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A Nationwide Survey and System Analysis of the Emergency Triage System in The Lao People's Democratic Republic

Lamngeun Silavong, MNS, DNS Student*, Ketsarin Utriyaprasit, Ph.D., RN*, Napaporn Wanitkun, Ph.D., RN*, Chukiat Viwatwongkasem, Ph.D.**

**Faculty of Nursing, Mahidol University, Bangkok 10700 Thailand, **Faculty of Public Health, Mahidol University, Bangkok 10400, Thailand.*

ABSTRACT

Objective: To assess the present status of the emergency department (ED) triage system in 162 hospitals across the Lao People's Democratic Republic (Lao PDR).

Materials and Methods: The nationwide survey participants were ED administrators of all hospitals in Lao PDR. The standard questionnaire package was used for data collection including patients' demographics and triage systemic factors. Descriptive analysis was applied to analysis the outcome of interest.

Results: A majority of triage officers were emergency room nurses (58.6%), general physicians (20.4%), or both (11.1%). Most hospitals (89.5%) used informal triage scales such as clinical experiences or colors to prioritize ED patients. Only 17 hospitals (10.5%) had a formal triage scale in their ED care systems and used it in their practice.

Conclusion: These findings provide knowledge of the ED triage system in the Lao PDR. The results indicate that the Lao PDR lacks a formal ED triage scale but uses a variety of informal scales. Thus, it is necessary to set up a standard triage system at all hospitals to standardize ED healthcare across the country.

Keywords: Health system; triage system; the Lao People's Democratic Republic (Siriraj Med J 2023; 75: 241-247)

INTRODUCTION

The Emergency Department (ED) is a pivotal healthcare entry point and is the busiest department in all hospitals worldwide.The ED has an excessive flow of complicated, often life-threatening cases and a high density of critical clinical decision-making.[1] Statistics of the Mahosot Hospital, the largest hospital in the Lao People's Democratic Republic (Lao PDR), showed the overall rise over five years (2011-2016) was 29.12%.[2] Triage is a treatment process for the timely delivery of emergency care, handling emergencies with an appropriate allocation of medical resources, and sorting for ED treatment.[3,4] The triage concept is used in modern healthcare systems worldwide.[5] The triage system helps patients with life-threatening illnesses access care first for medical services. It is volume management in the ED.

The triage system in the Lao PDR has been partially implemented since 2008 using the Look, Listen, Feel process.[6] Triage ensures resources are allocated where they are most needed.[3,4,7] Despite the well-established benefits of triage, no hospital has fully implemented the triage system.[8,9] The triage system in the Lao PDR employs three different models, the model of clinical experience (Look, Listen and Feel), three zones of patient screening (emergent, urgent, and non-urgent or color codes: red, yellow and green); or an emergency severity index (ESI

Corresponding author: Ketsarin Utriyaprasit
E-mail: ketsarin.utr@mahidol.ac.th
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ORCID ID:http://orcid.org/0000-0001-7932-3395
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with five scales). Different models have contributed to significant disorder in providing emergency service, increased length of stay and left patients feeling confused.[10] Enhancing patient safety through access to appropriate treatment is a crucial matter.

The pivotal triage system has never been examined to reform the Lao PDR's Emergency Medical Services (EMS) and ED processes. There is a lack of standard published articles on the triage system which explain the use and organization of different triage processes in the hospital ED of the Lao PDR. As a first step towards reforming the emergency medical service (EMS) system, a nationwide survey and system analysis to assess the current status and the problems of the ED triage system are needed to develop a formal triage system in Lao PDR hospitals.

MATERIALS AND METHODS

We employed a cross-sectional survey to collect data. All hospital EDs in the Lao PDR were surveyed between December 1, 2018 to March 11, 2019 to collect national data on triage methods. The study was approved by the Institutional Review Broad. (IRB-NS 2018/466.2711) There were totally 1,255 hospitals (1047 community, 148 primary/district, 17 secondary, 7 tertiary and 36 private hospitals) in the Lao PDR during the year 2018-2019. However, a total of 168 hospitals from 1255 hospitals provided emergency care. Since six district hospitals are used same ED service at the province hospital, thus only 162 hospitals participated in this study. These hospitals included 142 primary, 17 secondary, and three tertiary hospitals. Survey subjects were ED administrators or representative ED administrators (hospital directors, heads of EDs, and ED head nurses or nurse supervisors) from each hospital. Inclusion criteria for ED administrator were: 1) working full-time in an ED with at least one year of experience, and 2) responsibility as the official ED administrator.

This nationwide survey used a questionnaire developed by six emergency medicine departments of two institutions in Korea.[11] The survey instrument had an 8-item questionnaire related to the ED triage system. Four items were yes-no questions, and four were multiple-choice. A back-translation to Lao language was using technique by Brislin.[12] ED administrators of the 162 identified EDs were approached by mail invitation package to participate and provide study data. The package included an invitation letter, a brief proposal participant information sheet, and a written informed consent form. First, a representative ED administrator was designated to respond to the eight focus questions. The assigned person was contacted by telephone or face-to-face interview to receive project details and provide consent to participate by setting a schedule of interviews. Primarily telephone interviews were conducted in each hospital with a representative ED care manager (hospital director, head nurse, or assigned other); a face-to-face interview was sometimes used. Of the 162 hospitals, face-to-face interviews were conducted in 16 hospitals (three tertiary, four provincial, and nine district hospitals). Each interview took approximately 20-30 minutes.

The Statistical Package for Social Science (SPSS) for Windows version 23 was used for data entry and analysis.[13] We used descriptive analysis to characterize the findings. Frequency and percentage described categorical variables with mean or median values and standard deviations.

RESULTS

Characteristics of the Sample

Table 1 demonstrates the distribution of hospital levels across Lao PDR. Most of the one hundred and sixty-two hospitals surveyed were in the Lao PDR's northern region (42.6%). All tertiary hospitals were located in the central area. The highest percentage of secondary hospitals was in the southern region of the country (52.9%), while the primary hospitals were in the north of the Loa PDR (44.37%). Most respondents were hospital directors and general physicians who work in EDs (31.5%). The answers related to triage system in Lao PDR came from both hospital policymakers and clinicians, while only approximately 30% of respondents were not hospital directors.

Characteristics of the National Triage System

As shown in Table 2, most triage officers in primary and secondary hospitals (54.3 and 4.3%, respectively) were only emergency room (ER) nurses. Emergency physician specialists performed only 4.9% of triage (EPS). Approximately 50.6% of triage was not completed in separate triage rooms in the primary and secondary hospitals (44.4 and 6.2%, respectively). All three tertiary hospitals triaged their patients in specific triage rooms. One hundred forty-one hospitals (87%) initially triaged all visiting patients across primary, secondary, and tertiary hospitals (75.3, 9.9, and 1.9%, respectively). One hundred and forty-five of the 162 hospitals (89.5%) did not apply any formal triage scale in their ED care systems (80.2%, 8.6%, and 0.6% of primary, secondary, and tertiary hospitals, respectively). Of the 145 hospitals, seven hospitals (4.3%) had a formal scale but did not use it in their practice. While emergent symptoms are defined by law in the National Manual for Emergency Care (ESL), only 27

TABLE 1. The frequency and percentage of different hospitals by geographic region and numbers of respondent.

	Hospital level							
	Primary		Secondary		Tertiary		Total	
	n	%	n	%	n	%	n	%
Northern part	63	44.4	6	35.3	0	0.0	69	42.6
Middle	31	21.8	2	11.77	3	100	36	22.2
South	48	33.8	9	52.94	0	0.0	57	35.2
Total	142	100	17	100	3	100	162	100.0
Respondents								
HD	38	23.5			2	1.2	40	24.7
EPS	3	1.9	2	1.2			5	3.1
HN	21	13.0	4	2.5			25	15.4
GP	19	11.7					19	11.7
HD and EPS	4	2.5	4	2.5			8	4.9
HD and HN	5	3.1	2	1.2	10.6		8	4.9
HD and GP	51	31.5	4	2.5			55	34.0
HD, EPS, and HN			1	0.6			1	0.6
HD, EPS, and GP	1	0.6					1	0.6

Abbreviations: HD: Hospital Director; EPS: Emergency Physician Specialist; HN: Head Nurse; GP: General Physician

hospitals (16.7%) applied this practice guideline to their routine care. In contrast, 110 (67.9%) hospitals relied only on their clinical experience (CE). Only 2 of 162 (1.2%) hospitals applied a formal triage scale in their practice. All hospitals reported similar problems with Triage (45.1%). Most hospitals with triage difficulties, except in the tertiary hospitals (35.8%), used no formal triage scales.

Triage Duration across the Emergency Triage Scale

Time for triage estimated by administrators of the hospital EDs showed that CE for triage assessment took the longest time, with a formal scale requiring the shortest time. A comparison of triage methods showed a mean difference in triage duration across the three forms: CE, informal and formal scales, as shown in Table 3.

Quality Control of ED Triage

More than 52.5% of all EDs had no training plans for their ED staff. The primary hospital ED staff's was mostly significant lack of their training (48.8%). Among the remaining 77 EDs, 60 offered periodic training for their staff (37%) at an average of 1.65 times per year (SD = 0.92, range = 1– 4). Only 10% of EDs had a protocol as a part of initial job training. For quality improvement, all hospital representatives preferred to adopt a formal or standard scale and organize triage-training workshops to incorporate the triage system into their practice, as shown in Table 4.

DISCUSSION

Our nationwide survey investigated the prevailing conditions in all hospitals in the Lao PDR ED triage system. Hospital administrators from 162 hospitals reported (142 districts, 17 provinces, and three tertiary areas) patient emergency services. Eighty-seven percentage of ED hospitals were primary hospitals and located in the northern region (38.9%). In contrast, the secondary hospitals were mainly located in southern areas, and all tertiary hospitals were in the central region. Approximately 54.6% of Laotians live in rural areas, and 45.4% live in

TABLE 2. The frequency and percentage of emergency triage system characteristics in Lao PDR.

Characteristics	Hospital level							
	Primary		Secondary		Tertiary		Total	
	n	%	n	%	n	%	n	%
Who acts as a triage officer?								
ER Nurse	88	54.3	7	4.3			95	58.6
GP	33	20.4					33	20.4
GP and ER Nurse	14	8.6	3	1.9	1	0.6	18	11.1
EPS	4	2.5	3	1.9	1	0.6	8	4.9
EPS and ER Nurse	3	1.9	3	1.9	1	0.6	7	4.3
EPS, GP, and ER Nurse			1	0.6			1	0.6
Where is triage performed?								
In a separate triage room	70	43.2	7	4.3	3	1.9	80	49.4
In the treatment area	72	44.4	10	6.2			79	50.6
Who is triaged initially?								
All visiting patients	122	75.3	16	9.9	3	1.9	141	87.0
Waiting patients only	20	12.3	1	0.6			21	13.0
Is there an official triage scale?								
No	124	76.5	14	8.6			138	85.2
Yes, we use it	12	7.4	3	1.9	2	1.2	17	10.5
Yes, we did not use it	6	3.7			1	0.6	7	4.3
What model is the basis of your triage scale?								
CE	101	62.3	9	5.6			110	67.9
ESL	22	13.6	5	3.1			27	16.7
Color	14	8.6	3	1.9	2	1.3	19	11.7
CE& ESL	4	2.5					4	2.5
CTAS	1	0.6					1	0.6
ESI					1	0.6	1	0.6
Classifying levels								
Five levels					1	0.6	1	0.6
Problems with triage								
No	79	48.8	9	5.6	1	0.6	89	54.9
Yes	63	39.9	8	4.9	2	1.2	73	45.1
Vague context	10	6.2	1	0.6	1	0.6	12	7.4
Over triage	1	0.6	1	0.6	1	0.6	3	1.9
No formal triage scale	52	32.1	6	3.7			58	35.8

Abbreviations: GP: General physician; EPS: Emergency physician specialist; CE: Clinical experience; CTAS: Canadian triage acuity scale; ESL: Emergent symptoms defined in law; ESI: Emergency Severity Index

TABLE 3. The mean, standard deviation, minimum, and maximum of triage duration across the emergency triage scale and hospital level in Lao PDR.

Hospital level	Scale characteristics	N	Mean	SD	Min	Max
Primary	CE	101	9.53	7.37	1	30
	ESL	22	8.05	7.01	1	30
	Color	14	7.53	5.91	1	20
	CE and ESL	4	7.50	2.89	5	10
	CTAS	1	10.00		10	
	Total	142	9.04	7.08	1	30
Secondary	CE	9	8.22	5.60	1	20
	ESL	5	13	9.75	5	30
	Color	3	2.33	2.31	1	5
	Total	17	8.58	7.32	1	30
Tertiary	Color	2	7.50	3.54	5	10
	ESI	1	5.00		5	
	Total	3	6.67	2.89	5	10
Overall*	CE	110	9.43	7.23	1	30
	Informal scale	50	8.08	6.62	1	30
	Formal scale	2	7.50	3.54	5	10
	Total	162	8.94	7.03	1	30

Abbreviations: CE: Clinical experience; CTAS: Canadian triage acuity scale; ESL: Emergent symptoms defined in law; ESI: Emergency Severity Index

TABLE 4. The frequency and percentage of quality control of ED triage in Lao PDR.

Characteristics	Hospital level							
	Primary		Secondary		Tertiary		Total	
	n	%	n	%	n	%	n	%
Triage training								
No plan	79	48.8	6	3.7			85	52.5
Training availability								
As part of initial job training	16	9.9	1	0.6			17	10.5
As periodic training	47	29.0	10	6.2	2	1.2	59	36.4
As both					1	0.6	1	0.6
A review process of the triage scale								
No	136	84.5	16	9.9	2	1.2	154	95.7
Yes	6	3.7			1	0.6	7	4.3

urban areas.[14] As in other low-middle-income countries, healthcare facilities and resource infrastructure are unequal by region.[15]

The nationwide survey analyzed the situation in all Lao PDR ED triage system hospitals. Eighty-five percent of hospitals did not use an official and formal triage scale. Several triage scales have been used across hospital types in the ED triage system. Most triage scales were informal categorizations using clinical experiences (CE, 67.9%), the legally defined emerging symptoms based on the Lao PDR ED medical service (ESL, 16.7%), and by color (11.7%). The scales had different designs and materials, and no more than 80% were confirmed for the accuracy of their methods. The ED triage system in the Lao PDR applied two types of formal scales, including the CTAS and the ESI scales, and others used the CE & ESL (2.5%) mixed scale. Scaling variation made it impossible for patients across the country to receive the same treatment and made it extremely difficult to determine the efficacy and safety of different scales.[11,16]

The average triage time in the Lao PDR EDs was 8.94 ±7.03 minutes, 3-5 min longer than the triage time reported in previous studies.[11,17] CE for triage assessment required the most time, while the standardized scale required the least time at the hospital level. There was a mean difference in triage time across the three methods dropping from CE to informal and formal rankings. Using clinical experiences took longer than informal and formal scales for prioritizing ED patients. Ringström et al.[18] systematically reviewed the literature on triage for prioritization in EDs. Two studies recorded a 36-minute shorter length of stay and a significant reduction in waiting time for doctor assessment, with a mean difference of 16 minutes, contrasting formal triage with informal triage. Verified triage scales quickly enhanced critical access to care for ED patients, reducing waiting time and length of stay in the EDs. The triage scale usually is based on assessing conditions and determines how long the patient will wait before seeing a physician. The correct rating scale is essential to ensure the quality of ED care.[16] Van Der Wulp and Van Stel[19] compared clinical outcomes between triage models. A large Netherlands study reported that the 5-level ESI was more effective in predicting admission to a ward than the 5-level Manchester triage scale (MTS). No general conclusions are possible when comparing different triage models.[18]

Results showed that 58.6% of the EDs in the Lao PDR used an ER nurse, and 20% used a general physician (GP). Additional registered nurses (RNs) have also treated triage patients in other developed countries (the USA and Australia).[11,20] Triage is the first nursing activity occurring when a patient arrives at an ED. However, over 50% of all EDs had no training plan for their ED staff during this study. Many hospital ED personnel were deficient in their education (48.8%). The availability of triage-training facilities and personnel and the scientific verification of method accuracy assessed triage system quality. Quality-management proposals suggest that all hospital members wish to use a standard scale or have a triage learning session to improve triage methods. Government officials, stakeholders, and professionals must take action to establish policies that can resolve critical weaknesses in triage through standard hospital training and human resource development.[15,21]

Hospitals showed almost equivalent numbers for those using standard triage methods and those without (45.1% and 54.9%, respectively). The barriers against the use of a triage method were the absence of a standard scale (35.8 %), the vagueness of context (7.4 %), and over-triage (1.9 %), respectively, as disclosed by 69.7 % of the ED head directors. A tested and verified triage method can help minimize obstacles to successful triage. In addition, triage scale vagueness indicates that officers lack the experience and confidence to interpret the context of patient symptoms.[11] Incentives for professionals regarding ED triage system development skills are needed. Government policymakers should formulate specific policies to strengthen the ED triage system to enhance the professionalism of healthcare providers and ensure that the EMS curriculum includes the use of a triage system in the healthcare program.

Most ED systems in The Lao PDR apply informal triage systems to prioritize patient treatment. Many triage scales were used at different hospital levels in the ED triage system but were not based on a formal or standardized triage scale. ED nurses are the first to perform patient triage. The period of the prioritization process was 8.94±7.03 min., longer than the standard triage time of fewer than 3 minutes.

Limitations

Since only one hospital director in each hospital was interviewed, personal bias from triage experience may be present. Also, the predominant primary hospital findings may not have captured the triage processes of secondary and tertiary hospitals, limiting the generalizability of results. Finally, although valid and reliable instruments were used, data collection tools were developed, tested, and standardized in western populations; cultural differences may result in compromised or incomplete data in a different eastern culture.

CONCLUSION

Triage systems are methods for systematically prioritizing patients' treatment, but the design of these categorizations varies considerably among EDs hospital in the Lao PDR. Many head managers call for a formal triage scale and training plan for their ED staff. Establishing a standard triage system at all hospital levels in the Lao PDR are needed because it would be standardized ED health care throughout the Nation.

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The Potential of Vitamin-D-Binding Protein as a Urinary Biomarker to Distinguish Steroid-Resistant from Steroid-Sensitive Idiopathic Nephrotic Syndrome in Iraqi Children

Ali Mohammed Abd Alridha*, Dheyaa Jabbar Kadhim, Ayad Hussein Ali Alkhazrajy*****

**Department of Clinical Pharmacy and Therapeutics, Faculty of Pharmacy, University of Kufa, Najaf, Iraq, **Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq, ***Babylon Hospital for Maternity and pediatrics, Babylon, Iraq.*

ABSTRACT

Objective: To determine the ability of uVDBP to differentiate SRNS from steroid-sensitive nephrotic syndrome (SSNS) in Iraqi children.

Materials and Methods: This cross-sectional study enrolled children with SRNS (n=31) and SSNS (n=32) from the pediatric nephrology clinic of Babylon Hospital for Maternity and Pediatrics over three months. Patients' characteristics in terms of demographics, clinical data, and urinary investigations were collected. Quantitative analysis of uVDBP levels was undertaken via a commercially available ELISA kit.

Results: The median uVDBP values were significantly higher (p-value<0.001) in the SRNS group (median=10.26, IQR=5.91 µg/mL) than in the SSNS group (median=0.953, IQR=4.12 µg/mL). A negative correlation was noted between uVDBP levels and estimated glomerular filtration rate (eGFR) (Spearman's rho coefficient = −0.494, p=0.001). Nevertheless, the rise in uVDBP concentrations was still considerable in children with SRNS whose eGFR measurements were above 60 mL/min/1.73 m^2. The study revealed a good discriminatory power for uVDBP as a predicting parameter to distinguish SRNS from SSNS (AUC= 0.909, p<0.0001. The optimal uVDBP cut-off value of 5.781 µg/mL was associated with a sensitivity of 83.9% and specificity of 84.4% to differentiate SRNS from SSNS.

Conclusion: Considering its significant discriminatory strength, uVDBP can be considered as a potential marker to noninvasively distinguish children with SRNS from those with SSNS.

Keywords: Nephrotic syndrome; biomarker; vitamin D binding protein; steroid-sensitive nephrotic syndrome; steroid-resistant nephrotic syndrome (Siriraj Med J 2023; 75: 248-258)

INTRODUCTION

Nephrotic syndrome (NS) is a common glomerulopathy that occurs in children. The disorder is distinguished by episodic events of relapses that involve edema, proteinuria, and hypoalbuminemia.[1–3] The two prevalent forms of the disease often found in the histopathological study of an invasive renal biopsy, are minimal-change disease (MCD) and focal segmental glomerulo-sclerosis (FSGS).[4–7] Children with steroid-resistant nephrotic syndrome (SRNS) are at higher risk of the condition worsening and development of complications in comparison to children with steroid-sensitive nephrotic syndrome (SSNS).[8–12] Furthermore, reports indicated that the number of cases with SRNS is escalating which is likely attributed to the growing number of cases diagnosed with FSGS worldwide (including Iraq).[13–16] FSGS is the second leading cause of the end-stage renal disease (ESRD) and chronic renal failure in childhood.[17,18]

Corresponding author: Ali Mohammed Abd Alridha
E-mail: alim.abdalridha@uokufa.edu.iq
Received 11 January 2023 Revised 23 February 2023 Accepted 27 February 2023
ORCID ID:http://orcid.org/0000-0002-5580-9849
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Responsiveness to steroid therapy has been reported to provide a better prediction of prognosis as compared to a renal biopsy study.[1] Hence, children with idiopathic nephrotic syndrome (INS) complete an imperative trial of high-dose steroid therapy (for a variable duration of up to three months) which can be considered as both therapeutic and diagnostic intervention. If successful remission is not attained, the patient diagnosis is presumed SRNS and a biopsy study is warranted to identify the histopathological type.[19–22] On the other hand, identification of SRNS (specifically FSGS) is commonly missed with a single kidney biopsy because of the focal nature of the glomerular lesions, which mandate performing several biopsies for accurate diagnosis of FSGS.[23]

Vitamin D deficiency is a common complication in NS, which was reasoned to develop predominantly due to urinary losses of vitamin D binding protein (uVDBP).[24,25] In children with NS, a greater extent of the decline in serum vitamin D level was noted in SRNS as compared to SSNS suggesting that the severity of uVDBP losses is more prominent in SRNS than in SSNS.[26–28] In that regard, the uVDBP levels were assessed in SRNS and SSNS patients from India and the United States (US) and significantly higher concentrations were reported in SRNS as compared to SSNS.[29,30] However, SSNS subjects with proteinuria on urinalysis showed a higher trend of uVDBP levels than that in SSNS cases without proteinuria. It was questioned whether the increased levels of uVDBP were a reflection of more pronounced proteinuria rather than the disparity in steroid responsiveness in INS patients.[31]

Additionally, when the findings of the SRNS groups were examined separately, the reported uVDBP levels in the studied populations from the US and India were far from equivalent. The uVDBP levels in the SRNS groups from both studies (the American and the Indian, respectively) were 13659 (median; IQR 477–22,979) and 701.12 (mean; SD ± 371.64) ng/mL.

More studies in different populations are still required to provide further information about the capability of uVDBP in predicting steroid-responsiveness in children with INS. In Iraq, no research, to our knowledge, was undertaken to investigate the ability of uVDBP as a biomarker to differentiate children with SRNS from SSNS. Thus, we conducted this study to evaluate the potential of uVDBP as a noninvasive biomarker to predict steroid responsiveness in Iraqi children with INS.

MATERIALS AND METHODS

Setting and study design

This cross-sectional study was conducted in the department of pediatrics at Babylon Hospital for Maternity and Pediatrics from March to June 2022. The Human Research Committee of Babylon Directorate of Health (Decision number: 44 on 28/3/2022) and Research Ethics Committee of the University of Baghdad – College of Pharmacy (Approval number: RECAUBCP17102021A on 17/10/2021) approved the study protocol. Informed consent was acquired from all study participants (or parents/legal caretakers) before their enrollment in the study.

Participants

Patients aged 1-14 years, who were already diagnosed with steroid-sensitive or steroid-resistant INS, were recruited from the pediatric nephrology consultation clinic. Steroid-sensitive nephrotic syndrome (SSNS) was identified as succeeding in acquiring successful remission (<1+ proteinuria on early morning urine dipstick) after 4 weeks of daily prednisolone [2 mg/kg/d (maximum 60 mg/d)].

Steroid-resistant nephrotic syndrome (SRNS) was identified as failing to acquire successful remission after 8 weeks of daily prednisolone [2 mg/kg/d (maximum 60 mg/d)] or 4 weeks of daily prednisolone [2 mg/kg/d (maximum 60 mg/d)] then another 4 weeks of alternate day prednisolone [1.5 mg/kg/d (maximum 50 mg/d)] or 6 weeks of daily prednisolone [2 mg/kg/d (maximum 60 mg/d)] then another 6 weeks of alternate day prednisolone [1.5 mg/kg/d (maximum 50 mg/d)].

The exclusion criteria included patients with fever, gross hematuria, acute kidney injury, active or recurrent urinary tract infection, and nephrotic syndrome secondary to systemic diseases such as lupus nephritis, viral infections, or diabetes. Serum fasting blood glucose was documented to exclude diabetes mellitus. Additionally, patients were screened for viral antibodies (HIV, HBV, and HCV), autoantibodies (anti-double stranded DNA antibodies and anti-nucleic acid antibodies), and low serum complement C3 levels to exclude NS secondary to viral infections and autoimmune diseases such as systemic lupus erythematosus. The patients were approached during their routine follow-up visit to the clinic and were recruited consecutively after their consent and satisfaction with the study's inclusion and exclusion criteria.

Sample size estimation

An online calculator (https://sample-size.net/sample-size-ci-for-auroc/) was used to calculate the sample size.[32] The expected area under the ROC curve and the width of the confidence interval (0.90 and 0.16, respectively) was estimated based on the results of previous studies.[29,30]

A sample size of 63 was calculated when the proportion of the sample having the positive studied outcome (steroid resistance) is 50% of the sample size. Thus, 31 patients were included in the positive outcome group (SRNS) and 32 patients were recruited for the negative outcome group (SSNS).

Data collection

Data about the clinical and demographical characteristics of all the study participants were collected in a predetermined sheet at the time of enrollment. The glomerular filtration rate (eGFR) was calculated based on the participant's height and serum creatinine using the updated Schwartz equation.[33]

A commercially available ELISA kit (Bioassay Technology Laboratories, Zhejiang, China) was utilized to measure the VDBP levels in urine. Urine collection was performed as part of a routine clinic visit. After collection, the urine sample (early morning void) was subjected to centrifugation at 3000 RPM for 20 min, aliquoted, and stored at -80 °C. Repeated freeze-thaw cycles of more than two times were not allowed.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) statistics software (version 22) was used to execute the statistical analysis. The categorical data of demographical and clinical characteristics were described using frequencies and percentages and tested the differences using the Chi-square analysis. The normal data of both study groups (height, serum albumin, and eGFR) were compared using the unpaired t-test while the non-normal data were compared using the Mann-Whitney U test. The receiver operator characteristics (ROC) curve was also analyzed to determine the discriminatory power of uVDBP level to distinguish SRNS patients from SSNS patients. Spearman rank correlation analysis was performed to evaluate the association of the uVDBP levels with the renal function of the studied nephrotic syndrome patients, which was represented by eGFR. A finding was considered statistically significant if the p-value was lower than 0.05.

RESULTS

The patients' characteristics in both groups (SSNS and SRNS) were comparable except for serum albumin, serum creatinine, and blood urea (p-value <0.05; Table 1). The number of participants receiving concomitant treatment with ACEI and diuretics was higher in the SRNS group (n= 8 and 14, respectively) than in the SSNS group (n= 2 and 5, respectively). The mean values of the eGFR based on the Schwartz equation were significantly lower in the SRNS group (63.61 ± 14.31mL/min/1.73 m^2, p-value<0.05) in comparison to those in the SSNS group (72.89 ± 14.71mL/min/1.73 m^2).

The median uVDBP values were significantly higher (p-value<0.001) in the SRNS group (median=10.26, IQR=5.91 µg/mL) than in the SSNS group (median=0.953, IQR=4.12 µg/mL). The difference between the two groups was statistically significant (Fig 1).

A subgroup analysis was performed to examine the difference in the uVDBP level between the SSNS patients with proteinuria and those without proteinuria. The uVDBP median in SSNS patients with proteinuria was 2.63 (IQR=5.72) while the median in those without proteinuria was 0.85 (IQR=3.91). No statistically significant difference was found (p-value>0.05, Fig 2A).

Another subgroup analysis was conducted in the SRNS to determine if there is a difference in the uVDBP levels among children with calcineurin inhibitor (CNI) therapy and those without CNI therapy (Fig 2B). The difference was insignificant between the two subgroups (median [IQR] =10.26 [5.32] in CNI-treated children compared to 9.13 [6.53] in non-CNI treated children; p-value>0.05).

The median uVDBP values were negatively correlated with eGFR (the Spearman's rho coefficient = – 0.494, p<0.01), as illustrated by the increase of uVDBP levels in INS patients that was accompanied by a corresponding decline of renal function based on eGFR measurements. However, high levels of uVDBP were still present in SRNS subjects despite preserved renal function (eGFR>60 mL/min/1.73 m^2; Fig 3).

The receiver operator characteristic (ROC) curve analysis was conducted to assess the uVDBP capability as a predicting indicator of steroid responsiveness in INS. The levels of the uVDBP parameter showed a high discriminatory power (Fig 4) to characterize SRNS patients from SSNS patients with an AUC of 0.909 (p<0.0001). The analysis also revealed that the optimal cutoff value of 5.781 µg/mL yielded a sensitivity of 83.9% and a specificity of 84.4% to distinguish SRNS patients from SSNS patients (Fig 4 and Table 2).

DISCUSSION

Children with INS who are resistant to steroids are at a high risk of sustaining complications and progressing to end-stage kidney failure. The routine approach to diagnosing SRNS is to observe the outcome of a trial of a long-term prednisolone course, which is typically followed by an invasive kidney biopsy for the prediction of treatment responsiveness and disease progression. This approach entails that individuals with SRNS are being

TABLE 1. Demographic characteristics and clinical data of the study participants.

Characteristics	The study participants (n=63)		P-value
	SSNS (n=32)	SRNS (n=31)	
Age at enrollment [years; median (IQR)]	6.48 (3.4)	8.5 (6)	0.104§
Gender [male; frequency (%)]	20 (62.5)	21 (67.7)	0.432
Age at onset of disease [years; median (IQR)]	4 (2)	3 (5.5)	0.19§
Weight [Kg; median (IQR)]	21 (10.6)	25 (25)	0.132§
Height (cm; mean ± SD)	111.81 ± 17.14	118.77 ± 26.09	0.218‡
Serum albumin (gm/L; mean **± SD**)	37.92 ± 7.15	32.36 ± 11.29	**0.024‡**
Serum creatinine [umol/L; median (IQR)]	54 (22.8)	65 (32)	**0.007§**
Blood urea [mmol/L; median (IQR)]	2.8 (1.45)	4.1 (2.8)	**0.003§**
eGFR (mL/min/1.73 m²; mean ± SD)	72.89 ± 14.71	63.61 ± 14.31	**0.014‡**
Presence of hypertension (frequency, %)			
Systolic blood pressure >95 percentile	4 (12.5)	5 (16.1)	0.479*
Diastolic blood pressure >95 percentile	3 (9.4)	7 (22.6)	0.138*
Pathology upon biopsy (frequency, %)			
Focal segmental glomerular sclerosis	-	1 (3.2)	NA
Membranoproliferative glomerulonephritis	-	1 (3.2)	NA
Minimal change disease	-	3 (9.7)	NA
No biopsy	32 (100)	26 (83.9)	NA
Immunosuppressant regimen (frequency, %)			
Prednisolone	32 (100)	3 (9.7)	NA
Prednisolone and cyclosporine	0	18 (58.1)	NA
Prednisolone and tacrolimus	0	3 (9.7)	NA
Prednisolone and chlorambucil	0	1 (3.2)	NA
Prednisolone and mycophenolate mofetil	0	6 (19.4)	NA
Concomitant medications (frequency, %)			
ACEI	2 (6.3)	8 (25.8)	**0.036***
Statin	2 (6.3)	6 (19.4)	0.118*
Diuretic	5 (15.6)	14 (45.2)	**0.011**

* Significance value for Fisher's Exact Test. § Significance value for Mann-Whitney U test.
‡ Significance value for Independent samples t-test. Statistically significant p-values are in bold.
Abbreviations: SSNS: steroid-sensitive nephrotic syndrome; SRNS: steroid-resistant nephrotic syndrome; SD: standard deviation; IQR: interquartile range; eGFR: estimated glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitor.

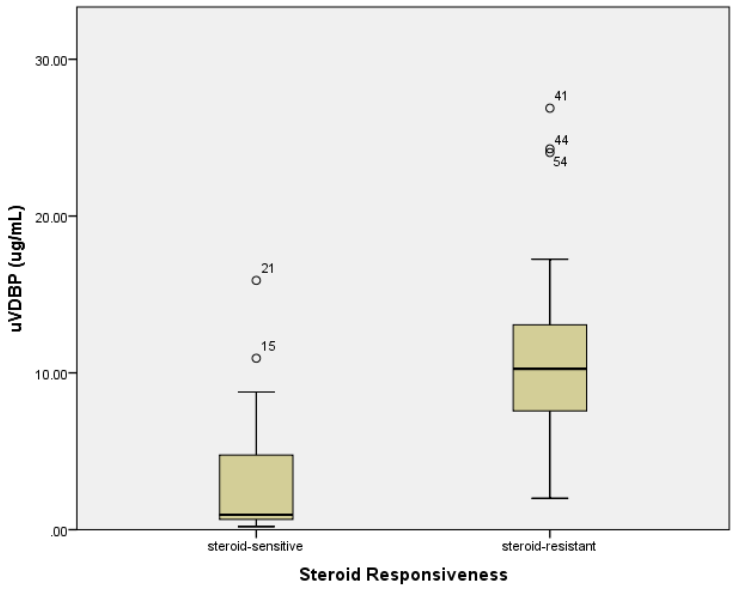
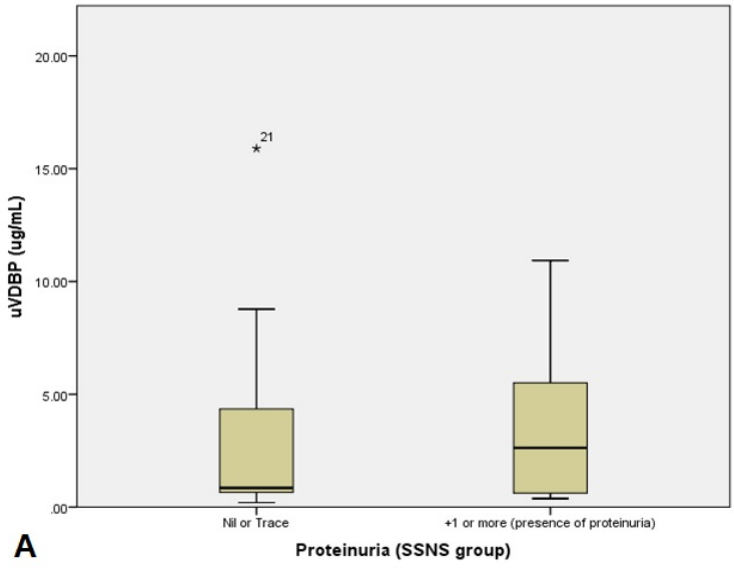


Fig 1. Urine vitamin D-binding protein (uVDBP) levels in the studied children with idiopathic nephrotic syndrome. Median uVDBP was significantly higher in the steroid-resistant group (median [IQR]= 10.26 [5.91]) than in the steroid-sensitive group (median [IQR]= 0.953 [4.12]; p-value<0.001).



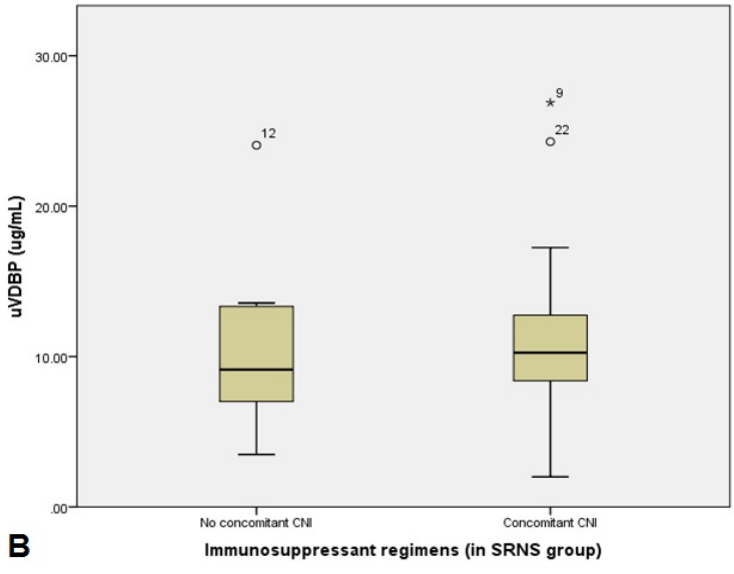


Fig 2. Subgroup analysis of uVDBP levels in children with SSNS and SRNS. A is a comparison of uVDBP levels in SSNS subgroups (SSNS patients with proteinuria and SSNS patients without proteinuria). B is a comparison of uVDBP levels in SRNS subgroups [SRNS patients with calcineurin inhibitor (CNI) use and SRNS patients without CNI use].

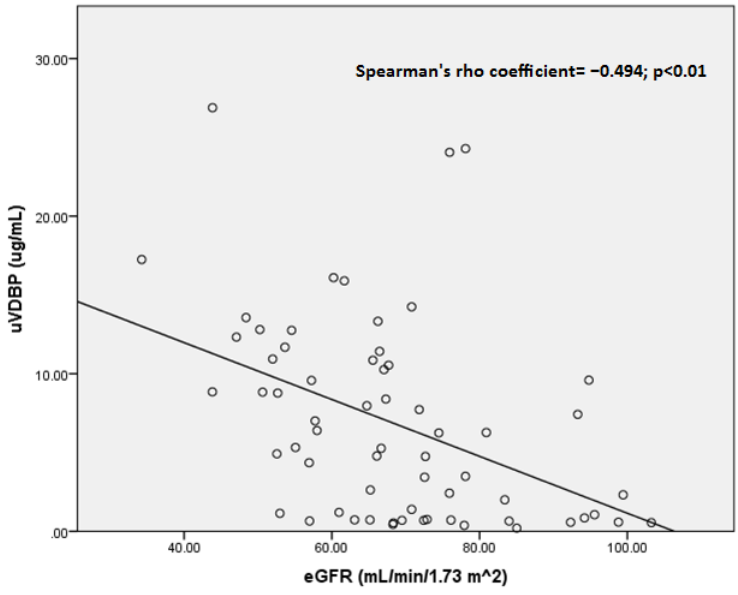


Fig 3. Correlation of uVDBP with renal function in children with idiopathic nephrotic syndrome (n=63). Median uVDBP is negatively correlated with estimated glomerular filtration rate (eGFR), as illustrated by the increase in uVDBP levels in nephrotic syndrome patients that is accompanied by a corresponding decline in renal function based on eGFR measurements.

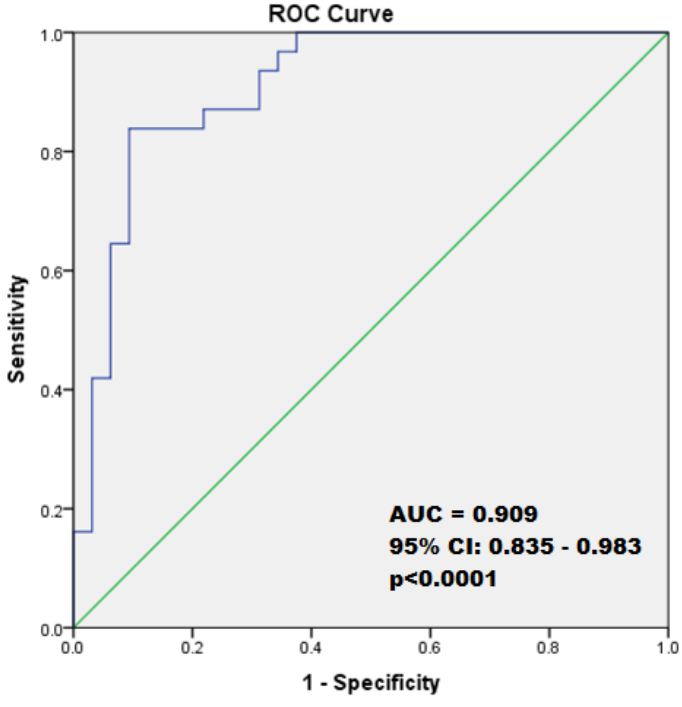


Fig 4. Receiver operator characteristic (ROC) curve analysis of uVDBP. The uVDBP parameter has good discriminatory power to distinguish SRNS from SSNS. ROC analysis revealed an AUC of 0.909 (95% CI: 0.835-0.983; p<0.0001) for the detection of SRNS. The optimal cut-off value was 5.781 µg/mL uVDBP, with a sensitivity of 83.9% and specificity of 84.4%.

exposed unnecessarily to high-dose steroid regimens, as well as prompting the postponement of administering alternative and potentially more effective regimens. Presently, there are no validated markers available for diagnostic purposes for SRNS. This study attempted to provide information to fill this gap by assessing the capability of uVDBP as a non-invasive biomarker to discriminate a priori between children with SRNS and those with SSNS.

In this study, the ROC curve analysis of uVDBP found a significantly reliable discriminatory power to discern patients with SRNS from patients with SSNS (AUC= 0.909, p<0.0001). This result was consistent with the results from similar studies in the United States and India (AUC= 0.87 and 0.897, respectively; p<0.0001).[29,30] We also investigated the impact of potentially interfering factors on the study findings, such as proteinuria status and CNI use. Although children with SRNS showed significantly higher uVDBP levels compared to those with SSNS, there were more patients with active proteinuria in the SRNS group (n=17) than in the SSNS group (n=7). Moreover, most SRNS patients (n=21) used a concomitant CNI, which is potentially nephrotoxic. Such interfering factors could further expand the difference in the uVDBP levels between the two groups. However, the subgroup analyses revealed no statistically significant differences in

TABLE 2. Results of the ROC curve analysis for uVDBP levels and the coordinates of the curve

Test result variable: urinary vitamin D binding protein level (μg/mL)				
Area Under the Curve				
Area	Standard Error[a]	Asymptotic Significance[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.909	0.038	<0.0001 (2.381E-8)	0.835	0.983
Coordinates of the Curve				
Positive outcome when the result is more than or equal to[c]			Sensitivity	1 – Specificity
-.8000			1.000	1.000
0.2890			1.000	0.969
0.4080			1.000	0.938
0.4865			1.000	0.906
0.5425			1.000	0.875
0.5615			1.000	0.844
0.5785			1.000	0.813
0.6160			1.000	0.781
0.6505			1.000	0.750
0.6745			1.000	0.719
0.6965			1.000	0.688
0.7040			1.000	0.656
0.7180			1.000	0.625
0.7260			1.000	0.594
0.7420			1.000	0.563
0.8035			1.000	0.531
0.9525			1.000	0.500
1.0980			1.000	0.469
1.1715			1.000	0.438
1.2960			1.000	0.406
1.6945			1.000	0.375
2.1565			0.968	0.375
2.3670			0.968	0.344
2.5225			0.935	0.344
3.0290			0.935	0.313
3.4605			0.903	0.313
3.9195			0.871	0.313
4.5500			0.871	0.281
4.7630			0.871	0.250
4.8465			0.871	0.219
5.0910			0.839	0.219
5.2920			0.839	0.188
5.7810			0.839	0.156
6.2560			0.839	0.125
6.3330			0.839	0.094
6.7035			0.806	0.094

TABLE 2. Results of the ROC curve analysis for uVDBP levels and the coordinates of the curve (Continued)

Test result variable: urinary vitamin D binding protein level (μg/mL)		
Coordinates of the Curve		
Positive outcome when the result is more than or equal to[c]	Sensitivity	1 – Specificity
7.2150	0.774	0.094
7.5725	0.742	0.094
7.8450	0.710	0.094
8.1780	0.677	0.094
8.5830	0.645	0.094
8.8045	0.645	0.063
8.8400	0.613	0.063
9.2105	0.581	0.063
9.5835	0.548	0.063
9.9270	0.516	0.063
10.3995	0.484	0.063
10.6980	0.452	0.063
10.8960	0.419	0.063
11.1770	0.419	0.031
11.5500	0.387	0.031
12.0025	0.355	0.031
12.5395	0.323	0.031
12.7775	0.290	0.031
13.0645	0.258	0.031
13.4440	0.226	0.031
13.9035	0.194	0.031
15.0710	0.161	0.031
15.9955	0.161	0.000
16.6720	0.129	0.000
20.6490	0.097	0.000
24.1675	0.065	0.000
25.5825	0.032	0.000
27.8800	0.000	0.000

[a] Under the non-parametric assumption

[b] Null hypothesis: true area = 0.5

[c] There is at least one tie between the negative actual state group and the positive actual state group for the test result variable [uVDBP (μg/mL)]. The smallest observed test value minus 1 is the lowest cutoff value. The highest observed test value plus 1 is the greatest cutoff value. The averages of two consecutively ordered observed test values are the remaining cutoff values.

uVDBP concentrations among SSNS patients with active proteinuria compared to those without active proteinuria, as well as among SRNS patients with concomitant CNI compared to those without concomitant CNI. Thus, the higher concentration of uVDBP in the SRNS group is not fully attributed to the patient's level of proteinuria or use of concomitant CNI. Valles et al. observed elevated uVDBP concentrations in patients with micro-albuminuria and chronic kidney disease (CKD) patients with macro-albuminuria. The uVDBP levels were still significantly higher even after maximal anti-proteinuric therapy and resolution of proteinuria. Proteinuria-independent levels of uVDBP are consistent with the findings of this study.[34]

Interestingly, the SRNS patients in this study had significantly lower eGFR compared to the SSNS group. Moreover, this study highlighted the presence of a negative correlation between uVDBP level and renal function. These findings may likely justify the higher uVDBP in the SRNS group. A plausible interpretation would be the fact that uVDBP is a low-molecular-weight protein that undergoes free filtration through the glomerulus, but the proximal convoluted tubules govern its reabsorption (via cubulin and megalin receptor-mediated transport).[24,35] Thus, a chronic process of tubular damage, such as that anticipated to occur in SRNS, most likely compromises the reabsorption and markedly increases the excretion of uVDBP.

Other markers have been investigated in an attempt to evaluate their ability to predict steroid responsiveness in NS patients. Woroniecki et al. assessed the potential of a urinary cytokine panel to distinguish steroid-resistant from steroid-responsive patients. The study demonstrated the ability of urinary TGF-beta[1] to discriminate FSGS from MCD but disclosed that a statistically significant difference in the marker expression was not found between SRNS and SSNS patients (p-value=0.21).[36] An earlier study discovered a distinct urinary proteome capable of predicting steroid responsiveness using mass spectrometry (surface-enhanced laser desorption/ionization). In the latter study, the proteomic profiling identified a 4.144 KD protein that identified all SRNS and SSNS patients with a positive predictive value of 96% and a negative predictive value of 88.2%. However, the significance of this discovery for clinical practice is hindered by the unavailability of such a mass spectrometry technique in most laboratories and the anonymity of the identifier protein sequence.[37] To our knowledge, this is the first study to determine the discriminatory ability of uVDBP as a non-invasive marker for the differentiation of SRNS from SSNS in Iraqi children with INS.

This study has several limitations that should be considered before drawing any conclusions. This pilot investigation was conducted in a single center and with a cross-sectional design. The sample in each group was small and included patients with ongoing steroid therapy at the time of recruitment. There was also a wide disparity among the uVDBP values of the SRNS patients. Variable data might be expected when treatment response is investigated in children with INS. Studying groups with small sample sizes could augment such variability. However, the normality of the uVDBP data distribution was analyzed, and non-parametric statistical tests were performed because the uVDBP data were not normally distributed. Moreover, we were led to believe that the analysis outcomes are indeed powerful because of the strength of the significant difference between the two groups (p-value<0.001).

To validate the results of this study, an investigation with a larger sample size and a prospective cohort design that is carried out in multiple centers is necessary. Furthermore, it is important to consider the possibility that the increase in uVDBP concentration is likely attributed to renal tubular damage, which may develop in various types of chronic kidney disease rather than being an underlying process that is distinctive to patients with SRNS. Nevertheless, in the context of INS, the findings of this study revealed that uVDBP has a promising potential to merit clinical applicability to identify patients with SRNS. The availability of a urinary marker with the capability of predicting steroid responsiveness in children with SRNS may help clinicians to personalize the management and improve the chances of controlling this serious and progressive form of the disease. Additionally, uVDBP may also be beneficial in preventing children from being exposed to unnecessary trials of high-dose steroids and other potent immunosuppressive regimens to which they are likely non-responsive.

CONCLUSION

The present study revealed that uVDBP can discriminate SRNS from SSNS in Iraqi children with significant reliability. The availability of a urinary marker with the capability of predicting steroid responsiveness can provide valuable information to develop more personalized therapy for children with INS.

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A Survey of Daily Genital Care Practices among Reproductive-aged Female Personnel at Siriraj Hospital

Khanin Hosiriphon*, Chenchit Chayachinda, M.D., M.Sc., Karit Keawpoonsub*, Kotchapun Taibowornpitak*, Duangrat Tuangrattanasirikun, B.Sc.****

**Medical students, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, **Unit of Gynaecologic Infectious Diseases and Female STDs, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.*

ABSTRACT

Objective: To demonstrate the genital cleansing habit and associating factors among reproductive-aged Thai women.

Materials and Methods: The survey was conducted at Siriraj Hospital between June and September 2022 (COA no. Si 370/2022). Twenty patient unit wards and 20 office units were randomly selected. Only active Siriraj female staff aged 18-50 were approached. The exclusion criteria included medical students and doctors, pregnant women, incomplete questionnaires, and women with immunocompromised conditions. Twenty sets of questionnaires, together with an information sheet as well as a box to return the questionnaire, were left at each unit. The primary outcome was the frequency of daily genital cleansing done outside of shower time. Associating factors and other genital care practices were secondary outcomes.

Results: Of the 800 distributed questionnaires, 611 were returned (response rate of 76.4%) and 504 were eligible for the study. The participants were 32.7±7.3 years old and most were in the 25-40 age group. Up to 90% reported genital cleansing outside shower time and 74.2% (374/504) of all respondents and 74.7% (236/316) of those with sexual experience cleansed >2 times daily. Twenty-four participants (4.8%) practiced vaginal douche. Water without genital care products is the most common method of cleansing. There was no association between sexual health risks and frequency of cleansing.

Conclusion: Three fourths of reproductive aged Thai women practice genital cleansing >2 times per day. Water without genital care products is the most common method of cleansing. There is no association between the habit and any demographic data and sexual health risks.

Keywords: Survey; genital care; women; reproductive age; Thai (Siriraj Med J 2023; 75: 259-265)

INTRODUCTION

The vagina is a pivotal part of all women as it is the route of menstruation and birth, sexual intercourse, and is a big commensal community of organisms. Together with *Lactobacilli spp*., which are facultative bacteria that protect the vagina, aerobic bacteria, anaerobic bacteria and fungus, particularly *Candida spp*., live in balance.[1] Other protective factors of the vagina are non-keratinizing, stratified squamous epithelium which contain innate immune cells, protein covering its surface, and secretion from surrounding glands.[2] The Society of Gynecologists and Obstetricians (SOGC) states that vaginal douche is not necessary and may negatively affect vaginal health.[3] Excessive vulvar cleansing during pregnancy may also

Corresponding to: Chenchit Chayachinda
E-mail: chenchit.cha@mahidol.ac.th
Received 11 January 2023 Revised 24 February 2023 Accepted 25 February 2023
ORCID ID:http://orcid.org/0000-0002-0153-2231
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lead to adverse perinatal outcomes.[4,5] At the moment, many genital care products are available in the market, but none provides strong evidence of improving the vaginal ecosystem. On the contrary, they may derange the ecosystem and increase the risk of infection.[4,5] The Canadian Women's Health Network recommends that water for vulvar cleansing should be adequate.[6]

Both vaginal candidiasis (VC) and bacterial vaginosis (BV), which are two forms of vaginal dysbiosis, account for the majority of abnormal vaginal discharge at gynaecologic clinics.[7] They markedly affect women's lives, both physically and mentally. VC causes marked vaginal/vulvar pruritus, increases the amount of vaginal discharge, dysuria and dyspareunia, while BV causes fishy-odor and/or increases amount of vaginal discharge.[8] Dysbiosis facilitates infections, including pelvic inflammatory disease (PID), human immunodeficiency virus (HIV) infection, and herpes genitalis.[9-11] Moreover, pregnant women with BV or VC tend to have adverse pregnancy outcomes such as preterm birth (PB), premature rupture of membranes (PROM) and chorioamnionitis.[4,5,12,13] Recently, aerobic vaginitis (AV) and cytolytic vaginitis (CV) have also been considered as other forms of vaginal dysbiosis.[8]

According to literature review, data regarding genital care is rarely studied since it may be influenced by culture and climate. A study of 220 Brazilian gynecologists with a mean age of 37 years who worked outside their home >10 hours per day showed that 17.8% did one-time external cleansing per day, while 52% did it twice per day. Their cleansing habits were as follows: 25.9% after voiding, 21.5% after defecation; 52.7% before having sex, and 78.5% after having sex.[14] Another study from Canada, which was an anonymous survey, included 1,435 participants.[15] In that study, genital care products used were vaginal moisturizer/lubricants (40.6%), vaginal tablets (34.8%), wet tissue paper (4.2%), and genital soap (4%). Women who used these products were three times as likely to experience vaginal symptoms. Besides, vaginal douche is also commonly practiced by women from specific regions and shows a negative impact on vaginal health.[16-18]

In 2011, a study was conducted among 400 young Thai women aged 20-35.[19] At that time, the prevalence of external genital cleansing and vaginal douche were 70.5% and 14.3%. Cleansing habits were linked to sexual experience, an unpleasant odor, or an increased amount of vaginal discharge. However, in the past decade, more genital care products have been launched and information online has become easily accessible. Moreover, the 2011 study of young Thai women does not represent other age groups. Therefore, the present study aims to demonstrate the prevalence of genital cleansing habit, current trends of genital care practice, and associating factors among reproductive-aged Thai women.

MATERIALS AND METHODS

The survey was conducted at Siriraj Hospital, which is the biggest hospital in Thailand, between June and September 2022. It was ethically approved by the Siriraj Institutional Review Board, Mahidol University (COA no. Si 370/2022).

Survey development

In brief, the survey took around 10 minutes to complete, was completely anonymous, and included controversial choices (no absolute right option). The survey about women's health and genital care practice was developed after literature review[14,15,19] and questions routinely asked at the Siriraj Female STD Clinic.[7] Four pages of questionnaires contained three parts, including demographic data, obstetric-gynecologic history, and genital care. In total, there were 48 questions.

Participants

Siriraj Hospital is a quaternary hospital with over 10,000 staff, including doctors, nurses, and back-office employees. Twenty patient ward units and 20 office units were randomly selected. Active Siriraj female personnel aged 18-50 were approached. The exclusion criteria included being medical students or doctors, pregnant women, or women with immunocompromised conditions such as diabetes mellitus (DM), systemic lupus erythematosus (SLE), or human immunodeficiency virus. Moreover, questionnaires without complete answers in the 'genital care' section were also excluded.

After receiving ethical approval and permission from the Director of Siriraj Hospital as well as the Head of Siriraj Nursing Department, the study team randomly chose 20 back-office units and 20 patient wards. The head of each sampled unit was approached to explain the details of the study and to ask for permission. If the head agreed, 20 sets of the questionnaire together with an information sheet were left at the unit. The study team provided a box for participants to return the questionnaires. As the survey was anonymous, informed consent was exempted. However, the return of questionnaires implied consent. After one week, the study team collected all the boxes to minimize identification. Next, the study team scanned completeness of the questionnaires and data was transferred to an Excel spreadsheet by two-blinded officers, and statistical analysis was carried out.

Outcome measures

The primary outcome was frequency of daily genital cleansing outside the shower. Internal cleansing was defined as use of water and/or soap to clean the inner side of labia majora or labia minora. External cleansing was defined as the use of water and/or soap to wash the mons pubis and/or outside of the labia majora. Vaginal douche was defined as using a syringe to push fluid into the vagina for cleansing. Other genital care practices and associating factors were secondary outcomes.

Sample size calculation and statistical analysis

Given the fact that 52% of Brazilian female gynaecologists practiced external genital cleansing at least two times per day[14] the sample size was 384 when alpha was set at 0.05. An additional 20% was added in case of incomplete questionnaires. Therefore, the required number of participants was 470.

Statistical analysis was done using Stata version 12.1 (Statacorp LP, College Station, Texas USA). Descriptive data was shown as n (%), mean±SD, and median with interquartile range (IQR). A Chi square test and Fisher's exact test were used to compare categorical data. The student T-test and Wilcoxon Ranksum test was used to compare parametric and non-parametric continuous data. P<0.05 was set as statistically significant.

RESULTS

From the 800 questionnaires distributed, 611 were returned (response rate 76.4%). Of the returned questionnaires, 504 were eligible for the study. There were three women aged >50, three with SLE, nine with diabetes mellitus, and 92 incomplete questionnaires.

Participants were aged 32.7±7.3, and most were in the 25-40 age group. Of all the participants, two thirds finished a bachelor's degree, half were nurses, and 58.5% had a normal BMI. Up to 40.2% of participants reported sitting behavior greater than 5 hours per day and 22.5% did not exercise at all. Consumption of sugar-rich diet included 59.5% of participants who drank ≥5 glasses of juice per week, and 71.6% who ate sweets ≥3 times per week. Only 18.5% had received the HPV vaccine (Table 1). Seventy-two experienced abnormal vaginal discharge in the prior one year. Of this group, 66 reported one episode of VC, one had two episodes of VC, and 57 had bacterial vaginitis. The route of preferred drug administration was oral (63.3%), vaginal (19.6%) or either (17.1%).

Fig 1 shows the frequency of genital cleansing per day. Almost 20% of participants reported internal cleansing while 90% reported external cleansing. Twenty-four (4.8%) participants practiced vaginal douche. Most used only water to cleanse (70%), followed by genital soap (34%), and other special products (11%). The median duration of genital cleansing was one[1,3] minute. Most participants (95.8%) used sanitary pads instead of vaginal cups or tampons during menstruation. Around half of all participants did nothing with pubic hair and 37.5% shaved regularly, followed by LASER (8.1%), waxing (6.7%) and chemical agents (2.6%). The reasons for pubic hair removal (n=277) included hygiene (225, 81.2%), cosmetics (30, 10.8%), and soothing (22, 7.9%). Only 32/504 (6.3%) reported using pads outside of menstrual periods.

The cleansing habits are shown in Fig 2. The majority of respondents reported cleaning every time in the following situations: before sex (65.7%), after sex (76.2%), bad-smelling discharge (75.4%), increased amounts of discharge (66.3%), itching (70.3%), after defecation (82.3%), and after voiding (68.9%).

Of the 316 participants who had sexual experience, 37 had a history of miscarriage; and 95 had children. Hormonal contraceptions were used by 160 respondents, including 83 instances of combined oral contraceptive pills, 24 progestin only pills, 21 implants, 19 depo-medroxy progesterone acetate, and 13 levonorgestrel intra-uterine system. Most participants had one lifetime sex partner; one partner in the prior three months; and a male sex partner. Twenty-four women experienced STIs, including 20 cases of herpes genitalis, one of gonorrhea, one of ano-genital wart, one of chlamydia cervicitis, and one of trichomoniasis.

When combining internal and external cleansing, 74.2% (374/504) of all respondents and 74.7% (236/316) of those with sexual experience cleansed more than two times outside of the shower each day. Table 2 demonstrates associating factors with daily cleansing habits. There was no association between sexual health risks and cleansing frequency.

DISCUSSION

The genital care survey in reproductive-aged Thai women shows that three-fourths of all participants cleansed more than two times per day. This was similar to a study in young Thai women aged 20-35[19], but higher than that reported in Brazilian gynaecologists.[14] As culture and personal belief comes before clinical evidence[20], habits of genital care are normally taught from one generation to the next. Since Thailand is near the equator where the climate is hot and humid, women may consider genital cleansing a routine practice. However, genital cleansing is more controversial than vaginal douche in that the

TABLE 1. Characteristics of the participants (n=504).

	Categories	N(%), mean and SD (n=504)
Age (year)		32.7±7.3
	<25	99 (19.6)
	25-40	320 (63.5)
	41-50	85 (16.9)
Education		
	High school	69 (13.7)
	Bachelor	338 (67.1)
	Master degree or more	91 (18.1)
	Philosophy degree	6 (1.1)
Body mass index (kg/m^2)		22.8±4.5
	<23	295 (58.5)
	23-30	174 (34.5)
	>30	35 (7.0)
Sedentary lifestyle (hr/d)	0	65 (12.9)
	1-3	129 (25.6)
	3-5	108 (21.4)
	>5	202 (40.1)
Exercise	No	114 (22.5)
	Sometimes	345 (68.5)
	Regular	45 (9.0)
HPV vaccine		93 (18.5)
Juice at least 5 glasses per week		300 (59.5)
Sweet at least 3 times per week		361 (71.6)
Social alcohol consumption		215 (42.7)

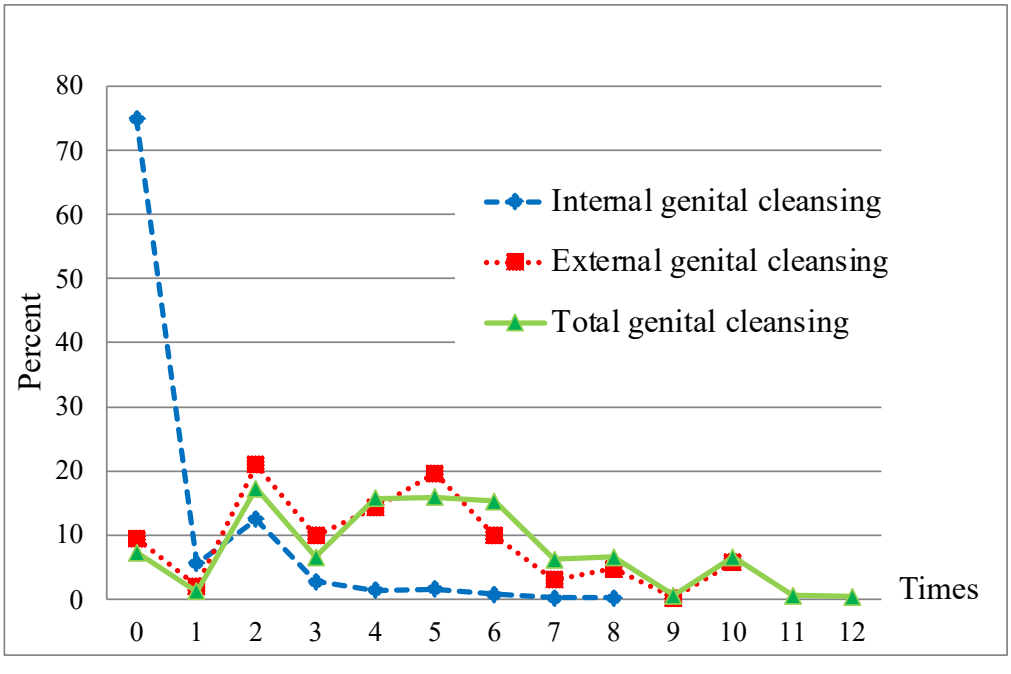

Fig 1. Frequency of internal and external genital cleansing per day (N=504).

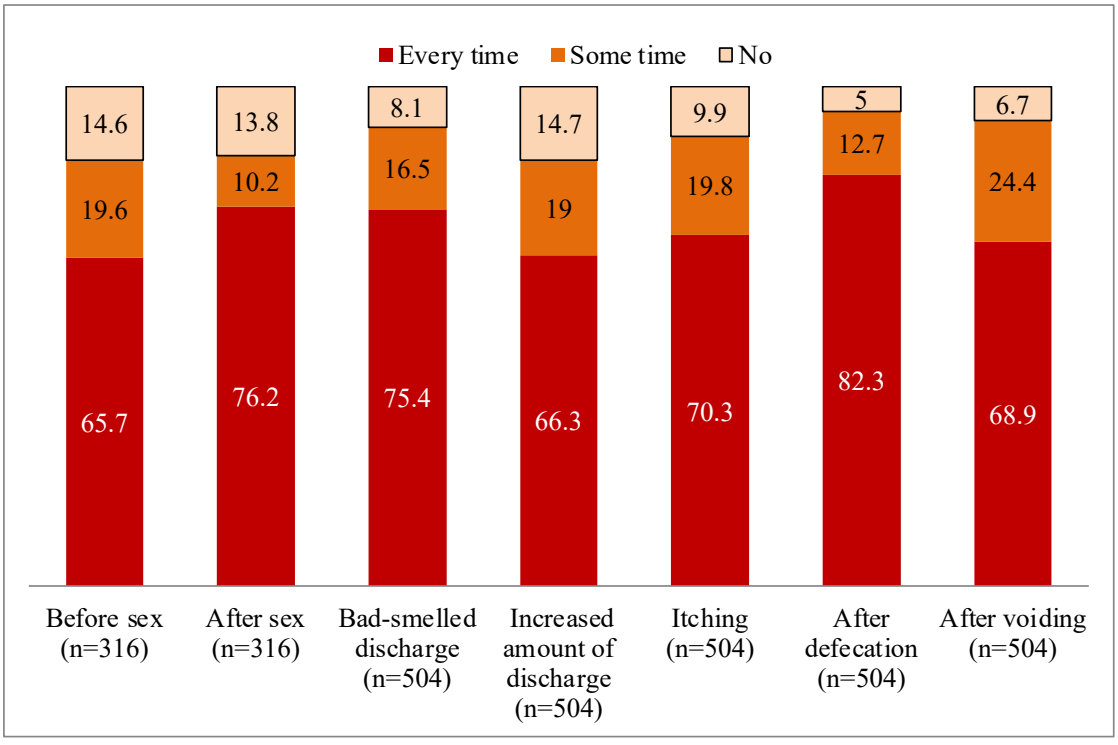

Fig 2. Cleansing habit.

TABLE 2. Sexual health risks (n=316).

	Categories	Total N (%)	Cleansing ≤2 /day	Cleansing >2 /day	P
All respondents (n=504)					
		N=504	N=130	N=374	
Age (years)	<25	99 (19.6)	23 (17.9)	76(20.2)	0.639
	25-40	320 (63.5)	88 (67.4)	232 (61.9)	
	41-50	85 (16.9)	19 (14.7)	66 (17.9)	
Sexual experience		316	80(61.1)	236(63.1)	0.934
Body mass index (kg/m²)	<23	295 (58.5)	84 (64.6)	211 (56.5)	0.278
	23-30	174 (34.5)	40 (30.7)	134 (35.7)	
	>30	35 (7.0)	6 (4.6)	29 (7.8)	
Experience of vaginal candidiasis		66 (13.1)	16 (12.3)	50 (13.4)	0.816
Experience of bacterial vaginitis		57 (11.3)	17 (13.1)	40 (10.7)	0.460
Respondents with sexual experience (n=316)					
		N=316	N=80	N=236	
Number of children	0	221 (70.0)	58 (72.5)	163 (69.1)	0.498
	1	60 (19.0)	16 (20.0)	44 (18.6)	
	≥2	35 (11.0)	6 (7.5)	29 (12.3)	
Having history of miscarriage		37 (11.7)	8 (10.0)	26 (11.0)	0.800
Number of lifetime sex partners	1	216 (68.4)	55 (68.8)	161 (68.2)	0.641
	2	40 (12.7)	8 (10.0)	32 (13.6)	
	≥3	60 (18.9)	17 (21.3)	43 (18.2)	
Currently being in relationship		257 (81.3)	65 (81.2)	192 (81.4)	0.949
Gender of partners	Male	291 (92.1)	69 (86.3)	222 (94.1)	0.076
History of STD		24/316(7.6)	8/80 (10.0)	16/236 (6.8)	0.552

vaginal douche can cause vaginal dysbiosis and harm vaginal microflora.[16] However, as BV and VC account for the majority of Thai women presenting abnormal vaginal discharge[7], reduction of cleansing habits should be included in a routine education session.

Compared to a study in Thai women aged 20-35[19], the respondents of the present study were three times less likely to practice vaginal douche. This may be explained by the fact that the present study surveyed women at work whereas the previous study included young patients at a gynecologic clinic. Although 10-20% of respondents reported experiencing BV or VC, and 7.6% had at least one STD, all reported being in good health at present. This supports previous studies that vaginal douche adversely affects vaginal ecosystem and brings about a variety of diseases.[16]

No associating factors with cleansing habits were demonstrated in the present study. This contrasts previous studies in young Thai women which showed that women with sexual experience tend to practice genital cleansing.[19] As young people tend to be more sexually active and have a higher incidence of STIs, vaginal douche may increase the risk of PID and its sequelae such as pelvic adhesion, chronic pelvic pain, and ectopic pregnancy.[21] Moreover, unplanned pregnancies are not uncommon at this age and vaginal dysbiosis from any cause, including excessive cleansing, results in PB, PROM and chorioamnionitis.[22] The present study suggests that education regarding sexual health for young Thai people should be enhanced.

Besides sexual experience, other sexual risks did also not affect cleansing habits. This may imply that genital care practice is generalized among Thai women as they demonstrated a high likelihood of frequent cleansing in many occasions such as after a period, before sex and after sex. The promotion of many genital products through multiple media streams using social idols as presenters has had a remarkable impact. Despite that, having been taught that the products are unnecessary, in line with the study in Brazil[14], most of the Siriraj female staff practiced genital cleansing using only water.

With increasing evidence showing that vulvar cleansing negatively affects the vaginal ecosystem[2], reducing genital cleansing habits may partly reduce the incidence of BV and VC. At the Siriraj Female STD Clinic, all patients with BV or VC were asked to explore their genital care practice and to minimize their cleansing habits. As a consequence, the recurrence of BV at 6-12 months was 6%[23] while a quarter of women with BV experienced recurrence in previous studies.[24] Compared to women in other countries[14,15,17,18,25], Thai women use less genital products and do not practice vaginal douche as often. As a result, our survey showed that only 13.1% and 11.3% of participants experienced VC and BV, whereas 80% of respondents in the Canadian survey[15] reported vaginal symptoms ≥1 times. There may not be the best practice that fits all; however, for those with any vaginal dysbiosis, reduction of cleansing habits is one of the musts to follow.

The guidance for proper female genital hygiene varies by regions. The Middle East and Central Asia (MECA) guideline one states that women of all ages require daily intimate hygiene which should be done before and after intercourse; and hypoallergic liquid wash is acceptable.[26] In contrast, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends shower rather bath and cleaning the vulva only once a day; and warns that washing with water can also cause dry skin.[27] An Australian health center suggests women limit genital washing to once a day using warm water with or without a pH adjusted soap and unperfumed moisturizer.[28] Adding to the genital cleansing with warm water, a clinic in the United States advice a thorough dry with a clean towel or a blow dryer set on cool.[29] As such, our findings are essential supporting data to form the Thai guideline which should be provided by domestic multidisciplinary care team.

This big survey on the unique issue of reproductive aged Thai women from different backgrounds is the strength of the study. Siriraj Hospital is a big hospital locating in the historical Thonburi area of Bangkok where many staff members are daily commuters from nearby provinces. The paper survey and clear understanding of the study enhanced its reliability. However information bias due to ambiguous questions could have occurred. As questions regarding genital care may be controversial, respondents, who were working in the hospital, possibly reported the answers they thought were correct, and not what they really did. Prospective studies using daily records of genital care practices should be further conducted.

CONCLUSION

Three fourths of reproductive aged Thai women practice genital cleansing more than two times per day, particularly the external one. Vaginal douche was less frequent. Water without genital care products is the most common method of cleansing. The cleansing habits are remarkable in the following situations: before and after sex, bad-smell discharge, increased amount of discharge, vulvar itching, after defecation and after voiding. There is no association between the habit and any demographic data or sexual health risks.

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Changes in Physical Components after Gastrectomy for Adenocarcinoma of Stomach and Esophagogastric Junction

Thikhamporn Tawantanakorn, M.D.*, Wanalee Phibalyart, M.D.*, Thammawat Parakonthun, M.D., Chawisa Nampoolsuksan, M.D.*, Tharathorn Suwatthanarak, M.D.*, Nicha Srisuworanan, M.D.*, Voraboot Taweerutchana, M.D.*, Atthaphorn Trakarnsanga, M.D.*, Chainarong Phalanusitthepha, M.D.*, Jirawat Swangsri, M.D., Ph.D.**, Thawatchai Akaraviputh, M.D.*, Asada Methasate, M.D., Ph.D.**, Vitoon Chinswangwatanakul, M.D., Ph.D.***

** Department of Surgery, ** Siriraj Upper Gastrointestinal Cancer Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: Enhanced Recovery After Surgery (ERAS) is a multidisciplinary approach that aims to optimize perioperative management, promote postoperative recovery, reduce postoperative complications, and improve long-term survival. The current study aimed to evaluate and compare the postoperative physical activity after gastrectomy between patients who underwent upper gastrointestinal surgery according to ERAS and those who underwent surgery based on the conventional care (CC) protocol.

Materials and Methods: This prospective and retrospective review enrolled 60 patients (n = 31, ERAS group; n = 29, CC protocol group) diagnosed with adenocarcinoma of the stomach and esophagogastric junction who underwent curative surgical resection. Physical outcomes, including body weight, body mass index, body fat percentage, basal metabolic rate, muscle mass, gait speed, and handgrip strength at the preoperative and immediate postoperative periods and at 1, 3, and 6 months postoperatively, were compared between the ERAS and CC protocol groups.

Results: One month after surgery, the ERAS group had a lower percentage of body weight loss than the CC protocol group. There was no significant difference in terms of muscle mass loss between the two groups. The hand grip strength of the ERAS group increased after surgery. Further, at 1 month postoperatively, the gait speed of patients who underwent total gastrectomy in the ERAS group was significantly higher than that of patients in the CC protocol group.

Conclusion: ERAS for gastrectomy was associated with a lower percentage of weight loss and a trend toward physical activity enhancement in the early postoperative period.

Keywords: Enhanced Recovery after Surgery (ERAS); gastrectomy; physical change (Siriraj Med J 2023; 75: 266-274)

INTRODUCTION

Gastric cancer is the fifth most common malignancy worldwide, the tenth most prevalent in Thailand, and the third leading cause of cancer-related mortality.[1,2] Gastrectomy is the mainstay treatment of gastric cancer. It is a high-risk procedure and is associated with a high rate of perioperative complications.[3,4] After surgery, patients experience a decline in physical status, muscle mass (MM), and body weight (BW), which lead to poor quality of life and loss to follow-up.

Enhanced Recovery After Surgery (ERAS) is a multidisciplinary approach that aims to optimize

Corresponding author: Thammawat Parakonthun
E-mail: t.parakonthun@gmail.com
Received 30 January 2023 Revised 10 February 2023 Accepted 21 February 2023
ORCID ID:http://orcid.org/0000-0002-2990-0649
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perioperative management, promote postoperative recovery, reduce postoperative complications, and improve long-term survival. The ERAS guideline for gastric surgery was introduced in 2014.[5] Several studies have shown that the ERAS protocol is significantly associated with a lower length of hospital stay, enhanced bowel function, decreased hospitalization costs, and decreased rate of major postoperative complications.[6-9] In terms of long-term outcomes, compared with the conventional care (CC) protocol, ERAS was significantly associated with a better 5-year cancer-specific survival rate.[10] Further, it was correlated with a better postoperative physical activity and lower percentage of weight loss.[6,11] However, there are no available data about postoperative changes in physical compositions, such as BW and muscle function and strength, which are correlated with postoperative recovery.

Siriraj Hospital developed an intensive care program and established ERAS for patients undergoing upper gastrointestinal surgery.[12] The current study aimed to evaluate and compare postoperative physical activity after gastrectomy between patients who underwent upper gastrointestinal surgery based on ERAS and those who had surgery according to the CC protocol.

MATERIALS AND METHODS

Study design

This prospective and retrospective review included patients diagnosed with adenocarcinoma of the stomach and esophagogastric junction (EGJ) between September 2019 and February 2022 at the Faculty of Medicine Siriraj Hospital, Mahidol University. The eligibility criteria of this study were patients aged 18 years who were pathologically diagnosed with adenocarcinoma and who underwent curative surgical resection. Prior to surgery, all patients received information about ERAS and the CC protocol.[8,12] Patients with active cancer other than gastric cancer and EGJ cancer or those who were for palliative surgery were excluded. Conventional perioperative care was defined as normal perioperative management in which the treatment is dependent on individual surgeons and based on the experience and knowledge of the surgeon. However, all patients also received standard surgical therapy and routine surveillance.

The ERAS protocols involve therapeutic interventions in the preoperative, intraoperative, and postoperative periods. Patients and their families received preoperative counseling and education about treatment planning and preoperative preparation. The nutritional status was assessed and improved to achieve the target calorie intake. The energy requirement was 25-30 kcal/kg/day of total calories, and 1.5 g/kg/day of protein. Nutrition supplement was given to moderately malnourished patients. Patients with severe malnutrition received nutritional support at least 2 weeks before surgery. The enteral feeding tube was inserted in patients who could not tolerate adequate oral intake. To improve lung function and decrease postoperative pulmonary complications, patients were advised to smoke cessation at least 2 to 4 weeks prior to surgery and breathing exercise were encouraged preoperatively. In the perioperative period, patients received information about cough training and positioning. Patients were allowed to intake normal meals until 6 hours before the operation and intake clear liquid until 3 hours before the operation. Oral carbohydrate loading with 50 grams of glucose or SI-CARB Drink solution was administered to all non-diabetic patients 3 to 4 hours before surgery. Patients with gastric outlet obstruction underwent gastric decompression and lavage at least 3 days prior to surgery. Postoperative nausea and vomiting (PONV) risk was assessed, and nausea and vomiting prophylaxis was adopted. Intraoperative period, compression stockings were used for thromboembolism prophylaxis. The air-warming blanket was applied to prevent hypothermia. If the duration of the operation was longer than 4 hours or if the estimated blood loss was more than 500 ml, an additional dose of antibiotic was administered. An epidural or intravenous patient-controlled analgesia (PCA) was given to provide adequate postoperative pain control. We avoided the placement of a nasogastric tube and unnecessary external drain. On postoperative day (POD) 1, the patients were promoted immediate mobilization and allowed to sip water. The patients started to drink liquid on POD 2, then were allowed to ingest a low residual soft diet on POD 3. Perioperative glycemic control was performed. All drains were early removed when they were considered unnecessary. The aim of discharge was on the postoperative day 4 if they met the discharge criteria which included a normal body temperature, hemodynamic stability, adequate pain relief with oral analgesics, normal bowel movement, tolerance of soft diet, and normal white blood cell count. Our team contacted patients by telephone 48 to 72 hours after discharge for follow-up. Patients could contact us at any time if they had a problem.

Data on preoperative clinicopathological characteristics (including age, sex, tumor location, pathological stage, operative approach, and extent of resection) and physical factors (such as BW, body mass index [BMI], MM, hand grip strength [HGS], gait speed [GS], basal metabolic rate [BMR], and body fat percentage [%BF]) were reviewed. Body composition was analyzed using the bioelectrical impedance analyzer[13], which can provide information

about BW (kg), BMI (kg/m^2), MM (kg), %BF, and BMR (Kcal). HGS was measured using a handheld dynamometry, which can obtain information about muscle strength. The patients were asked to hold a dynamometer with the dominant hand in an upright straight position while the arms were in abduction at 15°, and then to squeeze the dynamometer with maximum isometric effort.[14] GS was evaluated using the 10-m walk test.[15] The patients walked with or without a walking device at a 10-m walkway without any break to the endpoint. The time required to perform two trials was converted to walking speed. GS was calculated as distance (m) divided by time (s). All data were collected at the immediate postoperative period and then at 1, 3, and 6 months postoperatively (Fig 1). The current study primarily aimed to evaluate and compare changes in BW, BMI, %BF, BMR, MM, GS, and handgrip strength after gastric surgery between the ERAS and CC protocol groups.

Gastric resection and lymphadenectomy were performed in accordance with the Japanese gastric cancer treatment guidelines.[16] Subtotal gastrectomy (SG) was defined as proximal gastrectomy and distal gastrectomy. Total gastrectomy (TG) was defined as TG and extended gastrectomy. This study was approved by the Institutional Review Broad of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA no. Si 557/2019).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software version 21.0 (SPSS, Inc., Chicago IL, USA). Continuous data were compared using the *t*-test and reported as mean ± standard deviation. Categorical data were analyzed using the Chi-square test and presented as number and percentage. A p-value of <0.05 was considered statistically significant.

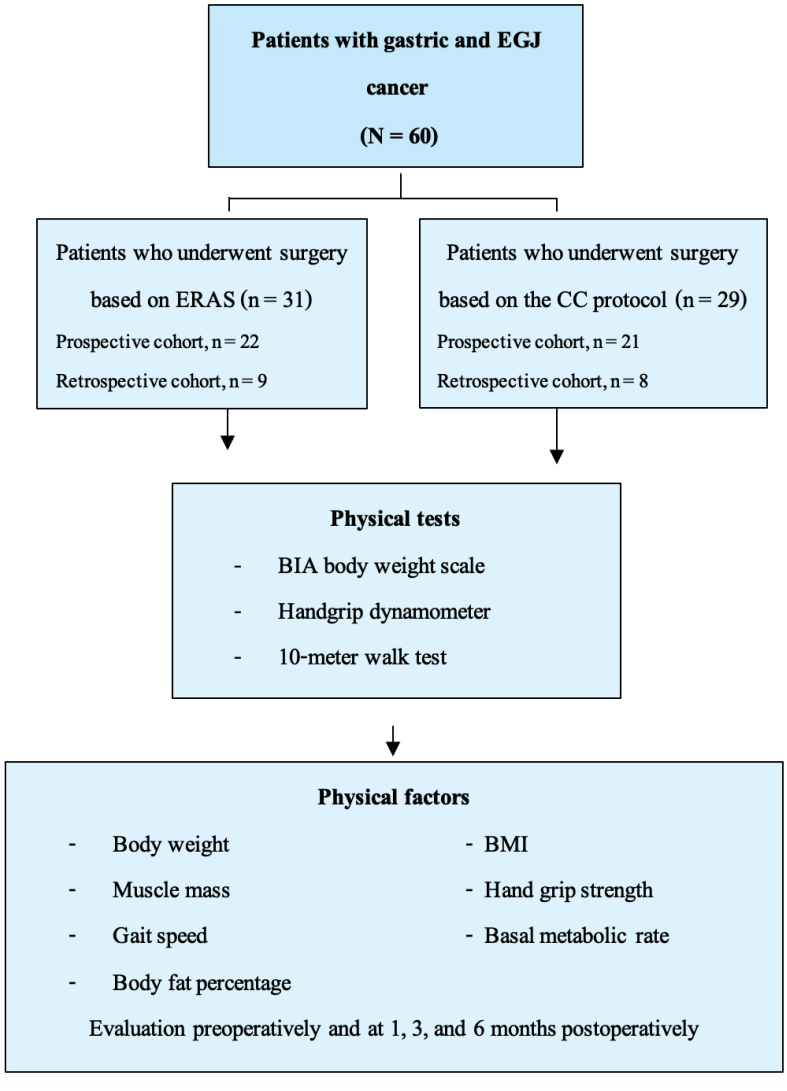

Fig 1. Study design and population

Abbreviations: EGJ, esophagogastric junction; n, number; ERAS, Enhanced Recovery after Surgery; CC, conventional care; BIA, bioelectrical impedance analysis; BMI, body mass index

RESULTS

The current study included 60 patients. Among them, 31 were enrolled in the ERAS group and 29 in the CC protocol group. The mean age of the participants was 63 years. Patients were diagnosed with adenocarcinoma of the stomach (n = 49, 81.67%) and EGJ (n = 11, 18.33%). There was no significant difference in terms of age, sex, tumor location, pathological staging, and operative approach. The proportion of patients who underwent TG was higher in the CC protocol group than in the ERAS group (p = 0.025). However, in the subgroup analysis, there was no significant difference in the extent of resection (Table 1) and baseline physical factors (BW, BMI, MM, HGS, GS, BMR, and %BF) (Table 2) between the CC protocol and ERAS groups.

Physical outcome

BW and BMI after gastrectomy decreased overtime in the CC protocol and ERAS groups (Figs 2 A–C). The ERAS group had a significantly lower percentage of BW loss (%BWL) at 1 month after surgery than the CC protocol group (6% vs. 9%, p = 0.036). Patients who underwent TG in the ERAS group had a significant lower %BWL than those who underwent TG in the CC group (5% vs. 9%, p = 0.043). There was no significant difference between the two groups in terms of %BWL at 3 and 6 months postoperatively. Moreover, both groups had lost MM overtime, and there was no significant difference in terms of changes in the percentage of MM (%MM) at 1, 3, and 6 months postoperatively (5.3% vs. 2.9%, p = 0.411; 4.5% vs. 7.2%, p = 0.618; and 6.5% vs. 11.7%, p = 0.450, respectively). The %BF loss did not significantly differ between the two groups. In the subgroup analysis, the %BF loss of patients who underwent TG in the ERAS group increased 6 months after surgery compared with that of patients who underwent TG in the CC protocol group (68% vs. 27%, p = 0.029) (Figs 2 D–F).

The BMR of the ERAS and CC protocol groups decreased after surgery. Further, there was no significant difference between the ERAS and CC protocol groups in terms of BMR at 1 month (65 vs. 62, p = 0.923), 3 months (91 vs. 112, p = 0.719), and 6 months (236 vs. 167, p = 0.244) postoperatively. The HGS (kg/BW) increased at 1, 3, and 6 months postoperatively in patients who underwent surgery based on ERAS (Fig 3A). However, in the TG subgroup analysis, there was no significant difference in terms of HGS at 1 month (0.002 vs. 0.02, p = 0.521), 3 months (0.11 vs. −0.68, p = 0.056), and 6 months (0.05 vs. −0.07, p = 0.252) postoperatively. The GS (m/s) of patients who underwent surgery based on ERAS increased at 1 month postoperatively (Figs 3B–C). There was no significant difference in terms of GS between the ERAS and CC protocol groups in all analyses (−0.69 vs. 0.14, p = 0.140). Nevertheless, the 1-month postoperative GS of patients who underwent TG in the ERAS group was significantly higher than that of patients who underwent surgery in the CC protocol group (−0.13 vs. 0.23, p = 0.018) (Figs 3D–F).

DISCUSSION

Previous studies have shown that ERAS for upper gastrointestinal surgery is beneficial in reducing length of hospital stay and promoting faster bowel function recovery.[6,17,18] Our study aimed to validate the application of ERAS based on its benefits in several aspects. Physical factors and body compositions can affect clinical outcomes in patients with cancer.[9,19] To validate the advantage of ERAS, we collected and compared data on muscle function performance and body composition between the ERAS and CC protocol groups. In terms of body compositions, this study found that after gastrectomy, the ERAS and CC groups had decreased BW, %BF, and MM. However, patients who underwent TG in the ERAS group had a lower %BWL at 1 month postoperatively compared with those who underwent TG in the CC protocol group. Our study result on BW change was in accordance with that of a previous study. A Japanese randomized controlled trial revealed that patients managed with ERAS had a lower %BWL. Further, the BW-to-preoperative weight ratio at 1 week and 1 month after surgery was higher in the ERAS group than in the CC protocol group.[6] Our previous prospective study[8] compared ERAS and the CC protocol in patients with upper gastrointestinal diseases who underwent curative resection at Siriraj Hospital. Results showed that BMI reduction was not significantly lower in the ERAS protocol group than in the CC protocol group. Nevertheless, the ERAS group had a faster BMI recovery than the CC group (3 vs. 6 months). In terms of MM and body fat loss, the ERAS group had a lower lean body mass loss (muscle and fat mass) than the CC group, probably due to the positive association between body mass and total %BWL.[20] Previous studies have shown that a lean BW loss of <5% at 1 month after surgery was an independent factor for predicting continuous treatment with adjuvant chemotherapy.[20]

HGS was strongly correlated with leg muscle power and calf cross-sectional muscle area. A low handgrip strength is a clinical marker of poor ambulation.[14] It has a linear association with inability to perform activities of daily living.[21] Our study has found that overall muscle strength (represented by HGS) and physical performance (indicated by GS) did not significantly differ between the

TABLE 1. Preoperative clinicopathological characteristics between the ERAS and conventional care groups.

Clinicopathological characteristics of the participants	Conventional care group (n = 29)	ERAS care group (n = 31)	P-value
Age, mean ± SD	63.76 ± 14.10	62.23 ± 13.48	0.669
Sex, n			0.170
Male	9 (31%)	15 (48.4%)	
Female	20 (69%)	16 (51.6%)	
Tumor location, n			0.379
Gastric cancer	25 (86.2%)	24 (77.4%)	
EGJ cancer	4 (13.8%)	7 (22.6%)	
pT stage, n			0.051
T0	1 (3.4%)	0 (0.0%)	
T1	5 (17.2%)	5 (16.1%)	
T2	6 (20.7%)	0 (0.0%)	
T3	7 (24.1%)	14 (45.2%)	
T4	10 (34.5%)	12 (38.7%)	
pN stage, n			0.170
N0	10 (34.5%)	10 (32.3%)	
N1	3 (10.3%)	8 (25.8%)	
N2	4 (13.8%)	7 (22.6%)	
N3	12 (41.4%)	6 (19.4%)	
pM stage, n			0.514
M0	27 (93.1%)	30 (96.8%)	
M1	2 (6.9%)	1 (3.2%)	
Operative approach, n			0.399
Open	25 (85.7%)	25 (80.6%)	
Laparoscopic	1 (3.4%)	4 (12.9%)	
Robotic-assisted	3 (10.3%)	2 (6.5%)	
Extent of surgery, n			0.025
Proximal gastrectomy	0 (0.0%)	4 (12.9%)	
Distal gastrectomy	7 (24.1%)	12 (38.7%)	
Total gastrectomy	16 (55.2%)	10 (32.3%)	
Extended gastrectomy	6 (20.7%)	5 (16.1%)	

A p-value<0.05 indicates statistical significance

Abbreviations: ERAS, Enhanced Recovery after Surgery; CC, conventional care; n, number; SD, standard deviation; n, number; EGJ, esophagogastric junction; pT, pathological primary tumor stage; pN, pathological lymph node stage; pM, pathological metastasis; Open, open surgery

TABLE 2. Preoperative physical factors compared between the ERAS and conventional care groups.

Physical factors	Conventional care group (n = 29)	ERAS care group (n = 31)	P-value
Body weight, mean ± SD	57.60 ± 10.74	60.13 ± 12.87	0.431
Body mass index, mean ± SD	22.57 ± 3.8	23.02 ± 4.33	0.687
Muscle mass, mean ± SD	39.61 ± 7.4	41.31 ± 8.11	0.597
Body fat percentage, mean ± SD	0.36 ± 0.12	0.39 ± 0.09	0.419
Hand grip strength, mean ± SD	0.76 ± 0.42	0.84 ± 0.26	0.586
Gait speed, mean ± SD	1205.22 ± 209.12	1328 ± 229.86	0.712
Basal metabolic rate, mean ± SD	30.42 ± 8.40	26.03 ± 12.13	0.336

A p-value<0.05 indicates statistical significance

Abbreviations: CC, conventional care; ERAS, Enhanced Recovery after Surgery; n, number; SD, standard deviation

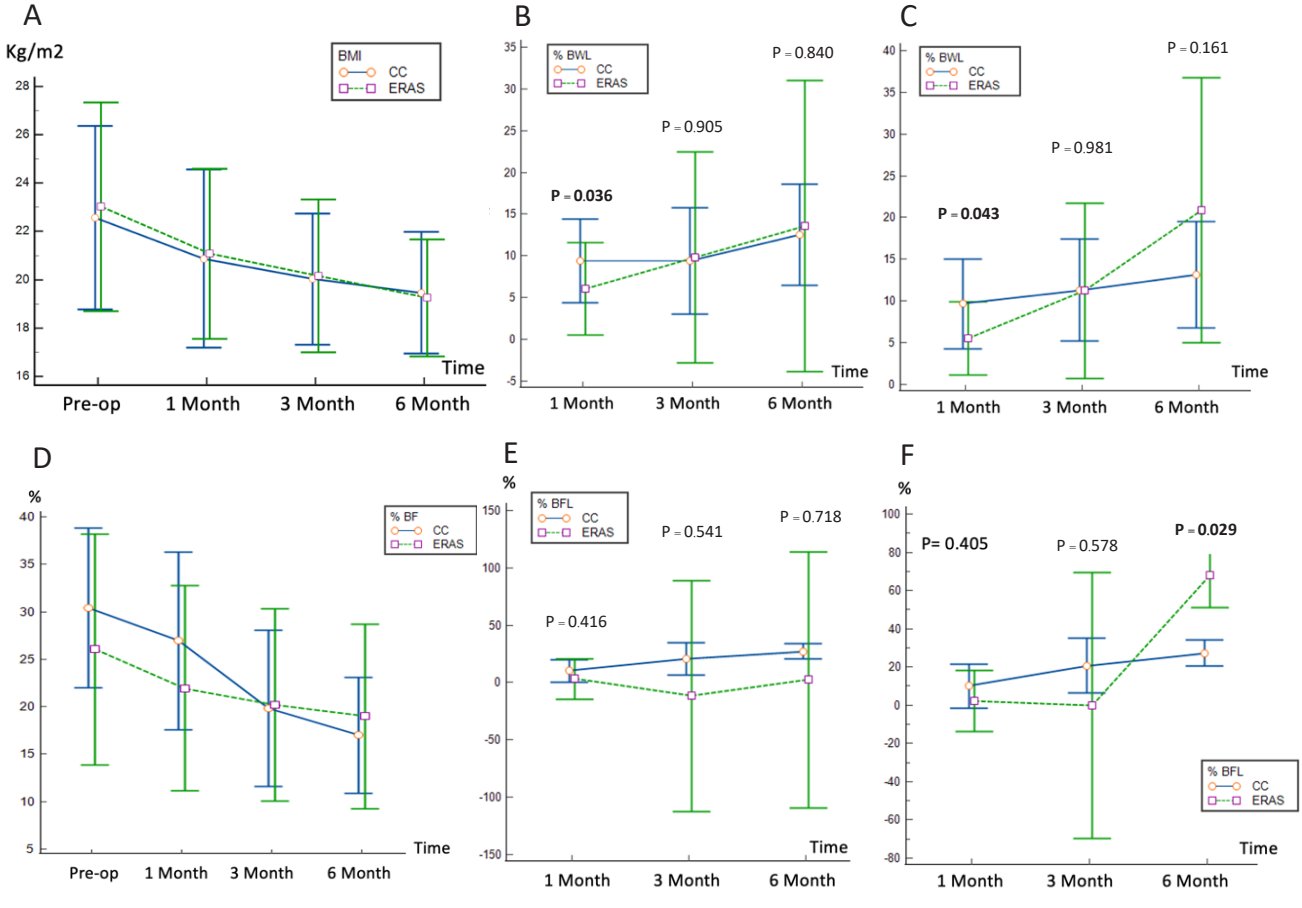

Fig 2. (A) BMI at the preoperative period and at 1, 3, and 6 months postoperatively, (B) % BWL in all group analyses, (C) % BWL in the total gastrectomy subgroup, (D) % BF at the preoperative period and at 1, 3, and 6 months postoperatively, (E) % BF loss in all group analyses, and (F) % BF loss in the total gastrectomy group

A p-value <0.05 indicates statistical significance

Abbreviations: CC, conventional care; ERAS, Enhanced Recovery after Surgery; BMI, body mass index; %BWL, percentage of body weight loss; % BF, percentage of body fat; %BFL, percentage of body fat loss; Pre-op, preoperative day

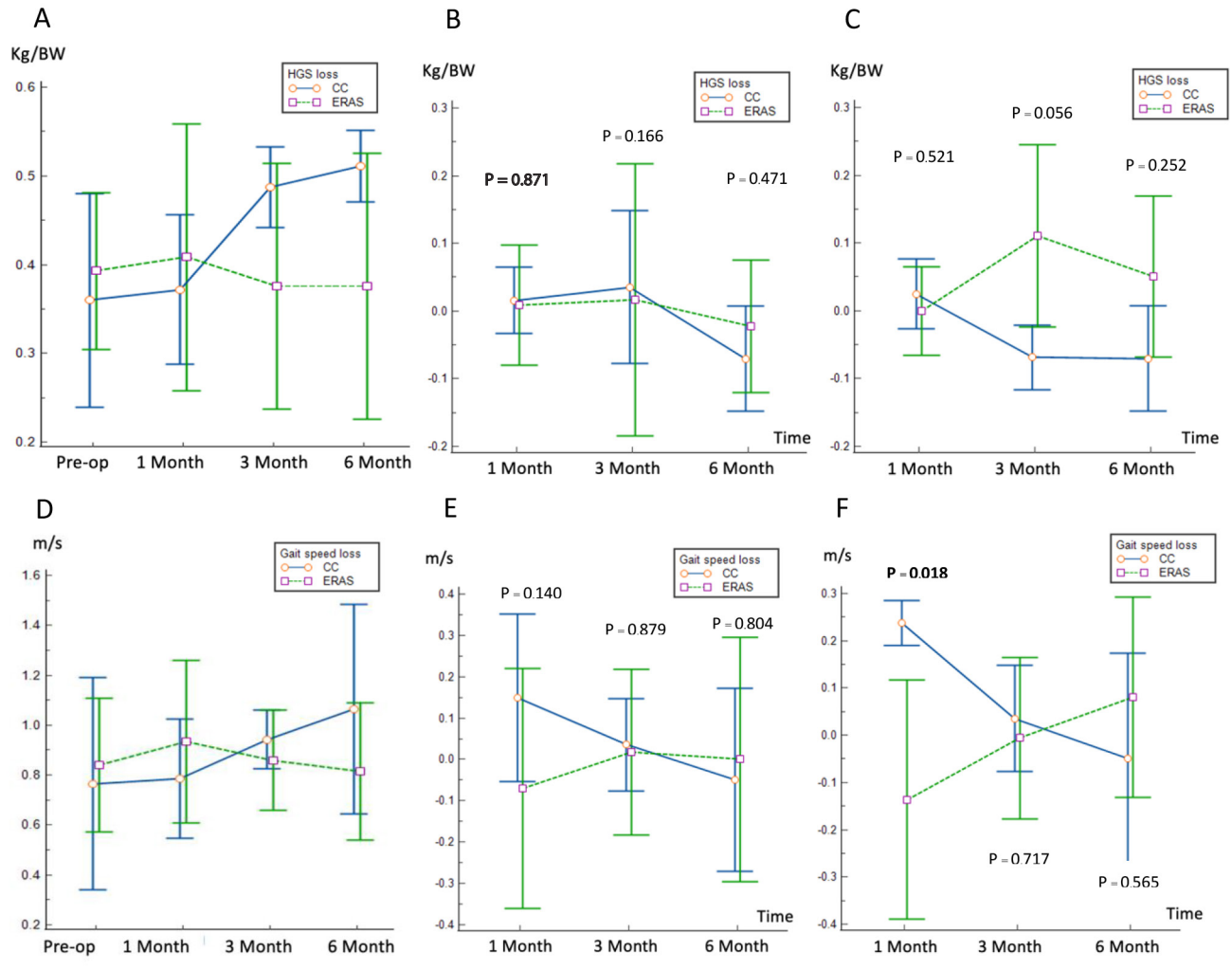

Fig 3. (A) HGS at the preoperative period and at 1, 3, and 6 months postoperatively, (B) HGS in all group analyses, (C) HGS in the total gastrectomy subgroup, (D) GS at the preoperative period and at 1, 3, and 6 months postoperatively, (E) GS loss in all group analyses, and (F) GS loss in the total gastrectomy subgroup

A p-value<0.05 indicates statistical significance

Abbreviations: CC, conventional care; ERAS, Enhanced Recovery after Surgery; HGS, hand grip strength; GS, gait speed; Pre-op, preoperative day

ERAS and CC groups. However, in the subgroup analysis of GS in patients who underwent gastrectomy, the ERAS group had a significantly better speed recovery at 1 month postoperatively than the CC group (0.13 vs. 0.23, p = 0.018). GS refers to physical performance.[22] Our data showed that the ERAS protocol promoted postoperative physical performance recovery. This finding was in accordance with that of another study[6] that facilitated more physical activities in the first week after surgery in the ERAS group.

Several clinical trials have shown that compared with surgery alone, adjuvant chemotherapy or chemoradiation therapy is associated with a better 5-year overall survival and 3-year disease-free survival.[23-25] There was a retrospective review about the long-term outcome of ERAS compared with the CC protocol. Results showed that the 5-year overall survival rates of the ERAS and CC protocol groups were 72.9% and 65.2%, respectively (p = 0.013).[10] Thus, the ERAS group had a better survival. Based on these data, the ERAS protocol had effects on BW and physical factors, and this could explain the association between ERAS and short- and long-term outcomes. Therefore, patients can receive adjuvant chemotherapy without delay, and this can contribute to improved survival.

This study has some mentionable limitations. First, our study cohort was small, and this might have limited the statistical power of our study in identifying all significant differences and associations. Second, there was variability in the surgical procedures. The majority of the conventional group underwent total gastrectomy which dominates the demographic data. The different types of gastrectomy and the reconstruction techniques

affected the post-operative condition. These were the factors that influence the nutritional status and post-gastrectomy sequence and affect this study. Therefore, further randomized controlled trials should be performed, and a larger sample size should be included to identify the benefits of ERAS.

CONCLUSION

ERAS for gastrectomy for adenocarcinoma of the stomach and EGJ can promote changes in physical compositions in the early postoperative period. Moreover, it is beneficial in reducing BW and promoting postoperative recovery.

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Conflict of interests: All authors have no conflicts of interest or financial support to declare.

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Specific Learning Objectives in the Form of Self-assessment to Facilitate Rehabilitation Residency Training Competency: A Prospective Cohort Study

Rinlada Pongratanakul, M.D., Waraporn Kanthanet, Kanda Sungkharuk, Sumana Srisoongnern, M.D.

Department of Rehabilitation Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To explore the benefits of rotation- and milestone-specific learning objectives in the form of self-assessment questionnaires to facilitate rehabilitation residency training.

Materials and Methods: Control and intervention groups were formed during academic years 2020 and 2021, respectively. The group participants were residents undergoing training in rehabilitation medicine. Before entering their rotations, the intervention group participants were provided rotation- and milestone-specific learning objectives in the form of self-assessment questionnaires. The participants of both groups self-assessed their confidence levels for each learning objective after the rotations, using a 5-level Likert scale. The self-rated scores of the 2 groups were compared.

Results: Twenty-five and 28 residents were enrolled in control and intervention groups, respectively. There were 12 sets of learning objectives (4 rotations; 3 milestones). Only 2 sets revealed higher self-rated scores for the intervention group (the pediatric and the pain rotations of the second-year residents). The groups' scores for Entrustable Professional Activities (EPAs) and tests of participants' knowledge of the learning objectives showed no differences.

Conclusion: Providing specific learning objectives in the form of self-assessment alone was not found to significantly improve residents' self-perceived learning achievement, particularly in the knowledge-based activities. The advantages of specific learning objectives might be enhanced when combined with other measures that support residency training.

Keywords: Learning objectives; residency training; self-assessment (Siriraj Med J 2023; 75: 275-281)

INTRODUCTION

Rehabilitation medicine is an extensive and diverse field. During training, residents are inundated with information and practices related to developing the skillsets needed to perform the job. We are interested in implementing an intervention that will help residents achieve their learning objectives and gain the most out of their 3 years of residency training.

Our hospital's rehabilitation residency core curriculum complies with the guidelines of the Royal College of Physiatrists of Thailand and is outcome-based.[1] New versions of Entrustable Professional Activities (EPAs) and the Workplace-Based Assessment (WPBA) were launched in 2020[2] to support competency-based training. To assist both learners and instructors in achieving the required competencies, the rehabilitation residency core curriculum and the EPAs are written in a milestone fashion, as required by the Next Accreditation System[3] of the Accreditation Council of Graduate Medical Education.[4]

Introducing the entire 3-year curriculum at the beginning of residency training might be too complex, thereby risking that residents would disregard the

Corresponding author: Rinlada Pongratanakul
E-mail: rinlada.p@gmail.com
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ORCID ID:http://orcid.org/0000-0001-7808-7749
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provided curriculum. Consequently, a strategy that could guide trainees through their residency training was launched. Motivation dictates human behavior and is a key to successful learning.[5] Knowing a goal or learning objective is one way to promote motivation in medical education.[5] As described by Mager in 1984, a learning objective is '...the description of a performance you want learners to be able to exhibit before you consider them competent.' This study therefore investigated whether learning outcomes are improved by using a self-assessment process to communicate learning objectives corresponding to residents' tasks and milestones (level of knowledge and skills).

MATERIALS AND METHODS

This questionnaire-based pilot study was conducted at the Department of Rehabilitation Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University. The intervention was provided to residents trained in academic year 2021. Those residents' learning outcomes were compared with those of residents trained in the preceding academic year (2020), when no intervention was given. The research coordinators invited the participation of all first- to third-year residents via an online platform. The inclusion criterion was residents undertaking training in rehabilitation medicine during academic years 2020 and 2021. Once residents voluntarily agreed to enroll in the study, their informed consent was obtained electronically. There were no exclusion criteria at enrollment. However, the analysis did not include residents in academic year 2021 who did not provide pre- and postintervention responses. Before this research began, the Siriraj Institutional Review Board approved its protocol (COA no. Si 755/2021). The study followed the Helsinki Declaration of 1964 and subsequent amendments.

Rehabilitation residency clinical rotations

In Thailand, residency training in rehabilitation medicine takes 3 years. At Siriraj Hospital, clinical rotations are divided into 5 major blocks, 4 of which are specific to particular illnesses (cardiopulmonary, pediatric, geriatric, and pain). The other rotation was excluded because it includes various fields of study including general rehabilitation, prosthesis-orthosis, urodynamic studies, etc. This precludes the formation of specific learning objectives. In each of the 3 academic years, the first- to third-year residents perform all 5 clinical rotations, with individual rotations lasting 4 weeks.

Interventions

Rotation-specific learning objectives were provided to residents before entering each rotation. The learning objectives were provided in the form of self-assessment questionnaires and were listed as items. Residents were required to read and self-assess their confidence in each task. Participants in academic year 2020 were requested to complete the questionnaires after each rotation. However, participants in academic year 2021 were required to respond to the questionnaires before and after each rotation. As there were 3 years of training with 4 specific clinical rotations each year, there were 12 sets of learning objectives. In addition, tests were given to determine participants' knowledge of the learning objectives.

Questionnaires and tests

Questionnaire 1: Self-assessment of the learning objectives (the intervention)

The learning objectives complied with the core curriculum of the Royal College of Physiatrists of Thailand of 2018[1] and the original and revised versions of EPAs and WPBA of 2020 and 2021.[2,6] The objectives were formulated in accordance with the concepts of "SMART" (specific, measurable, attainable, relevant, and time-bound)[7] and "ABCD" (audience, behavior, condition, and degree of independence).[8] Faculty educators specializing in the medical fields reviewed and approved the learning objectives.

For the self-rated questionnaires, the participants used a 5-level Likert scale (1=not at all confident, 2=slightly confident, 3=moderately confident, 4=quite confident and, 5=extremely confident)[9] to rate how confident and competent they considered they were in each objective. The rating system was presented as an online Google form. Between 4 and 13 items were assessed per objective.

Tests on knowledge of the learning objectives

Tests were given to assess whether the intervention helped participants become informed about the learning objectives. There were 3 sets of tests, one for each year of training. Residents of both academic years 2020 and 2021 took the tests at the end of the year after completing all clinical rotations. The tests were in addition to the residents' routine academic examinations, and the test scores were used for this research only.

Questionnaire 2: Participant satisfaction with the intervention

Participants rated their satisfaction with the intervention on a 5-level Likert scale (1=not at all satisfied; 5=extremely satisfied).[9] Only the participants of academic year 2021 were administered Questionnaire 2, which was given at the end of the study period.

EPA and WPBA evaluation results

In all, there are 13 EPAs, and each has 3 milestones. EPAs that were related to the rotations in this study were selected. The EPA score for "overall actual performance" was used; scores were graded into 4 levels: "good," "pass," "borderline," and "fail."

The baseline demographic data that was recorded consisted of age, sex, number of postgraduate internship years, grade point average during medical school, and scores for the first and second steps of the national medical licensing examination.

The study's primary endpoint was the benefits of the intervention assessed by the achievement of the rotation-specific learning objectives. The Questionnaire-1 scores of the participants in academic years 2020 and 2021 were compared. In the case of the intervention group, the pre- and postrotation questionnaires had to be completed to be eligible for analysis.

Statistical analysis

Demographic data and results are described using descriptive statistics. Categorical data are presented as numbers with percentages. Normally distributed continuous data are presented as the means ± standard deviations. Comparisons between groups were made using the chi-squared test for categorical data and the independent t-test for normally distributed continuous data. The internal consistency reliability of the Questionnaire 1 (the intervention) was analysed with Cronbach's alpha coefficients. The level of significance for all tests was set at 0.05. The analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Twenty-eight and 30 residents were enrolled in the rehabilitation-medicine training program during academic years 2020 and 2021, respectively. Of those, 89% (25/28) and 93% (28/30) residents enrolled in the study. However, not all participants responded to all of the study questionnaires and tests. For the primary outcome (Questionnaire 1), the response rates were 80% (80/100) and 65% (73/112) for academic years 2020 and 2021, respectively.

The participants' characteristics are summarized in Table 1. The residents in academic years 2020 and 2021 had mean ages of 29 and 28, respectively. Although there was only a 1-year difference in the mean ages, the difference was statistically significant (P = 0.01). Both groups were similar in terms of grade point averages, and scores for the first and second steps of the national medical licensing examination.

Table 2 details the participants' self-assessment scores for their confidence and competency in each learning objective. The mean scores are categorized by rotation and year of residency. The intervention group achieved higher self-rated scores than the control group for only 2 of the 12 assessment sets: the pediatric and the pain rotations of the second-year residents (P = 0.02 and 0.02, respectively). The scores for the 4 clinical

TABLE 1. Demographic data of participants.

	Academic year 2020 (N=25)	Academic year 2021 (N=28)	*P* value
Number of participants	25	28	0.81
1st year residents (n)	10	9	
2nd year residents (n)	8	11	
3rd year residents (n)	7	8	
Age, years (mean±SD)	29.24±1.10	28.50±0.92	0.01*
Years of internship (mean±SD)	2.92±0.64	3.07±0.60	0.38
3 years, n (%)	18 (72%)	21 (75%)	0.72
Sex, female, n (%)	15 (60%)	14 (50%)	0.47

*= P value < 0.05

TABLE 2. Scores for self-assessment of the learning objectives test (Questionnaire 1), categorized by 4 clinical rotations and 3 levels of residency training.

	Academic year 2020		Academic year 2021			
	No.	Mean score±SD[#]	No.	Mean score±SD[#]	*P* value	Mean difference (95% CI)
1st year residents						
Cardiopulmonary rotation	8	3.67±0.64	5	3.55±0.44	0.72	-0.12 (-0.84, 0.60)
Pediatric rotation	8	3.63±0.43	6	3.85±0.27	0.28	0.23 (-0.21, 0.67)
Geriatric rotation	8	3.44±0.81	5	3.75±0.25	0.43	0.31 (-0.52, 1.14)
Pain rotation	8	3.88±0.69	5	3.90±0.30	0.94	0.03 (-0.70, 0.75)
Overall score		3.68±0.49		3.77±0.32	0.57	0.09 (-0.23, 0.41)
2nd year residents						
Cardiopulmonary rotation	5	3.58±0.60	6	4.25±0.61	0.10	0.68 (-0.15, 1.50)
Pediatric rotation	5	2.98±0.32	5	3.96±0.64	**0.02***	**0.98 (0.20, 1.76)**
Geriatric rotation	5	3.80±0.67	8	4.29±0.37	0.12	0.49 (-0.14, 1.10)
Pain rotation	5	3.23±0.49	7	4.13±0.63	**0.02***	**0.90 (0.18, 1.62)**
Overall score		3.35±0.46		4.16±0.54	**0.01***	**0.82 (0.25, 1.38)**
3rd year residents						
Cardiopulmonary rotation	7	4.24±0.43	6	4.09±0.20	0.47	-0.15 (-0.57, 0.28)
Pediatric rotation	7	3.35±0.51	6	3.82±0.41	0.10	0.47 (-0.10, 1.04)
Geriatric rotation	7	4.29±0.55	6	4.04±0.25	0.34	-0.24 (-0.78, 0.29)
Pain rotation	7	3.71±0.71	8	3.71±0.49	0.99	0.00 (-0.67, 0.68)
Overall score		3.79±0.45		3.90±0.38	0.51	0.11 (-0.23, 0.46)
Rotation-specific scores without residency sublevels						
Cardiopulmonary rotation	20	3.85±0.61	17	3.99±0.52	0.45	0.14 (-0.24, 0.52)
Pediatric rotation	20	3.37±0.49	17	3.87±0.42	**0.002***	**0.51 (0.20, 0.81)**
Geriatric rotation	20	3.83±0.76	19	4.07±0.36	0.21	0.24 (-0.14, 0.63)
Pain rotation	20	3.66±0.68	20	3.91±0.51	0.20	0.25 (-0.13, 0.63)

[#] Scores are rated on a 5-level Likert scale (1=not at all confident; 5=extremely confident).

* *P* value < 0.05.

rotations were also compared holistically, i.e., without a breakdown by year of residency. This analysis revealed that the intervention group had a significantly higher self-rated score for the pediatric rotation than the control group ($P = 0.002$).

In addition to the residents self-evaluating their confidence levels, they were tested on their knowledge of the learning objectives. For all 3 years of residency, the participants in the control and intervention groups had similar scores.

EPA assessment scores were obtained as a means of objectively assessing the intervention. Unfortunately, not all learning objectives had a corresponding EPA assessment. Moreover, not all participants underwent an EPA assessment during their rotation period. For some assessments, scores were available for only 20% of the participants. Based on the available data, there were no significant differences in the performance scores of the control and intervention groups for any of the EPA assessments (Table 3).

During the academic year 2021, self-rated scores were obtained from the participants before and after their rotations. For all 3 years of residency and all 4 clinical rotations, the participants gave significantly higher ratings after than before the rotations (all $P < 0.05$; data not shown).

The internal consistency reliability of the Questionnaire 1 was analysed with Cronbach's alpha coefficients. In 12 sets of learning objectives, Cronbach's alpha coefficients ranged from .891 to .965, all of which exceeded .70, indicating acceptable values.[10]

Questionnaire 2 investigated participant satisfaction with the intervention. On a Likert scale of 1 to 5, the mean scores for the 5 aspects of satisfaction that were examined ranged between 3.6 and 4.0. Over 80% of the residents gave scores ≥ 4.0 when asked if they wished to have the learning objectives routinely provided as part of their training program (Table 4).

TABLE 3. Scores from the EPA assessments, categorized by rotation and milestone level.

	Academic year 2020		Academic year 2021		*P* value
	No.	Mean score±SD#	No.	Mean score±SD#	
1st year residents					
Cardiopulmonary rotation		No responses*			
Pediatric rotation	7	3.07±0.19	2	3.00±0.00	0.63
Geriatric rotation		No assessments**			
Pain rotation	7	3.07±0.19	6	3.17±0.41	0.59
2nd year residents					
Cardiopulmonary rotation	6	3.33±0.52	8	3.00±0.00	0.09
Pediatric rotation	7	3.00±0.00	3	3.00±0.00	NA
Geriatric rotation		No assessments**			
Pain rotation		No assessments**			
3rd year residents					
Cardiopulmonary rotation	6	3.17±0.41	8	3.50±0.53	0.23
Pediatric rotation	1	3.00±0.00	8	3.13±0.35	0.75
Geriatric rotation	6	3.33±0.52	8	3.63±0.52	0.32
Pain rotation		No assessments**			

Scores range from 1–4 (*4=good, 3=pass, 2=borderline, and 1=fail*).
* No responses = although there was an EPA assessment that matched the rotation and milestones, no assessments were performed during the study period.
** No assessments = no EPA assessment matched the rotations or milestones.
NA = not applicable

TABLE 4. Satisfaction with having learning objectives (Questionnaire 2).

Questions	Mean score±SD[#]	Participants with scores ≥ 4 (%)
Beneficial for self-learning	3.75±0.55	70%
Beneficial for learning in the clinic	3.75±0.55	70%
More confident in caring for patients	3.60±0.60	55%
Helps with self-reflection and stimulates learning	4.00±0.56	85%
Wish to have learning objectives announced periodically	4.00±0.65	80%

[#] Scores are rated on a 5-level Likert scale (1=not at all satisfied; 5=extremely satisfied).

DISCUSSION

Learning goals are the foundation of self-regulated learning and enhance learner motivation, reinforcing each aspect and contributing to successful learning.[11-14] However, while using goals is vital, having medical residents set effective goals for themselves has been reported to be challenging.[15] A study on the learning obstacles faced by family-medicine residents found that they yearned for external motivation and guidance.[16] One form that can be implemented relatively easily is the communication of specific learning objectives, which is the technique that this study investigated. Goals that are well written and proximal (relating to the near future) are more effective than general or long-term goals.[14] By giving residents rotation-specific objectives, we hypothesized that the scores of the residents in academic year 2021 would be higher. Although the self-rated confidence scores were slightly higher in academic year 2021 than in 2020 for almost all learning objectives, only the pediatric rotation showed statistical significance ($P = 0.002$).

Research has been undertaken to determine whether self-evaluation can accurately rate clinical skills and knowledge. Some studies claimed that self-assessment was more accurate when used to assess skills or clinical performance rather than knowledge or cognitive aspects. In contrast, other studies found no differences.[17] In the present study, most learning objectives were related to knowledge-based activities. Only the pediatric rotation had more skills-based than knowledge-based learning outcomes. This may have limited the apparent benefits of our intervention.

Self-evaluation is a well-established method of self-reflection.[18,19] However, its accuracy is questionable, with most studies finding that it is limited compared with external standards.[17,20,21] Several factors influence self-evaluation accuracies, for example, sex and learner insight.[17] Meta-analysis of the association between self-assessment and external evaluation reported that external validation is still needed while self-assessment is used.[21] Consequently, the current study applied EPAs and tests (the tests on the participants' knowledge of the learning objectives) as an external standard. Unfortunately, only a minority of participants obtained EPA assessments, which limited our ability to detect score differences. Tests of the participants' knowledge of the curriculum's learning objectives were also administered and the results were negative. Given the negative findings of the self-rated scores and the 2 external standards, the benefits of the intervention seemed negligible.

Moreover, we obtained self-rated scores before and after the rotations of the intervention group. The scores were all significantly higher for the postrotation evaluations. However, this finding more likely reflects the benefits of the training rather than the intervention.

The study aimed to guide residents through residency training with effectively written learning objectives combined with a process of self-reflection. Nevertheless, because self-evaluation accuracy is restricted, other measures should be incorporated, for example, feedback, performance benchmarking,[17,22] experience, and external measurement.[21-23] In addition, as monthly self-evaluations might have burdened the residents with extra work, participant satisfaction was obtained; the results were quite positive. Consequently, strategies to provide rotation-specific learning objectives should be continued. In conclusion, providing specific learning objectives in the form of self-assessment alone was not found to significantly improve residents' self-perceived learning achievement, particularly in the knowledge-based activities.

Limitations

As it was a pilot study, the number of participants enrolled was small, which might have limited the study's power. Moreover, the number of respondents to the questionnaire was not constant. Both factors could obscure the full benefits of the intervention. Another limitation was the EPA assessments. Being workplace-based evaluations, they were difficult to obtain. Another concern was the history threat to internal validity as the participants of the control and the intervention groups were from different academic years. The training process between the 2 years might not be absolutely identical. In addition, it should be noted that this study has limited generalizability as it was performed in a rehabilitation residency training setting at only 1 institution. Therefore, the study's results might not apply to other academic institutions or residency training programs. More positive outcomes might be identified via a larger sample size coupled with a study design that better engages participants throughout the study and draws upon EPA evaluations.

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Pathological and Oncologic Outcomes of Consolidation Chemotherapy in Locally Advanced Rectal Cancer after Neoadjuvant Chemoradiation

Thikhamporn Tawantanakorn, M.D.*, Thawatchai Akaraviputh, M.D.*, Vitoon Chinswangwatanakul, M.D.*, Suthinee Ithimakin, M.D., Janjira Petsuksiri, M.D.***, Atthaphorn Trakarnsanga, M.D.***

**Minimally Invasive Surgery Unit, Division of General Surgery, Department of Surgery, , **Division of Radiation Oncology, Department of Radiology, ***Division of Medical Oncology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: The current standard of care for locally advanced rectal cancer is associated with multimodality therapy. Neoadjuvant chemoradiation significantly decreased the locoregional recurrence rate and improved survival. However, distant metastasis develops rather than local recurrence, which becomes the leading cause of death. This study aimed to evaluate the oncological outcomes of total neoadjuvant therapy (TNT) in locally advanced rectal cancer.

Materials and Methods: This retrospective study recruited 18 patients diagnosed with locally advanced rectal adenocarcinoma (cT3-4 or cN1-2), treated with consolidation TNT. The primary endpoint was pathological complete response (pCR). The secondary endpoint included postoperative outcomes, local recurrences, and distant metastases.

Results: The pathologic complete response was observed in 27.8% of consolidation therapy cases and 25% of induction therapy cases. Downstaging of the T-category was achieved in 10 (55.6%) patients, and downstaging of the N-category was achieved in 14 (77.8%) patients. Only one patient who achieved pCR developed distant metastasis, whereas all patients with pathological stage III developed distant metastasis.

Conclusion: TNT is a promising approach for patients with locally advanced rectal cancer. This strategy improved complete pathologic response rates in TNT, and pCR was found to be associated with fewer local recurrences and greater disease-free survival.

Keywords: Consolidation chemotherapy; total neoadjuvant therapy; rectal cancer; pathologic complete response
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INTRODUCTION

In Thailand, colorectal cancer is the third most common cancer in men and the fourth in women,[1] with an estimated of over 10,000 new cases annually. Rectal cancer accounts for 40%–52% of all colorectal adenocarcinoma.[2] The current standard of care for locally advanced rectal cancer is associated with multimodality therapy, consisting of neoadjuvant chemoradiotherapy (CRT) that included either preoperative long-course CRT or short-course radiotherapy, followed by surgical resection with total mesorectal excision and adjuvant chemotherapy.[3]

Neoadjuvant chemoradiation significantly decreased the locoregional recurrence rate and improved survival.[4,5] Nevertheless, distant metastasis occurs rather than local recurrence, which becomes the leading cause of death.[6] A systemic spread was presumed to be caused by clinically undetectable micrometastases in a distant area.

Total neoadjuvant therapy (TNT) is an alternative treatment option to provide systemic therapy for patients

Corresponding author: Atthaphorn Trakarnsanga
E-mail: atthaphorn.tra@mahidol.ac.th
Received 10 February 2023 Revised 22 February 2023 Accepted 1 March 2023
ORCID ID:http://orcid.org/0000-0002-1980-7782
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with locally advanced rectal cancer and aims to reduce distant metastases. TNT refers to the administration of CRT plus chemotherapy followed by surgery, including induction and consolidation chemotherapy.[7] Moreover, a previous study showed that TNT achieved improved local control and reduced the duration of a diverting ileostomy.[8]

The benefits of this therapeutic strategy are increased downstaging, improved resectability by the downsizing of the tumors, potentially decreased sphincter-preservation rate, and reducing a significantly higher rate of pathological complete response (pCR).[9,10] Early systemic therapy allows for chemosensitivity assessment and eliminates micrometastatic disease before surgery, which would lead to better survival. This study aimed to evaluate the oncological outcomes of consolidation chemotherapy in poor responders after neoadjuvant chemoradiation.

MATERIALS AND METHODS

Patient populations

This single-center retrospective cohort study recruited 22 patients with locally advanced rectal adenocarcinoma who were treated with TNT and underwent elective surgery during the period from January 2012 to December 2020 at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Consolidation chemotherapy was completed by 18 patients, whereas 4 patients received induction chemotherapy.

The inclusion criteria were as follows: age 18 years or older at the time of diagnosis, received consolidation TNT, histologically proven rectal adenocarcinoma located up to 10 cm from the anal verge, locally advanced stage of T3/T4, or node-positive disease confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Patients who received palliative treatment, refused CRT, had a previous history of cancer, and received pelvic radiotherapy or systemic chemotherapy were excluded. Ethical approval for this study was obtained from Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 600/2022).

Data collection

The data collected included patient demographics, age at diagnosis, sex, performance status, tumor size, and location. Preoperative clinical assessments included physical examination, colonoscopy, abdominal MRI, chest CT, and serum carcinoembryonic antigen measurement. The clinical stage was classified according to the American Joint Committee on Cancer (AJCC) 8th staging system.[11] Initial evaluation was performed by a surgeon, medical oncologist, and radiation oncologist, and the CRT regimen was selected at the discretion of the treating physician.

Clinical response was evaluated by digital rectal examination and endoscopy. Restaging MRI was performed 6–8 weeks after the completion of concurrent chemoradiation and TNT. The chemotherapy regimen, radiation dose, operative approach, surgical procedure, pathological staging, adverse reactions of chemoradiation, and postoperative complications were reviewed. The histology of surgical specimens was reviewed and confirmed by pathologists and was classified based on the modified Ryan scheme for the tumor regression score.[12] Patients were classified as complete responders (TRG0), near-complete responders (TRG1), partial responders (TRG2), and poor responders (TRG3).

The primary endpoint was pCR. pCR or ypT0N0 was defined as the absence of residual tumor cells in the surgical specimen. The secondary endpoints included postoperative outcomes, Clavien–Dindo classification of complications,[13] sphincter preservation, mortality, local recurrences, and distant metastases.

The study was performed with the approval of the Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 517/2022), and the requirement for informed consent was waived.

Statistical analysis

All data were analyzed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The descriptive analysis was performed. Quantitative variables with normal distribution were summarized as mean and standard deviation (SD), whereas non-normal variables were presented as median and interquartile range (IQR). Qualitative variables were reported as frequency and percentage. The pCR of each clinicopathological variable was evaluated by univariate and multivariate logistic regression analyses. A p-value < 0.05 was considered significant.

RESULTS

Patient characteristics

A total of 22 patients with locally advanced rectal cancer who received consolidation TNT were enrolled, and the baseline characteristics of the study population are shown in Table 1. The mean age of the patients at the initial diagnosis was 61.2 years, with a SD of 12.9 years (range, 34–81 years), and approximately 66.7% of the cases occurred in men. The median distance of the tumor from the anal verge was 5.0 cm (IQR 3–6), and 72.2% of tumors were located at the site 5 cm below the anal verge. The majority of cases were classified as clinical

TABLE 1. Demographic data (n = 22).

Characteristics	
Age (years), mean ± SD (range)	59.9 ± 11.5 (range 34–81)
Sex, n (%)	
Male	14 (63.6)
Female	8 (36.4)
ASA classification, n (%)	
ASA I	1 (4.6)
ASA II	18 (81.8)
ASA III	3 (13.6)
Body mass index(kg/m^2), mean ± SD	23.7 ± 2.7
Clinical T stage, n (%)	
cT1	1 (4.5)
cT2	0
cT3	17 (77.3)
cT4	4 (18.2)
Clinical N stage, n (%)	
cN0	2 (9.1)
cN1	18 (81.8)
cN2	2 (9.1)
AJCC clinical stage, n (%)	
Stage 2	2 (9.1)
Stage 3	20 (90.9)
Preoperative diversion	6 (27.3)
Raised preoperative CEA level*	14 (63.6)
Distance from anal verge, n (%)	
≤5 cm	15 (68.2)
5.1–10 cm	7 (31.8)
Total radiation dose (Gy), median (IQR)	50.4 (50.1–54)
Induction regimen, n (%)	4 (18.2)
Consolidation regimen, n (%)	18 (81.8)
Operation, n (%)	
LAR	4 (18.2)
TaTME	6 (27.3)
APR	12 (54.5)
Approach, n (%)	
Open	8 (36.4)
Laparoscopic	13 (59.1)
Robot	1 (4.5)

Abbreviations: ASA, American Society of Anesthesiologists physical status classification

* Serum carcinoembryonic antigen (CEA) levels >5 ng/mL are considered elevated.

T3 (88.9%) based on the AJCC. Approximately 88.9% were clinical node-positive cases. The nodal status was N1 in 14 (77.8%) and N2 in 2 (11.1%) patients.

Total neoadjuvant therapy

Two cases (11.1%) were classified as clinical stages II, and 16 (88.9%) cases were classified as stage III at initial diagnosis. All patients received long-course radiotherapy, with a median radiation dose of 50.4 Gy (IQR 50–54). About two-thirds of the patients (72.2%) received preoperative radiotherapy with concurrent capecitabine, and 5 (27.8%) patients received concurrent 5-fluorouracil-based chemotherapy. A poor responder was defined as follows: threaten margin or positive circumferential margin (70.6%). After the completion of CRT, poor responders received either consolidation chemotherapy with capecitabine and oxaliplatin (CAPOX; 66.7%) or fluorouracil, leucovorin calcium, and oxaliplatin (FOLFOX; 33.3%) regimen. Induction chemotherapy was completed by 4 patients, who received chemotherapy with various regimens in the form of CAPOX, FOLFOX, or FOLFIRINOX. After completing the induction chemotherapy, concurrent CRT with capecitabine or FOLFOX was given.

Response to treatment

Therapeutic response was assessed by clinical examination, colonoscopy, MRI, and histopathology. Clinical response was evaluated after induction or consolidation chemotherapy, and restaging was performed 6–8 weeks after concurrent chemoradiation, in which the median time of restaging was 53 (IQR 45–59) days following the completion of radiation. Tumors were gradually downstaged after received TNT. Two patients had a clinical complete response (cCR), as shown in Fig 1.

Surgery

The standard surgical procedure for locally advanced rectal cancer is abdominoperineal resection (APR) and low anterior resection (LAR) with total mesorectal excision. All patients underwent curative surgical resection, and the mean time from completion radiation to operation was 251.6 ± 68.6 days. During the preoperative period, diverting loop colostomy was performed in 5 (27.8%) patients Moreover, 11 (61.1%), 2 (11.1%), and 5 (27.8%) patients underwent APR, LAR, and transanal total mesorectal excision, respectively.

None of the patients had 30-day postoperative mortality. Postoperative complications occurred in 2 (11.1%) patients, which were classified as Clavien–Dindo grade III complications. One of them developed colostomy necrosis and underwent resection and relocation of the stoma. Another patient had postoperative intra-abdominal hemorrhage, who underwent re-exploration for bleeding control.

The anal sphincter preservation rate was 38.9%, and protective ileostomy or colostomy was performed in all cases. However, the rate of permanent stoma after sphincter-saving surgery was 42.8%, which was associated with tumor recurrence. One patient developed a 1-cm liver nodule during preoperative restaging; thus, these

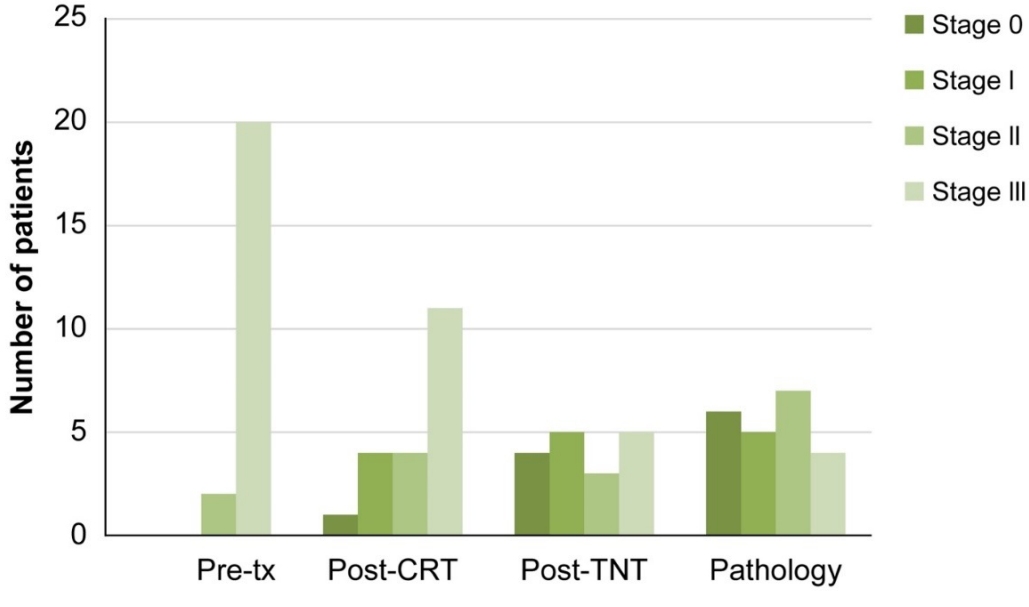

Fig 1. Response to treatment over time including pretreatment clinical stage (pre-tx), clinical response after chemoradiation completion (post-CRT; 54-day median time from radiation completion), clinical response after total neoadjuvant therapy completion (post-TNT), and pathological stage.

patients underwent hepatectomy. Laparoscopic and robotic-assisted surgery was performed in 11 (61.1%) and 1 (5.6%) patient, respectively.

Treatment efficacy

The pCR was observed in 27.8% of the patients receiving consolidation therapy. The histopathological results are summarized in Table 2. The final pathology revealed ypT2N0 in 4 (22.2%), ypT3N0 in 7 (38.9%), and ypT3N1 in 2 (11.1%) patients. Downstaging of the T-category was achieved in 10 (55.6%) patients, and downstaging of the N-category was achieved in 14 (77.8%) patients, whereas stable disease was observed in 2 (11.1%) patients. The mean number of retrieved lymph nodes was 10.9 ± 6.9. The resection margins were 83.3% for the negative margin (R0) and 16.7% for the microscopic-positive margin (R1). Perineural invasion was present on histopathological assessment in 5 (27.8%) patients, and lymphovascular invasion was reported in 3 (16.7%) patients. Tumor regression was evaluated according to the modified Ryan scheme as TRG0 in 5 (27.8%) patients, TRG1 in 2 (11.1%), TRG2 in 3 (16.7%), and TRG3 in 5 (27.8%). The univariate analysis was used to assess the predictive value of variables for achieving pCR. Clinicopathological factors were not significantly associated with pCR including age, gender, comorbidities, body mass index, clinical stage, tumor location, positive circumferential resection margin (CRM), radiation dose, and chemotherapy type. The results of the analyses are summarized in Table 3.

Survival and recurrence

The mean follow-up time was 36.8 ± 15.8 (range, 16.3–72.1) months. Recurrence was recorded in 6 (33.3%) patients. The mean recurrent time was 23.1 ± 14.5 (range, 2.1–45.7) months. Locoregional recurrences of rectal cancer occur in 2 (11.1%) patients, and 4 (22.2%) patients developed distant metastases. The lung and liver were the most common sites of distant metastasis (Table 4).

DISCUSSION

Neoadjuvant CRT followed by total mesorectal excision remains a standard treatment for stage II and III rectal cancer. We found that TNT improved

TABLE 2. Pathological features.

	Total	Consolidation (N = 18)	Induction (N = 4)
Pathologic T stage, n (%)			
ypT0	6 (27.3)	5 (27.8)	1 (25)
ypT1	0	0	0
ypT2	5 (22.7)	4 (22.2)	1 (25)
ypT3	11 (50)	9 (50)	2 (50)
ypT4	0	0	0
Pathologic N stage, n (%)			
ypN0	18 (81.8)	16 (88.9)	2 (50)
ypN1	3 (13.6)	2 (11.1)	1 (25)
ypN2	1 (4.6)	0	1 (25)
Pathologic stage, n (%)			
Stage 0 (ypT0N0)	6 (27.3)	5 (27.8)	1 (25)
Stage 1 (T2N0)	5 (22.7)	4 (22.2)	1 (25)
Stage 2 (T3N0)	7 (31.8)	7 (38.9)	0
Stage 3 (T3N1/T3N2)	4 (18.2)	2 (11.1)	2 (50)
Pathologic response, n (%)			
TRG 0	6 (27.3)	5 (27.8)	1 (25)
TRG 1	2 (9.1)	2 (11.1)	0
TRG 2	4 (18.2)	3 (16.7)	1 (25)
TRG 3	6 (27.3)	5 (27.8)	1 (25)

Abbreviation: TRG, tumor regression grade.

TABLE 3. Univariate analysis of clinicopathological factors associated with pathological complete response.

Variable	Univariable analysis		
	OR	95% CI	*P*-value
Age	0.98	0.90–1.07	0.72
Sex	1.20	0.16–8.65	0.85
ASA classification	0.46	0.03–5.41	0.53
Body mass index	0.76	0.52–1.11	0.16
Distance from anal verge (≤5 cm, 5.1–10 cm.)	1.10	0.14–8.12	0.92
Preoperative diversion	2.27	0.20–24.88	0.50
Raised preop CEA	2.20	0.32–14.97	0.42
Clinical T stage	1.36	0.25–7.43	0.71
Clinical N stage	0.25	0.02–3.11	0.28
AJCC Clinical stage	0.61	0.09–4.03	0.61
TNT therapy (induction, consolidation)	1.15	0.09–13.87	0.91
Positive CRM	0.66	0.09–4.92	0.69
Concurrent chemoradiation	0.54	0.06–4.56	0.57
Total radiation dose	1.39	0.82–2.38	0.21
Consolidation chemotherapy	0.55	0.24–1.23	0.14

TABLE 4. Complications and recurrence.

	Total	Consolidation (N = 18)	Induction (N = 4)
Mortality, n (%)	0	0	0
Major complication, n (%)	2 (9.1)	2 (11.1)	0
Recurrent, n (%)			
No recurrent	15 (68.2)	12 (66.7)	3 (75)
Local recurrent	2 (9.1)	2 (11.1)	0
Distant metastasis	5 (22.7)	4 (22.2)	1 (25)
Distant metastatic site, n (%)			
Lung	3 (37.5)	3 (16.7)	0
Liver	3 (37.5)	3 (16.7)	0
Pancreas	1 (12.5)	0	1 (25)
Brain	1 (12.5)	1 (5.6)	0

complete pathologic response rates. Previous studies have revealed that 15%–20% of the treated patients achieved pCR after conventional neoadjuvant chemoradiation therapy,[14,15] whereas our study revealed that 27.8% of patients who received TNT had higher pCR. A pCR is associated with fewer local recurrences (odds ratio (OR) 0.25; $p = 0.002$), distant metastases (OR 0.23; $p < 0.001$), and greater disease-free survival at 5 years (OR 4.33; $p < 0.001$) than standard therapy.[16,17] In a previous systematic review, the pooled 5-year DFS and 5-year OS rates were 65% and 74%, respectively.[18]

TNT improved pCR rates in both consolidation and upfront therapies. In our study, pCR was observed in 27.8% of the patients on consolidation therapy, which is comparable to the recent meta-analysis.[18,19] However, The OPRA trial demonstrated slightly higher pCR rates than our study which could be attributed to the lymph node staging.[20] Downstaging of the T-category was achieved in approximately half of our patients, whereas downstaging of the N-category was observed in more than two-thirds of the patients. Downsizing of rectal cancer in response to TNT can change a previously inoperable tumor to an operable tumor. Thus, consolidation chemotherapy should be an option in poor responders to neoadjuvant therapy.

Among five patients who achieved pCR, one developed distant lung and brain metastasis at 30.2 months, whereas among two patients with pathological stage III cancer who poor responders to TNT developed distant metastasis. Furthermore, 33.3% of the patients with microscopic residual tumor had distant metastasis at 2.1 months without local recurrence. Distant metastasis remains the major reason for treatment failure in TNT.

The cCR was evaluated by digital rectal examination, colonoscopy, and radiographic images. After the completion of CRT, two patients had cCR; however, all of them achieved a pCR. The disconcordance of the pCR and cCR is associated with the accuracy of the examinations and imaging findings.[21]

Our data showed that the mean time from the completion of radiation therapy to operation was 35.9 weeks. A prolonged interval between radiation to surgery may increase the risk of radiation-induced pelvic fibrosis but does not increase the surgical technical difficulty and complications.[21,22] In this study, there was no conversion to open surgery, and surgical complications (Clavien–Dindo grade III; 11.1%) were comparable to those in previous studies.[10] Therefore, laparoscopic surgery is feasible in long-waiting time cases after CRT.

We achieved a sphincter-preservation rate of 45.5% in low rectal cancers, especially in two-thirds of tumors located within 5 cm from the anal verge. The sphincter-preservation surgery improves the patient's quality of life and allows an early return to work. A previous study showed no difference in the proportion of sphincter-preserving surgery when compared with conventional therapy.[8]

This study has some limitations. First, this is a preliminary retrospective review with a small population, which presents potential selection bias. The randomization of the patients is ethically challenging, and some drug regimens were based on health insurance. Second, the follow-up time was short. Thus, more patients should be analyzed. A prospective randomized controlled trial with longer follow-up periods for survival analysis is warranted.

CONCLUSION

TNT is a promising approach for patients with locally advanced rectal cancer. This strategy improved complete pathologic response rates in both consolidation and upfront therapies, and pCR was found to be associated with fewer local recurrences and greater disease-free survival. However, distant metastasis remains the predominant cause of treatment failure. Long-term follow-up can provide estimates of the effectiveness of systemic therapy.

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Declaration of Conflicting interest: The Authors declare that there is no conflict of interest.

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Effects of an Integrated Rehabilitation Program on Fatigue in Patients with Pulmonary Tuberculosis

Sunisa Nguantad, R.N., M.N.S*, Wimolrat Puwarawuttipanit, R.N., Ph.D., Pichitra Lekdamrongkul, R.N., Ph.D.**, Yong Rongrungruang, M.D., FRCP (T)*****

**Master of Nursing Science Program in Adult and Gerontological Nursing, Faculty of Nursing, Mahidol University, Bangkok 10700, Thailand, **Department of Medical Nursing, Faculty of Nursing, Mahidol University, Bangkok 10700, Thailand, ***Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: This study aimed to assess the effect of a six weeks integrated rehabilitation program on fatigue in pulmonary tuberculosis patients.

Materials and Methods: Sixty-eight participants were diagnosed with pulmonary tuberculosis receiving antituberculosis drugs treated for two weeks or more and have experienced fatigue. Participants were randomly selected into experimental and control groups with 34 participants each. The experimental group received usual care plus an integrated rehabilitation program that consisting of walking exercises (perform at least three times a week, light to moderate intensity and 20-30 min in duration), nutrition education and management of adverse reactions from antituberculosis drugs, and support from healthcare workers through the LINE application for a period of six weeks. The control group received the usual care with given the option to engage in activities to reduce their own fatigue for a period of six weeks. Fatigue symptoms were assessed with PFS-12 at baseline, at week 3 and week 6 and using the Repeated measure ANOVA for statistical analysis.

Results: The study found that the experimental group had a lower mean fatigue score at week 3 than at the baseline. At week 6, the mean fatigue score decreased significantly compared that at the baseline and compared to the control group with statistical significance ($F = 9.698$, $p < .001$), while no statistically significant differences were found in the control group ($F = 1.687$, $p = .200$)

Conclusion: The integrated rehabilitation program statistically and significantly reduced the levels of fatigue in pulmonary tuberculosis in 3-6 weeks.

Registration number: This study was registered at the Thai Clinical Trials Registry (TCTR20221202001).

Keywords: Pulmonary tuberculosis; integrated program; fatigue; line application (Siriraj Med J 2023; 75: 290-298)

INTRODUCTION

Fatigue is a symptom that can be found in patients with pulmonary tuberculosis at up to 88%.[1] This symptom is believed to be caused by chronic inflammatory processes and the functioning of the immune system,[2,3] including adverse reactions from the treatment received by the patient, which can also result in fatigue. Studies have shown that adverse reactions from antituberculosis drugs can directly and indirectly cause fatigue in 53 to 55% of patients.[4,5] Physical and mental factors that contribute to the occurrence of fatigue have also been found, including malnutrition, poor sleep quality, and depression.[1] In addition, studies have found that fatigue was a common symptom in 47% of post-tuberculosis patients.[6] This is caused by scarring of the lung tissue and can lead to limited lung expansion and obstructive

Corresponding author: Wimolrat Puwarawuttipanit
E-mail: wimolrat.puw@mahidol.ac.th
Received 11 January 2023 Revised 23 February 2023 Accepted 1 March 2023
ORCID ID: https://orcid.org/0000-0001-5274-9943
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airway disorders may be observed, or a combination of both in some cases.[7,8] This results in inefficient gas exchange, causes patients to experience shortness of breath or difficulty breathing for a long period of time, thereby resulting in patient fatigue.

According to the review, Fatigue is a symptom that occurs continuously for months or years. This affects long-term lung rehabilitation and also significantly affects the patient's daily functioning and well-being. There are restrictions on activities, dependence on others, deteriorating health, discomfort, boredom, discouragement and hopelessness.[5] Patients might have to take time off work, lose income and feel a decrease in self-esteem. Moreover, if patients feel fatigue during the course of receiving antituberculosis drugs in combination with other adverse reactions, the result may be a decrease in cooperation with medication adherence.[9] Therefore, fatigue is considered an important problem that needs to be corrected before it affects the patient's body, mind, society, and economy. Encouraging patients to deal with their fatigue in the right way is, therefore, very essential for the care of patients with pulmonary tuberculosis.

Integrated rehabilitation programs combine physical and mental care rather than a single program, which covered the management of factors causing fatigue in pulmonary tuberculosis and the program also corresponded with the WHO's guidelines for patient care.[10,11] Based on a review of previous research, there have been no direct studies on the management of fatigue in patients with pulmonary tuberculosis at domestic or international. Thus, the researchers' interest is in studying the effects of an integrated rehabilitation program by applying Dodd's symptom management model,[12] which consists of three interrelated components: symptom experience, symptom management strategies, and symptom management outcomes. In the present study, the program included walking exercises, nutrition education and management of adverse reactions from antituberculosis drugs with support from health care provider and use of the LINE application to monitor patient care and keep up with the 4.0 technology era to achieve comprehensive care and to manage fatigue in patients with pulmonary tuberculosis effectively and sustainably in the long term. The present study aimed to study the effect of a six weeks integrated rehabilitation program on fatigue in pulmonary tuberculosis patients at the outpatient department, an advanced tertiary hospital in Bangkok, Thailand.

MATERIALS AND METHODS

Study design and participants

This study was a single-blind randomized controlled trial. The Study population consist of both male and female patients with pulmonary tuberculosis. Eligible participants were (a) aged at least 18 years old, (b) Who have been treated with anti-TB drugs for 2 weeks or more, (c) And have experienced fatigue (Use the method of asking about the experience of fatigue, For example: feeling tired, lethargic, sluggish, uncomfortable, sleepy all the time, lack of energy, exhaustion, lack of motivation, decreased activity etc.), (d) With ability to continue daily routines for at least 6 minutes without getting tired, (e) Have no restrictions on walking and exercising, (f) And have no cognitive impairment, (g) And are able to use the LINE application, and (h) Are also able to read and write in Thai. The exclusion criteria applied to patients with comorbidities causing simple fatigue, such as Acquired Immune Deficiency Syndrome, Chronic obstructive pulmonary disease, Asthma, Congestive heart failure, Cancer with chemotherapy or radiotherapy, a history of coronavirus disease 2019, and obstructive sleep apnea.

The sample size was calculated using power analysis. The required sample size calculation for repeated measures analysis of variance (ANOVA) test indicated a sample of 68 participants (34 per group), with a power (p) of 0.80, significance level (α) of 0.05, medium effect size (f) of 0.25, and attrition rate of 20%. The researcher prepares for the sampling process by the research assistant who is not involved in this research project is responsible for preparing numbers 1-68 that use a computer program to randomize by specifying which number is group one or group two and packed in a sealed brown envelope prepared, with group one being the control group and group two being the experimental group. After that, the researcher had the sample randomly select an envelope and the researcher opens a sealed brown envelope containing the number and grouped the samples into the control group and the experimental group according to the number inside the envelope. (Fig 1).

Intervention

Both groups received usual care for patients with pulmonary tuberculosis attending the Outpatient. The experimental group received an integrated rehabilitation program created by the researchers based on the application of the pulmonary rehabilitation program and the use of the symptom management model of Dodd. The integrated rehabilitation program has been reviewed for content accuracy, format and language used from five experts. The program consisted of walking exercise, nutrition education and management of adverse reactions from antituberculosis drugs with reinforcement of support from health care provider via the LINE application for

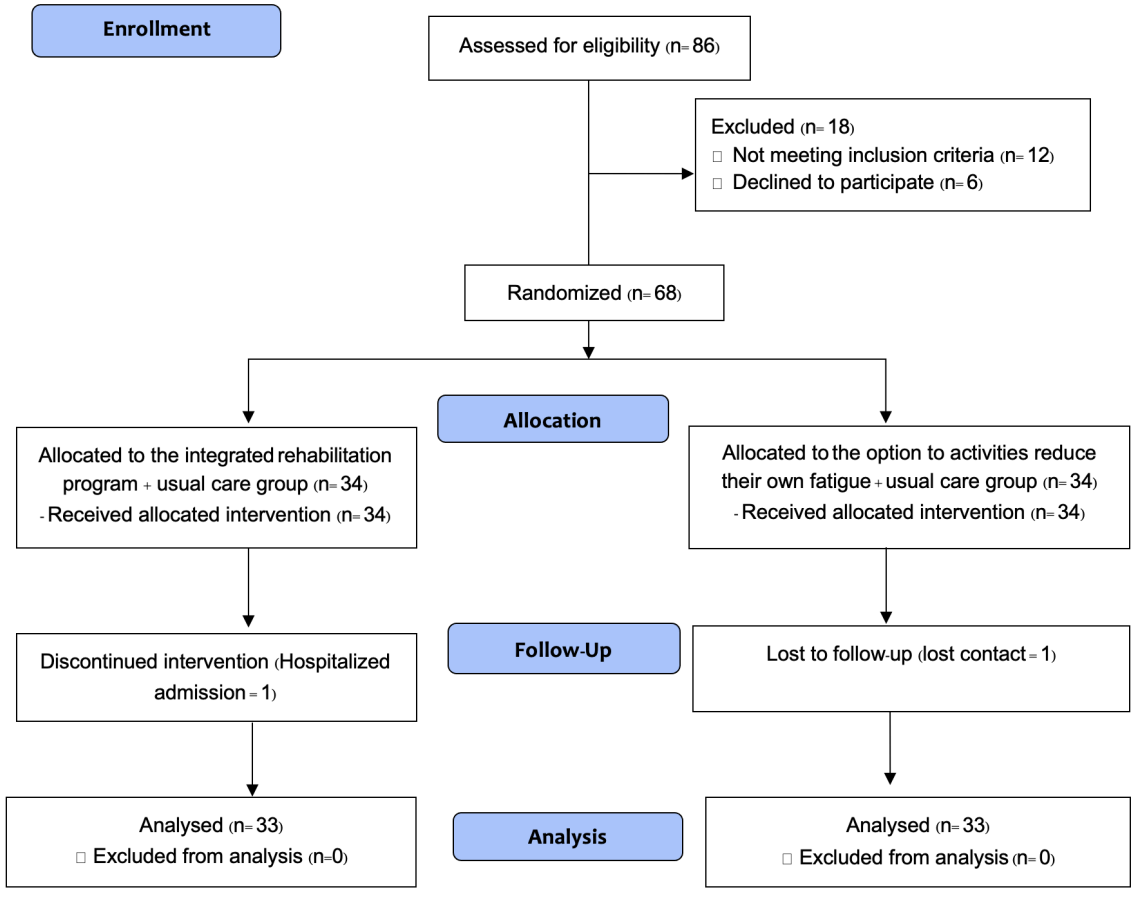

Fig 1. Flow diagram of participant eligibility and randomization process

a period of six weeks. The researchers described fatigue reduction programs and added participants to the TB care LINE account, which includes animated knowledge clips and exercise video clips for participants to study and for training researchers in skills for assessing the intensity of exercise by estimating the percentage of the highest heart rate. Participants were advised to check their pulse rates during the most exhausting periods of exercise, optimal pulse rates were calculated for each patient, and the participants were allowed to practice checking their own pulse rates until they had the confidence to return to practice at home. Furthermore, appropriate exercise goals were set for the participants with a frequency of at least three times a week, light to moderate intensity and a duration of 20-30 minutes. The participants were then given walking diaries. When walking at home as recommended, the participants were instructed to record their walking exercise. At the end of each week, the participants were instructed to send the record of their workout data to the researchers via the TB care LINE account to monitor and assess their walking exercise trends to determine whether or not set goals had been met. After the researchers obtained recorded exercise data from the participants, they sent the messages and stickers of encouragement to the participants. Next, the researchers called to follow up with the participants via the LINE application to inquire about problems. During the week, the participants received infographic knowledge through the TB care LINE account, three times a week, on Monday, Wednesday and Friday at 10 am, to encourage participants to perform their activities and review their knowledge any time.

The control group received a manual "Learning and Understanding Tuberculosis" of the Department of Disease Control. And were given a diary to record the activities they selected to reduce the occurrence of fatigue over a 6-week period.

Outcome measurement

The study outcomes included fatigue (using the Piper Fatigue Scale-12 [PFS-12][13] and the Thai-translated versions).[14] A total of 12 questions were answered via Google FORM via the LINE application for the baseline (T1) and evaluated at Week 3 (T2) and at Week 6 (T3) at the end of the study and demographic characteristics, history of illness and treatment (using the questionnaire developed by the researchers and patient's medical records) Furthermore, to monitor walking exercise adherence

to program (perform at least 3 times a week, light to moderate intensity and 20-30 min in duration), including problems and obstacles in participating in the program.

The PFS-12 tool was tried in 30 patients with similar characteristics to the participants in the present study by using Cronbach's alpha coefficient formula. The reliability value was .90 and the reliability value in the 68 participants in this study was .90.

Statistical analysis

All data analyses were performed using SPSS v.25. Descriptive statistics were used to analyze demographic characteristics and history of illness and treatment, followed by comparison of the differences between the experimental and control groups at baseline by using Chi-square testing or fisher's exact test and independent t-test. Analysis of the differences in mean fatigue scores at baseline, week 3 and week 6 between the experimental and control groups by using repeated measures ANOVA.

RESULTS

Demographic characteristics and history of illness and treatment

Overall, 68 participants completed the baseline. Of these, 1 and 1 from the intervention and control groups withdrew from the study, respectively. In contrast, 66 participants completed at the end of the study (33 and 33 from the experimental and control groups, respectively). Furthermore, there was no difference between the two groups at baseline (Tables 1 & 2).

Comparison of mean fatigue scores of patients with pulmonary tuberculosis at baseline, week 3 and week 6 within groups and between groups

When comparing the differences in mean fatigue scores over time in the experimental group and control groups (within group) at (baseline, week 3 and week 6), the mean fatigue score in the control group had no statistically significant difference when compared over time ($F = 1.687$, $p = .200$). In the experimental group, the mean fatigue scores had statistically significant differences ($F = 29.866$, $p < .001$) when comparing pairwise differences over time in the experimental group, the mean fatigue scores were found to vary in three pairs: The mean fatigue score at week 3 was lower than at baseline (difference of 0.90 points), and the mean fatigue score at week 6 was lower than week 3 (difference of 1.04 points) and the mean fatigue score at week 6 was statistically and significantly lower than baseline (difference of 1.95 points) ($p < .001$) over time, while no such difference was found in the control group .

When comparing the differences in mean fatigue scores between the experimental and control groups over time (between groups) at (baseline, week 3 and week 6), it was found that the time effect changed from T1 (baseline) to T3 (week 6). In addition, the interaction between time and group variables (time * group interactions) were statistically significantly different ($F = 9.698$, $p < .001$) While the control group had a relatively stable mean fatigue score. In the experimental group, the mean fatigue score continued to decrease. (Fig 2).

TABLE 1. Demographic characteristics of the experimental and control groups at baseline.

Demographic characteristics	Experimental Group (n=34) n (%) or mean ± SD	Control Group (n= 34) n (%) or mean ± SD	P - value
Gender (male)	15 (44.1)	17 (50)	0.627[a]
Age (years)	57.21 ± 17.30	52.88 ± 18.22	0.319[c]
Body Mass Index (kg/m^2)	20.57 ± 3.04	19.95 ± 3.88	0.464[c]
Marital Status (Married)	20 (58.8)	22 (64.7)	0.618[a]
Education (Primary school)	21 (61.8)	13 (38.2)	0.104[a]
Occupation (Hired Labor)	7 (20.6)	10 (29.4)	0.302[a]
Income (baht/month)	12,058.82 ±16,118.08	13,057.06 ±10,725.92	0.765[c]
Healthcare Scheme (Universal Coverage)	19 (55.9)	16 (47.1)	0.482[b]
Have a Caregiver	34 (100)	33 (97.1)	1.000[b]
Never Exercise	14 (41.2)	20 (58.8)	0.146[a]

[a]Chi-square test, [b]Fisher's exact test, [c]Independent *t* test.

TABLE 2. History of illness and treatment of the experimental and control groups at baseline.

History of Illness & Treatment	Experimental Group (n=34) n (%) or mean ± SD	Control Group (n= 34) n (%) or mean ± SD	P - value
Tuberculosis Patient (New Case)	32 (94.1)	27 (79.4)	0.150[b]
Extrapulmonary Tuberculosis (No)	31 (91.2)	30 (88.2)	1.000[b]
Duration of tuberculosis illness (months)	4.47 ± 3.71	5.63 ± 4.36	0.241[c]
Duration of taking anti-tuberculosis drugs (months)	4.31± 3.83	5.46 ± 4.42	0.256[c]
Chronic Disease/Comorbidities*			
Diabetes Mellitus	6 (17.6)	10 (29.4)	0.253[a]
Dyslipidemia	10 (29.4)	8 (23.5)	0.582[a]
Hypertension	10 (29.4)	12 (35.3)	0.604[a]
Antituberculosis Drug Regimen (2HRZE/4-7HR)	21 (61.8)	20 (58.8)	0.812[b]

[a] Chi-square test, [b] Fisher's exact test, [c] Independent *t* test. *Top three most common comorbidities (more than 1 answer possible).

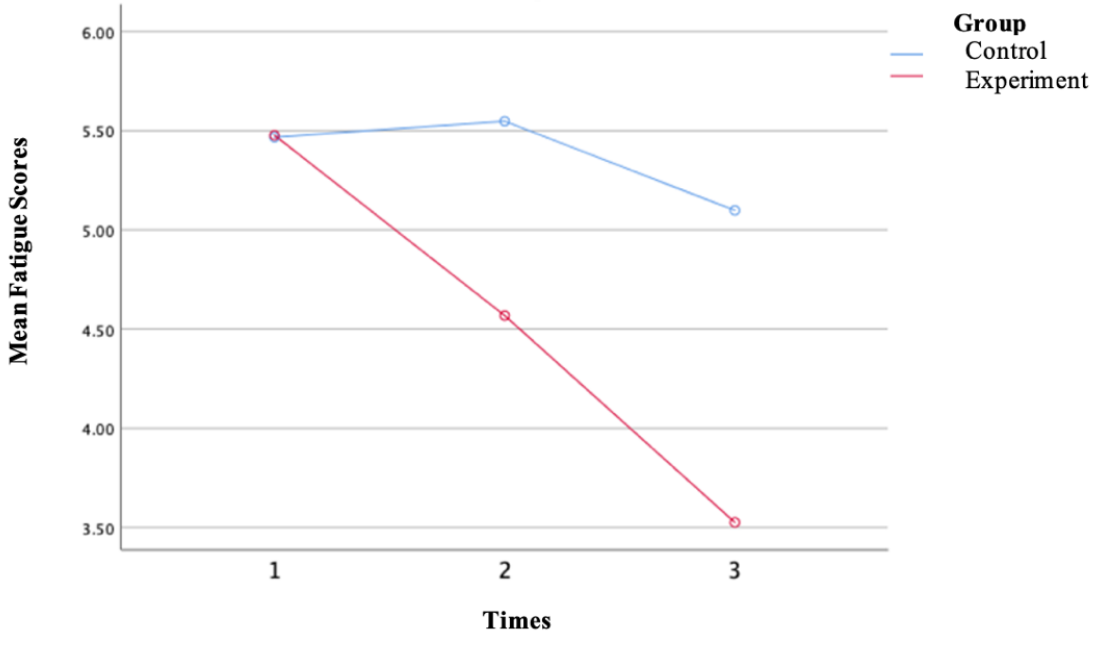

Fig 2. The graph shows the changes in mean fatigue scores at baseline (Time 1) week 3 (Time 2) and week 6 (Time 3) between the experimental and control groups.

Walking exercise adherence to program

Overall, 34 participants received the intervention (Integrated rehabilitation program); of these, 33 (97.05%) completed the study, and 1 (2.9%) did not complete the planned follow-up because of hospitalized admission. In the intervention group, 28 (84.84%) of the participants were able to engage in walking exercise for the number of days meeting the set goal (Perform at least 3 times/week). Otherwise, the participants were able to exercise more than or equal to 18 days in a 6-week period and exercising on average 6 days per week. Designating light to moderate walking intensity (57-76% of maximum heart rate), 30 (90.90%) of the participants were able to perform walking exercise at the designated intensity. And the recommended goal is 20 - 30 minutes at a time. A total of 19 participants, or 57.58 %, were able to exercise for a

specified duration (20-30 minutes/session). The study also found the participants to exercise for an average in the range of 11 to 56 minutes per time. In addition, Problems & obstacles to participating the program include: Some weeks, the participants are inconvenient, not having time from work that must travel, etc. Some elderly people feeling very tired when exercising towards a specific goal or after increasing the intensity and duration of walking exercise. The participants were slightly tired, slightly swollen legs when resting, the symptoms improved and no adverse events were found in this study, such as arrhythmia, dyspnea, rapid and shallow breathing, and severe muscle pain, etc.

DISCUSSION

The results of this study, finding that patients with pulmonary tuberculosis had statistically significant decreases in fatigue after receiving the integrated rehabilitation program and the decreases were substantial when compared to the control group and with statistical significance ($p < .001$). That the integrated rehabilitation program can reduce fatigue in patients with pulmonary tuberculosis is the result of the three components in the program, which included the following: walking exercise, nutrition education and management of adverse reactions from antituberculosis drugs, support from health care provider together with the use of the LINE application in health care monitoring that covers physical and mental care rather than a single program format. Thus, the program covers the main causes or contributing factors involved fatigue in pulmonary tuberculosis. The program style in this study is consistent with a study by Xu et al.[15] of a holistic nursing model combined with breathing exercises. As a result, tuberculosis patients can take better care of themselves and improve lung function and the quality of life improved statistically and also consistent with previous studies on pulmonary rehabilitation programs in patients with pulmonary tuberculosis that require components a variety of programs, including exercise, breathing exercises, education, nutrition support, and psychological support.[16] Thus, fatigue can be managed effectively and is beneficial in reducing residual pulmonary impairment.[17,18]

The present study was based on the Symptom Management Model of Dodd[12] consisting of three main dynamic components applied in the integrated rehabilitation program, which can be described as follows: Experiencing fatigue among patients with pulmonary tuberculosis is an individual differently perception. It is therefore necessary to create a common understanding that fatigue is a manageable condition. Understanding these elements was the starting point for raising awareness and building confidence for participants to manage symptoms, thereby leading to effective management of fatigue. Managing symptoms well requires a health care team that can develop appropriate symptom management strategies for patients. In the present study, For the control group, even though they were not given the integrated rehabilitation program, they were given the option to engage in activities to reduce their own fatigue. This study found that most of the participants in the control group chose to use the method of rest and relaxation when fatigued and others engaged in prayer, meditation, and exercise sometimes, etc. This finding corresponded with previous studies found that sleep was the most frequently chosen symptom management method for the managing fatigue.[19] The outcome was that this method was able to help alleviate some of the symptoms but might not have been sufficiently effective due to the fact that the fatigue in patients with pulmonary tuberculosis is caused by a variety of reasons. In addition, the fatigue in patients with pulmonary tuberculosis is classified as chronic fatigue in which sleep and relaxation may not yield optimal outcomes.[2] The experimental group implemented an integrated rehabilitation program to reduce fatigue and affecting the perceived experience of reduced fatigue symptoms. The experimental group therefore continued to use strategies to manage fatigue symptoms to help control symptoms from recurring. This is in line with the symptom management concept of Dodd[12], which is a dynamic process. As a result, the integrated rehabilitation program can statistically significant reduce fatigue in pulmonary tuberculosis patients.

When describing each component of an integrated rehabilitation program that can reduce fatigue in pulmonary tuberculosis patients, it can be described as follows: People who exercise regularly will help stimulates immune function, strengthens the body, reducing dyspnea, fatigue and improving the physical performance.[18,20] and causes the body to level up the neurotransmitter monoamine, leading to the balancing of the nervous and limbic systems associated with emotions and sensations. It also improves mood, relieves depression, reduces anxiety, and promotes better sleep quality.[21] Furthermore, educating patients about nutrition and the management of adverse reactions from antituberculosis drugs in an easy-to-understand format can be described through videos, illustrated manuals, and the knowledge sent in an infographic format to the participants in order to remind the participants to review their knowledge. This is consistent with the study that the use of multimedia to inform TB patients

results in knowledge skills and behavior modification can take better care of themselves.[22] It also gives them understanding about choices of food intake and helps them recognize the benefits of proper dietary intake, which will help encourage patients to have better nutrition or maintain good nutrition[23,24] that it plays an important role in reducing fatigue and strengthens the body's immune system, helping to promote recovery from illness with tuberculosis[24,25] Including the knowledge of adverse reaction management strategies from antituberculosis drugs will help patients apply the knowledge gained in the event of an adverse reaction and help adherence to treatment include make patient feel truly comprehensive care[26,27] and educating is also another form of social support in the field of information. It is very important and necessary to take care of tuberculosis patients.[28]

Reinforcing support from health care provider through the use of LINE applications to monitor, assess activity performance, communication and is a channel for transmitting information about multimedia knowledge.[29] It is the nurse's role in social support for evaluation by providing feedback in the form of sending messages and stickers of appreciation and encouragement. Which tells the participants about the results of the exercise after the participants saw the results of their own performance. It will help motivate and encourage the participants to continue to exercise continuously. Including emotional support and information for tuberculosis patients with encouragement show empathy, concern and empathy as a caregiver for tuberculosis patients.[28] Consistent with the study found this support would make tuberculosis patients under stress, anxiety during treatment feel warm and comfortable in being closely cared for and make patients feel self-worth encourage patients to be more aware of self-care.[30]

The results of this study, finding that participation adherence to program was as high as 97.05%, as a result of a follow-up calls via LINE application were made once a week throughout the research period to inquire about problems and obstacles in exercising including general symptoms of the participants. Makes it possible to track and evaluate the trend of exercise whether it meets the goals set or not and can plan together each week and can help manage and modify exercises flexibly according to individual suitability. It is similar to many previous studies in the use of the telephone follow-up method. It was found that phone calls follow up on activities and give advice periodically contributing to the participants group's cooperation and persistence in the program.[31,32] It is therefore a part that helps to make the integrated rehabilitation program more effective.

This study has some limitations. The integrated rehabilitation program conducted through the LINE application was available only to participants with smartphones who were able access the program. This study collected data at advanced tertiary care hospital in a single urban area. There may be limitations to the use of research results in generalize to the entire tuberculosis patient population.

CONCLUSION

The integrated rehabilitation program statistically and significantly reduced the levels of fatigue in pulmonary tuberculosis in 3-6 weeks.

Recommendations and implications

1. Nurses and health care teams can implement the integrated rehabilitation program to care for patients with pulmonary tuberculosis such as nutrition education, managing adverse reactions to antituberculosis drugs and promoting exercise together with Dodd's symptom management concept. The patient's fatigue was assessed, and sufficient information is provided to patients and there should be a plan for periodic follow-up visits and encourages patients to manage fatigue appropriately.

2. Studies should be conducted on the effects of the integrated rehabilitation program on fatigue in patients with pulmonary tuberculosis in different locations and contexts from this study. Furthermore, longitudinal studies (e.g., 3 months, 6 months, or 1 year) can be generalized extensively in the care of patients with pulmonary tuberculosis.

3. Clinical outcomes, such as pulmonary function, respiratory and skeletal muscle strength, subjective perception exertion, and dyspnea, body weight, serum albumin level or quality of life should be measured in patients with pulmonary tuberculosis to further monitor the effectiveness of such programs.

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Correlation between Postmortem Ethanol Production and Low Molecular Weight Volatiles (LMWVs) in a Thai Population

Sutara Hengcharoen, M.D.*,, Darunrat Kaeomun, M.Sc.**, Peerayuht Phuangphung, M.D., Ph.D.****

**Paholpolpayuhasena Hospital, Ministry of Public Health, Kanchanaburi Province, Thailand., **Department of Forensic Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: To determine the relationship between postmortem ethanol production and low molecular weight volatiles (LMWVs) in a Thai population.

Materials and Methods: A retrospective study was conducted on 157 Thai cadavers. Various subject data were recorded, including degree of postmortem changes (transition period group vs. decomposition group classified by the total body score [TBS]) and blood profiles of ethanol, acetaldehyde, and 1-propanol concentrations from femoral blood samples. Blood ethanol concentrations were diagnosed as postmortem production by vitreous humor analysis. Linear regression analysis was performed to determine the correlations between these three analytes and the TBS and between postmortem ethanol and the other two analytes.

Results: This study comprised 44 females and 113 males with a mean age at death of 47.79 years old. Postmortem ethanol, acetaldehyde, and 1-propanol concentrations escalated along with the increased TBS ($p<0.001$). These three analytes were significantly correlated with the TBS ($p<0.001$) and the correlations of determination (R^2) for postmortem ethanol and 1-propanol were better than for acetaldehyde ($R^2 = 0.488$ and 0.414 vs. 0.269). Acetaldehyde and 1-propanol were positively correlated with postmortem ethanol ($p<0.001$). The correlations between postmortem ethanol and acetaldehyde, 1-propanol, and the combination of these two analytes produced R^2 values of 0.413, 0.480, and 0.544, respectively.

Conclusion: Acetaldehyde and 1-propanol concentrations were significantly correlated with postmortem ethanol concentrations in Thai cadavers, and the combination of these two markers produced a better correlation with the postmortem ethanol concentration.

Keywords: Postmortem ethanol; acetaldehyde; 1-propanol; Thai population (Siriraj Med J 2023; 75: 299-305)

INTRODUCTION

Ethanol (alcohol) is the most common substance detected in forensic autopsy cases.[1] Ethanol plays an important role in many causes of death in medico-legal cases. In addition, a blood ethanol concentration beyond the legal limit for vehicle control is important for the diagnosis of driving under the influence of alcohol. In Thai legislation, Ministerial Regulations No. 16 B.E. 2537 (1994) and No. 21 B.E. 2560 (2017) by virtue of the provisions of Section 5 of the Road Traffic Act B.E. 2522 (1979) set the statutory cut-off point for blood ethanol concentration at 50 mg/dL for the general population

Corresponding author: Peerayuht Phuangphung
E-mail: peerayuht.phu@mahidol.ac.th
Received 26 December 2022 Revised 1 March 2023 Accepted 4 March 2023
ORCID ID:http://orcid.org/0000-0003-4139-9997
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and 20 mg/dL for people in some specific groups, for example, people who are under 20 years old. This cut-off may result in difficulty in blood ethanol interpretation, particularly in postmortem cases due to postmortem ethanol production from the time since death.

A previous study suggested that postmortem ethanol production commonly occurs in decomposed bodies, bodies retrieved from water, and bodies with extensive trauma because of the increasing risk of bacterial activities.[2] A review article suggested that blood ethanol concentrations less than 30 mg/dL in dead bodies were mainly caused by postmortem ethanol production.[1] The majority of postmortem ethanol blood concentrations have been reported to be not greater than 70 mg/dL.[2,3] There are only a few reports of postmortem ethanol production greater than 100 mg/dL.[3-6] Postmortem ethanol productions at 120 mg/dL and 160 mg/dL have been reported in decomposed bodies.[3,4] The diagnosis of postmortem ethanol production in these decomposed bodies was based on their vitreous humor (VH) ethanol concentrations that were less than 10–20 mg/dL, leading to inconsistent ratios of VH-to-blood ethanol concentrations (VH/B ratio).[3,4,7] Dead bodies with severe trauma can have a postmortem ethanol production of 180 mg/dL and 190 mg/dL.[5,6] Thus, the VH/B ratio is an important parameter for the interpretation of postmortem ethanol production.

Low molecular weight volatiles (LMWVs), such as acetaldehyde, 1-propanol, 2-propanol, and 1-butanol, were also reported to be useful for the diagnosis of postmortem ethanol production.[8-10] Ceciliason et al. and Boumba et al. indicated that 1-propanol was correlated with the degree of decomposition.[8-10] Chen et al. suggested that acetaldehyde was also positively correlated with postmortem ethanol production and this marker was more sensitive than 1-propanol.[9] Thus, 1-propanol and acetaldehyde are two potential markers to determine postmortem ethanol production.

The synthesis of LMWVs in dead bodies can vary depending on the postmortem interval (PMI), environmental factors, internal conditions of the dead bodies, and types of intestinal microbes.[11] There is still no current information about the association between postmortem ethanol production and LMWVs in Thai postmortem cases. Consequently, the aim of this study was to determine the correlation between postmortem ethanol production and LMWVs in a Thai population. This finding would be useful for the interpretation of postmortem ethanol production and the prediction of blood ethanol concentrations generated in postmortem periods, leading to the benefit of better understanding the states of dead bodies for legal procedures.

MATERIALS AND METHODS

Study design and data collection

A retrospective study was conducted of medico-legal cases sent for autopsy at the Department of Forensic Medicine, Siriraj Hospital, Mahidol University between January 1, 2021 and December 31, 2021. This study was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University (COA no. Si 061/2022, SIRB protocol No. 016/2565(IRB4)). The inclusion criteria were: Thai people who were 18 years old or over and their postmortem changes ranged from the transition period before decomposition to the decomposition period. Femoral blood and VH must be collected from each case in a sodium fluoride tube for the analysis of ethanol, acetaldehyde, and 1-propanol. The positive ethanol concentrations were considered as postmortem ethanol production according to two criteria[1,3,4,7]:

1. Blood ethanol concentrations were less than 30 mg/dL and VH ethanol concentrations were negative.

2. Blood ethanol concentrations were equal to or greater than 30 mg/dL and VH ethanol concentrations were less than 10 mg/dL.

Sex, age, underlying disease, cause of death, and postmortem changes were recorded for each case. The external findings of postmortem changes were classified into two groups based on two periods:

1. Transition period (before decomposition) group: presence of secondary flaccidity of rigor mortis and partial or total fixation of livor mortis without external signs of decomposition.

2. Decomposition group: presence of external signs of decomposition, including chromatic phase and gaseous phase (Table 1).

The decomposition group was scored by the total body (decomposition) score (TBS) adapted from previous works.[12-14] The scoring system based on the starting number of zero for the state of no decomposition was derived from Moffatt et al.[12] The body descriptions for the decomposition state were adapted from Megyesi et al.[13] and Gelderman et al.[14] Our TBS is described in Table 1.

The summation of all the TBS points from each area was calculated. For the decomposition group, this meant the scoring would be from 1 to 10 points. Next, decomposition group was categorized into three groups based on the degree of TBS: 1–3 points, 4–7 points, and 8–10 points, respectively.

Analyses of ethanol, acetaldehyde, and 1-propanol

Ethanol, acetaldehyde, and 1-propanol analyses were

TABLE 1. Developed TBS method for the body decomposition.

TBS	Points	Description
TBS_Head and Neck	0	No signs of decomposition
	1	Greenish discoloration of the face and neck
		Marbling of the face and neck
	2	Bloating of the face and neck
	3	Skin bleb and/or skin slippage of the face and neck
TBS_Torso (Trunk)	0	No signs of decomposition
	1	Greenish discoloration of the chest and/or abdomen
		Marbling of the upper trunk
	2	Bloating of the chest and abdomen
	3	Skin bleb and/or skin slippage of the chest and abdomen
TBS_Limb	0	No signs of decomposition
	1	Greenish discoloration of the upper limbs
		Marbling of the upper limbs
	2	Greenish discoloration of the lower limbs
		Marbling of the lower limbs
	3	Bloating of the upper and/or lower limbs (limb spreading)
	4	Skin bleb and/or skin slippage of the upper and/or lower limbs

performed by the method adapted from the previous study[15] using a headspace gas chromatography-flame ionization detector (HS-GC-FID) in an Agilent 7890A GC system. The GC was equipped with the RTX-BAC2 RESTEK capillary column (30 m × 0.32 mm × 1.2 µm). Helium gas was used as the carrier gas at a flow rate of 2 mL/min. GC introduction was carried out using split injection with a ratio of 10:1. The HS preparation was done using an Agilent G1888 HS with an oven temperature of 80 °C, transfer line temperature of 120 °C, and vial equilibration time of 5 minutes. The oven temperature was set at 47 °C. The FID temperature was set at 235 °C with the flow rates of hydrogen gas, air zero, and make-up gas (nitrogen) at 45, 450, and 8 mL/min, respectively. The analysis was performed in duplicate using isocratic elution with a total run time of 7.5 minutes.

Method validation was performed following the SWGTOX 2013 guidelines.[16] Selectivity and interference studies were conducted to ascertain there were no interference peaks at retention times of acetaldehyde, ethanol, and 1-propanol at 2.27, 3.36, and 5.93 minutes. The limit of detection (LOD) and lower limit of quantitation (LLOQ) for ethanol, acetaldehyde, and 1-propanol were 1.5/2.5, 0.5/1, and 0.5/1 mg/dL, respectively. Calibration curves for ethanol were performed from 2.5 to 100 mg/dL (2.5, 5, 10, 20, 50, and 100 mg/dL). Calibration curves for acetaldehyde and 1-propanol were performed from 1 to 50 mg/dL (1, 2, 5, 10, 20, and 50 mg/dL). Calibration curves were generated using Agilent ChemStation Software® Version B.04.03 from back-calculated concentrations for each calibrator to achieve $R^2 > 0.99$ and acceptable accuracy. Three spiked QC samples for ethanol at 8, 25, and 80 mg/dL and for acetaldehyde/1-propanol at 3, 15, and 40 mg/dL were analyzed for assessing the accuracy and precision. The accuracy and precision for each QC were within acceptable criteria at ±15% accuracy and ±15% coefficient of variation (%CV).

Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics for Windows version 25. Descriptive statistics, including the mean, median and standard deviation (SD), were calculated. The Kruskal–Wallis H-test was performed for comparison of these three analytes and each TBS group. Linear regression analysis was performed for assessing the correlation between the TBS and each compound. Then, linear regression and multiple regression analyses were performed for assessing the correlation between ethanol and the other two compounds. Regression diagnostics and multicollinearity testing were performed for acetaldehyde and 1-propanol with the variance inflation factor (VIF) converged to 1.

RESULTS

According to two criteria for postmortem ethanol production stated above, there were 157 cases recruited in this study, comprising 44 females (28.03%) and 113 males (71.97%). The mean age at death was 47.79 ± 15.77 years old (range, 18–84 years old). The main causes of death were coronary artery disease (35.67%, 56/157), drowning (15.92%, 25/157), hanging (13.38%, 21/157), closed head injuries from falling (5.10%, 8/157), and cirrhosis (4.46%, 7/157), respectively. There were 34 cases (21.66%) that were in the transition period and 123 cases (78.34%) that presented with external signs of decomposition.

Overall, there were 47.13% (74/157) acetaldehyde-positive samples and 35.03% (55/157) 1-propanol-positive samples. There were a small number of positive cases for acetaldehyde (14.71%, 5/34), and no positive cases for 1-propanol in the transition period group; in contrast, there were 56.10% (69/123) acetaldehyde-positive cases and 44.72% (55/123) 1-propanol-positive cases in the decomposition group. The concentration ranges of ethanol, acetaldehyde, and 1-propanol in the decomposition group escalated with the increasing extent of decomposition. The comparison of ethanol, acetaldehyde, and 1-propanol between the three different TBS groups presented with significant differences for all three compounds ($p < 0.001$). The ranges and median concentrations of ethanol, acetaldehyde, and 1-propanol in the subjects classified by the postmortem changes are shown in Table 2.

In the decomposition group, all three analytes were positively correlated with the TBS ($p < 0.001$), but the coefficients of determination (R^2) for ethanol and 1-propanol were better than for acetaldehyde. The regression analysis results for these three analytes are shown in Fig 1 and Table 3.

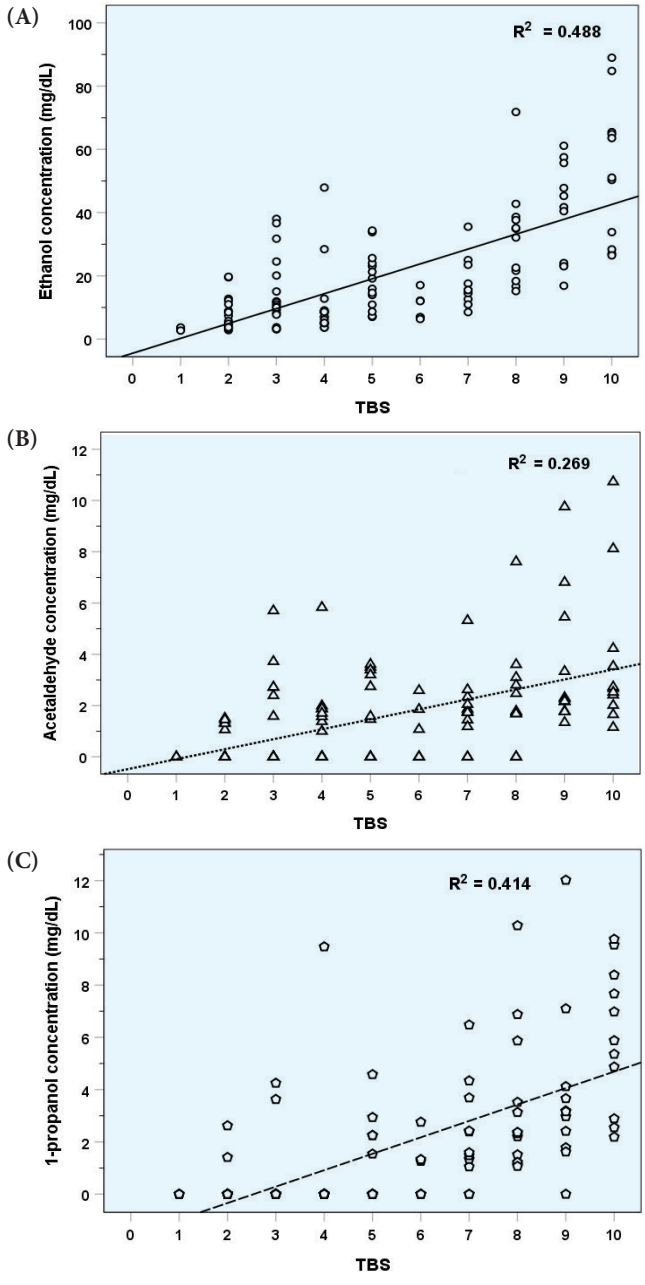

Fig 1. Regression analyses between TBS and (A) ethanol, (B) acetaldehyde, and (C) 1-propanol.

TABLE 2. Blood ethanol, acetaldehyde, and 1-propanol concentrations in the studied subjects.

Postmortem changes	Ethanol (mg/dL)		Acetaldehyde (mg/dL)		1-propanol (mg/dL)	
	Range	Median	Range	Median	Range	Median
Transition period group	2.71–22.78	6.56	ND–3.64	ND	ND	ND
Decomposition group	2.72–88.96	14.56	ND–10.73	1.34	ND–12.02	1.75
TBS 1–3 points	2.72–38.01	8.37	ND–5.70	ND	ND–4.25	ND
TBS 4–7 points	3.66–47.90	12.00	ND–5.83	1.18	ND–9.47	ND
TBS 8–10 points	15.18–88.96	38.14	ND–10.73	2.36	ND–12.02	3.18

*ND = Not detected (<LOD)

TABLE 3. Regression analyses for the correlation between all three analytes and TBS.

Regression equation	R	R^2	p-value
Ethanol = (4.704 × TBS) – 4.455	0.699	0.488	<0.001
Acetaldehyde = (0.389 × TBS) – 0.479	0.518	0.269	<0.001
1-propanol = (0.629 × TBS) – 1.598	0.643	0.414	<0.001

There were highly significant correlations between postmortem ethanol and acetaldehyde and 1-propanol ($p < 0.001$) with approximately equivalent R^2 values. The correlation between the combination of these two analytes and postmortem ethanol produced better results than using each marker alone. The regression curves and equations are shown in Fig 2 and Table 4, respectively.

DISCUSSION

Postmortem ethanol production can occur from the transition period to decomposition state in a cadaver because postmortem ethanol could be generated from several pathways and there are many substrates that are utilized in microbial activities.[11] This finding was consistent with a previous review that indicated the susceptibility to postmortem ethanol production in cadavers that had the postmortem intervals greater than 12-24 hours due to the invasion of intestinal bacteria to bloodstream.[17] Subjects in the transition period group also had the postmortem intervals greater than 12 hours because of the criteria of postmortem changes in this study. Therefore, subjects in the transition period group could present with some degree of postmortem ethanol production. In the decomposition group in the present study, ethanol concentrations increased following the increased scores of the TBS, and this finding was consistent with previous studies.[7,9] This finding indicated that ethanol concentrations in blood and VH samples obtained from postmortem

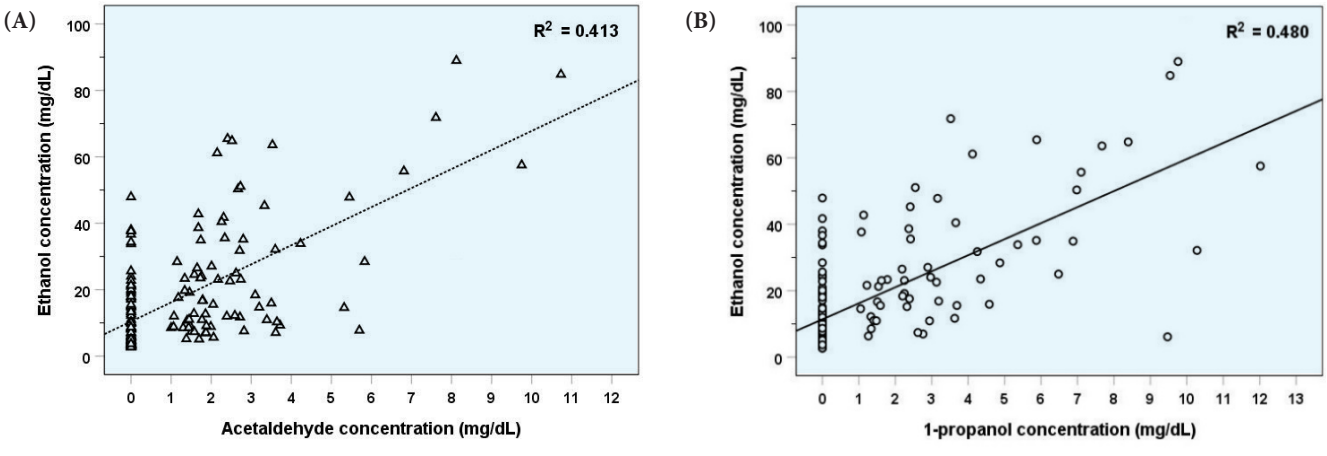

Fig 2. Regression analyses between ethanol and (A) acetaldehyde and (B) 1-propanol.

TABLE 4. Regression analyses for the correlation between postmortem ethanol and LMWVs.

Regression equation	R	R^2	p-value
Ethanol = (5.737 × acetaldehyde) + 10.425	0.643	0.413	<0.001
Ethanol = (4.826 × 1-propanol) + 11.379	0.693	0.480	<0.001
Ethanol = (2.981 × acetaldehyde) + (3.317 × 1-propanol) + 9.517	0.738	0.544	<0.001

cases were critical for the diagnosis of postmortem ethanol production using two criteria stated above. This study also showed that acetaldehyde and 1-propanol were positively correlated with the TBS. However, the R^2 values of postmortem ethanol and 1-propanol with the TBS were superior to acetaldehyde and this pattern was similar to in a previous study.[7] Although our R^2 values for postmortem ethanol and 1-propanol were relatively low (0.488 and 0.414), they were slightly better than in a previous study, which reported R^2 values of 0.16 and 0.29 for postmortem ethanol and 1-propanol, respectively.[7] This finding might have resulted from the difference in case recruitment because 78.34% of the cadavers in this study were decomposed cases, whereas the decomposed cases accounted for only 49% of the cadavers in the previous study.[7] Previous studies suggested that 1-propanol was a strong marker for the putrefactive state, whereas the other LMWVs could be variable[7,8,10,11], because 1-propanol was mainly generated from the amino acid pathway in bacteria and yeast and this production did not depend on the presence of glucose and carbohydrate metabolism.[11] Thus, 1-propanol produced a better correlation with the TBS than acetaldehyde and may be suitable for TBS evaluation in Thai postmortem cases.

Acetaldehyde (47.13%) was more commonly found than 1-propanol (35.03%) in the overall cases and this finding was consistent with previous studies.[8,10] Chen et al. found that 1-propanol was generated *in vitro* at a slower rate and lower amount than acetaldehyde and this explanation was congruent with our results that 1-propanol was only found in the decomposition group.[9] However, the acetaldehyde concentrations in this study were not as high as stated in the previous study because Chen et al. indicated that acetaldehyde beyond 14 mg/dL could be used as a marker for postmortem ethanol production[9], but the concentration range for acetaldehyde in this study was only ND–10.73 mg/dL.

Our study showed that acetaldehyde and 1-propanol were positively correlated with postmortem ethanol with equivalent R^2 values (R^2 = 0.413 and 0.480). When these two markers were combined for the regression analysis with postmortem ethanol, the R^2 value was improved compared with each marker alone (R^2 = 0.544). This finding was consistent with a previous study employing multiple markers (1-propanol, n-butanol, isobutanol, and methyl-butanol).[18] However, our R^2 was relatively moderate compared with the previous study that reported a high R^2 value (>0.7).[18] This result could be caused by differences in the data collection because the previous study derived the equation and R^2 from experiments using single bacteria in each experimental condition, whereas our study obtained the equation and R^2 from authentic cases. Although the previous study showed that their models from *C. perfringens* and *E. coli* were suitable for postmortem ethanol prediction, they estimated the postmortem ethanol concentrations with a standard error of <40% for approximately 63%–68% of the total cases.[18] This implied that postmortem ethanol production came from complex pathways and there were likely several microorganisms involved in this process. Furthermore, postmortem ethanol and LMWVs produced by microbial activities could vary due to the different substrates used and different types of microorganisms and this may be dependent on the cadaver condition.[11] Thus, the interpretation of postmortem ethanol concentrations using LMWVs should be carefully performed.

CONCLUSION

Acetaldehyde and 1-propanol were positively correlated with postmortem ethanol concentrations. The combination of these two markers in the regression analysis produced a better correlation with postmortem ethanol concentrations than employing each marker alone. Thus, postmortem ethanol concentration could be determined by using blood and VH ethanol concentrations coupled with acetaldehyde and 1-propanol concentrations that were correlated with blood ethanol concentrations.

ACKNOWLEDGEMENTS

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Conflict of Interest

None.

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Comparative Effectiveness of Video and Face-to-Face Sessions to Educate Hospitalized Patients on Cancer Pain Management

Suratsawadee Wangnamthip, M.D. *, Isaraporn Tip-apakoon, BNS*, Natinee Benjangkhaprasert, M.D. *,, Nattaya Bunwatsana, B.Sc. *, Skaorat Panchoowong, BNS*, Pramote Euasobhon, M.D.***

**Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, **Ramadhibodi Chakri Naruebodindra Hospital, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.*

ABSTRACT

Objective: Patients' lack of knowledge of cancer pain management affects pain outcomes. This study compared the effectiveness of cancer pain management achieved in a previous retrospective study ("P-group"), in which hospitalized cancer pain individuals received no pain education, with the pain management achieved by 2 study groups. One group received pain management information via video sessions ("V-group") and the other via face-to-face coaching ("F-group"). The study's secondary aims were to compare the 2 interventions' psychological, quality-of-life, and opioid-consumption impacts.

Materials and Methods: This single-blinded, randomized, controlled trial enrolled hospitalized cancer pain patients aged between 18 and 70 with an Eastern Clinical Oncology Group performance status < 4. They were assigned to V- and F-groups to receive information on managing cancer pain. "Successful pain control" was defined as "no to mild pain" or a numerical rating scale score < 4 on Day 6. Pain intensity and opioid consumption (morphine-equivalent daily dosage) were recorded daily from baseline to Day 6. Psychological status (Hospital Anxiety and Depression Scale) and quality of life (Functional Assessment of Cancer Therapy–General) were assessed at baseline and Day 6.

Results: Fifty-nine participants were analyzed (V-group: 31; F-group: 28). Both groups had significantly higher successful pain outcomes than the P-group ($P < .001$). The V- and F-groups had no significant differences in successful pain control (20 [65%] vs 19 [68%]; $P = .787$), psychological effects, quality of life, or opioid consumption.

Conclusion: Video sessions are an alternative means of educating hospitalized cancer pain patients and reducing healthcare providers' workloads.

Keywords: Cancer pain; hospitalization; humans; neoplasm; pain management; patient education; randomized controlled trial (Siriraj Med J 2023; 75: 306-315)

INTRODUCTION

Pain remains a prevalent symptom in patients with cancer despite the availability of opioids and current guidelines.[1–3] Cancer-related pain is common across the cancer spectrum, with reported incidences between 40% and 75% of patients.[4,5] The risk factors are disease stage, comorbidities, treatment regimen, and efficacy of pain treatment.[2,4,6] Despite guidelines for managing cancer pain, pain control in cancer patients and survivors is underperformed. Fifty-five percent of all patients with cancer are undertreated for their pain, as are 66% of patients with advanced, metastatic, or terminal diseases.[5] Decreasing the pain and suffering of cancer individuals is fundamental to delivering quality care. Pain experienced

Corresponding author: Isaraporn Tip-apakoon
E-mail: Isaraporn.tip@mahidol.ac.th
Received 27 February 2023 Revised 2 March 2023 Accepted 10 March 2023
ORCID ID:http://orcid.org/0000-0003-4436-4570
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by adults with cancer affects their physical functioning, social functioning, concentration, and mental health.[2] If the pain is compounded by anxiety, the deleterious effects on quality of life and disability are exacerbated.[2]

In Thailand, many factors are associated with inadequate cancer pain management. They include hospital remoteness, limited healthcare providers, and insufficient understanding by patients and healthcare providers of cancer pain management. In 2014, research by Wangnamthip et al revealed that only 35% of hospitalized patients at Siriraj Hospital given no pain education had excellent pain responses.[1] Patients' negative attitudes toward opioid use are one of the barriers to managing cancer pain. A study examined factors influencing nonadherence to potent opioids by Thai cancer individuals. The authors reported that 39.6% of patients were nonadherent to opioid therapy. The barriers to compliance were fear of the possible long-term outcomes, concern about opioid side effects, and a poor understanding of their illness.[7]

A meta-analysis by Bennett showed that educational interventions on cancer pain improve patients' knowledge of and attitudes toward pain and analgesia. It was also found that the interventions increased medication adherence, thereby minimizing pain intensity.[8] Educational support has therefore become a standard component of cancer care to enhance pain management.[9,10] Many interventions have been employed to overcome barriers to patient understanding of cancer pain management.[11] Among them are face-to-face coaching, video sessions, audiotapes, information sheets, booklets, and web-based information.[12,13] The traditional approach is face-to-face coaching, usually for 30 to 60 minutes. Video presentations are an interesting alternative. They are more flexible, cost-effective, and time-efficient than face-to-face coaching.[14]

Due to the unsatisfactory prevalence of poor cancer pain management at Siriraj Hospital, the authors conducted a single-blinded, randomized, controlled trial. Its primary aim was to compare the efficacy of providing hospitalized cancer pain individuals with no pain education (the historical approach) and with pain education. Two educational interventions were separately tested: video sessions ("V-group") and face-to-face coaching ("F-group"). The secondary aims were to evaluate the psychological, quality-of-life, and opioid-consumption impacts of the 2 interventions.

MATERIALS AND METHODS

Study design and setting

A single-blinded, randomized, controlled trial was conducted from August 2017 to April 2022 at Siriraj Hospital, Bangkok, Thailand. Before this research began, the Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University, approved the study protocol (COA no. Si 231/2017). The clinical trial registration number was NCT03205579.

Participants

Participants were recruited from patients assigned to receive pain control during their hospital stay. The inclusion criteria were an age of 18 through 70 years, an Eastern Clinical Oncology Group (ECOG) performance status of < 4, and fluency in Thai. The exclusion criteria were patients with cognitive dysfunction or clinical instability, and denial of consent to participate in the study.

Interventions

During the study, all participants received standard care from pain physicians. The educational interventions were provided within 24 hours after a pain specialist prescribed pain management therapy. Each participant in the F-group was given 30 minutes of face-to-face pain education with a trained nurse, while participants in the V-group received 14 minutes of video education. The video was developed by the hospital's medical education technology center under the close supervision of pain specialists. The information provided to both groups was drawn from the WHO analgesic ladder. It encompassed the causes and effects of cancer pain, using a numerical rating scale (NRS) to estimate pain intensity, pain treatment goals, truths and myths about opioids, opioid side effects, and pain management.

This study had 2 primary objectives. The first was to compare the efficacy of face-to-face and video educational interventions for controlling pain as of Day 6 with historical data ("P-group"). To this end, the finding of the 2014 study by Wangnamthip et al was used: only 35% of hospitalized patients given no pain education had excellent pain responses. The other primary objective was to compare the efficacy of the 2 trial methods (face-to-face approach and video). The secondary objectives were to evaluate the following:

- psychological status, including anxiety and depression, via the Thai version of the Hospital Anxiety and Depression Scale (HADS)
- quality of life via the Thai version of the Functional Assessment of Cancer Therapy–General (FACT-G)
- opioid consumption via the 2 groups' morphine-equivalent daily dosages (MEDD)[15]

Data collection and outcome measures

Data were collected at baseline and on the following

6 consecutive days (7 full days). Records were made of baseline demographic data (age, sex, marital status, and education level) and clinical characteristics (body mass index, functional status [ECOG score], cancer diagnosis, primary tumor, cancer stage and grade, and pre-existing comorbidities). Other variables (pain intensity [NRS score], opioid consumption [MEDD], and analgesic usage) were evaluated before the interventions and every day from baseline to Day 6. Emotional status (HADs) and quality of life (FACT-G) were assessed before and after the intervention (baseline and Day 6). Data were collected by nurses and physicians and entered onto paper case report forms.

Functional status

ECOG performance status scores are typically used to identify patients' functional status. The scores range from 0 (fully active; able to carry on all pre-disease performance without restrictions) to 5 (deceased).[16]

Primary outcome

The NRS for pain uses an 11-point scale (0–10), with 0 signifying "no pain" and 10 denoting "the worst pain imaginable."[17] The daily patient-reported scores were combined to determine the maximum, average, and minimum experienced by each intervention group during each preceding 24-hour period. "Successful pain control" was defined as patients with a pain intensity of less than 4 (no to mild pain) on Day 6. The proportions of patients in the V-group, F-group, and P-group who achieved successful pain control were compared.

Secondary outcomes

Psychological status

The HADS uses a 14-item scale, with 7 items relating to anxiety and 7 to depression. Each item is scored from 0 to 3. Scores of 0 to 7 determined a "normal" psychological status, and scores of 8 to 10 indicated a "borderline abnormal" status. The cut point for clinical anxiety or depression was a score of 11.[18]

Quality of life

The FACT-G consists of 27 items covering 4 domains: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well-being (7 items). Each of the 27 items is scored from 0 ("not at all") to 4 ("very much"). Negatively worded items are reverse-scored prior to summing. Each domain score was calculated, and the FACT-G total score was determined by summing the 4 domain scores. Higher scores indicated a better quality of life.[19]

Opioid consumption

Opioid consumption levels were calculated as the MEDD.[15] The consumption included the maintenance dosage and the total breakthrough dose.

Sample size calculation and statistical analysis

One of the 2 primary objectives of this study was to establish the degree of successful pain outcomes following video-based and face-to-face-based educational interventions on pain management. We theorized that the successful pain control level resulting from each intervention strategy would be 60%, which is higher than the historical value achieved without pain education (35%, as reported by Wangnamthip et al in 2014[1]). The sample size was determined using nQuery Advisor (version 6.0; Statistical Solutions, Saugus, MA, USA). With a type 1 error of .05 (1-tailed) and a statistical power of 80%, the estimated sample size was 30 participants per intervention group (one group of tests in which the proportion equals a user-specified value [normal approximation]). The second primary objective of the current investigation was to compare the efficacy of the video-based and face-to-face-based educational interventions. We assumed that the degree of successful pain control achieved with the face-to-face approach would be 1.5-fold higher than that of the video-based intervention. According to the formula for 2 groups of tests of equal proportion, F-group's proportion was 0.9 (p1 = .90), and V-group's proportion was 0.6 (p2 = .60). Considering a type 1 error of .05 and a statistical power of 80%, the sample size was increased to 32 participants per group. After allowing for a 10% dropout rate, the final sample size was calculated as 35 participants per intervention group.

Randomization and allocation

The participants were randomly allocated to the 2 intervention groups using simple random sampling. First, 70 slips of paper were divided equally among the F-group and V-group. Each slip was placed in separate sealed envelopes, which were then stored in an enclosed box. Only research assistants who were not involved in any other aspect of the study were notified by the research team that a patient had consented to participate in the trial. The same research assistant randomly selected an envelope from the storage box, thereby determining the intervention group to place the patient in. A suitably trained nurse subsequently arranged the appropriate intervention for the patient. The other trial staff and outcome assessors were blinded to the intervention group allocations.

Statistical analysis

Data analyses were performed with PASW Statistics for Windows, version 18 (SPSS Inc, Chicago, IL, USA) and Number Cruncher Statistical Software (NCSS version 10.0.19; NCSS, Kaysville, Utah, USA). Descriptive statistics were used to summarize the baseline characteristics (age, sex, education, ECOG score, cancer type and stage, reason for admission, baseline pain intensity, quality of life [FACT-G], and psychological status [HADS]). A Shapiro–Wilk normality test was used to evaluate skewness, with $P = .05$. Due to the skewness of the data, continuous variables are presented as medians (IQRs), and categorical variables are reported as numbers (percentages). The Mann–Whitney U test was used to evaluate the differences in the continuous data of the groups. Pearson's chi-square or Fisher's exact test was used for categorical group comparisons.

The exact binomial test was used to evaluate the improvement in cancer pain management achieved by each intervention relative to the previous historical study (P- vs V-group; P- vs F-group). Next, pre-post testing of the HADS and FACT-G scores within groups was undertaken using a marginal homogeneity test and the Wilcoxon signed-rank test, respectively. Finally, the repeated measure variables, including average pain intensity and MEDD, were analyzed, and imbalanced baseline variables were adjusted using repeated ANOVA. A P value < .05 determined a statistically significant difference.

RESULTS

Study population

Seventy hospitalized patients with cancer pain were enrolled. They were randomly allocated to 2 groups: 35 to the V-group and another 35 to the F-group. Eleven patients dropped out, primarily due to functional decline and a resulting inability to focus on the protocol (Fig 1). Consequently, 59 participants (31 in the V-group and 28 in the F-group) were analyzed.

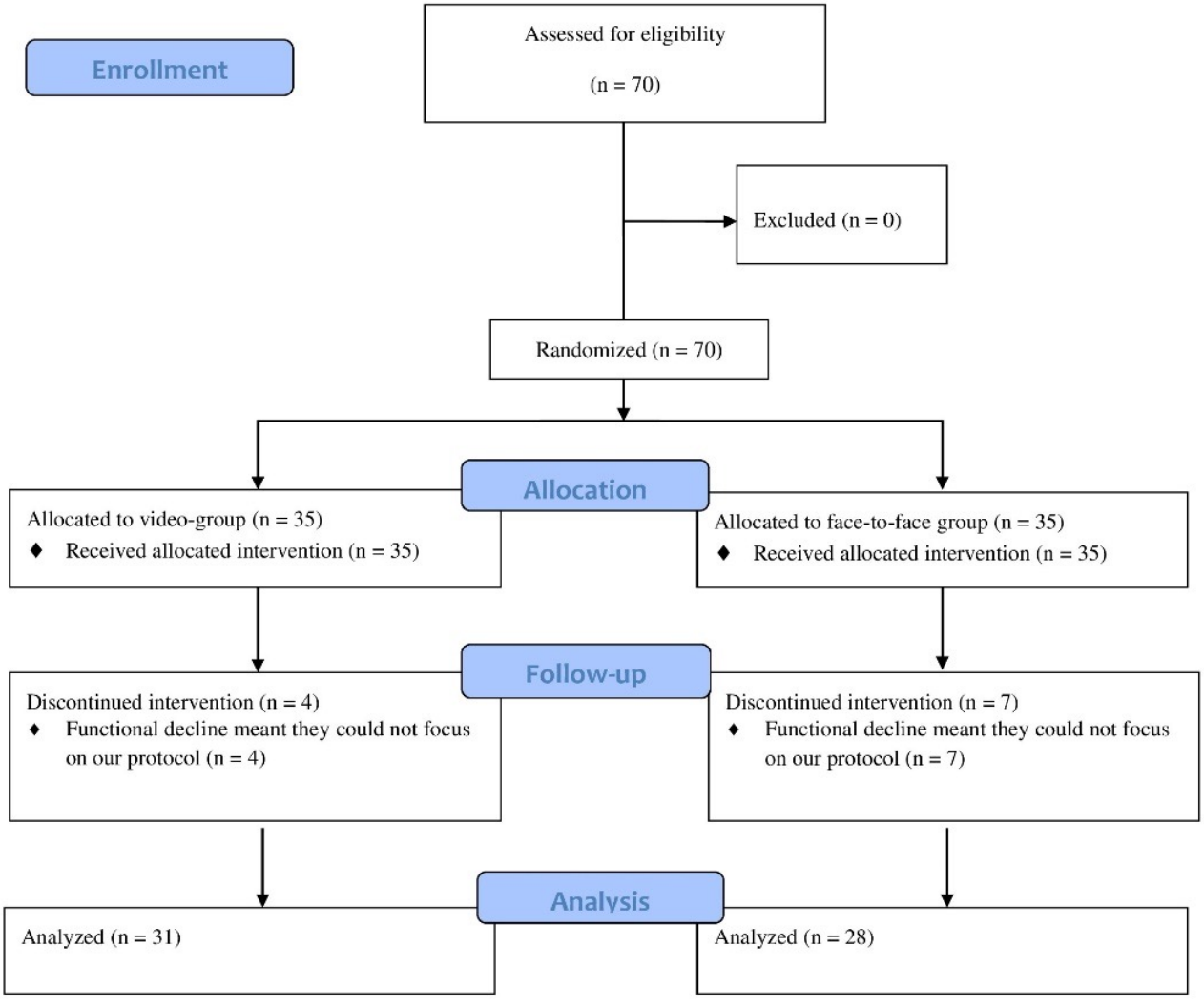

Fig 1. CONSORT 2010 Flow Diagram.

Baseline characteristics

The baseline characteristics of the study groups are detailed in Table 1. The groups had no significant differences in age, body mass index, marital status, education level, comorbidities, cancer status, primary cancer, or baseline pain intensity ($P > .05$). However, the sex profiles and ECOG scores of the groups differed significantly. The F-group had a higher proportion of females than the V-group (78.6% vs 41.9%; $P = .004$), and the distribution of the ECOG scores showed a significant difference ($P = .008$). The frequency of ECOG score 3 in the V-group was significantly lower than that in the F-group (6 patients [19.4%] vs 17 patients [60.7%]; $P = .001$). Conversely, the frequency of ECOG score 2 in the V-group was significantly greater than that in the F-group (12 patients [38.7%] vs 3 patients [10.7%]; $P = .014$).

Primary outcome

The exact binomial test evaluated the variations in the proportion of patients achieving successful pain control in the historical group (P-group) and the 2 educational intervention groups. A statistically higher proportion of patients achieved pain control in the V-group than in the P-group (65% [95% CI, 45%–81%] vs 35% [95% CI, 27%–0.43%]; $P < .001$). Similarly, there was a higher proportion in the F group than in the P-group (68% [95% CI, 48%–84%] vs 35% (95% CI, 27%–0.43%]; $P < .001$). The successful pain control levels achieved by the 2 educational interventions as of Day 6 were similar but without statistical significance (V-group, 20 patients [65%]; F-group, 19 patients (68%); $P = .787$).

Secondary outcomes

Pain intensity (maximum, average, and minimum) decreased from baseline to Day 6 in both intervention groups. There were no significant differences in the values for the 2 groups at any time point (Table 2).

Depression, anxiety, and quality of life were assessed by the HADS and FACT-G (Table 3). The 2 study groups had no significant differences in their psychological statuses (anxiety and depression) or quality of life on Day 6 ($P = .594$, .278, and .461, respectively). Moreover, there were no significant differences in the pre-post test results of the groups for psychological status or quality of life. The 2 groups had comparable levels of use of analgesics, including anticonvulsants, antidepressants, and NSAID/COX-2 inhibitors, during the trial period.

Repeated ANOVA was applied to the repeating variables (average pain intensity and MEDD). Imbalanced baseline data (sex and ECOG scores) were also adjusted. There were different average pain intensities over time ($P = .348$; no interaction between time points and factors). However, there was an interaction between ECOG scores and intervention ($P = .023$). Therefore, we analyzed the pain education groups' effects on pain intensity for each ECOG score. We found that the F-group had a significantly lower average pain intensity than the V-group for ECOG score 2 ($P = .015$; Fig 2). Repeated ANOVA for MEDD found no effect of pain education group, time, sex, or ECOG score on MEDD; nevertheless, only baseline MEDD found a significant difference (Fig 3).

DISCUSSION

Our study demonstrated that pain control improved after pain education through video and face-to-face sessions compared to a historical-conventional method without pain education. Moreover, there were no differences between the video and face-to-face methods regarding pain improvement, psychological status, quality of life, or opioid consumption.

Advancing pain education in cancer pain

Although pain treatment has become more diverse, cancer pain control remains an important issue. The main barriers to effective pain management include concerns about using pain medications, knowledge deficits, negative beliefs and attitudes, an unsupportive ambiance, and psychological distress.[20] Other research on healthcare providers revealed that nurses fear administering opioids because of the potential for patient addiction and harmful side effects. Moreover, healthcare staff may have inadequate knowledge and training on opioids, may not follow guidelines, and may focus on cancer treatment rather than pain management. Patients' opioid phobias are related to a fear of becoming addicted and a concern about possible opioid-induced side effects. Myths about the management of cancer pain and the associated symptoms contribute markedly to patients' opioid phobias.[21]

A meta-analysis by Oldenmenger et al showed that education statistically affected pain in 31% of the studies and that 66% reported a significant improvement in participants' knowledge. However, due to the heterogeneity of the studies, no recommendation on intervention types could be endorsed.[14] Capewell et al investigated a DVD-based educational intervention for palliative care patients and their caregivers. They found benefits for the participants and the caregivers within a short period. There was a median reduction in pain scores of 18% based on the Patient Pain Questionnaire and 9.4% based on the Brief Pain Inventory.[22] Additionally, participants

TABLE 1. Demographic data.

	Video group (n = 31)	Face to face group (n = 28)	*P* value	*P* group (n = 231)
Age (years), median (IQR)	54.0 (50.0–60.5)	49.0 (37.0–59.5)	.058	52.0 (40.0–61.0)
Sex, n (%)			**.004**	
Male	18 (58.1)	6 (21.4)		120 (51.9)
Female	13 (41.9)	22 (78.6)		111 (48.1)
BMI (kg/m^2), median (IQR)	19.2 (18.4–23.6)	20.9 (18.8–23.1)	.818	22.0 (19.0–24.0)
Marital status, n (%)			.583	
Married	22 (71.0)	18 (64.3)		159 (68.8)
Single/divorced/widowed	9 (29.0)	10 (35.7)		72 (31.2)
Education, n (%)			.055	
Below high school	10 (32.3)	16 (57.1)		–
High school and higher	21 (67.7)	12 (42.9)		–
Comorbidities, yes n (%)	11 (34.4)	6 (21.4)	.267	64 (27.7)
ECOG, n (%)			**.008**	–
0	2 (6.5)	1 (3.6)		–
1	11 (35.5)	7 (25.0)		–
2	12 (38.7)	3 (10.7)		–
3	6 (19.4)	17 (60.7)		–
Cancer site, n (%)			.245	
GI	9 (29.0)	4 (14.3)		–
Bronchus &Lung	4 (12.9)	1 (3.6)		–
Breast	2 (6.5)	1 (3.6)		–
Head & neck	5 (16.1)	3 (10.7)		–
Hematological	2 (6.5)	3 (10.7)		–
Gynecological	2 (6.5)	10 (35.7)		–
Urological	2 (6.5)	2 (7.1)		–
Musculoskeletal	3 (9.7)	3 (10.7)		–
Other	2 (6.5)	1 (3.6)		–
Cancer staging, n (%)			.539	
Local	10 (32.3)	7 (25.0)		48 (20.8)
Advanced	21 (67.7)	21 (75.0)		183 (79.2)
Reason to admission, n (%)			.774	
Pain control	4 (12.9)	2 (7.1)		–
Chemotherapy	5 (16.1)	8 (28.6)		–
Surgery	14 (45.2)	12 (42.9)		–
Radiation therapy	6 (19.4)	5 (17.9)		–
Others	2 (6.5)	1 (3.6)		–
Baseline pain intensity, median (IQR)				
Minimum pain score	2.0 (0.0–3.0)	2.0 (0.0–3.0)	.688	
Average pain score	4.0 (2.8–5.0)	4.5 (3.0–5.0)	.976	7.0 (6.0–10.0)
Maximum pain score	7.0 (5.5–8.0)	7.0 (6.0–10.0)	.348	

P < .05 indicates statistical significance using the chi-square or Fisher's exact test for categorical data and the Mann–Whitney U test for continuous data.

Abbreviations: BMI: body mass index, ECOG: Eastern Clinical Oncology Group

P-group is data from the previous study by Wangnamthip S, Euasobhon P, Siriussawakul A, Jirachaipitak S, Laurujisawat J, Vimolwattanasarn K. Effective Pain Management for Inpatients at Siriraj Hospital: A Retrospective Study. J Med Assoc Thai. 2016 May;99(5):565-71. PMID: 27501612.

TABLE 2. Pain intensity.

Time	Minimum pain score			Average pain score			Maximum pain score		
	V-group	F-group	*P* value (MWU)	V-group	F-group	*P* value (MWU)	V-group	F-group	*P* value (MWU)
BL	2.0 (0.0–3.0)	2.0 (0.0–3.0)	.840	4.0 (2.8–5.0)	4.5 (3.0–5.0)	.815	7.0 (5.5–8.0)	7.0 (6.0–10.0)	.306
D1	0.0 (0.0–3.0)	1.5 (0.0–2.0)	.624	3.0 (2.0–5.0)	3.0 (2.0–4.5)	.848	6.0 (4.5–8.0)	5.0 (4.0–7.0)	.396
D2	1.0 (0.0–3.0)	2.0 (0.0–2.5)	.898	3.0 (2.0–4.0)	3.5 (1.0–5.0)	.585	6.0 (4.0–7.0)	5.5 (3.0–7.5)	.760
D3	1.0 (0.0–2.5)	0.0 (0.0–3.0)	.532	3.5 (1.0–5.0)	2.5 (1.0–4.0)	.505	6.0 (4.0–7.0)	4.0 (2.5–7.0)	.292
D4	1.0 (0.0–2.0)	0.0 (0.0–3.0)	.531	3.0 (2.0–4.5)	3.0 (1.0–4.5)	.878	6.0 (4.0–7.0)	5.0 (2.0–8.0)	.830
D5	0.0 (0.0–2.5)	0.0 (0.0–2.5)	.632	2.5 (1.0–5.0)	2.0 (2.0–3.5)	.939	5.0 (3.0–6.5)	5.0 (2.5–7.5)	.842
D6	2.0 (0.0–3.0)	0.0 (0.0–3.5)	.968	3.0 (1.0–4.0)	2.0 (1.0–5.0)	.957	5.0 (2.5–7.0)	5.0 (2.5–7.0)	.825

P < .05 indicates statistical significance using the Mann–Whitney U test (MWU)
Abbreviations: BL: baseline; D1–D6: Day 1–Day 6

TABLE 3. Psychological status and quality of life.

	Group V (n = 31)	Group F (n = 28)	*P* value (ChS)
Psychological status			
Pre-test HADS-A			.123
Normal 0–7	14 (45.2)	20 (71.4)	
Borderline 8–10	10 (32.3)	5 (17.9)	
Abnormal 11–21	7 (22.6)	3 (10.7)	
Post-test HADS-A			.594
Normal	17 (54.8)	15 (53.6)	
Borderline 8–10	7 (22.6)	9 (32.1)	
Abnormal 11–21	7 (22.6)	4 (14.3)	
P-value (MHT)	.564	.090	
Pre-test HADS-D			.170
Normal	20 (64.5)	21 (75.0)	
Borderline	2 (6.5)	4 (14.3)	
Abnormal	9 (29.0)	3 (10.7)	
Post-test HADS-D			.278
Normal	23 (74.2)	18 (64.3)	
Borderline	3 (9.7)	7 (25.0)	
Abnormal	5 (16.1)	3 (10.7)	
P-value (MHT)	.058	.257	
Quality of life			*P* value (MWU)
Pre-test for FACT-G	58.0 (53.0–66.5)	58.0 (51.5–62.0)	.600
Post-test for FACT-G	56.0 (49.5–63.0)	55.0 (49.5–60.0)	.461
P value (WSR)	.227	.122	

P < .05 indicates statistical significance using the chi-square test (ChS), Mann–Whitney U test (MWU), marginal homogeneity test (MHT), and Wilcoxon signed-rank test (WSR)
Abbreviations: HADS-A: Hospital Anxiety and Depression Scale for anxiety; HADS-D: Hospital Anxiety and Depression Scale for depression, FACT-G: Functional Assessment of Cancer Therapy–General

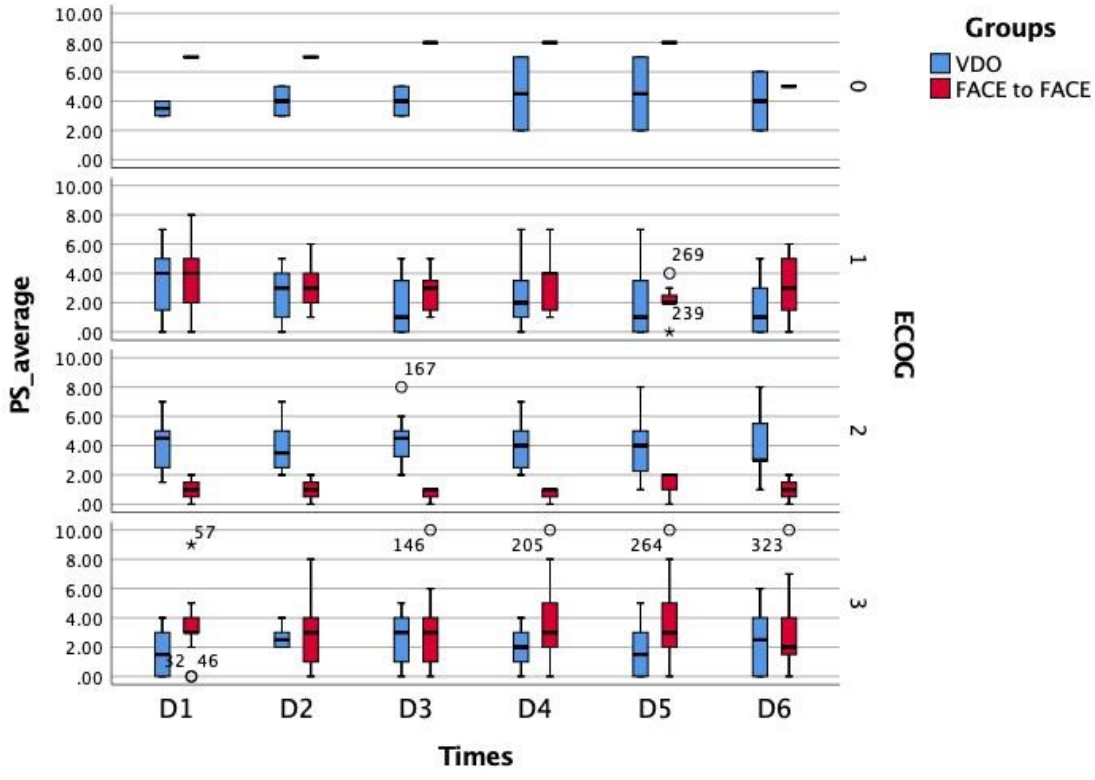

Fig 2. Demonstrates the median pain intensity on average after adjusting the baseline in repeated ANOVA.

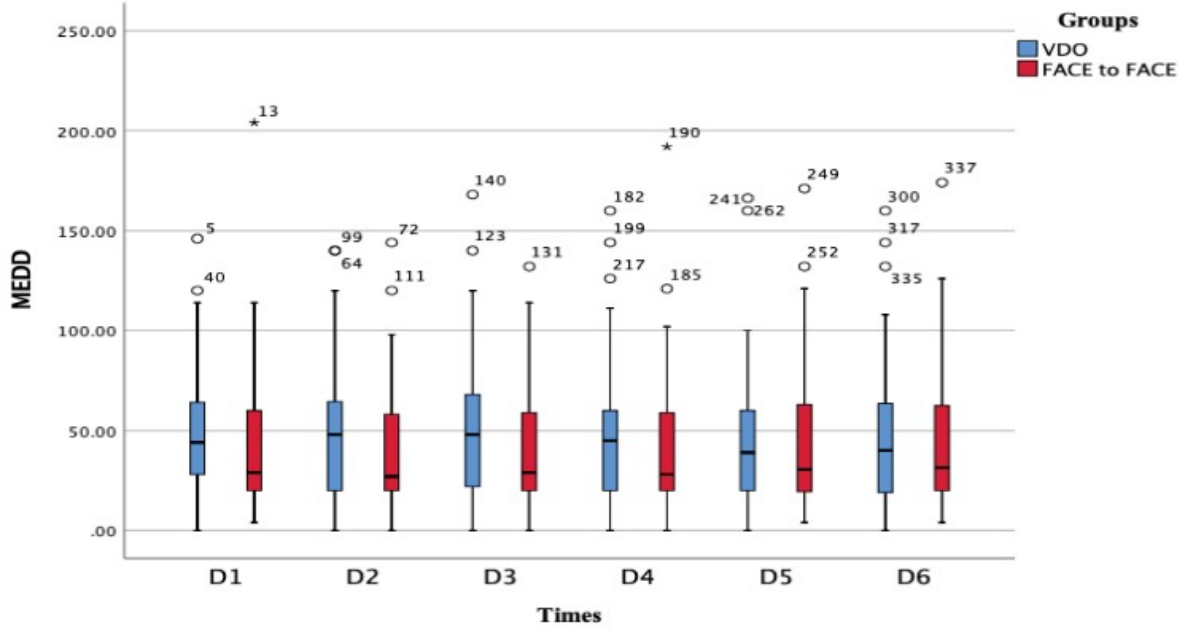

Fig 3. Demonstrates the median morphine-equivalent daily dosage (MEDD) after adjusting the baseline for sex and ECOG score with repeated ANOVA.

who received pain education reported greater degrees of pain reduction than those without pain education. Therefore, gaining knowledge through an educational intervention increases confidence in prescribed pain management medicines and heightens the likelihood of successful pain control.

Technology can assist efforts to improve care quality

Due to the limited number of healthcare personnel in Thailand, the ratios of doctors and nurses to the national population were 1:1680 and 1:353, respectively, in 2022.[23] In addition, a review reported that system factors such as the use of locums and work overloads are risk factors

for irresponsible care and medical errors.[24] A different study evaluated healthcare providers' compliance with guidelines aimed at preventing the mislabeling of blood samples in collection tubes, which results in the incorrect identification of patients. The investigation found that work overload was an independent risk factor.[25] Another qualitative review of the linkage between workplace stressors and the quality of care reported that both have negative associative factors. For example, work overloads lead to prolonged waiting times for examinations and admissions, shorter times for conversations, and fewer opportunities to explain symptoms. The researchers suggested that work-related stress prevention, such as improvements to the workplace atmosphere and culture, would positively impact the quality of patient care.[26]

Technology such as video and social media has been accepted as a tool for caring for patients, learning about diseases, and self-care. Information technology has become more critical to healthcare operators, with their mission of keeping patients safe and providing satisfying service. Nurses are responsible for giving close attention to patients. Information technology has been introduced in healthcare settings to enable nursing staff to increase patient safety and help prevent mistakes stemming from human error.[27] A review found that collaborating with relevant community groups to create educational videos with appealing content and an appropriate length can significantly impact society. This approach can be emulated to educate the public about various diseases.[28] Conversely, face-to-face coaching is a practical approach to improving cancer pain management; additionally, it enables the exploration of individual points of view, beliefs, and behaviors affecting cancer pain management. However, face-to-face coaching is time-consuming, costly, and laborious.[29] In contrast, video sessions only provide one-way communication. Nevertheless, they can lessen the time, costs, and effort needed to educate cancer patients.[30] Therefore, technology, especially videos, can be applied to educate hospitalized cancer pain patients instead of face-to-face coaching, which requires substantially more human resources.

Limitations

The generalizability of these results is subject to certain limitations. First, our population was hospitalized cancer patients. Such patients often have poor physical status, declined cognitive function, and, eventually, attention deficits. Therefore, pain education might benefit participants with greater functional levels. Second, we collected data for only 7 days. The observed outcomes might not be representative of hospitalized cancer patients with extended hospital stays. Further research is necessary to explore the longer-term effects of video and other high-technology media to determine whether they should be extended to other populations, such as patients with chronic non-cancer pain.

CONCLUSION

This study established that educating hospitalized patients about pain management via video presentations and face-to-face coaching improves the effectiveness of cancer pain management. Additionally, video sessions can be utilized to counter myths about pain management among hospitalized cancer pain patients and to decrease healthcare providers' workloads. Future research should:

- explore video educational sessions' longer-term effects;
- investigate the adoption of user-friendly technology with appealing content;
- identify new and alternative educational methods; and
- consider customizing material to enhance the application and effectiveness of video sessions in various populations.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Primary Cardiac Electrical Diseases: Baseline and Retrospective Outcomes of a Multicenter Registry from Thailand

Satchana Pumprueg, M.D.*, Tomon Thongsri, M.D., Chaninart Phongsri, M.D.*, Krisada Kriengkraikul, M.P.A*****

**Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. **Department of Medicine, Buddhachinaraj Hospital, Ministry of Public Health of Thailand, ***Research and Innovation Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.*

ABSTRACT

Objective: Primary cardiac electrical diseases are the leading cause of sudden cardiac arrest in patients with apparently normal structured heart. The purpose of this study was to assess the distribution of primary cardiac electrical diseases, as well as to assess the prognosis and predictive factors for future ventricular arrhythmia in Thai patients.

Materials and Methods: Patients with primary cardiac electrical diseases who came for clinic visit at Siriraj Hospital, Buddhachinarat hospital, and Chonburi hospital were enrolled. History was acquired from interview and medical record.

Results: There were 120 patients in the study. The most prevalent primary cardiac electrical disease was Brugada syndrome. Sixty nine patients experienced prior sudden cardiac death episode and all of the patient in this group had ICD implanted. None of the patient with ICD died after a median follow up of 8.59+5.01 years. Recurrent ventricular arrythmia rate was 47.8%. Among patients who had ICD implanted for primary prevention, none had sudden cardiac arrest/ new ventricular arrythmia episode detected. The only predictor of future lethal arrythmia is history of prior sudden cardiac arrest.

Conclusion: Brugada syndrome is the most common etiologic cause of primary cardiac electrical disease in Thailand. ICD is extremely effective for secondary prevention of sudden cardiac arrest.

Keywords: Primary cardiac electrical disease; Brugada syndrome (Siriraj Med J 2023; 75: 316-320)

INTRODUCTION

Primary cardiac electrical diseases are the leading cause of sudden cardiac arrest in patients with apparently normal structured heart.[1] Several reports have been published since 1981 regarding the incidence of sudden unexplained deaths in Southeast Asian refugees, immigrant workers, immigrants, and other subpopulations in Thailand.[2-5] Brugada syndrome, early repolarization syndrome, and long QT syndrome are among the most common cause of sudden cardiac death in Thailand.[6] Based on global publications, prognosis of Brugada syndrome varies.[7-10] *Makarawate et al* reported a very high recurrence of lethal arrhythmia in the northeastern Thai population, or 32% in 12 months.[11] There are no reports regarding prognosis of asymptomatic patients with this disease in the Thai population. The purpose of this study was to assess the distribution of primary cardiac electrical diseases, as well as to assess the prognosis and predictive factors for future ventricular arrhythmia in Thai patients.

Corresponding author: Satchana Pumprueg
E-mail: drsatchana@gmail.com
Received 16 January 2023 Revised 10 March 2023 Accepted 10 March 2023
ORCID ID:http://orcid.org/0000-0002-4111-9695
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MATERIALS AND METHODS

Study population

Patients diagnosed with primary cardiac electrical disease who had a follow-up at Siriraj Buddhachinaraj, and Chonburi Hospitals were enrolled.

The inclusion criteria were:

1. Patients who survived cardiac arrest with normal structural heart or
2. Patients diagnosed with primary cardiac electrical disease, including Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, pulseless monomorphic ventricular tachycardia, and primary ventricular fibrillation

The exclusion criteria were:

1. Patients with structural heart diseases identified as the etiology of cardiac arrest such as acute coronary syndrome, hypertrophic cardiomyopathy, and dilated cardiomyopathy
2. Patients with severe comorbidities with an expected survival time of less than three years
3. Patients who refused to participate in the study

Baseline characteristics of patients were recorded in an electronic database. Recorded variables included age at diagnosis, sex, hometown, diagnosis, history of sudden cardiac arrest, history of syncope, family history of sudden cardiac arrest, coronary artery disease, baseline hypertension, baseline diabetes mellitus, left ventricular ejection fraction, and current medication. Hometown was classified as northeastern Thailand or not northeastern Thailand. History of sudden cardiac arrest was defined as cardiac arrest from ventricular arrhythmia with successful cardiopulmonary resuscitation. History of syncope was defined as syncopal episodes from cardiac/ presumed cardiac arrhythmia. The etiologic diseases were diagnosed either during initial clinic visit, by retrospective chart review, or during follow up.

Patients had follow-up visits at arrhythmia clinic every six months. Both retrospective and prospective data was collected from electronic databases at a hospital. Implantable cardioverter defibrillator (ICD) programming depended on the implant physician. In ICD patients, an episode of sustained ventricular arrhythmia was collected from device interrogation. Data of patients who had their follow-up visit outside the study sites was collected from telephone interviews. Here, we reported baseline characteristics, including etiologic diseases of sudden cardiac arrest, as well as follow-up data acquired from the electronic database.

Statistical analysis

Continuous variables are presented as mean±S.D or median±SD. Categorical variables are presented as frequency and percentage of the population. Comparisons of characteristic variables were done using the Chi-square test or t-test for continuous variables. All statistical tests were two-tailed, with a p-value <0.05 considered statistically significant. Variables with a p-value of ≤0.1 were included in multivariate analysis. Logistic regression analysis was used for multivariate analysis. Effect of significant variables was reported by the odds ratio and 95% confidence interval. All statistical analyses were performed using SPSS version 18.

RESULTS

Between October 2017 and October 2020, a total of 120 patients were enrolled. The majority (83, 69.2%) of patients were male. The mean age was 47.8±14.1. Hypertension, and diabetes, were diagnosed in 16 (13.3%), and six (5.0%) patients, respectively. Four (0.3%) patients had a history of coronary artery disease. Brugada syndrome was the most common cause of primary cardiac electrical disease in this study, as 84 (70.0%) patients were diagnosed with this disease. Long QT syndrome, monomorphic ventricular tachycardia, and primary ventricular fibrillation was diagnosed in 10 (8.3%), 14 (11.7%), and 11 (9.1%) patients, respectively. One patient with ventricular fibrillation had pre-excitation syndrome. The patient underwent successful radiofrequency ablation without any recurrent ventricular arrhythmia; hence, ICD was not implanted in this patient. Twenty-four (20.0%) patients had a family history of unexplained sudden cardiac arrest. Sixty-nine (57.5%) patients experienced prior sudden cardiac arrest episodes. Regarding current medication, 54 (45.0%) patients were prescribed beta-blockers. Amiodarone was the only antiarrhythmic agent used, and was prescribed to 16 (19.2%) patients. Ninety-nine (96.0%) patients underwent ICD implantation. From this group, 27 (28.1%), had ICD implanted for primary prevention. All patients with primary prevention were diagnosed with Brugada syndrome. The baseline characteristics of patient are presented in Table 1.

After a median follow-up time of 8.59±5.01 years, 119 (99.2%) patients survived. One patient denied treatment and died from recurrent ventricular fibrillation. Recurrent ventricular arrhythmia was found in 33 (47.8%) patients who experienced prior cardiac arrest. For patients who did not have prior cardiac arrest, 27 (52.9%) had ICD implanted, and there was no new ventricular arrhythmia detected by the device. Six (22.2%) patients who had ICD

TABLE 1. Baseline characteristics of patients.

Baseline characteristics	Total N=120
Age (years)	47.8±14.1
Sex (male)	83 (69.2%)
Home town (Northeastern Thailand)	36 (29.0%)
Diagnosis	
Brugada syndrome	85 (70.8%)
Long QT syndrome	10 (8.3%)
Monomorphic ventricular tachycardia	14 (11.7%)
Ventricular fibrillation	11 (9.1%)
History of sudden cardiac arrest	69 (57.5%)
History of presumed cardiac syncope	38 (31.7%)
Family history of sudden cardiac arrest	24 (20%)
History of diabetes mellitus	6 (5.0%)
History of hypertension	16 (13.3%)
Coronary artery disease	4 (0.3%)
Left ventricular ejection fraction (%)	66.4±6.6
Cardiac electrophysiologic study	19 (15.8%)
Inducible ventricular arrhythmia	15 (78.9%)
Medication	
Beta-blocker	54 (45%)
Amiodarone	16 (19.2%)
ICD implanted	95 (79.1%)
Primary prevention	27 (28.1%)

Data presented as mean±S.D. or total number (%). All patients had structurally normal heart proven from echocardiogram. Other cardiac investigations including coronary angiogram, cardiac magnetic resonance imaging, exercise test, and genetic test were done according to clinical indication.

implanted for primary prevention suffered inappropriate ICD therapy. From univariate analysis, age, amiodarone usage, and previous cardiac arrest were identified as predictors for future ventricular arrhythmia. However, previous cardiac arrest was the only predictor identified from multivariate analysis. Table 2 describes detailed information regarding univariate analysis of predictors for recurrent event.

DISCUSSION

Among primary cardiac electrical disease in the Thai population, Brugada syndrome is the most common etiologic disease in both symptomatic and asymptomatic patients. This finding gives additional information as a previous study only included survivors of sudden cardiac arrest.[6] Furthermore, Brugada syndrome is not only common in Northeastern Thailand, but also in other parts of the country. The prevalence may possibly be higher, as we included only patients with spontaneous type 1 ECG and no challenge test was performed. There was not any early repolarization syndrome in this study. In fact, all patients with an initial diagnosis of early repolarization syndrome had spontaneous type 1 Brugada ECG during long term follow-up. For long QT syndrome, the prevalence was low. This could be explained by the relatively high age of patients in this study. Most patients with abnormally long QT intervals were excluded from the study due to identifiable causes, such as QT prolonging medication. It is still uncertain if genetic testing can increase the prevalence of long QT syndrome. Pulseless monomorphic ventricular tachycardia is the third most common cause. All patients in this study had idiopathic ventricular tachycardia from the outflow tract. In general, patients with idiopathic ventricular tachycardia have a good prognosis. However, the disease could be fatal, and there were several reports of cardiac arrest.[12,13] Idiopathic ventricular fibrillation is a rare cause of cardiac arrest and 11 (9.1%) patients from

TABLE 2. Baseline characteristics of patients.

Patient characteristics	No recurrent/ new event	Recurrent/ new event	O.R. (95% CI) Univariate analysis	P value	O.R. (95% CI) Multivariate analysis	P value
Age (years)	51.0±14.6	43.9±13.5	0.95 (0.93-0.99)	0.02*	0.96 (0.91-1.01)	0.13
Sex (male)	36 (43.4%)	47 (56.6%)	0.90 (0.34-2.36)	0.83		
Hometown in northeastern Thailand	18 (50%)	18 (50%)	1.12 (0.41-3.02)	0.82		
Diagnosis (Brugada syndrome)	51 (60.7%)	33 (39.3%)	0.88 (0.45-1.86)	0.31		
History of sudden cardiac arrest	19 (26.1%)	50 (73.9%)	20.15 (5.65-71.84)	0.00*	12.16 (2.22-66.75)	0.00*
History of presumed cardiac syncope	19 (50%)	19 (50%)	1.54 (0.66-3.59)	0.31		
Family history of sudden cardiac arrest	11 (45.8%)	13 (54.2%)	1.06 (0.37-2.99)	0.91		
Beta-blocker used	22 (40.7%)	32 (59.2%)	0.95 (0.42-2.20)	0.91		
Amiodarone used	5 (31.2%)	11 (68.7%)	4.00 (1.51-13.90)	0.03*	2.36 (0.42-13.29)	0.33

Data presented as mean±S.D. or n: O.R. = Odds ratio
*Statistically significant

this study fit into this category. Some of these patients may have been diagnosed with Brugada syndrome had the challenge test been done. Another possibility is that patients with ST segment elevation myocardial infarction had spontaneous reperfusion.

Regarding medication, 45% of patients were treated with beta-blockers. This concurs with guidelines for long QT syndrome and ventricular arrhythmia. However, 26% of Brugada syndrome patients were also prescribed beta-blockers. The rational for using beta-blockers for Brugada syndrome was based on findings from a study of sudden cardiac death patients which did not only include Brugada syndrome, but also patients with other causes of ventricular arrhythmia.[14] Whether beta-blockers are effective for Brugada syndrome is questionable. Nineteen percent of patients were prescribed amiodarone for suppression of recurrent ventricular arrhythmia. None of the patients underwent catheter ablation. The procedure might be more effective with less complication in the long term.

We found that 47.8% of patients with previous cardiac arrest from ventricular arrhythmia had a recurrent event. Implantable cardioverter defibrillators (ICD) are extremely effective as only one patient who refused treatment died after a median follow-up of 8.59±5.01 years. This could be explained by the age group of the patients, which was rather young with low co-morbidity. The finding concurs with several reports which have shown that unsuccessful defibrillation in a structurally normal heart is rare.[15,16] We could not identify other predictors for lethal ventricular arrhythmia in Brugada syndrome patients who did not experience prior sudden cardiac arrest. Patients who did not have prior cardiac arrest, who had strong family history of sudden cardiac arrest/ unexplained syncope, or inducible ventricular arrhythmia, did not experience any appropriate ICD therapy. The data is reliable as 52.9% of patients in this group had an ICD implanted (All patients in this group were diagnosed with Brugada syndrome). Moreover, besides the lack of benefit, 10 (37%) patients suffered inappropriate ICD shock. The finding implies that ICD implantation for primary prophylaxis is not cost-effective. This is different from the current recommendation for Brugada syndrome. Previous guidelines recommended ICD implantation for patients with presumed arrhythmic syncope without documented ventricular arrhythmia.[17,18] Recently, guidelines have recommended implantable loop recorder (ILR) for arrhythmia detection in this group of patients.[19] Regarding the risk stratification method, genetic testing might be helpful. However, only 20-30% of Brugada syndrome patients have known genetic mutations.[20,21] For Long QT syndrome, monomorphic ventricular tachycardia, and ventricular fibrillation, ICD implants are for secondary prophylaxis only and the rate of recurrent ventricular arrhythmia is comparable to Brugada syndrome.

CONCLUSION

Brugada syndrome is the most prevalent primary cardiac electrical disease in Thailand. Recurrent ventricular arrhythmia rate is high. ICD therapy is very effective for this group of patients.

Study limitations

There are several limitations of this study. First, it only includes patients who had a follow-up at the study center. There was potential selection bias as not all patients came to the hospital, especially patients who did not have prior cardiac arrest. Second, the number of patients in the study was low and enrolment of more patients, especially asymptomatic patients, would allow us to identify other risk factors for future events. Third there was missing/ erroneous data, as some was taken from incomplete medical records or interviews about symptoms in the past, for which the patients may not be able to remember the details after several years.

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