study in 2012 performed percutaneous RF ablation in 20 patients with HCC in the caudate lobe, which also showed similar results, with a 100% technical success rate without major complications. In these cases, however, the local recurrence rate was relatively high (22.3%) compared to at the other locations (4.5%).<sup>7</sup>

With regard to an alternative treatment of HCC in the caudate lobe with transarterial chemoembolization (TACE), Kim et al. showed that the key to achieving treatment efficacy was a successful super-selection of the caudate artery. However, local tumor progression (LTP) was still relatively high (about 64%).<sup>8</sup>

In terms of combined treatment using TACE and RF ablation for treating HCC in the caudate lobe, Fujimori et al. (2012) and Hyun et al. (2016) also used a single straight electrode needle in both studies.<sup>9,10</sup> Similar results were noted, without significant difference in the results between RF ablation used alone and in combined treatment regarding the local tumor control. However, with regard to the survival rate, the combined treatment was seen to be better.<sup>11,12</sup> For some small HCCs, combined treatment is effective that are not visible in unenhanced CT and ultrasound.<sup>13</sup>

Since relatively fewer studies have been reported regarding the use of percutaneous RF ablation for the treatment of HCC in the caudate lobe, and all the prior

studies used a non-expandable RF ablation electrode, the purpose of this study was to evaluate the outcome of RF ablation using an expandable electrode in the treatment of HCC located in the caudate lobe in experienced hands.

## MATERIALS AND METHODS

This is a retrospective study performed over the period January 2011 to April 2017. After approval from the institutional review board, with protocol number (Si 109/2017 (EC2)), the electronic records in the radiological information system (RIS) were searched for patients with HCC in the caudate lobe who had underwent RF ablation.

Out of a total of 1,292 ablation procedures in the liver, including 1,251 RF ablations, 19 IRE (irreversible electroporation), and 22 microwave ablations, the records of 29 patients with HCC at the caudate lobe treated with RF ablation by an expandable electrode were obtained. The patients included 21 males and 8 females with mean age of  $65.4 \pm 10.8$  years old. All the patients had liver cirrhosis, mostly with an etiology of hepatitis B ( $n = 13$ ) (Table 1). Child-Pugh classifications A and B were obtained in 24 patients and 5 patients, respectively. Serum alpha-fetoprotein (AFP) levels with the mean and median values of 109.0 and 5.69 ng/ml, respectively, (range, 1.0-2,444.0 ng/ml) were noted.

### Tumor characteristics

The diagnosis of HCC at the caudate lobe was based on either the imaging criteria or the pathological results. The mean size of the tumor was  $1.78 \pm 0.80$  cm (range 0.7 - 4.0 cm). Tumor size was classified into two categories (size  $\leq 2$  cm;  $n = 18$ , and  $> 2$  cm;  $n = 11$ ). Location of the tumor was classified according to three sub-segments of the caudate lobe: Spiegel's lobe (48.3%), paracaval portion (41.4%), and caudate process (10.3%) (Table 1). There were 7 lesions (24.1%) that underwent TACE before the ablation treatment.

### RF ablation procedure

Percutaneous RF ablation procedures were performed by one of the five interventional radiologists in our institution, who had at least three years' experience. The procedures were performed under intravenous sedation, using expandable RF electrodes (Leveen needle electrode; Boston Scientific, Marlborough, Massachusetts, USA). All the procedures were performed under combined ultrasound (iU22; Philips Healthcare, Amsterdam, the Netherlands) and CT (Optima CT660; GE Healthcare, Chicago, Illinois, USA) guidance, as the standard protocol in the institution. Depending on the tumor size and

**TABLE 1.** Patient demographics and tumor characteristics.

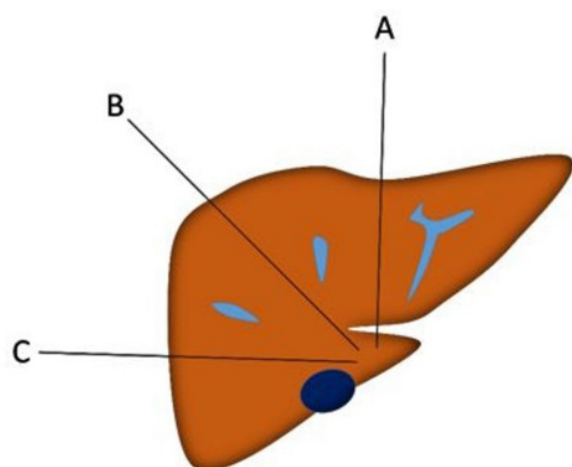
Patients' characteristics	
Age (years)	65.4 ± 10.8 (range, 34–84)
Sex (male: female)	21:8
Etiology of liver cirrhosis	
Chronic hepatitis B	13 (44.8%)
Chronic hepatitis C	7 (24.1%)
Cryptogenic cirrhosis	6 (20.7%)
NASH	2 (6.9%)
Alcoholic cirrhosis	1 (3.5%)
Child-Pugh classification	
A	24 (82.8%)
B	5 (17.2%)
AFP Median	5.69 ng/ml (range, 1.0–2,444.0)
Tumor characteristics	
Mean tumor size (cm)	1.78 ± 0.80 (range, 0.7–4.0)
Size classified	
≤ 2 cm	18 (62.1%)
> 2 cm	11 (37.9%)
Tumor location	
Spiegel's lobe	14 (48.3%)
Paracaval portion	12 (41.4%)
Caudate process	3 (10.3%)
Prior TACE treatment of the lesion	7 (24.1%)
Subcapsular location	18 (64.3%)
Perivascular location	16 (57.1%)

**Abbreviations:** NASH, Non-alcoholic steatohepatitis; AFP, Alpha-fetoprotein; TACE, Transarterial chemoembolization

the depth from the skin, the diameter and the length of the RF electrode were determined by the performing physicians. Three types of access route were used: supine approach through the left lobe, right anterior approach, and right posterior approach (Fig 1). The aim of the ablation treatment was to cover the visualized tumor area and to generate a sufficient ablation zone of at least 5 mm margin, which was could be as an echogenic cloud

on the real-time ultrasonography.

The imaging assessment protocol at this institution includes multiphase CT of the liver or MRI of the liver with a hepatocyte specific agent; performed at 1, 3, 6, 9, and 12 months after the ablation, and thereafter every 3-6 months. The treatment response definitions were based on the Society of Interventional Radiology Standardization of Terminology and Reporting.<sup>14</sup>



**Fig 1.** Schematic diagram showing three access sites for the caudate lobe approach;

- A. – left lobe approach
- B. – right anterior approach
- C. – right posterior approach

### Treatment response assessment

Technical success was determined as complete ablation of a targeted tumor at one month imaging follow-up. Primary efficacy was achieved if there was disappearance of the tumor at the ablation site without evidence of a residual viable tumor at three months imaging follow-up. Local tumor progression (LTP) was determined as any imaging follow-up after three months showing evidence of a recurrent tumor. Secondary efficacy was defined as successful local tumor control by re-ablation of the LTP using RF ablation.

Follow-up concluded at the time of death, liver transplantation, or the last clinical follow-up evaluation. The primary endpoints of the study were LTP and control of the tumor growth. The secondary endpoint of the study was the overall survival rate.

Complications were analyzed by imaging findings, clinical symptoms, and laboratory examinations after treatment and were ranked according to the SIR standard classification.<sup>15</sup>

### Risk factors analyzed

Risk factors related to LTP include the tumor size, location of the tumor, proximity to the large vessels, and proximity from the liver capsule and the adjoining critical organs that might be injured during ablation. Perivascular location was established as the tumor abutting vessels >3 mm in diameter. Subcapsular location was defined as a tumor located less than 10 mm from the liver capsule. Adjoining critical organs at risk were contemplated if located <10 mm from the tumor.

### Statistical analysis

Analysis of the data was done by using the chi-square test to determine whether technical success, primary efficacy, secondary efficacy, and local tumor progression were related to the size of the tumor (classified as  $\leq 2$  cm and  $> 2$  cm), access route, and location of the tumor, prior to TACE treatment, and the Child–Pugh classification. Kaplan–Meier analysis was used to assess the survival rate and local tumor progression rate.

All the statistical analyses were performed using IBM SPSS Statistics for Windows version 23.0 (IBM Corporation, Armonk, New York). A difference with  $p < 0.05$  was considered to be statistically significant.

## RESULTS

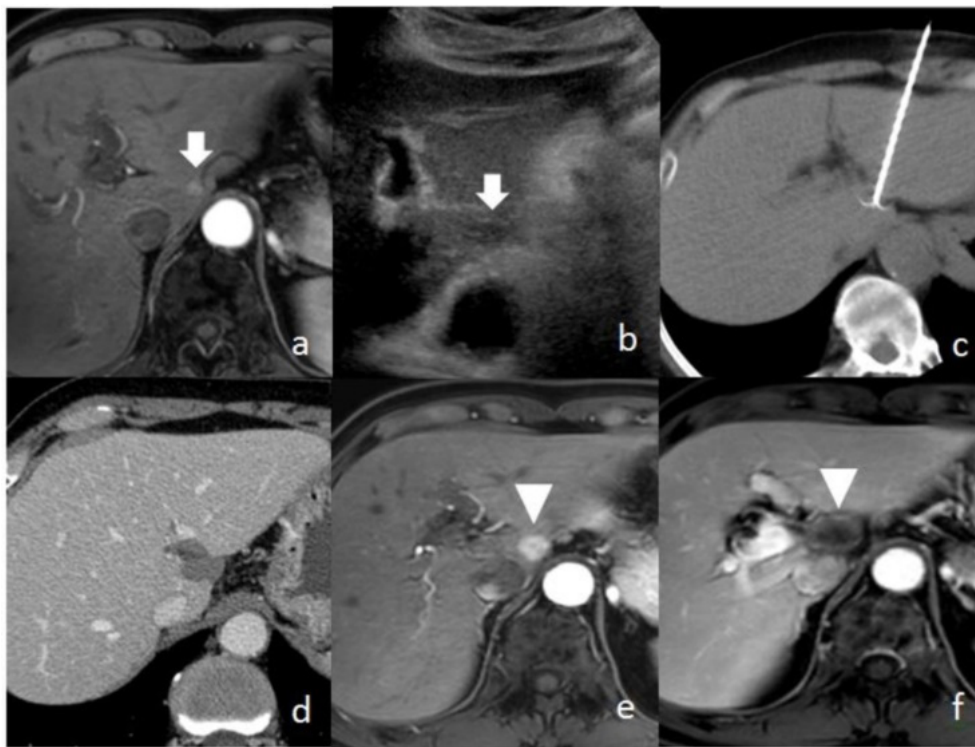
### Primary efficacy and technical success rate

Among the 29 patients treated by RF ablation using expandable electrodes, four lesions demonstrated residual disease upon imaging at one month after ablation. The technical success rate of the first session was 86.2%. One lesion had another RF ablation session and achieved complete tumor ablation within three months (Fig 2). Two lesions had re-ablation but the follow-up imaging still showed residual disease. In one lesion, re-ablation treatment was not performed because of multiple intrahepatic distant recurrence; hence TACE was performed instead. The primary efficacy rate was 89.7%, as 26 of the 29 tumors had complete tumor control at three months follow-up imaging.

Univariate analysis (Table 2) showed better technical success ( $p = 0.014$ ) and primary efficacy ( $p = 0.045$ ) in the smaller tumor group ( $\leq 2$  cm), as compared to the larger tumor group ( $> 2$  cm). With regard to the location (Table 3), the technical success was statistically significant in the tumor located at Spiegel's lobe and in the caudate process (100% technical success;  $p = 0.042$ ). In terms of the access site (Table 3), the primary efficacy was significantly better in the left lobe approach (100% primary efficacy;  $p = 0.033$ ) compared to the right anterior or right posterior approach. The rest of the various tumor-related prognostic factors, such as the patient's age and sex, Child–Pugh score, prior TACE treatment of the lesions, perivascular or subcapsular location, vessel in ligamentum venosum, and the depth from the skin, showed no statistically significant results in both technical success and primary efficacy.

### Local tumor progression rate and secondary efficacy rate

Local tumor progression (LTP) occurred in five of the 29 tumors. Two tumors were successfully treated by additional RF ablation with a secondary efficacy



**Fig 2.** A 71 year-old man with a 1 cm HCC in Spiegel portion of caudate lobe (arrow in a, b) RF ablation was performed via anterior left lobe approach (c). CT after ablation showed complete ablation (d). At two years follow up, MRI showed local tumor progression (arrowhead in e). Second RF ablation was performed by using the same technique and complete ablation was achieved (arrowhead in f).

**TABLE 2.** Univariate analysis of the tumor characteristics and results between tumor size.

Variables	Tumor size ≤2 cm	Tumor size >2 cm	P-value
No. tumors	18	11	
Age (years)	68.6 ± 9.2	60.1 ± 11.6	.291
Sex			
Male	13 (72.2%)	8 (72.7%)	.976
Female	5 (27.8%)	3 (27.3%)	
Child–Pugh score			
A	13 (72.2%)	11 (100%)	.126
B	5 (27.8%)	0 (0%)	
Prior TACE treatment	2 (28.6%)	5 (71.4%)	.071
Location of tumor			
Spiegel lobe	11 (61.1%)	3 (27.3%)	.024
Paracaval portion	4 (22.2%)	8 (72.7%)	
Caudate process	3 (16.7%)	0 (0%)	
Perivascular	7 (41.2%)	9 (81.8%)	.054
Subcapsular	10 (58.8%)	8 (72.7%)	.689
Vessel in ligamentum venosum	2 (11.1%)	3 (27.3%)	.339
Access site			
Left lobe	14 (77.8%)	5 (45.5%)	.267
Right anterior	2 (11.1%)	3 (27.3%)	
Right posterior	2 (11.1%)	3 (27.3%)	
Results			
Technical success	18 (100%)	7 (63.6%)	.014
Primary efficacy	18 (100%)	8 (72.7%)	.045
LTP	3 (16.7%)	3 (37.5%)	.330
Secondary efficacy	17 (94.4%)	7 (63.6%)	.054

**Abbreviations:** TACE, Transarterial chemoembolization; LTP, Local tumor progression

**TABLE 3.** Univariate analysis of the prognostic factors for technical success, primary efficacy, and local tumor progression.

Variable	Technical success		Primary efficacy		Local tumor progression (LTP)	
	(%)	( <i>P</i> -value)	(%)	( <i>P</i> -value)	No LTP (%)	( <i>P</i> -value)
Prior TACE treatment						
Present	71.4%	0.238	85.7%	1.000	2 (33.3%)	0.596
Absent	90.9%		90.9%		4 (20.0%)	
Location of tumor						
Spiegel's lobe	100%		100%		4 (28.6%)	
Paracaval portion	66.7%	0.042	75%	0.136	2 (22.2%)	0.829
Caudate process	100%		100%		0 (0%)	
Vessel in ligamentum venosum						
Present	80%	0.553	80%	0.446	2 (50%)	0.218
Absent	87.5%		91.7%		4 (18.2%)	
Perivascular						
Present	75%	0.113	81.3%	0.238	5 (29.4%)	0.624
Absent	100%		100%		1 (12.5%)	
Subcapsular						
Present	88.9%	0.601	94.4%	0.284	3 (23.1%)	1.000
Absent	80%		80%		3 (25%)	
Access site						
Left lobe	94.7%		100%		5 (26.3%)	
Right anterior	60%	0.105	60%	0.033	0 (0%)	1.000
Right posterior	80%		80%		1 (25%)	

**Abbreviation:** TACE, Transarterial chemoembolization

rate of 82.8%. Three patients with LTP had no further ablation treatment due to disease progression. One developed pulmonary metastasis, another had concomitant cholangiocarcinoma proven by tissue biopsy and both were subjected to systemic chemotherapy. Another patient had deterioration of liver function and was treated with palliative care. Kaplan–Meier analysis showed LTP rates of 12.3% at one year and 31.5% at two years. The median time of LTP was 6.9 months (Fig 3A).

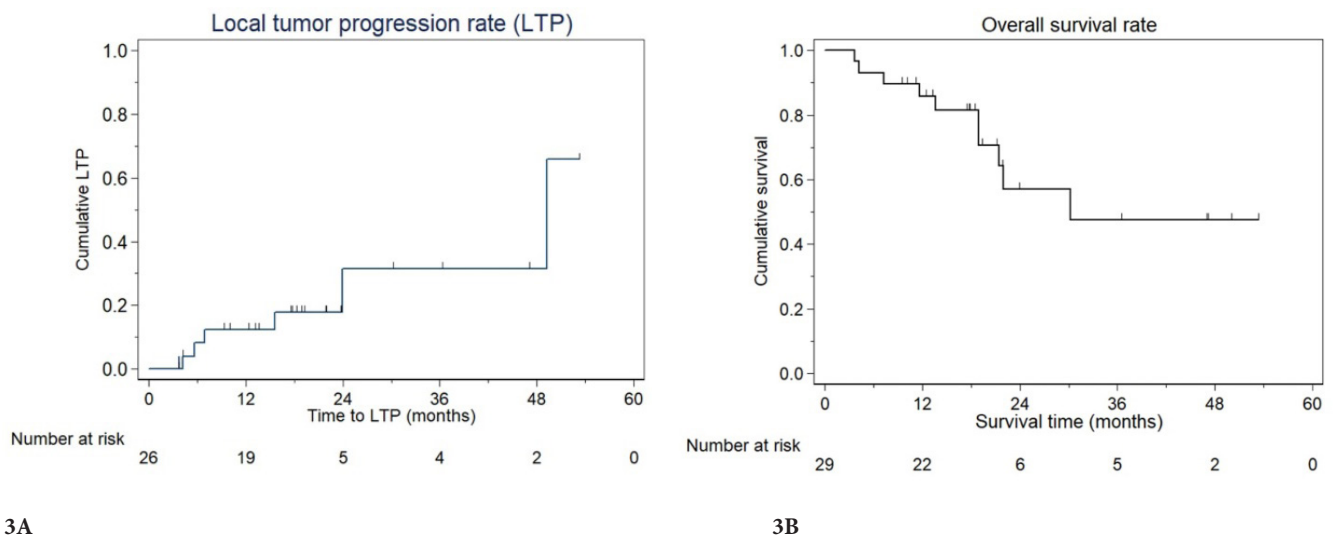
Univariate analysis also showed a high LTP rate and low secondary efficacy in the larger tumor group (>2 cm), but not significant statistically ( $p = 0.054$ ). (Table 2).

### Follow-up period and overall survival rate

The mean follow-up period was  $22.5 \pm 14.3$  months (range, 3.6–53.2 months). Ten patients died during the follow-up period. One patient underwent liver transplantation. The overall survival rate was computed by using Kaplan–Meier analysis, which showed survival rates of 85.8% at one year and 57.1% at two years (Fig 3B).

### Complications

There were no major complications encountered. No procedure-related death occurred. Only one case developed a minor complication of asymptomatic biloma (3.5%), which resolved spontaneously.



**Fig 3.** Kaplan-Meier analysis; (A) Local tumor progression rate (B) Overall survival rate

## DISCUSSION

For the curative treatment of HCC, RF ablation is an alternative to surgical resection. Nevertheless, the treatment of HCC located in the caudate lobe is still challenging to date due to the complex anatomy and deep location.<sup>1-4</sup>

This study showed an 86.2% technical success rate and 89.6% primary efficacy rate, which are comparable with the prior study by Seror et al. (2005), where treatment was done by RF ablation alone using non-expandable electrodes.<sup>5</sup> This study also used a combination of ultrasound and CT guidance for the needle electrode placement in all cases, which may have been a major key in achieving the technical success of the RF ablation in the tumors deeply situated in the caudate lobe. The advantage of the expandable electrode seems to be allowing a more precise estimation of the ablation zone, which can be visualized in the image guidance from the reconstructed non-contrast CT scan. However, a disadvantage is the difficulty to deploy the expandable electrode in the limited space of the caudate lobe.

This study demonstrated the advantage of the RF ablation of tumors in the caudate lobe using expandable electrodes in the smaller tumor group ( $\leq 2$  cm), which showed better results with statistical significance for technical success ( $p = 0.014$ ) and the primary efficacy ( $p = 0.045$ ) compared to the larger tumor group ( $> 2$  cm). Similar results were reported by Hyun et al. using combined transarterial treatment with RF ablation.<sup>10</sup>

The LTP rate of the present study (12.3% at one year and 31.5% at two years) showed a higher rate compared to RF ablation done in other locations.<sup>5-7</sup> These could be due to multifactorial causes, like inadequate ablation

margins, difficulty of needle repositioning in the limited space of the caudate lobe, and the heat sink effect due to the proximity to the large vessels, including the IVC and the main portal vein.

Regarding the access route of the RF electrode, this study mainly involved the use of the left lobe approach (65.5%), which was probably due to the majority of the tumors being located in the Spiegel's lobe (48.3%), which could be accessed by using this approach. The technical success rate of the left lobe approach also was the highest (94.7%) as long as the primary efficacy was 100%, also showing statistical significance ( $p = 0.033$ ). This might be due to the tumors in the Spiegel's lobe seemingly able to be well-visualized in the ultrasonography, probably as the depth from the skin was mostly shorter compared to the other locations. Also there is likely less heat sink effect for tumors in the Spiegel's lobe because of the greater distance to the large vessels.

The left lobe approach may increase the risk of bleeding, due to the needle piercing the liver capsule twice and also penetrating the ligamentum venosum, in which an accessory/replaced left hepatic artery or accessory left gastric artery may be present.<sup>5</sup> A variant artery in ligamentum venosum causing a limitation for the left lobe approach was observed in five patients; comprising accessory left hepatic artery in four patients and accessory left gastric artery in one patient. Four of these were accessed by using the left lobe approach. There was no evidence of bleeding, but we need to be cautious in this matter.

Limitations of this study include its retrospective design, non-randomized control, and small number of patients, which may have caused some selection bias

and a difference in the results. Multivariate analysis also itself has inherent limitations that need to be taken into account. A longer follow-up period should be achieved for a better evaluation of the overall survival and LTP.

In conclusion, radiofrequency ablation using expandable electrodes is feasible and safe in treating HCCs located in the caudate lobe, especially for small-sized tumors ( $\leq 2$  cm).

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# Predictors of Depressive Symptoms among Family Caregivers of Patients with Dementia in Java, Indonesia

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## ABSTRACT

**Objective:** Depressive symptoms are common mental health problems among the family caregivers of patients with dementia. However, little is known about the prevalence of depressive symptoms among the family caregivers of patients with dementia in Indonesia. This study aimed to examine: 1) the factors predicting depressive symptoms, 2) the mediating role of social support in the relationship between burden and depressive symptoms, and 3) the association between depressive symptoms and healthcare utilization among family caregivers.

**Methods:** This was a cross-sectional study involving 250 family caregivers of patients with dementia recruited from four hospitals in Java, Indonesia. Data were collected by Zarit Burden Interview (ZBI); the Neuropsychiatric Inventory Questionnaire (NPI-Q), the Mastery scale, the Multidimensional Scale of Perceived Social Support, and the Center for Epidemiologic Studies Depression (CES-D) Scale. Descriptive statistics, chi-square test, hierarchical multiple linear regression, and Baron and Kenny's regression method were used to analyze the data.

**Results:** The results revealed that about a quarter of the participants (24.8%) experienced depressive symptoms. Caregiver burden, mastery, behavioral and psychological symptoms of dementia, and social support explained 45.5% of the variance in the prevalence of depressive symptoms among family caregivers ( $R^2=0.455$ ). Social support also partially mediated the association between caregiver burden and depressive symptoms. There was no association between depressive symptoms and the use of healthcare services among the family caregivers.

**Conclusion:** The findings revealed that social support is a mediating factor affecting the relationship between caregiver burden and depressive symptoms. Interventions targeting social support to help alleviate caregiver burden would be effective in helping reduce depressive symptoms in the family caregivers of patients with dementia.

**Keywords:** Depressive symptoms; dementia; caregiver; burden; social support (Siriraj Med J 2021; 73: 549-558)

## INTRODUCTION

Alzheimer's Disease International reported that almost 50 million people worldwide have dementia, and projections indicate that the number of people with dementia will be 152 million in 2050, having more than tripled since 2015.<sup>1</sup> In Indonesia, which is the fourth

most populous country in the world, the proportion of older people in the population is dramatically growing, and thus the number of patients with dementia (PWDs) is likely to rise. Indonesia had an estimated 1.2 million patients with dementia in 2016, with 2 million forecast by 2030 and 4 million by 2050.<sup>2</sup> PWDs are affected by

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a progressive and significant deterioration that results in impaired memory, judgment, communication, and function.<sup>3,4</sup> Over time, PWDs become more and more dependent on their family for support alongside the progression of the illness and their gradual deterioration. Family caregivers provide comprehensive care to the increasing and demanding circumstances experienced by PWDs,<sup>5</sup> leading them to face chronic stress, which can contribute to them experiencing poor mental health, including depressive symptoms.<sup>6</sup>

A meta-analysis of 13 studies reported an aggregate prevalence of depressive symptoms among 34% of PWD caregivers.<sup>6</sup> If left untreated, depressive symptoms can lead to major depressive disorder. A prospective cohort study in the USA examining the incidence of depression and anxiety disorders among the caregivers of PWDs without clinical depression or anxiety disorder at baseline showed that 60% of the caregivers developed a depressive and/or anxiety disorder within 24 months.<sup>7</sup> Furthermore, the need to assume a caregiving role can leave depressed caregivers at a high risk of developing poor health outcomes, such as a decline in their health status,<sup>8</sup> cognitive decline,<sup>9</sup> and even having suicidal thoughts.<sup>10</sup> Depressive symptoms can also exacerbate caregivers' preexisting disease or even increase their susceptibility to other diseases, while there is evidence that family caregivers of PWDs tend to have a high rate of healthcare use.<sup>11</sup> Consequently, a high prevalence of depressive symptoms among PWD caregivers will also have a wider impact on society, impacting economic development, social welfare, and public health awareness.

The present study was guided by the Stress Process Model<sup>12</sup> which explains stress through the relationship patterns among four domain and mediating factors. The domains consist of the: 1) background and context, 2) stressors, 3) stress mediators, and 4) stress outcomes. The background and context refer to stress related to sociodemographic, family, and network information. The stressors are conceptualized into primary and secondary stressors; whereby primary stressors are related directly to the caregiver activity in providing care, while secondary stressors do not directly stem from the illness and caregiving but are rather split into role strain, such as family conflict, work conflict, and constriction of social life, and intrapsychic strain, such as self-esteem and mastery. Coping and social support are identified as mediators to describe how these factors provide a buffering effect to the outcomes through direct and indirect pathways. The interrelationship between the caregiver background and context, stressors, and mediators leads to the stress outcomes, as the fourth

domain. All these factors may lead to a decline in the family caregiver's physical health and mental health and can impact the family caregiver's overall health, such as restricting their physical activities and causing depression.<sup>12</sup>

Attempts have been made to examine the factors influencing the prevalence of depressive symptoms in the family caregivers of PWDs, including the caregiver's characteristics, caregiver burden, behavioral problems of the PWD, mastery, and social support. There is mixed evidence regarding the caregiver's characteristic and depressive symptoms; for instance, older caregivers, female, the caregiver relationship, and employment status are predictors of depressive symptoms arising among family caregivers,<sup>13–15</sup> while some studies have found that age, gender, caregiver relationship, and employment status could not predict depressive symptoms.<sup>15–17</sup> Few studies have investigated the relationship between the caregiving duration and prevalence of depressive symptoms among caregivers, although one study reported that caregiving duration was a predictor of depressive symptoms among caregivers.<sup>15</sup> Caregiving duration is a critical factor in the context of care as caregivers may take on the caregiving role for lengthy periods and this might play a major role in their mental health.

Despite the extensive research in this area, no previous study has been done in an Indonesia context, with most research to date conducted in Western countries, where the cultural beliefs and norms might differ. Moreover, this scarce research on dementia caregiving in Indonesia means that uncertainty exists regarding the risks and protective factors of depressive symptoms among family caregivers of PWDs in Indonesia. Understanding these issues is important to enable suitable interventions to be made to address family caregivers' needs in ways that are culturally appropriate.

Consequently, to fill the gap, the aims of this study were to examine, in an Indonesian context, the: 1) prevalence of depressive symptoms among family caregivers; (2) caregiver's sociodemographic factors, BPSD, caregiver burden, mastery, and social support as predictors of depressive symptoms among family caregivers of PWDs; (3) mediating role of social support on the relationship between burden and depressive symptoms; and (4) relationship between depressive symptoms and the utilization of healthcare services among family caregivers of PWDs.

## MATERIALS AND METHODS

A cross-sectional study was conducted of the family caregivers of PWDs who attended four outpatient tertiary

hospitals on the island of Java, Indonesia, between April to September, 2019. All the participants were more than 18 years old, had assumed the primary caregiver's role without receiving any reward or salary for this service for at least six months, and were living with the PWD in the same household. Family caregivers over 60 years old were excluded if they had cognitive impairment with a Six-item Cognitive Impairment Test (6CIT)<sup>18</sup> score of >7. The patients were diagnosed with dementia according to the International Statistical Classification of Diseases (ICD-10).<sup>19</sup>

Approval to conduct the study was obtained from the Institutional Review Board Faculty of Nursing at Mahidol University (COA No. IRB-NS 2019/488.0603) and the Ethics Committee of Nursing Research, Faculty of Nursing, Universitas Indonesia (138/UN2.F12. D/HKPP.02.04/2019). The sample size calculation was based on a previous study with an estimated  $R^2=0.30$ ,<sup>20</sup> and an estimated sample size for varying numbers of predictor variables.<sup>21</sup> With nine predictors and an estimated  $R^2=0.30$ , 250 family caregivers were recruited for this study.

In addition to the demographic characteristics and clinical information collected from the family caregivers, the study participants were also asked to complete a questionnaire about their healthcare utilization in the preceding 6 months, such as which healthcare services they had visited in the preceding 6 months, as well as five self-reporting questionnaires that addressed separate conditions. All the instruments were back-translated into Bahasa (Indonesia language) with permission from the instruments' developers.

Burden was assessed by Zarit Burden Interview (ZBI),<sup>22</sup> which consisted of 22 items with total scores ranging from 0-88, where a higher score indicated a higher burden. The Cronbach's alpha coefficient obtained from our sample was 0.91. MAPI Research Trust granted permission to use this instrument and back-translated it into Bahasa.

Behavioral and psychological symptoms of dementia were assessed by the Neuropsychiatric Inventory Questionnaire (NPI-Q), a shorter version of the Neuropsychiatric Inventory (NPI).<sup>23</sup> The range of scores for severity was 12-36, while the caregiver distress score ranged from 0-60. Here, a higher score pointed to a higher severity of neuropsychiatric symptoms (NPS) of the PWDs and caregiver distress. The Cronbach's alpha coefficient obtained from our sample was 0.90.

Mastery was assessed by the Mastery scale developed by Pearlin and Schooler, and consisted of 7 items.<sup>24</sup> The total possible scores ranged from 7-28, where a higher score indicated a higher level of mastery or a stronger

sense of caregiver control over their own lives. The Cronbach's alpha coefficient obtained from our sample was 0.66.

Social support was assessed by the Multidimensional Scale of Perceived Social Support (MSPSS), which is a 12-item questionnaire, developed by Zimet et al.<sup>25</sup> The total possible score ranged from 12-84, where a higher score indicated a higher level of perceived social support. The Cronbach's alpha coefficient obtained from our sample was 0.87.

Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression (CES-D) scale, which is a 20-item questionnaire developed by Radloff.<sup>26</sup> The total possible score ranged from 0-60; scores of 16 or higher are a cutoff point indicating depressive symptoms. The Cronbach's alpha coefficient obtained from our sample was 0.87.

## Data analysis

Data were analyzed using the SPSS 18.0 software program. Descriptive statistics were used to assess the demographic characteristics and study variables. To identify the relationship between depressive symptoms and healthcare service utilization, analysis was performed using the chi-square test. Hierarchical regression analysis was used to identify the predicting factors of depressive symptoms. To examine the mediating role of social support on the association between burden and depressive symptoms in the family caregivers of PWDs, Baron and Kenny's method was used.<sup>27</sup>

## RESULTS

### Characteristics

**Caregivers.** The average age of the participants was 50.2 years old (SD=14.26; range, 20-92). The majority of family caregivers were females (74.4%), Muslim (86.0%), and married (89.6%). Considering the relationship to the PWD, the highest proportion was adult children (47.2%), with an average caregiving duration of 22.6 months (SD=16.85), and had other family members living in the same house. About 40% graduated from senior high school. Over half the caregivers were unemployed (53.2%), and the majority of participants reported having sufficient family income (74%). The majority of participants cared only for PWDs (89.6%) and had health insurance (89.2%). Regarding health status, over half the family caregivers (52.8%) rated themselves as very healthy, as shown in Table 1.

**Patients.** The average age of the PWDs was 67.2 years old (SD=9.25; range, 43-92). Most of the PWDs were male (56.8%) and married (73.2%). The majority of the

**TABLE 1.** Characteristics of family caregivers of patients with dementia (n = 250).

Demographics characteristics	Number (%)
<b>Gender</b>	
Male	64 (25.6)
Female	186 (74.4)
<b>Age (Years)</b>	
20 - 39	59 (23.6)
40 - 59	123 (49.2)
60 - 79	66 (26.4)
80 - 92	2 (8)
Mean = 50.2, SD = 14.26, Min = 20, Max = 92	
<b>Education level – top level reached</b>	
No formal education	5 (2)
Primary school	64 (27.2)
Senior high school	101 (40.4)
College/University	76 (30.4)
<b>Religion</b>	
Muslim	215 (86)
Christian	33 (13.2)
Other	2 (0.8)
<b>Marital Status</b>	
Married	224 (89.6)
Single	19 (7.6)
Widowed, divorced, or separated	7 (2.8)
<b>Employment status</b>	
Employed	117 (46.8)
Unemployed	133 (53.2)
<b>Family income (rupiah/month)</b>	
≤ 1,000,000	48 (19.2)
1,000,001-4,000,000	112 (44.8)
4,000,001-8,000,000	62 (24.8)
> 8,000,000	28 (11.2)
Mean = 4,177,200, SD = 4,097,839.59, Min = 200,000, Max = 27,000,000 (14,400 rupiah = 1 USD)	
<b>Income adequacy</b>	
Sufficient	185 (74)
Insufficient	65 (26)
<b>Relationship to the PWD</b>	
Adult children	118 (47.2)
Spouse	115 (46)
Relatives	17 (6.8)
<b>Duration of caregiving (months)</b>	
6 - 12	112 (44.8)
13 - 24	69 (27.6)
25 - 36	38 (15.2)
37 - 48	13 (5.2)
≥ 49	18 (7.2)
Mean = 22.6, SD = 16.85, Min = 6, Max = 84	
<b>Number of members in the household</b>	
1 - 3	112 (44.8)
4 - 6	118 (47.2)
≥ 7	20 (8)
Mean = 4, SD = 1.69, Min = 1, Max = 11	
<b>Caring for other family members</b>	
No	224 (89.6)
Yes	26 (10.4)
<b>Caregiver with health insurance</b>	
Yes	223 (89.2)
No	27 (10.8)
<b>Self-rated health</b>	
Very healthy	132 (52.8)
Somewhat healthy	36 (14.4)
Somewhat unhealthy	80 (32)
Very unhealthy	2 (0.8)

PWDs were Muslim (85.6%), and just under one-third (20.4%) had attended college or university. The average length of dementia was 24.0 months (SD=17.82), and almost all (93.2%) the PWDs had health insurance, as shown in Table 2.

The average CES-D score was 11.70 (SD=8.03). The majority of the family caregivers (75.2%) had a CES-D score of less than 16, while 24.8% of the family caregivers had a CES-D score of more than 16, indicating that they were suffering from depressive symptoms.

### Predictors of depressive symptoms

Except for the caregivers' characteristics, other

independent variables also made a significant contribution to explaining the variance in caregivers' depressive symptoms. The incremental changes in  $R^2$ , the proportion of variance explained by each block of variables, were 3.3%, 5.6%, and 36.5% for the caregivers' characteristics, social support, and stressors in caregiving. Social support ( $b=-0.003$ ,  $p=0.043$ ), BPSD ( $b=0.002$ ,  $p=0.014$ ), caregiver burden ( $b=0.010$ ,  $p<0.01$ ), and mastery ( $b=-0.027$ ,  $p<0.001$ ) were significantly related to the caregivers' depressive symptoms. These factors explained 45.5% of the variance in the family caregivers' depressive symptoms, as shown in Table 3.

**TABLE 2.** Characteristics of the patients with dementia (n = 250).

Characteristics	Number (%)
<b>Gender</b>	
Male	142 (56.8)
Female	108 (43.2)
<b>Age (years)</b>	
41 - 60	59 (23.6)
61 - 80	172 (68.8)
≥ 80	19 (7.6)
Mean = 67.2, SD = 9.25, Min = 43, Max = 92	
<b>Marital status</b>	
Married	183 (73.2)
Widowed, divorced, or separated	64 (25.6)
Single	3 (1.2)
<b>Education level</b>	
No formal education	21 (8.4)
Primary school	98 (39.2)
Senior high school	80 (32)
College/university	51 (20.4)
<b>Religion</b>	
Muslim	214 (85.6)
Christian	33 (13.2)
Hindu	1 (0.4)
Other	2 (0.8)
<b>PWD with health insurance</b>	
Yes	233 (93.2)
No	17 (6.8)
<b>Duration of dementia (months)</b>	
6–12	107 (42.8)
13–24	66 (26.4)
> 25	77 (30.8)
Mean = 24.0, SD = 17.82, Min = 6, Max = 84	

**TABLE 3.** Hierarchical multiple regression analysis for factors predicting depressive symptoms (n = 250).

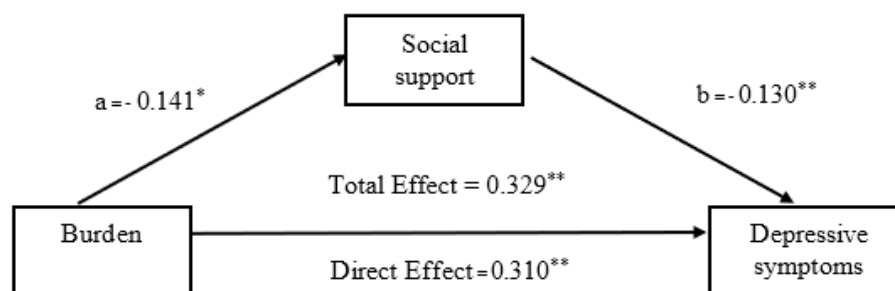
Predictor	Block 1			Block 2			Block 3		
	<i>b</i>	SE ( <i>b</i> )	<i>p</i> -value	<i>b</i>	SE ( <i>b</i> )	<i>p</i> -value	<i>b</i>	SE ( <i>b</i> )	<i>p</i> -value
Age	0.001	0.002	0.737	0.001	0.002	0.619	- 0.001	0.001	0.389
Gender	0.073	0.048	0.130	0.072	0.047	0.123	0.026	0.037	0.480
Employment status	- 0.094	0.041	0.024	- 0.088	0.040	0.031	- 0.038	0.032	0.230
Duration of caregiving	- 0.095	0.074	0.200	- 0.063	0.073	0.387	0.010	0.057	0.861
Children	- 0.014	0.056	0.800	0.004	0.055	0.935	- 0.049	0.044	0.267
Relatives	0.016	0.083	0.847	0.041	0.081	0.617	- 0.022	0.063	0.728
Social support				- 0.007	0.002	< .001	- 0.003	0.001	<b>0.043</b>
BPSD							0.002	0.001	<b>0.014</b>
Burden							0.010	0.001	<b>&lt; 0.001</b>
Mastery							- 0.027	0.006	<b>&lt; 0.001</b>
R <sup>2</sup>	0.033			0.090			0.455		
ΔR <sup>2</sup>				0.056			0.365		
ΔF				15.006*			53.352*		

Significance level: \* $p < 0.05$ **Mediating effects of social support**

From multiple regression analyses, it was found that the caregivers' social support partially mediated the relation between the caregiver burden and depressive symptoms (Fig 1). In the first regression model (path c), caregiver burden independently predicted depressive symptoms in a significant manner ( $b=0.329, p<0.001$ ). In the second regression model (path a), caregiver burden independently predicted social support ( $b=-0.141, p=0.002$ ). In the third regression model (path b), social support independently predicted depressive symptoms ( $b=-0.130, p<0.001$ ). In the fourth regression model

(path c') and after controlling for the effect of social support (mediator variable), caregiver burden remained a significant independent predictor of depressive symptoms ( $b=0.310, p<0.001$ ). These bootstrapping results verified the significant indirect effect of social support,  $b=0.018$ , 95%CI (0.002–0.045), suggesting a partial mediating effect of social support on the relation between the caregiver burden and depressive symptoms.

With regard to healthcare utilization, the relation between depressive symptoms and healthcare utilization was not statistically significant as shown in Table 4.

**Fig 1.** Mediation effects of social support on the relationship between the caregiver burden and depressive symptoms.

**TABLE 4.** Correlation between depressive symptoms and healthcare utilization.

Variable	Healthcare utilization		Chi-square ( $\chi^2$ )	p-value
	No (%)	Yes (%)		
No Depression (0 -15)	168 (89.4)	20 (10.6)	1.87	<b>0.171</b>
Depression (16 -40)	59 (95.2)	3 (4.8)		

## DISCUSSION

Depressive symptoms were evident in nearly a quarter of the family caregivers (24.8%) of PWDs in Indonesia, which was a lower prevalence than reported in other countries. For instance, the rate was 34.2% among Japanese informal caregivers of community-dwelling elderly persons,<sup>28</sup> in Taiwan, the rate of depressive symptoms was 43.8%,<sup>29</sup> and the rate of depressive symptoms in the USA was found to be 47%.<sup>30</sup> A possible explanation for this may be related to the different cultural beliefs in Indonesia regarding the caregiving role as well as due to some characteristics of the caregivers. In Indonesia, caring for ill family members is considered the moral responsibility of the whole family. Indonesia's collectivist culture emphasizes the interdependence between family members. Caregiving is thus not the sole responsibility of a single individual; other family members pitch in with assistance, advice, and support as needed.<sup>31</sup> It is also important to consider the stage of dementia of the patient. On average, in our study the PWDs had been diagnosed for two years or less, likely reflecting an early stage of dementia. Thus, the PWDs in our study may have had relatively less memory and behavioral problems and a minimal need for support in their daily activities at this stage of their dementia, which could have meant less psychological distress on the caregivers.

BPSDs were found to be predictors of depressive symptoms. The finding is similar to that of previous studies, which revealed that behavioral and psychological symptoms of dementia (BPSDs) are strong predictors of depressive symptoms.<sup>17,32,33</sup> As indicated by the Stress Process Model,<sup>12</sup> the primary stressors related to caring for PWDs impact caregiver depression. As behavioral problems of the PWDs increase in frequency and severity, the family caregivers will face increasing stress and difficulty in providing care. Neuropsychiatric symptoms in PWDs are varied and intrinsically unpredictable in terms of emotional experience, thought content, insight, and motor function appearance. These problematic

behaviors of PWDs are challenging to treat and are often embarrassing, contributing to the caregiver's depression.

Caregiver burden is found to be a predictor of depressive symptoms. The finding is consistent with previous studies, which found that caregiver burden is a strong predictor of depressive symptoms.<sup>16,34</sup> A possible explanation for this may be related to the care demands of the PWD. Burden is a subjective perception in terms of negative feelings of caregivers on the stressors in the caregiving situation.<sup>22</sup> In this study, caregivers may have little control over those demands since dementia is an incurable, progressive disease and may arise in the caregiving responsibilities. Also, demands from other family needs, social obligations, and work contribute to increasing the burden on caregivers. One previous study revealed that constraints on a caregiver's life due to caring can cause a more significant impairment to their mental health.<sup>5</sup> The uneasiness of family caregivers' increases as the PWD condition worsens, along with the onset of BPSDs in the PWD and a consequent reduction of the PWD's independence in daily life. As a result, there is a higher burden on family caregivers, leading to more stress and more depression.

The finding that mastery is a negative predictor of depressive symptoms is similar to in a previous study.<sup>35</sup> Mastery is the extent to which an individual believes that life chances are under his/her own control,<sup>24</sup> thus, it is related to a sense of control. The more frequently family caregivers' efforts result in higher task achievement, the more intensely the caregiver believes that he/she has control over what occurs in their life in common with the PWD. However, caring for a PWD can contribute to a caregiver's feelings of lack of control since dementia is a devastating chronic illness with no known cure that leads to the PWD manifesting unsettling alterations, which may decrease the caregiver's feeling of mastery. When caregivers feel adaptive in their role, they can develop a higher sense of mastery, which will reduce their depressive symptoms.<sup>35</sup>

Social support appears to be a significant predictor in our study. This result is congruent with previous studies.<sup>15</sup> Social support is the perception that one is accepted, cared for, and provided with assistance from certain individuals or a specific group.<sup>36</sup> Social support can decrease depressive symptoms among family caregivers of PWDs through providing emotional support, information about dementia care, and by helping to solve the family caregiver's problems.<sup>15</sup> Furthermore, most family caregivers in this study lived in extended-family households, which should ease the family caregiver's burden by having others share in the informal caregiving demands and reinforcing the caregiver's feeling of not being left to cope alone in a difficult situation. Social support plays an important role in improving family caregivers' mental health outcomes.<sup>15</sup>

The results revealed a mediating role of social support on the relationship between the caregiver burden and depressive symptoms. This findings are similar to that of another study, which found that social support mediated the relationship between the burden and general health of caregivers.<sup>37</sup> The findings affirmed the role of social support as a buffer against caregiver burden, and this was in line with the Stress Process Model.<sup>12</sup> Caring for the PWD also consumes the family caregiver's resources. Social support can alleviate the situational caregiving burden and the caregiver's emotional responses to those burdens, thereby directly reducing the physical and psychological consequences of these stressors. When a family caregiver is under stress, social support can lead to the family caregivers underestimating the caregiving burden and the vagaries of stress.<sup>15</sup> That is, social support reduces the relationship between the caregiver burden and depressive symptoms. However, this study found a partial mediating effect of social support, which suggests that additional factors are also important regarding this relationship.

This study found that depressive symptoms had no relationship with healthcare utilization among the family caregivers of PWDs during the six months preceding the study. Our finding is contrasted to that of a previous study, which found that caregivers were 1.023-1.044 times more likely to visit the doctor, have outpatient tests and procedures, and take over the counter and prescription medications.<sup>11</sup> In addition, depressed caregivers were more likely to use healthcare services, including outpatient tests, procedures, and medical appointments, than non-depressed caregivers.<sup>11</sup> One possible explanation for this may actually be due to the failure of chi-square statistics. The assumption in the chi-square test is that the expected value in each cell is

greater than 5.<sup>38</sup> In the present study, the observed value in those who were depressed and who utilized healthcare services involved only 3 cases. However, most caregivers in this study were female, middle aged (an average of 50 years old), and married. Also, over half rated their health status as "healthy" (67.2%). A previous study showed that self-rated health is significantly associated with an individual's perceived need to use healthcare services.<sup>39</sup>

### Limitations

In summary, this study revealed more about the phenomenon of the family caregivers of PWDs experiencing depressive symptoms but in an Indonesian context. The findings support the concepts represented in each domain proposed in the Stress Process Model.<sup>12</sup> However, the key limitation of this study is its cross-sectional design. Depressive symptoms experienced at any one point in time may not reflect the experience of depressive symptoms over time. Thus, a longitudinal study may help identify the impact of specific episodes as the symptoms of depression change significantly throughout the caregiving experience.

### CONCLUSION

Based on the study findings, this study utilized theory-based research to inform nursing practice in Indonesia. It identified specific factors (including caregiver burden and BPSDs) that place some family caregivers at a higher risk of developing depressive symptoms. It has been suggested that nurses should implement a caregiver screening tool to help identify vulnerable family caregivers, which would enable them to provide appropriate and timely interventions. An effective intervention targeting social support for dealing with caregiver burden would help reduce the depressive symptoms in family caregivers. Further studies should be carried out on the family caregivers of PWDs who are in the middle and more advanced stages of dementia. Such studies will help nurses understand the caregiving experience and symptoms of depression among family caregivers in each stage of dementia progression. In addition, an intervention study targeting the depressive symptoms of family caregivers of PWDs is required.

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# Changes in HbA<sub>2</sub> Levels May Signify Hemoglobin Defects in Infants

## To the editor:

The hemoglobin profile has been utilized as a clue for the diagnosis of thalassemia and hemoglobinopathy. Fetal hemoglobin (HbF,  $\alpha_2\gamma_2$ ) is highly expressed as the major functional hemoglobin during the fetal stage. Following hemoglobin switching, HbF declines to less than 1% of the total hemoglobin within one year of age. Adult hemoglobin (HbA,  $\alpha_2\beta_2$ ) therefore predominates over total hemoglobin in combination with 2-3% of HbA<sub>2</sub> ( $\alpha_2\beta_2$ ) and trace amounts of HbF throughout adult life. Hemoglobin can routinely be analyzed using chromatography or electrophoresis. Relative alterations of these hemoglobin types have been shown to be associated with abnormal globin production in adults. For instance, hemoglobin E (HbE,  $\alpha_2\beta_2^{26\text{Glu}\rightarrow\text{Lys}}$ ), the hallmark hemoglobinopathy of Southeast Asia, exists in a range from 25-90% of the total hemoglobin in adults with HbE inheritance; however, HbE levels present less than 25% of total hemoglobin in heterozygous HbE patients who co-inherit with  $\alpha$ -thalassemia. Moreover, HbA<sub>2</sub> is markedly raised between 3.5 and 9.9% in adult heterozygous  $\beta$ -thalassemia. In contrast, relative changes in hemoglobin types are unnoticeable by routine hemoglobin analysis in adults with one or two  $\alpha$ -globin gene defects.<sup>1</sup> To broaden the knowledge and illustrate the effects of globin disorders on hemoglobin profile in infants, leftover blood samples from 142 unrelated individuals aged between 8 and 12 months with a mean corpuscular volume (MCV) less than 80 fL were subjected to thalassemia screening and diagnosis. Hemoglobin analysis was performed regarding the Bio-Rad Variant II Hemoglobin Testing System with  $\beta$ -Thalassemia Short Program (BioRad, Hercules, CA). The diagnosis of thalassemia was performed according to standard diagnostic guidelines used in Thailand.<sup>2-4</sup> In addition, common deletion types of  $\alpha^+$ -thalassemia ( $-\alpha^{3.7}$  and  $-\alpha^{4.2}$ ) and  $\alpha^0$ -thalassemia ( $--^{\text{SEA}}$  and  $--^{\text{THAI}}$ ) were genotyped as described in previous studies.<sup>5,6</sup> The protocols in this study were approved by the ethics committee of the Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand (ethical approval reference number AMSEC-63EM-001). The results revealed that 59 (41.5%) were negative for the common thalassemias (hereafter so called normal), 37 (26.1%) were heterozygous for  $\beta$ -thalassemia, 19

(13.4%) were heterozygous for HbE, 18 (12.7%) were heterozygous for  $\alpha$ -thalassemia 1, and 9 (6.3%) were deletional HbH disease caused by compound heterozygous  $\alpha$ -thalassemia 1 with  $\alpha$ -thalassemia 2 (Table 1). Complete blood count (CBC) showed hypochromic microcytic anemia with reduced total Hb level, Hct, MCV, and mean corpuscular hemoglobin (MCH) (Table 1). On average, the hemoglobin profile of normal infants was similar to that of normal adults, suggesting that the hemoglobin switching had completed in these subjects. Conversely, a significant increase in HbA<sub>2</sub> and HbF levels was observed in infants with heterozygous  $\beta$ -thalassemia and heterozygous HbE (Table 1). The elevated HbA<sub>2</sub> levels were similar to those of adults with heterozygous  $\beta$ -thalassemia. Regardless of age, this suggested that increased HbA<sub>2</sub> levels determine the inheritance of  $\beta$ -thalassemia. Interestingly, elevated HbF levels were absent in adults with either heterozygous  $\beta$ -thalassemia or heterozygous HbE,<sup>7,8</sup> suggesting a developmental stage-specific effect. This finding is comparable to previous studies in which the delayed HbF to HbA switching is remarkably shown in infants with  $\beta$ -globin defects.<sup>9,10</sup> Although the mechanisms underlining HbF to HbA switching are unclear, the prolonged HbF levels in infants with a  $\beta$ -globin defect maybe due to the primary compensation of  $\beta$ -like globin gene expression and total hemoglobin during development in affected infants. Similar to those of adults with homozygous  $\beta^0$ -thalassemia and compound heterozygous  $\beta^0$ -thalassemia with HbE disease, the increase in  $\gamma$ -globin gene expression has been shown to associate with milder clinical manifestations as it is able to substitute for the inadequate  $\beta$ -globin gene expression and yields increased HbF levels. In contrast to  $\beta$ -globin gene defects, heterozygous  $\alpha^0$ -thalassemia demonstrated comparable hemoglobin types to the normal in our finding. Despite insignificance, infants with two  $\alpha$ -globin gene defects displayed reduced HbA<sub>2</sub> and modestly increased HbF levels in the previous study.<sup>9</sup> The decrease in HbA<sub>2</sub> levels was clearly noticed in infants with three  $\alpha$ -globin gene defects or deletional HbH disease in our study. Together, the results suggested that HbA<sub>2</sub> levels may be considered as valuable markers for the inheritance of globin gene defects in infants.

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**TABLE 1.** Hematological data of the infants participated in this study.

Characteristic	Age (Month), Mean ± SD	Sex (No.), Boy/Girl	RBC (10 <sup>12</sup> /L), Mean ± SD	Hb (g/dL), Mean ± SD	Hct (%), Mean ± SD	MCV (fL), Mean ± SD	MCH (pg), Mean ± SD	MCHC (g/dL), Mean ± SD	HbA <sub>2</sub> /E (%), Mean ± SD	HbF (%), Mean ± SD	HbA (%), Mean ± SD	Hb Bart's	HbH
Normal (n = 59)	11.6 ± 1.0	27/32	5.1 ± 0.5	9.9 ± 1.2	32.0 ± 3.5	62.5 ± 4.4	19.3 ± 2.1	30.9 ± 1.6	2.6 ± 0.4	1.1 ± 0.8	91.5 ± 5.8	Absent	Absent
Heterozygous β-thalassemia (n = 37)	12.0 ± 0.2	21/16	5.6 ± 0.5	10.0 ± 0.7	31.9 ± 2.4	56.8 ± 3.0	17.9 ± 1.1	31.5 ± 1.4	5.5 ± 0.5	6.1 ± 3.8	83.3 ± 6.8	Absent	Absent
Heterozygous HbE (n = 19)	11.9 ± 0.2	11/8	5.0 ± 0.6	10.6 ± 2.2	31.8 ± 4.9	64.1 ± 6.1	21.3 ± 3.4	33.1 ± 3.8	24.7 ± 4.2	4.2 ± 2.4	66.7 ± 7.1	Absent	Absent
Heterozygous α <sup>0</sup> -thalassemia (-- <sup>SEA</sup> /αα) (n = 18)	12.0 ± 0.0	10/8	6.0 ± 0.5	10.4 ± 1.2	34.0 ± 3.6	57.2 ± 6.2	17.5 ± 2.2	30.5 ± 1.3	2.5 ± 0.3	1.2 ± 0.8	92.7 ± 5.5	Absent	Absent
HbH disease (-- <sup>SEA</sup> /-α <sup>3.7</sup> ) (n = 9)	12.0 ± 0.0	4/5	5.8 ± 0.6	9.1 ± 0.7	30.8 ± 2.7	53.0 ± 2.9	15.7 ± 1.5	29.5 ± 1.8	1.6 ± 0.5	1.4 ± 1.1	92.7 ± 3.5	Present	Present

**Abbreviations:** RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.