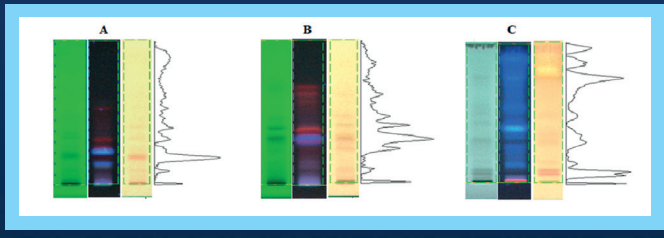
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By Rattana Phadungrakwittaya, et al.

ORIGINAL ARTICLE

175 **Managing Difficult Cannulations in Endoscopic Retrograde Cholangiopancreatography: A Prospective Randomized Control Trial Study of Precut Needle Knife Sphicterotomy versus Transpancreatic Sphicterotomy Technique**
Surachai Siripornadulsilp, Nisit Tongsiri

181 **Mosapride Reduces Prolonged Postoperative Ileus after Open Colorectal Surgery in the Setting of Enhanced Recovery after Surgery (ERAS): A Matched Case-Control Study**
Varut Lohsiriwat

189 **Cardiaovascular Disease Risk Factors in Thai Natural Menopause with First-Time Diagnosis of Low Bone Mass Density**
Kitirat Techatraisak, Pattra Wisarnsirirak

196 **Comparative Study of Health-Related Quality of Life between Colorectal Cancer Patients with Temporary and Permanent Stoma**
Natharom Chutikamo, et al.

201 **An Agreement of Two Tonometers: Goldmann Applanation and Non-Contact Scheimflug Technology in Healthy, Ocular Hypertension and Open-angle Glaucoma Patients**
Sakaorat Petchyim, et al.

207 **The Use of Dual Energy Computerized Tomography to Detect Residual Viable Hepatocellular Carcinoma after Transarterial Chemoembolization**
Pharida Pengwan, et al.

214 **The Effects of the Thai Traditional Medicine of Abdominal Massage on Defecation in Post Lumbar Laminectomy Patients**
Prapapin Siripohn, et al.

220 **Prevalence and Factors Associated with Abnormal Cervical Cell among the Hmong and Mien Hill Tribe Women in Pha Yao Province, Thailand**
Supansa Kuntasorn, et al.

228 **Resilience in Medical Doctors within the Areas of the Southern Thailand Insurgency**
Chonnakarn Jatchavala, Jarurin Pitanupong

234 **Detection of Specific Autoantibodies in Sera with Negative Antinuclear Antibody by Indirect Immunofluorescence Assay but Positive by Enzyme Immunoassay**
Ronnachai Viriyataveekul, Jaruda Kobkitjaroen

240 **Identification of Apigenin and Luteolin in *Artemisia annua* L. for the Quality Control**
Rattana Phadungrakwittaya, et al.

REVIEW ARTICLE

246 **Telemedicine – Meaning, Challenges and Opportunities**
Ittipong Khemapech, et al

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Detection of Specific Autoantibodies in Sera with Negative Antinuclear Antibody by Indirect Immunofluorescence Assay but Positive by Enzyme Immunoassay

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ABSTRACT

Objective: The aim of this study was to investigate the predictive value of positive enzyme immunoassay (EIA) for detection of specific autoantibodies in sera negative for antinuclear antibody (ANA) by indirect immunofluorescence (IIF) assay, but positive for ANA by EIA.

Methods: Eighty sera that tested negative for ANA by IIF, but positive for ANA by EIA were included. All sera were tested for specific autoantibodies by line immunoassay (LIA). The positive predictive value (PPV) of EIA was calculated using LIA result as a reference standard. Medical records of patients were reviewed. Clinical findings at the time of blood sampling for ANA testing and at 5 years after sampling were obtained.

Results: Twenty-eight sera (35%) were found to be positive by LIA. The PPV of EIA for detection of specific autoantibodies at the manufacturer's recommended cut-off was 35.0% (95% CI: 24.5-45.5%). The most prevalent antibodies were anti-SSA/Ro60 (64.3%, 95% CI: 46.5-82.0%), anti-Ro52 (25.0%, 95% CI: 9.0-41.0%), and anti-SSB/La (10.7%, 95% CI: 0-22.2%). A diagnosis of systemic autoimmune rheumatic disease was established in 7 patients (25%) at the time of blood sampling, and 4 patients (14.3%) were diagnosed with non-rheumatic autoimmune disease.

Conclusion: EIA testing in IIF-ANA negative sera yielded a chance to detect antinuclear antibodies. However, the poor PPV of EIA may have low benefit in real-life clinical practice. Anti-SSA/Ro60 was the most prevalent antibody detected. A high proportion of LIA-ANA positive patients were not diagnosed as autoimmune disease at the time of antibody detection.

Keywords: Antinuclear antibody; extractable nuclear antigen; enzyme immunoassay; indirect immunofluorescence assay (Siriraj Med J 2019;71: 234-239)

INTRODUCTION

Antinuclear antibodies (ANA) are essential autoantibodies for screening and diagnosis of systemic autoimmune rheumatic diseases (SARD), such as systemic lupus erythematosus (SLE), as well as non-rheumatic autoimmune diseases.[1-5] Certain specific antibodies are included in the diagnostic criteria for certain specific diseases.[6-9] Indirect immunofluorescence (IIF) assay is the gold standard method that is most commonly used for detection of ANA.[10] IIF uses Hep-2 cells as

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a substrate, which provides almost all of the antigens that are required for ANA testing. However, enzyme immunoassay (EIA) is more rapid and simple than IIF for detecting ANA. EIA contains disease-relevant native or recombinant antigens that are coated on a microtiter plate. IIF using Hep-2 cells could yield a false-negative result for anti-Ro and anti-Jo-1 antibodies, while EIA could detect them.[11,12] However, EIA has been associated with both false-positive and false-negative results.[13] During 2010, the Clinical Pathology Laboratory at Siriraj Hospital implemented a protocol that calls for IIF to be used for initial screening of ANA. In cases of negative result by IIF, secondary screening is performed using EIA. We observed that among sera positive for ANA by EIA, some sera samples were positive and some were negative for specific antibodies subsequently requested by the physician.

Accordingly, the aim of this study was to investigate the predictive value of positive EIA for detection of specific autoantibodies in sera negative for ANA by IIF, but positive for ANA by EIA. The secondary objective was to determine and report the prevalence and clinical findings of certain antibodies.

MATERIALS AND METHODS

Patient sera

Sera negative for ANA by IIF, but positive for ANA by EIA were randomly selected from stored sera sent to the Clinical Pathology Laboratory at Siriraj Hospital for ANA testing during 2010. Sera were stored at -20°C before analysis. Siriraj Hospital is Thailand's largest national tertiary referral center.

Medical records of patients whose sera were included in this study were reviewed. Clinical findings at the time of blood sampling for ANA testing and at 5 years after sampling were obtained and recorded.

The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 211/2557).

IIF assay

IIF assay was performed using a Mosaic HEp-20-10/Liver (Monkey) Kit (Euroimmun AG, Lübeck, Germany). Briefly, sera were diluted to 1:100 and then incubated with Hep-20-10 cells. The Hep-20-10 cells contained an increased spectrum of Hep-2 cells in the mitotic phase. After staining with fluorescent conjugate, slides were visualized under a fluorescent microscope at 400x. Fluorescence intensity was compared with that of the end-point positive control. Fluorescence intensity equal to or greater than the fluorescence intensity of the end-point positive control was considered a positive result.

EIA testing

EIA testing was performed using an IMTEC-ANA Screen Kit (Human Diagnostics, Wiesbaden, Germany). The microtiter strips came coated with HeLa cell nuclei. Sera were diluted to 1:101 before being added to the plates. The manufacturer defined any value above 55 U/ml as being a positive result.

Antigen-specific assays

Line immunoassay (LIA) was performed using an IMTEC-ANA-LIA Kit (Human Diagnostics). The strips contain the following antigens: nucleosomes, histones, SmD1, nRNP, SSA/Ro60, Ro52, SSB/La, Scl-70, CENP-B, Jo-1, and ribosomal P proteins (Rib-P). Sera showing positive reactivity on the Human Diagnostics LIA were tested again using a EUROLINE ANA Profile 3 Kit (Euroimmun AG) to confirm the result. The strips in that kit contain the following antigens: nRNP, Sm, SSA/Ro60, Ro-52, SSB/La, Scl-70, PM/Scl, Jo-1, CENP-B, PCNA, dsDNA, nucleosomes, histones, Rib-P, and AMA M2. Sera were diluted to 1:101 before incubation with the strips. Positive reactivity on both LIA kits for at least 1 identical antibody (Ab) type was considered a positive result.

Statistical analysis

All data were collected and analyzed using Microsoft Excel 2016 spreadsheet software (Microsoft Corporation, Redmond, WA, USA). Rate of positive or negative LIA, predictive value of positive EIA, prevalence of each specific antibody, and 95% confidence interval (CI) were calculated.

RESULTS

Eighty sera that tested negative for ANA by IIF, but that tested positive for ANA by EIA were included. An overview of LIA results from both LIA test kits is shown in Fig 1. Seven sera with positive LIA by only the Human Diagnostics LIA (samples 31-37), and 2 sera positive for different antibody types using either the Human Diagnostics LIA or the Euroimmun LIA (samples 29-30) were considered negative LIA (Table 1). Therefore, 28 sera (35%) were considered positive LIA (samples 1-28).

The manufacturer's recommended cut-off value of 55 U/mL could not discriminate positive from negative LIA (Fig. 2). Using the LIA result as a reference standard, the

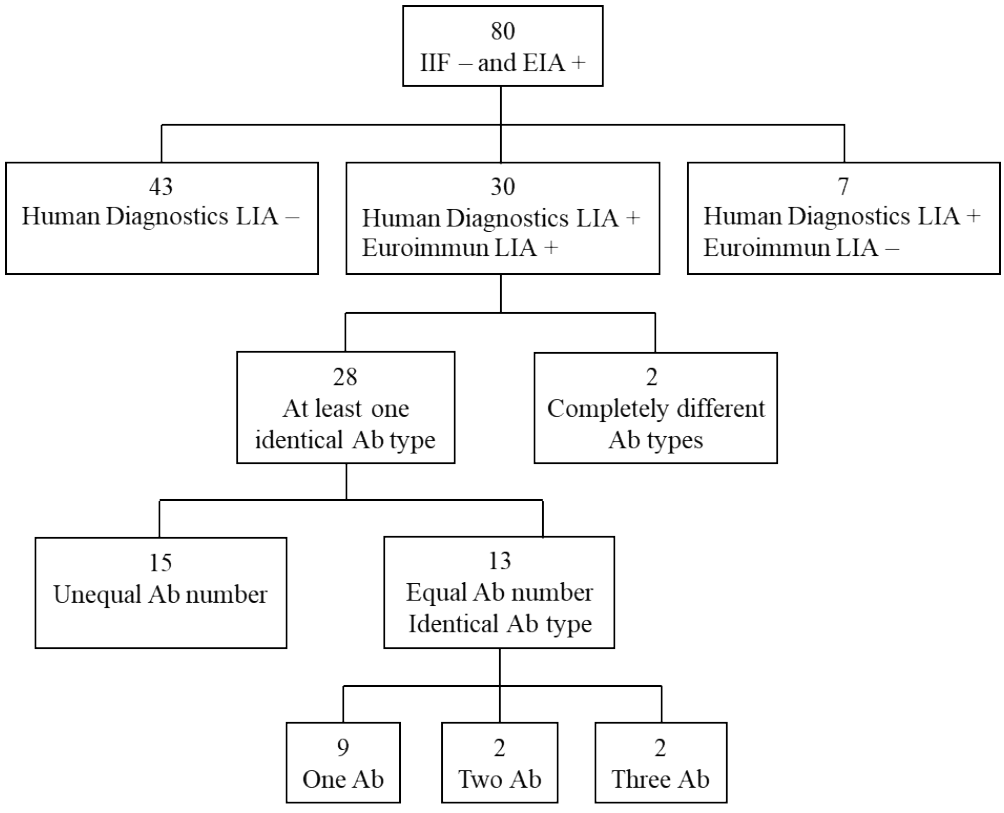


Fig 1. Overview of LIA results of 80 sera negative for ANA by IIF, but positive for ANA by EIA.
Abbreviations: Ab = antibody; EIA = enzyme immunoassay; IIF = indirect immunofluorescence assay; LIA = line immunoassay, - = negative; + = positive

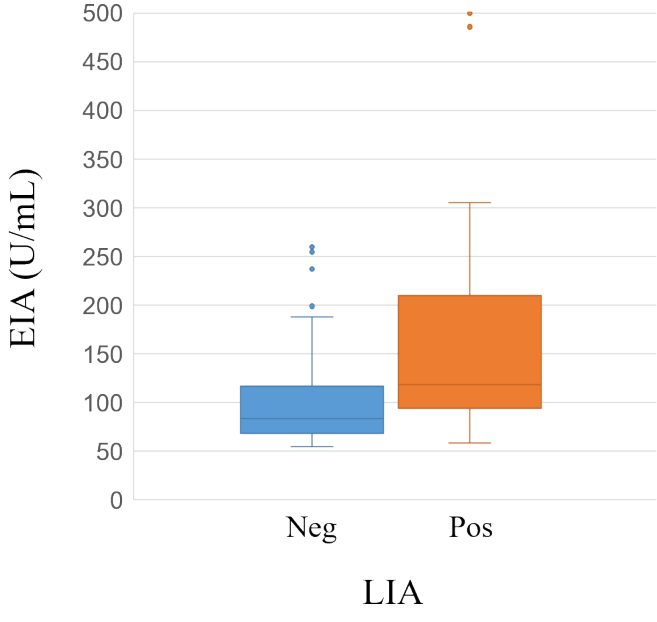


Fig 2. Comparison of EIA values between positive and negative LIA.
Abbreviations: EIA= enzyme immunoassay; LIA= line immunoassay; Neg= negative; Pos= positive

positive predictive value (PPV) of EIA for the detection of specific autoantibodies at this value was 35.0% (95% CI: 24.5-45.5%). The PPV of different EIA values are shown in Table 2.

The most prevalent antibodies were anti-SSA/Ro60 (64.3%, 95% CI: 46.5-82.0%), anti-Ro52 (25%, 95% CI: 9.0-41.0%), and anti-SSB/La (10.7%, 95% CI: 0-22.2%) (Table 1). A diagnosis of SARD was established in 7 of 28 patients (25%) at the time of blood sampling. Four patients (14.3%) were diagnosed with non-rheumatic autoimmune disease. Seventeen patients had insufficient evidence for diagnosing autoimmune disease (60.7%).

TABLE 1. EIA values, specific antibodies, and clinical findings of 37 sera showing reactivity on LIA.

Sample no.	EIA (U/ml)	Human Diagnostics LIA	Euroimmun LIA	Clinical findings
1	95	Ro60	Ro60	Urticarial vasculitis
2	98	Ro60	Ro60	Chronic urticaria, allergic rhinitis
3	94	Ro60	Ro60	Tubulointerstitial disease of unknown cause
4	305	Ro60, Ro52	Ro60, Ro52	Dead fetus in utero at 13 weeks
5	252.57	Ro60, Ro52, La	Ro60, Ro52, La	SLE
6	113.63	Ro60, SmD1, Rib-P	Ro60, Sm, Rib-P	Discoid LE, lupus profundus
7	>500	Ro60	Ro60, Ro52	SLE
8	139	Ro60	Ro60, Ro52	Amaurosis fugax
9	114	Ro60	Ro60, Ro52	RA, secondary Sjogren syndrome
10	193.41	Ro60	Ro60, AMA-M2	Primary biliary cirrhosis
11	>500	Ro60	Ro60, histone	Nonalcoholic steatohepatitis
12	486	Ro60	Ro60, Rib-P	AIH
13	206	Ro60	Ro60, Ro52, AMA-M2	Nephrotic syndrome (FSGS)
14	198.6	Ro60	Ro60, Ro52, La, CENP-B	RA, leukopenia
15	120.3	Ro60, nRNP	Ro60	DM, AKI on top of CKD
16	211	Ro60, Ro52	Ro60, Ro52, PM/Scl	Chronic ITP
17	90	Ro60, SmD1, nucleosome	Ro60, Ro52	Alopecia areata
18	288.3	Ro60, histone, nucleosome	Ro60, dsDNA	Lupus nephritis type IV
19	58.41	Ro52	Ro52	Myofascial pain syndrome
20	106	Ro52	Ro52, Ro60	Common variable immune deficiency
21	63	Ro52	Ro52, AMA-M2	Chronic hepatitis C
22	117	Ro52, Jo-1	Ro52, Jo-1	RA
23	148.54	CENP-B	CENP-B	Suspected AIH
24	72	Jo-1	Jo-1	Progressive obstructive jaundice of unknown cause
25	88.9	La	La	Beta-thalassemia/Hb E disease, AIHA
26	83	La	La, Jo-1	Erythema nodosum
27	124.29	Scl-70	Scl-70	Chronic urticaria
28	96.87	SmD1	Sm	Unilateral posterior uveitis
29	78.9	SmD1	Ro60	N/A
30	146	nRNP	Sm	N/A
31	68	Ro60	-	N/A
32	72	SmD1	-	N/A
33	77.8	SmD1	-	N/A
34	135	Histone	-	N/A
35	158	nRNP	-	N/A
36	107.4	SmD1, Ro60	-	N/A
37	81	Nucleosome, histone, nRNP	-	N/A

Abbreviations: Ab= antibody; AIH= autoimmune hepatitis; AKI= acute kidney injury; AIHA= autoimmune hemolytic anemia; CKD= chronic kidney disease; DM= diabetes mellitus; FSGS= focal segmental glomerulosclerosis; ITP= immune thrombocytopenia; LE= lupus erythematosus; N/A= not applicable; RA= rheumatoid arthritis; SLE= systemic lupus erythematosus

TABLE 2. Positive predictive values of different EIA values.

EIA value (U/mL)	Positive LIA n	Negative LIA n	PPV (95% CI)
>260	5	0	100% (100-100)
>250	6	2	75.0% (45.0-100)
>200	8	3	72.7% (46.4-99.0)
>150	10	9	52.6% (30.2-75.1)
>100	18	19	48.6% (32.5-64.8)
>55	28	52	35.0% (24.5-45.5)

Abbreviations: EIA= enzyme immunoassay; LIA= line immunoassay; PPV= positive predictive value; CI= confidence interval

Five years later, 13 of those (76.5%) had not developed autoimmune disease, and 4 patients (samples 19, 21, 23, and 28) had missing data.

DISCUSSION

The present study set forth to investigate for specific antibodies in sera negative for ANA by IIF, but positive for ANA by EIA. We found a higher rate of positive specific antibodies than previous study (35% vs. 16.9%).[14] Compared to previous studies that performed antigen-specific assay in all IIF-ANA negative sera and who found a rate of positivity of 0.7-14%[15-17], we demonstrated that screening with EIA-ANA before performing antigen-specific assay in IIF-ANA negative sera may increase the probability of identifying specific antibodies.

The manufacturer's recommended cut-off value yielded a low PPV. Even though the EIA value was as high as 250 U/mL, the PPV of 75% was not sufficiently high. Therefore, a positive result from this EIA kit may not be applicable to real-life clinical practice. However, reporting the EIA result along with its specific PPV may provide benefit relative to a decision to request or not request antigen-specific assay.

Similar to previous studies[14,16], the most prevalent antibodies identified in this study were anti-SSA/Ro60, anti-Ro52, and anti-SSB/La, and these antibodies have been recognized as being associated with Sjogren syndrome and SLE.[18] Anti-SSA/Ro60 was shown to have association with both subacute cutaneous lupus erythematosus[19] and neonatal lupus erythematosus.[20,21] In the present study, a large proportion of patients with positive LIA were not diagnosed as autoimmune disease by the 5-year follow-up. However, the presence of autoantibodies often portends the development of disease that does not fully clinically manifest until years into the future. Anti-SSA/Ro60 could be detected before the onset of symptoms and diagnosis of SLE at intervals as long as 9.1 and 10.4 years, respectively.[22,23]

This study has some mentionable limitations. First and consistent with the retrospective nature of this study, some data was missing or incomplete. Second, the number of included samples was relatively small. Third, random samples were selected from routine ANA testing; therefore, our findings may not be generalizable to patients tested in specialized clinic. Fourth and last, we investigated only one EIA kit that uses HeLa cell nuclear extract, which may be different from other EIA kits that use different combinations of defined native or recombinant antigens.

CONCLUSION

EIA testing in IIF-ANA negative sera yielded a chance to detect antinuclear antibodies. However, the poor PPV of EIA may have low benefit in real-life clinical practice. Anti-SSA/Ro60 was the most prevalent antibody detected. A high proportion of LIA-ANA positive patients were not diagnosed as autoimmune disease at the time of antibody detection.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Ms. Jintana Jaiyen for assistance with specimen collection, and the laboratory technicians in the Clinical Pathology Serology Laboratory of Siriraj Hospital for performing the LIA test.

Conflict of interest: The LIA kits used in this study were provided free of charge by their distributors. The authors declare no other conflicts of interest.

REFERENCES

1. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
2. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
3. Solomon DH, Kavanaugh AJ, Schur PH, American College of Rheumatology Ad Hoc Committee on Immunologic Testing G. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. Arthritis Rheum 2002;47:434-44.
4. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-38.
5. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-76.
6. Alarcon-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. J Rheumatol 1989;16:328-34.
7. Tanimoto K, Nakano K, Kano S, Mori S, Ueki H, Nishitani H, et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol 1995;22:668-74.
8. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2012;64:475-87.
9. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747-55.
10. Agmon-Levin N, Damoiseaux J, Kallenberg C, Sack U, Witte T, Herold M, et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Ann Rheum Dis 2014;73:17-23.
11. Blomberg S, Ronnblom L, Wallgren AC, Nilsson B, Karlsson-Parra A. Anti-SSA/Ro antibody determination by enzyme-linked immunosorbent assay as a supplement to standard immunofluorescence in antinuclear antibody screening. Scand J Immunol 2000;51:612-7.
12. Bahrt KM, McCarty GA. A negative fluorescent antinuclear antibody test in a patient with Jo-1 antibody. J Rheumatol 1985;12:624-5.
13. Bayer PM, Fabian B, Hubl W. Immunofluorescence assays (IFA) and enzyme-linked immunosorbent assays (ELISA) in autoimmune disease diagnostics--technique, benefits, limitations and applications. Scand J Clin Lab Invest Suppl 2001;235:68-76.
14. Dahle C, Skogh T, Aberg AK, Jalal A, Olcen P. Methods of choice for diagnostic antinuclear antibody (ANA) screening: benefit of adding antigen-specific assays to immunofluorescence microscopy. J Autoimmun 2004;22:241-8.
15. Hoffman IE, Peene I, Veys EM, De Keyser F. Detection of specific antinuclear reactivities in patients with negative anti-nuclear antibody immunofluorescence screening tests. Clin Chem 2002;48:2171-6.
16. Lee SA, Kahng J, Kim Y, Park YJ, Han K, Kwok SK, et al. Comparative study of immunofluorescent antinuclear antibody test and line immunoassay detecting 15 specific autoantibodies in patients with systemic rheumatic disease. J Clin Lab Anal 2012;26:307-14.
17. Sener AG, Afsar I, Demirci M. Evaluation of antinuclear antibodies by indirect immunofluorescence and line immunoassay methods': four years' data from Turkey. APMIS 2014;122:1167-70.
18. Provost TT. Anti-Ro(SSA) and anti-La(SSB) antibodies in lupus erythematosus and Sjogren's syndrome. Keio J Med 1991;40:72-7.
19. McCauliffe DP. Cutaneous diseases in adults associated with anti-Ro/SS-A autoantibody production. Lupus 1997;6:158-66.
20. Cimaz R, Spence DL, Hornberger L, Silverman ED. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. J Pediatr 2003;142:678-83.
21. Jaeggi E, Laskin C, Hamilton R, Kingdom J, Silverman E. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. J Am Coll Cardiol 2010;55:2778-84.
22. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526-33.
23. Eriksson C, Kokkonen H, Johansson M, Hallmans G, Wadell G, Rantapaa-Dahlqvist S. Autoantibodies predate the onset of systemic lupus erythematosus in northern Sweden. Arthritis Res Ther 2011;13:R30.

Identification of Apigenin and Luteolin in *Artemisia annua* L. for the Quality Control

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ABSTRACT

Objective: To identify active compounds and establish the chemical fingerprint of *Artemisia annua* L. for the quality control.

Methods: Thin-layer chromatography (TLC) conditions were developed to screen for 2 common flavonoids (apigenin and luteolin). Three mobile phases were used to isolate these flavonoids in 80% ethanolic extract of *A. annua*. Hexane : ethyl acetate : acetic acid (31:14:5, v/v) and toluene : 1,4-dioxane : acetic acid (90:25:4, v/v) were used in normal phase TLC (NP-TLC), and 5.5% formic acid in water : methanol (50:50, v/v) were used in reverse phase TLC (RP-TLC). Chromatograms were visualized under visible light after spraying with Fast Blue B Salt. Apigenin and luteolin bands were checked by comparing their Rf values and UV-Vis absorption spectra with reference markers.

Results: Apigenin and luteolin were simultaneously detected with good specificity in RP-TLC condition, while only apigenin was detected in NP-TLC condition. Apigenin band intensity was higher than luteolin band intensity in both conditions.

Conclusion: This knowledge can be applied to the development of quality control assessments to ensure product efficacy and consistency.

Keywords: *Artemisia annua* L.; TLC fingerprint; apigenin; luteolin (Siriraj Med J 2019;71: 240-245)

INTRODUCTION

Artemisia annua L., commonly known as sweet wormwood, is an annual plant in the Asteraceae (Compositae) family. This herb is native to Asia and throughout much of China. It flourishes in the temperate zone, and also grows wild in central Europe. Aqueous preparations of dried *A. annua* have traditionally been used to treat fever, malaria, skin diseases, jaundice, and hemorrhoids in China. In Thailand, *A. annua* has been used to treat fever, asthma, skin disease, circulatory disorders (e.g., dizziness), and as an expectorant and an anthelmintic.[1] *A. annua* is also used as an herbal ingredient in some Thai herbal recipes that are published in The National List of Essential Medicines.[2] Several previous studies reported that *A. annua* possesses various pharmacological activities, including antimalarial, antinociceptive, anti-inflammatory, antioxidant, anticancer, and antimicrobial actions.[3-10] Moreover, the essential oil from this plant is postulated to inhibit the growth of Gram-positive bacteria, Gram-negative bacteria, and yeast, and to depress the central nervous system.[11-13] These reported findings support the historical claims and traditional belief that *A. annua* is an effective herbal medicine for treatment of different diseases. The chemical component of *A. anuua*

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that makes it effective for treating the parasitic diseases of malaria is artemisinin, a sesquiterpene lactone.[4-5] A large number of flavonoides, including apigenin, luteolin, kaempferol, quercetin, casticin, and artemetin, have also been reported to be present in *A. annua*.[14-15] Reported vital pharmacological activities effectuated by flavonoids in *A. annua* include antioxidant, inhibition of immune mediators of angiogenesis, prophylactic effects in malaria and related fevers, and antimalaria parasite.[8,16-20]

Luteolin and apigenin are flavonoids that are commonly found in different plant species that are associated with a broad spectrum of pharmacological activities, including antimalarial, anti-inflammatory, antioxidant, and anticancer.[20-23] However, the efficacy of drugs that contain flavonoids can vary according to environmental conditions and season of harvest or growth stage.[24-26] Thin-layer chromatography (TLC) is currently the method of choice for identifying a wide variety of substance classes, because it is a simple, rapid, inexpensive, and substances are identified visually. A new method for simultaneously quantifying apigenin and luteolin using reverse-phase TLC in some medicinal plants was recently reported.[27] The development of a screening method that could reliably identify the presence of apigenin and luteolin in *A. annua*, and then a chromatogram fingerprint of *A. annua* would facilitate quality control assessments of harvested *A. annua* to ensure the reproducibility of ingredients and the consistent efficacy of the product. Accordingly, the aim of this study was to develop a screening method to identify apigenin and luteolin in *A. annua*, and then establish a chromatogram fingerprint of *A. annua*.

MATERIALS AND METHODS

Chemicals and plant materials

All reagents used were of analytical grade. Methanol, ethanol, and hexane were purchased from Scharlau (Barcelona, Spain), and toluene, formic acid, and acetic acid were purchased from Merck (Darmstadt, Germany). Ethyl acetate was purchased from Riedel-de Haen (Seelze, Germany), and 1, 4 dioxane was purchased from Carlo Erba Reagents, (Val de Reuil, France). Apigenin, luteolin, and Fast Blue B Salt were purchased from Calbiochem (San Diego, California, USA), Extrasynthese, (Genay, France), and Sigma-Aldrich (St. Louis, Missouri, USA), respectively. HPTLC Silica gel 60 F_{254} (NP-TLC) and TLC Silica gel 60 RP-18 F_{254S} (RP-TLC) were purchased from Merck (Darmstadt, Germany). Pulverized aerial plant material of *A. annua*, was obtained from the Manufacturing Unit of Herbal Medicines and Products, Center of Applied Thai Traditional Medicine (CATTM), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Instruments

The CAMAG TLC system (CAMAG Chemie-Erzeugnisse & Adsorptionstechnik AG, Muttenz, Switzerland) consisted of a CAMAG Linomat 5 sample applicator, a CAMAG Automatic Developing Chamber (ADC2), and a CAMAG TLC Scanner 3. Densitometry documentation was performed under UV light (254 and 366 nm) and visible light using Reprostar 3 densitometer with CCD camera. CAMAG winCATS software was used to control the system and analyze the data.

Preparation of standard solutions

One milligram of apigenin was dissolved in 2 milliliters of methanol, and 1 mg of luteolin was dissolved in 1 milliliter of methanol. Stock solutions were maintained in a refrigerator at -20°C until use.

Preparation of sample solutions

To obtain the optimal solvent for the extraction of *A. annua*, three common solvents were used, including 100% methanol, 100% ethanol, and 80% ethanol. Ten milliliters of each solvent was added to 1 gram of pulverized aerial plant material of *A. annua* and sonicated for 60 minutes. The 3 mixtures were then centrifuged at 4,000 rpm for 10 minutes at 25°C. The supernatant was separated and evaluated using the TLC systems.

TLC analysis

We employed 3 different mobile phase systems – two normal-phase (NP) and one reverse-phase (RP) TLC. The 2 NP-TLC mobile phase systems consisted of hexane : ethyl acetate : acetic acid (31:14:5, v/v) and toluene : 1,4-dioxane : acetic acid (90:25:4, v/v). The RP-TLC mobile phase system consisted of 5.5% formic acid in water : methanol (50:50, v/v). Sample volumes of *A. annua* extracts applied on HPTLC and RP-TLC plates were varied to obtain the best separation and the most obvious chromatogram fingerprints. One microliter (μL) of luteolin and 2 μL of apigenin were mixed and loaded alongside the sample as markers. Development duration was approximately 20 minutes or the solvent migration distance was at least 7.5 cm. Developed plates were dried in cold air for approximately 5 minutes. Extracted chromatogram fingerprints were visualized under both ultraviolet light (UV) (254 and 366 nm) and visible light after spraying with Fast Blue B Salt (FBS). Chromatograms were further sprayed with 10% NaOH to intensify the result. Presence of apigenin and/

or luteolin was determined by comparing rate of flow (Rf) values and absorption spectra with those of their respective markers.

RESULTS

Chromatogram fingerprints of ethanol, methanol, and 80% ethanol extracts of the aerial part of *A. annua* after FBS staining are shown in Fig 1. Eighty percent ethanol was determined to be the optimal extraction solvent. Chromatogram fingerprints of *A. annua* extract under UV light (254 and 366 nm) and visible light after FBS staining of NP-TLC and RP-TLC are shown in Fig 2. The Rf values in NP-TLC (2 solvent systems) and RP-TLC (1 solvent system) were 0.21, 0.24, and 0.09 for apigenin marker, and 0.10, 0.13, and 0.15 for luteolin marker, respectively (Fig 3, Table 1). Bands identified in the chromatogram of *A. annua* using RP-TLC expressed migration distance, color, and absorption spectrum similar to that of apigenin and luteolin markers. Using NP-TLC, only bands of apigenin was identified (Fig 4). Accordingly, RP-TLC was found to be the most suitable method for simultaneously identifying both apigenin and luteolin in 80% ethanolic extract of *A. annua*. The band intensity of apigenin was higher than that of luteolin in both NP-TLC and RP-TLC.

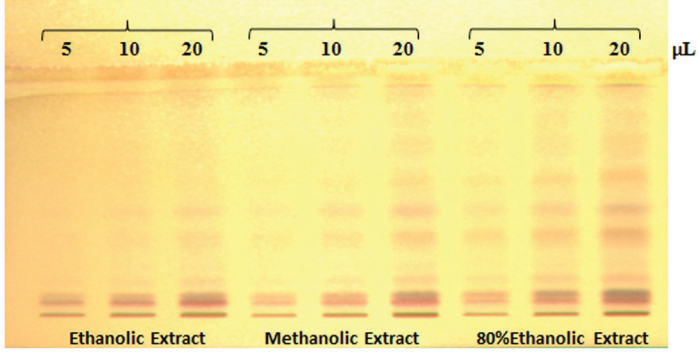


Fig 1. RP-TLC chromatogram of ethanol, methanol, and 80% ethanol extracts of the aerial part of *A. annua* detected under visible light after spraying with FBS and intensification by spraying with 10% NaOH.

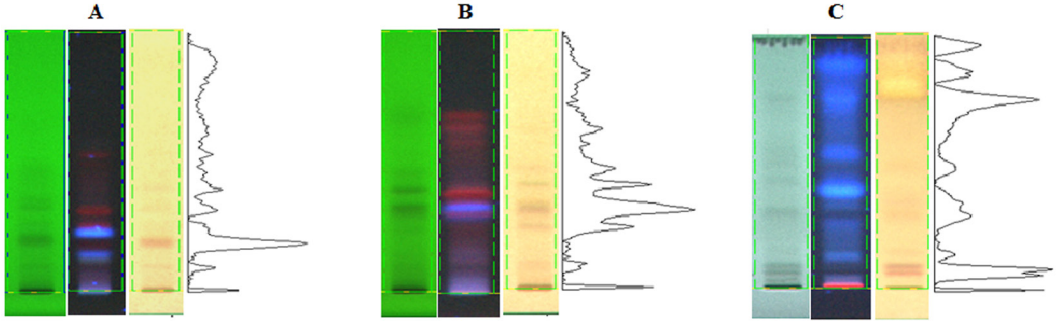


Fig 2. Chromatogram fingerprint of *A. annua* developed in a NP-TLC plate with **A)** hexane : ethyl acetate : acetic acid (31:14:5 v/v); **B)** toluene : 1,4-dioxane : acetic acid (90:25:4, v/v); and, **C)** in an RP-TLC plate with 5.5% formic acid in water : methanol (50:50, v/v). Visualization was performed under UV light (254 and 366 nm) and visible light after spraying with FBS.

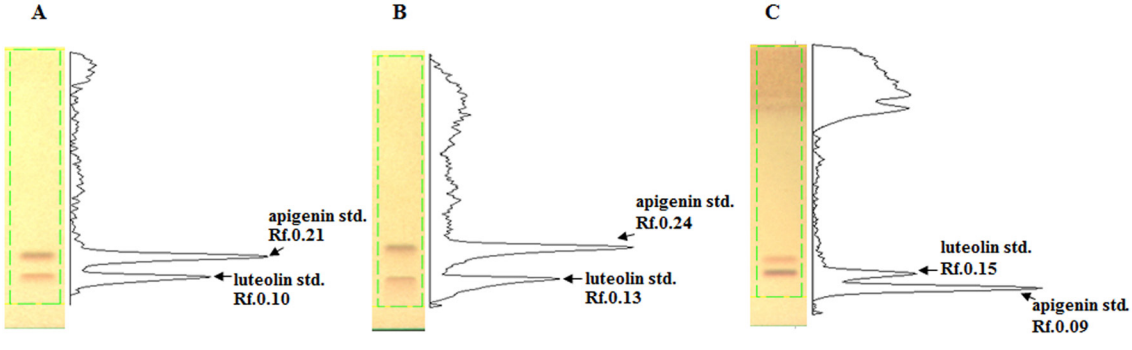


Fig 3. Chromatograms of apigenin and luteolin in a mixed marker solution developed in a NP-TLC plate with **A)** hexane : ethyl acetate : acetic acid (31:14:5, v/v); **B)** toluene : 1,4-dioxane : acetic acid (90:25:4, v/v); and, **C)** in an RP-TLC plate with 5.5% formic acid in water : methanol (50:50, v/v). Bands were detected under visible light after FBS staining.

TABLE 1. Rf values of reference markers by mobile phase

Mobile phase	Marker	Plate type	Rf
Hexane : ethyl acetate : acetic acid	Apigenin	NP-TLC	0.21
(31:14:5, v/v)	Luteolin	NP-TLC	0.10
Toluene : 1,4-dioxane : acetic acid	Apigenin	NP-TLC	0.24
(90:25:4, v/v)	Luteolin	NP-TLC	0.13
5.5% formic acid in water: methanol	Apigenin	RP-TLC	0.09
(50:50, v/v)	Luteolin	RP-TLC	0.15

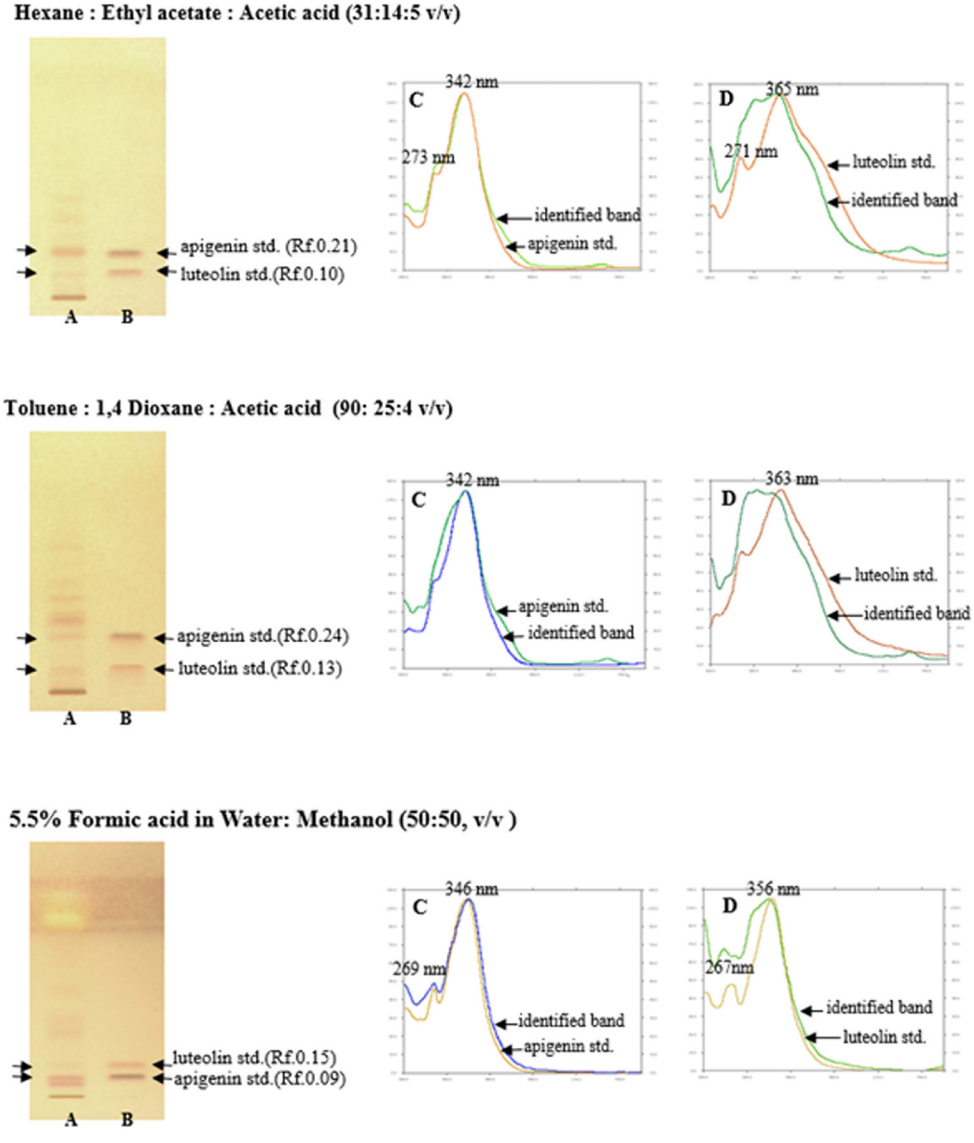


Fig 4. Detection of apigenin and luteolin in *A. annua* under visible light after spraying with FBS and intensification with 10% NaOH in 3 condition systems: **A)** 80% ethanolic extract of *A. annua*; **B)** mixed marker solution; **C)** absorbent overlay of apigenin marker along with the sample; and, D) absorbent overlay of luteolin marker along with the sample.

DISCUSSION

Artemisinin is a potent antimalarial drug against *Plasmodium falciparum* that can be found at a range of concentration of 0.01-0.5% of dry weight of *A. annua*.[4] That study also reported for flavonoid compounds in this plant. Apigenin and luteolin were 2 of several flavonoids identified in the leaves and stems of *A. annua*. These compounds were isolated and characterized by comparing their UV, MS, and 1H NMR spectra with the literature and reference compounds.[14] Luteolin and apigenin are reported to be associated with a broad spectrum of pharmacological activities, including antimalarial, anti-inflammation, antioxidant, and anticancer.[20-23] Thin-layer chromatography (TLC) is suitable for initial identification of substances prior to more advanced analysis using more sophisticated analytical instruments. The optimal yield of apigenin and luteolin found in 80% ethanolic extract allowed for further identification of apigenin and luteolin in *A. annua* using the three mobile systems. In this study, RP-TLC enabled simultaneous detection of apigenin and luteolin with specificity while NP-TLC could detect with specificity only for apigenin compound. A previous study reported the use of RP-TLC to identify various flavonoids, including apigenin and luteolin.[27] However and based on our review of the literature, no comparison has been made between the efficiency of NP-TLC and RP-TLC. Our finding showed that RP-TLC can identify the two substances of interest and established that RP-TLC is more suitable for detecting the presence of apigenin and luteolin in *A. annua*. The superiority demonstrated by RP-TLC over NP-TLC can be explained by the low selectivity of NP-TLC. The UV-Vis absorption profile of the similar in position band to luteolin reference compound under NP-TLC condition was not similar to that of standard. This indicates that the band might not be free of any interference that was present in the extract. In this study, the fact that the band of apigenin appeared more intensely than the band of luteolin suggests that the aerial parts of the *A. annua* used in this experiment contained more apigenin than luteolin. This result contrasts with the result of a previous study that reported the same amount of luteolin and apigenin isolated from ethyl acetate extract of the leaves and stems of *A. annua* (0.015% on dry weight).[14] In addition to different types of sample preparations and different methods of analysis being the cause of variations in flavonoid content, variation may also be due to geographical area, season of harvest, or phenological growth stages. The previous study on the effects of geographical area and polluted environment on flavonoid contents in *Artemisia vulgaris* and *Veronica chamaedrys* by using TLC technique reported that apigenin in *V. chamaedrys* was increased at the alpine regions, while the content of quercetin 3,7,3'-trimethyl ether in *A. vulgaris* appeared to be independent of altitude, but it was influenced positively by environmental pollution.[24] The study on the seasonal variation in 15 phenolic compounds of 80% ethanolic extract of *Rhododendron tomentosum* leaf found that the quantity of all fifteen phenolic compounds showed significant seasonal variation, but there was no seasonal variation of their total sum.[25] The qualitative and quantitative flavonoid aglycones variations in relation to the different phenological stages were also observed in *Artemisia absinthium* and *Artemisia vulgaris* by using HPLC. The detected flavonoids in *A. absinthium* were stable in their qualitativem but different in their contents while the flavonoid profiles of *A. vulgaris* exhibited qualitative and quantitative variability during the life cycle.[26]

CONCLUSION

This study found RP-TLC to be most suitable for simultaneously identifying both apigenin and luteolin in 80% ethanolic extract of *A. annua*. This knowledge can be applied to the development of quality control assessments of harvested *A. annua* to ensure the reproducibility of ingredients and the consistent efficacy of the product.

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Conflict of interest: The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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REFERENCES

1. Bunyapraphatsara N, Chokchaicharoenporn O, editors. Indigenous medicinal herbs (1). 1st ed. Bangkok: Prachachon Press; 1996.
2. National Essential Drug List 2009, National Drug Committee,

Ministry of Public Health, Thailand, List of Herbal Medicinal Products A.D. 1999, 2006, 2012.
3. Mesa LE, Lutgen P, Velez ID, Segura AM, Robledo SM. *Artemisia annua* L., Potential Source of Molecules with Pharmacological Activity in Human Diseases. AJPCT 2015;3:436-50.
4. Woerdenbag HJ, Lugt CB, Pras N. *Artemisia annua* L.: a source of novel antimalarial drugs. Pharm Weekbl Sci 1990;12:169-81.
5. Elfawal MA, Towler MJ, Reich NG, Golenbock D, Weathers PJ, Rich SM. Dried whole plant *Artemisia annua* as an antimalarial therapy. PLoS One 2012;7:e52746.
6. Favero Fde F, Grando R, Nonato FR, Sousa IM, Queiroz NC, Longato GB, Zafred RR, Carvalho JE, Spindola HM, Foglio MA. *Artemisia annua* L.: evidence of sesquiterpene lactones' fraction antinociceptive activity. BMC Complement Altern Med 2014;14:266.
7. Kim WS, Choi WJ, Lee S, Kim WJ, Dong Lee C, Sohn UD, et al. Anti-inflammatory, antioxidant and antimicrobial effects of artemisinin extracts from *Artemisia annua* L. Korean J Physiol Pharmacol 2015;19:21-27.
8. Iqbal S, Younas U, Chan KW, Zia-Ul-Haq M, Ismail M. Chemical composition of *Artemisia annua* L. leaves and antioxidant potential of extracts as a function of extraction solvents. Molecules 2012;17:6020-32.
9. Kim MH, Seo JY, Liu KH, Kim JS. Protective effect of *Artemisia annua* L. extract against galactose-induced oxidative stress in mice. PLoS One 2014;9:e101486.
10. Appalasamy S, Lo KY, Ch'ng SJ, Nornadia K, Othman AS, Chan LK. Antimicrobial activity of artemisinin and precursor derived from in vitro plantlets of *Artemisia annua* L. Biomed Res Int 2014;2014:215872.
11. Marinas IC, Oprea E, Chifiriuc MC, Badea IA, Buleandra M, Lazar V. Chemical composi tion and antipathogenic activity of *Artemisia annua* essential Oil from Romania. Chem Biodivers 2015;12:1554-64.
12. Bilia AR, Santomauro F, Sacco C, Bergonzi MC, Donato R. Essential oil of *Artemisia annua* L.: An extraordinary component with numerous antimicrobial properties. Based Complement Alternat Med 2014;2014:159819.
13. Perazzo FF, Carvalho JC, Carvalho JE, Rehder VL. Central properties of the essential oil and the crude ethanol extract from aerial parts of *Artemisia annua* L. Pharmacol Res 2003;48: 497-502.
14. Yang SL, Roberts MF, O'Neill MJ, Bucar F, Phillipson JD. Flavonoids and chromenes from *Artemisia annua*. Phytochemistry 1995;38:255-7.
15. Bhakuni RS, Jain DC, Sharma RP, Kumar S. Secondary metabolites of *Artemisia annua* and their biological activity. Curr Sci 2001; 80:35-48.
16. Song Y, Desta KT, Kim GS, Lee SJ, Lee WS, Kim YH, et al. Polyphenolic profile and antioxidant effects of various parts of *Artemisia annua* L. Biomed Chromatogr 2016; 30:588-95.
17. Zhu XX, Yang L, Li YJ, Zhang D, Chen Y, Kostecká P, et al. Effects of sesquiterpene, flavonoid and coumarin types of compounds from *Artemisia annua* L. on production of mediators of angiogenesis. Pharmacol Rep 2013;65:410-20.
18. Ogwang PE, Ogwal JO, Kasasa S, Ejobi F, Kabasa D, Obua C. Use of *Artemisia annua* L. infusion for malaria prevention: mode of action and benefits in a Ugandan community. Br J Pharm Res 2011;1:124-132.
19. Ferreira JF, Luthria DL, Sasaki T, Heyerick A. Flavonoids from *Artemisia annua* L. as antioxidants and their potential synergism with artemisinin against malaria and cancer. Molecules 2010; 15:3135-70.
20. Lehane AM, Saliba KJ. Common dietary flavonoids inhibit the growth of the intraery throcytic malaria parasite. BMC Res Notes 2008;1:26.
21. Funakoshi-Tago M, Nakamura K, Tago K, Mashino T, Kasahara T. Anti-inflamma tory activity of structurally related flavonoids, apigenin, luteolin and fisetin. Int Immunopharmacol 2011;11: 1150-9.
22. López-Lázaro M. Distribution and biological activities of the flavonoid luteolin. Mini Rev Med Chem 2009;9:31-59.
23. Patel D, Shukla S, Gupta S. Apigenin and cancer chemoprevention: progress, potential and promise (review). Int J Oncol 2007;30: 233-45.
24. Nikolova MT, Ivancheva SV. Quantitative flavonoid variations of *Artemisia vulgaris* L. and *Veronica chamaedrys* L. in relation to altitude and polluted environment. Act Biol Szeg 2005;49: 29-32.
25. Black P, Saleem A, Dunford A, Guerrero-Analco J, Walshe-Roussel B, Haddad P, et al. Seasonal variation of phenolic constituents and medicinal activities of Northern Labrador tea, *Rhododendron tomentosum* ssp. *subarcticum*, an Inuit and cree First Nations traditional medicine. Planta Med 2011;77: 1655-62.
26. Nikolova M, Velickovic D. Phenological variations in the surface flavonoids of *Artemisia vulgaris* L. and *Artemisia absinthium* L. Turk J Bot 2007;31:459-62.
27. Bhandari P, Kumar N, Gupta AP, Singh B, Kaul VK. A rapid RP-HPTLC densitometry method for simultaneous determination of major flavonoids in important medicinal plants. J Sep Sci 2007;30:2092-6.

Telemedicine – Meaning, Challenges and Opportunities

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ABSTRACT

Medical service is one of the crucial policies and decent medical service is required by the population in every country. There are three main obstacles which prevent people from obtaining proper medical cares and treatments. First, the deficiency of medical staffs especially physicians which occur even in the developed countries. Second, regarding an important demographic issue, an increase in the number of the elderly makes the medical services more demanding. Finally, geographical aspect also plays a major role in healthcare inequality. The population dwelling in rural or remote areas struggle from accessing proper medical services. Information and communication technologies have become an important infrastructure upon which several domains can build in order to achieve more effective solutions. Integrating such technologies into the medical discipline results in telemedicine which is currently available across the globe. This article describes telemedicine in three key aspects including current state, challenges and opportunities based upon existing studies and implementations.

Keywords: Health monitoring; telehealth; telemedicine (Siriraj Med J 2019;71: 246-252)

INTRODUCTION

Population has been regarded as the most valuable asset in every country. Apart from several aspects such as education, health-related issues are crucially responsible for the governmental agencies in order to provide proper medical services. There are many obstacles to achieving such goals including economic, demographic and geographical points of view. Deficiency of qualified medical staff significantly causes uncovered medical services, especially in the developing areas. In the global point of view, according to the currently reported density of physicians defined as a total number per ten thousand population, all of the countries have such ratios which are lower than 60.[1] Most of the African countries have the ratios which are lower than 5. On the other hand, countries in Europe and in North America have higher ratios. However, higher ratio does not demonstrate an equivalent access to the medical services in all areas. People dwelling in rural areas experience several difficulties in obtaining the same services compared to those living in urban areas.

Such problem has been worsened by an ongoing aging society transformation. The elderly require medical monitoring and warning system in order to avoid feasible injuries and losses. According to the report conducted by the United Nations[2], some key findings have been concluded as follows:

- The number of people aged 60 years or over is projected to grow by 56 percent between 2015 and 2030 and will be double or approximately 2.1 billion by the year 2050.
- According to the prediction, the number of people aged 60 years or over is expected to increase fastest in Latin America and the Caribbean (71 percent), followed by Asia (66 percent),

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Africa (64 percent), Oceania (47 percent), Northern America (41 percent) and Europe (23 percent).
- The ratio of the elderly aged 80 years or over is predicted to increase from 14 percent in 2015 to over 20 percent in 2050.
- Aging society transformation is occurring faster in urban areas than in rural areas.
- The growth of aging society in many developing countries is currently faster than that occurred in developed countries.

Both requirements on deficiency of medical personnel and aging society transformation can be realized as a key driver on leveraging health and well-being strategies in order to provide decent and proper medical services to the whole population.

Computer hardware and software technologies have been playing a major role in introducing automated systems from which several domains such as medical aspect can benefit from. Several benefits include increasing operation reliability, accuracy and efficiency, which results from the computer system. Furthermore, communication technologies tackle the services which mainly rely on the physical distances and other environmental impacts. People in the rural or difficult areas are thus able to access medical services.

Leveraging computer-related technologies onto medical disciplines has been conducted and the outcome was initially one part of the "Health Telematics". An international Group Consultation on World Health Organization (WHO)'s Telemedicine Policy in relation to the Development of the Health-for-All Strategy in the 21st Century was established and assembled in 1997. The definition of telemedicine is accordingly proposed as follows.[3]

"Telemedicine is the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communications technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities."

Telemedicine can be determined as an integration of several components including information and communication technologies, hardware and software technologies and medical services operating together in order to provide required features or services to users as shown in Fig 1. The underlying technologies are seen as a black box to the users and they are responsible for facilitating processes of each proposed service.

Information and communication technologies have been regarded as a key infrastructure for facilitating data exchange among relevant parties located at different locations. Several domains deploy both technologies in order to make their services more accessible. With recent advancement in hardware and software technologies,

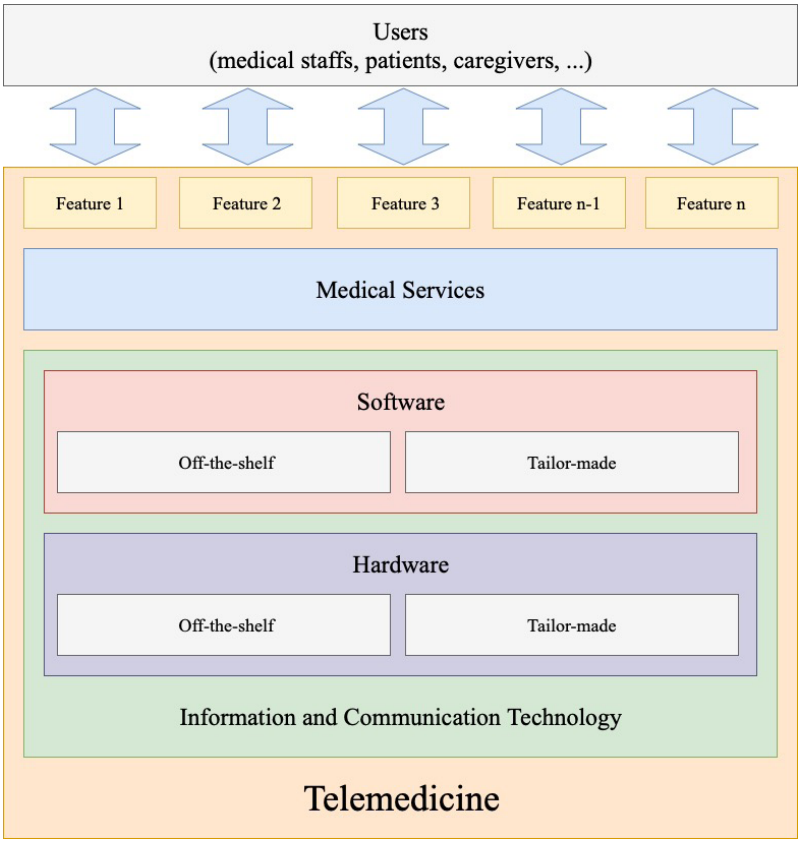


Fig 1. Concept of telemedicine which consists of several components. Medical services deploy digital technology to provide more efficient services regardless of distance and time. Information and communication technologies play a major role as an underlying infrastructure. Hardware and software technologies can be considered as a medical service provider via several features. The technologies are black box to users.

multimedia can be delivered via the Internet in real-time. Such breakthrough enables the communications between physicians or medical staff and patients or their family members. Preliminary diagnosis and corresponding medical consultancy can be performed and delivered. Hence, the patients do not always need to personally meet their physicians.

Apart from tackling distance limitation by communication technology, a computerized system is implemented and deployed in order to facilitate operational procedures. Several components are developed and work together. For example, mobile or web applications consisting of several features are developed for both physician and patient sides. Captured photos by the patients via their mobiles are stored in the database server and retrieved later by the physicians. In case of emergency, the medical staff interrogate the patients or the caregivers through the applications, then diagnose and provide first-aid suggestions online. Furthermore, telemedicine can be used as a learning tool where the physicians around the globe discuss and exchange their opinions. Both distance and time limitations are therefore overcome by telemedicine.

This article focuses on the telemedicine regarding as an application of information and communication technologies to the medical disciplines. Key issues including its challenges and opportunities based upon existing case studies are addressed. The remaining parts of this article are organized as follows: current state of telemedicine focusing on aging society is given in Section 2. Section 3 outlines key challenging issues on telemedicine based upon existing applications. Several opportunities of telemedicine system deployment are addressed in Section 4. Finally, conclusions are provided in Section 5.

Current state of telemedicine

Telemedicine is regarded as an integration of medical services and information and communication technologies. Underlying computer-based technologies can be pictured as medical service delivery channels. Hence, several existing medical services benefit from such technologies in order to tackle various limitations. This section focuses on addressing current state of telemedicine application, especially to aging society domain.

Telemedicine has been deployed or of interest in many regions including developed countries[4] and developing countries.[5,6] A wide range of medical services is currently provided via telemedicine such as telelaboratory service, telehealth education and ambulance.[7] The elderly normally experience several common health issues such as chronic health conditions, cognitive health and mental health which make ability to move or travel to hospital become more difficult, impractical or sometimes impossible. The elderly have become one of the major target groups for telemedicine. Remote medical diagnosis, care and treatment can be performed at the elderly's houses or nearby hospitals via telemedicine. Not only providing remote medical services, telemedicine also gives the elderly a feeling of reassurance and safety.[8]

A study based upon in-depth review and interview outlines current state and future trends in telemedicine application to aging society in Europe.[4] According to the findings, both devices and their associate services are categorized into several generations. Basic services using ordinary sensors such as alarm system including safety and security monitoring[8] are in the first generation whereas detectors and tracking devices are in the second generation. More advanced devices which use more than one technology and provide additional functions are in the third generation. More complex services such as monitoring, consultation, diagnostic and tele-education are found in the third generation. Furthermore, key trends include medical services based upon mobile devices, personal digital assistants, interactions between devices and prediction.

Like other countries, Thailand is transforming into an aging society. According to the latest information, current ratio of the population aged 60 or over is approximately 17%.[9] Moreover, in 2017, a physician and a nurse are responsible for taking care of 1,843 and 405 Thai people, respectively.[10] In order to increase an opportunity for Thai people for obtaining medical and health services with equality, eHealth strategy for 2017 – 2026 is outlined by the Ministry of Public Health.[11] Regarding the strategy, eHealth development in Thailand has four phases as follows:

- Investing and building a foundation for eHealth development phase which is planned to take 1 year and 6 months.
- eHealth inclusion phase aims at involving all sector of Thailand to eHealth operations. This phase is planned to spend 5 years.
- eHealth transformation phase aims to leverage digital innovation to propose innovative medical services. It is estimated to take 10 years to achieve such goal.
- eHealth leadership phase to creating real economic value in public health system and to provide good quality of life to Thai people. This big step will take 20 years.

Even telehealth or telemedicine is also one of the focused components as described in the strategy, it requires

underlying information and communication technologies for delivering reliable medical services. eHealth foundations are essential and thus firstly operated. Furthermore, several plans for developing eHealth applications are based upon the survey conducted in 2009. In case of telemedicine, major barriers to implementing solutions include lack of legal policies/regulation, organizational culture not supportive, competing priorities, lack of knowledge of applications and lack of technical expertise. In summary, four information is required to support telemedicine development including cost, infrastructure, legal and ethical issues and patients' perception.

There are two approaches to implementing telemedicine. The first one is to join the existing communities. Thailand has been associated with the Telemedicine Development Center of Asia (TEMDEC) since 2005. The first hospital that joined telemedicine program is Siriraj Hospital. As of 2017, in total 144 programs have been recently conducted in Thailand. Moreover, most of the program associations are conducted in Bangkok. Endoscopy and surgery are the two main activities which performed via telemedicine.[12] The other scheme is building our own system. Even eHealth foundations development is in progress, over 30 applications have been built by the Ministry of Public Health and launched for public use. Most of them provide useful health-related information such as first aid, medical institutions and diseases.[13]

Challenges

Telemedicine has been recently deployed in many countries both developed and developing ones. Like other system applications, several challenges have been arisen and they are outlined in this section. In total 5 key issues based upon economic, technological and social sides together with some existing studies are described.

- System Development Cost – Apart from the required medical issues, enabling the population especially those dwell in remote or developing areas to benefit from the information and communication technologies generates additional costs. Such requirement can be considered as a key policy in the 21st century[3] and it needs to be driven by the government.[11] Both technologies are core infrastructure and a large amount of budget is required to invest in necessary computer equipment and developing tools.[8] Hardware and software installation and maintenance together with qualified manpower and knowledge transfer demonstrate one-time and periodic investment.
- System Implementation – Several parties within and across institutes are involved in an implementation of telemedicine services.[11] Like other domains, telemedicine implementation is not only technological but also managerial prospects. Prior to implementing a telemedicine project, several issues including technological and societal aspects have to be carefully considered.[8] As telemedicine services are built upon existing digital technologies, developing teams are normally required to understand the underlying infrastructure and the users' requirements. Advancement in digital technologies including hardware and software has been occurring and they are utilized for transformation in several domains in order to yield better solutions and competitive advantages. Developing tools and devices have been created and continuously improved to conform to the latest advancement. The system developers are always expected to properly select and use the tools and the devices in order to develop the next generation of telemedicine solutions which conform to the requirements.[4] Moreover, obtaining precise requirements are challenging as they need proper communication and collaboration skills between groups of people with different expertise and background. Telemedicine affects traditional medical care processes and several social concerns may arise. Key concerns including legal, regulatory, security and human resources issues together with successful implementation of the telemedicine services are addressed.[11,14] Building a telemedicine service is therefore not only about completing the system implementation but also about the impacts of system utilization.
- Digital Literacy – This issue mostly affects the elderly as they were born before the "digital disruption" age where most systems or services are integrated with the digital technology. Unlike the following generations that digital technology has become one of the major parts of their lives, the elderly has to learn how to use some devices such as smartphone and interact with applications such as health technology-based applications. Results show that the users aged over 65 years old produce lower success rate and higher error on assigned computer-based tasks compared to the younger ones.[8] Several studies on technology acceptance by the elderly including stakeholders' perspectives, factors influencing technology and dynamics in technology have been conducted.[15]

According to survey on digital technology usage, 71 percent of the elderly aged over 65 years access the Internet every day or almost every day.[16] Moreover, 27 and 18 percent of them own tablet or e-book reader and smartphone, respectively. Telemedicine service may build upon some existing applications or has its own applications. Therefore, the user uses its services via several devices.

- Digital Technology Acceptance – Even digital technology has been integrated to many activities in our daily lives, some people including the elderly still do not accept it regarding several issues such as privacy and security.[8,11] A large number of firms such as banks are developing their own financial services on web or mobile applications in order to decrease operation costs. Several campaigns or privileges are offered to persuade their customers to go online. However, different realization may be observed in the healthcare domain. First, health-related personal data is required to be securely transmitted over digital networks and accurately destined to predefined receivers. Second, additional devices such as wearable devices capable of measuring heart rate or blood pressure are deployed to sense and transmitted the measurements to the receiving nodes. Such devices' performance especially their accuracy compared to standard medical equipment is one of the major concerns. Scope of the offering telemedicine services should thus be concisely defined for the users' accurate understandings.[4,8] Under some circumstances, telemedicine can be used as a monitoring tool for early detection and warning.[4] Hence, devices available in the market can be used. Results indicate acceptance of telemedicine to improve quality of care in rural areas and during emergency situations.[17]
- Diagnostic Accuracy – Accuracy of the diagnosis is one of the key concerns especially when the physicians and the patients are at different locations. Face-to-face medical care usually brings confidence to patients, especially the elderly.[8] However, a short period of medical interrogation and vital sign measurement performed at a hospital may not reflect current symptoms due to the white coat syndrome.[18] Physicians may obtain more accurate results by applying continuous health monitoring based upon electronic healthcare approach. Several studies have been undertaken in order to investigate the diagnostic accuracy of the telemedicine applied to the emergency department and ophthalmology.[19,20] The results demonstrate telemedicine as a viable alternative to the in-person and a valuable tool where medical service is in high demand.

Opportunities

Most countries have been experiencing deficiency of physicians and aging society transformation. Population dwelling in remote or developing areas tends to have lower opportunities of decent medical care than those residing in an urban or developed areas. Such limitations worsen the situations especially in an emergency where urgent help is needed. Telemedicine can be used to deliver medical services regardless of distance and time via information and communication technologies. Several studies and reviews of applying telemedicine in developing countries have been undertaken.[21-24] This section outlines feasible opportunities of telemedicine.

- Cost Reduction – One of the main objectives of digital technology integration is to provide better services at lower cost. In case of telemedicine, several operation costs such as traveling can be reduced as the patients are able to get medical services online. Several results indicate cost effectiveness of telemedicine compared to other methods.[25-27] Telemedicine can thus be considered as an alternative diagnosis and treatment methods in several cases. For example, it can be used for the first diagnosis or an emergency to provide an urgent help. Moreover, hospitals benefit from applying telemedicine. Hospital bed or space occupancy and resource utilization can be improved as patients receive medical cares at any places and anytime.
- Preventive Medicine Promotion – People sometimes have symptoms which can be prevented. One of the key benefits of practicing preventive medicine is to decrease feasible illnesses. It can be conducted by several levels ranging from the governmental agencies to individuals.[28] Health monitoring concept together with telemedicine are the main driver of applying preventive medicine. In order to obtain the real-time vital sign readings, wearable devices available in the market can be used to sense and transmit the readings to the medical staff.[29] Preliminary diagnosis and following procedures are performed by using telemedicine. Possible illnesses can thus be prevented or found at an early stage.
- Medical Education – Most countries are still

experiencing the lack of medical staff and specialists. Remote areas do not have professionals to provide specific medical cares or treatments. Such problems are worsened in case of emergency. Apart from being a medical treatment platform, telemedicine can be used as a continuing medical education where medical staff and professionals meet, learn and exchange their knowledge and experiences. Successful cases of telemedicine as an education platform are reported.[30,31] Sessions can be conducted at any convenient sites where attendees gather and participate an assigned workshop.

- Healthcare Equality – Limitations of distance and time are tackled by the information and communication technologies. Telemedicine is built on top of such technologies in order to provide medical services. People around the world can therefore access the services as soon as they are connected to the Internet. Medical services are not only delivered by local physicians. Professionals residing at other areas can provide diagnoses and treatments. Local or novice physicians are capable of learning from medical specialists. In order to achieve healthcare equality, collaboration, regulation and standardization are required. Governmental agencies and private institutes have to cooperate and agree upon a set of requirements. Regarding the digital technologies related issues, several predefined standards such as communication protocols can be adopted.
- Service Diversity – With an advancement of recent digital technology, data delivery and processing are considerably improved. Instead of basic data type, multimedia streaming over the Internet is now more efficient. Processing power is also remarkably increased while the hardware price is continually decreased. Such improvements support a variety of medical services and enable real-time applications. A variety of telemedicine services such as tele-pathology, tele-dermatology, tele-nursing and tele-surgery and their performance acceptance are addressed.[32] The key consideration on offering new service is to select a set of suitable tools and technologies.

CONCLUSION

Two major indices reflecting good quality of life are healthiness and access to decent medical services. Lack of medical personnel, demographical and geographical problems are significant barriers of medical service improvement. Telemedicine can be applied to aging society transformation which causes higher demand of remote medical care and treatment.Telemedicine is officially defined by the World Health Organization (WHO) as the delivery of health care services where distance is a critical factor. Major challenges of telemedicine utilization include system development cost, system implementation, digital literacy, digital technology acceptance and diagnostic accuracy. Building a telemedicine service requires information and communication technologies as the underlying infrastructure. System integration needs some specialists who can address users' requirements and develop the required system. Users' acceptance of technology is crucial to acquiring the advantages of telemedicine. A revision of generated results is essential in order to avoid diagnostic errors. Several opportunities of telemedicine include cost reduction, preventive medicine promotion, medical education, healthcare equality and service diversity. Studies show that telemedicine significantly reduces cost of treatment as hospital visit is no longer necessary. Regarding cost issues, not only the patients but also the medical institutes benefit from telemedicine. Moreover, telemedicine facilitates health monitoring and thus promotes preventive medicine. Knowledge and experience transfer and exchange are feasible via telemedicine. Medical personnel and corresponding services are thus improved, and it is possible for the population to have an equality in medical services. Finally, a variety of medical services is observed, and additional services can be offered due to technological advancement.

Telemedicine has been realized by many countries as major tool to delivering decent and improved medical services with equality. It is therefore included in national healthcare strategies outlined by several nations. In order to achieve the same operating standards, all of the relevant parties have to involve and make agreements. Telemedicine consists of several systems connected by universally pre-defined data formats and protocols. Making all medical institutes follow such formats will definitely be time-consuming as some of them have their own formats. Standard protocols have to be also applied. Hence, telemedicine is not only building the new system but also adjusting the legacy systems. Apart from technological issue, several aspects must be taken into consideration including economical and societal ones. Inaccurate diagnosis and personal data leakage lead to legal and ethical issues. Proper preparation and operating procedures are significantly required to successfully apply telemedicine.

REFERENCES

1. Who.int [Internet].Global health observatory data repository – medical doctors [updated 2017; cited 2019Apr14] Available from http://apps.who.int/gho/data/node.main HWFGRP_0020?lang=en.
2. Un.org [Internet]. World population ageing [updated 2015; cited 2019 Apr 13]. Available from http://www.un.org/en/development/desa/population/publications/pdf/ageing/ WPA2015_Report.pdf.
3. Who.int [Internet]. A health telematics policy [updated 1997; cited 2019 Apr 13]. Available from http://apps.who.int/iris/bitstream/handle/10665/63857/WHO_DGO_98.1.pdf?sequence=1&isAllowed=y.
4. Pacitaproject.eu [Internet]. Telecare technology for an ageing society in Europe – current state and future developments [updated 2013; cited 2019 Apr 13]. Available from http://www.pacitaproject.eu/wp-content/uploads/2012/11/Telecare-description-web.pdf.
5. Ganapathy K, Chawdhry V, Premanand S, Sarma A, Chandralekha J, Kumar KY, et al. Telemedicine in the Himalayas: operational challenges – a preliminary report. Telemed J E Health 2016;22:821-35.
6. Chandwani RK, Dwivedi YK. Telemedicine in India: current state, challenges and opportunities, Transforming Government: People. Process and Policy 2015;9:393-400.
7. Rogers H, Madathil KC, Agnisarman S, Narasimha S, Ashok A, Nair A, et al. A systematic review of the implementation challenges of telemedicine systems in ambulances. Telemed J E Health 2017;23:707-17.
8. Bujnowska-Fedal MM, Grata-Borkowska U. Use of telemedicine-based care for the aging and elderly: promises and pitfalls. Smart Homecare Technology and TeleHealth. 2015;8:91-105.
9. Thailandometers.mahidol.ac.th [Internet]. Thailandometers [updated 2019 Apr 12; cited 2019 Apr 12]. Available from http://www.thailandometers.mahidol.ac.th.
10. Social.nesdb.go.th [Internet]. The number of Thai populations per medical staff 1994 – 2017 [updated 2018 Nov 5; cited 2019 Apr 13] Available from http://social.nesdb.go.th/ SocialStat/StatReport_Final.aspx?reportid=662&template=1R2C&yeartype=M&subcatid=18
11. Moph.go.th [Internet]. eHealth strategy 2017 – 2026 [updated 2017 Aug; cited 2019 Apr 13] Available from https://ehealth.moph.go.th/index.php/resources/draft-ehealth-strategy-ministry-of-public-health-2016-2021?download=7:eng.
12. Shimizu S, Kudo K, Tomimatsu S, Moriyama T, Moriyama T, Sadakari Y, et al. International telemedicine activities in Thailand. Siriraj Med J 2018;70:471-5.
13. Moph.go.th [Internet]. MoPH Application [cited 2019 Apr 10]. Available form https://www.moph.go.th/index.php/home/app_moph.
14. Paho.org [Internet]. Framework for the implementation of a telemedicine service [updated 2016; cited 2019 Apr 13]. Available fromhttp://iris.paho.org/xmlui/bitstream/handle/123456789/28414/9789275119037_eng.pdf;sequence=1.
15. Sebastian Peek. Understanding technology acceptance by older adults who are aging in place: a dynamic perspective, Ph.D. Thesis, Tilburg University, 2017.
16. Pewresearch.org [Internet]. Older adults and technology use [updated 2014; cited 2019 Apr 13]. Available from http://www.pewresearch.org/wp-content/uploads/sites/9/ 2014/04/PIP_Seniors-and-Tech-Use_040314.pdf.
17. Thomas GP, Christian AB, Suzanne KP, Renald L. Social acceptance and population confidence in telehealth in Quebec. B MC Health Services Research 2015;15:72.
18. Briana C, Kelly H-Zolnierek, Krista H. White coat hypertension: improving the patient-health care practitioner relationship, Phychol Res Behav Manag 2015;8:133-41.
19. Izzo JA, Bhat R, Blumenthal J, Hoffman D, Watson J, et al. Diagnostic accuracy of a rapid telemedicine encounter in the emergency department. Ann Emerg Med 2017; 70(4):S127-S128.
20. Ausayakhun S, Skalet AH, Jirawison C, Keenan JD, Khouri C, Nguyen K, et al. Accuracy and reliability of telemedicine for diagnosis of cytomegalovirus retinitis. Am J Ophthalmol 2011;152:1053-8.
21. Carlo C, Gabriele P, Giuseppe P. Telemedicine for developing countries – a survey and some design issues. Appl Clin Inform 2016;7:1025-50.
22. Who.int [Internet]. Telemedicine – Opportunities and developments in member states [updated 2010; cited 2019 Apr 13]. Available from http://www.who.int/goe/publications /goe_telemedicine_2010.pdf.
23. Aparajita D, Soumya D. Telemedicine: a new horizon in public health in India. Indian J Community Med 2008;33:3-8.
24. Richard W, Nivritti GP, Richard ES. Telehealth in the developing world. Royal Society of Medicine Press Ltd. London; 2009.
25. Connectwithcare.org [Internet]. Assessment of the feasibility and cost of replacing in-person care with acute care telehealth services [updated 2014; cited 2019 Apr 13]. Available from http://www.connectwithcare.org/wp-content/uploads/2014/12/Medicare-Acute-Care-Telehealth-Feasibility.pdf.
26. Agha Z, Schapira RM, Maker AH. Cost effectiveness of telemedicine for the delivery of outpatient pulmonary care to a rural population. Telemed J E Health 2002;8:281-91.
27. Stensland J, Speedie SM, Ideker M, House J, Thompson T. The relative cost of outpatient telemedicine services. Telemed J 1999;5:245-56.
28. Clarke EA. What is preventive medicine? Can Fam Physician 1974;20:65-68.
29. Leelaloetphanit W, Leelaloetphanit W, Srikhuanjai K, Chomanan P, Khemapech I. UbiNurSS on Mobile: a ubiquitous nursing support system on mobile devices, Proceedings of the 5th IIAI International Congress on Advanced Applied Informatics, 2016.p.71-76.
30. Randriambelonoro M, Bagayoko CO, Geissbuhler A. Telemedicine as a tool for medical education: a 15-year journey inside the RAFT network. Ann N Y Acad Sci 2018;1434:333-341.
31. Michael AER, Michael PC, Peter WC, Mary G. The use of telemedicine for delivering continuing medical education in rural communities. Telemedicine and e-Health 2005; 11:124-9.
32. Hassibian MR, Hassibian S. Telemedicine Acceptance and Implementation in Developing Countries: Benefits, Categories, and Barriers. Razavi International Journal of Medicine [Internet]. Kowsar Medical Institute; 2016 Aug 21 [cited 2019 Apr 13];4(3). Available from: http://dx.doi.org/10.17795/rijm38332.

Managing Difficult Cannulations in Endoscopic Retrograde Cholangiopancreatography: A Prospective Randomized Control Trial Study of Precut Needle Knife Sphincterotomy versus Transpancreatic Sphincterotomy Technique

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ABSTRACT

Objective: To evaluate the success rate of cannulations and rate of procedure-related complications between needle knife sphincterotomy (NKS) and transpancreatic sphincterotomy (TPS) techniques, and to evaluate the most effective cannulation time to proceed with NKS or TPS.

Methods: This study recruited 52 patients with inaccessible bile ducts by the standard cannulation at Khon Kaen Hospital from May 2012 to May 2015. Patients were randomly allocated to the NKS group (N=21) or the TPS group (N=21). Successful cannulations, and complications between NKS and TPS were collected and assessed.

Results: Successful cannulations by TPS and NKS were achieved in 14 cases (53.8%) and 13 cases (50%) respectively (p value = 0.781). Post ERCP pancreatitis was found in 2 cases using TPS, and in 3 cases using NKS. There were 3 cholangitis cases in TPS group, and 2 cholangitis cases in NKS group. Perforations were found in 3 cases and 1 case in TPS and NKS group, respectively. There were 4 deaths in this study, one case in TPS group and 3 cases in NKS group. Complications and mortality between TPS and NKS were not statistically significant (P>0.05). After 40 minutes of the ERCPs, there was less chance for a successful cannulation. Unsuccessful cannulations between TPS and NKS was not statistically different according to the Kaplan-Meier analysis.

Conclusion: TPS and NKS are able to increase successful cannulations. There are no significant differences in the cannulation success rate and rate of complications between the TPS and NKS. The appropriate time to terminate a cannulation in difficult cases is found to be 40 minutes.

Keywords: ERCP; Transpancreatic precut sphicterotomy; needle knife sphicterotomy; difficult cannulation; time for successful cannulation (Siriraj Med J 2019;71: 175-180)

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is challenging endoscopic procedure which has a long learning curve. ERCP operators need to perform 180 ERCPs under supervision to achieve a 70-80% successful cannulation.[1] A successful cannulation is defined as the passing guide wire from the duodenal papilla to the common bile duct which is the key to success in the ERCP procedure.[2,3] According to a study of the outcomes of ERCP at Khon Kaen Hospital, the success rate for

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cannulations using the standard cannulation technique at Khon Kaen Hospital was 78%.[4] This success rate was low in comparison with expert ERCP centers which have a successful cannulation rate of 90-95%.[5] Therefore, Khon Kaen Hospital has to increase its successful cannulation rate in ERCP by using a special technique to overcome difficult cannulations. There are many cannulation techniques to deal with difficult cannulations such as precut needle knife sphicterotomy, transpancreatic sphicterotomy technique, needle knife fistulotomy, and endoscopic ultrasound-guide cholangiography.[3,6]

At Khon Kaen Hospital, we are familiar with the needle knife sphicterotomy (NKS) technique and the transpancreatic sphicterotomy (TPS) technique. NKS has been used to overcome difficult cannulations by many institutions for a long time with evidence of an increasing successful cannulation rate to 92-96.9%[7-9], and TPS, a newer technique, described by Goff in 1995[10], has also been used by ERCP operators with 72.5-97.3% cannulation success rate.[11-15] According to previous studies, the procedural related complications in NKS and TPS were 10-24.2%[7-9] and 11.1-5.8%[11,15] respectively. There were several studies that evaluated successful cannulation rates and complication rates between NKS and TPS techniques. The randomized controlled trial from Catalano et al.[16] demonstrated higher a successful cannulation rate in TPS than with NKS while the complication rate was the same; a study from Lee et al.[15] showed a similar successful cannulation rate and complication rate between TPS and NKS. Therefore, the use of NKS or TPS to achieve a successful cannulation rate is still being debated.

There are several studies stating that prolonged a cannulation time was associated with an increased rate of post-ERCP pancreatitis (PEP).[17-20] Therefore, the appropriate cannulation time should be balanced between successful cannulation rates and complications, so the most effective cannulation time to increase the chances of a successful cannulation should be investigated.

The objectives of this study are to evaluate successful cannulation rates and procedures related to complications between the NKS and TPS techniques; to evaluate the most effective required time for proceeding with either NKS or TPS in an attempt to increase the chances of a successful cannulation.

MATERIALS AND METHODS

This study was approved by Khon Kaen Hospital Ethics Committee (issue number 56/01/2555) and registered in the Thai Clinical Trials Registry (TCTR number 20150224003). Patients who had been treated with ERCP procedure at the Endoscopic Unit, Department of Surgery, Khon Kaen Hospital during May 2012 to May 2015 were recruited into the study. All of the patients were treated with ERCP by the first author (S. Siripornadulsilp). Patients with unstable vital sign, post-sphincterotomy patients, patients with gastric outlet obstructions, and patients with surgically altered anatomy were excluded. There were 286 patients who did not meet the exclusion criteria and participated in the study. All the participants gave informed consent before undergoing ERCP. Of the 286 participants, 52 had difficult cannulations which were defined as lasting more than 10 minutes in attempting to cannulate after visualization of ampulla of Vater, or there were more than three unintended pancreatic duct cannulations.[21] The patients with difficult cannulation conditions were randomly allocated to either the NKS or the TPS group by sealed envelopes. There were 26 patients in each group. NKS was defined as using a needle-knife, specifically a MicroKnife XL 5.5F, Boston Scientific, El Coyol, Alajuela, Costa Rica, to perform an incision at the upper margin of the papilla orifice toward the direction of bile duct until the underlying biliary sphincter was visualized. TPS was defined as cutting the septum between the pancreatic duct and bile duct by sphicterotome toward the direction of the bile duct after selective cannulation of the pancreatic duct.

In our institution, ERCP patients were given intravenous prophylactic antibiotic 15 minutes before the ERCP procedure. The videoduodenoscopes were Olympus TJF 140, Olympus TJF 140R, Fujinon EO-250XT5, Olympus TJF130, and Olympus TJF150. The patients were given 2% lidocaine viscus as a local anesthetic agent. During ERCP, the patient's vital signs and oxygen saturation were monitored with a pulse oximetry by endoscopic nurses. After ERCP, the patients were sent to the surgical ward for observation for at least 24 hours. In this study, a successful cannulation was defined as the insertion of a sphincterotome to the common bile duct.[21] The ERCP-related complications were defined as the "consensus criteria" described by Cotton et al[23]; PEP was abdominal pain with an increase in serum amylase of more than three times the normal upper limit 24 hours after ERCP. Post-ERCP cholangitis was defined as abdominal pain with fever of more than 38 degree Celsius that lasted more than 24 hours after ERCP and a demonstration of obstructive jaundice in a liver function test. Hemorrhage was clinical evidence of bleeding with a hemoglobin drop of more than 2 g/dL. Perforation was the presence of fluid leakage or contrast media in the abdominal cavity or retroperitoneal cavity during ERCP procedures or from imaging studies.

The characteristics of the participants was demonstrated with descriptive statistic. The Chi-square test and the Fisher exact test were used in comparing categorial data between NKS and TPS. The effective required time for a successful cannulation was estimated by the Kaplan-Meier method.

RESULTS

Baseline characteristics of the patients are shown in Table 1.

There was no difference in the baseline characteristics between the TPS patients and NKS patients. (Table 2)

There was no difference in successful cannulations and procedural related complications between the TPS and NKS patients. In this study, there were 4 procedural related mortality cases. The indications for ERCP in these patients were 2 CBD stone cases and 2 malignancy cases. There were 3 death cases in the NKS group and 1 death case in TPS group. The causes of death are described in Table 3.

There were 51 patients of 52 patients that had complete cannulation time data. The cannulation time was not recorded in one patient. The patients were allocated and treated with TPS or NKS according to the study protocol. The median survival time (the median cannulation time) was 30 minutes, and the 95% confidence interval was 6.8-53.2 minutes. The majority of successful cannulations were in the first 30 minutes. There were only a few successful cannulations after 40 minutes as only one successful cannulation occurred in the 40th to 60th minute of the cannulation.

Fig 2 shows a comparison of non-successful cannulations between TPS and NKS by using the Kaplan-Meier method. After the 20th minute, there were 15 cases in TPS group and there were 13 cases in the NKS group who did not have successful cannulations. After the 40th minute, there were 6 cases in the TPS group and 8 cases in NKS group that did not have successful cannulations. The unsuccessful cannulations between TPS and NKS showed no statistical significance.

TABLE 1. Baseline characteristics of the patients between the TPS and NKS group.

Characteristics	TPS (N=26)	NKS (N=26)	P-value
Gender			
Female N (%)	11 (42.3)	18 (69.2)	0.05*
Male N (%)	15 (57.7)	8 (30.8)	
Age			
Mean (SD)	61 (11.3)	59.6 (15.5)	
Median (Min-Max)	61.5 (36-82)	61 (21-85)	
Diabetes mellitus N (%)	5 (19.2)	6 (23.1)	1.00**
Hypertension N (%)	4 (15.4)	3 (11.5)	1.00**
IH N (%)	1 (3.8)	0 (0)	1.00**
CBD stone N (%)	6 (23.1)	9 (34.6)	0.36*
Biliary stricture N (%)	4 (15.4)	2 (7.7)	0.67**
Malignancy N (%)	16 (61.5)	14 (53.8)	0.58*
Bile Leakage N (%)	0 (0)	1 (3.8)	1.00**

*P-value from Chi-square test, **P-value from fisher exact test

Abbreviations: IH = Ischemic heart disease, CBD = Common bile duct, TPS = transpancreatic sphicterotomy, NKS = needle knife sphicterotomy

TABLE 2. Successful cannulation and complications between TPS and NKS group.

Techniques	TPS (N =26)	NKS (N =26)	P-value
Successful cannulation N (%)	14 (53.8)	13 (50)	0.78*
Complications			
Pancreatitis N (%)	2 (7.7)	3 (11.5)	1.00**
Cholangitis N (%)	3 (11.5)	2 (7.7)	1.00**
Perforation N (%)	3 (11.5)	1 (3.8)	0.61*
Bleeding N (%)	0 (0)	0 (0)	NA
Hypoxia N (%)	0 (0)	1 (3.8)	1.00**
Subcutaneous emphysema N (%)	1 (3.8)	0 (0)	1.00**
Death N (%)	1 (3.8)	3 (11.5)	0.61*

*P-value from Chi-square test, **P-value from fisher exact test
Abbreviations: NA = Not applicable, TPS = transpancreatic sphicterotomy, NKS = needle knife sphicterotomy

TABLE 3. Causes of death.

Case	Age	Indication	Technique	Complication
1	41	CBD stone	TPS	Pancreatitis
2	57	CBD stone	NKS	Cholangitis
3	47	Malignancy	NKS	Pancreatitis and perforation
4	74	Malignancy	NKS	Pancreatitis and cholangitis

Abbreviations: CBD = Common bile duct, TPS = transpancreatic sphicterotomy, NKS = needle knife sphicterotomy

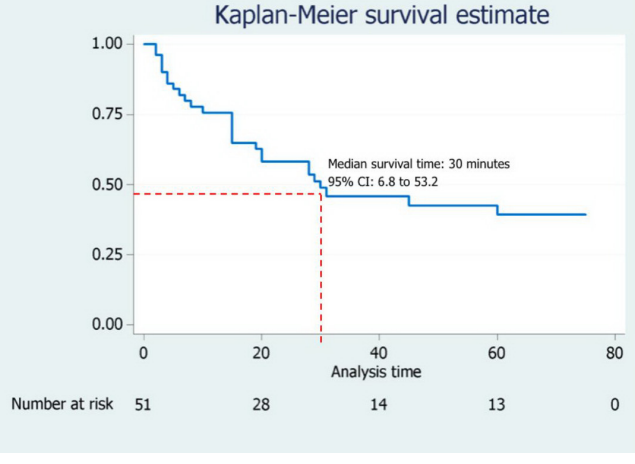


Fig 1. Kaplan-Meier Curve of All Patients.

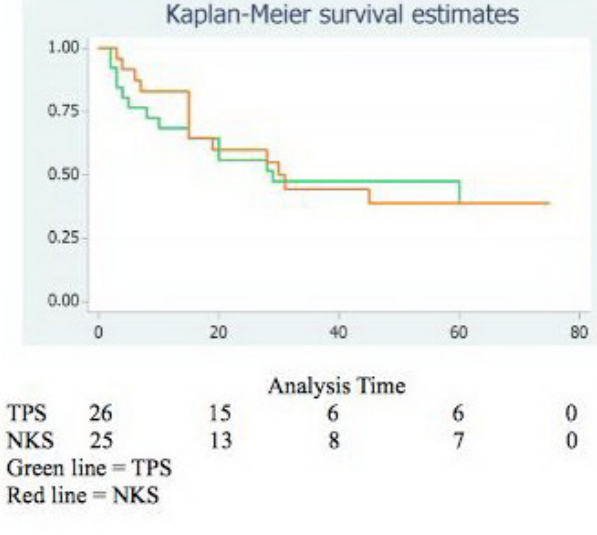


Fig 2. Kaplan-Meier Curve of TPS and NKS.

DISCUSSION

In this study, successful cannulations in difficult cannulation cases between TPS and NKS were the same as the result of the previous study from Lee et al.[15] The procedural related complications between TPS and NKS were similar as the previous studies from Lee et al.[15], Catalano et al.[16], and Zang et al.[24] Although TPS was not shown to be better than NKS in increasing the rate of successful cannulations, both cannulation techniques could increase the rate of successful cannulations in difficult cannulation cases. In this study, there were 286 participants who met the inclusion criteria and 52 (18.2%) of them were difficult cannulation cases. According to the results of this study, for TPS and NKS, each technique could increase the cannulation rate by at least 50%; therefore, these techniques could raise successful cannulation rates in ERCP patients in our institution to over 90%. The crossover of TPS and NKS techniques was reported to improve the final successful cannulation rates to 95.3%[15]; however, this study did not decide to evaluate TPS and NKS in a crossover regime.

Although the successful cannulations and complications between TPS and NKS were not statistically different, there were more procedural related deaths in the NKS group; moreover, technically, it is relatively easy to perform pancreatic duct cannulations[16,25] and there is no special instrument and additional time for placing special instruments for TPS while NKS needs special instruments such as a needle-knife (MicroKnife XL) and additional time to place the needle-knife to the ampulla. As a result, TPS is a more attractive method to overcome difficult cannulation in comparison with NKS. However, according to the European Society of Gastrointestinal Endoscopy (ESGE), clinical guideline for papillary cannulation and sphincterotomy techniques at ERCP, in difficult cannulation cases that had no unintentional pancreatic guide wire insertion, the initial technique that should be used to overcome difficult cannulation is NKS.[26]

The most common complications in this study were PEP and cholangitis. In this study, PEP occurred in 7.7% and 11.5% in the TPS and NKS groups respectively, the rate of PEP was comparable with the rate of PEP in the previous study from Lee et al.[15] which reported a 10.7% PEP occurrence in the TPS group and 5.3% in the NKS group, while Zang et al.[24] reported 9.6% and 10.5% of PEP in the TPS and NKS group respectively. In this study, the rate of cholangitis was 11.5% and 7.7% in TPS and NKS respectively. The cholangitis rate was high in comparison with the study from Lee et al.[15], which reported a cholangitis rates of 3% in TPS and no cholangitis in NKS. In the study from Catalano et al., there was no reported cholangitis as a procedural related complication.[16] The high rate of cholangitis in this study might be due to the high incidence of hilar cholangiocarcinoma in northeastern Thailand.[27] Therefore, the rate of palliative biliary drainage for malignant cases was also high. According to previous studies, palliative endoscopic biliary drainage for hilar cholangiocarcinoma was responsible for a high rate of cholangitis, ranging from 8.8-40.7%.[28-31]

The second objective of this study is to define the most effective required time for proceeding with either NKS or TPS to increase the rate of successful cannulations. In this study, the majority of successful cannulations were in the first 30 minutes. There was only one successful cannulation occurred in the 40th to 60th minute of the cannulation. However, we did not evaluate the correlation between increasing cannulation time and ERCP-related complications.

CONCLUSION

In this study, both TPS and NKS increased successful ERCP cannulations, but there was no difference in successful cannulations and procedural-related complications between TPS and NKS. There was little chance to make a successful cannulation after the 40th minute before a cannulation.

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REFERENCES

1. Jowell PS, Baillie J, Branch MS, Affronti J, Browning CL Bute BP. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. Ann Intern Med 1996;125:983-9.
2. Baron TH, Peterson BT, Mergener K, Chak A, Cohen J, Deal SE, et al. Quality indicators for endoscopic retrograde Cholangiopancreatography. Gastrointest Endosc 2006;63: S29-S34.
3. Qayed E, Reid AL, Willingham FF, Keilin S, Cai Q. Advances in endoscopic retrograde cholangiopancreatography cannulation. World Journal of Gastrointest Endosc 2010;2:130-7.
4. Siripornadulsilp S, Tongsiri N, Wongrach L, Piriyakarnon A, Reangwannasak S, Tipsunthonsak N. Outcomes of Endoscopic Retrograde Cholangiopancreatography in 942 cases. KKMJ 2011;35:35-39.
5. Huibregtse K. Complications of endoscopic sphincterotomy and their prevention. N Engl J Med 1996;335:961-3.
6. Udd M, Kylanpaa L, Halttunen J. Management of difficult bile duct cannulation in ERCP. World J Gastrointest Endosc 2010;2:97-103.
7. Gullichen R, Lavonius M, Laine S, Gronroos J. Needle knife

assisted ERCP. Surg Endosc 2005;19:1243-5.
8. Kasmin FE, Cohen D, Batra S, Cohen SA, Siegel JH. Needle knife sphincterotomy in a tertiary referral center: efficacy and complications. Gastrointest Endosc 1996;44:48-53.
9. Miao L, Li QP, Zhu MH, Ge XX, Yu H, Wang F, et al . Endoscopic transpancreatic septotomy as a precutting techinque for difficult bile duct cannulation. World J Gastroenterol 2015;21:3978-82.
10. Goff JS. Common bile duct pre-cut sphincterotomy: transpancreatic sphincter approach. Gastrointest Endosc 1995;41:502-6.
11. Kahaleh M, Tokar J, Mullick T, Bickston SJ, Yeaton P. Prospective evaluation of pancreatic sphicterotomy as a precut technique for biliary cannulation. Clin Gastroenterol Hepatol 2004; 2:971-7.
12. Kapetanos D, Kokozidis G, Christodoulou D, Mistakidis K, Dimakopoulos K, Katodritou E, et al. Case series of transpancreatic septotomy as precutting technique for difficult bile duct cannulation. Endoscopy 2007;39:802-6.
13. Weber A, Roesch T, Pointner S, Born P, Neu B, Meining A, et al. Transpancreatic precut sphincterotomy for cannulation of inaccessible common bile duct: a safe and successful technique. Pancreas 2008;36:187-91.
14. Halttunen J, Keranen I, Kylanpaa L. Pancreatic sphincterotomy versus needle knife precut in difficult biliary cannulation. Surg Endosc 2009;23:745-9.
15. Lee YJ, Park YK, Lee MJ, Lee KT, Lee KH, Lee JK, et al. Different Strategies for Transpancreatic Septotomy and Needle Knife Infundibulotomy Due to the Presence of Unintended Pancreatic Cannulation in Difficult Billiary Cannulation. Gut Liver 2015;9:534-9.
16. Catalano MF, Linder JD, Geene JE. Endoscopic transpancreatic papillary septotomy for inaccessible obstructed bile ducts: Comparison with standard pre-cut papillotomy. Gastrointest Endosc 2004;60:557-61.
17. Borges AC, Almeida PC, Furlani SMT, Cury MS, Pleskow. ERCP performance in a tertiary Brazilian center: focus on new risk factors, complications and quality indicators. Arq Bras Cir Dig 2018;31:e1348.
18. Funatsu E, Masuda A, Takenaka M, Nakagawa T, Shiomi H, Yoshinaka H, et al. History of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis and Acute Pancreatitis as Risk Factors for Post-ERCP Pancreatits. Kobe J Med Sci 2017;63:E1-E8.
19. Wang P, Li ZS, Liu F, Ren Xu, Lu NH, Fan ZN, et al. Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol 2009;104:31-40.
20. Sofuni A, Maguchi H, Mukai T, Kawakami H, Irisawa A, Kubota K, et al. Endoscopic pancreatic duct stents reduce the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients, Clin Gastroenterol Hepatol 2011; 9:851-8.
21. Laohavichitra K, Akaraviputh T, Methasate A, Leelakusolvong S, Kachinton U. Comparison of early pre-cutting vs standard technique for biliary cannulation in endoscopic retrograde cholangiopancreatography: A personal experience. World J Gastroenterol 2007;13:3734-7.
22. Baron TH, Peterson BT, Mergener K, Chak A, Cohen J, Deal SE, et al. Quality indicators for endoscopic retrograde Cholangiopancreatography. Gastrointest Endosc 2006;101: 892-7.
23. Cotton PB, Lehman G, Vennes J, Geenen JE, Russel RCG, Meyers WC, et al. Endoscopic sphincterotomy complications and their management: An attempt at consensus. Gastrointest Endosc 1991;37:383-93.
24. Zang J, Zhang C, Gao J. Guidewire-assisted transpancreatic sphincterotomy for difficult biliary cannulation: a prospective randomized controlled trial. Surg Laparosc Ensosc Percu Tech 2014;24:429-33.
25. Yoo YW, Cha SW, Lee WC, Kim SH, Kim A, Cho YD. Double guidewire technique vs transpancreatic precut sphincterotomy in difficult biliary cannulation. World J Gastroenterol 2013;19: 108-14.
26. Green A, Uttaravichien T, Bhudhisawadi V, Chartbanchahai W, Elkins DB, Marieng EO, et al. Cholangiocarcinoma in North East Thailand. Trop Geogr Med 1991;43:193-8.
27. Riesco-Lopez JM, Vazquez-Romero M, Rizo-Pascual JM, Rivero-Fernandez M, Manzano-Fernandez R, Gonzalez-Alonso R, et al. Efficacy and safety of ERCP in a low-volume hospital. Rev Esp Enferm Dig (Madrid) 2013;105:68-73.
28. de Palma G. D, Galloro G, Siciliano S, Iovino p, Catanzano C. Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. Gastrointest Endosc 2001;53:547-53.
29. Pisello F, Geraci G, Modica G, Sciume C. Cholangitis prevention in endoscopic Klatskin tumor palliation: air cholangiography technique. Langenbeck Arch Surg 2009;394:1109-14.
30. Walter T, Ho CS, Horgan AM, Warkentin A, Gallinger S, Greg PD, et al. Endoscopic or percutaneous biliary drainage for klatskin tumors. J Vasc Interv Radiol 2013;24:113-21.

Mosapride Reduces Prolonged Postoperative Ileus after Open Colorectal Surgery in the Setting of Enhanced Recovery after Surgery (ERAS): A Matched Case-Control Study

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ABSTRACT

Objective: To evaluate the effects of mosapride, a selective 5-hydroxytryptamine-4 agonist, on gastrointestinal recovery in patients undergoing open colorectal surgery.

Methods: A prospectively collected database of the patients undergoing elective 'open' colorectal resection under enhanced recovery after surgery (ERAS) from May 2013 to April 2017 was reviewed. From April 2016, mosparide was routinely given from postoperative day 1 to discharge date. Eighty-four patients receiving mosapride were matched to 168 control patients (historical comparison with a ratio of 1:2). Surgical outcomes and postoperative gastrointestinal recovery was compared.

Results: The patient characteristics were comparable except more patients in control group had perioperative administration of NSAIDs. The mosapride group had a 1.5% higher compliance rate of ERAS protocol. The control group had higher incidences of prolonged postoperative ileus (17.3% vs 7.1%; p=0.029) and prolonged postoperative ileus requiring nasogastric tube decompression (8.9% vs 3.6%; p=0.19). Overall complication, clinical intestinal transit and length of hospitalization were not significantly different between groups. However, the patients with prolonged postoperative ileus had significantly prolonged hospitalization (p<0.001). Median length of hospital stay was 4 days (IQR 4-5) in those without prolonged ileus (n=217), 5 days (IQR 5-6) in those with prolonged ileus without a need of gastric decompression (n=17) and 10.5 days (IQR 7-14.5) in those with prolonged ileus requiring nasogastric tube decompression (n=18) (p<0.001). A multivariate analysis showed that administration of mosapride was only a protective factor for prolonged postoperative ileus (OR=0.37, 95% CI=0.15-0.93, p=0.029).

Conclusion: Postoperative administration of mosapride reduced the incidence of prolonged postoperative ileus after open colorectal surgery.

Keywords: Mosapride; postoperative ileus; colon; rectum; enhanced recovery after surgery; ERAS; prokinetic drug; prevention (Siriraj Med J 2019;71: 181-188)

INTRODUCTION

Postoperative ileus (POI) is a physiologic hypomotility of the gastrointestinal tract occurring immediately after major abdominal or non-abdominal surgery. The pathophysiology of POI is multifactorial and complex. It is known to be associated with inflammatory, neurological and hormonal responses to surgery.[1] Prolonged POI refers to this gastrointestinal dysfunction continuing

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past the expected timeframe – usually beyond 3 days after laparoscopic abdominal surgery and 5 days after open abdominal surgery.[22] Prolonged POI is one of the most frequent and challenging complications following colorectal surgery especially open procedure[3] because it was associated with increased hospital cost and length of hospital stay.[4] Patients with POI were also more likely to develop other postoperative complications and to be readmitted.[5] The incidences of prolonged POI following colorectal surgery vary widely depending on the definition and cut-off limit.[6] For example, a recent French cohort of colorectal patients undergoing surgery with enhanced recovery after surgery (ERAS) program showed the rate of prolonged POI ranged from 10% for a cut-off of 5 days to 40% for a cut-off of 3 days.[7]

Since treatment options for prolonged POI are limited, several methods of preventing or minimizing POI have been advocated such as laparoscopic surgery[3], epidural analgesia[8], administration of selective cyclooxygenase-2 inhibitors[9], and ERAS pathway.[7] Regarding pharmacological intervention, various prokinetic drugs such as metoclopramide, erythromycin and cisapride have been used to improve postoperative gastrointestinal motility. In a systematic review of the aforementioned agents, only cisapride showed a significant reduction in POI.[10] However, cisapride – a 5-hydroxytryptamine-4 (5-HT4) receptor agonist – was withdrawn from the market worldwide because it caused potentially lethal cardiac arrhythmia via its high affinity blockade of cardiac potassium channel.[11]

Mosapride citrate (mosapride) is another prokinetic drug that selectively activates 5-HT4 receptors on the efferent cholinergic neurons of the gastrointestinal tract, leading to increased acetylcholine release and hence increased bowel contraction – without cardiac side effects.[11] Mosapride has been shown to reduce the duration of POI after hand-assisted laparoscopic colectomy[12] and laparoscopic colectomy.[13] However, its effect on POI after open colorectal surgery has not been assessed especially in the setting of ERAS pathway. The aim of the present study was therefore to evaluate whether mosapride reduced the incidence of prolonged POI and shorten the duration of gastrointestinal recovery after open colectomy and/or proctectomy.

MATERIAS AND METHODS

Patients

This was a review of prospectively collected database of patients undergoing elective 'open' segmental resection (colectomy and/or proctectomy) within an ERAS pathway from May 2013 to April 2017 in the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Patients with clinical peritonitis or acute colonic obstruction were excluded. The study was approved by the institutional ethics committee (Si 014/2013) and written informed consent was obtained from each patient.

ERAS protocol and pharmacologic intervention

All of the studied patients were operated on and treated by a board-certified colorectal surgeon (the author) who has applied an ERAS pathway into colorectal surgery since 2010. ERAS strategies in our institute were adopted from the ERAS society recommendations for perioperative care in elective colorectal surgery.[14,15] Some details of our ERAS program have been described previously.[9,16-18] Briefly, a practice of perioperative pain control with a preferential use of non-opioid analgesia, mechanical bowel preparation for left-sided colon and rectal surgery, prophylactic antibiotic regimen, prophylaxis of postoperative nausea and vomiting, selective use of diverting stoma after colorectal anastomosis, no insertion of nasogastric tube (NGT), early enteral feeding and immediate mobilization was standardized. There was no postoperative administration of laxative and other prokinetic drugs *except* ondansetron and/or metoclopramide for treating postoperative nausea and vomiting. Of note, from 1 April 2016 mosparide (mosapride citrate 15 mg; about 0.75 USD/tablet) was routinely given to every patient three times a day on postoperative day 1 until the patients were discharged. There is no significant change in our ERAS protocol during the study period *except* the routine postoperative administration of mosapride from April 2016.

If patients met the criteria of prolonged POI (defined systematically by the combination of at least two of the following five criteria on or after the fourth operative day: nausea or vomiting, abdominal distension, inability to tolerate oral diet over 24 hours, absence of gas or stool passing over 24 hours, and radiological evidence of ileus)[6], rescue agents such as intravenous metoclopramide and/or suppository bisacodyl would be given for reducing the duration of ileus. For patients with vomiting and distention, the placement of NGT was performed to provide symptomatic relief. The NGT was placed until patients had decreased drainage volume - together with clinical or radiological improvement. Patients would be discharged from the hospital if they had no fever, good appetite, satisfactory gastrointestinal recovery and a good level of ambulation. All of the patients were scheduled for follow-up at 7-10 days and 30 days after an operation.

Data collection

Data including patient characteristics, operative details, and postoperative outcomes were prospectively collected. Patient characteristics included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (CR-POSSUM) score[19], and preoperative nutritional status based on the subjective global assessment (SGA).[20] Operative details included type of operation and operative time. Overall ERAS protocol compliance of each case was determined based on the ERAS society recommendations for perioperative care in elective colorectal surgery.[14,15]

Postoperative outcomes included postoperative complications (graded I-V according to the Clavien-Dindo classification system)[21], time to global resumption of intestinal transit (defined as interval from surgery to the tolerance of solid food intake in association with passage of stool)[22], the incidence of prolonged POI (as aforementioned criteria)[6], the length of postoperative stay, death and readmission within 30 days after the operation. Impact of prolonged POI on postoperative hospitalization was also determined.

Sample size calculation

For 1-to-2 comparison, a minimum sample size of 81 patients in mosapride group and 162 patients in control group was estimated to show a 50% reduction in the incidence of prolonged POI with a power of 90% and a significance level of 0.05.[13] Sample size calculations were based on a recent prospective study in France[22] indicating that 39.6% of patients undergoing colorectal surgery within an ERAS protocol experienced prolonged POI using the clinical definition of prolonged POI purposed by Vather et al.[6] We calculated the sample size based on this French study because a well-established ERAS pathway was fully applied in this French university hospital - like ours. Patients receiving mosapride were matched with historical control patients on potentially confounding factors for prolonged POI such as age, co-morbidity, site of operation (colon vs rectum), stoma formation and extension of surgical treatment.

Statistical analysis

All statistical analyses were performed using the PASW Statistics software (SPSS version 18.0 for Windows, Illinois, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile; IQR), and were compared using the Student t-test or Mann-Whitney U test. Categorical data were expressed as number (percentage) and were compared using the Pearson Chi-square test or Fisher exact probability test. Factors potentially associated with or protective of prolonged POI were analyzed using a univariate analysis. Only significant variables from the univariate analysis were included in a multivariate model of logistic regression (forward stepwise logistic regression analysis), and the odds ratio with 95% confidence intervals (95% CI) for each variable was determined. A p-value of <0.05 was considered statistically significant.

RESULTS

After case-matching from a database of 305 cases, 252 patients were included - 84 in the mosapride group and 168 in the historical control group (Fig 1). Patient characteristics were comparable except more patients in control group had perioperative administration of NSAIDs, and mosapride group had a 1.5% higher compliance rate of ERAS protocol (Table 1). Overall complication, global resumption of intestinal transit and length of hospitalization were not significantly different between the two groups (Table 2). However, the control group had more incidence of prolonged POI and prolonged POI requiring NGT insertion (17.3% vs 7.1%; p=0.029 and 8.9% vs 3.6%; p=0.19), respectively. Clinical factors associated with prolonged POI were shown in Table 3. A multivariate model of logistic regression showed that postoperative administration of mosapride was *only* a protective factor for prolonged POI (OR=0.37, 95% CI=0.15-0.93, p=0.029).

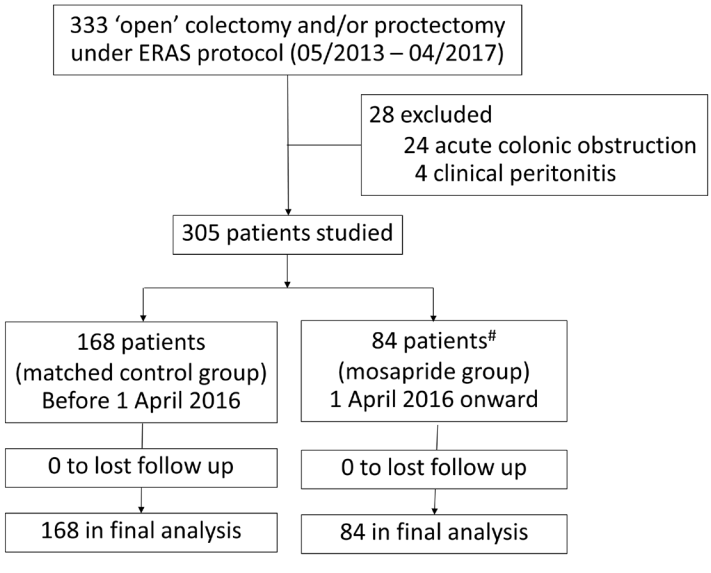


Fig 1. Flow diagram of participant enrollment and analysis.

#There was no patient refusing consent to receive the drug or excluding from analysis

TABLE 1. Patient's characteristics and intraoperative parameters.

	Mosapride (n=84)	Control (n=168)	*P*-value
Age, year	62.4 ± 12.9	64.1 ± 11.8	0.306
Male	44 (52.4)	95 (56.5)	0.531
BMI, kg/m^2	22.6 ± 4.1	22.9 ± 4.1	0.630
ASA class ≥ 3	13 (15.5)	42 (25.0)	0.084
CR-POSSUM predictive mortality, %	1.90 (1.30-2.60)	1.83 (0.98-2.58)	0.426
Hematocrit, %	37.4 ± 5.7	36.8 ± 5.4	0.335
Preoperative malnutrition[#]	16 (19.0)	46 (27.4)	0.148
Previous laparotomy	7 (8.3)	13 (7.7)	0.869
Previous abdominal/pelvic irradiation	6 (7.1)	8 (4.8)	0.437
Cancer surgery	79 (94.0)	152 (90.5)	0.334
Tumor staging ≥ 3	41 (51.9)	89 (57.4)	0.422
Rectal surgery	47 (56.0)	93 (55.4)	0.929
Stoma creation	16 (19.0)	33 (19.6)	0.910
Major multi-organ resection[##]	4 (4.8)	15 (8.9)	0.315
Detailed procedure			0.930
(Extended) right hemicolectomy	13 (15.5)	26 (15.5)	
(Extended) left hemicolectomy	9 (10.7)	8 (4.8)	
Sigmoidectomy	13 (15.5)	36 (21.4)	
Hartmann procedure	7 (8.3)	16 (9.5)	
(Sub) total colectomy	2 (2.4)	6 (3.6)	
(Low) anterior resection	34 (40.5)	65 (38.7)	
Abdominoperineal resection	6 (7.1)	11 (6.5)	
Epidural analgesia	22 (26.2)	41 (24.4)	0.758
Duration of surgery, minute	184 ± 57	189 ± 77	0.577
Blood loss, mL	120 (50-200)	150 (100-250)	0.090
Perioperative administration of NSAIDs	34 (40.5)	91 (54.2)	0.040*
Total IV morphine consumption, mg/kg	0.43 (0-0.71)	0.26 (0.01-0.79)	0.964
Overall ERAS protocol compliance[###], %	83.6 ± 4.4	82.1 ± 4.7	0.010*

*P-value < 0.05

Values are expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

[#]Malnutrition was defined as subjective global assessment (SGA) class B and class C.

[##]Major multi-organ resection excluded the resection of appendix, gallbladder, ovaries and fallopian tubes, small bowel, and part of urinary bladder (partial cystectomy).

[###]Overall compliance of each patient was determined based on the ERAS® society recommendations for perioperative care in elective colorectal surgery.

Abbreviations: ASA = American society of Anesthesiologists, BMI = body mass index, CR-POSSUM = ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, ERAS = enhanced recovery after surgery, NSAIDs = non-steroidal anti-inflammatory drugs

TABLE 2. Postoperative outcomes.

	Mosapride (n=84)	Control (n=168)	*P*-value
Prolonged POI	6 (7.1)	29 (17.3)	0.029*
Prolonged POI requiring NGT insertion	3 (3.6)	15 (8.9)	0.193
Overall complication	12 (14.3)	34 (20.2)	0.249
Serious complication#	4 (4.8)	8 (4.8)	1.000
Time to off intravenous fluid, days	2 (2-3)	2 (2-3)	0.412
Global resumption of intestinal transit, days	3 (2-3.5)	3 (2-4)	0.868
Length of hospitalization, days	4 (4-5)	4 (4-5)	0.474
30-day readmission	1 (1.2)	7 (4.2)	0.275

*P-value < 0.05
Values are expressed as number (percentage) or median (interquartile range).
#Serious complication was defined as the Clavien-Dindo classification of surgical complication grade III-V. Mosapride group had 4 patients with serious complications as following: intraabdominal collection requiring reoperation, adhesive small obstruction requiring relaparotomy, upper gastrointestinal bleeding requiring endoscopic intervention, and distal duodenal obstruction requiring endoscopic management. Control group had 8 patients with serious complications as following: anastomotic leakage (3) requiring reoperation, pelvic collection requiring percutaneous drainage, anastomotic bleeding requiring endoscopic clipping, upper gastrointestinal bleeding requiring endoscopic intervention, and life-threatening congestive heart failure (1) and liver failure (1) requiring intensive care unit management.

Abbreviations: NGT = nasogastric tube, POI = postoperative ileus

TABLE 3. Clinical factors associated with prolonged postoperative ileus (PPOI).

	No PPOI (n=217)	PPOI (n=35)	*P*-value	Odds ratio (95% CI)
Serious complication#	8 (3.7)	4 (11.4)	0.068	3.37 (0.96-11.86)
ASA ≥ 3	44 (20.3)	11 (31.4)	0.138	1.80 (0.82-3.96)
ERAS compliance > 80%	117 (53.9)	15 (42.9)	0.224	0.64 (0.31-1.32)
Administration of NSAIDs	111 (51.2)	14 (40.0)	0.221	0.64 (0.31-1.32)
Administration of mosapride	78 (35.9)	6 (17.1)	0.029*	0.37 (0.15-0.93)

*P-value < 0.05
Values are expressed as number (percentage).
#Serious complication was defined as the Clavien-Dindo classification of surgical complication grade III-V.

Abbreviations: ASA = American society of Anesthesiologists, ERAS = enhanced recovery after surgery, NSAIDs = non-steroidal anti-inflammatory drugs

The length of hospitalization in patients with prolonged POI was significantly longer than those without such a condition (p<0.001). Median length of postoperative stay was 4 days (IQR 4-5) in those without prolonged POI (n=217), 5 days (IQR 5-6) in those with prolonged POI without a requirement of NGT decompression (n=17), and 10.5 days (IQR 7-14.5) in those with prolonged POI requiring NGT decompression (n=18) – which was significantly different between groups (Fig 2).

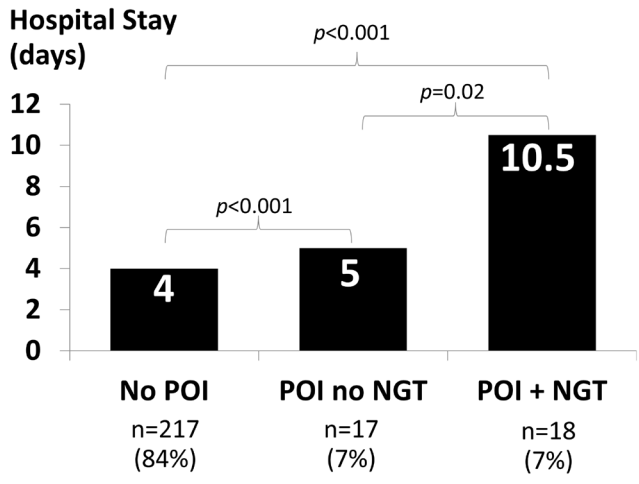


Fig 2. Association between postoperative ileus and length of hospitalization.
Abbreviations: NGT = nasogastric tube, POI = postoperative ileus

DISCUSSION

Prolonged POI is one of the most common problems after intra-abdominal surgery especially open laparotomy. Since treatment options for prolonged POI are limited, preventive measures of POI such as multimodal analgesia[9], application of ERAS pathway[7] and administration of prokinetic drugs are essential.[12,13] This study demonstrated that within an ERAS pathway postoperative administration of mosapride reduced the incidence of prolonged POI after open colorectal surgery. To the best of our knowledge, this is the first clinical study examining the beneficial effects of mosapride on bowel function following open colorectal operation – after its favorable effects on shortening time to gastrointestinal recovery have been shown in hand-assisted laparoscopic colectomy and laparoscopic colectomy for colon cancer.[12,13]

Mosapride is a relatively new prokinetic drug available in Asian countries such as Japan and Thailand. It is a highly selective 5-HT4 receptor agonist facilitating acetylcholine release from the enteric cholinergic neurons within myenteric and submucosal plexus. It has been shown to accelerate gastric emptying rate[12], shorten small bowel transit[23], stimulate colonic motility[24] and augment rectal contraction.[25] Interestingly, in a recent animal study mosapride has been shown to exert anti-inflammatory effects on the muscular wall of gastrointestinal tract after intestinal manipulation and therefore dramatically inhibit POI.[26] Unlike other 5-HT4 receptor agonists such as cisapride and tegaserod, mosparide has no effect on cardiac potassium channels, dopamine receptors or other 5-HT receptors thus resulting in a high profile of safety.[11]

Several prokinetic agents have been used to prevent or reduce POI. Among the most common drugs used are cisapride and metoclopramide. An animal study comparing the prokinetic activities of mosapride with these two drugs showed that all agents promoted gastric emptying but only mosapride enhanced small bowel and large bowel motility in a dose-response relationship.[27] In another animal model, electrointestinography was used to measure intestinal motility after jejunocecostomy. The authors found that bowel motility significantly reduced following surgery. However, in the treated group with mosapride (daily for 5 days after surgery), the contractile amplitude of the small intestine was significantly higher than in the controls indicating that mosapride could overcome the decline of intestinal motility after bowel anastomosis.[28] So far, there have been several animal and human studies supporting the administration of mosapride for facilitating bowel movement or reducing POI after gastrointestinal surgery.[12,13,27,28]

The present study showed that patients receiving mosapride had a lower incidence of prolonged POI and a less requirement of NGT decompression for treating prolonged POI. However, we failed to demonstrate a faster time to global resumption of intestinal transit (time to tolerance of solid food intake *and* passage of stool after an operation) in the mosapride group. The reason for the absence of a significant difference in gastrointestinal recovery between groups could be partly explained by that an ERAS pathway markedly shortens time to postoperative gastrointestinal recovery especially in patients with high compliance[7] – like our patients. Also, the sample size calculation of this study was based on the hypothesis that mosapride could reduce an incidence of prolonged POI by half - not based on time to tolerate solid food or first bowel movement. An ability to tolerate solid food or passing stool may indicate only gastric and rectal emptying and not necessarily the function of the entire gastrointestinal tract. Given the limitations of these individual endpoints, we used a combination of clinical and radiologic grounds for defining prolonged POI as our primary endpoints.[6]

It could be argued that a lower incidence of prolonged POI in mosapride group was associated with a slightly higher compliance of ERAS protocol since ERAS compliance ≥ 85% was shown to be a protective factor for prolonged POI.[7] In our univariate analysis, high ERAS compliance, perioperative use of NSAIDs and administration of mosapride were associated with a lower incidence of prolonged POI. However, in a multivariate analysis the postoperative administration of mosapride was *only* factor associated with a decrease in the incidence of prolonged POI.

The beneficial effects of mosapride on postoperative gastrointestinal recovery in this study (open colorectal

surgery) were in line with the findings of 2 randomized control trials (minimally invasive surgery for colon cancer) by Narita et al[12] and Toyomasu et al.[13] In addition to a decreased incidence of prolonged POI by mosapride in the present study, the two prospective clinical trials revealed that mosapride reduced the duration of POI (i.e. a faster time to first bowel movement). It is worth noting that the present study was conducted within a full ERAS setting whereas the two trials were not - since the scheme of early oral feeding was not applied. Moreover, colorectal operations for malignancy and benign diseases were included in the present study whereas only patients with colon cancer were included in the others. Notably, in all studies mosapride citrate (15 mg tablet three times a day) was given from postoperative day 1 until patients were discharge or a maximum period of 7-10 days.[12,13] It is interesting to determine whether preoperative administration of mosapride will further facilitate postoperative gastrointestinal recovery.

This study revealed that patients experiencing prolonged POI had a significantly longer postoperative stay (e.g. 4 days in no prolonged POI vs 10.5 days in prolonged POI requiring NGT) - which could affect patient's quality of life and increase in-hospital expense.[4] Since the overall incidence of prolonged POI in this study was lower than we expected, the effect of POI on length of hospitalization may be not clearly seen between the study groups. However, prolonged POI remains a challenging clinical reality for achieving early discharge in the ERAS setting. Even in a European university hospital with well-established ERAS protocol, the incidence of prolonged POI requiring NGT decompression was as high as 24.7% and the median length of hospital stay increased from 5 days to 13 days if prolonged POI occurred.[29] We acknowledge that other pharmacological interventions such as perioperative administration of the opioid receptor antagonist alvimopan (12 mg before surgery and 12 mg twice daily until discharge) could reduce POI but this drug is more expensive (63 USD per 12 mg capsule) than mosapride tablet (0.75 USD per tablet).[30] Chewing gum, a cheaper intervention, may be a safe and well tolerated method to reduce POI but the degree of improvement is small and of limited clinical significance.[31]

This study has two major strengths. First, all patients were operated on by single colorectal surgeon under a well-established ERAS program. Moreover, there is no significant change in the ERAS protocol during the study period *except* the routine postoperative administration of mosapride from April 2016. It could suggest that a decreased incidence of prolonged POI in the intervention group is a direct effect of prokinetic drug administration - as shown in our analysis. Second, the criteria for a diagnosis of prolonged POI were defined and sample size was appropriately calculated. A matched case-control analysis was also used in this study.

However, some limitations of this study needed to be addressed. First, it is non-randomized trial which could lead to risk of bias. However, using the validated criteria of prolonged POI and matched case-control analyzing a prospectively collected database with well-established ERAS protocol could in part cover the drawback of non-randomized study and may reflect more realistic estimates of treatment outcomes. We acknowledge that a prospectively randomized controlled trial is a better way to study the effect of this prokinetic drug and the present study could allow for a power analysis to define an appropriately-sized trial in the future. Second, only clinical grounds and radiologic evaluation on or after the fourth operative day were used for diagnosing prolonged POI.[6] Ones could argue that other definitions of prolonged POI and sophisticated methods of assessment e.g. intraluminal pressure and migration of radiopaque markers may be used. Since it is clear that a 'standard' definition and diagnosis of prolonged POI remains elusive[32], we used a widely-accepted and validated clinical definition of prolonged POI based on a recent systematic review and global survey in 2013 due to its simplicity and reproducibility.[6] Third, we recruited only patient undergoing open colorectal surgery. Whether the beneficial effect of mosapride on postoperative gastrointestinal recovery will be evident in other intraabdominal operations needs to be examined. In conclusion, although laparoscopic surgery has become a standard operation for colorectal diseases in many countries, open laparotomy remains a common approach in some regions of the world especially in the developing or underdeveloped areas. Consistent with the findings from laparoscopic colon surgery[12,13], this study demonstrated that postoperative administration of mosapride reduced the incidence of prolonged POI after open colorectal surgery. This prokinetic drug could potentially become a part of ERAS protocol to reduce postoperative ileus.

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Conflict of Interest: The author declares that he has no completing interest.

REFERENCES

1. Venara A, Neunlist M, Slim K, Barbieux J, Colas PA, Hamy A, et al. Postoperative ileus: Pathophysiology, incidence, and prevention. J Visc Surg 2016;153:439-46.
2. Delaney CP, Kehlet H, Senagore AJ, Bauer AJ, Beart R, Billingham R, et al. Clinical Consensus Update in General Surgery: Postoperative Ileus: Profiles, Risk Factors, and Definitions-A Framework for Optimizing Surgical Outcomes in Patients Undergoing Major Abdominal and Colorectal Surgery. Clinical Consensus Update in General Surgery, http://www.clinicalwebcasts.com/pdfs/GenSurg_WEB.pdf2006.
3. Delaney CP, Marcello PW, Sonoda T, Wise P, Bauer J, Techner L. Gastrointestinal recovery after laparoscopic colectomy: results of a prospective, observational, multicenter study. Surg Endosc 2010; 24:653-61.
4. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. J Manag Care Pharm 2009;15:485-94.
5. Murphy MM, Tevis SE, Kennedy GD. Independent risk factors for prolonged postoperative ileus development. J Surg Res 2016;201:279-85.
6. Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. J Gastrointest Surg 2013;17:962-72.
7. Barbieux J, Hamy A, Talbot MF, Casa C, Mucci S, Lermite E, et al. Does enhanced recovery reduce postoperative ileus after colorectal surgery? J Visc Surg 2017;154:79-85.
8. Fotiadis RJ, Badvie S, Weston MD, Allen-Mersh TG. Epidural analgesia in gastrointestinal surgery. Br J Surg 2004;91:828-41.
9. Lohsiriwat V. Opioid-sparing effect of selective cyclooxygenase-2 inhibitors on surgical outcomes after open colorectal surgery within an enhanced recovery after surgery protocol. World J Gastrointest Oncol 2016;8:543-9.
10. Luckey A, Livingston E, Tache Y. Mechanisms and treatment of postoperative ileus. Arch Surg 2003;138:206-14.
11. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. Neurogastroenterol Motil 2008;20:99-112.
12. Narita K, Tsunoda A, Takenaka K, Watanabe M, Nakao K, Kusano M. Effect of mosapride on recovery of intestinal motility after hand-assisted laparoscopic colectomy for carcinoma. Dis Colon Rectum 2008;51:1692-5.
13. Toyomasu Y, Mochiki E, Morita H, Ogawa A, Yanai M, Ohno T, et al. Mosapride citrate improves postoperative ileus of patients with colectomy. J Gastrointest Surg 2011;15:1361-7.
14. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg 2013;37:259-84.
15. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg 2013;37:285-305.
16. Lohsiriwat V. Enhanced recovery after surgery vs conventional care in emergency colorectal surgery. World J Gastroenterol 2014;20:13950-5.
17. Lohsiriwat V. The influence of preoperative nutritional status on the outcomes of an enhanced recovery after surgery (ERAS) programme for colorectal cancer surgery. Tech Coloproctol 2014;18:1075-80.
18. Lohsiriwat V. Impact of an enhanced recovery program on colorectal cancer surgery. Asian Pac J Cancer Prev 2014;15:3825-8.
19. Tekkis PP, Prytherch DR, Kocher HM, Senapati A, Poloniecki JD, Stamatakis JD, et al. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). Br J Surg 2004;91:1174-82.
20. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987;11:8-13.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
22. Barbieux J, Hamy A, Talbot MF, Casa C, Mucci S, Lermite E, et al. Does enhanced recovery reduce postoperative ileus after colorectal surgery? J Visc Surg 2017;154:79-85.
23. Nakamura M, Ohmiya N, Miyahara R, Ando T, Watanabe O, Kawashima H, et al. Are symptomatic changes in irritable bowel syndrome correlated with the capsule endoscopy transit time? A pilot study using the 5-HT4 receptor agonist mosapride. Hepatogastroenterology 2011;58:453-8.
24. Kanazawa M, Watanabe S, Tana C, Komuro H, Aoki M, Fukudo S. Effect of 5-HT4 receptor agonist mosapride citrate on rectosigmoid sensorimotor function in patients with irritable bowel syndrome. Neurogastroenterol Motil 2011;23:754-e332.
25. Liu Z, Sakakibara R, Odaka T, Uchiyama T, Uchiyama T, Yamamoto T, et al. Mosapride citrate, a novel 5-HT4 agonist and partial 5-HT3 antagonist, ameliorates constipation in parkinsonian patients. Mov Disord 2005;20:680-6.
26. Tsuchida Y, Hatao F, Fujisawa M, Murata T, Kaminishi M, Seto Y, et al. Neuronal stimulation with 5-hydroxytryptamine 4 receptor induces anti-inflammatory actions via alpha7nACh receptors on muscularis macrophages associated with postoperative ileus. Gut 2011; 60:638-47.
27. Okamura K, Sasaki N, Yamada M, Yamada H, Inokuma H. Effects of mosapride citrate, metoclopramide hydrochloride, lidocaine hydrochloride, and cisapride citrate on equine gastric emptying, small intestinal and caecal motility. Res Vet Sci 2009;86:302-8.
28. Okamura K, Sasaki N, Kikuchi T, Murata A, Lee I, Yamada H, et al. Effects of mosapride on motility of the small intestine and caecum in normal horses after jejunocaecostomy. J Vet Sci 2009;10:157-60.
29. Grass F, Slieker J, Jurt J, Kummer A, Sola J, Hahnloser D, et al. Postoperative ileus in an enhanced recovery pathway-a retrospective cohort study. Int J Colorectal Dis 2017;32:675-81.
30. Kraft M, Maclaren R, Du W, Owens G. Alvimopan (entereg) for the management of postoperative ileus in patients undergoing bowel resection. P T 2010;35:44-9.
31. Su'a BU, Pollock TT, Lemanu DP, MacCormick AD, Connolly AB, Hill AG. Chewing gum and postoperative ileus in adults: a systematic literature review and meta-analysis. Int J Surg 2015;14:49-55.
32. Wolthuis AM, Bislenghi G, Fieuws S, de Buck van Overstraeten A, Boeckxstaens G, D'Hoore A. Incidence of prolonged postoperative ileus after colorectal surgery: a systematic review and meta-analysis. Colorectal Dis 2016;18:O1-9.

Cardiaovascular Disease Risk Factors in Thai Natural Menopause with First-Time Diagnosis of Low Bone Mass Density

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ABSTRACT

Objective: To evaluate the prevalence of initial cardiovascular disease (CVD) risk factors in naturally postmenopausal Thai women with first-time diagnosis of low bone mass density (BMD), and compare with those reported among general Thai women of the same age range during the same studied time.

Methods: A retrospective cross-sectional study of initial CVD risk factors of 473 naturally postmenopausal Thai women (45-60 years) with the first-time diagnosis of osteopenia or osteoporosis without previous treatment for CVD risk factors, except for hypertension(HT) and diabetes mellitus(DM), was performed. Only subjects with all available initial CVD risk factors were recruited. Data included age, weight, height, waist circumference(WC), and underlying diseases. Extracted initial CVD risk factors were: HT, DM, body mass index(BMI), cholesterol level, triglyceride, high density lipoprotein , and family history of CVD. The main outcome was prevalence of initial CVD risk factors with 95%CI. Results were compared with data of previous Thai reports in women of the same age during the same time period.

Results: All subjects (86.3% osteopenic, 13.7% osteoporotic) had on average 3.6 years since menopause. Prevalence of women with initial CVD risk factors was 73.8%. The three most common risk factors were high BMI (48.6%), high WC (37.8%) and high cholesterol (22.2%). Only high BMI was more prevalent than previously reported. In contrast, the other factors were lower than previously published data.

Conclusion: With the exception of high BMI, initial CVD risk factors in this study were comparable to or lower than those reported in general Thai women of the same age during the same time period.

Keywords: CVD risk factors; low BMD; natural menopause; Thai (Siriraj Med J 2019;71: 189-195)

INTRODUCTION

Osteopenia or osteoporosis is a condition that is characterized by low bone mineral density (BMD) and reduced bone strength increases risk of bone fractures. However, the overall prevalence of osteoporosis, the more severe condition, in postmenopausal Thai women was approximately 39%.[1] Many studies found cardiovascular disease (CVD) to be associated with osteoporosis.[2] Tanko, *et al*. reported that this increase in risk is proportional to the severity of osteoporosis at the time of diagnosis.[3] Thai women diagnosed with low BMD (osteopenia/osteoporosis) are usually prescribed calcium supplementation because typical Thai diet is low in calcium. Calcium is also a key player in coagulation, and muscle and myocardial contraction. Thus, a change in calcium metabolism may participate in the development of CVD.[4]

Traditional CVD risk factors are categorized as either un-modifiable risk factors (e.g. age, gender) or modifiable risk factors [e.g. hypertension (HT), diabetes mellitus (DM), dyslipidemia (DLP), and obesity or overweight status]. With an increase in older population and the adoption of more and more Western lifestyle behaviors,

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Thailand is replacing its traditional high-carbohydrate diets, consisting largely of rice and vegetables, with a diet high in fat and sugar.[5] As a result, we can expect to see commensurate increases in the prevalence of CVD. The prevalence of several initial CVD risk factors has not been simultaneously studied in naturally postmenopausal Thai women with first time diagnosis of osteopenia/osteoporosis and crucially needed calcium supplementation.

Accordingly, the primary aim of this study was to investigate the prevalence of initial traditional CVD risk factors in naturally postmenopausal Thai women at the first-time diagnosis of osteopenia/osteoporosis. The secondary objective was to compare our findings with results from previous studies in Thai women in the same age range during the same time period.

MATERIALS AND METHODS

This retrospective cross-sectional study was performed at the Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. After the institutional ethical board approval (Si 276/2014) was obtained, data were collected from medical records between 1997 and 2014. Sample size calculation was ~500, which number included 10% for data loss by using the formula $n = \frac{Z^2_{1-\alpha} P(1-P)}{d^2}$. P was the prevalence of HT, which was one of the CVD risk factors (p=0.276) from the latest studied Thai population in 2012.[6] Allowable error (d) was 0.0414 and relative error was 15%. The collected data were from the first participation in this unit. About 1,000 out-patient charts were reviewed and only 473 charts, as in Fig 1, were finally included when the following inclusion criteria were met: natural menopause, 45-60 years, the first-time diagnosis of osteopenia or osteoporosis without previous treatment. Patient charts with a history of metabolic bone disorders, drug affecting calcium and bone metabolism, congenital or valvular heart disease, or cancer with bone metastasis were excluded. Reviewed data included age, weight, height, waist circumference (WC), and underlying diseases. CVD risk factors consisted of DM, HT, body mass index (BMI), cholesterol (Chol), triglyceride (TG), high density lipoprotein (HDL) and family history of CVD (female <65 years, male <55 years).

Statistical analysis

PASW (SPSS) version 18 (SPSS Inc., Chicago, IL, USA.) was used. The results were reported as mean±SD, minimum, maximum and percentage with 95%CI. T- test was used to compare continuous variables eg. BMI, Wt, Ht, etc. Categorical data, eg. BMI≥ 23 kg/m^2 etc. was analyzed by Pearson Chi-square test, and p-value <0.05 was statistically significant. The data were also compared with previously reported data of Thai population.

RESULTS

473 patients with complete data were included in the final analysis. The mean age of patients was 53.5±4.1 years. All subjects were non-smoking with an average 3.6 years since menopause. Demographic data and clinical characteristics are shown in Table 1. Mean WC, Chol, TG, and HDL levels were all within normal ranges. Only mean high BMI for Asian women (≥ 23.0 kg/m^2) in this study was higher than previously reported in Thai women. The overall prevalence of patients with traditional initial CVD risk factors was 73.8%. While approximately one-fourth of the subjects had no risk factor, 61 patients (12.9%) had 4-6 risk factors, and only one patient had all seven risk factors. The 3 most common risk factors were high BMI (48.6%), high WC (37.8%), and Chol ≥ 240 mg/dl (22.2%). The vast majority of women were osteopenic (408 patients, 86.3%), with only 65 (13.7%) women having osteoporosis (Fig 1).

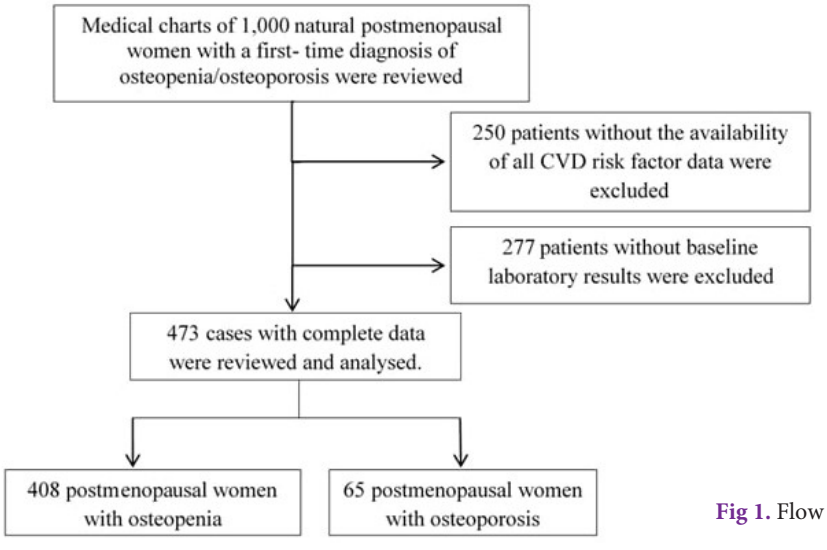


Fig 1. Flow diagram of subject selection process.

TABLE 1. Clinical characteristics, and prevalence and number of CVD risk factors, overall and by BMD group.

	All subjects (n = 473) Mean±SD	Osteopenia (n = 408) Mean±SD	Osteoporosis (n=65) Mean±SD	*P*-value*
Age (yrs)	53.5±4.1	53.4±4.0	53.7±4.1	0.595
Wt (kg)	55.7±8.7	56.0±8.6	53.8±8.5	0.066
Ht (cm)	154.7±5.2	154.8±5.1	154.3±5.7	0.501
BMI (kg/m^2)	23.3±3.4	23.4±3.4	22.6±3.4	0.104
WC (cm)	78.1±8.3	78.3±8.3	76.6±8.1	0.113
Chol (mg/dl)	212.4±38.6	211.5±38.0	218.1±42.3	0.200
TG (mg/dl)	103.3±50.5	103.9±51.5	100.1±44.3	0.573
HDL (mg/dl)	65.5±15.9	64.6±16.0	67.5±15.4	0.177
Number of risk factor, cases (%)				
HT	67 (14.2%)	48 (11.8%)	19 (29.2%)	<0.001
DM	22 (4.7%)	17 (4.2%)	5 (7.7%)	0.210
BMI ≥ 23.0 (kg/m^2)	230 (48.6%)	201 (49.3%)	29 (44.6%)	0.486
Chol ≥ 240 mg/dl	106 (22.2%)	85 (20.8%)	20 (30.8%)	0.073
TG ≥ 150 mg/dl	59 (12.5%)	53 (13%)	6 (9.2%)	0.394
HDL < 50 mg/dl	49 (10.4%)	46 (11.3%)	3 (4.6%)	0.102
WC > 80 cm	179 (37.8%)	159 (39%)	20 (30.8%)	0.205
Family history of CVD	94 (19.9%)	76 (18.6%)	18 (27.7%)	0.089
Number of risk factors, cases (%)				
0-1	237 (50.1%)	207 (50.8%)	30 (46.2%)	0.462
2-3	174 (36.8%)	149 (36.5%)	25 (38.4%)	
4-6	61 (12.9%)	51 (12.5%)	10 (15.4%)	
7	1 (0.2%)	1 (0.2%)	0 (0%)	

**P*-value <0.05 indicates statistical significance

Abbreviations: BMD=bone mineral density, Wt=weight, Ht=height, BMI=body mass index, WC=waist circumference, Chol=cholesterol, TG=triglyceride, HDL=high density lipoprotein cholesterol, HT=hypertension, DM=diabetes mellitus, CVD=cardiovascular disease

Results of analysis between the osteopenia and osteoporosis subgroups are shown in Table 1. Average age, anthropometric parameters, and baseline laboratory results were not significantly different between groups. HT, DM, high Chol and family history of CVD were higher in the osteoporosis group than in the osteopenia group. Of those, HT was the only risk factor that was statistically significantly higher in the osteoporosis group than in the osteopenia group (p <0.001). Also, prevalence of high BMI, high TG, low HDL and high WC were lower in the osteoporosis group, but without statistical significance. The number of cases with 0-1, 2-3, 46 and 7 CVD risk factors were comparable between groups.

The prevalence of each initial CVD risk factor with 95% CI, and the prevalence reported from other studies in Thai women conducted during the same period are shown in Table 2. BMI ≥23.0 kg/m^2 was more prevalent in this study than in the 2010 report. HT, DM, high WC, high TG, and low HDL were also lower than in the previously published data. High Chol was also much lower than one previously published study, but the cut-off levels differed between the two studies (240 mg/dl vs 200 mg/dl, respectively). Family history of CVD was comparable with the 2006 report. Prevalence of DLP was also relatively high in this study, but without available previous data for comparison. Data from the National Health Examination Survey (NHES) V for the year 2015 was not available for comparison at the time that this manuscript was being prepared.

DISCUSSION

This study set forth to investigate the prevalence of initial CVD risk factors in naturally postmenopausal Thai women with low BMD who crucially need calcium supplementation after the first-time diagnosis of osteopenia/osteoporosis at a large tertiary care hospital in Thailand. Only naturally postmenopausal women were studied, because surgically postmenopausal women would likely be younger and would likely not yet have developed low BMD. Moreover, low BMD is not always identifiable soon after oophorectomy in younger women. Given that the average age of subjects was in the early naturally postmenopausal period, osteopenia was found to be more prevalent than osteoporosis. Interestingly, 26% of the subjects at the average age of 53.5 years still did not have any identifiable traditional CVD risk factors, and one-fourth of the cases had only one factor. However, half of the patients in this study had ≥ 2 risk factors and 12.5% had ≥ 4 risk factors.

The cross-sectional data from the NHES III in 2004, revealed a prevalence of overweight and obesity of 4.0% in a sample of Thai adults aged 35-59 years.[7] In another report, Thai women aged 46-55 years had the highest risk of being overweight or obese, and this may be due to the weight gain during important life transition events like retirement and menopause.[8] In a study conducted in Bangkok at another tertiary-care hospital, risk factors of hypercholesterolemia increased among Thai women: advanced age (OR:3.19), and family history of DLP (OR:1.59). It also reported that total Chol and TG were strongly associated with age, BMI and family history of DLP, while HDL was inversely associated with BMI.[9] In that study, women aged 40-59 years had an OR of 1.77 (95%CI: 1.27-1.48) of developing hypercholesterolemia compared to women aged <40 years. However, a positive association between increasing age and BMI and total Chol, TG and total Chol/HDL ratio were also noted. Undoubtedly, overweight and obese women had higher TG (p <0.001). A study in Taiwan by Tsai WL., also found that the risk of hypercholesterolemia increased with increasing BMI in both genders.[10] In addition, women with a family history of DLP had a mean total Chol higher than those without a family history of DLP (p <0.001). In a study from Japan, Kawada T. observed that odd ratios for hypercholesterolemia (≥ 240 mg/dl) also increased across higher BMI quartiles (OR:1.0-4.6).[11]

The average baseline characteristics of the patients in this study were mostly within normal ranges and approximately one fourth of the women had no initial CVD risk factors. Regarding HT and DM in Thailand, the age-specific prevalence of individuals having one or both conditions increased as age increased and peaked at later age, ≥80 years. Prevalence of coexisting HI and DM was reported to be highest in the 60-69 years' age group.[6] Total prevalence of DM was higher in urban residents than in rural residents for both men and women (p <0.001).[7] However, the proportions of DM cases with HT did not significantly decrease for either gender.

This study revealed some other interesting outcomes. Firstly, the prevalence of high BMI, high Chol, and family history of CVD, were comparable with the results of other Thai studies in patients of comparable ages. In Thailand, a significant increase in the prevalence of overweight and obesity was observed, from 1991 (25%) to 2004 (48%) among Thai adults aged 35-59 years.[13] Also, from 2004 to 2009, the proportion of women with DM and abdominal obesity increased 18% and the proportion of women who had DM and high Chol increased 23.5%.[14] The increase in BMI and prevalence of obesity in Thailand were reported to be consistent with rates of increase in other Asian countries.[15] It is known that the risk of developing CVD increases twofold after

TABLE 2. Prevalence of each CVD risk factor compared with previous Thai reports.

CVD risk factors	Prevalence (%)	95%CI	The other National Thai studies	
			Population	Prevalence (%)
HT	14.2	11.3-17.6	Thai women aged 45-59 years Central, Northern, North, South Survey (urban/rural area) NHES III[7]	34.6
DM	4.7	3.1-6.9	Thai women aged 45-59 years Central, Northern, North, South Survey (urban/rural area) NHES III[7]	12.8
BMI ≥23 kg/m^2	48.6	44.2-53.1	3,275 women, average age 40.8 ±16.6 years (women aged 36-45, 46-55, 56-65 with OR for overweight 2.5 (1.6-3.9), 4.8 (3.0-7.6), 2.9 (1.8-4.8) respectively, p <0.001) Nationally representative sample covering all geographic regions of Thailand[8]	44.9
DLP	44.4	40-48.9		NA
Cholesterol ≥ 240 mg/dl	22.2	18.7-26.2	510 women aged 40-59 who participated in annual health examination at a tertiary-care hospital, Bangkok (cholesterol ≥200 mg/dl)[9]	71.9
TG ≥ 150 mg/dl	12.5	9.8-15.8	Thai women aged 40-59 years Sampling by province, region, district, village, the sex and agespecific group. NHES IV[12]	40-49 years: 29.6% 50-59 years: 42.9%
HDL > 50 mg/dl	10.4	7.9-13.4	Thai women aged 40-59 years Sampling by province, region, district, village, the sex and agespecific group. NHES IV[10]	40-49 years: 56.4% 50-59 years: 58.4%
WC > 80 cm	37.8	33.6-42.3	Thai women aged 40-59 years Sampling by province, region, district, village, the sex and age- specific group. NHES IV[12]	40-49 years: 51.0% 50-59 years: 57.6%
Family history of CVD	19.9	16.5-23.7	851 women with known family history of CVD who participated in annual health examination at a tertiary-care hospital, Bangkok[9]	19.8

Abbreviations: CVD=cardiovascular disease; CI=confidence interval; HT=hypertension; NHES=National Health Examination Survey; DM=diabetes mellitus; BMI=body mass index; OR=odds ratio; DLP=dyslipidemia; NA=not available; Chol=cholesterol; TG=triglycerides; HDL=high density lipoprotein cholesterol; WC=waist circumference
Thai NHES III= 2004 (Multistage, probability sampling of Thai population aged ≥ 15 years) Thai NHES IV = 2009 (Multistage, stratified sampling of Thai population aged ≥ 20 years) Thai NHES V = 2015 (Published data not available at the time this manuscript was drafted)

menopause. Decreased estrogen level may be associated with CVD risk.[16,17] Prevalence of family history of CVD in this study was similar to the other Thai study conducted during the same time period to which we compare our results. This may explain why subjects in both studies were homogenous Thai Indochina population.

Secondly, the prevalence of HT, high WC, high TG and low HDL were much lower in this study than in the other studies to which each was compared. This may be explained by the reason that the women in this study were early naturally postmenopausal women who had received the first-time diagnosis of osteopenia/osteoporosis. This interesting finding should be studied more extensively. Many studies reported that postmenopausal women have increased total Chol, increased LDL, increased TG, increased lipoprotein (a), and decreased HDL. The change in lipid profile may also be partly attributed to increased abdominal adiposity in menopausal women.[16] Unfortunately, prevalence of DLP from previous study was not available for comparison in this report.

Menopause causes a significant increase in total peripheral resistance and loss of arterial vasodilatation. This may contribute to increases in BP.[10] Differences in the prevalence in this study and the comparative studies shown in Table 2 could also be differences in study design. The population in this study was derived from a single-center, tertiary care hospital. The proportions of subjects with numbers of CVD risk factors (i.e. 0-1, 2-3, 4-6 and 7) were not significantly different between the two groups. However, the prevalence of HT in the osteoporosis group was significantly higher than the osteopenia group (p <0.001). This difference may be explained by the older mean age of patients in the osteoporosis group (p >0.05).

Family history of CVD is an un-modifiable risk factor, and other modifiable risk factors, such as HT and DM might increase in prevalence as women age. The prevalence of HT reported from the NHES III study in 2004 and reported in 2008 among Thai women increased from 34.6% (45-59 yr), to 48.1% (60-69 yr) and 54.1% (70-79 yr). Also, the prevalence of DM in that study increased from 12.8% (45-59 yr), to 19.1% (60-69 yr) and 16.1% (70-79yr).[18] The cross-sectional data from the NHES IV reported in 2009 showed that high WC also increased as Thai women aged, from 51.0% (40-49 yr) to 57.6% (50-59yr). Result from the same report in 2009 showed, TG ≥150 mg/dl also increased with age, from 29.6% (40-49 yr) to 42.9% (50-59 yr), while HDL <50 mg/dl showed only a slight increase in prevalence from 56.4% (40-49 yr) to 58.4% (50-59 yr). Results from the National Thai Food Consumption Survey in 2010 of other samples covering all geographic regions of Thailand, showed that women aged 46-55 year had the highest OR for BMI ≥23.0 kg/m^2 compared to women aged <45 years and 56-65 years (OR:2.5 vs 2.9, respectively). The results from previous Thai reports imply that as Thai women age, they may have more traditional CVD risk factors.

This study showed that naturally postmenopausal Thai women with osteopenia/osteoporosis had initially comparable or lower CVD risks than Thai women in the general population of the same ages during the same study time frame. However, the CVD risk factors were different among the osteopenia and osteoporosis groups and need future study.

This study has some mentionable limitations. First and consistent with the retrospective nature of this study, some patient data may have been missing or incomplete which they were excluded from the final analysis. Second, the patients we studied were hospital-based, from a single center referred with mainly menopausal symptom complaints. Behavioral and lifestyle characteristics such as alcohol consumption, and exercise habits should also be collected for analysis.

CONCLUSION

Prevalence of initial CVD risk factors in this study was 73.8%. With the exception of high BMI, initial CVD risk factors in this study subjects were comparable to or lower than those found in Thai women in the general population of the same age during the same time period.

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REFERENCES

1. Limpaphayom KK, Taechakraichana N, Jaisamrarn U, Bunyavejchevin S, Chaikittisilpa S, Poshyachinda M, et al. Prevalence of osteopenia and osteoporosis in Thai women. Menopause 2001;8:65-9.
2. Warburton DE, Nicol CW, Gatto SN, Bredin SS. Cardiovascular disease and osteoporosis: Balancing risk management. Vasc Health Risk Manag 2007;3:673-89.
3. Tanko LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J Bone Miner Res 2005;20:1912-20.
4. McGreevy C, Williams D. New insights about vitamin D and cardiovascular disease. Ann Intern Med 2011;155:820-6.
5. Kosulwat V. The nutrition and health transition in Thailand. Public Health Nutr 2002;5:183-9

6. Tiptaradol S, Aekplakorn W. Prevalence, awareness, treatment and control of coexistence of diabetes and hypertension in Thai population. Int J Hypertens 2012;2012:386453.
7. Aekplakorn W, Abbott-Klafter J, Premgamone A, Dhanamun B, Chaikittiporn C, Chongsuvivatwong V, et al. Prevalence and management of diabetes and associated risk factors by regions of Thailand: third National health examination survey 2004. Diabetes Care 2007;30:8-12.
8. Jitnarin N, Kosulwat V, Rojroongwasinkul N, Boonpragerm A, Christopher KH, Walker SCP. Risk factor for overweight and obesity among Thai adults: Results of the National Thai Food Consumption Survey. Nutrient 2010;2:60-74.
9. Le D, Garcis A, Lohsoonthorn V, Williams WA.Michelle. Prevalence and risk factors of hypercholesterolemia among Thai men and women receiving health examinations. Southeast Asian J Trop Med Public Health 2006;37:1005-14.
10. Tsai WL, Yang CY, Lin SF, Fang FM. Impact of obesity on medical problems and quality of life in Taiwan. Am J Epidemiol 2004;160:557-65.
11. Kawada T. Body mass index is a good predictor of hypertension and hyperlipidemia in a rural Japan population. Intl J Obes Relat Metab Disord 2002;26:725-9.
12. Aekplakorn W, Kessomboon P, Sangthong R, Chariyalertsak S, Putwatana P, Inthawong R, et al. Urban and rural variation in clustering of metabolic syndrome components in the Thai population: results from the fourth National Health Examination Survey 2009. BMC Public Health 2011;11:854.
13. Ministry of Public Health, Bureau of Policy and Strategy. Thailand Health Profile, 2005-2007; Printing Press, the War Veterans Organization of Thailand: Bangkok, Thailand, 2008.
14. Aekplakorn W, Chariyalertsak S, Kessomboon P, Sangthong R, Inthawong R, Puttawatana P, et al. Prevalence and management of diabetes and metabolic risk factors in Thai adults. Diabetes Care 2011;34:1980-5.
15. Aekplakorn W, Inthawong R, Kessomboon P, Sangthong R, Charityalertsak S, Puttawattana P, et al. Prevalence and trends of obesity and association with socioeconomic status in Thai adults: National health examination surveys, 1991-2009. J Obes 2014;2014:410259.
16. Molly CC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 2003;88:2404-11.
17. Hanah NP, Alex JP. Metabolic implications of menopause. Semin Reprod Med 2010;28:426-34.
18. Porapakkham Y, Pattaraarchachai J, Aekplakorn W. Prevalence, awareness, treatment and control of hypertension and diabetes mellitus among the elderly: the 2004 National Health Examination Survey III, Thailand. Singapore Med J 2008;49:868-73.

Comparative Study of Health-Related Quality of Life between Colorectal Cancer Patients with Temporary and Permanent Stoma

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ABSTRACT

Objective: To compare the health-related quality of life (HRQOL) between colorectal cancer (CRC) patients with temporary and permanent stoma.

Methods: This survey was a cross-sectional study that was conducted on 110 CRC patients living with stoma. A validated Thai version of Padilla and Grant's HRQOL (as a cancer nursing outcome variable) was used. Enrolled patients must have age between 40-60 years and live with stoma over a period of 3 months.

Results: There were 83 patients with temporary stoma and 27 patients with permanent stoma. The majority was male and got married. The common indication for temporary and permanent stoma was low anterior resection and abdominoperineal resection, respectively. Overall mean HRQOL index was not significantly different between groups. There was also no difference in the mean QOL of each domain - namely physical well-being, psychological well-being, body image concerns about stoma, social support concern, and diagnosis/treatment response between those with temporary and permanent stoma. Notably, the domain of body image concern had the lowest QOL index in both groups.

Conclusion: Postoperative health-related quality of life was not different between Thai colorectal cancer patients with temporary or permanent stoma. However, the patients with permanent stoma appeared to have non-significant higher score in every domain of health-related quality of life than those with temporary stoma.

Keywords: Health-related quality of life; colon cancer; rectal cancer; colostomy; ileostomy; stoma; temporary; permanent; surgery (Siriraj Med J 2019;71: 196-200)

INTRODUCTION

Colorectal cancer (CRC) is one of major health problems across the globe. A significant increase in its incidence has been observed worldwide in the recent years.[1] In Thailand CRC is now the third most commonly diagnosed cancer in males and the fourth in females.[2] Currently, CRC-related death has reduced due to an improvement in early detection and advances in cancer treatment. However, some curative operations would have stoma formation either temporary or permanent purpose. Not surprisingly, the number of CRC survivors with stoma is growing significantly.[3] Presence of stoma (colostomy/ileostomy) has been shown to adversely affect patient's wellbeing in several phases such as physical and psychological aspects, social function, work and productive life, relationships with partners and friends, social activities and personal interests.[5]

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Since temporary and permanent stoma is one of viable treatment options for CRC[3], it creates many challenges for CRC patients especially in terms of health-related quality of life (HRQOL). The patients with stoma formation face the loss of sphincter control and inability to control gas[4] and may have several other prolems including anxiety or fear of future living with relationships and family[5], difficulty in social and sexual activities, sleep disturbance[5], the restriction of food intake and physical activities[6] and changes in lifestyle.[7] All of these sequelae impacted their HRQOL.[8] In CRC patients, non-sphincter preserving operation (i.e. colostomy formation) was also shown to negatively impact patients' HRQOL.[9]

HRQOL for patients with stoma is one of important patient-reported outcome measures and could be regards as one of the long-term comprehensive outcomes in CRC patients. The World Health Organization defines HRQOL as individuals' perception of their life's position in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[10] HRQOL in CRC patients with stoma is a multidimensional construct measuring patients' perception in several domains including physical well-being, psychological well-being, body image concerns about colostomy, social support concern, and diagnosis/treatment (surgical) response.[11]

Most published literatures about HRQOL of CRC patients with stoma were conducted in Western or developing countries - with some conflicting results. For example, Grumann et al[12] compared HRQOL in German patients undergoing anterior resection (AR), low anterior resection (LAR) and abdominoperineal resection (APR) for rectal cancer. They found that patients undergoing APR did not have a poorer HRQOL than those undergoing AR but patients undergoing LAR had a lower HRQOL than those undergoing APR. In the Netherlands, Gooszen et al[13] studied HRQOL in those with a temporary stoma (37 loop ileostomy and 39 loop colostomy) and found that stoma leakage, peristomal dermatitis, and stoma retraction or prolapse had significant impact on patients' HRQOL. In Brazil, Fortes et al[14] and de Gouveia Santos et al[15] evaluated HRQOL in CRC patients with temporary and permanent colostomy and found that patients with temporary stoma suffered the same affection and poor HRQOL as those with permanent colostomy.

In Thailand, there have been some studies examining HRQOL or factors related to HRQOL in patients with stoma[16-18], but there is no comparative study of HRQOL in CRC patients with temporary or permanent stoma. We believe that the information of HRQOL in those with temporary or permanent stoma will help surgeons and other related healthcare personals more understanding and could improve patient's care in such individuals in the future. Therefore, this study aimed to examine and compare HRQOL in CRC patients with temporary or permanent stoma in Thai population.

MATERIALS AND METHODS

This study was a cross-sectional study examining HRQOL in 110 CRC adult patients with either temporary or permanent stoma.[18] Data were collected from July 2016 to October 2016 at 3 tertiary referral centers in Bangkok, Thailand - namely 1) Faculty of Medicine Siriraj Hospital, Mahidol University, 2) King Chulalongkorn Memorial Hospital and 3) National Cancer Institute. The patients were systematically and randomly enrolled with inclusion criteria of patient age between 40-60 years and having stoma over a period of 3 months. The correspondents must have no symptoms and signs of critical illness during interviewing, and understand and response properly to the questionnaires. The eligible cases were randomly enrolled. All subjects granted a signed inform consent before an enrollment.

The interview questionnaires had 2 parts: general details and HRQOL. The general details included patients' demographics, level of education, income, tumor characteristics and operative details, their general knowledge of CRC, self-care behaviors and social support. For HRQOL, a validated Thai version of Padilla and Grant's HRQOL (as a cancer nursing outcome variable) was used[18], including the domains related to physical, mental, emotional and social functioning. The HRQOL index ranges from 0 to 100 as the higher score the better HRQOL. This index of HRQOL was divided into 3 levels: low (HRQOL 0-33.33), moderate (33.34-66.67) and high (66.68-100) level of HRQOL. Data were analyzed using computer-based statistical program (SPSS/Window version 17). Demographic data and HRQOL index were analyzed using descriptive statistics and independence student t-test to compare between HRQOL index of adult CRC patients with temporary and permanent stomas. A P-value < 0.05 was considered a statistical significance.

RESULTS

Demographic data of patients with temporary and permanent stoma

There were 27 patients with permanent stoma with mean age of 54.4 years. Seventeen (63%) were males and 25 patients (92.6%) were married. Stage III and IV rectal cancer were the most common indication for stoma formation as two-third had abdominoperineal resection. At the time of HRQOL evaluation, the two-third of

patients had permanent stoma was more than 1 year. In the other group, there were 83 patients with temporary stoma with mean age of 54.9 years. Fifty-five (66.3%) were males and 78 patients (94%) were married. Stage III colorectal cancer was the most common indication for temporary stoma formation (mostly in case of low anterior resection). At the time of HRQOL evaluation, the two-third of patients had temporary stoma less than 1 year. Demographic data of patients with temporary and permanent stoma are summarized in Table 1.

Health-related quality of life between colorectal cancer patients with temporary and permanent stoma

Overall mean HRQOL index was not significantly different between groups. There was also no difference in the mean QOL of each domain between those with temporary and permanent stoma. Notably, the domain of body image concern had the lowest QOL index in both groups. Table 2 shows and compare the HRQOL index between CRC patients with temporary and permanent stoma.

DISCUSSION

This cross-sectional study of CRC patients with stoma in Thailand found that the overall HRQOL index and its detailed domains were not significantly different between those with temporary and permanent stoma. However, it is worth noting that Thai CRC adult patients with permanent stoma had non-significantly higher overall HRQOL index and HRQOL indexes of each domain - namely physical well-being, psychological well-being, body image concerns about stoma, social support concern, and diagnosis/treatment response than those with temporary stoma. These results are similar to those reported from Western countries. For example, Smith et al[19] conducted a small cross-sectional study of patients

TABLE 1. Patients' demographic data (n=110). The data are shown as mean ± standard deviation, or number (percentage).

Variables	Permanent (n=27)	Temporary (n=83)
Age (years)	54.4 ± 6.1	54.9 ± 5.5
Male	17 (63.0%)	55 (66.3%)
Marital status: Married	25 (92.6%)	78 (94.0%)
Education		
No education	1 (3.7%)	1 (1.2%)
Primary school	11 (40.7%)	41 (49.3%)
High school	3 (11.1%)	13 (16.8%)
Bachelor degree or higher	12 (44.4%)	27 (32.5%)
Income (Bahts)		
Less than 10,000	7 (25.9%)	21 (25.3%)
10,001-30,000	18 (66.7%)	54 (65.1%)
30,001-50,000	2 (7.4%)	8 (9.6%)
Cancer staging		
Stage II	5 (18.5%)	10 (8.2%)
Stage III	11 (37.0%)	47 (42.7%)
Stage IV	11 (37.0%)	26 (23.6%)
Presence of stoma more than 1 year	18 (66.7%)	28 (33.7%)
Operative details		
Low anterior resection	4 (14.8%)	53 (63.9%)
Abdominoperinal resection	18 (66.7%)	2 (2.4%)
Hartmann's procedure	3 (11.1%)	11 (13.3%)
Colectomy	2 (7.4%)	17 (20.5%)

TABLE 2. Index score and level of health-related quality of life among patients with temporary and permanent stoma.

	Type of stoma	N	Mean	SD	Level*	P-value
Overall HRQOL	Temporary stoma	83	66.41	14.32	Moderate	0.372
	Permanent stoma	27	69.31	15.37	High	
Physical well-being	Temporary stoma	83	69.08	16.68	High	0.474
	Permanent stoma	27	71.74	16.65	High	
Psychological well-being	Temporary stoma	83	64.68	16.43	Moderate	0.525
	Permanent stoma	27	67.06	18.22	High	
Body image concern	Temporary stoma	83	54.56	21.98	Moderate	0.596
	Permanent stoma	27	57.22	24.32	Moderate	
Social concern	Temporary stoma	83	76.83	13.52	High	0.427
	Permanent stoma	27	79.26	14.50	High	
Surgical response	Temporary stoma	83	69.28	17.80	High	0.369
	Permanent stoma	27	72.72	15.30	High	
Nutrition response	Temporary stoma	83	68.73	18.14	High	0.176
	Permanent stoma	27	74.07	16.30	High	

*__Note:__ Level of HRQOL: low (0-33.33), moderate (33.34-66.67) and high (66.68-100)

with stoma in the United States and found that patients with permanent stoma had high HQOL scores than patients with temporary stoma. These finding suggested that patients with irreversible colostomies would adapt more fully than would those with colostomies that were potentially reversible. Our previous study indicated that patient's self-esteem, self-care and knowledge were also significant factors for determining HRQOL.[18]

Regarding the physical well-being dimension of HRQOL in Thai CRC adult patients with stoma, both groups had a comparable and high level of HRQOL. This result was partly explained by the fact that almost of patients with stoma already had good recovery from surgery and/or adjuvant therapy although some patients with a temporary stoma were in the middle of chemotherapy or radiation session. Fortes et al14 reported that chemotherapy or radiotherapy might have numerous influences on HRQOL in patients with stomas and the adverse symptoms may last up to 1 year after treatment.

Although there was no significant difference in the score of psychological well-being dimension between groups, patients with permanent stoma was regarded to have a high level of QOL while those with temporary stoma had a moderate level. These results were consistent with other studies in Thailand.[17,20] The most frequent coping strategy employed by individuals with temporary stoma was escape and avoidance which was not so effective because it did not permit the subject to approach the problem directly. In contrast, the most frequent coping strategy employed by patients with permanent stoma was problem-solving which provided a more proactive and mature behavior - allowing greater autonomy and responsibility when coping with their stoma.[15]

The body image concern dimension had the lowest score in Thai CRC adult patients with temporary and permanent stoma. It is well known that stoma surgery is a mutilating procedure and could affect their body image directly and negatively. We found that patients with stoma had some anxiety about stoma and fear of stoma leakage (especially during performing physical activities or sleep) which were consistent with other reports.[15,21] In Thailand, Teerathongdee[20] reported that CRC patients with colostomy had a moderate level of QOL in component of body image concern. Meanwhile, Ransriwong[22] reported a low level of QOL in component of self-image in those with stoma. However, the results were extracted from early postoperative period (within 3 months after surgery) - where the patients may not cope with the body change.

Regarding the social concern dimension, both groups had a high level of QOL. It could be explained by the fact that, in Thai culture, patients with stomas

were taken care of their stoma by their caregivers such as their family members or spouses. Patients often come to clinic with their relatives and did not feel lonely or abandoned.[17] For the dimension of surgical response and nutrition, patients with either temporary or permanent stoma dimension had a high level of QOL which was not significant different between groups. It is possible that HRQOL in each dimension could gradually improve as the time goes by because the patients can learn, adapt and cope with stoma and their activities of daily living such as eating and moving.[5,17]

The strength of this study included a relative larger sample size of enrolled patients than those previously reported from Thailand. The data were also collected from 3 tertiary care centers where colorectal surgeons, ostomy nurse specialists and psychologists are available. There are also a dedicated ostomy clinics and specialized medical supplies in these centers. However, it is unknown about the HRQOL in Thai CRC adult patients with stoma who were operated on by non-colorectal surgeons or taken care of by non-specialist nurses.

CONCLUSION

Postoperative health-related quality of life was different between Thai colorectal cancer patients with temporary or permanent stoma. However, the patients with permanent stoma appeared to have non-significant higher score in every domain of health-related quality of life than those with temporary stoma. We believed that, apart from focusing on oncological outcomes, healthcare personals should aim to improve patient's health-related quality of life overall and in each domain - partly by integrating knowledge, self-care as well as patient-centered program in patients with stoma.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:359-86.
2. Imsamran W, Chaiwattana A, Wiangnon S, Pongnikorn D, Suwanrungrung K, Sangrajrang S, et al. Cancer in Thailand Vol.VIII, 2010-2012 [Cited 2015 December 8]. Available from: http://www.nci.go.th/en/index1.html.
3. American Cancer Society Colorecral cancer 2016 [Cited 2016 November 24]. Available from: http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-what-is-colorectal-cancer.
4. Burch J. Stoma Care. Singapore: Markono Print Media Ptd Ltd; 2008.
5. Arndt V, Merx H, Stegmaier C, Ziegler H, Brenner H. Quality of life in patients with colorectal cancer 1 year after diagnosis compared with the general population: a population-based study. J Clin Oncol 2004;22:4829-36.
6. Zajac O, Spychala A, Murawa D, Wasiewicz J, Foltyn P, Polom K. Quality of life assessment in patients with a stoma due to rectal cancer. Rep Prac Oncol Radiother 2008;13:130-4.
7. Ang SG, Chen HC, Siah RJ, He HG, Klainin-Yobas P. Stressors relating to patient psychological health following stoma surgery: An integrated literature review. Oncol Nurs Forum 2013;40:587-94.
8. King CR. Health related quality of life issues for individual with colorectal cancer. In: Berg DT, editor. Contemporary issues in colorectal cancer: A nursing perspective. London: Jones and Bartlett Publishers; 2011.
9. Vonk-Klaassen SM, de Vocht HM, den Ouden ME, Eddes EH, Schuurmans MJ. Ostomy-related problems and their impact on quality of life of colorectal cancer ostomates: a systematic review. Qual Life Res 2016;25:125-33.
10. World Health Organization. Quality of life 2016 [Cited 2016 December 1]. Available from: http://www.who.int/mental_health/media/68.pdf.
11. Padilla GV, Grant MM. Health related quality of life as a cancer nursing outcome variable. ANS Adv Nurs Sci 1985;8:45-60.
12. Grumann MM, Noack EM, Hoffmann IA, Schlag PM. Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer. Ann Surg 2001;233:149-56.
13. Gooszen AW, Geelkerken RH, Hermans J, Lagaay MB, Gooszen HG. Quality of life with a temporary stoma: ileostomy vs. colostomy. Dis Colon Rectum 2000;43:650-5.
14. Fortes RC, Monteiro TMRC, Kimura CA. Quality of life from oncological patients with definitive and temporary colostomy. J Coloproctol 2012;32:253-9.
15. de Gouveia Santos VL, Chaves EC, Kimura M. Quality of life and coping of persons with temporary and permanent stomas. J Wound Ostomy Continence Nurs 2006;33:503-9.
16. Chitmon N. Health-related quality of life patients with permanent colostomy. Bangkok: Chulalongkorn University; 2006.
17. Decha W, Navicharern R. Predicting factors of quality of life among colorectal cancer patients with colostomy recieving chemotherapy. Kuakarun J Nurs 2016;23:113-47.
18. Chutikamo N, Navicharern R, Lohsiriwat V. Predicting factors of quality of life in colorectal cancer adult patients with colostomy. Royal Thai Navy Med J 2017;44:103-16.
19. Smith DM, Loewenstein G, Jankovic A, Ubel PA. Happily hopeless: Adaptation to a permanent, but not to a temporary, disability. Health Psychol 2009;28:787-91.
20. Teerathongdee K. Factors predicting quality of life in aged patients with colorectal cancer after stomal surgery. Thai Cancer J 2014;34:68-78.
21. Gracia Pereira M, Figueiredo AP, Fincham FD. Anxiety, depression, traumatic stress and quality of life in colorectal cancer after different treatments: A study with Portuguese patients and their partners. Eur J Oncol Nurs 2012;16:227-32.
22. Ransriwong P. Quality of life in colorectal cancer patient after stoma surgery. Suan Dok J 2549;15:22-6.

An Agreement of Two Tonometers: Goldmann Applanation and Non-Contact Scheimflug Technology in Healthy, Ocular Hypertension and Open-angle Glaucoma Patients

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ABSTRACT

Objective: The primary objective was to find an agreement of intraocular pressure (IOP) assessed by Goldmann applanation tonometry (GAT) and Corvis in healthy, ocular hypertension (OHT) and primary open-angle glaucoma (POAG). The secondary objective was to find a reliability of intra-examiner and inter-examiner IOP measurement by GAT and Corvis.

Methods: Fifty three eyes from 53 participants were included and were divided into healthy (N=20), OHT (N=13) and POAG group (N=20). Only right eyes were selected for further statistical analysis except one patient with only left eye eligible. The eyes with corneal pathologies, greater than 2.5 diopters astigmatism, or recent ocular surgery were excluded. Randomized examining sequence between GAT and Corvis was applied. To minimize an after measurement IOP fluctuation, five minutes and two minutes gap between measurements were strictly applied for Corvis and GAT respectively. The first ten patients had 3 measurements per measurer and two measurers were assigned per machine to evaluate intra-examiner and inter-examiner reliability. Intraclass correlation coefficient was used to analyze the reliability of the IOP measuring machine. Bland & Altman plot was used to analyze an agreement between the machines.

Results: High ICCs were found in both measurers using GAT (ICC of measurer 1 = 0.954, measurer 2 = 0.977) and Corvis (ICC of measurer 1 = 0.920, measurer 2 = 0.927) which indicated excellent intra-examiner reliability. High ICCs were found when comparing IOP between 2 measurers who used the same machine (GAT ICC = 0.928, Corvis ICC = 0.915) which indicated excellent inter-examiner reliability. GAT tends to yield higher IOP reading. The mean IOP were 13.93±3.849 by GAT and 12.15±4.030 by Corvis. The mean IOP differences were 1.8, 1.7, 1.4 and 2.2 mmHg in total, healthy, OHT and POAG group respectively. POAG had highest mean difference and widest standard deviation which might result from poor agreement between 2 machines. According to Bland & Altman plot the values were scattered and no trend was found indicating higher or lower average IOP would result in higher or lower difference between the two machines. From the clinical point of view, 71.7% and 47.2% fall into IOP difference range of ±3 and ±2 mmHg respectively.

Conclusion: Corvis-IOP is a good parameter with excellent intra-examiner and inter-examiner reliability. In clinical practice, the usefulness of Corvis-IOP is limited especially in POAG patients according to the poor agreement with gold standard GAT-IOP.

Keywords: Corvis; comparison; tonometry; tonometer; intraocular pressure measurement; repeatability (Siriraj Med J 2019;71: 201-206)

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INTRODUCTION

Introcular pressure (IOP) measurement is crucial for glaucoma diagnosis and management. Gold standard instrument is Goldmann applanation tonometer. Unfortunately, there were some drawbacks using this machine such as well-trained user is required to take measurement, required anesthetic and fluorescein eye drops, need to calculate central corneal thickness (CCT)-corrected IOP, CCT and corneal biomechanical properties should be taken separately by different machine. Corvis ST (Corneal visualization scheimflug technology, Oculus, Wetzlar, Germany) is an IOP measurement machine approved by FDA in the year 2013. IOP and CCT from Corvis demonstrated excellent repeatability from previous studies.[1-3] They do not need eye drops or well-trained user. Corvis is an interesting new machine that should be considered. Moreover, plenty of data such as CCT, corneal biomechanical properties and IOP are retrieved at same time. There are insufficient clinical studies to conclude that these two machines showed acceptable agreement. There is controversy since some studies showed good agreement,[1,2,4] but some did not.[5] The primary aim of the study was to assess the usefulness of Corvis by evaluating an agreement with gold standard GAT in healthy, ocular hypertension (OHT) and primary open-angle glaucoma (POAG).

MATERIALS AND METHODS

The study was a cross-sectional study approved by the Ethics Committee (Si 622/2014) of our institution which followed the tenets of the Declaration of Helsinki and signed inform consent were obtained.

We included subjects who were 18 years old or older in the study. Participant with corneal pathologies, for example corneal edema or keratoconus was excluded. Participant who had more than 2.5 diopters astigmatism, recently underwent corneal or glaucoma surgery within 3 months, nystagmus and uncooperative were excluded.

In this study, we classified all participants into 3 groups which were healthy, ocular hypertension (OHT) and primary open-angle glaucoma (POAG). Healthy participant was defined as participant who had no evidence of glaucoma or ocular hypertension from medical record and complete eye examination by ophthalmologist. Ocular hypertension was defined as participant who had intraocular pressure (IOP) of 21 mmHg or more with no evidence of glaucoma. Primary open angle glaucoma was defined as participants who were diagnosed with POAG.

Subject allocation was done in each participant group by randomizing into 2 different examining sequences as displayed in the diagram 1, in order to minimize the effect of machine sequence on IOP measurement. The sequence was created using http://www.randomization.com.

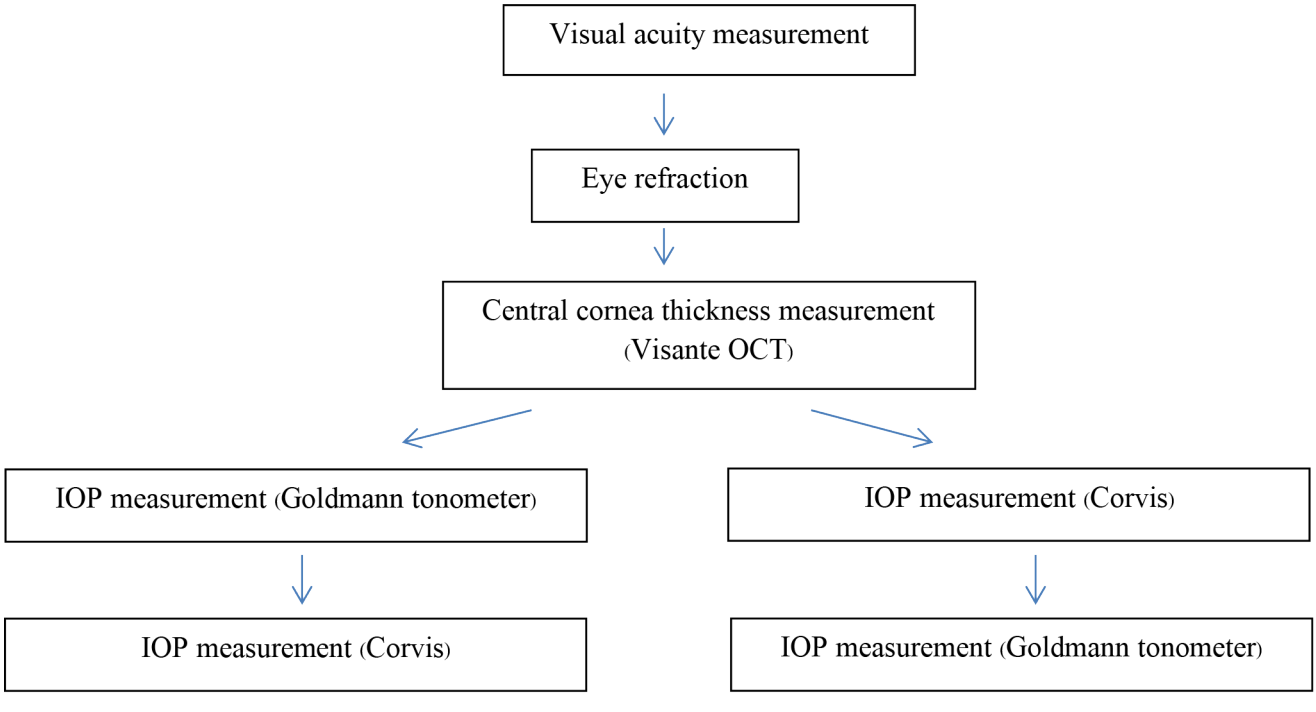


Diagram 1. Examining sequence

Two experience opticians (Measurer 1 and 2) who worked in special equipment room and trained for using Corvis machine were responsible for Corvis measurement. Meanwhile, GAT was done by two ophthalmologists (S.P. as measurer 1 and S.K. as measurer 2) during an eye examination. Visual acuity, eye refraction and central corneal thickness (CCT) by using Visante OCT were done by one experienced optician.

CCT is the main parameter that could affect IOP measurement. There is no best CCT-corrected equation for GAT when comparing with Dynamic contour tonometer (DCT).[6] To minimize the effect of central corneal thickness (CCT), corrected GAT IOP was calculated from GAT IOP and CCT (Visante OCT) by using Doughty & Zaman equation. This equation came from meta-analysis and big database. Meanwhile, corrected Corvis IOPs were automatically generated and collected. The study selected only corrected IOPs from both devices for statistical analysis.

For the first 10 eyes, we took three different IOP measurements by using each machine to assess intra-examiner reliability and all measurements were repeated by another examiner to assess inter-examiner reliability. The intra-examiner and inter-examiner ICCs were excellent in both GAT and Corvis group, as showed in Table 1. For the rest of participants, GAT and Corvis measurements were done by only measurer 1.

Two minute and 5 minute gaps between each measurement were applied for GAT and Corvis respectively, to minimize the effect on IOP from previous measurement. Only the data from right eye was analyzed, except one patients who had only left eye eligible for the study so the data from left eye was used.

Sample size and statistic

Intraclass correlation coefficients (ICC) is used to assess interrater and intrarater reliability. In order to compare an agreement of two measurement devices, Bland and Altman plot was applied. All the statistical analyses were performed using SPSS version 18.0 software.

Aiming for excellent correlation between Goldmann applanation tonometer (GAT) and Corvis, we used the following statistical formula to calculate sample size for intraclass correlations coefficients of 0.75. At a confident level 95%, SD 0.15 resulted in sample size of 131.

$$n = 8z^2\alpha/2\ \{(1-\rho I)^2(1+(k-1)\rho I)^2\}/\{k(k-1)w^2\}+1$$

RESULTS

The study ended up with 53 eyes from 53 participants (female = 36) which included 3 groups healthy (N=20), OHT (N=13) and POAG (N=20). Mean age of participants was 62.40±10.132 years old. Mean IOP from three different measurements by 2 measurers were shown in Table 1. Intraclass correlation coefficients were calculated from first ten participants for both intra-examiner and inter-examiner as shown in Table 2. The excellent reliability was found according to ICC level ≥ 0.75 in all parameters.

As shown in Table 3, mean IOP was lowest in POAG group. This result was from a treatment that aimed for low target IOP in this group. OHT group had highest mean IOP which was consistent with a key feature of the disease and treatment was not aimed for as low as the IOP in POAG. GAT tended to yield higher IOP reading than Corvis in total participants and in each group. ICC in total participants reflected fair to excellent correlation between GAT and Corvis. However, in each group, POAG group had poor correlation as ICC level < 0.4 and ICC in OHT and healthy group were <0.4 as well if consider a lower bound of 95%CI.

Mean IOP difference result from GAT IOP was minus Corvis IOP which positive value means that GAT tends to give higher IOP than Corvis. Mean IOP differences were 1.8, 1.7, 1.4 and 2.2 mmHg in total, healthy, OHT and POAG respectively. POAG had highest mean difference and widest standard deviation which

TABLE 1. Mean IOP of GAT and Corvis by two measurers of first ten participants.

	GAT IOP (mmHg)		Corvis IOP (mmHg)	
	Measurer 1 mean ± SD	Measurer 2 mean ± SD	Measurer 1 mean ± SD	Measurer 2 mean ± SD
First time	14.81± 3.823	15.10± 4.795	12.41± 4.307	12.05± 4.995
Second time	14.63± 3.856	15.30± 4.218	11.99± 4.033	12.30± 5.321
Third time	14.40± 3.831	15.10± 4.067	11.93± 4.071	11.53± 4.309

TABLE 2. Intra-examiner and inter-examiner Intraclass correlation coefficients.

	Intra-examiner				Inter-examiner	
	GAT		Corvis		GAT	Corvis
	Measurer 1	Measurer 2	Measurer 1	Measurer 2		
ICC	0.954	0.977	0.920	0.927	0.928	0.915
95%CI	0.929-0.972	0.937-0.994	0.877-0.950	0.835-0.982	0.728-0.982	0.665-0.979

TABLE 3. The correlation between GAT and Corvis in IOP measurements.

Group	GAT (mmHg) Mean±SD	Corvis (mmHg) Mean±SD	GAT-Corvis (mmHg) Mean±SD	ICC (95%CI)
Total	13.93±3.849	12.15±4.030	1.78±2.944	0.793(0.520-0.899)
Healthy	12.91±3.393	11.22±3.191	1.69±2.371	0.797(0.353-0.927)
OHT	17.90±2.611	16.45±3.559	1.45±2.860	0.701(0.107-0.906)
POAG	12.11±2.984	9.96±2.620	2.15±3.675	0.207(-0.648-0.674)

Abbreviations: OHT=Ocular hypertension, POAG=Primary open angle glaucoma

may result from poor agreement between 2 machines. The value was scattered with no trend for which higher or lower average IOP will result in higher or lower difference between the two machines. From clinical point of view, 71.7% and 47.2% fall into IOP difference range of ±3 and ±2 mmHg respectively.

DISCUSSION

From the study, both Corvis and GAT demonstrated excellent repeatability and reproducibility by different examiners for IOP measurement. This is consistent with previous studies that IOP from Corvis is a parameter that showed excellent intra-examiner and inter-examiner reliability both in healthy and glaucoma eyes.[1-3]

Interestingly, there was no difference or tendency of IOP from the first to the third measurement (Table 1). That means repeated measurement with 5 minutes and 2 minutes gap for Corvis and GAT respectively was sufficient to lessen the IOP effect from previous measurements. There was no study about how long should the gap be, but air-puff technology as Corvis should take longer than an applanation for the effect of prior measurement to be vanished. The gap could be smaller, so a well-designed study will answer this question.

According to the results, IOP acquired from GAT tends to be higher than Corvis in all groups of participants. Hong et al.,[1] who enrolled healthy volunteers and glaucoma patients in their study to investigate an agreement between GAT and Corvis found the same bias, approximately 1.3 mmHg higher when acquiring IOP from GAT. From the study of Tejwani et al., GAT showed overestimated IOP from GAT when compared to other machines including Corvis.[7] However, there were some studies which reported higher IOP readings from Corvis when compared to GAT.[5,8] It is to be noted that this study, Hong et al. and Tejwani et al. studies had randomized an examination sequence. In contrast, Smedowski et al., use fixed examination sequence which could result in a bias from after-IOP measurement fluctuation.

Although, ±3 mmHg IOP difference seems to be acceptable, but for precise decision making in the clinic ±2 mmHg range is more reasonable. From Bland and Altman, only 47.2% of all participants fall in to ±2 mmHg range of IOP difference which indicated that Corvis and GAT could not be used interchangeably in the clinic. It is to be highlighted that POAG group demonstrated highest mean IOP difference and widest standard deviation. Keep in mind that this study used CCT-corrected IOP, assuming

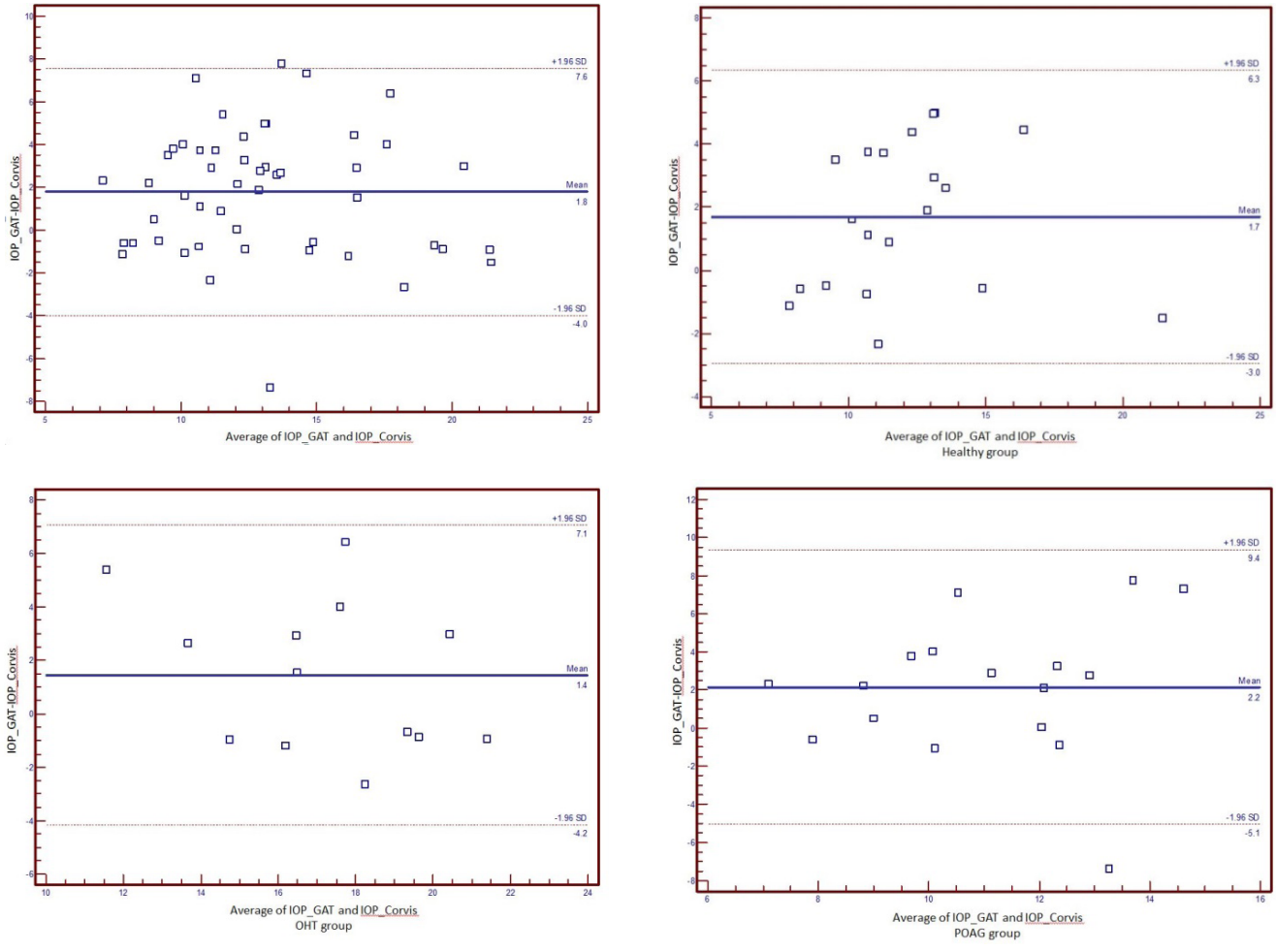


Fig 1. Bland-Altman plot, an agreement of IOP measurement between GAT and Corvis.

CCT effect should be minimal. Biomechanical corneal properties might be the reason, as POAG patients still using topical anti-glaucoma medications. Several studies showed that topical prostaglandin cause an effect on corneal biomechanical properties by increasing corneal hysteresis.[9-12] It could affect accuracy of IOP measurement including IOP fluctuation which finally resulted in more variation of IOP. Unfortunately, there is no study about the direct effect of long term usage of topical prostaglandin analogues on IOP measurement at this time.

The limitation of this study was a small sample size and corneal biomechanical properties were not taken into account. By the way this study's primary aim was to assess the clinical usefulness of the new machine, Corvis by comparing with GAT rather than to analyze factors that could affect IOP measurement.

In conclusion, Corvis-IOP is a good parameter with excellent level of reliability. In the clinic, the usefulness of Corvis-IOP is limited especially in POAG patients according to the poor agreement with gold standard GAT-IOP.

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REFERENCES

1. Hong J, Xu J, Wei A, Deng SX, Cui X, Yu X, et al. A new tonometer-the Corvis ST tonometer: clinical comparison with noncontact and Goldmann applanation tonometers. Invest Ophthalmol Vis Sci 2013;54:659-65.
2. Reznicek L, Muth D, Kampik A, Neubauer AS, Hirneiss C. Evaluation of a novel Scheimpflug-based non-contact tonometer in healthy subjects and patients with ocular hypertension and glaucoma. Br J Ophthalmol 2013;97:1410-4.
3. Salvetat ML, Zeppieri M, Tosoni C, Felletti M, Grasso L, Brusini P. Corneal Deformation Parameters Provided by the Corvis-ST Pachy-Tonometer in Healthy Subjects and Glaucoma Patients. J Glaucoma 2015;24:568-74.

4. Bañeros-Rojas P, Martinez de la Casa JM, Arribas-Pardo P, Berrozpe-Villabona C, Toro-Utrera P, García-Feijoó J. Comparison between Goldmann, Icare Pro and Corvis ST tonometry. Arch Soc Esp Oftalmol 2014;89:260-4. [Article in Spanish]
5. Smedowski A, Weglarz B, Tarnawska D, Kaarniranta K, Wylegala E. Comparison of three intraocular pressure measurement methods including biomechanical properties of the cornea. Invest Ophthalmol Vis Sci 2014;55:666-73.
6. Ang GS, Nicholas S, Wells AP. Poor utility of intraocular pressure correction formulae in individual glaucoma and glaucoma suspect patients. Clin Exp Ophthalmol 2011;39: 111-8.
7. Tejwani S, Dinakaran S, Joshi A, Shetty R, Roy AS. A cross-sectional study to compare intraocular pressure measurement by sequential use of Goldman applanation tonometry, dynamic contour tonometry, ocular response analyzer, and Corvis ST. Indian J Ophthalmol 2015;63:815-20.
8. Lanza M, Iaccarino S, Cennamo M, Irregolare C, Romano V, Carnevale UA. Comparison between Corvis and other tonometers in healthy eyes. Cont Lens Anterior Eye 2015;38:94-8.
9. Tsikripis P, Papaconstantinou D, Koutsandrea C, Apostolopoulos M, Georgalas I. The effect of prostaglandin analogs on the biomechanical properties and central thickness of the cornea of patients with open-angle glaucoma: a 3-year study on 108 eyes. Drug Des Devel Ther 2013;7:1149-56. .
10. Liehneová I, Karlovská S. The glaucoma pharmacological treatment and biomechanical properties of the cornea. Cesk Slov Oftalmol 2014;70:167-76. [Article in Czech]
11. Bolivar G, Sanchez-Barahona C, Teus M, Castejon MA, Paz-Moreno-Arrones J, Gutierrez-Ortiz C, et al. Effect of topical prostaglandin analogues on corneal hysteresis. Acta Ophthalmologica 2015;93:e495-8.
12. Wu N, Chen Y, Yu X, Li M, Wen W, Sun X. Changes in Corneal Biomechanical Properties after Long-Term Topical Prostaglandin Therapy. PloS One 2016;11:e0155527.

The Use of Dual Energy Computerized Tomography to Detect Residual Viable Hepatocellular Carcinoma after Transarterial Chemoembolization

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ABSTRACT

Objective: To determine the value of the dual energy computerized tomography (DECT) for detection of residual viable hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE).

Methods: Single-source (ss) DECT of liver was performed in adult patients who were diagnosed as HCC and treated with TACE at Siriraj Hospital during October 1st, 2013- December 31st, 2014. The diagnostic 5-point performance score of conventional liver CT imaging set (CCTI) and iodinated material density imaging set (IMDI) obtained simultaneously by using DECT, were evaluated by two radiologists. The follow up imaging at 6 months was regarded as gold standard. The sensitivity and specificity were calculated by assigned score 4 or 5 lesions as positive for the presence of HCC, assigned score 1 or 2 lesions as negative for viable tumor and assigned score 3 lesions as uncertain diagnosis. McNemar's test was used to compare the sensitivity and specificity between CCTI and IMDI. The reading time of both technique and radiation dose were recorded and the mean reading time were compared using a paired *t-test*.

Results: Out of total 21 patients with 66 lesions, 81% were male and 19% were female with mean age 61.8 ± 10.2 years old. After monitoring for 6 months, 35 of the total 66 lesions were still viable HCCs and 31 lesions became non-viable HCCs. CCTI had excellent inter-observer agreement while IMDI had moderate agreement (K = 0.931 and 0.534, respectively). The sensitivity of CCTI and IMDI for detection of viable tumor were 88.6% and 100%, respectively (p-value cannot be computed). The specificity of CCTI and IMDI were 96.8% and 93.5%, respectively (p-value = 1.000). The mean reading time of two radiologists for CCTI was 151.2 ± 134.7 seconds and 123.2 ± 126.8 seconds for IMDI (p-value = 0.048). Total radiation dose of dynamic liver CT was 1194.22 ± 179.44 mGy cm.

Conclusion: IMDI has higher sensitivity for detection of viable HCCs after TACE and consumes less reading time than CCTI.

Keywords: Dual energy CT; viable HCC; transarterial chemoembolization (Siriraj Med J 2019;71: 207-213)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of liver and is the second leading cause of cancer mortality worldwide.[1,2] There are more than 700,000 newly diagnosed cases each year and more than 600,000 deaths each year throughout the world in which the major risk factors are hepatitis C virus and hepatitis B virus infection.[3] The treatment of HCC depends on patient status, Child pugh score, number of tumors and tumor staging.

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Transarterial chemoembolization (TACE) is an effective palliative treatment for unresectable tumor which interrupts arterial blood supply by chemoembolic agent and results in ischemic tumor necrosis. Dynamic computed tomography (CT) or Magnetic Resonance Imaging (MRI) of the liver are commonly used for assessing tumor response after TACE. However, due to limitation of MRI availability in Thailand, most patients are followed up with CT modality.

Dual-energy imaging is a new development in CT which improves lesion detection and characterization. Using two different simultaneous energy settings in dual-energy CT (DECT), allows the differentiation of materials on the basis of their energy-related attenuation characteristics (material density). A single x-ray tube is used in single-source DECT (ssDECT) with the fast kVp switching between 80 kVp and 140 kVp to generate computed monochromatic images, which have less beam hardening, pseudo enhancement and provide a higher contrast-to-noise ratio than polychromatic images obtained by conventional CT.[4] The obtained data from DECT can be reconstructed to virtual unenhanced images as well as iodinated contrast material density images. Radiation dose savings are possible if virtual unenhanced images replace true unenhanced images.[5]

Detection of viable tumor around the ethiodized oil-laden lesions after TACE is usually difficult. Prior study found that the color-coded iodine CT imaging (CICT) generated by dual-detector DECT, is comparable to conventional liver CT protocol for detecting viable HCCs and can reduce mean radiation dose by 18.3% when omitting the unenhanced phase CT.[6]

The purpose of the present study is to determine the value of DECT to detect viable HCC after TACE by comparing two imaging sets of conventional liver CT (CCTI) and iodinated material density imaging (IMDI), obtained simultaneously by using DECT.

MATERIALS AND METHODS

Patient population

This study was a preliminary and prospective study that was approved by Siriraj Institutional Review Board (Si 546/2013). A total of 68 adult patients (age >18 years old) who had been diagnosed as HCC and treated with TACE in Siriraj Hospital during 1 October 2013 to 31 December 2014 were recruited and written informed consent was obtained. The patients with infiltrative or hypovascular HCC, those who were treated with combination therapy, no availability of follow up imaging, or loss to follow up were excluded from the study. Finally, 21 patients were included. Demographic and clinical data of patients were recorded including age, sex, AFP level, date and number of TACE treatments.

DECT scanning and post-processing

All included patients were followed up with liver CT imaging by using ssDECT scanner (Discovery CT750HD; GE Healthcare Technologies, Milwaukee, WI, USA) after TACE treatment about 4-6 weeks. DECT scan was performed only in arterial phase by using Gemstone Spectral Imaging (GSI) abdomen protocol number 3 with following scan protocol: detector coverage 40 mm., helical thickness 5.0 mm., pitch and speed 1.375:1 mm/rotation, rotation time 0.5 second, display FOV 35 cm., CTDI Vol 18.33 mGy. Reconstruction option (GSI ASiR 20%) and standard reconstruction type with slice thickness 1.25 mm. and interval 1.25 mm. were used.

Pre-contrast phase and portovenous phase were performed by using single energy CT of 120 kVp with following scan protocol: detector coverage 40 mm., pitch and speed 1.375:1 mm/rotation, rotation time 0.5 second, auto mA (min 200 mA, max 500 mA), noise index 20, and reconstruction 1.25 mm.

For iodine contrast medium adminstration, we used Iopamiro (370 mg Iodine/ml) with Medrad-XDS Stellant CT injection system (Bayer Healthcare LLC, Whippany, New Jersey, USA). Dose of contrast medium was 2 ml/kg. Flow rate and delayed scanning time for arterial phase was adjusted by patient body weight in order to obtain late arterial phase. Flow rate 3 cc/min and delayed time of 40 sec for patient body weight < 50 kg, flow rate 3.5 cc/min and delayed time of 38 sec for patient body weight 50-70 kg and flow rate 4 cc/min and delayed time of 35 sec for patient body weight >70 kg. Portovenous phase was obtained at a fixed delayed time at 80 seconds after contrast medium injection.

The computed monochromatic images at 70 keV were generated for arterial phase of CCTI at post-processing workstation. Then, the iodinated material density images were created by processing of the 70 keV computed monochromatic image using mono material density compare technique of GE workstation.

Data collection and interpretation

Two CT imaging sets were independently reviewed by two radiologists who had experience of 13 years for reader 1 and 5 years for reader 2. CCTI set included pre-contrast phase, arterial phase computed monochromatic image at 70 keV and portovenous phase. For IMDI set, post-processing iodinated material density images were

used for arterial phase. Two radiologists reviewed each imaging set at time interval about 8 weeks to exclude recognition bias.

The number of tumor, tumor size, and reading time of two radiologists for each imaging set, radiation dose and type of follow-up imaging were recorded. Five-point performance score was used to evaluate post TACE response.

Score 1: Dense iodized oil uptake with or without a thin marginal rim enhancement.

Score 2: Suggestive of a non-viable tumor with a mildly thickened, smooth marginal rim enhancement, but without nodular enhancement.

Score 3: Suspicious for viable tumor seen as equivocal nodular enhancement or an irregularly thickened marginal rim enhancement.

Score 4: Suggestive of viable tumor with more prominent abnormal findings

Score 5: Definite viable tumor

The discordant performance score for each imaging set was consensus by two radiologists and undetected lesion was rated as score 0.

To compare the diagnostic performance of both imaging sets, the present study used imaging follow up with hepatic angiogram, liver MRI or liver CT until 6 months as gold standard. A viable tumor was defined as hypervascularized and neovascularized tumor staining on hepatic angiogram, or a lesion that demonstrated arterial enhancement or portovenous washout on liver CT/MRI. Non-viable tumor was defined as lesion without hypervascularized and neovascularized staining on hepatic angiogram, or dense lipiodol staining lesion without arterial enhancement or portovenous washout on liver CT/ MRI.

Statistical analyses

Agreement between two radiologists for each imaging set were determined using weighted kappa (quadratic weight, K) which was classified as; K of 0.00-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80 and 0.81-1.00 for poor, fair, moderate, good and excellent agreement, respectively. To calculate the sensitivity and specificity for each modality, lesions assigned to score 4 or 5 were regarded as positive for the presence of HCC and lesions assigned to score 1 or 2 were regarded as negative for viable tumor. Lesions assigned to score 3 was regarded as uncertain diagnostic lesions. McNemar's test was used to compare the sensitivity and specificity between CCTI and IMDI. A paired *t-test* was applied to compare mean reading time between CCTI and IMDI. The radiation dose was reported using descriptive statistics. All statistical data analyses were performed using SPSS 18.0. P-value of less than 0.05 indicated a statistically significant difference.

RESULTS

A total of 21 patients, 17 patients (81%) were male and 4 patients (19%) were female with mean age 61.8 ± 10.2 years old (range 42-82 years). At the time of the TACE, the mean serum alfa-fetoprotein (AFP) level was about 165.9 ± 498.9 IU/ml (Max= 2248 and Min= 2.3 IU/ml). Episodes of TACE treatment were 1st time in 7 patients (33.3%), 2nd-4th times in 12 patients (57.1%) and ≥ 5th times in 2 patients (9.5%). Number of lesions treated with TACE was single lesion in 8 patients (38.0%), 2-5 lesions in 11 patients (52.4%) and > 5 lesions in 2 patients (9.6%). Mean duration of CT after TACE was about 6.57 ± 3.27 weeks. There were 66 lesions in these 21 patients. Tumor size ranged from 0.5-16.3 cm., mean 2.71 ± 2.97 SD.

At 6 months follow-up, 14 patients underwent conventional liver CT, 3 patients underwent hepatic angiogram with TACE, 3 patients underwent both of conventional liver CT and hepatic angiogram with TACE and only one patient underwent liver MRI with Primovist. There were 35 viable HCCs lesions and 31 non-viable HCCs lesions.

Table 1 showed diagnostic 5-point performance score of overall ethiodized oil-laden lesions and viable HCCs. The lesion detection rate of overall ethiodized oil-laden lesions and viable HCCs were excellent (97.1% - 100%) by both imaging sets. The inter-observer agreement between both radiologists for overall ethiodized oil-laden lesions were excellent. However, the inter-observer agreement for viable HCC lesions by CCTI was excellent (K = 0.931), but the inter-observer agreement by IMDI was moderate (K =0.534).

Table 2 showed diagnostic 5-point performance score of overall ethiodized oil-laden lesions of both imaging sets after consensus by two radiologists. The iodinated material density image detected more viable tumor (score 4 and 5, n=35 vs. n=31) but less uncertain diagnosis (score 3, n=2 vs. n=4) and non-viable tumor (score 1 and score 2, n= 29 vs. n= 30) than conventional CT image.

Of the total 35 viable HCC lesions, IMDI correctly defined as viable tumor in all lesions (score 4 and 5, n = 9 and 26; sensitivity = 100%) whereas CCTI defined as viable tumor in 31/35 lesions (score 4 and 5, n = 6 and 25; sensitivity = 88.6%). There was one missed viable tumor (Fig 1) and three uncertain diagnostic lesions (score 3) by CCTI (Fig 2). McNemar p-value cannot be computed to compare the sensitivity between IMDI and CCTI due

TABLE 1. Diagnostic 5-point performance score of overall ethiodized oil-laden lesions and viable HCCs.

Type of lesion	Imaging set		Score						Lesion detection rate	Weighted K value
			0	1	2	3	4	5		
Overall ethiodized oil-laden lesions (n=66)	CCTI	Reader 1	1	20	11	5	3	26	98.5%	0.968
		Reader 2	1	21	6	7	7	24	98.5%	
	IMDI	Reader 1	0	23	6	7	2	28	100%	0.942
		Reader 2	0	28	0	1	13	24	100%	
Viable HCCs (n=35)	CCTI	Reader 1	1	0	1	4	3	26	97.1%	0.931
		Reader 2	1	0	0	3	7	24	97.1%	
	IMDI	Reader 1	0	0	0	5	2	28	100%	0.534
		Reader 2	0	0	0	0	12	23	100%	

TABLE 2. Diagnostic 5-point performance score of overall ethiodized oil-laden lesions (n= 66) of both imaging sets after consensus by two radiologists.

	IMDI score						Total
CCTI score	0	1	2	3	4	5	
0	0	0	0	0	1	0	1
1	0	22	0	0	0	0	22
2	0	3	4	1	0	0	8
3	0	0	0	1	3	0	4
4	0	0	0	0	3	3	6
5	0	0	0	0	2	23	25
Total	0	25	4	2	9	26	66

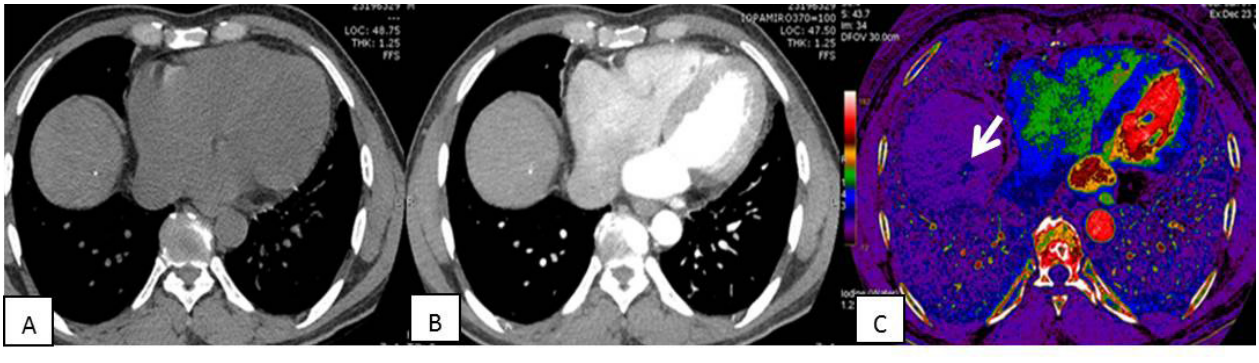


Fig 1. Demonstrated missed viable tumor by CCTI but could detected by IMDI.

A. Unenhanced CT image showed a tiny ethiodized oil-laden lesion near liver dome.

B. Arterial phase computed monochromatic image at 70 keV showed no definite arterial enhancement (score 0)

C. Arterial phase iodinated material density image showed nodular arterial enhancement (arrow) surrounding ethiodized oil-laden lesion (score 4).

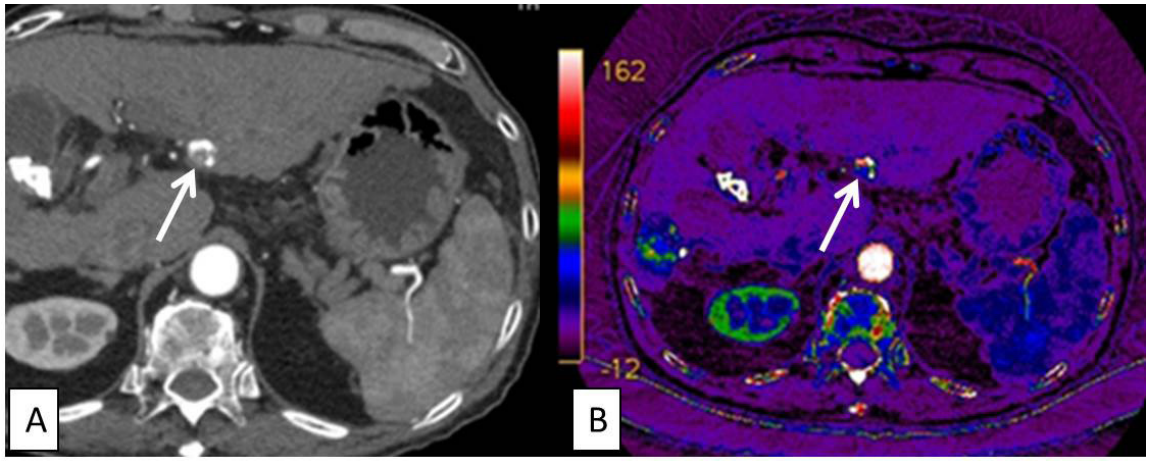


Fig 2. Demonstrated uncertain diagnostic lesion by CCTI but defined as viable tumor by IMDI.

A. Arterial phase computed monochromatic image at 70 keV showed a partial ethiodized oil-laden lesion with equivocal nodular enhancement (arrow); score 3.

B. Arterial phase iodinated material density image showed nodular arterial enhancement (arrow); score 4. Another viable HCC was also seen at hepatic segment VI (score 5).

to 100% sensitivity of IMDI. Among 31 non-viable HCC lesions, IMDI was defined as non-viable tumor in 29/31 lesions (score 1 and 2, n= 25 and 4; specificity=93.5%) and uncertain diagnosis (score 3) in 2/31 lesions. CCTI defined as non-viable tumor in 30/31 lesions (score 1 and 2, n= 22 and 8; specificity=96.8%). The remaining one case was defined as uncertain diagnosis (score 3). Fig 3 showed a non-viable HCC lesion which was defined as uncertain diagnosis (score 3) by both imaging sets. There was no statistically significant difference of the specificity between IMDI and CCTI (McNemar p-value = 1.000).

The overall mean reading time of two radiologists for CCTI was 151.2 ± 134.7 seconds and 123.2 ± 126.8 seconds for IMDI (p-value = 0.048).

Table 3 showed the mean radiation dose of dynamic liver CT. Mean total radiation dose was 1194.22 ± 179.44 mGycm. Mean value of the CTDI Vol were 12.17 ± 2.09 mGy, 13.33 mGy, and 12.17 ± 2.06 mGy for unenhanced, arterial and portovenous phases, respectively.

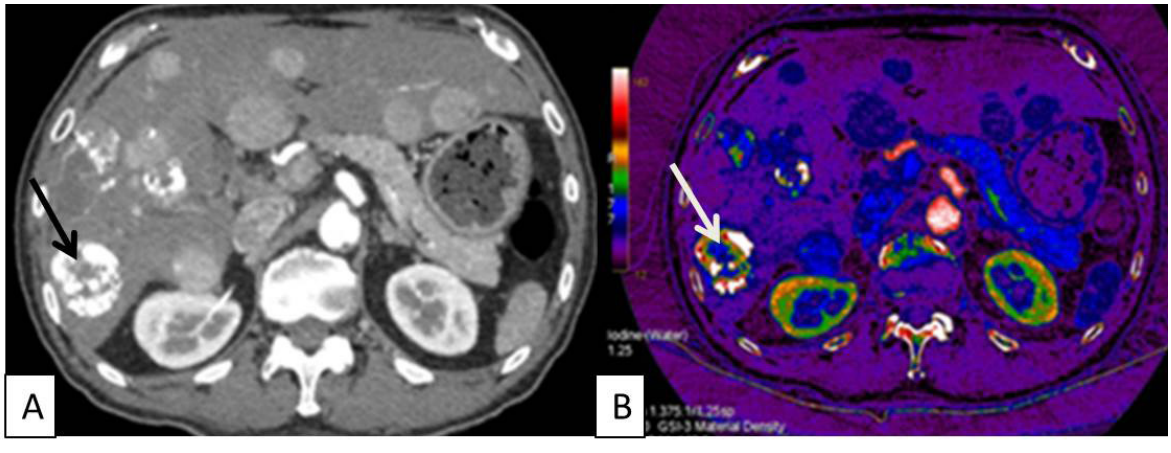


Fig 3. Demonstrated a non-viable HCC lesion which was defined as uncertain diagnosis (score 3) by both imaging sets.

A. Arterial phase computed monochromatic image at 70 keV showed a partial ethiodized oil-laden lesion with equivocal nodular enhancement (arrow) at central part of lesion.

B. Arterial phase iodinated material density image also showed equivocal nodular enhancement (arrow) at central part of lesion.

After 6 months follow-up, this lesion was confirmed a non-viable tumor. All of other remaining lesions seen on both imageswere correctly defined as viable tumors (score 5).

TABLE 3. Mean radiation dose of dynamic liver CT.

Phase	Mean ± SD	
	CTDI Vol (mGy)	DLP (mGy cm)
Unenhanced	12.17 ± 2.09	384.21 ± 79.49
Arterial	13.33	423.39 ± 33.76
Portovenous	12.17 ± 2.06	386.63 ± 77.46
Total DLP		1194.22 ± 179.44

DISCUSSION

Due to lack of MRI availability, conventional CT of liver is usually used to assess therapeutic response of HCC after TACE. However, it has only 43% accuracy, 36% sensitivity and 57% specificity for evaluation of tumor viability after TACE.[7] DECT has potential benefit to detect hypervascular hepatic lesions including HCC. Based on the fact that contrast material has higher attenuation at lower peak voltage[8], computed monochromatic images obtained from ssDECT at lower keV levels can provide greater conspicuity of hypervascular hepatic lesions with less noise than polychromatic images from conventional CT.[4] However, evaluation of viable HCC after TACE is usually difficult because ethiodized oil in the chemotherapeutic agent used in TACE contains iodine which can mimic focal hepatic enhancement on iodinated material density image.[4] Therefore, unenhanced images must be obtained and interpreted in conjunction with enhanced images.[9, 10]

The present study showed that IMDI had only moderate inter-observer agreement. This could be from both readers had little experience in IMDI. It would be better if the third radiologist with high experience was assigned to judge a discordant performance score. The reading time of IMDI was reduced by 28 seconds when compare with CCTI (p-value = 0.048). IMDI had sensitivity of 100% and specificity of 93.5% for detection of viable HCC after TACE while the sensitivity and the specificity of CCTI were 88.6% and 96.8%, respectively. Calculation of the sensitivity and the specificity was done by assigning the score 3 lesions as uncertain diagnosis. If the authors assigned the score 1 or 2 lesions as negative for viable tumor and lesions with score 3, 4, or 5 as positive for the presence of HCC, the sensitivity and the specificity of CCTI will be 97.1% and 96.8%, respectively while the sensitivity and the specificity of MDCI will remain unchanged. CCTI in the present study had much higher sensitivity and specificity than prior study[7] because it used computed monochromatic image at 70 keV during arterial phase instead of polychromatic images from conventional CT. The possible explanation of very high sensitivity and specificity in the present study could be that almost all of viable lesions (34/35 lesions) had area of ethiodized oil staining < 90%. This resulted in untroubled differentiation between viable tumor and ethiodized oil.

Radiation dose is a concerned issue of DECT. Radiation dose minimizing is possible if obviating unenhanced CT acquisition.[4,5] However, unenhanced CT is essential for assessing therapeutic response of HCC after TACE. The present study shown that mean value of the CTDI Vol of arterial phase obtained from ssDECT (13.33 mGy) was slightly higher than the CTDI Vol of unenhanced and portovenous phases performed by single energy CT (12.17 ± 2.09 mGy and 12.17 ± 2.06 mGy). Prior study tried to develop a method to discriminate viable HCC from ethiodized oil by limiting the window setting of the color-coded iodine map of DECT without unenhanced images.[6] Result showed that the color-coded iodine CT is comparable to conventional CT for detection of viable HCC after TACE, while it allows a reduction in radiation dose. However, the range of Hounsfield unit (HU) in viable HCC is partially overlapped with normal hepatic parenchyma. A further study is needed.

The present study had some limitations. First, it was a preliminary study with a small number of population. Second, the readers had little experience in interpretation of the material density images and there was only moderate inter-observer agreement between both readers. It is required to have more experience in the interpretation skill of DECT images. Third, there was no pathological confirm of viable HCC.

CONCLUSION

IMDI has higher sensitivity for detection of viable HCCs after TACE with less consumed reading time than CCTI. DECT including unenhanced and enhanced acquisitions has high sensitivity and specificity to detect viable HCC after TACE with slightly higher radiation dose than conventional liver CT. Further research is needed to develop a method for radiation dose reduction.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485-91.
3. Shariff MI, Cox IJ, Gomaa AI, Khan SA, Gedroyc W, Taylor-Robinson SD. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis and therapeutics. Expert Rev Gastroenterol Hepatol 2009;3:353-67.
4. Silva AC, Morse BG, Hara AK, Paden RG, Hongo N, Pavlicek W. Dual energy (Spectral) CT: applications in abdominal imaging. Radio Graphics 2011;31:1031-46.
5. Ho LM, Yoshizumi TT, Hurwitz LM, Nelson RC, Marin D, Toncheva G, et al. Dual energy versus single energy MDCT: measurement of radiation dose using adult abdominal imaging protocols. Acad Radiol 2009;16:1400-7.
6. Lee JA, Jeong WK, Kim Y, Song SY, Kim J, Heo JN, et al. Dual-energy CT to detect recurrent HCC after TACE: initial experience of color-code iodine CT image. Eur J Radiol 2013;82:569-76.
7. Hunt SJ, Yu W, Weintraub J, Prince MR, Kothary N. Radiologic monitoring of hepatocellular carcinoma tumor viability after transhepatic arterial chemoembolization: estimating the accuracy of contrast-enhanced cross-sectional imaging with histopathologic correlation. J Vasc Interv Radiol 2009;20:30-8.
8. Yeh BM, Shepherd JA, Wang ZJ, Teh HS, Hartman RP, Prevrhal S. Dual energy and low-kVp CT in the abdomen. AJR Am J Roentgenol 2009;193:47-54.
9. Kim HC, Kim AY, Han JK, Chung JW, Lee JY, Park JH. Hepatic arterial and portal venous phase helical CT in patients treated with transcatheter arterial chemoembolization for hepatocellular carcinoma: added value of unenhanced images. Radiology 2002;225:773-80.
10. Kim SH, Lee WJ, Lim HK, Lim JH. Prediction of viable tumor in hepatocellular carcinoma treated with transcatheter arterial chemoembolization: usefulness of attenuation value measurement at quadruple-phase helical computed tomography. J Comput Assist Tomogr 2007;31:198-203.

The Effects of the Thai Traditional Medicine of Abdominal Massage on Defecation in Post Lumbar Laminectomy Patients

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ABSTRACT

Objective: This prospective study examined the defecation enhancement effects in post-lumbar laminectomy patients who received Thai traditional medicine of abdominal massage (TTMAM) in combination with standard nursing care, compared with patients receiving only standard nursing care.

Methods: This prospective, randomized, controlled trial was conducted at Siriraj Hospital between 2011 and 2015. Eighty-eight patients with spinal stenosis scheduled for lumbar laminectomy with or without fusion were enrolled. The patients were randomly assigned to two groups: the first group underwent standard nursing care combined with TTMAM (the TTMAM group), and the second group underwent standard nursing care (the non-TTMAM group). The clinical outcomes regarding the first defecation within 3 days after surgery, abdominal distension, and patient satisfaction with defecation care were evaluated.

Results: When comparing the first defecation within 3 days after surgery, no significant differences were found in the number of patients between the two groups. The number of the patients who had their first defecation within 3 days after surgery was higher in the TTMAM group (46.5%) than the non-TTMAM group (27.3%). There was significantly less abdominal distension on the third day after surgery in the TTMAM group than in the non-TTMAM group. Moreover, the mean score of patient satisfaction of the TTMAM group was higher than that of the non-TTMAM group.

Conclusion: Thai traditional medicine of abdominal massage tends to help defecation in post-lumbar laminectomy patients as it relieves abdominal distension and increases satisfaction with defecation care. Therefore, the use of TTMAM with other bowel care methods could provide additional benefit for lumbar laminectomy patients.

Keywords: Thai traditional medicine of abdominal massage; defecation; post lumbar laminectomy patient (Siriraj Med J 2019;71: 214-219)

INTRODUCTION

Lumbar laminectomy is a surgical procedure to enlarge the spinal canal and relieve pressure on the spinal cord or nerve roots caused by spinal stenosis.[1] Constipation is a common problem for many people recovering from back surgery.[2,3] Phataranavic et al. suggested that 9% of postoperative orthopedic patients have constipation.[4] Even though constipation is not life-threatening, the absence of any treatment may cause discomfort, abdominal distention, abdominal pain, and the loss of appetite, with the possibility of fever, vomiting, and delirium.[5,6,7]

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The use of the common constipation treatments (stool softeners, laxatives, and enemas) sometimes leads to harmful side-effects like abdominal distention, nausea, fluid and electrolyte loss, and defecation-reflex loss, particularly with patients with chronic diseases.[8] There have been studies on constipation prevention programs that have utilized high fiber foods and the drinking of water.[9,10] However, such programs require careful administration in the case of elderly patients with heart, lung, or kidney diseases in order to avoid water and electrolyte imbalances.[11]

The use of complementary approaches like abdominal massage to relieve constipation has been suggested since the 19th century.[12] Several studies on patients with spinal injuries found that abdominal massage reduced the colonic transit time and abdominal distention, increased the frequency of defecation, and improved continence.[13,14,15]

The Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University has much experience with the administration of a range of traditional healing approaches. The Thai traditional medicine of abdominal massage (TTMAM) is one of the treatments which is normally administered to patients with constipation, most of whom had improved defecation as a result. However, to our knowledge, there is no data or research available relating to the effects of TTMAM on defecation in post lumbar laminectomy patients. The present study was designed to examine the effects of TTMAM in post lumbar laminectomy patients in terms of defecation.

MATERIALS AND METHODS

This single-center, prospective, randomized, controlled trial was conducted during the 2011 to 2015 study period. The Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, approved the study protocol (Si. 095/2011). The enrolled subjects were spinal stenosis patients who were scheduled to undergo a decompressive laminectomy with or without fusion. Patients were excluded if they had any of the following conditions: abdominal aortic aneurysm; aortic dissection; palpable pulsatile intra-abdominal mass; previous abdominal surgery; preexisting medical diseases which could interfere with defecation, such as hypothyroidism, delirium, and stroke; or the need to be placed in the ICU post-operatively.

Patients were randomized into two groups (44 patients per group) using simple randomization. The control group (non-TTMAM) consisted of patients who received standard nursing care only. The intervention group (the TTMAM group) was comprised of patients who were provided with the TTMAM in addition to standard nursing care. After being provided with verbal and written information regarding the procedure, 88 patients were accepted to participate in this study. Written informed consent was obtained from all 88 participants.

Postoperatively, the non-TTMAM group received standard nursing care. This consisted of a deep breathing exercise every 4 hours, and at least 100 times per day; turning the patients every 2 hours; an ankle pumping exercise at least 100 times per day; and the drinking of at least 1,000 cc of water per day.

By comparison, the TTMAM group received standard nursing care combined with the TTMAM on Days 1 to 3 postoperatively; twenty minutes of the TTMAM was performed two hours after dinner. The TTMAM was conducted by certified, applied-Thai traditional medicine therapists from the Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital. The TTMAM maneuver is described in Fig 1.

The clinical outcomes that were evaluated comprised the first defecation within 3 days after surgery and the abdominal symptoms after surgery. The latter were assessed daily using the abdominal distention evaluation form (modified from Wattanawetch[16]); belching, flatus excretion, the perception of fullness, bowel sounds, and increases in abdominal girth were examined. Patient satisfaction was evaluated by the level of satisfaction with defecation care, which was determined by questionnaires administered on the fourth day after surgery.

Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows, version 18. A chi-square test was used to compare the number of participants in the two groups who first defecated within 3 days after surgery, and the degree of abdominal distention experienced by the experimental and control groups. An independent t-test was used to compare the level of satisfaction with the defecation care reported by patients in the two groups. A p-value of 0.05 or less was considered statistically significant.

RESULTS

The forty-four patients in the TTMAM group consisted of thirty females and fourteen males, with an average age of 62.8 years. The forty-four patients in the non-TTMAM group, comprised of thirty-five females and nine males, had an average age of 63.8 years. The demographic data are shown in Table 1. All patients

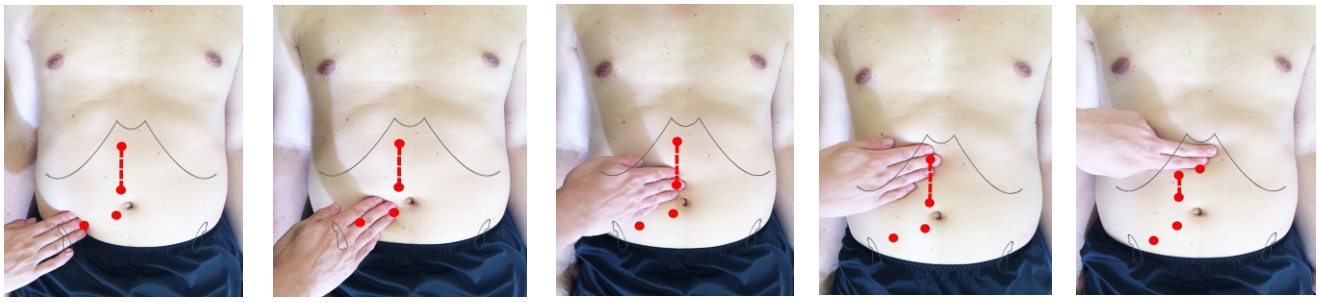


Fig 1A split motion

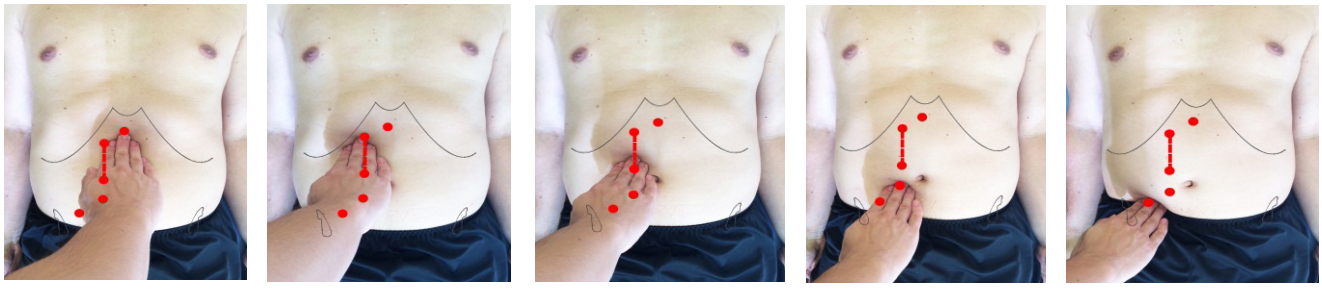


Fig 1B pressing motion



Fig 1C scooping motion

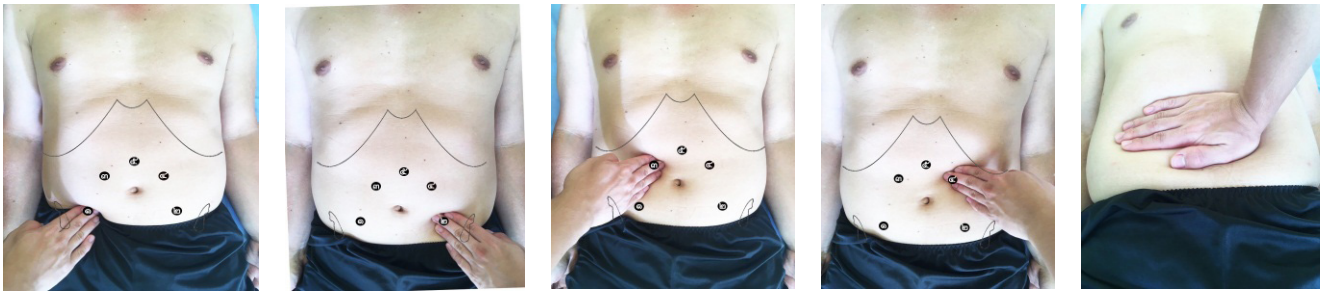


Fig 1D massage important abdominal points

Fig 1. The Thai traditional medicine abdominal massage maneuver. The subject is placed in a supine position. The massage therapist stands beside the subject and uses the thumb, finger tips and hand to massage along the muscles via 4 motions; the split motion (1A); the pressing motion (1B); the scooping motion (1C); and the soft massage of 5 important abdominal points, to about 70% of the maximum weight (1D).

completed the study protocol. There were no statistically significant differences between the two groups, and no complications were found in either group.

When comparing the number of patients with a first defecation within 3 days after surgery, no significant differences were found in the figures for the two groups. However, the number was higher for the TTMAM group (n = 20, 46.5%) than for the non-TTMAM group (n = 12, 27.3%; p = 0.063).

On the other hand, there was a significant difference between the intervention and control groups in terms of the degree of abdominal distention and abdominal discomfort on the third day after surgery (Table 2). In addition, there was a statistically significant difference in the mean scores for satisfaction with the defecation care reported by the patients in the two groups (Table 3).

TABLE 1. Baseline characteristics of 88 patients with spinal stenosis who randomly received standard nursing care (non-TTMAM group) versus TTMAM in addition to standard nursing care (TTMAM group).

	Non-TTMAM Group (n = 44)	TTMAM Group (n = 44)
Gender (male: female)	9:35 (20.5%:79.5%)	14:30 (31.8%:68.2%)
Age (years)	63.8	62.8
Laminectomy	14(31.8%)	24(54.5%)
Laminectomy with fusion	30(68.2%)	20(45.5%)
Volumes of drinking water		
1st day after surgery (mL)	1278.6±470.2	1254.3±504.3
2nd day after surgery (mL)	1351.6±496.3	1277.1±462.6
3rd day after surgery (mL)	1305.4±475.3	1381.1±496.0
Morphine	34(77.2%)	30(68.2%)

Abbreviation: TTMAM = Thai traditional medicine of abdominal massage

TABLE 2. Comparison of the number and percentage of patients with abdominal distention and of the level of abdominal distention on the 3rd day after surgery in the control and experimental groups.

	Non-TTMAM Group (n = 44)	TTMAM Group (n = 44)	P-value
Belching / 4 hours			0.70
No belching	12 (27.3%)	16 (36.4%)	
1-10 times	30 (68.1%)	27 (61.3%)	
> 11 times	2 (4.5%)	1 (2.3%)	
Flatus excretion			0.92
No flatus excretion	1 (2.3%)	1 (2.3%)	
1-6 times	34 (77.3%)	33 (75.0%)	
≥ 7 times	9 (20.5%)	10 (22.7%)	
Perception of fullness			0.04*
Severe	1 (2.3%)	1 (2.3%)	
Moderate	29 (65.9%)	16 (36.4%)	
Mild	14 (31.8%)	27 (61.4%)	
Bowel sounds			0.66
< 3 times / minute	7 (15.9%)	5 (11.4%)	
> 3 times / minute	37 (84.1%)	39 (88.6%)	
Increased abdominal girth			0.41
> 3.9 centimeters	16 (36.4%)	11 (25.0%)	
< 3.9 centimeters	28 (63.6%)	33 (75.1%)	
Degree of abdominal distention			0 .01*
Mild	10 (22.7%)	21 (47.7%)	
Moderate	34 (77.3%)	21 (47.7%)	
Severe	0 (0.0%)	2 (4.5%)	

* = statistical significance level of ≤0.05
Abbreviation: TTMAM = Thai traditional medicine of abdominal massage

TABLE 3. Comparison of the mean scores for patient satisfaction with defecation care for the non-TTMAM and TTMAM groups.

	Non-TTMAM Group (n = 44)	TTMAM Group (n = 44)	P-value
Satisfaction score	2.34 ± 1.92	4.09 ± .86	< 0.001***

*** = statistical significance level of ≤0.001
Abbreviation: TTMAM = Thai traditional medicine of abdominal massage

DISCUSSION

This study found that constipation, defined as a first defecation later than 3 days after surgery, is a common problem among lumbar laminectomy patients (72.7% in the standard nursing care, or non-TTMAM, group). Pain after surgery encourages patients to remain in bed after surgery, which causes the sympathetic nervous system to become dominant. In turn, this inhibits the bowel functions, slows bowel movements, affects digestion, causes poor absorption, and promotes abdominal distention and constipation.[6] Moreover, pain after surgery is often treated with opioids, such as morphine, thereby reducing the patient's bowel movements.[3]

The results of the present study on the number of defecations within the first 3 days after surgery found that there was no statistically significant difference between the group that received the TTMAM and the group that received standard bowel care. Even though previous studies have reported that the use of the TTMAM has enhanced defecation, most of those studies were done on spinal injury patients who had chronic constipation.[13,14] On the other hand, the patients in the present study were in a different situation because of their recent spinal surgery; they had limited mobility and acute pain, which led to an acute change in the habit of constipation rather than to the chronic constipation reported in the aforementioned studies that had enrolled chronic spinal cord injury patients.

With regard to abdominal distention on the third day after surgery, the present study demonstrated that the group that had received TTMAM had less severe abdominal distention than the group that had only been treated with standard nursing care, with statistical significance. This finding is in line with a study on the effects of abdominal massage on the gastrointestinal function in patients with spinal injuries[13]; it found that abdominal massage improved bowel movements, reduced the colonic transit time, and reduced abdominal distention, as massaging increases pressure in the abdomen. Massaging also stimulates the somato-autonomic reflexes, which in turn reduce the colonic transit time.[14] Furthermore, abdominal massage stimulates the parasympathetic system, which is responsible for the stomach and the intestinal functions, thereby reducing abdominal distention.[17]

The analysis of the level of patient satisfaction with defecation care revealed that the group receiving the TTMAM were more satisfied than the group given standard nursing care, with statistical significance. An earlier study of the effects of Swedish abdominal massage on constipation found that patients felt satisfied and safe while the massage was being given.[18] Another study on the effects of the TTMAM together with a soap rectal suppository on spinal injury patients determined that none rejected the massage, they felt relaxed during the abdominal massage, and there were no feelings of distention or discomfort.[15] After the TTMAM, those subjects were able to pass flatus for longer durations, had less abdominal distention and no nausea, and were able to defecate more easily. These findings can be explained by the fact that abdominal massage is a type of touch that is meaningful and stimulates a profound feeling. Massage inhibits the hypothalamic function, which works with the autonomic system to stimulate the secretion of norepinephrine and acetylcholine in the sympathetic and parasympathetic systems. Norepinephrine has a positive effect on a person's mood. In addition, massage reduces the function of the sympathetic system and stimulates the parasympathetic system, which causes relaxation.[18,19]

The limitations of this study are related to uncontrollable factors, such as the amount of high-fiber food eaten, the degree of patient mobility, and the level of stress arising from the surgery. Bowel movements and abdominal pressure were not measured. Moreover, the volume and consistency of the feces were not evaluated.

CONCLUSION

The Thai traditional medicine of abdominal massage tends to help post-laminectomy patients to defecate. Furthermore, this procedure reduces abdominal distention and increases patient satisfaction. It should therefore be employed with other defecation stimulation methods.

REFERENCES

1. Chiengthong K, Bunmaprasert T. Degenerative disease of the spine. Chiang Mai: Faculty of Medicine, Chiang Mai University; 2007. (In Thai)
2. Pamela E. Verkuilen. Preventing Constipation After Back Surgery. (Internet). 2007 (Cited 2017 July 22). Available from: http://www.spine-health.com/treatment.
3. Cassinelli EH, Eubanks J, Vogt M, Furey C, Yoo J, Bohlman HH. Risk factors for the development of perioperative complications in elderly patients undergoing lumbar decompression and arthrodesis for spinal stenosis. Spine J. 2007;32:230-35.
4. Phataranavic P, Okmaen R, Kuntisomboon S. A study of symptom disturbances and postoperative complications in orthopaedic patients. Journal of Orthopaedic Nursing. 2005;10: 85-99. (In Thai.)
5. Eberhardie C. Constipation: Identifying the problem. Nurs Older People. 2003;15:22-6.
6. Khumtaveeporn P. Pathophysiology of movement. In: Unnapirak L, editor. Pathophysiology in nursing. 8th ed. Bangkok: Boonsiri; 2009. p.170-98. (In Thai)
7. Norton C. Constipation in older patients: Effects on quality of life. Br J Nurs. 2006; 15:188-92.
8. Tack J, Muller-Lissner S. Review Treatment of Chronic Constipation: current Pharmacologic approaches and future direction. Clin Gastroenterol Hepato. 2009;7:502–8.
9. Stumm RE, Thomas MS, Coombes J, Greenhill J, Hay J. Managing Constipation in Elderly orthopaedic patients using either pear juice or a high fiber supplement. Aust J Nutr Diet. 2001;58: 181-5.
10. Monmai P. The effectiveness of a constipation prevention program for hospitalized elderly with hip surgery [master's thesis]. Bangkok: Mahidol University; 2009.p.154 (In Thai)
11. Hinrichs M, Huseboe J. Research-based protocol management of constipation. J Geronto Nurs. 2001;27:17-28.
12. Thai massage restoration project. The manual of Thai massage in primary health care. Bangkok: Ruenkaew; 1992. (In Thai)
13. Lämås K, Lindholm L, Stenlund H, Engström B, Jacobsson C. Effects of abdominal massage in management of constipation—A randomized controlled trial. Int J Nurs Stud. 2009;46:759-67.
14. Ayas S, Leblebici B, Sozay S, Bayramoglu M, Niron EA. The effect of abdominal massage on bowel function in patients with spinal cord injury. Am J Phys Med Rehabil. 2006;85:951-5.
15. Vatthakavarn P. Effectiveness of abdominal massage combined with soap rectal suppository on stimulating bowel movement in spinal cord injury patients [master's thesis]. Khon Kaen: Khon Kaen University; 2002.p.75 (In Thai)
16. Wattanawech T. The influence of selected factors and self-care behavior on abdominal distention in patients with abdominal surgery (master's thesis). Bangkok: Mahidol University; 2002. p.124 (In Thai)
17. Diego MA, Field T. Moderate pressure massage elicits a parasympathetic nervous system response. Int J Neurosci. 2009;119:630-8.
18. Lamas K, Graneheim UH, Jacobsson C. Experiences of abdominal massage for constipation. J Clin Nurs; 2012;21:757-65.
19. Boonsawat W. Effects of Thai traditional massage on pain reduction in cancer patients [master's thesis]. Songkla: Prince of Songkla University; 2005.p.173 (In Thai)

Prevalence and Factors Associated with Abnormal Cervical Cell among the Hmong and Mien Hill Tribe Women in Pha Yao Province, Thailand

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ABSTRACT

Objective: To estimate the prevalence and to determine factor associated with abnormal cervical cell among the Hmong and Mien hill tribe women.

Methods: A cross-sectional study aimed to estimate the prevalence and to determine the factors associated with abnormal cervical cell among the Hmong and Mien hill tribe women living in Pha Yao province, Thailand was conducted. The data from validated questionnaires and Papanicolaou (Pap) smear test results were collected. Logistic regression was used to detect the associations between variables and abnormal cervical cell at the significant level of alpha = 0.05.

Results: Totally, 450 Hmong and Mien women were recruited into the analysis. The overall prevalence of abnormal cervical cell was 2.2%; 1.2% were atypical squamous cells of undetermined significance (ASC-US), 0.4% were atypical squamous cells-cannot exclude HSIL (ASC-H), 0.4% were cervical intraepithelium neoplasia-I (CIN-I) and 0.2% were cervical intraepithelium neoplasia-II (CIN-II). Two variables, the number of their sexual partners and the number of husbands' sexual partners, were significantly associated with abnormal cervical cell. The women who had ≥ 4 sexual partners had a 7.09 times (95%CI=1.85-27.17) more likely to have abnormal cervical cell than those who had < 4 sexual partners. The women whose husbands had ≥ 4 partners had a 5.63 times (95%CI=1.51-20.90) more likely to have abnormal cervical cell than those whose husbands had < 4 sexual partners.

Conclusion: The number of sexual partners is significantly associated with abnormal cervical cell among the Hmong and Mien hill tribe women. Health interventions regarding safe sex should be promoted in the hill tribe people.

Keywords: Abnormal cervical cell; Hmong; Mien; hill tribe; prevalence (Siriraj Med J 2019;71: 220-227)

INTRODUCTION

Cancer is a major threat to human life in worldwide. In 2015, there were 17.5 million cases worldwide and 8.7 million deaths.[1] This number is expected to increase to 24 million by 2035.[2] Cervical cancer is the significant leading cause of death globally in women including Thailand.[3] The human papillomavirus (HPV) is the cause of cervical cancer which involved sexual behavior.[4-6] Consequently, personal suffering and economic loss are the major impacts to an individual health and family.

In 2016, the Ministry of Public Health reported that cervical cancer was ranked the second overall cause of death in women in Thailand with the prevalence at 608/100,000 population.[7] The northern region of Thailand reported the highest prevalence and accounted for 12.1% of all female cancer. The average age-standardized incidence

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rate (ASR) was 17.0 per 100,000.[8] In 2016, Pha Yao province was ranked second followed by Chiang Rai province with the ASR at 25.0/100,000 pop which was higher than the average ASR of northern Thailand.[9] Besides, the trend of cervical cancer is rising yearly, and it has become a significant health problem in Pha Yao province.[10] However, only 55.9% of women aged 30-60 were screened for cervical cancer by a Pap smear test, and less than 20.0% among the hill tribe women in 2015.[11]

A number of the hill tribe people live in Pha Yao province which is located in northern Thailand. Most hill tribe people living in Pha Yao province are Hmong and Mien.[12] These two tribes have their own culture, and lifestyles including sexual behaviors.[13] Most Hmong and Mien men and women have their first sexual intercourse at young age, and get married at early age as well.[14] Moreover, these tribes have a unique culture of polygamy.[15] Regarding their economic status, they are living under the poverty line of Thailand.[16] Hmong and Mien women did not favor a regular Pap smear test.[17] Therefore, a few data are available on cervical cancer among the hill tribe population particularly the Hmong and Mein women. This study aimed to assess the prevalence and to determine the factors associated with cervical cancer among the Hmong and Mien women. The data could be used to develop public health policy and also health promotion intervention in the area.

MATERIALS AND METHODS

Study design

A cross sectional study was used to assess the prevalence and to determine the factors associated with abnormal cervical cell among the Hmong and Mien women.

Study setting

The study was conducted in 13 Hmong and Mien villages in Pong, and Chiang Kham districts, Pha Yao province. Seven villages were selected from Pong district; Ban Pang Kha, Ban Pang Ma-O, Ban Sip Song Pattana, Ban Kun Kam Lang, Ban San Ti Suk, Ban Saeng Sai, and Ban Hwauy Khok Moo villages. Another 6 villages were selected from Chiang Kham district; Ban Mai Rom Yen, Ban Pra Cha Pak Dee, Ban Hwauy Poom, Ban Pra Cha Pattana, Ban Roung San, and Ban Hwauy Diar Doi Nang villages.

Study population

Hmong and Mien women aged 30-60 years old and their husbands who lived in the study settings were the study population.

Inclusion criteria

a) Those that self-identified as Hmong or Mien tribe women, b) aged between 30 and 60 years old, c) married, d) lived in the study area for at least 1 year.

Exclusion criteria

a) Those that could not provide essential information due to any causes such as ability to communicate in Thai, b) women who had a period at the date of Pap smear test, c) women who were pregnant.

Study sample and sample size calculation

Hmong and Mein women aged 30-60 and their husbands were the target population. In 2016, there were 2,038 couples living in the 13 villages.[8] The sample size was calculated by the following formula[19];

$$n=(Z^2\ P(1-P))/d^2$$

At the confidence level 95%, d = 0.05, P=12.2%[14], at least 405 samples were required. Adding for any errors during the study for 10.0%, then, 450 samples were needed for the analysis.

Research instruments

A validated questionnaire and Pap smear test were used for data collection in the study. There were 5 parts in the questionnaire. Part I asking about the general information which consisted of five questions; age, tribe, education, religion, income, etc. Part II consisted of six questions regarding the risk factors such as what age they got married, number of partners, history of sexually transmitted infections (STIs), history of Pap screening test previous year, etc. Part III consisted of four questions, asking about risk behaviors of husband such as number of partners, history of STIs, etc. Part IV consisted of six questions regarding health behaviors such as smoking, alcohol drinking, etc. Part V consisted of thirty short questions regarding knowledge, attitude, and practice for cervical cancer prevention.

Questionnaire was developed from the literature review and consulting with experts in relevant fields. Questionnaire was tested for validity by Index of Item Congruence (IOC) method which was assessed by three external experts. Questions that resulted in IOC score of less than 0.5 were excluded. After that, a pilot test was done with 30 participants with similar characteristics with the study sample. The purposes of the pilot test were to determine the reliability, feasibility, and possibility of collecting the data from the participants. Questions in part V were tested for reliability from the pilot test using Cronbach's alpha. Questions that had Cronbach's alpha less than 0.5 were deleted due to less reliability.

Resulting, the overall Cronbach's alpha was 0.76. Moreover, Kuder-Richardson (KR)[20] was used to detect the quality of questions regarding the knowledge. The overall KR score was 0.71.

Pap smear (The Bethesda 2001 Cytology Report) was used to collect the specimen. The process of collecting the specimen was done by two trained nurses. All specimens were sent to Chiang Kham, which has the only standard institute with medical laboratory in Pha Yao province for detection the cervical cancer. Abnormal cervical cell was defined according to the Bethesda system 2001 as; atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude high grade squamous intraepithelial lesion (ASC-H), low grade squamous intraepithelial lesion (LSIL) encompassing human papillomavirus change/cervical intraepithelial neoplasia I (CIN I), high grade squamous intraepithelial lesion (HSIL) encompassing cervical intraepithelial neoplasia II (CIN II)/ cervical intraepithelial neoplasia III (CIN III)/with feature suspicious for invasive, squamous cell carcinoma, atypical glandular cell, atypical glandular cells favor neoplasia, endocervical adenocarcinoma in situ, adenocarcinoma endocervical cells/endometrials, other malignants.

Data collection procedures

After getting the ethical approval from the Human Research Committee from Mae Fah Luang University, Pha Yao Public Health Office was contacted to request their approval to conduct the study and also information regarding the hill tribe villages in Pha Yao province including the contact number of all health promoting hospitals in the study area. Four health promoting hospitals located at the hill tribe villages were contacted; Pang Kha, Khun Kwaun, Hwauy Khok Mhoo and Rom Yen health promoting hospitals. Two trained nurses on Pap smear technique were contacted for to help in collecting specimen. A one-day training course was provided for two trained nurses and all health promoting hospitals staff regarding research objectives and procedures.

All targeted village leaders were contacted and asked for their cooperation to conduct the study. Lists of women who met the inclusion criteria were sent to the researcher who was supported by the village headman. A simple random sampling was used to select the study samples. Appointments were made with all the selected samples at the health promoting hospitals close to their resident.

On the day of collecting data, all the participants and their husbands were provided the essential information and the researcher obtained the informed consent form from both of them before interview. The interviews were done separately in a private and confidential room. Each interview lasted for 20 minutes for woman, and 10 minutes for husband. After the interview, a trained nurse collected specimen from the women.

Statistical analysis

Data were coded and double-entered into Microsoft Excel 2010. The analysis was conducted by using SPSS (version 20; IBM, Armonk, NY). Descriptive statistics was used to explain the characteristics of the participants; percentage, mean, SD. Logistic regression was used to detect the associations between variables and abnormal cervical cell as an outcome at the significant level α=0.05. All independent variables were detected the association with the outcome in simple logistic regression model. Afterward, all significant variables in simple logistic regression model were considered to put into the multivariate analysis by using "ENTER" mode. Variables remaining a significant association with the outcome, were determined as factors association with abnormal cervical cell in the final model.

Ethical considerations

The study was approved by the Ethics Committee for Human Research, Mae Fah Laung University, Chiang Rai, Thailand (No.REH-60022). All information was kept in the private and secured code only the researcher could access. After the analysis was complete, data were deleted including the questionnaire and laboratory results. A small gift was given to all participants to appreciate their cooperation. The laboratory results were sent to all participants with the guideline for future medical care required particularly those who were abnormal.

RESULTS

Characteristics of women

A total of 450 women were recruited into the analysis. More than half were Hmong (63.6%), average age was 45 (SD=8), and majority were aged 51-60 years (36.2%). Most participants graduated primary school (50.0%), worked as farmers (77.3%), and had monthly income ≤ 3,000 Bath (55.3%). Most participants had free access to health care. More than half had their first sexual intercourse while aged < 18 years (53.8%), and married while aged < 18 years (52.4%). Almost all the participants had < 4 sexual partners (90.0%), and only 17.5% were screened for cervical cancer previous year. A few of the participants had congenital problem; 13.3% had yellow or green or offensive odour leucorrhoea, and 8.9% had a history of genital ulcer. Regarding health behaviors;

44.0% smoked, and 37.3% drank alcohol. Regarding the knowledge, attitude, and practice on cervical cancer prevention; 46.4% had low level of knowledge, 28.0% had negative, neutral or positive attitude towards cervical cancer prevention, and 26.4% had incorrect practice of cervical cancer prevention, respectively (Table 1).

Characteristics of husband

Majority had < 4 partners (76.9%), none of them had a genital discharge. A few of them had a history of genital ulcer (3.3%), and some of them had experience of having sexual intercourse with sex workers (11.6%) (Table 2).

The overall prevalence of abnormal cervical cell was 2.2%; 1.2% were atypical squamous cells of undetermined significance (ASC-US), 0.4% were atypical squamous cells and cannot exclude high grade squamous intraepithelial lesion (ASC-H), 0.4% were low grade squamous intraepithelial lesion (LSIL) encompassing cervical intraepithelial neoplasia I (CIN I), and 0.2% were high grade squamous intraepithelial lesion (HSIL) encompassing cervical intraepithelial neoplasia II (CIN II) (Table 3). There were 7 participants positive among 286 Hmong women (2.5%), and 3 positive participants among 164 Mien women (1.8%). There was no statistically significant difference between tribes (χ^2=0.17, p-value=0.675).

Three variables were significantly associated with abnormal cervical cell in the univariate analysis: women's number of partners, husband's number of sexual partners, and husband's history of sexual intercourse with sex workers (Table 1).

In the multivariate model, two variables were still significantly associated with abnormal cervical cell; women's number of partners, and husband's number sexual partners. Women who had ≥ 4 partners had a 7.09 time (95%CI=1.85-27.17) more likely to have abnormal cervical cell than those who had < 4 partners. Women whose husbands had ≥ 4 partners had a 5.63 time (95%CI=1.51-20.90) more likely to have abnormal cervical cell than those whose husbands had < 4 partners (Table 1).

DISCUSSION

The study found that Hmong and Mien in Pha Yao province are living in low socio-economic condition. The overall prevalence of abnormal cervical cell among our study subjects was 2.2%. Number of partners both in women and men are the factors associated with cervical cancer in the Hmong and Mien women in Pha Yao province. In our study, it was found that the prevalence of cervical cancer between Hmong and Mien women was not statistically different. However, a study in Iran[21] reported some ethnicity related trends in cervical cancer. The study of Akram Husain[22] also reported that some groups of Indian women in the south were at a greater risk of cervical cancer than women who lived in other regions in India. In terms of the prevalence of cervical cancer among these two hill tribe women is higher than Thai national rate at 23/100,000 population.[23] The rate of screening for cervical cancer is also lower than Thai targeted women at 60.2%.[23]

In our study we found that women's number of partners was a significant factor associated with abnormal cervical cancer. Liu, et al[24] reported that number of partners was highly associated with cervical cancer from the meta-analysis. Whereas several studies[25-27] reported that women's number of partners and history of STIs were associated with cervical cancer among the women in South Africa. However, the study of Obiri-Yeboah[28] reported that age of women and circumcision status of main sexual partner were associated with cervical cancer, but no association was found with number of partners.

We also found that number of partner of husband related to the occurrence of cervical cancer in women. This coincides with the study which was conducted in Shanxi province, China reported that number of partners of women and her husband were associated with cervical cancer of women.[29]

Some limitations were found in the study. First, at the beginning of the interview process, both male and female participants were interviewed by a female interviewer. However, upon completing 3 interviews; it was found that the husbands were not comfortable to provide information. Afterwards, the process was adjusted and interviews were conducted by same sex. Another point is the ability to communicate in Thai. It was found that 3 women were excluded from the study due to limitation in use of Thai. They could not provide the essential information to the interviewer. The study could not use a translator for gathering information from the participants since all information required are sensitive. Moreover, 7 selected women were excluded from the study because 5 were on their period, and 2 were pregnant. However, the researcher believes that it did not impact the study results since an excess of 20 couples had been selected at the stage of sample selection by a random method.

CONCLUSION

The hill tribe women are at risk for abnormal cervical cell. The number of partners of both women and the number of partners of their husband are identified as the

TABLE 1. Univariate and multivariate analyses of factors associated with abnormal cervical cell.

Characteristics	Total n (%)	Abnormal n (%)	Normal n (%)	OR	95% CI	P-value	OR_{adj}	95% CI	P-value
Tribe									
Hmong	286 (63.6)	7 (2.4)	279 (97.6)	1.34	(0.34-5.28)	0.670			
Mien	164 (36.4)	3 (1.8)	161 (98.2)	1					
Age (years)									
30-40	152 (33.8)	4 (2.6)	148 (97.4)	2.17	(0.39-12.05)	0.374			
41-50	135 (30.0)	4 (3.0)	131 (97.0)	2.45	(0.44-13.63)	0.303			
51-60	163 (36.2)	2 (1.2)	161 (98.8)	1					
Education									
Illiterate	151 (33.6)	4 (2.6)	147 (97.4)	0.98	(0.17-5.47)	0.981			
Primary school	225 (50.0)	4 (1.8)	221 (98.2)	0.65	(0.11-3.63)	0.625			
High school	74 (16.4)	2 (2.7)	72 (97.3)	1					
Occupation									
Farmer	348 (77.3)	6 (1.7)	342 (98.3)	0.39	(0.07-2.01)	0.264			
Merchant	55 (12.2)	2 (3.6)	53 (96.4)	0.84	(0.11-6.27)	0.873			
Labor	47 (10.5)	2 (4.3)	45 (95.7)	1					
Income (bath/month)									
≤ 3,000	249 (55.3)	3 (1.2)	246 (98.8)	0.22	(0.04-1.15)	0.075			
3,001-5,000	142 (31.6)	4 (2.8)	138 (97.2)	0.54	(0.11-2.49)	0.431			
≥ 5001	59 (13.1)	3 (5.1)	56 (94.9)	1					
Religion									
Buddhist	401(89.1)	9 (2.2)	392 (97.8)	1.10	(0.13-8.88)	0.927			
Christian	49 (10.9)	1 (2.0)	48 (98.0)	1					
Rights of free access health care									
Yes	368 (81.8)	7 (1.9)	361 (98.1)	1		0.338			
No	82 (18.2)	3 (3.7)	79 (96.3)	1.95	(0.49-7.74)				
Age at first sexual intercourse (years)									
<18	242 (53.8)	3 (1.2)	239 (98.8)	2.77	(0.70-10.86)	0.143			
≥18	208 (46.2)	7 (3.4)	201 (96.6)	1					
Age at marriage (years)									
<18	236 (52.4)	3 (1.3)	233 (98.7)	2.62	(0.67-10.28)	0.166			
≥18	214 (47.6)	7 (3.3)	207 (96.7)	1					
Number of partners (persons)									
<4	405 (90.0)	6 (1.5)	399 (98.5)	1			1		
≥4	45 (10.0)	4 (8.9)	41 (91.1)	6.48	(1.75-23.93)	0.005*	7.09	(1.85-27.17)	0.004*
Method of contraception use									
None	261 (58.0)	5 (1.9)	256 (98.1)	1					
Orally	57 (12.7)	1 (1.8)	56 (98.2)	0.91	(0.10-7.97)	0.935			
Injection	58 (12.9)	3 (5.2)	55 (94.8)	2.79	(0.64-12.03)	0.168			
Tubal ligation	74 (16.4)	1 (1.4)	73 (98.6)	0.70	(0.08-6.09)	0.748			
History of yellow or green or offensive odour leucorrhoea									
Yes	62 (13.8)	3 (4.8)	59 (95.2)	2.76	(0.69-11.00)	0.148			
No	388 (86.2)	7 (1.8)	381 (98.2)	1					

TABLE 1. Univariate and multivariate analyses of factors associated with abnormal cervical cell.

Characteristics	Total n (%)	Abnormal n (%)	Normal n (%)	OR	95% CI	P-value	OR_{adj}	95% CI	P-value
History of genital ulcer									
Yes	40 (8.9)	2 (5.0)	38 (95.0)	2.64	(0.54-12.90)	0.229			
No	410 (91.1)	8 (2.0)	402 (98.0)	1					
Smoking									
Yes	198 (44.0)	7 (3.5)	191 (96.5)	3.04	(0.77-11.91)	0.110			
No	252 (56.0)	3 (1.2)	249 (98.8)	1					
Alcohol use									
Yes	168 (37.3)	3 (1.8)	165 (98.2)	0.71	(0.18-2.80)	0.629			
No	282 (62.7)	7 (2.5)	275 (97.5)	1					
History of cervical cancer of family member									
Yes	28 (6.2)	2 (7.1)	26 (92.9)	3.98	(0.80-19.70)	0.090			
No	422 (93.8)	8 (1.9)	414 (98.1)	1					
Exercise									
Yes	203 (45.1)	3 (1.5)	200 (98.5)	1					
No	247 (54.9)	7 (2.8)	240 (97.2)	1.94	(0.46-7.61)	0.340			
Knowledge									
Low	209 (46.4)	5 (2.4)	204 (97.6)	1.05	(0.12-9.25)	0.962			
Moderate	197 (43.8)	4 (2.0)	193 (98.0)	0.89	(0.09-8.17)	0.919			
High	44 (9.8)	1 (2.3)	43 (97.7)	1					
Attitude									
Low	126 (28.0)	4 (3.2)	122 (96.8)	2.78	(0.30-25.37)	0.363			
Moderate	238 (52.9)	5 (2.1)	233 (97.9)	1.82	(0.21-15.83)	0.586			
High	86 (19.1)	1 (1.2)	85 (98.8)	1					
Practice									
Low	119 (26.4)	2 (1.7)	117 (98.3)	0.82	(0.11-5.93)	0.845			
Moderate	233 (51.8)	6 (2.6)	227 (97.4)	1.26	(0.25-6.39)	0.773			
High	98 (21.8)	2 (2.0)	96 (98.0)	1					
Number of sexual partners of husband (persons)									
<4	346 (76.9)	4 (1.2)	342 (98.8)	1			1		
≥4	104 (23.1)	6 (5.8)	98 (94.2)	5.23	(1.44-18.92)	0.012*	5.63	(1.51-20.90)	0.010*
Condom use with other women (n=271)									
Never	132 (48.7)	5 (3.8)	127 (96.2)	1.65	(0.18-14.55)	0.650			
Sometimes	96 (35.4)	4 (4.2)	92 (95.8)	1.82	(0.19-16.83)	0.595			
Always	43 (15.9)	1 (2.3)	42 (97.7)	1					
Husband's history of genital ulcer									
Yes	15 (3.3)	1 (6.7)	14 (93.3)	3.38	(0,40-28.54)	0.263			
No	435 (96.7)	9 (2.1)	426 (97.9)	1					
History of sexual intercourse with sex workers									
Yes	52 (11.6)	4 (7.7)	48 (92.3)	5.44	(1.48-19.98)	0.011*			
No	398 (88.4)	6 (1.5)	392 (98.5)	1					

* Significant level at α =0.05

TABLE 2. General characteristics of husbands.

Characteristics	n (%)
Number of partners (persons)	
<4	346 (76.9)
≥4	104 (23.1)
Condom use while having sex with other women (n=271)	
Never	132 (48.7)
Sometimes	96 (35.4)
Always	43 (15.9)
History of genital discharge	
Yes	0 (0.0)
No	450 (100.0)
History of genital ulcer	
Yes	15 (3.3)
No	435 (96.7)
Sexual intercourse with sex worker	
Yes	52 (11.6)
No	398 (88.4)

TABLE 3. Prevalence of abnormal cervical cancer.

Characteristics	N (%)
Negative for intraepithelial lesion or malignancy (NIL)	**345 (76.7)**
Organism	
Trichomonas *spp*.	3 (0.7)
Fungus	26 (5.8)
Coccobacilli shift in vaginal flora	32 (7.1)
Others	2 (0.4)
Other non-neoplastic findings	
Inflammation	29 (6.4)
Atrophy	3 (0.7)
Epithelial cells abnormalities	
Squamous cells	**10 (2.2)**
Atypical squamous cells of undetermined significance (ASC-US)	5 (1.2)
Atypical squamous cells-cannot exclude HSIL (ASC-H)	2 (0.4)
Low grade squamous intraepithelial lesion (LSIL)	
Cervical Intraepithelium Neoplasia I (CIN-I)	2 (0.4)
High grade squamous intraepithelial lesion (HSIL)	
Cervical Intraepithelium Neoplasia II (CIN-II)	1 (0.2)

factors associated to abnormal cervical cell of Hmong and Mien women. Public health intervention which is focused on minimizing the number of partners among these hill tribe population should be implemented to reduce the possibility of having abnormal cervical cell.

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REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. JAMA Oncology 2017;3: 524-48.
2. World Cancer Research Fund International (WCRF International). Cancer facts & figures worldwide data. Available from http://www.wcrf.org/int/cancer-facts- gures/worldwide- data.
3. World Health Organization (WHO). Cancer situation in SEAR countries. Available from: http://www.searo.who.int/thailand/news/cancer-sear/en/
4. Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. Int J Women's Health 2015;7:405-14.
5. Centers for Disease Control and Prevention (CDC). Gynecologic cancers: cervical cancer. Available from: https:// www.cdc.gov/cancer/cervical/
6. World Health Organization (WHO). Cervical cancer prevention and control saves lives in the Republic of Korea. Available from: http://www.who.int/news-room/feature- stories/detail/cervical-cancer-prevention-and-control-saves- lives-in-the-republic-of-korea.
7. Sawatdimongkol S. Annual report of non-communicable diseases 2015. Available from: http://www. thaincd.com/document/le/download/paper manual/Annual-report-2015.pdf
8. Lampang Cancer Hospital. Cancer incidence in northern Thailand, 2012-2016. Available from: http://www.lpch.go.th/lpch/lpch_attachment/20151016085144134377.pdf
9. Lampang Cancer Hospital. Cancer incidence in Pha Yao province. Available from: http://www. lpch.go.th/lpch/lpch_attachment/20151202100952874252.pdf
10. Thitibordin B. Reporting system of cancer service plan in Pha Yao province, Thailand. Available from: http:// bie.moph.go.th/eins59/upload/2559A12103114.doc
11. Pha Yao Provincial Public Health Office, Thailand. Cervical cancer screening report. Available from: http://203.209.96.247/chronic/rep_cancer_vagina. php
12. Hill Tribe Development Center of Pha Yao Province, Thailand. Hill tribe population data in 2016-2017. Available from: http://www.sdc31.go.th/index.php?name=download& le=readdownload&id=19
13. Apidechkul T. A 20-year retrospective cohort study of TB infection among the Hill-tribe HIV/AIDS populations, Thailand. BMC Infect Dis 2016;16:72.
14. Kritpetcharat OW, Sirijaichingkul S, Kritpetcharat P. Comparison of Pap smear screening results between Akha hill tribe and urban women in Chiang Rai province, Thailand. Asian Pac J Cancer Prev 2012;13:5501-4.
15. Thawongma S, Maneewan K. Roles of adolescents Hmong and sexual behavior modification. Hill Tribe's Health Development Center, Chiang Mai, Thailand. 2006.
16. Apidechkul T, Laingoen O, Suwannaporn S. Inequity in accessing health care service in Thailand in 2015: A case study of the Hill tribe people in Mae Fah Luang district, Chiang Rai, Thailand. J Health Res 2016;30 67-71.
17. Khirisuntikul S. Development of a health promotion model for cervical cancer prevention among hill tribe women aged 30-60 years. Available from: https://wwwnno.moph. go.th/research/index.php/2559/item/274-2559-1
18. Pha Yao Provincial Public Health Office, Thailand. Hill tribe population in 2016. Pha Yao Provincial Public Health Office, Pha Yao, Thailand, 2016.
19. Naing L, Winn T, Rusli BN. Practical issues in calculating the sample size for prevalence studies. Arch Orofac Sci 2006;1:9-14.
20. Mohaffyza MM, Sulaiman L, Sern LC, Salleh KM. Measuring the validity and reliability of research instruments. Procedia Soc Behav Sci 2015;204:164-71.
21. Michaan N, Gortzak-Uzan L, Grisario D, Laskov I. Ethnicity-related trends in gynecologic malignancies in Israel, 1993-2013. Int J Gynaecol Obstet 2018;142:176-81.
22. Akram Husain RS, Rajakeerthana R, Sreevalsan A, Prema Jayaprasad P, Ahmed S, Ramakrishnan V. Prevalence of human papilloma virus with risk of cervical cancer among south Indian women: A genotypic study with meta- analysis and molecular dynamics of HPV E6 oncoprotein. Infect Genet Evol 2018;62:130-40.
23. The HPV Information Center, Thailand. Human papilloma virus and related disease report. Available from: http://www.hpvcentre.net/statistics/reports/THA.pdf
24. Liu ZC, Liu WD, Liu YH, Ye XH, Chen SD. Multiple sexual partners as a potential independent risk factor for cervical cancer: a meta-analysis of epidemiological studies. Asian Pac J Cancer Prev 2015;16:3893-900.
25. Jolly PE, Mthethwa-Hleta S, Padilla LA, Pettis J, Winston S, Akinyenmiju TF, et al. Screening, prevalence, and risk factors for cervical lesion among HIV positive and HIV negative women in Swaziland. BMC Public Health 2017;17:218.
26. Okunade KS, Nwogu CM, Oluwole AA, Anorlu RI. Prevalence and risk factors of genital high-risk human papillomavirus infection among women attending the out-patient clinics of a university teaching hospital in Lagos, Nigeria. Pan Afr Med J 2017; 28:227.
27. Mbulawa ZZA, van Schalkwyk C, Hu NC, Meiring TL, Barnabas S, Dabee S, et al. High human papillomavirus (HPV) prevalence in South Africa adolescents and young women encourages expanded HPV vaccination campaigns. PLoS One 2018;13(1): e0190166.
28. Obiri-Yeboah D, Akakpo PK, Mutocheluh M, Adje-Danso E, Allornuvor G, Amoako-Sakyi D, et al. Epidemiology of cervical human papillomavirus (HPV) infection and squamous intraepithelial lesion (SIL) among a cohort of HIV-infected and uninfected Ghanaian women. BMC Cancer 2017;17:688.
29. Shi N, Lu Q, Zhang J, Li L, Zhang J, Zhang F, et al. Analysis of risk factors for persistent infection of asymptomatic women with high-risk human papilloma virus. Hum Vaccin Immunother 2017;13:1404-11.

Resilience in Medical Doctors within the Areas of the Southern Thailand Insurgency

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ABSTRACT

Objective: This study aimed to examine resilience and its' associated factors among medical doctors who worked at hospitals, either in the restive areas of the southern Thailand insurgency, or non-restive areas of nearby provinces.

Methods: This cross-sectional study was conducted for all medical doctors who worked at the hospitals located in the lower southern part of Thailand from January to April 2018. All of the participants completed the personal information and Thai resilience questionnaires (Thai-RQ) by themselves. The data was analyzed by descriptive statistics, whilst the factors associated with resilience were analyzed using logistic regression analysis.

Results: From 245 medical doctors, most were female (58.0%), single (50.2%) and worked more than 40 hours per week (30.2%). The average resilience scores were at a normal level (62.3 ± 7.8) as well as most of them being (67.3%). The highest section of resilience was coping skills, with the lowest being emotional stability. There were no differences in resilience between those who worked in restive areas, or those who worked in non-restive areas of the southern Thailand insurgency. Perceived sleep/rest quality and family relationships were significantly associated with their resilience.

Conclusion: Most of the medical doctors, who worked at hospitals either in the restive or non-restive areas of the southern Thailand insurgency, were at normal levels of resilience. No difference of resilience was found between these two areas. The factors associated with resilience were perception of sleep/rest quality and family relationships.

Keywords: Resilience; medical doctor; south Thailand insurgency (Siriraj Med J 2019;71: 228-233)

INTRODUCTION

Since 2004, the Thailand's southern insurgency, which is a part of a complicated political conflict, has continuingly deteriorated, generating violence in the 3 provinces of southern Thailand: Patani, Yala and Narathi, in addition to some parts of Songkhla province, which the Thai media has dubbed as the SBP (Southern border Providences) of Thailand.

From the 1st of January 2004 to the 31st of August 2018; 19,993 violent situations were officially reported with; 6,848 people killed and another 13,443 injured in total.[1] Local people, including medical professionals working in these areas, have to live under these ongoing, stressful circumstances and embody a substantial escalation in psychological distresses.[2] They are at risk of many mental illnesses; not only burnout syndrome which is commonly found among health care professionals, but also more severe psychiatric disorders, such as; post-traumatic stress disorder.[3]

However, Charoenwong and the co-authors[2] found that most, local people in the restive areas represented as having normal levels of stress. Even a survey among widows whose husbands died due to the violent situations in the SBP, revealed stable stress management, spiritual and physical strength.[4]

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The remarkable question is: 'Exactly how do they live under these continuing stressful conditions?' Especially medical doctors, who normally already work in demanding settings as is the nature of their profession. the researchers focused on the medical doctors 'resilience', as this is the capacity to recover quickly from any difficulties.[5] Within Thailand's context, resilience and resilience assessment were conceptually based on 3 sources of: "I AM", "I HAVE" and "I CAN". Therefore, the Thai version of resilience quotient was divided into 3 parts: emotional stability, will power and coping skills.[6] Previous studies of resilience promotion reported that; the extrinsic factors that are associated to the level of resilience were quality of family relationship and governmental/social support.[7] As well as which intrinsic factors were self- esteem, faith and high cognitive functionality, however; physical illnesses could interfere with resilience, particularly among patients with an abnormal cortisol level, which is also related to stress.[8]

For these reasons, the researchers emphasized both resilience and associating factors among medical doctors, who work in government hospitals in the restive areas of SBP, and the other 4 southern provinces of Thailand for comparison. This was in order for the collection of principal data for promoting mental health among Thai health care professionals, and to develop psychological support systems for public health organizations in Thailand.

MATERIALS AND METHODS

This study was a cross-sectional survey; designed to determine the level of resilience and its' associated factors among medical doctor, working at secondary and tertiary-care hospitals in the restive areas of Narathiwas, Patani, Yala, and 4 the non-restive provinces of Songkhla, Satun, Trang and Phatthalung, from January to April 2018. Additionally, this research also compared resilience between the restive areas of the Thailand's southern insurgency, and the non-restive areas in 4 nearby provinces. After the research proposal was endorsed by the ethic committee of Prince of Songkla University (REC number: 60-262-03-1), the researchers contacted human resource officers at each secondary and tertiary hospitals in both the restive and non-restive areas of the Thailand's southern insurgency. Upon contact, we asked for permission from the directors of each hospital for help in the administration all of the sealed envelopes of the self-administered questionnaires: Thai resilience questionnaires (Thai-RQ)[9], to all medical doctors, who were employed at that time. Consensus to participate in the study had to be individually agreed upon.

Whilst the estimated size of our target population is at least 320 medical doctors[10], according to region 12, from the Ministry of Public health records, there are 1,592 physicians on duty.[11] Then, the data were performed using the R software package, and were analyzed by using descriptive statistics. The primary results were presented as: frequency, percentage, average and standard deviation. Therefore, associated factors of resilience were analyzed by using logistic regression.

RESULTS

Of the 245 medical doctors, who participated in this study (19.3% responded from a total of 1270 questionnaires); 55.9% of them worked in restive areas of the SBP. Participants were mostly females (58.0%) Buddhist (80.0%), healthy (74.7%) and single (50.2%). The mean age±SD was 35.9±9.5 years old, with the mean±SD amount of working hours per week being 63.0±26.4. Around half of the participants reported that they perceived adequate rest and sleep, but more of them perceived this to be inadequate (48.6% and 49.0% respectively). Most of them revealed that the most important reason in the choice of their workplace location was so as to be near their homes, and families (55.1%). They also assessed their own family relationships as being good or excellence (48.6% and 40.0% respectively). However, 86.9 % of them reported that they perceived considerable stress form their work. (Table 1)

Regarding levels of resilience (Table 2), no significant difference was found between medical doctors who worked in either the restive or non-restive areas of Thailand's southern insurgency. Only 15.7% of the medical doctors in restive areas, and 14.7% of those who worked in non-restive ones, had less levels of resilience than that of a normal population. Whilst the domain showed, the highest prevalence of normal to above average levels of resilience, was coping skills (91.7% in restive areas, and 88.2% in non-restive areas). The domain of emotional stability represented the lowest prevalence; as 14.8% in restive areas and 15.4% in non-restive area, were reported as lower levels of resilience than normal people. (Table 3)

On the subject of associated factors to resilience (Table 4), perception of sleeping/rest quality (p -value=0.067) and family relationships (p-value<0.001) were found to be statistically significantly associated to the levels of resilience among medical doctors, working in both the restive and non-restive areas of Thailand's southern insurgency. According to Table 5, both groups of medical doctors, who perceived adequate rest/sleep, showed 2.5 greater levels of resilience than those who perceived this

TABLE 1. Demographic characteristics (n=245).

Demographic characteristics	Number (%)
Gender	
Male	103 (42.0)
Female	142 (58.0)
Age (year)	
Mean±S.D.(min-max)	35.9±9.5 (24-60)
Hometown	
3 southern border provinces	89 (36.3)
Other southern provinces	124 (50.6)
Others provinces	31 (12.7)
Missing valued	1 (0.4)
Religion	
Buddhism	196 (80.0)
Islam	44 (18.0)
Christianity	2 (0.8)
Others	3 (1.2)
Marital status	
Single	123 (50.2)
Married/couple	115 (46.9)
Divorced /widow	3 (1.2)
Missing value	4 (1.6)
Hospitallocation	
Non-SBP	137 (55.9)
SBP	108 (44.1)
Work hour (per week)	
Mean±S.D. (min-max)	63.0±26.4 (6-120)
≤ 40	74 (30.2)
41-60	62 (25.3)
61-80	36 (14.7)
>80	55 (22.4)
Missing value	18 (7.3)
Perceived quality of resting or sleeping	
Adequate	119 (48.6)
Not adequate	120 (49.0)
Not sure	1 (0.4)
Missing valued	5 (2.0)
Perceived work stress	
No	30 (12.2)
Yes	213 (86.9)
Missing value	2 (0.8)
History of physical illness	
No	183 (74.7)
Yes	59 (24.1)
Missing value	3 (1.2)
Family relationship	
Excellent	98 (40.0)
Good	119 (48.6)
Fair	26 (10.6)
Missing value	2 (0.8)
Initial reasons of working in the hospital	
Near home	135 (55.1)
Reimbursement education fund	39 (15.9)
Follow couple or family	20 (8.2)
Have a chance for study programming	15 (6.1)
Others	33 (13.5)
Missing value	3 (1.2)

Abbreviations: S.D. = standard deviation, GPA = grade point average

TABLE 2. Level of resilience categorized by working area.

Resilience Quotient screening test	Total (%)	Non-restive (%) n=136	Restive (%) n=108	Chi2 P-value
Level of resilience				0.675
Less than normal range (<55)	37 (15.1)	20 (14.7)	17 (15.7)	
Normal range (55-69)	165 (67.3)	90 (66.2)	75 (69.4)	
Higher than Normal range (>69)	42 (17.1)	26 (19.1)	16 (14.8)	
Mean±S.D. (min-max)	62.3±7.8 (40-80)	62.5±7.8 (42-80)	61.9±7.8 (40-78)	

TABLE 3. Three domain of Resilience Quotient by working area (n=244).

Domain of resilience	Total (%)	Non-restive (%) n=137	Restive (%) n=108	Chi2 P-value
Emotional stability				0.721
Less than normal range	37 (15.1)	21 (15.4)	16 (14.8)	
Normal range (27-34)	173 (70.6)	94 (69.1)	79 (73.1)	
Higher than normal range	34 (13.9)	21 (15.4)	13 (12.0)	
Mean±S.D. (min-max)	30.2±4.1 (19-40)	30.3±4.2 (20-40)	30.1±3.9 (19-38)	
Will power				0.501
Less than normal range	27 (11.0)	13 (9.6)	14 (13.0)	
Normal range (14-19)	177 (72.2)	98 (72.1)	79 (73.1)	
Higher than normal range	40 (16.3)	25 (18.4)	15 (13.9)	
Mean±S.D. (min-max)	16.7±2.5 (10-20)	16.8±2.4 (10-20)	16.6±2.5 (10-20)	
Coping skill				0.462
Less than normal range	25 (10.2)	16 (11.8)	9 (8.3)	
Normal range (13-18)	197 (80.4)	106 (77.9)	91 (84.3)	
Higher than normal range	22 (9.0)	14 (10.3)	8 (7.4)	
Mean±S.D. (min-max)	15.4±2.3 (9-20)	15.5±2.3 (9-20)	15.2±2.2 (9-20)	

to be inadequate (95%CI=1.1,5.8). Whereas, those who appraised their family relationship as being excellence, were found to have resiliency levels 6.5 higher than those who did not (95%CI=2.1,19.9).

DISCUSSION

Previous studies of mental health, in the SBP of Thailand, mostly focused on mental difficulties and psychiatric diseases, in valuable populations, such as; patients with substance dependence.[12] However, it is questionable as to why some groups of people can produce positive consequences in specific situations at risk, for example; medical doctors in the areas of Thailand's southern insurgency as well as nearby provinces. Compared with a study among patients with substance-related disorders in the restive areas of SBP, 15.7% of medical doctors who worked in the same area were found to have lower levels of resilience than that of a normal population. Whereas, 28.3% of these patients reported the same level.[13] The different results may clarify the phenomenon of different social and occupational functioning. Oppositely, dissimilar physical and mental strength between the two groups of the population may explain the difference on the outcomes of resilience.

However, the authors found that 99.6% of the same group of medical doctors were suffering from burnout syndrome.[14] This survey of resilience, which found 84.4% of the total medical doctors, and 84.2% of those who worked in the restive areas had normal to higher than normal levels of resilience, and this may explain the reason why these medical doctors could work as per usual in situations with surrounding violence, while suffering

TABLE 4. Association between demographic variables and level of resilience.

Demographic characteristics	Level of resilience <55 (n=37)	Level of resilience >=55 (n=207)	Chi2 P-value
Gender			0.161
Male	20 (54.1)	83 (40.1)	
Female	17 (45.9)	124 (59.9)	
Age (year)			0.579
<30	13 (35.1)	58 (28.2)	
30-40	14 (37.8)	96 (46.6)	
41-60	10 (27.0)	52 (25.2)	
Religion			0.679
Buddhism	31 (83.8)	164 (79.2)	
Islam/Christianity	6 (16.2)	43 (20.8)	
Marital status			0.175
Single/ divorced / widow	23 (63.9)	102 (50.0)	
Married/couple	13 (36.1)	102 (50.0)	
Work hours (per week)		0.131	
≤ 40	6 (18.2)	68 (35.1)	
41-60	8 (24.2)	54 (27.8)	
61-80	8 (24.2)	28 (14.4)	
>80	11 (33.3)	44 (22.7)	
Perceived quality of resting or sleeping			0.067
Adequate	12 (34.3)	107 (52.7)	
Not adequate	23 (65.7)	96 (47.3)	
Perceived work stress			0.271[a]
No	2 (5.7)	28 (13.5)	
Yes	33 (94.3)	179 (86.5)	
History of physical illness			0.977
No	27 (77.1)	155 (75.2)	
Yes	8 (22.9)	51 (24.8)	
Family relationship			<0.001
Excellent	8 (22.9)	90 (43.5)	
Good	17 (48.6)	101 (48.8)	
Fair	10 (28.6)	16 (7.7)	

[a] = p-value from Fisher's exact test
Level of resilience <55 = below average
>=55 = average and above average

TABLE 5. Analyzed Factors associated with resilience (n=221).

Factors	Crude OR (95%CI)	Adjusted OR (95%CI)	P LR-test
Perceived quality of resting or sleeping			0.021
Not adequate	1	1	
Adequate	2.9 (1.3, 6.3)	2.5 (1.1, 5.8)	
Family relationship			0.005
Fair	1	1	
Excellent	7.3 (2.4, 22.1)	6.5 (2.1, 19.9)	
Good	3.5 (1.4, 9.1)	3.3 (1.3, 8.8)	

Abbreviations: OR= Odds ratio, LR = Likelihood Ratio

from burnout syndrome. In so saying, a secondary data analysis study for correlation should be undertaken.

Regarding the associated factors of resilience, quality of rest/sleep and family relationships showed to have a significant association. To promote resilience in medical doctors, especially those who work in situations at risk; policy makers should emphasize the working hours, work-load and work-place location, so as to provide for adequate rest/sleep and non-disturbance of such family relationships. Additionally, medical doctors themselves should be aware of their quality of sleep/rest, family relationships along with other resources to face both the mental and physical difficulties from their work.

Strength and limitation

Even though this study was the first study of resilience among Thai medical doctors, especially in the restive areas of southern Thailand's insurgency, the response rate was below 20.0%. However, the sample size determination for finite populations was 320 medical doctors; therefore, 245 participants were 76.5% of calculated sample size, which is adequate for this resilience study.

The design of this study was that of a cross-sectional survey; the results could not summarize the process of medical doctors' adaptation in spite of adversities. Thus, a cohort coupled with long-term, follow-up studies in this group of the population should be conducted. Moreover, the data came from a quantitative designed research, which explains only individual traits of the participants could also be tabled. To understand the paradigm of resilience, we have to study contextual interactions between their inner strengths and contributions within the environment, therefore; a qualitative- designed study is required.

CONCLUSION

Most medical doctors, who worked at secondary and tertiary-care hospitals in both the restive areas of Thailand's southern insurgency as well as the non-restive areas of nearby provinces, were at normal or higher than normal levels of resilience. No difference of resilience was found between the restive and the non-restive areas of the Thailand's southern insurgency. The factors associated to resilience were: perception of sleeping/rest quality and family relationships. Medical doctors who perceived adequate rest/sleep showed a 2.5 greater level of resilience, while those who estimated excellent family relationships were found to have a resiliency level of 6.5 higher.

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REFERENCES

1. Deep South watch. Summary of incidents in Southern Thailand, august 2018 [Internet]. Deepsouthwatch.org. 2018 [cited 2018 Oct 3]. Available from: https://deepsouthwatch.org/en/node/11862
2. Charoenwong S, Kongsuwan V, Taogani M. Stress and psychological self-care behaviors of the people in the unrest area of Narathiwat Province, Thailand. Bangkok: Mental Health in the City; 2007.
3. Maslach C, Jackson S. Burnout in health professions: a social psychological analysis. In: Sanders G, Suls J, editors. Social psychology of health and illness. New Jersey: Lawrence Erlbaum; 1982. p. 227-51.
4. Udomlapsakul S, Intanon T, Suttharangsee W. Mental health promotion of widows from situation of unrest in the three southernmost provinces, Thailand. PNU J 2011; 3:29-40.
5. Oxford University Press. Resilience | Definition of resilience in English by Oxford Dictionaries [Internet]. Oxford Dictionaries | English. 2018 [cited 2018 Oct 4]. Available from: https://en.oxforddictionaries.com/definition/resilience
6. Maneerat S, Isaramalai S- arun, Boonyasopun U. A conceptual structure of resilience among Thai elderly. The Journal of Behavioral Science [Internet]. 2011 [cited 2018 Oct 5];6(1): 24-40. Available from: https://www.tci-thaijo.org/index.php/IJBS/article/view/514
7. Rutter M. Psychosocial resilience and protective mechanisms. Am J Orthopsychiat 1987; 57(3):316-31.
8. Simeon D, Yehuda R, Cunill R, Knutelska M, Putnam F, Smith L. Factors associated with resilience in healthy adults. Psychoneuroendocrinology 2007; 32:1149-52.
9. Mental Health Center Region 10. Mental health screening tool [Internet]. Ubon Ratchathani: Mental Health Center Region 10; 2018 [cited 2018 Dec 4]. Available from: http://www.mhc10.go.th/evaluation.php
10. Yamane, Taro. Statistics, An Introductory Analysis, 2nd ed., New York: Harper and Row, 1967.
11. Ministry of public health, Thailand. Information of staffs [Internet]. Sasuk12.com. 2017 [cited 5 August 2017]. Available from: http://www.sasuk12.com/index3.php
12. Jatchavala C, Vittayanont A. Post-traumatic stress disorder symptoms among patients with substance-related disorders in the restive areas of south Thailand insurgency. Songkla Med J 2017; 35(2):121-32.
13. Jatchavala C, Ngamkajornwiwat A. Resilience among patients with substance-related disorders in the restive area of south Thailand insurgency. J Psychiatr Assoc Thailand 2016; 61(4):307-18.
14. Pitanupong J, Jatchavala C. A study on the comparison of burnout syndrome, among medical doctors in the restive areas and non-restive areas of the South Thailand Insurgency. J Health Sci Med Res 2018; 36(4):279-89.