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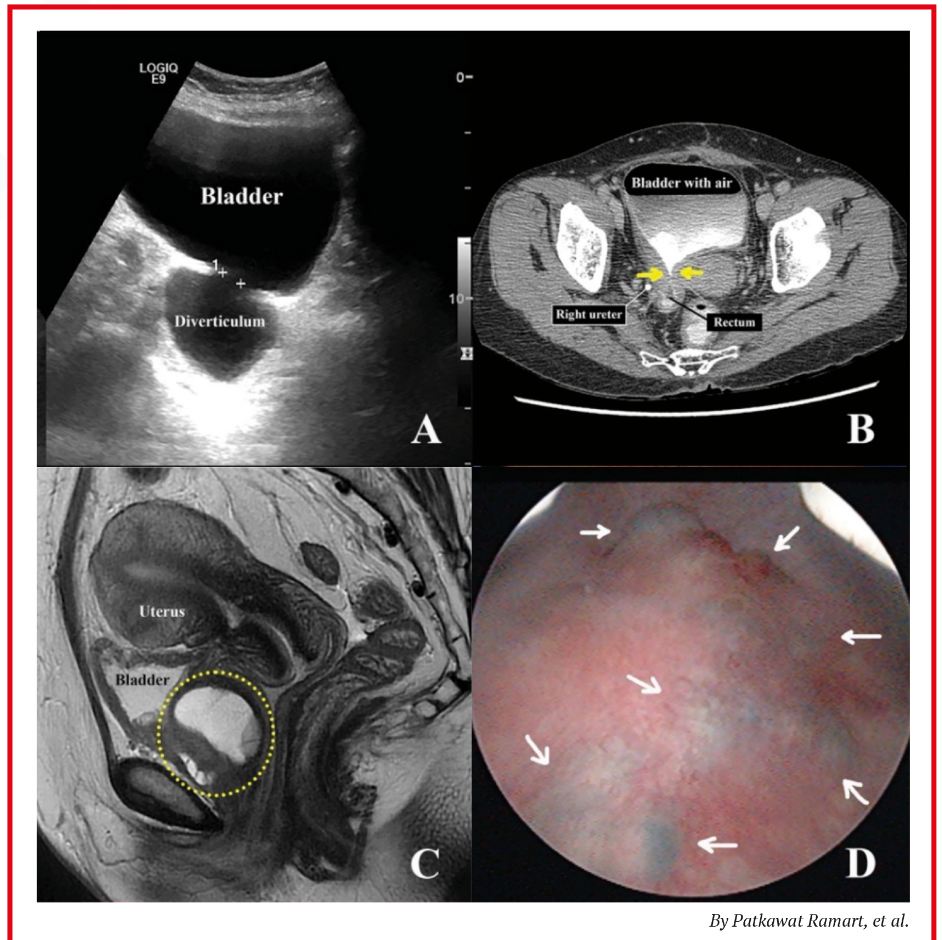

By Patkawat Ramart, et al.

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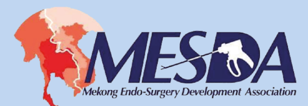

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Evaluation of Clinical Knowledge Regarding Geriatric Skin Conditions among Thai Physicians

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ABSTRACT

Objective: Assess the knowledge of common geriatric skin conditions in Thai physicians.

Materials and Methods: This retrospective study was conducted among Thai physicians attending annual dermatology courses by the Dermatological Society of Thailand from 2016 to 2019. Data was assessed based on knowledge of diagnosis and management of common geriatric skin conditions.

Results: A total of 197 participants, mainly general practitioners, were included. The highest percentage of correct diagnoses were benign erythematous, eczematous lesions (35.5%, senile purpura; 36.0%, xerotic eczema), and malignant diseases (35.5%, basal cell carcinoma; 27.4%, squamous cell carcinoma; 11.7%, subungual melanoma; 24.4%, acral lentiginous melanoma). In contrasts, the lowest percentage of correct diagnosis were premalignant diseases (0.5%, arsenical keratosis; 4.6%, actinic keratosis; 1.0% Bowen's disease) and benign hypopigmented lesion (0.5%, stellate pseudoscar; 7.6%, idiopathic guttate hypomelanosis). Harmful treatment with systemic antifungal therapy was used in subungual melanoma (58.0%). Harmful management of senile comedone, subungual melanoma and acral lentiginous melanoma was significantly found in physicians given the incorrect diagnosis. ($p = 0.027$, $p < 0.001$, $p = 0.014$, respectively).

Conclusion: Most physicians recognized malignant lesions, benign erythematous or eczematous diseases in elderly skin. Surprisingly, almost all physicians couldn't diagnose premalignant lesions and benign hypopigmented lesions.

Keywords: Geriatric skin conditions; physician (Siriraj Med J 2023; 75: 1-6)

INTRODUCTION

A major global trend in population aging is rapidly occurring. By 2050, the proportion of the world's population aged 60 years will increase from 12% to 22%.[1] Thailand has also become an aging society, with 18.24% of the population aged over 60 years in 2021.[2] The emergence of senile dermatosis in the aging population is expected. Elderly skin goes through changes that are both intrinsic and extrinsic. Intrinsic changes result from chronological aging, such as thinning of the epidermis, reduction in the function of sweat and apocrine glands. Extrinsic changes result from UV and other environmental pollutants. Both changes are responsible for the susceptibility of skin conditions in the elderly.[3,4]

Diagnosis and management of skin conditions in the elderly are challenging due to many aspects, such as ordinary physiologic change, atypical disease presentation, and multiple comorbidities. Yet, there was no prior assessment report on the knowledge of geriatric skin conditions among Thai physicians. This knowledge gap will help identify potential improvements in understanding skin conditions in the elderly. Many studies have shown an increase in diagnostic capabilities and proper referral in general practitioners after providing educated sessions.[5,6]

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For these reasons, this study aims to assess the knowledge of common geriatric skin conditions in Thai physicians.

MATERIALS AND METHODS

Study design

This retrospective study was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The protocol was approved by the Siriraj Institutional Review Board (COA no. Si 456/2012). The data includes knowledge of diagnosis and management of common dermatological conditions in the elderly, as seen in Table 2. We conducted a retrospective review of physicians' demographic data and working experiences derived from records at the annual short dermatology course for general practitioners. Which was held by the dermatological society of Thailand from 2016 to 2019.

We compiled a reviewed list of differential diagnoses and management. Management was categorized as proper, disadvantageous, and harmful. Proper management was defined as necessary, beneficial actions for patients, such as tissue biopsy in premalignant or malignant lesions. Disadvantageous management was defined as the actions which provided no benefits, had no, or only minor adverse effects on patients. Such as the use of topical steroids in premalignant or malignant lesions, which might cause some delay in tissue diagnosis. Defining harmful management encompasses actions causing severe adverse reactions or worsening skin conditions.

Statistical analysis

The PASW Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA), was used for data analysis. Categorical data, such as the numbers of physicians who answered correctly for diagnosis or differential diagnoses and the number of each management category, were described using frequency and percentage. Evaluating the relationship between physicians' confidence level, the number of patients with skin conditions the physicians treated per week, and harmful management used a Chi-Squared analysis or Fisher's exact test. The difference in the proportion of harmful management between those who had correct and incorrect diagnoses were evaluated using Chi-Squared tests or Fisher's exact test.

RESULTS

Analysis of 197 physicians' records with complete data was conducted. Approximately half of the physicians were between 26-30 years old, and most were general practitioners (83.0%). For the working setting, 66.7% of the physicians worked at public hospitals, while 20.3% and 19.8% worked at private hospitals and clinics, respectively. Regarding the experience in treating patients with dermatologic conditions, most physicians (67.4%) treated 0 to 10 patients per week (Table 1).

Benign erythematous, eczematous, and malignant lesions represented the highest percentage of correct diagnoses (Table 2). Among benign erythematous lesions, 36% of physicians gave a correct diagnosis for xerotic eczema, followed by 35.5% for senile purpura. Malignant lesions showed only 35.5% of physicians made accurate diagnoses for basal cell carcinoma, 27.4% for squamous cell carcinoma, and 24.4% for acral lentiginous melanoma. However, less than 10% of physicians had the correct answers in premalignant and benign hypopigmented lesions.

Harmful treatment was commonly found in subungual melanoma (58%). Principally, 174 physicians who had an incorrect diagnosis of this lesion, and 93 physicians (53%) misdiagnosed the lesions as onychomycosis. Therefore, many patients with melanoma were prescribed systemic antifungal therapy (Table 2).

Physicians with more than 30 patients per week recommended harmful management when diagnosing seborrheic keratosis and actinic keratosis, as seen in Table 3, which was significantly higher compared to physicians with 11-30 patients per week (11.8, 4.8, and 0.9%, respectively, with a p-value of 0.035 in seborrheic keratosis and 16.7, 8.6, and 3.3%, respectively with a p-value of 0.048 in actinic keratosis). In contrast, there was no difference in the percentage of harmful management among physicians with different confidence levels.

Table 4 compares the proportion of harmful management in correct and incorrect diagnoses. In all diseases, physicians with incorrect diagnoses tend to prescribe damaging solutions compared to correct diagnoses. There was no statistical significance between both groups except in senile comedone, subungual melanoma, and acral lentiginous melanoma.

DISCUSSION

This study shows that Thai general practitioners rarely recognize common skin conditions in the elderly. Additionally, premalignant skin lesions and benign hypopigmented lesions were the most common uncorrected diagnosis. The largest proportion of physicians recommended systemic antifungal therapy for subungual melanoma. For Thai general practitioners, these findings will improve their knowledge in recognizing skin conditions in the elderly.

In this study, physicians rarely recognized premalignant skin lesions compared to other benign and malignant skin lesions except for hypopigmented lesions. For premalignant lesions, actinic keratosis and Bowen

TABLE 1. Demographic data.

Characteristics	Number/total (%)
Age group	
20 – 25 years old	27/196 (13.8%)
26 – 30 years old	108/196 (55.1%)
31 – 45 years old	61/196 (31.1%)
Gender	
Female	137/196 (69.9%)
Previous dermatology short course taken	
No	164/168 (97.6%)
Yes	4/168 (2.4%)
Status of the doctors	
General practitioner	161/194 (83.0%)
Specialist other than dermatologists	22/194 (11.3%)
Diploma or M.Sc in dermatology	3/194 (1.5%)
Medical student	3/194(1.5%)
Others	5/194 (2.6%)
Workplace*	
Public hospitals	128/192 (66.7%)
Private hospitals	39/192 (20.3%)
Private clinic	38/192 (19.8%)
Number of patients treated (per week)	
0 – 10 patients/week	126/187 (67.4%)
11 – 30 patients/week	42187 (22.5%)
> 30 patients/week	19/187 (10.1 %)
Confidence in treating patients with dermatologic problems	
Very low confidence	53/194 (27.3%)
Low confidence	101/194 (52.1%)
Moderate confidence to High confidence	40/194 (20.6%)

*One subject could have more than one work place
Abbreviation: M.Sc, Master of Science

TABLE 2. Pretest answers of participants at the beginning of dermatology short course training.

Diseases	Total (n = 197) Correct differential diagnosis n (%)	Correct diagnosis n (%)	Management n	Proper (%)	Disadvantageous (%)	Harmful (%)
Benign disease						
Hypopigmented lesion						
Stellate pseudoscar	1 (0.5)	1 (0.5)	149	37 (24.8)	84 (56.4)	28 (18.8)
Idiopathic guttate hypomelanosis	15 (7.6)	15 (7.6)	131	32 (24.4)	89 (67.9)	10 (7.6)
Erythematous/eczematous lesion						
Senile purpura	81 (41.1)	70 (35.5)	143	121 (84.6)	20 (14.0)	2 (1.4)
Xerotic eczema	94 (47.7)	71 (36.0)	165	154 (93.3)	8 (4.8)	3 (1.8)
Progressive pigmentary dermatosis	4 (2.0)	2 (1.0)	130	59 (45.4)	56 (43.1)	15 (11.5)
Lump and bump lesion (Tumor and plaque)						
Seborrheic keratosis	51 (25.9)	34 (17.3)	176	168 (95.5)	3 (1.7)	5 (2.8)
Solar lentigo	20 (10.2)	12 (6.1)	141	56 (39.7)	77 (54.6)	8 (5.7)
Senile comedone	46 (23.4)	41 (20.8)	121	46 (38.0)	59 (48.8)	16 (13.2)
Premalignant disease						
Arsenical keratosis	3 (1.5)	1 (0.5)	163	78 (47.9)	74 (45.4)	11 (6.7)
Actinic keratosis	14 (7.1)	9 (4.6)	151	20 (13.2)	122 (80.8)	9 (6.0)
Bowen's disease	3 (1.5)	2 (1.0)	137	36 (26.3)	86 (62.8)	15 (10.9)
Malignant disease						
Basal cell carcinoma	90 (45.7)	70 (35.5)	186	179 (96.2)	5 (2.7)	2 (1.1)
Squamous cell carcinoma	71 (36.0)	54 (27.4)	173	162 (93.6)	9 (5.2)	2 (1.2)
Subungual melanoma	30 (15.2)	23 (11.7)	162	35 (21.6)	33 (20.4)	94 (58.0)
Acral lentiginous melanoma	62 (31.5)	48 (24.4)	152	126 (82.9)	13 (8.6)	13 (8.6)

disease typically present with an erythematous patch with a dry scale that sometimes resembles other skin conditions. As in this study, physicians mostly misdiagnosed premalignant lesions as psoriasis or chronic eczema. Similarly, a previous study showed general practitioners provided correct diagnosis of benign skin tumor lesions (seborrheic keratosis, melanocytic nervus) better than premalignant (actinic keratosis, nervous dysplasia).[7] Most primary care physicians from selected countries provide acceptable diagnosis of basal cell carcinoma than actinic keratosis (90% VS 74%).[8] Yet, both studies had significantly higher overall correct diagnoses, including premalignant skin lesions, compared to this study. This study highlights the need for educational intervention for Thai general practitioners who can't recognize common skin lesions in the elderly. The need for intervention is especially evident when diagnosing premalignant and benign hypopigmented lesions. Subungual melanoma is a severe subtype of acral lentiginous melanoma commonly presented with longitudinal melanonychia. The presence of Hutchinson's sign, ulceration, and broad heterogenous band appearance suggested the diagnosis of subungual melanoma.[9,10] Subungual melanoma is common among Asians and Blacks.[11] Our study demonstrated a low correct diagnosis for these lesion types. Table 4 also shows that harmful management was concordant with misdiagnosis. Thus, Thai general practitioners need to recognize the alarming features for correct diagnosis to avoid delayed or harmful treatment.

Limitations of this retrospective study include collected data that may have some bias and missing data. Management was dependent on the diagnosis. Therefore,

TABLE 3. Comparison of harmful management among physicians with different level of experience according to the average numbers of dermatologic patients per week.

Diseases	Number of dermatologic patients per week			*P*-value
	0-10 patients n (%)	11-30 patients n (%)	> 30 patients n (%)	
Benign disease				
Hypopigmented lesion				
Stellate pseudoscar	19/88 (21.6)	3/38 (7.9)	4/16 (25)	0.132
Idiopathic guttate hypomelanosis	7/79 (8.9)	2/33 (6.1)	1/14 (7.1)	1.000
Erythematous/eczematous lesion				
Senile purpura	1/88 (1.1)	1/34 (2.9)	0/17 (0.0)	0.416
Xerotic eczema	2/102 (2.0)	1/37 (2.7)	0/18 (0.0)	
Progressive pigmentary dermatosis	9/76 (11.8)	4/33 (12.1)	2/17 (11.8)	1.000
Lump and bump lesion				
Seborrheic keratosis	1/110 (0.9)	2/42 (4.8)	2/17 (11.8)	0.035*
Solar lentigo	5/90 (5.6)	3/32 (9.4)	0/15 (0.0)	0.742
Senile comedone	12/72 (16.7)	2/30 (6.7)	2/15 (13.3)	
Premalignant				
Arsenical keratosis	7/101 (6.9)	1/39 (2.6)	2/17 (11.8)	0.308
Actinic keratosis	3/92 (3.3)	3/35 (8.6)	3/18 (16.7)	0.048*
Bowen's disease	8/81 (9.9)	6/37 (16.2)	1/14 (7.1)	0.591
Malignant disease				
Basal cell carcinoma	2/116 (1.7)	0/42 (0.0)	0/19 (0.0)	0.687
Squamous cell carcinoma	1/108 (0.9)	1/40 (2.5)	0/18 (0.0)	0.578
Subungual melanoma	63/100 (63.0)	19/39 (48.7)	9/16 (56.3)	0.294
Acral lentiginous melanoma	6/94 (6.4)	5/38 (13.2)	2/16 (12.5)	0.369

*A p-value less than 0.05 indicated statistical significance, Chi-squared test.

an incorrect diagnosis leads to inappropriate treatment. In reality, physicians should observe or refer patients to dermatologists for proper diagnosis. In conclusion, benign erythematous/eczematous diseases and malignant lesions, including xerotic eczema, basal cell carcinoma, senile purpura, squamous cell carcinoma, and acral lentiginous melanoma, were the elderly skin conditions that the physicians most recognized. In contrast, premalignant lesions and benign hypopigmented lesions couldn't be diagnosed by almost all physicians.

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

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TABLE 4. Comparison of harmful management in participants given correct and incorrect diagnosis.

Diseases	Harmful management in correct diagnosis n (%)	Harmful management in incorrect diagnosis n (%)	*P*-value
Benign disease			
Hypopigmented lesion			
Stellate pseudoscar	0/1 (0.0)	28/148 (18.9)	1.000
Idiopathic guttate hypomelanosis	0/13 (0.0)	10/118 (8.5)	0.275
Erythematous/eczematous lesion			
Senile purpura	0/62 (0.0)	2/81 (2.5)	0.505
Xerotic eczema	0/67 (0.0)	3/98 (3.1)	0.272
Progressive pigmentary dermatosis	0/2 (0.0)	15/128 (11.7)	1.000
Lump and bump lesion (Tumor and plaque)			
Seborrheic keratosis	0/30 (0.0)	5/146 (3.4)	0.590
Solar lentigo	0/9 (0.0)	8/132 (6.1)	0.447
Senile comedone	1/36 (2.8)	15/85 (17.6)	0.027*
Premalignant disease			
Arsenical keratosis	0/1 (0.0)	11/162 (6.8)	1.000
Actinic keratosis	0/8 (0.0)	9/143 (6.3)	0.464
Bowen's disease	0/2 (0.0)	15/135 (11.1)	1.000
Malignant disease			
Basal cell carcinoma	0/70 (0.0)	2/116 (1.7)	0.528
Squamous cell carcinoma	0/54 (0.0)	2/119 (1.7)	1.000
Subungual melanoma	1/23 (4.3)	93/139 (66.9)	<0.001*
Acral lentiginous melanoma	0/45 (0.0)	13/107 (12.1)	0.014*

*A p-value less than 0.05 indicated statistical significance, Chi-squared test.

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SARS-CoV-2 Detection on Artificially Contaminated Surfaces by Rapid Antigen Test

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ABSTRACT

Objective: Evaluation of an antigen-based rapid test for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on artificially contaminated objects in comparison with a real-time reverse transcription-polymerase chain reaction (RT-qPCR) standard method.

Materials and Methods: Artificial surface contamination with inactivated SARS-CoV-2 was tested on ten different objects comprising fruits and common materials. Three contamination levels with virus titers of 10^3, 10^4, and 10^5 pfu/100 µl were studied. Each object was spiked with 200 µl of virus suspension, samples were then collected by swabbing and evaluated by rapid antigen test and RT-qPCR. Additionally, 3- and 5-day contamination with SARS-CoV-2 at 10^5 pfu/100 µl was tested for some materials.

Results: The detection rate obtained by the rapid antigen test with 10^3, 10^4, and 10^5 pfu/100 µl of SARS-CoV-2 was 10%, 90%, and 90%, respectively for the tested objects. RT-qPCR showed a detection rate of 100% at all virus titers. Furthermore, both rapid antigen test and RT-qPCR were able to detect the 3- and 5-day extended contamination with SARS-CoV-2.

Conclusion: The collected data suggests that the evaluated rapid antigen test is suitable for detection of SARS-CoV-2 adhered to non-human samples as a screening method. This simple method can reduce costs and turnaround time when compared to a standard molecular assay. It may be applied to enhance safety policies for COVID-19 prevention in public health and international export-businesses.

Keywords: SARS-CoV-2; COVID-19; Rapid antigen test; RT-qPCR, screening method; surface contamination

(Siriraj Med J 2023; 75: 7-12)

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the pandemic coronavirus disease 2019 (COVID-19). Transmission of infectious SARS-CoV-2 to the human respiratory tract occurs through two major pathways: by aerosols/droplets in direct person-to-person contact and via exposure to contaminated fomites in indirect contact. Viable SARS-CoV-2 has been shown to survive on different surfaces for days or weeks depending on temperature, relative humidity, and light.[1]

High safety standards are a must in the food industry, including in food processing and distribution to maintain consumer trust and confidence in its products. However, infected food workers, either unaware of hygiene guidelines or not following them, might contaminate food during processing and packaging by touching it with contaminated hands or via infectious droplets released when talking, coughing, or sneezing.[2] SARS-CoV-2 contamination of food products and packaging materials can lead to serious economic loss in food export businesses. For example, China, known for its strict COVID-19 policy,

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temporarily banned durian from Thailand due to several positive SARS-CoV-2 detection results during random testing.[3] Although the contact with SARS-CoV-2 adhered on food, including fruits and vegetables, or food packaging materials is highly unlikely to cause COVID-19, such contaminations must always be tracked, particularly in the actual context where the virus is spreading in the countries.[4]

Real-time reverse transcription polymerase chain reaction (RT-qPCR) is recognized as the gold standard method for the detection of SARS-CoV-2 in clinical and non-clinical samples. However, it is limited by a long turnaround time due to nucleic acid extraction and amplification and requires trained staff, expensive instruments, and a laboratory setting with adequate biosafety. These resources are not always available in all countries and in this case a rapid antigen test might be an alternative to RT-qPCR. While it is less sensitive, it is faster, easier to perform, more affordable and allows for decentralized testing at field areas.[5]

At the present time, data on the use of rapid antigen tests to detect SARS-CoV-2 in food or environmental samples are limited. Thus, this study aimed to evaluate the performance of an antigen-based rapid test for detection of SARS-CoV-2 on artificially surface-contaminated objects in comparison with a RT-qPCR standard method.

MATERIALS AND METHODS

Inactivated SARS-CoV-2 virus preparation

An inactivated clinical isolate of SARS-CoV-2/01/human/Jan2020/Thailand was used in this study. It represented the original Wuhan strain isolated from a confirmed COVID-19 patient at Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand.

The inactivated virus was prepared by two methods, heating and UV-C radiation. Stock SARS-CoV-2 virus of 10^6 pfu/ml was divided into two sets for incubation at 65°C, 15 min, and for exposure by UV-C for 15 min. Subsequently, the virus was inoculated onto Vero E6 cells to confirm the complete inactivation of the virus by absence of cytopathic effects (CPE).

All processes involving inactivated SARS-CoV-2 were performed under Enhanced BSL-2 (BSL-2+) in accordance with the biosafety guidelines. The project was approved by the Thammasat University Institutional Biosafety Committee (101/2564).

Artificial-surface contamination and sample collection

Serial dilutions of 10^3, 10^4, and 10^5 pfu/100 µl were prepared from the stocks of heat- and UV-C-inactivated SARS-CoV-2. Samples of pooled inactivated virus at each dilution were prepared by combining 100 µl each of heat- and UV-C-inactivated SARS-CoV-2. Ten different objects comprising common fruits and packaging materials were selected for analysis. They were durian, rambutan, orange, apple, leather, parcel box, fruit foam net, foam box, foil, and plastic.

Inoculation and swab processes were performed by different persons. Pooled inactivated virus of each dilution was randomly spiked, by making tiny drops with pipette like droplets from sneezing, onto the entire surface of each object and the objects were then completely dried at room temperature. The objects were collected by randomly swabbing without knowledge of previous inoculation site at an area of 100 to 225 cm^2 or entire area for smaller ones at day 0, 3 and 5. Two swabs were used for SARS-CoV-2 detection by rapid antigen test and RT-qPCR.

SARS-CoV-2 testing

Nucleocapsid (NP) protein antigen of SARS-CoV-2 was detected by a Rapid Surface Ag 2019-nCov Kit (Prognosis Biotech, Larissa, Greece). Briefly, the collected swab was placed in extraction buffer for 30 seconds and was then discarded. Afterwards, a test strip was immersed into the extraction buffer for 10 min. Detection of SARS-CoV-2 resulted in visible colored bands at both Test (T) and Control (C) lines. As shown in the test manual, cross-reactivity with 4 different human coronavirus strains is not found, and the limit of detection (LOD) is 2.5 ng/ml of NP or 5.75 x 10^3 $TCID_{50}$/ml of inactivated SARS-CoV-2.[6]

Collected swabs for RT-qPCR assay were kept in HiViral™ transport medium (HiViral™ Transport Kit, HiMedia, Mumbai, India). Swabs were vortexed and 200 µl of HiViral™ transport medium was used to extract RNA by using a PureLink viral RNA/DNA mini kit (Cat no. 12280050, Invitrogen, USA) according to the manufacturer's instructions. The concentration of the purified RNA was measured as ng/µl and the RNA was kept at −80°C before RT-qPCR detection. Following the manufacturer's instructions and interpretations, SARS-CoV-2 RNA targeting ORF1ab, N, and E genes was detected by an ANDiS FAST SARS-CoV-2 RT-qPCR Detection Kit (Cat no. 3103010069, 3DMed, Germany).

Positive (SARS-CoV-2) and negative (human coronavirus strain OC43) controls were used to validate results in all experiments.

Statistical analysis

Descriptive analysis as mean, standard deviation (SD), detection rate (%) was performed and compared between rapid antigen test and RT-qPCR at each viral dilution.

RESULTS

Detection of SARS-CoV-2 by rapid antigen test and RT-qPCR on artificially contaminated objects was compared and the results obtained on the day of inoculation and sample collection (day 0) are shown in Table 1 and Fig 1. RT-qPCR, the gold standard method, had a higher sensitivity than the rapid antigen test and detected SARS-CoV-2 contamination on all objects at all virus dilutions. The detection rate obtained with the rapid antigen test was 10%, 90% and 90% at 10^3, 10^4 and 10^5 pfu/100 µl, respectively (Fig 1). The sensitivity of the rapid test was poor at the lowest virus titer but was much improved at 10^4 and 10^5 pfu/100 µl. Likewise, the intensity of the detected T-band seemed to depend on the virus titer (Fig 2). However, we observed that the type of material affected the detection. Detection of SARS-CoV-2 contamination was most difficult for both methods on the parcel box made from paper. Indeed, even contamination with virus titer at 10^4 and 10^5 pfu/100 µl showed negative results when detected by the rapid test. Although it could be detected by RT-qPCR, the Ct values of all target genes were shifted over ten cycles (Table 1). Additionally, plastic was the only object out of the ten spiked objects that could be detected by the rapid test at 10^3 pfu/100 µl SARS-CoV-2.

Next, we investigated the detection rate after the artificially contaminated objects were left for 3 and 5 days. All objects spiked with 10^5 pfu/100 µl SARS-CoV-2 could be detected by rapid test and RT-qPCR after 3 and 5 days (Table 2). The results were consistent with the same day testing (day 0).

Further comparison of RT-qPCR and rapid antigen test showed the latter to have a limit for detection of SARS-CoV-2 NP when the Ct values (mean±SD) of RT-qPCR targeting the ORF1ab, N, and E genes were in the range of 30.77±3.74, 27.02± 3.64, 26.54±9.72, respectively (Table 1).

DISCUSSION

This study used pooled heat and UV-C inactivated SARS-CoV-2 to contaminate ten different materials. Heat-inactivation at 65°C for 15 min will denature viral proteins but not the genomic RNA, while UV-C-inactivation for 15 min has a deleterious effect on the RNA but not on the viral structure.[7] Thus, the pooled inactivated SARS-CoV-2 used in this study allowed parallel application of the two detection methods, i.e., antigen-based rapid test and nucleic acid-based RT-qPCR and minimized the risk of false negative results.

The used rapid chromatographic immunoassay intended for qualitative detection had a lower sensitivity in SARS-CoV-2 detection in comparison to the gold standard method RT-qPCR. Our data showed that the limit of detection of the rapid antigen test was at 10^4 pfu/100 µl. At this amount of virus RT-qPCR showed average Ct values for ORF1ab, N, and E genes, across the analyzed samples in the range of 30.77±3.74, 27.02±3.64, 26.54±9.72, respectively.

However, the results of the rapid test showed that detection sensitivity depended on the kind of investigated material. SARS-CoV-2 NP could be still detected at 10^3 pfu/100 µl on plastic, whereas it could not be detected at a titer as high as 10^5 pfu/100 µl on other materials like parcel box. Interestingly, Ct values from SARS-CoV-2 detection by RT-qPCR showed the highest value at all virus titers on parcel box. Previous research supports these findings.[8-9] Most of the enveloped viruses like SARS-CoV-1 or influenza virus were found to survive and persist in stable form longer on plastic and stainless steel (1–7 days) than on paper and tissue (3–8 h).[9-11] SARS-CoV-2 was found to be inactivated much faster on paper than on plastic. No virus could be detected after 3 hours of being inoculated on paper.[8,10] Corpet hypothesized that dryness would inactivate SARS-CoV-2 like found on water absorbent porous materials.[10] Since an enveloped virus has a lipid bilayer membrane that needs water on both sides to maintain an intact structure dryness might lead to oxidation of lipids and Maillard reactions of proteins.[10] While smooth and waterproof materials would protect the virus by keeping the moisture from micro-droplets of water on the surface.[12] This would explain the stability of SARS-CoV-2 on non-absorbent materials, including durian, leather, and plastic on which it could be detected after many days by both, rapid test and RT-qPCR.

Taken together, our pilot study on artificially contaminated objects suggests that the used rapid antigen test would be a valuable method for screening of different materials. In comparison to RT-qPCR it is easier to perform, would cost less, save time, and is suitable for a large number of samples. Its application may enhance safety policies in public health and international export-businesses. However, the limitations in this study were using only artificial samples under controlled conditions and no testing with control group of inoculation with non-infected fluid on samples that might develop interpretation bias on an antigen-based rapid test. Thus, these concerns should be considered for future study. Real-world samples should be done with and always in comparison with a gold standard RT-qPCR assay.

TABLE 1. Comparison of SARS-CoV-2 detection results on artificially contaminated objects by rapid antigen test and RT-qPCR on same day testing (day 0).

Samples	Cycle threshold (Ct) value (Interpret result) of RT-qPCR detection[a]					Rapid antigen test result
	ORF1ab	N gene	E gene	Internal control	Conclusion result[b]	
A. Virus titer at 10^5 pfu/100 µl						
SARS-CoV-2[c]	11.94 (+)	12.27 (+)	9.38 (+)	34.03 (+)	+	+
HCOV-OC43[d]	> 40 (-)	> 40 (-)	> 40 (-)	> 40 (-)	-	-
Durian	27.1 (+)	23.47 (+)	25.83 (+)	> 40 (-)	+	+
Rambutan	28.84 (+)	26.49 (+)	27 (+)	> 40 (-)	+	Weak +
Orange	26.55 (+)	23.05 (+)	25.12 (+)	> 40 (-)	+	+
Apple	24.14 (+)	21.52 (+)	22.6 (+)	> 40 (-)	+	+
Leather	21.46 (+)	20.27 (+)	20.07 (+)	> 40 (-)	+	+
Parcel box	37.56 (+)	34.2 (+)	35.62 (+)	39.71 (+)	+	-
Fruit foam net	25.44 (+)	22.8 (+)	24.33 (+)	38.89 (+)	+	+
Foam box	25.49 (+)	23.11 (+)	24.12 (+)	39.79 (+)	+	+
Foil	24.95 (+)	21.96 (+)	25.33 (+)	> 40 (-)	+	+
Plastic	23.57 (+)	20.61 (+)	23.12 (+)	> 40 (-)	+	+
Mean±SD (Positive-Ct)	**26.51±4.37**	**23.75±4.07**	**25.31±4.10**	**11.84±19.06**		
B. Virus titer at 10^4 pfu/100 µl						
SARS-CoV-2	16.35 (+)	16.05 (+)	15.16 (+)	37.19 (+)	+	+
HCOV-OC43	> 40 (-)	> 40 (-)	> 40 (-)	> 40 (-)	-	-
Durian	31.57 (+)	28.57 (+)	29.93 (+)	38.15 (+)	+	Weak +
Rambutan	32.63 (+)	30.32 (+)	31.54 (+)	> 40 (-)	+	Weak +
Orange	31.17 (+)	26.45 (+)	29.16 (+)	38.64 (+)	+	Weak +
Apple	36.06 (+)	28.69 (+)	> 40 (-)	> 40 (-)	+	Weak +
Leather	27.36 (+)	22.63 (+)	27.24 (+)	37.43 (+)	+	Weak +
Parcel box	36.95 (+)	34.45 (+)	35.63 (+)	> 40 (-)	+	-
Fruit foam net	30.13 (+)	26.71 (+)	30.2 (+)	38.19 (+)	+	Weak +
Foam box	29.46 (+)	25.62 (+)	28.96 (+)	35.99 (+)	+	Weak +
Foil	26.06 (+)	23.33 (+)	26.48 (+)	> 40 (-)	+	Weak +
Plastic	26.32 (+)	23.42 (+)	26.27 (+)	> 40 (-)	+	+
Mean±SD (Positive-Ct)	**30.77±3.74**	**27.02±3.64**	**26.54±9.72**	**18.84±19.87**		
C. Virus titer at 10^3 pfu/100 µl						
SARS-CoV-2	19.89 (+)	19.30 (+)	18.44 (+)	> 40 (-)	+	+
HCOV-OC43	> 40 (-)	> 40 (-)	> 40 (-)	> 40 (-)	-	-
Durian	36.99 (+)	32.73 (+)	35.11 (+)	38.32 (+)	+	-
Rambutan	31.79 (+)	29.71 (+)	31.21 (+)	> 40 (-)	+	-
Orange	34.39 (+)	30.10 (+)	33.49 (+)	> 40 (-)	+	-
Apple	28.46 (+)	25.27 (+)	27.67 (+)	> 40 (-)	+	-
Leather	32.39 (+)	28.17 (+)	32.75 (+)	> 40 (-)	+	-
Parcel box	37.48 (+)	36.47 (+)	36.27 (+)	> 40 (-)	+	-
Fruit foam net	35.49 (+)	29.06 (+)	> 40 (-)	> 40 (-)	+	-
Foam box	33.45 (+)	30.03 (+)	33.04 (+)	37.40 (+)	+	-
Foil	31.97 (+)	28.31 (+)	32.31 (+)	37.58 (+)	+	-
Plastic	32.01 (+)	28.97 (+)	32.11 (+)	> 40 (-)	+	Weak +
Mean±SD (Positive-Ct)	**33.44±2.73**	**29.88±2.98**	**29.40±10.58**	**11.33±18.24**		

[a] "+" when Ct value ≤ 40, and "-" when Ct value ≥ 40.
[b] Conclusion results were interpreted following the manufacturer's instruction. In brief, positive when at least 2/3 of SARS-CoV-2 specific RNA targets were detected without relying on internal control detection.
[c] Positive control from inactivated SARS-CoV-2.
[d] Negative control from inactivated human coronavirus strain OC43 (HCOV-OC43).

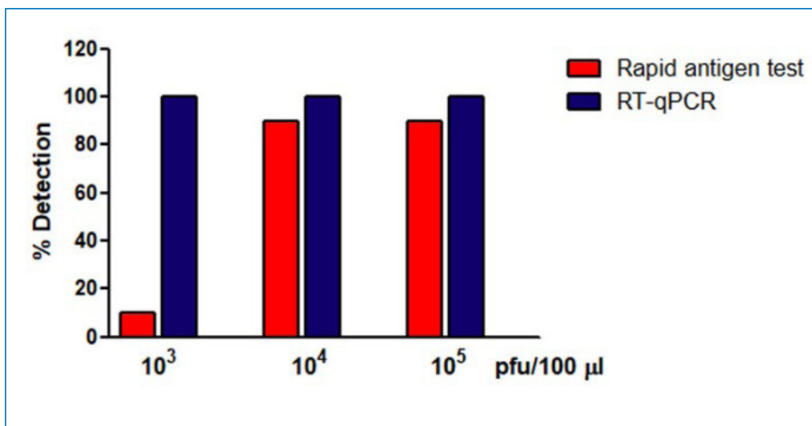

Fig 1. Comparison of detection rate (%) between rapid antigen test and RT-qPCR.
The relative number of positive results per total samples at each tested virus titer is shown as percentage of detection.

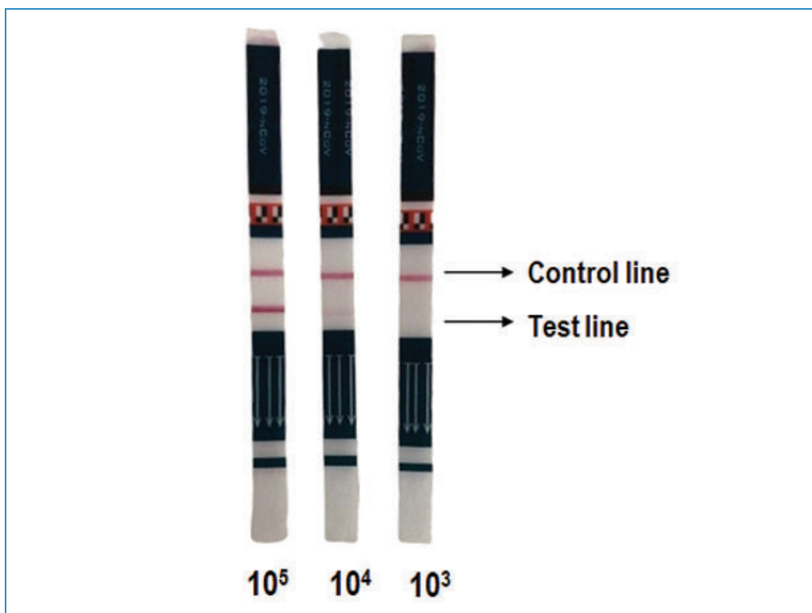

Fig 2. Test line intensity of rapid antigen test. From left to right, 10^5, 10^4, and 10^3 pfu/100 µl SARS-CoV-2 virus titers were evaluated by rapid antigen tests. The observed test line intensity depended on the virus titer. The results were interpreted as positive, weak positive, and negative, respectively.

TABLE 2. Comparison of SARS-CoV-2 detection results on artificially contaminated objects by rapid antigen test and RT-qPCR after 3 and 5 days of inoculation.

Samples	Cycle threshold (Ct) value (Interpret result) of RT-qPCR detection[a]					Rapid antigen test result
	ORF1ab	N gene	E gene	Internal control	Conclusion result[b]	
Day 3-Virus titer at 10^5 pfu/100 µl						
Durian	21.91 (+)	20.88 (+)	21.14 (+)	> 40 (-)	+	+
Leather	30.08 (+)	26.27 (+)	31.09 (+)	> 40 (-)	+	+
Plastic	24.60 (+)	21.11 (+)	25.54 (+)	33.21 (+)	+	+
Day 5-Virus titer at 10^5 pfu/100 µl						
Durian	24.77 (+)	23.27 (+)	23.73 (+)	> 40 (-)	+	+
Leather	28.97 (+)	24.96 (+)	30.08 (+)	> 40 (-)	+	+
Plastic	23.88 (+)	20.53 (+)	24.84 (+)	39.01 (+)	+	+

[a] "+" when Ct value ≤ 40, and "-" when Ct value ≥ 40.
[b] Conclusion results were interpreted following the manufacturer's instruction. In brief, positive when at least 2/3 of SARS-CoV-2 specific RNA targets were detected without relying on internal control detection.

CONCLUSION

This study suggests the rapid antigen test as a first screening assay to identify SARS-CoV-2 contamination on various material types. It would reduce the demand for the expensive and time-consuming RT-qPCR assay in non-clinical samples.

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Conflict of interest statement: The authors do not have any conflict of interest to declare.

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Effects of Music on Preoperative Anxiety in Patients Undergoing Hair Transplantation: A Preliminary Report

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ABSTRACT

Objective: To study the effects of music on anxiety in patients undergoing hair transplantation.

Materials and Methods: This randomized controlled trial enrolled patients undergoing hair transplantation. The patients were randomized into a music group, who listened to music for 15 minutes during the preoperative period, and a control group, who were not exposed to music. Two scales were used to measure anxiety. One was the State-Trait Anxiety Inventory (STAI), comprised of a state anxiety scale (STAI-S) and trait anxiety scale (STAI-T). The other was the Visual Analog Scale for Anxiety (VASA). Demographic and physical parameters (blood pressure, heart rate, and respiratory rate) were recorded.

Results: The 26 patients had a mean age of 40.8 ± 10.4 years. Twenty-three (88.5%) were men. The 2 groups had no significant differences in their STAI-S or VASA scores, or physical parameters before and after intervention. The STAI-S score of the control group significantly increased with time ($P = 0.027$). Additionally, a significant decrease in the VASA score was observed after the intervention for the music group ($P = 0.039$). No adverse events were noted.

Conclusion: Listening to music is an easy, effective, and safe method of reducing preoperative anxiety in patients undergoing hair transplantation. The method should be employed during the preoperative period for patients undergoing hair transplantation. It may also be considered for use in similar procedures.

Keywords: Anxiety; hair transplantation; music; state-trait anxiety inventory; preoperative (Siriraj Med J 2023; 75: 13-19)

INTRODUCTION

The preoperative period is a worrying event for patients and creates emotional, cognitive, and physiological responses.[1] Waiting for surgery or invasive procedures has been reported to create stress and anxiety, which aggravate and affect physiological and psychological parameters.[2] Preoperative anxiety is a major concern in patients undergoing surgery. It may be attributed to a fear of complications, unfamiliar environments, needles, injections, pain, bleeding, or separation from friends and family.[3] Anxiety has a considerable impact on surgical outcomes. It is associated with an increased requirement for postoperative pain control, a prolonged recovery time, and an increase in postoperative complications.[4]

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Pharmacological and nonpharmacological interventions have been employed to alleviate preoperative anxiety. Pharmacological interventions, such as sedatives and anti-anxiety drugs, are widely used, easy to administer, and effective.[5] However, these drugs frequently cause adverse events like drowsiness and respiratory depression, and they may impair decision-making. As well, patients should not drive as the drugs can affect their judgment.[5,6] Because of the various drawbacks, a pharmacological intervention may not be appropriate for ambulatory surgery. In comparison, nonpharmacological interventions, such as preoperative education and the use of relaxation techniques and music, are being increasingly used.[7] In particular, music is a safe, easy, and noninvasive method of reducing anxiety. Additionally, listening to music has proven to decrease anxiety sufficiently to allow the total dose of sedatives to be reduced.[8]

Hair transplantation, an outpatient procedure performed under local anesthesia, is a treatment option for patients who have failed to respond to standard medical treatment.[9] Although hair transplantation is a minimally invasive surgery, patients have reported severe anxiety levels before the procedure.[10,11] Since preoperative anxiety has substantial adverse influences on postoperative outcomes and given the ease of use, low cost, and safety of music, this study aimed to evaluate the effects of music in reducing preoperative anxiety in patients undergoing hair transplantation. This study used the State-Trait Anxiety Inventory (STAI) questionnaire and the Visual Analog Scale for Anxiety (VASA) to evaluate the effects of music on preoperative anxiety in patients undergoing hair transplantation.

MATERIALS AND METHODS

This prospective, single-blind, randomized controlled trial was conducted at the Hair Clinic, Outpatient Dermatology Unit, in a tertiary hospital in Thailand between February 2018 and August 2021. The study protocol was approved by the Institutional Review Board (COA no. Si 077/2019) and was registered with the Thai Clinical Trials Registry (TCTR20210820004). All patients gave their written informed consent.

Participants

The study enrolled patients aged 18 years or older who underwent hair transplantation with the follicular unit transplantation or follicular unit excision technique and had a waiting time of at least 45 minutes before surgery. Exclusion criteria were patients with any psychological disease, regular use of antidepressant or anxiolytic drugs, an inability to read and understand Thai, a visual impairment or hearing loss that impaired their ability to communicate, and an unwillingness to participate or listen to music. The patients were divided into 2 groups using a simple random sampling method. Participants in a music group received a preoperative music intervention for 15 minutes, whereas those in a control group did not receive the music intervention.

Data collection

Demographic and clinical data were collected using face-to-face interviews. Anxiety levels in the patients were assessed using an STAI questionnaire and a VASA. The STAI is a 40-item, self-report questionnaire developed by Spielberger et al that uses a 4-point Likert-type scale for each item.[12] It comprises 2 parts: a state anxiety scale (STAI-S), which measures the current state of anxiety ("state anxiety"); and the trait anxiety scale (STAI-T), which assesses the general state of anxiety ("trait anxiety"). Each scale has 20 items. The score for each item ranges from 1 ("not at all") to 4 ("very much"), and the total score for each part ranges from 20 to 80 points. Higher scores indicate a greater severity of anxiety.[12,13] The STAI was translated into Thai by Nonthasak and colleagues.[14] The reliability of Thai STAI has been documented (Cronbach's alpha = 0.89).[15,16] With regard to the VASA, it uses a 10-cm horizontal line with a scale ranging from 0 to 10, indicating "not anxious at all" and "extremely anxious," respectively. The scores are categorized to indicate mild (≤ 3), moderate (4–6), and severe (≥ 7) degrees of anxiety.[17] Patients were instructed to indicate their level of anxiety on the line. The distance was then measured and noted.

Intervention

All patients were requested to answer the STAI questionnaire (both the STAI-S and STAI-T components) and rate the VASA independently before the intervention. Nursing staff also recorded the physical parameters of each patient: heart rate, systolic blood pressure, diastolic blood pressure, and respiratory rate. After that, members of the music group were invited to listen to music on YouTube via headphones through mobile telephones that were made available to them. They were allowed to choose 1 set of classical music from a list using the keyword "relaxing instrumental music" and listen for 15 minutes during the preoperative period. The volume of the music was modified by each patient according to their personal preference. In contrast, the members of the control group were instructed to wait in a silent room and were not allowed to listen to any music for 15 minutes. Subsequently, all patients independently redetermined their STAI-S and VASA scores, and the

nursing staff remeasured their physical parameters. The patients then had a 5- to 15-minute wait before the hair transplantation procedure commenced. All processes were performed before the surgery and were completed in a single visit.

Statistical analyses

Demographic data were calculated using descriptive statistics. Categorical data are presented as numbers (percentages). Continuous data with normal distributions are shown as the mean ± SD and were compared by an independent t-test. The Wilcoxon signed-rank test was used to determine the differences between each group before and after the intervention. Spearman's rank correlation coefficient was used to calculate the association between pairs of variables. Data were analyzed using PASW Statistics for Windows (version 18; SPSS Inc., Chicago, IL., USA).

RESULTS

A total of 30 patients were evaluated for eligibility. Four were excluded: 2 had a waiting time less than 45 minutes, 1 regularly used anxiolytic drugs, and 1 declined to participate (Fig 1) Therefore, 26 patients were included in the study (control group, n =14; music group, n = 12). The mean age of the patients was 40.8 years, and 23 of the 26 (88.5%) were men. Most of the patients (96.2%) were diagnosed with androgenetic alopecia, and 1 (3.8%) had scarring alopecia from burns. All patients had educational levels higher than primary school grade 9. The mean trait anxiety scores of the control and music groups were 46.2 ± 4.5 and 47.5 ± 2.7, respectively. There were no statistically significant differences in any of the demographic parameters of the groups, except age and marital status. The demographic data of the 26 patients are detailed in Table 1.

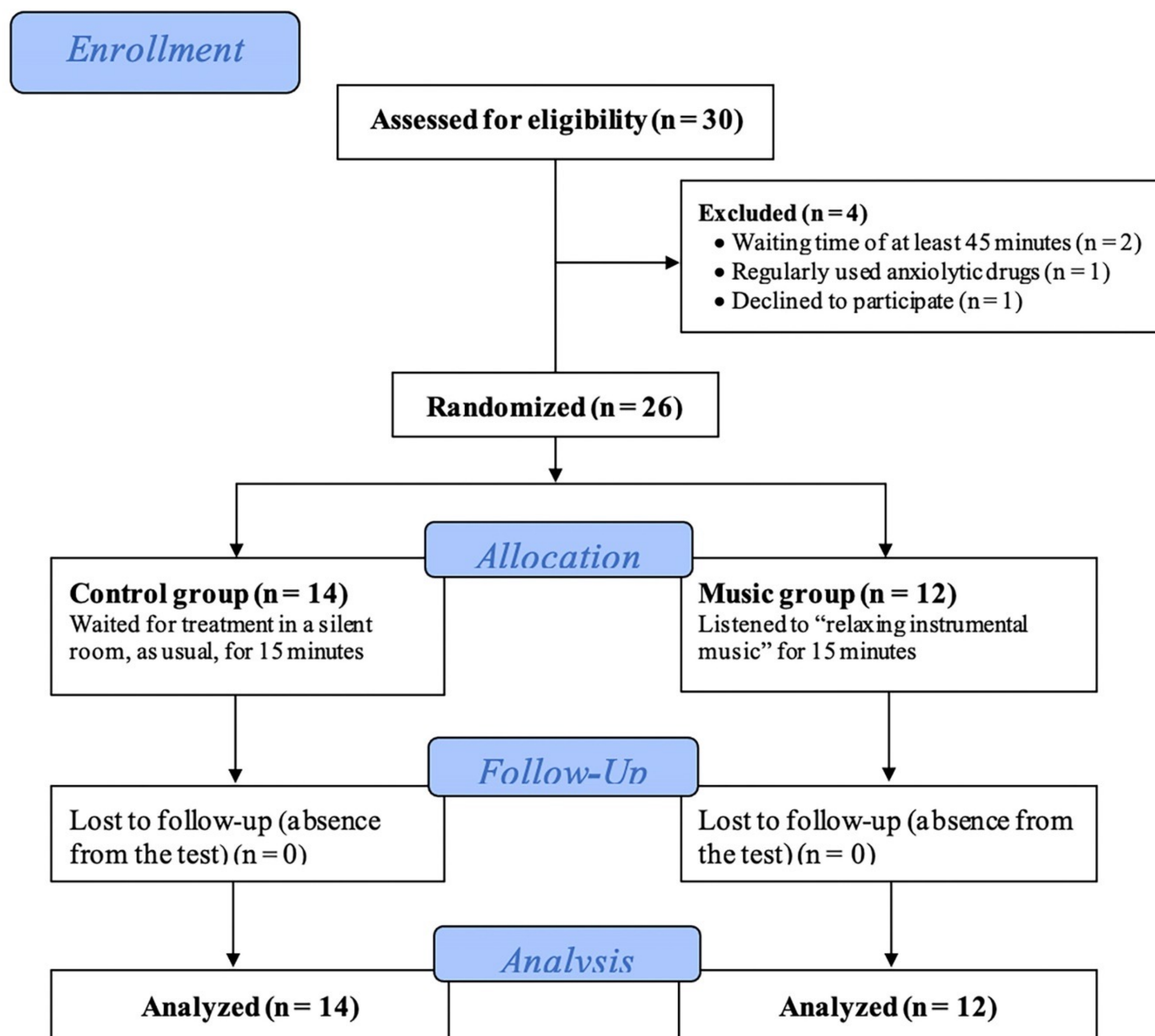

Fig 1. Flowchart outlining patient enrollment, randomization, follow-up, and analysis.

TABLE 1. Demographic data of patients undergoing hair transplantation.

Characteristic	Total (N, 26)	Control group (n, 14)	Music group (n, 12)	P value
Sex				
Male	23 (88.5)	12 (85.7)	11 (91.7)	1.000
Female	3 (11.5)	2 (14.3)	1 (8.3)	
Age (years)	40.8 ± 10.4	45.0 ± 9.8	35.9 ± 9.1	0.022*
Age onset (years)	24.2 ± 10.0	25.1 ± 12.5	23.1 ± 6.0	0.609
Body mass index (kg/m^2)	23.5 ± 2.2	23.3 ± 2.4	23.7 ± 2.0	0.653
Marital status				
Single	14 (53.8)	5 (35.7)	9 (75.0)	0.045*
Married	12 (46.2)	9 (64.3)	3 (25.0)	
Living				
With family	20 (76.9)	12 (85.7)	8 (66.7)	0.365
Alone	6 (23.1)	2 (14.3)	4 (33.3)	
Previous hair transplantation				
No	12 (46.2)	4 (28.6)	8 (66.7)	0.052
Yes	14 (53.8)	10 (71.4)	4 (33.3)	
Hair transplantation in this visit				
FUE	19 (73.1)	10 (71.4)	9 (75.0)	1.000
FUT	7 (26.9)	4 (28.6)	3 (25.0)	
Trait anxiety score	46.8 ± 3.8	46.2 ± 4.5	47.5 ± 2.7	0.395

The data are presented as mean ± SD or number (%)
*, statistically significant ($P < 0.05$)
Abbreviations: FUE: follicular unit excision; FUT: follicular unit transplantation

Although patients in the music group were 10 years younger than those in the control group, age was not associated with the baseline STAI-S scores of the music and control groups ($r = 0.049$; $P = 0.812$). Similarly, while most of the patients were single, there was no difference in the baseline STAI-S scores of single and married patients ($P = 0.413$). At baseline, the mean state anxiety scores, mean VASA scores, and physical parameters of the 2 groups were similar. After the intervention, there were no statistical differences in any of the data items of the 2 groups ($P > 0.050$; Table 2). However, a comparison of the changes in the pre- and postintervention values within each group revealed significant differences for 2 items. On the one hand, the mean state anxiety score of the control group significantly increased after the patients waited in the silent room for 15 minutes (before, 45.6 ± 3.5; after, 48.4 ± 4.3; $P = 0.027$). On the other hand, the VASA score of the music group significantly decreased as a result of listening to music (before, 2.7 ± 2.3; after, 1.9 ± 2.0; $P = 0.039$). No other significant differences within the groups were revealed. Moreover, no side effects were reported during the study period.

DISCUSSION

Regarding the cognitive behavioral model of social anxiety, exposure to a feared social situation activates assumptions that have been formed by past experiences. These assumptions activate socially anxious individuals to regard certain social situations as dangerous, leading to low self-esteem.[18] According to this theory, the loss of hair can create anxiety and affect self-esteem and self-image. Consequently, effective treatments are sought for patients with hair loss.[19] Several studies have reported hair transplantation to be an effective way to potentially reverse psychosocial problems by reducing anxiety and improving self-confidence.[19,20] However, effective strategies

TABLE 2. Comparison of first- and second-measured state anxiety scores, VASA scores, and physical parameters of control and music groups.

Variable	Mean ± SD Control group (n, 14)	Music group (n, 12)	*P* value
State anxiety score			
1st measurement	45.6 ± 3.5	45.7 ± 3.6	0.946
2nd measurement	48.4 ± 4.3	46.3 ± 3.5	0.173
VASA (n = 19)			
1st measurement	2.2 ± 2.4	2.7 ± 2.3	0.652
2nd measurement	1.6 ± 1.7	1.9 ± 2.0	0.730
Heart rate			
1st measurement	82.6 ± 12.8	82.1 ± 12.9	0.924
2nd measurement	76.8 ± 15.9	80.4 ± 10.9	0.518
Respiration rate			
1st measurement	15.9 ± 0.9	15.5 ± 1.2	0.339
2nd measurement	15.8 ± 1.0	16.2 ± 0.6	0.415
SBP			
1st measurement	126.1 ± 11.2	129.4 ± 13.4	0.495
2nd measurement	126.5 ± 12.3	129.4 ± 10.2	0.535
DBP			
1st measurement	79.3 ± 11.9	78.3 ± 6.2	0.788
2nd measurement	81.2 ± 15.5	77.4 ± 11.7	0.510

The data are presented as mean ± SD
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; VASA, visual analog scale for anxiety

to decrease preoperative anxiety in hair transplant patients have not been explored.

Previous studies demonstrated that listening to music significantly reduced anxiety in patients undergoing dermatological procedures.[21-23] Vachiramon and associates found significant reductions in the anxiety of patients who listened to self-selected music while waiting for physicians and during the first stage of Mohs micrographic surgery. This was especially the case for patients undergoing the surgery for the first time.[21] Sorensen and others concluded that listening to classical music during an injection of local anesthesia significantly decreased pain and anxiety in non-Mohs dermatologic procedures.[22] Similarly, Deivasigamani and colleagues found that music intervention reduced anxiety in patients undergoing dermatosurgery under local anesthesia.[23] In contrast, Alam and coauthors reported that relaxing music was not associated with any significant differences in pain, anxiety, blood pressure, or heart rate in patients undergoing excisional surgery for basal and squamous cell carcinoma.[24]

In the present study, listening to music was not associated with reducing the anxiety of the patients undergoing hair transplantation, and it did not affect their physical parameters. There are several possible reasons for this. First, the state anxiety score of the patients in this study was only slightly higher than 40, which is the cutoff score used to detect anxiety symptoms.[25] Similarly, anxiety levels measured by VASA showed mild anxiety. This is contrary to the work by Ahmad and Mohmand, who reported moderate to severe anxiety in patients undergoing hair transplantation.[10] This difference from our study may be because individuals are increasingly using the Internet to access a wide range of health information. Their internet research may cause them to perceive that hair transplantation is a safe and minor surgical procedure with very few complications, leading

them to worry less.[26] Listening to music may therefore be unable to measurably decrease their low level of state anxiety. On the other hand, the patients in our study had a high mean trait anxiety score.[27] This may be because the patients had previous personality or mental health problems. Patients who suffer severely from hair loss experience multiple feelings and emotions due to personal and social pressures. The hair loss may lead to psychological stress out of proportion to the problem.[28] Accordingly, such patients are more likely to have high expectations for their hair transplant results. Therefore, these expectations might also impact the effects of music on their pre-intervention anxiety.

Second, the patients were instructed to listen to classical music and were unable to select the music of their choice. Although classical music was shown to offer greater benefits than other musical genres, some authors reported that the greatest anxiolytic effect may be achieved when patients select familiar music that they enjoy.[6,21] Third, the duration of music intervention in the current investigation may have been a contributing factor. This study administered a 15-minute music intervention. This is shorter than the intervention period of previous studies, in which patients listened to 30 minutes of music in the preoperative setting.[29,30] Further studies with larger sample sizes and longer music interventions may be required to elucidate the effects of music on anxiety in hair transplant patients.

Although this study did not detect significant differences between the music and control groups, significant differences within the groups were reported. There was a significant increase in anxiety measured by STAI-S in the control group. This could be attributed to an increasing trend of preoperative anxiety over time.[31] Additionally, a reduction in anxiety using VASA was demonstrated by the music group after listening to music. The theoretical basis of music in terms of anxiety reduction lies in the impact of music on the autonomic nervous system, which enhances relaxation. The auditory stimulation of music is believed to affect a number of neurotransmitters and alter the experience of anxiety, fear, and pain. Consequently, more positive perceptual experiences, including stimulation of stress and anxiety reduction, are achieved. Additionally, music promotes feelings of physical and mental relaxation by refocusing attention on pleasurable emotional states.[32] While listening to music, patients' awareness of time passing was distracted because their attention was on the music, resulting in greater relaxation.[33] This study demonstrated a trend of reduction in anxiety through music listening. Since music listening is a noninvasive, easy-to-administer, effective, and safe method, its introduction should be considered as a means of reducing the anxiety of patients undergoing hair transplantation or similar procedures.

This study has some limitations. As it was a preliminary study, only 26 patients were included. In addition, the prevalence and severity of androgenetic alopecia have been reported to be higher in males than in females.[34] Consequently, most of the hair transplant patients in this study were men. Validation through a larger sample size and a sex-balanced distribution is needed to conclusively demonstrate the effects of music on preoperative anxiety in patients undergoing hair transplantation. Moreover, the patients in our study could not be blinded to the group assignments. This may have affected their evaluations, resulting in bias. In addition, the unequal waiting times before the commencement of the procedures may have affected the patients' pre- and post-surgery anxiety scores.

In conclusion, music is an easy-to-administer, effective, and safe method to reduce preoperative anxiety in patients undergoing hair transplantation surgery. During the preoperative period, listening to music should be recommended to the patients. The method may also be considered for use in similar procedures.

Conflicts of Interest: All authors declare that there are no conflicts of interest related to any aspect of this research.

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Functional Status of the Elderly and their Rehabilitation Needs: A Mixed-Method Study in a Slum of Kolkata, West Bengal

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ABSTRACT

Objective: A comprehensive understanding of the requirements of elderly is necessary to preserve their "functional capacity", an important indicator of their health status. This study aimed to assess the functional status of the elderly and their rehabilitation needs.

Materials and Methods: A mixed-method study was conducted from November 2021 to June 2022 at a health centre in Chetla, West Bengal, India. Quantitative data, collected from 172 elderly persons using a pretested questionnaire, were analyzed by logistic regression analysis. Qualitative data, collected via focus group discussions, were analyzed thematically.

Results: Overall, 11.62% and 66.86% participants were functionally dependent in one or more activities of daily living (ADL) and instrumental activities of daily living (IADL), respectively. Significant association of age ≥70 years (AOR = 4.06, 95% CI= 1.13-14.63), male gender (AOR= 5.21, 95% CI= 1.57-17.28) and assistive device use (AOR= 6.92, 95% CI= 1.85-25.83) was found with ADL limitations. Increasing age (AOR= 1.29, 95% CI= 1.13-1.50), female gender (AOR= 13.97, 95%CI= 3.61-54.00), residence in joint family (AOR= 3.95, 95%CI=1.47-10.61), without spouse (AOR= 3.59, 95% CI= 1.12-11.44) and daily intake of multiple medications (AOR= 4.99, 95%CI= 1.45-17.13) were factors significantly associated with IADL limitations. Major identified needs of the elderly were related to development of peer support groups, transportation systems and delivery of services from the health system.

Conclusion: Rehabilitative services like providing assistive devices to the needy, developing elderly support groups, undertaking household visits for bedridden and those with restricted mobility, and building supportive environments within families and communities should be ensured.

Keywords: Activities of daily living; elderly; functional status; instrumental activities of daily living; rehabilitation (Siriraj Med J 2023; 75: 20-28)

INTRODUCTION

The unprecedented increase in human longevity in the 20th century has led to a global rise in the elderly population. India is soon destined to become home to the second-largest number of elderly persons in the world. The Census data has demonstrated a steady increase in the proportion of older people from 7.7% of the total population in 2001 to 10.1% in 2021, which is estimated to reach 300.96 million by 2051.[1]

Over the past decade, 'Healthy aging' has emerged as an important concept concerning health issues of the elderly. It has been defined as "not only the mere absence

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of a disease but the process which enables older people to continue to do the things that are important to them".[2] Data provided by the United Nations has shown that more than 46% of the global elderly population (≥60 years of age) live with disabilities.[3] Disabilities are the negative aspects of the interaction between the individual and the environment, i.e., deficits, limitations in the activity and restrictions in his/her social participation.[4] Thus, maintenance of functional capacity becomes an important indicator of health status in the elderly.[5]

Activities of daily living (ADL) are considered as those activities that are essential for an independent life while instrumental activities of daily living (IADL) are more complex tasks that involve decision making and greater interaction with the environment.[6] Studies conducted previously across different countries have assessed the functional capacity of the elderly and have demonstrated varying prevalence of limitations in activities of daily living (ADL) ranging from 17.3% to 34.6% while limitations in instrumental activities of daily living (IADL) ranged from 35.75% to 59.3%.[7-10] Although laudable efforts have been made by the researchers for assessing the functional status, the issue of social and healthcare needs of the elderly required for healthy ageing has been largely overlooked. Therefore, a comprehensive understanding of the requirements of our elderly population is needed to preserve their functional capacity and promote healthy aging so that they can continue to make their positive contributions towards the society. With this backdrop, this mixed method study was undertaken to assess the functional status of the elderly residing in an urban slum in West Bengal and to explore their unmet needs from the health system for rehabilitation

MATERIALS AND METHODS

This cross-sectional study with convergent parallel mixed method design (QUAN+QUAL) was conducted from November 2021 to June 2022 among the elderly persons (age≥60 years) attending the non-communicable disease (NCD) clinic at Urban Health Unit and Training Centre, Chetla, Kolkata, West Bengal. Participants who did not give written informed consent were excluded from the study.

Sampling

For the quantitative strand of the study, considering the prevalence of ADL disability and IADL disability among the study population to be 53.6%[11] and 48%[9] respectively and relative error of 20% with a confidence level of 95%, the sample size was calculated separately using the standard Cochran's formula.[12] It came to be 84 and 105 respectively. Taking into account the larger value, that is 105, the final sample size was estimated by adding a design effect of 1.5 and 10% non-response rate allowance which came to be 172.

Data collection was performed on 1 day per week. So, for estimated sample size of 172, it took approximately 12 weeks for data collection. Study participants were selected by systematic random sampling technique for the quantitative strand. Approximately 30 elderly persons attended the NCD clinic per day. Study piloting revealed that only 15 patients could be interviewed per day. Therefore, taking sampling interval of 30/15= 2, every 2nd patient attending the NCD clinic was interviewed.

Separate days were taken to conduct Focus group discussions (FGDs) for collecting data for the qualitative strand of our study. Data was collected till the point of data saturation which was reached after conduction of 2 FGDs. Each FGD constituted 6 members who were recruited purposively from the patients visiting the NCD clinic.

Study Tools and Parameters Used

Medical records were checked and face-to-face interview technique was performed using pre-tested, pre-designed structured questionnaire to collect data for the quantitative strand of our study. Pretesting was done on 15 elderly patients diagnosed with NCDs in a different setting who were not included in the study. Reliability of the scales used within the questionnaire was checked with Cronbach's alpha along with inter-item correlation. Face & construct validity of the scales used was checked by public health experts. The questionnaire consisted of the following domains:

(a) Independent variables

i. *Socio-demographic variables*: age, religion, caste, gender, marital status, living arrangement, education, employment status, financial status, socioeconomic status, availability of medical insurance

ii. *Physical health status*: body mass index (BMI), pain on visual analog scale (VAS), number of chronic diseases (from medical records), number of daily medicine intake (from medical records)

iii. *Environmental characteristics*: presence of assistive technology (handrails, grab bars, hearing aid, glasses, walker wheelchair etc.), home modifications (widened doors, lowered cabinets) and material adjustments (removing throw rugs, rearranging furniture etc.)

iv. *Multidimensional scale of perceived social support (MSPSS)*: It was assessed via a 12-item tool for measuring perceptions of support from 3 sources: family, friends,

and significant others. [Cronbach's alpha= 0.87].[13] A mean score of 1-2.9 meant low support, 3-5 indicated moderate support and 5.1-7 indicated high support.

v. *Geriatric depression scale 15 (GDS 15)* consisted of a 15-item preliminary screening tool for depression in elderly [Cronbach's alpha= 0.71].[14] Scores of 0-4 were considered normal, 5-8 indicated mild depression; 9-11 as moderate depression; and 12-15 indicated severe depression.

(b) Dependent variable

i. *Katz Index of Independence in Activities of Daily Living (ADL)*: It assessed the client's ability to independently perform six activities of daily living i.e bathing, dressing, toileting, transferring, continence, and feeding.[15] Participants were given 1 point if they required no assistance in performing their daily activities and 0 point if they required help, personal assistance or total care for the same. (Cronbach's alpha=0.79). Study participants were categorized into two groups according to their summary scores:

1. Independent (score of 6, needed no assistance in any of the activities)

2. Dependent (score 0-5, assistance needed in some or the other activity)

ii. *Lawton- Brody Instrumental Activities of Daily Living Scale (IADL)*: It measured the client's ability to perform independent living skills, measured across 8 domains.[16] Women were scored on all 8 areas of function; whereas, for men, the areas of food preparation, housekeeping, laundering were excluded [Cronbach's alpha= 0.82]. Participants were given 1 point if they required no assistance in performing the activities and 0 point if they required help, personal assistance or total care for the same. Study participants were categorized into two groups according to their summary scores:

For *females*: 1. Independent (score of 8, needed no assistance in any of the activities)

2. Dependent (score of 0-7, assistance needed in some or the other activity)

For *males*: 1. Independent (score of 5, needs no assistance in any of the activities)

2. Dependent (score 0-4, assistance needed in some or the other activity)

For the qualitative part of the study, two FGDs were conducted among the study participants to find out their expectations from the health system with respect to their healthcare needs, using a predesigned FGD guide, audio recorder and field notes.

Data analysis

Quantitative data was analysed using Microsoft Excel 2016 and Statistical Package for Social Sciences software (version 16). Descriptive statistics were shown by frequency table, mean, median and interquartile range. After excluding multicollinearity (variance inflation factor>10), factors were analyzed by test of significance (p-value< 0.05) at 95% confidence interval via univariate regression model. All the biologically plausible significant factors in the respective univariate analysis where then included in the final multivariable model.

For qualitative data, thematic analysis approach was undertaken. The recorded statements from the FGD were first transcribed in verbatim format and translated back to English language. Simultaneously, field notes were reviewed. Appropriate codes were then generated from the transcripts. Similar codes were put together to generate subthemes followed by the generation of appropriate themes.

Ethical approval

Permission was taken from Institutional Ethics Committee of All India institute of Hygiene and Public Health, Kolkata. All the ethical principles as per Declaration of Helsinki were strictly adhered to. Informed written consent was taken from each participant before data collection. Confidentiality was maintained throughout the process.

RESULTS

Among the 172 study participants, 118 were females and 54 were males with a median age of 62.50 years (IQR =61.00- 67.75). Majority of the male participants were married (81.5%) whereas only 36.4% females were married. Around 30.8% of the participants had two children. 47.1% of elderly were living with 'spouse and other members'. Almost 55.2% of the participants had no formal education and considered themselves to be financially dependent on their family members. Around one-fourth (25.6%) of the study participants were formally retired. More than half (60.5%) of the study participants belonged to class V of B.G Prasad's socioeconomic scale. The median per capita income was Rs 1,000/-. More than half of the participants (52.3%) were covered under state government financed medical insurance schemes like 'Swasthya Sathi'.

With regard to their health status, as many as 56.9% of individuals suffered from multiple chronic diseases and 55.8% were taking multiple medicines daily. Around 44.8% individuals reported to be suffering from moderate pain on Visual Analogue Scale (VAS).

On the part of environmental modifications, only 0.6% and 5.8% of participants had special equipment attached to their home structure and did material adjustments

respectively, for unhindered movement. Assistive devices were used by 24.4% of the elderly. None of the participants had the interior of their homes modified as per their necessity of old age.

Almost 65.7% of the elderly received moderate social support (friends, family and significant other combined) with median score of 4(IQR= 3.44-5.04).

Majority (82.6%) of study participants were suffering from some or other form of depression with a median score of 6(IQR= 5-9) as measured by GDS 15.

Functional Status of the elderly:

The respondents reported at least one problem with IADL (66.86 %) more frequently than with ADL (11.62 %). Among the female participants 7.6% and among males 20.4% were dependent in one or more ADL while 80.5% of females and 37% of males were found to be one or more IADL (Fig 1 & 2).

The most frequent problem in ADL was related to transferring (6.4%) followed by continence (4.7%) and toileting (4.7%). The most frequent problem associated with IADL was food preparation (61.9%) among the females and shopping in males (52.3%).

Factors associated with functional limitations among the study participants

Significant factors associated with functional limitations in ADL were age of ≥70 years {Adjusted odds ratio (AOR) = 4.06, 95% CI= 1.13-14.63}, male gender (AOR= 5.21, 95% CI= 1.57-17.28) and use of assistive devices (AOR= 6.92, 95% CI= 1.85-25.83) (Table 1).

With respect to IADL limitations, increasing age (AOR= 1.29, 95% CI= 1.13-1.50), female gender (AOR= 13.97, 95% CI= 3.61-54.00), participants residing in joint family (AOR= 3.95, 95% CI= 1.47-10.61) without spouse (AOR= 3.59, 95% CI= 1.12-11.44) and taking multiple medicines daily (AOR= 4.99, 95% CI= 1.45-17.13) were the factors that came to be statistically significant (Table 2).

The models examining the influences of factors on ADL and IADL explained 16.6%-32.3% and 39.7%-55.1% of the variance respectively.

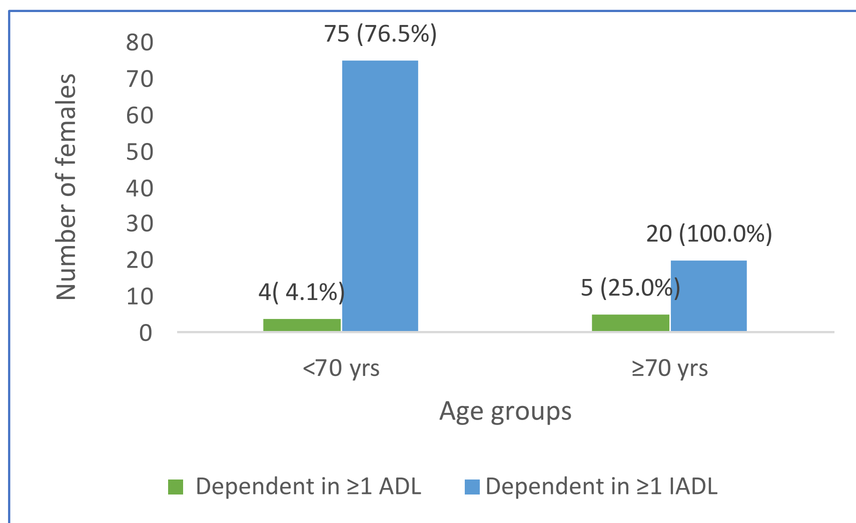

Fig 1. Multiple bar diagram showing functional status of female participants across age groups (n=118).

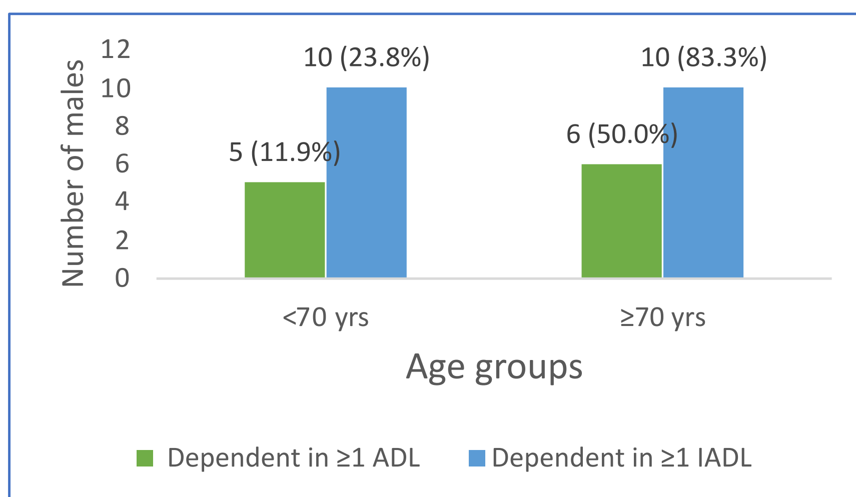

Fig 2. Multiple bar diagram showing functional status of male participants across age groups (n=54).

TABLE 1. Factors associated with functional limitation in ADL among study participants: Univariate and Multivariable logistic regression analysis (n=172).

Parameters	Total number (n)	Dependent in ≥1 ADL (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age				
<70 yrs	140	9(6.4)	1(Ref)	1(Ref)
≥70 yrs	32	11(34.4)	7.62(2.82-20.60)	4.06(1.13-14.63)
Gender				
Female	118	9(7.6)	1(Ref)	1(Ref)
Male	54	11(20.4)	3.09(1.19-8.00)	5.21(1.57-17.28)
Number of chronic diseases				
<2	74	4(5.4)	1(Ref)	1(Ref)
≥2	98	16(16.3)	3.41(1.09-10.68)	0.57(0.09-3.61)
Number of medicines taking daily				
<2	76	4(5.3)	1(Ref)	1(Ref)
≥2	96	16(16.7)	3.60(1.15-11.26)	3.04(0.52-17.83)
Use of assistive devices (hearing aid, wheelchair, walker etc)				
Absent	130	8(6.2)	1(Ref)	1(Ref)
Present	42	12(28.6)	6.10(2.29-16.24)	6.92(1.85-25.83)
Material adjustments at residence (removing through rugs, rearranging furniture, adjusted lighting etc.)				
Absent	162	16(9.9)	1(Ref)	1(Ref)
Present	10	4(40.0)	6.08(1.55-23.85)	0.81(0.12-5.35)

Hosmer-Lemeshow test statistic=0.669, Cox and Snell's R^2=0.166, and Nagelkerke's R^2=0.323.

Qualitative exploration of the unmet needs of the elderly from the health system for rehabilitation

The FGDs revealed three major themes: (I) need to cater to service issues (II) need to cater to transportation issues (III) need for development of peer support group. Under the first theme the major sub themes identified were 'Homebased services', 'Supplies and logistics', 'Social protection schemes' and 'Other health services'.

Under the 'Homebased services' subtheme, the need for domiciliary visits at least once every month by trained healthcare workers for routine health check-ups was identified. In this context P4 (60 years, female) reiterated:

"If it was possible that once or twice in a month the health workers come and visit us in our house and do a checkup of our sugar, pressure it would have been very very helpful."

The major 'Supplies and logistics' need identified was ensuring the availability of medicines and assistive devices such as glasses, hearing aids etc. from the health centre, better if free of cost. P3 (61 years, female) said in this regard:

"Sometimes they ask us to buy medicines from outside but we cannot buy them due to our economic constraint. So, we miss the dose for that month."

Under the 'Social protection schemes', the need for old age pension, increase in pension amount, and health insurance schemes were identified. P2 (62 years, female) said in this respect:

"I get old age pension of ₹1,000 per month. But you tell me, in these days does ₹1,000 have any value?"

The study participants also highlighted the need for provision of 'Other health services' such as dental facility, ophthalmology, psychiatry, otorhinolaryngology and investigations such as thyroid profile from the PHC. P1 (64 years, male) & P2 said in this regard:

"I hear less in one ear. If facility for ear check-up was present over here I would go for the same."

TABLE 2. Factors associated with functional limitation in IADL among study participants: Univariate and Multivariable logistic regression analysis (n=172).

Parameters	Total number (n)	Dependent in ≥1 IADL (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age(↑)*			1.14(1.05-1.24)	1.29(1.13-1.50)
Gender				
Female	118	95(80.5)	7.20(3.43-14.36)	13.97(3.61-54.00)
Male	54	20(37.0)	1(Ref)	1(Ref)
Type of family				
Joint	99	78(78.8)	3.61(1.85-7.03)	3.95(1.47-10.61)
Nuclear	73	37(50.7)	1(Ref)	1(Ref)
Marital Status				
No spouse	83	70(84.3)	5.26(2.55-10.85)	3.59(1.12-11.44)
Married	89	45(50.6)	1(Ref)	1(Ref)
Education				
No formal education	95	70(73.7)	2.06(1.07-3.96)	0.79(0.28-2.17)
Educated (any form)	73	42(57.5)	1(Ref)	1(Ref)
Socioeconomic status †				
Class V	104	83(79.8)	4.44(2.26-8.73)	0.87(0.31-2.41)
Class IV & below	68	32(47.1)	1(Ref)	1(Ref)
Pain				
Severe pain	27	24(88.9)	4.74(1.36-16.51)	5.56(0.93-33.18)
Less than severe pain	145	91(62.8)	1(Ref)	1(Ref)
Number of chronic diseases				
≥2	98	73(74.5)	2.22(1.16-4.24)	0.60(0.16-2.23)
<2	74	42(56.8)	1(Ref)	1(Ref)
Number of medicines taking daily				
≥2	96	75(78.1)	3.21(1.66-6.22)	4.99(1.45-17.13)
<2	76	40(52.6)	1(Ref)	1(Ref)
Multidimensional scale of perceived social support				
Lower support	131	96(73.3)	3.17(1.53-6.56)	0.71(0.23-2.11)
High support	41	19(46.3)	1(Ref)	1(Ref)

Hosmer-Lemeshow test statistic=0.095, Cox and Snell's R^2=0.397, and Nagelkerke's R^2=0.551.

*Continuous variables, OR=odds ratio, CI=confidence interval

† According to Revised B.G Prasad Scale for January 2021 based on labour bureau statistics of November 2020

"I have pain in my gums and teeth but no dental facility is available here".

Under the second theme, the distant location of tertiary care hospitals, poor access to accessible, comfortable and reliable transport services were reported to cause hindrance to patients' journey to hospitals for specialized care. Notable verbatim by P7 (61 years, female) in this aspect is:

"Sometimes we are said to go to specialized hospitals since all the treatment is not available here. But our old age and restricted mobility prevent us from going there and getting better treatment"

The third theme highlighted the 'need for development of peer support groups'. The elderly valued peer support as an important source of happiness, information and companionship as stated by P8 (65 years, male):

"It feels good to talk among your friends and relieve your mental burden. You can hear their side of their stories as well as you can express your concerns."

DISCUSSION

The study findings revealed the overall prevalence of ADL and IADL limitations among the elderly to be 11.62% and 66.86% respectively, which is comparable to the findings from other studies. A study done in Nepal by Chalise et al.[18] showed around 30% & 52% elderly aged 65 yrs and older were having functional limitation on at least one ADL and IADL respectively. In a study done in India by Patel et al. 22% & 48% of the older adults reported some form of ADL and IADL disability respectively. [9]

Increasing age showed significant association with functional limitations, both ADL and IADL in elderly proving that it can be the most important risk factor for the deterioration of the functional state in the elderly.

The current study showed that males were more dependent in ADL than females which is in contrast to other studies that showed female gender to be more predisposed to functional limitations in ADL.[7,19,20] This may be attributed to the fact that there were more older male participants (22.2%) compared to females (6.9%) in this study.

With respect to IADL limitations and gender differences, this study is in line with findings from other studies that showed that female elderly are significantly more dependent in one or more IADL.[7,19,20] This can be explained by the fact that in an Indian society, which is predominantly male dominated, women are traditionally bound to do household work whereas their male counterparts do work outside and are mainly responsible to handle finances.

Participants residing in joint family reported to have more dependency in IADL in our study. This finding substantiates the fact that those who live with others have the opportunity to depend on them for shopping, food preparation, housekeeping etc., than those who live alone.

Significant association between functional limitation of IADL and absence of spouse can be explained by the fact that loss of significant other in the extreme of age has a huge emotional impact on the surviving elderly to the extent that it can lead to depression. Many previous studies have also found a positive correlation between depression and worsened mobility in elderly.[21,22]

As disability and mobility problems increase with age, use of assistive devices such as canes, crutches, and walkers, increase a patient's base of support, improves balance, increased activity and independence, proving that significant association between functional dependency in ADL and assistive device use among the elderly may exist, as found in our study.

Significant association between dependency in IADL and intake of multiple medicines has been found in our study which can be ascribed to the fact that advancing age brings increased number of comorbidities and thereby increasing number of daily medicines intake.

The findings from the qualitative part of our study also substantiates our quantitative findings (Table 3). Subjective needs assessment is required for addressing the complexity of needs of dependent older people. Due to limitations in mobility and economic constraints, older people cannot access health facilities located far away from home or buy medicines from outside. There is a paramount need for provision of various rehabilitative and healthcare services like home visits, ensuring all-time supply of medicines and logistics, service delivery nearer to homes, easy availability and accessibility of social protection schemes and development of peer support groups.

CONCLUSION

This study revealed that emotional health is as important as physical health of the elderly. With advancing age there is not only an increasing limitation in the functional capacity of the elderly but also an increasing requirement of meaningful relationships and experiences. Declining agility and unsteadiness may result in falls and devastating injuries among the aged population. Similarly feeling of loneliness, isolation and lack of self-worth may result in depression among elderly. Health care administrators and policy makers should take into note the physical and emotional needs of the elderly while implementing strategies for their rehabilitation.

TABLE 3. Joint Display of health care needs of elderly with respect to their functional status.

Themes	Sub themes	Qualitative results (Codes)	Quantitative results
Service issues	Need for home based services	domiciliary visits by health workers for health check up	11.62% & 66.86% elderly are dependent in ADL & IADL respectively, hindering their regular visit to health centre. 15.7% participants reported severe body pain
	Need for supplies and logistics	ensure availability of medicines, insulin supply, supply of hearing aids, glasses, cane	56.9% and 55.8% participants respectively, were having ≥2 chronic diseases and taking ≥2 medications daily. 24.4% elderly required assistive devices in their daily activities.
	Need for Social Protection Schemes (SPS)	provision of government health insurance scheme, increment in amount of old age pension schemes, financial dependence on children	More than half of the study participants (55.2%) were financially dependent and belonged to lower socio-economic group (60.5%). 47.7% were not covered by any medical insurance.
	Other services	dental facility, psychiatry, Eye and ENT doctors, thyroid profile test	17.4% elderly had visual impairment, 6.4% had impaired hearing, 1.2% had dental problems, 1.2% had thyroid disorder.
Transportation issues		inconvenient and distant location of tertiary care hospitals providing specialized care and treatment	11.6% were found to be dependent on 'mode of transportation' item of Lawton Brody IADL Scale.
Peer support groups		isolation & neglect of family, loss of spouse, feeling of burden on children, no one to share emotional feelings	82.6% suffered from some form of depression in GDS 15 scale 8.7% participants reported to have low social support in MSPSS scale.

Tailor-made interventions are the need of the hour for holistically addressing the rehabilitative needs- both physical and emotional, of our elderly. Availability of various services such as mental health clinics, dental clinics, ophthalmology and otorhinolaryngology services etc, provision of assistive devices to the needy, developing elderly support groups, undertaking household visits for bedridden elderly, counseling about improved care-seeking, and increasing supportive environment in families and community should be ensured at the primary care level.

Limitations

This study was done in an outpatient clinic and hence elderly who are bedridden, too sick to attend OPD could not be interviewed. While most of the responses were recall-based, bias might be possible.

Conflict of interest : Nil

Funding: Nil

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Comparative Effectiveness of Court-Type Thai Traditional Massage and Ultrasound Therapy in Patients with Neck Pain: A Randomized Controlled Trial

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ABSTRACT

Objective: Neck pain is a common problem. *Lomplaipattakad Sanyan-4-Lang* (LPP-S4L) disease is a frequent cause of neck pain in Thai traditional medicine. Thai traditional medicine recommends treating neck pain with court-type Thai traditional massage (CTTM). Meanwhile, in conventional medicine, ultrasound modality (US) is used to treat neck discomfort. However, there is no scientific evidence if CTTM has potential analgesic advantages on LPP-S4L compared to ultrasound therapy. The study aims to evaluate the efficacy of CTTM compared to US and find body elements of participants based on aspects of Thai traditional medicine.

Materials and Methods: Sixty-six participants were diagnosed with LPP-S4L, with a numerical rating scale (NRS) ≥ 4. Patients were randomly assigned to one of two groups (33 per group). Participants underwent CTTM or US therapy eight times in total (twice a week). Pain intensity, pressure pain threshold, Range of motion (ROM), quality of life, and a body element questionnaire were used to assess patients.

Results: Both treatments showed a significant reduction in pain intensity, increase in pain threshold, increase in ROM, and improvement in quality of life in patients with LPP-S4L. The current study found that CTTM is more effective than US in most parameters, except Quality of life (QoL). Moreover, a decrease in pain intensity is related body elements, which indicates the influence of CTTM, or mostly the fire element.

Conclusion: We recommend employing CTTM, an alternative therapy, to treat patients with neck pain caused by LPP-S4L disease.

The trial was registered at thaiclinicaltrials.org (number: TCTR20211004008).

Keywords: Musculoskeletal pain; myofascial pain syndrome; Thai traditional medicine; massage; ultrasound therapy; body elements (Siriraj Med J 2023; 75: 29-37)

INTRODUCTION

Neck pain is a problem that affects both individuals and families, the healthcare system, and organizations.[1] The prevalence of neck pain in adults is significant, with the problem affecting up to 75% of the global population.[1,2] Neck pain is a type of discomfort that originates at the posterior of the neck and extends to the head, scapula, shoulder, trunk, and upper limbs.[3] Pain usually lasts more than three months and is commonly characterized by hyperalgesia in the skin, ligaments, and muscle palpations,

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as well as a limitation of the range of motion (ROM) of the neck and shoulder joints.[4] A variety of risk factors are thought to play a role in the development of neck pain. These risk factors can be divided into three main categories: physical, psychosocial, and individual-related risk factors. Although physical risk factors for neck pain are generally emphasized, psychosocial risk factors appear to play a more important role in the development of neck pain. In fact, neck pain is associated with multiple psychological risk factors such as having a demanding job, poor social support, and low job security.[4] This can also affect the quality of life.[5] In Thailand, a study reported a significant prevalence of neck pain in both adults and teenagers, with the main causes being poor body posture and stress.[6]

Neck pain is also a prevalent condition in individuals with musculoskeletal pain, according to traditional medicine, especially Thai traditional medicine where the condition is known as *Lomplaipattakad Sanyan 4 Lang* (LPP-S4L) disease. *Lomplaipattakad* are diseases caused by a defect in the wind element in the body while *Sanyan 4 Lang* defines the location of disease. When combined, LPP-S4L is a muscular discomfort of the posterior neck region, with a painful spot and muscle tightness above the 7th cervical vertebra (C7). The discomfort might be perceived in the scapula region, the anterior chest wall, and the upper limbs. Therefore, the practitioner must carry out a physical examination to assess range of motion (ROM) of the neck and palpation.

LPP-S4L is also frequently associated with neck myofascial pain syndrome (MPS). The Thai traditional medicine practice guidelines for neck pain recommend massage, hot herbal compression[7], or combination treatment.[8] Thai massage, also known as *Nuad Thai* in Thailand, has various styles. It is classified based on characteristics and the goal of the massage. The court-type Thai traditional massage (CTTM) is typically used for therapeutic purposes, while the general type is used for relaxation.[9,10] CTTM focuses on rehabilitation and treatment of musculoskeletal complaints and disorders. Its technique relies on the application of pressure on muscles with thumbs or palms, with a goal to reduce muscular tension, joint stiffness, and pain.[9] The principal focus of CTTM is major signal points (MaSPs) since anatomical examinations of each MaSP have shown that the majority of points are linked to muscles connected to branches of arteries and nerves. The effectiveness of CTTM therapy is the result of effective massage of MaSPs.[11,12] Massage has proven to have an impact on the musculoskeletal system, nervous system, cardiovascular system, and the mind. Several previous CTTM studies have revealed that a massage results in a rise of skin temperature and blood flow rate, indicating that it targets both local and systemic circulation.[13] Meanwhile, other studies show that each CTTM massage session should last between 30 and 60 minutes to relieve neck pain.[14-20] CTTM reduces pain intensity in the upper trapezius MPS more than topical diclofenac.[14, 15] Furthermore, CTTM also reduces the pain score and improves pain threshold in patients with chronic myofascial pain syndrome. It has also been suggested that CTTM be used with *Ruesi dad ton* (hermit doing body contortion) exercise to increase neck and shoulder joint ROM.[16] Last but not least, CTTM alleviates discomfort and reduces the need for medication in chronic headaches.[17-20]

In conventional medicine, most MPS patients receive various therapies[21], including medicine, ultrasound[22], acupuncture[23], stretching exercises[24], and massage.[15,16,25] One of the most common therapies is ultrasound (US), which uses high frequency acoustic vibrations convert to heat at the tissue level.[26] The thermal and non-thermal effects of US increase muscle fiber, tendons, ligaments, and joint capsule flexibility, and in the process reduce pain intensity and joint stiffness.[27] In a previous clinical study, US was able to rapidly reduce trigger point stiffness in the upper trapezius muscle in the US treatment group.[22] One study found that combining US, massage, and exercise for treatment of myofascial pain was not differ from a sham-US group combining massage and exercise.[28] However, there is no scientific clinical trial data to demonstrate that CTTM has potential analgesic effects on LPP-S4L compared to US.

The aim of this study was to compare the efficacy of CTTM and US on pain reduction in patients with LPP-S4L by measuring pain intensity, neck ROM, pressure pain threshold, and quality of life after 4-weeks of treatment. The secondary objective was to discover a relationship between body elements, based on Thai traditional medicine, and pain severity. We hypothesized that CTTM would provide more pain relief than US in LPP-S4L disease.

MATERIALS AND METHODS

Subjects were recruited between May 2019 and November 2020 at the Ayurved Clinic and Rehabilitation Center, Faculty of Medicine Siriraj Hospital. All study participants were randomized by computerized block randomization. There were 33 per group. The research was approved by the ethical committee of the Faculty of Medicine Siriraj Hospital (COA no. Si 648/2018).

The inclusion criteria was participants aged between 18-60 with chronic neck pain, and moderate to severe pain intensity (NRS ≥ 4). All subjects were screened and

diagnosed for LPP-S4L by a licensed Thai Traditional medicine practitioner with over 10 years clinical experience.

Participants were excluded if they met the following criteria: open wound on the neck and related areas, fever with temperature over 38.5°C, history of trauma or surgery involving bones of the neck, shoulder and/or back, inflammatory arthritis, neuropathic pain, pregnant, uncontrolled hypertension (BP>140/90mmHg), use of medication such as analgesics or muscle relaxants within one week of the experiment. Researcher enrolled and assigned participants after signed inform consent.

Court-type Thai traditional massage (CTTM)

Five licensed Thai traditional medicine massage therapists with at least 10 years of clinical experience massaged patients in this study. They were trained using the same massage protocol.[17,48] The massage therapists were in a standing position while patients were in the sitting position during massage. CTTM therapy was carried out for 30 minutes per session, twice a week for a total of four weeks as per standard protocol in clinical practice guideline. CTTM starts as a basic massage of the shoulder, neck and pressure on major signal points on both sides. The treatment targets the trapezius muscle, levator scapulae muscle, splenius muscle and suboccipital muscle. The therapists were randomized for each round of treatment (Fig 1).

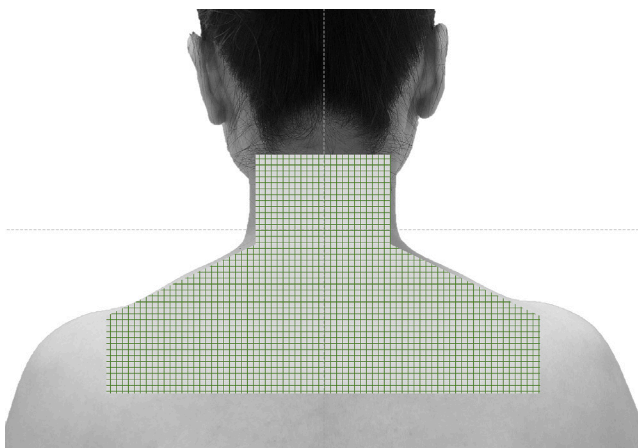

Fig 1. Treatment area.

Ultrasound treatment (US)

Two licensed physical therapists with 10 years of clinical experience underwent training sessions for this study. Ultrasound treatment was set at an intensity of 0.8 W/cm^2 and the frequency was 1 Mhz. Physical therapists were also in the standing position while patients were in the sitting position. Ultrasound treatment was carried out for 10 minutes in each session, twice a week for four weeks following the standard protocol as per clinical practice guidelines. The treatment area covered the common source of neck pain such as trapezius, levator scapulae, splenius and suboccipital muscles (Fig 1).

Outcome measurement

Pain intensity

Pain intensity was measured by the numerical rating scale (NRS). Participants self-assessed pain intensity using a numerical rating scale (0-10). During the study, an assistant researcher inquired about the pain before and after treatment (eight visits). A score of 0 meant no discomfort while 10 indicated maximum pain.

Pressure pain threshold (PPT)

Algometry is a method to measure pain sensitivity. This study used pressure algometry (Algomed algometry, Compass medical technologies, Inc. Medoc advance medical system, U.S.). The PPT was evaluated on the trigger point or the most hard tendon in the upper trapezius muscle which was the major diagnosis area of LPP-S4L. An assistant researcher put algometry force (kg/cm^2) slowly on the point until the participant pressed a button on the algometer response unit to stop the pressure. Data from the same area was collected an average of two times or before and after of treatment.

Range of Motion (ROM)

Two assistant researchers underwent a training session for measuring the ROM of the neck, including flexion, extension, lateral flexion and rotation of both sides using a goniometer. The ROM was collected before and after treatment during the study (eight visits).

Quality of life (SF-36)

SF-36 (short form 36) is a health survey questionnaire that assesses quality of life. SF-36 has thirty-six questions covering eight important points of quality of life, including physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional and mental health. SF-36 is administered before and after the last treatment. This study used SF-36 version 2 (Thai version).[29]

Percentage usage of rescue drug

Each participant received 20 tablets of 500mg acetaminophen (paracetamol). They were asked to state the remaining in each visit.

Dominant body element questionnaire

Participants were evaluated using the dominant

body element questionnaire[30] in their first visit. The body element questionnaire determines innate body elements and present body elements of participants. The innate body elements, including fire, wind, water and earth were obtained by birth month. Meanwhile, present body elements, including Pitta, Vata, Semha, and mixed elements were obtained from 33 questionnaire items. The present body element can be indicated by a higher percentage score.[30]

Statistical analysis

Data was analyzed by using SPSS version 18. Data is presented as the mean, mean difference, SD, changes in value, and percent difference. This study was parallel or independent-group study. Comparison between groups was performed by an unpaired T-test, while a paired Student's t-test was used to compare within group. A comparison of NRS and PTT over the time points was performed by repeated measures ANOVA with the Bonferroni method for the differences within group, and effect of times. The difference between group used unpaired T-test. A *p-value* of less than 0.05 was considered statistically significant.

RESULTS

A total of 69 patients with LPP-S4L were recruited. Three participants were excluded due to low pain score and hypertension. A total of 66 patients with LPP-S4L were enrolled and received treatment twice a week for four weeks, or a total of eight times, with 33 patients per group (Fig 2). The demographic characteristics are presented in Table 1. There was no significant difference in demographic findings between CTTM and US.

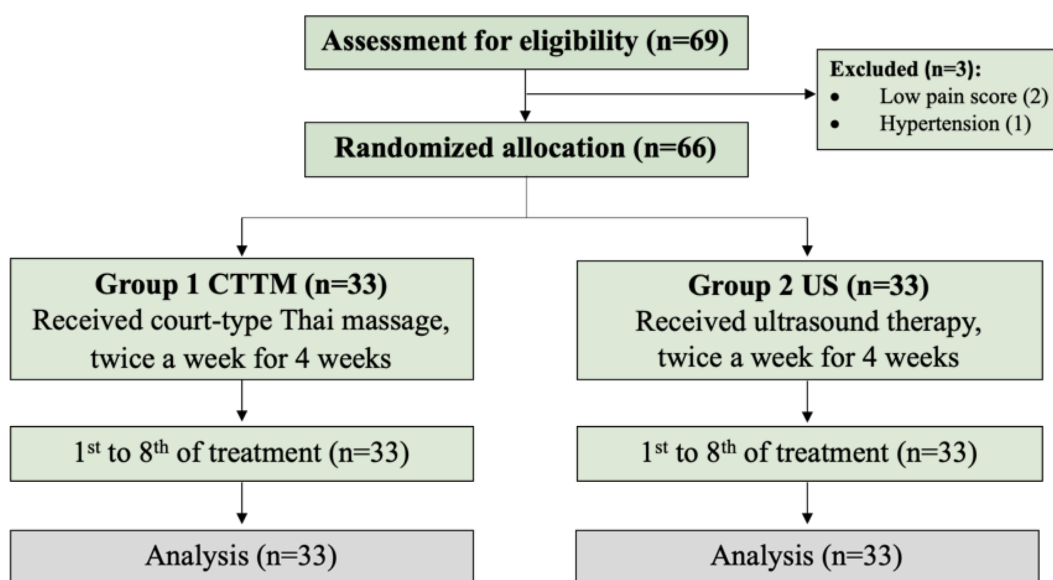

Fig 2. Study flowchart.

TABLE 1. Demographic data of participants.

Characteristics	Total (n=66)	CTTM group (n=33)	US group (n=33)	P-value
Gender; n (%)				
Female	46 (69.70)	23 (69.70)	23 (69.70)	1.000[a]
Age (years);				
Mean ± SD	32.92 ± 6.46	33.8 ± 6.5	32.0 ± 6.3	0.265[b]
Min, Max	24, 48	25, 44	24, 48	
Weight (kg); Mean ± SD	61.86±11.29	59.6±10.2	64.1±12.0	0.102[b]
Height (kg); Mean ± SD	162.62±8.37	161.9±8.6	163.3±8.2	0.494[b]
BMI (kg/m^2); Mean ± SD	23.33±3.59	22.7±3.2	24.0±3.7	0.141[b]

[a] Fisher's exact test, [b] Independent T test.

Pain intensity

Baseline NRS in both groups was not significantly different (Table 2). NRS significantly decreased after treatment at the four-week point in both groups (p<0.05). In the CTTM group, the level of pain relief was lower than the US group and significantly different at all time points of treatment over the course of four weeks (Fig 3A).

Pressure pain threshold

Baseline PPT in both groups was not significantly different (Table 2). PPT significantly increased after treatment at the four-week point in both groups (p<0.05). In the CTTM group, the level of pain increased more than the US group and was significantly different all time points of treatment over four weeks (Fig 3B).

Neck range of motion

The baseline of neck flexion and neck rotation was significantly different between both groups (Table 2). Both groups showed improved ROM of the neck, including flexion, extension, lateral flexion, and rotation at four weeks. At the four-week point, lateral flexion and rotation improved by 7.56±3.84 and 10.29±5.78 degrees, indicating a significant difference between CTTM and US group (p=0.038 and 0.005, respectively).

Quality of life

The baseline of quality of life was acquired from SF-36 in both groups, but it was not significantly different in all parameters (Table 2). There were significant improvements in physical, bodily pain, general health, vitality, social function, and mental health after four weeks of treatment in the CTTM group. In the US group, bodily pain improved significantly after four weeks of treatment. However, after four weeks, there were no significant differences in any other parameters.

Percentage of rescue drug use

No significant differences between the two groups were noted regarding the percentage of use of rescue drug over four weeks. During the eight visits for treatment, only one (3.03%) patient in the CTTM group used two tablets of rescue drug during the third visit because of

TABLE 2. Clinical parameters of patients in both groups before and after the fourth week.

Outcomes	CTTM group (n=33)			US group (n=33)			P-value[b]	P-value[b]
	Before	After (4th week)	P-value[a] before vs after	Before	After (4th week)	P-value[a] before vs after	CTTM vs US Before	CTTM vs US After
VAS	5.58±1.23	0.94±0.93	<0.001*	5.33±0.98	2.42±1.44	<0.001*	0.380	<0.001*
PPT	3.73±1.90	5.91±2.42	<0.001*	2.97±1.46	3.83±1.94	0.003*	0.074	<0.001*
ROM								
Flexion	36.97±10.13	42.09±10.85	<0.001*	44.82±13.60	51.85±8.60	<0.001*	0.010*	0.010*
Extension	36.36±11.02	38.27±9.80	<0.001*	39.42±8.62	37.06±8.74	0.031*	0.214	0.120
Lateral flexion	23.21±5.79	23.83±5.34	<0.001*	20.97±5.06	23.47±4.31	<0.001*	0.099	0.105
Rotation	58.55±9.51	66.61±7.94	<0.001*	68.27±8.55	75.29±9.28	<0.001*	<0.001*	0.025*
SF-36								
Physical function	69.55±20.13	70.91±17.48	0.702	73.48±20.90	74.55±21.04	0.745	0.438	0.448
Role physical	72.73±17.32	78.98±14.97	0.024*	74.05±19.46	78.22±17.48	0.155	0.711	0.851
Bodily pain	32.29±18.07	55.68±17.70	<0.001*	29.92±13.60	50.38±19.13	<0.001*	0.550	0.247
General health	50.21±17.3	59.67±18.19	0.002*	54.79±16.54	57.00±17.49	0.380	0.276	0.546
Vitality	49.06±15.85	60.41±12.85	<0.001*	50.95±15.32	56.25±17.54	0.072	0.625	0.275
Social function	61.36±15.74	75.38±15.14	<0.001*	68.94±17.43	72.35±22.48	0.348	0.069	0.523
Role emotional	75.76±19.80	79.29±18.99	0.364	76.77±20.70	74.49±24.47	0.514	0.840	0.377
Mental health	61.06±14.62	68.33±11.30	0.001*	63.48±12.96	64.67±16.63	0.538	0.479	0.303

[a] Paired t-test. [b] Unpaired t-test. Significant (p-value<0.05).

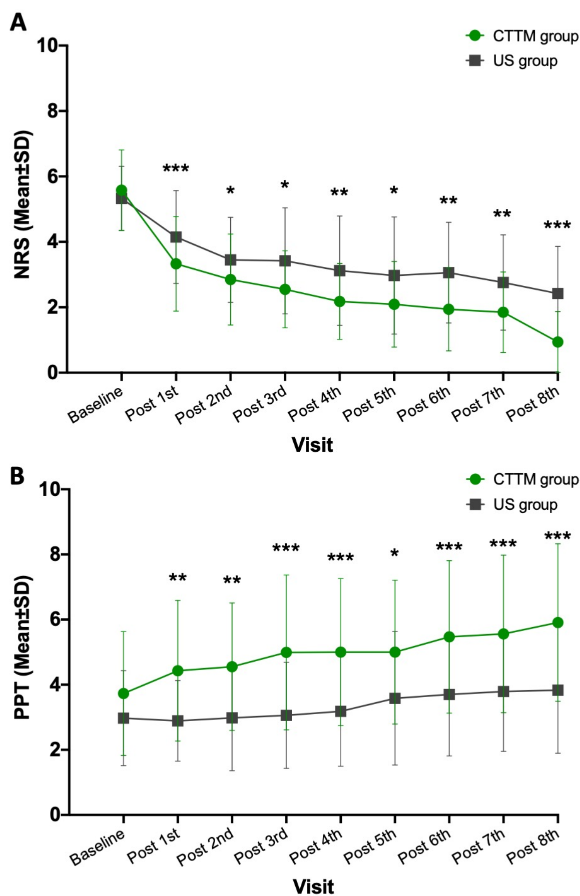

Fig 3. Pain parameters over four weeks of treatment (twice a week). (A) pain score measured by numeric rating scale (0-10). (B) pressure pain threshold (0-10 kg/cm^2). Data compared with mean differences ± SD between CTTM and US groups (n=33 each group). Significant differences between groups are * p-value<0.05, ** p-value<0.01, *** p-value<0.001, unpaired T-test. There were significant differences compared before with over time of NRS and PPT, repeated measured ANOVA with Bonferroni ($^{\#}$p-value <0.001).

menstrual pain. One (3.03%) patient in the US group also used four tablets of rescue drug on the fourth visit due to headache. No side effects were linked to intervention during the study.

Relationship between body elements based on Thai traditional medicine

Both groups showed a similar proportion of innate body elements (Fig 4A). Using the innate body elements to stratify the pain difference (Fig 4B). NRS different for fire, wind, water, and earth elements of CTTM group were 4.75±0.89, 5.20±1.10, 4.55±2.20, 4.33±1.73, respectively. NRS different for fire, wind, water, and earth elements of US group were 2.30±1.42, 2.40±1.34, 4.00±1.41, 3.00±1.61, respectively. Patients with the fire element in the CTTM group showed a greater decrease compared to US group (p<0.001). There were no significant different between group for wind, water, and earth (p-value 0.07, 0.53, 0.09). Both groups also showed a high proportion of the Pita-Vata-Semha element for present body elements (Fig 4C).

DISCUSSION

This study examined the impact of CTTM and US on neck pain relief in patients with LPP-S4L disease. Although the outcomes of massage have been investigated in patients with neck pain, the majority of whom had MPS[16], it was a broader diagnosis than Thai traditional medicine. MPS in the neck can be identified with LPSS-4L disease, LPSS-5L disease, *Lompakang* disease, and *Koh-tok-mhon* disease, among others. Each condition has its own set of treatment regions and protocols. Our study found that LPP-S4L patients in the CTTM as well as US group experienced significant improvements in pain intensity, pressure pain threshold, neck ROM, and quality of life. According to clinical practice guidelines of Thai Traditional Medicine[8], treatment should last at least four weeks. This helps maintain pain relief, muscle tightness, and improves daily life.[31]

Over the course of the study, patients with LPP-S4L who experienced moderate levels of chronic pain were examined for pain intensity. When comparing the before and after treatment across all time points, both treatments exhibited statistically significant reductions in pain intensity. When comparing CTTM to US, the study found a statistically significant difference in impact in terms of lower pain intensity in CTTM across all time points. CTTM can reduce pain by around 50% after the first session and by 80% of baseline after four weeks, indicating clinical therapeutic effects. CTTM treatment claims to be a muscle relaxant.[32] Pain alleviation is achieved by lowering muscular pain and tension in the

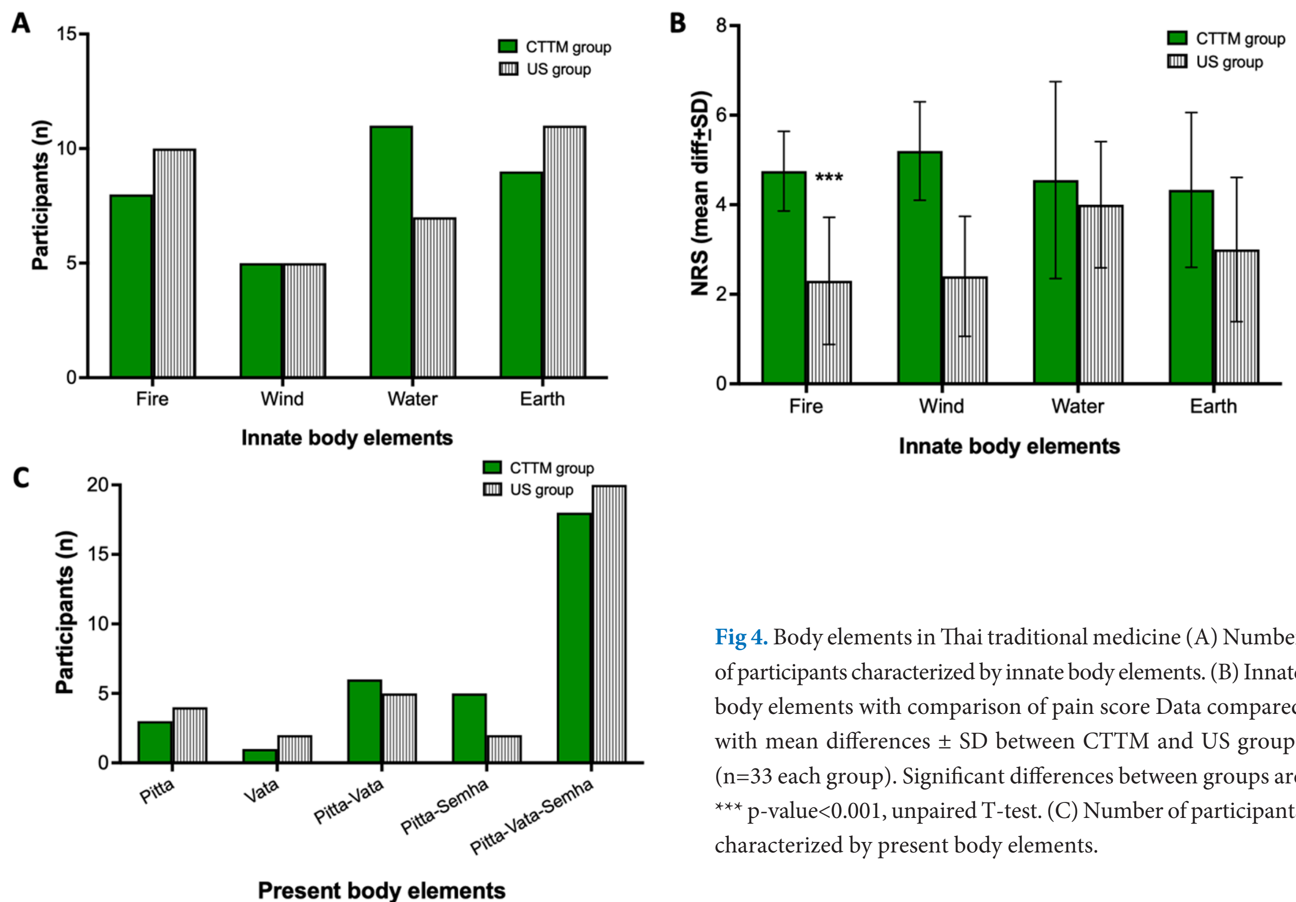

Fig 4. Body elements in Thai traditional medicine (A) Number of participants characterized by innate body elements. (B) Innate body elements with comparison of pain score Data compared with mean differences ± SD between CTTM and US groups (n=33 each group). Significant differences between groups are *** p-value<0.001, unpaired T-test. (C) Number of participants characterized by present body elements.

back of the neck and upper back. These findings were consistent with reports that after four weeks of CTTM and US, the pain response increased.[16,33] In this study, the CTTM group had a higher pain threshold than the US group. The decrease in pain intensity and increase in pain threshold suggests efficacy and pain relief. CTTM is more efficient than the US. This could be because CTTM treatments primarily target tender points and press deeply into the muscle. Its therapeutic effect is derived from various pathways such as stress reduction, increased relaxation, muscle soreness reduction, and improved circulation. While ultrasound therapy works primarily by increasing temperature and improving circulation. Perhaps CTTM is more effective because it has more pain-reduction mechanisms. It may result in less muscle tension than in the US.

The current study found that an increase in ROM in all directions at all time-points was statistically significant when comparing the before and after treatment in the CTTM group. Our findings were similar to those of previous studies. A single course of CTTM treatment for LPP-S4L reduced pain intensity, raised the pain threshold, and increased cervical ROM.[33] However, when compared to US, a different result was reported in a previous study.[34] There was no difference in cervical ROM or VAS between the two treatments. In individuals with cervical MPS, both Thai massage and ultrasonography can dramatically raise cervical ROM while decreasing the pain rating and suffering during activities of daily life. When compared to ultrasound, Thai massage improved patients' capacity to complete daily activities and improve clinical satisfaction.[34]

According to the current study, both therapies can improve quality of life. In the CTTM group, there were significant differences in six out of eight categories, including role physical, bodily pain, general health, vitality, social function, and mental health. However, no statistically significant variations in physical function or emotion were found. There were differences only in the physical pain category in the US group. When comparing the before and after results in the US group, there was no statistically significant difference in other categories. There were also no statistically significant differences between the CTTM and US groups in any category. The findings were comparable to those of a previous report.[15] Participants with neck pain in the CTTM group have higher quality of life in all domains, although there are no statistically significant differences when compared to the control group. The results suggest that CTTM improves quality of life more than US. In this study, no

significant change of quality of life in both groups might be from a ceiling effect of the SF-36 in detecting change before and after treatment.

As per Thai traditional medicine, this investigation evaluated innate and present body elements and found that patients'innate body elements were not dominant, but that both groups had a similar proportion. When the pain intensity was assessed before and after the study, participants with the fire element in the CTTM group had the greatest reduction in pain intensity compared to the US group. Meanwhile, the water and earth elements provided comparable pain alleviation. The present body elements were mostly of the mixed-type (Pitta-Vata-Semha). According to Thai traditional theory, the wind element is the primary cause of pain. It may impact the fire, water, and earth components, resulting in muscle spasms. Thus, people who have the wind element may be more affected than others.[32] CTTM can help reduce muscle spasms and restore normal wind element flow. A large population must be investigated in order to collect all elements for analysis to understand the body elements.

Participant bias may have occurred due to a lack of blind treatment intervention in each group. Since the majority of participants were young, the findings cannot be generalized to all age groups. The proportion of patients with different body elements may not fully represent the relationship between the type of element and the severity of pain. In contrast, this study indicated the overall makeup of patients' body elements. With body elements and age-classified inclusion, a larger sample size should be observed. The effect of CTTM on patients' suffering from various diseases should be investigated further. Also, CTTM's effectiveness beyond a period of three to six months should be established for future clinical trials.

This study determined that a four-week course of CTTM is an appropriate amount of time to treat LPP-S4L and reduce pain intensity. CTTM, a recognized alternative and integrative medicine, can be used as a primary treatment for people suffering from neck pain. However, cost of treatment for CTTM and US differs. While CTTM costs around 300 baht/session (30 minutes), US costs 200 baht/session (20 minutes). Both treatments have minimal side effects. A patient can select his or her treatment based on preference, confidence, risk factors, precaution, and practitioner experience.

CONCLUSION

This study suggests that CTTM and US treatment on the neck muscle twice a week for four weeks is effective in decreasing pain intensity, increasing pain threshold, increasing cervical ROM, and improving quality of life of patients with LPP-S4L. Both treatments are non-drug interventions with no side effects. In addition, the findings in the present study found that CTTM is more effective than US across all domains in patients with LPP-S4L. Moreover, we found that a change in pain intensity relates to differences in the body element in the patient, especially the wind and fire element. Consequently, we recommend using CTTM, an alternative therapy, to treat neck pain caused by LPP-S4L disease. Future research should be conducted to determine the efficacy of CTTM and US for diseases that last longer than three to six months.

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A Comparison of Serum Copper Levels in Patients with Papillary Thyroid Carcinoma, Nodular Goiter, and Healthy Volunteers

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ABSTRACT

Objective: Serum copper (Cu) is an essential trace element that plays a key role in thyroid hormone production. An inappropriate level of serum Cu might be related to development of both benign and malignant thyroid neoplasm. Nodular goiter and papillary thyroid carcinoma (PTC) are common benign and malignant tumors of the thyroid, respectively. This study aims to compare the serum Cu levels of healthy women with women with PTC or nodular goiter.

Materials and Methods: A total of 205 Thai women were recruited for this cross-sectional study. The reference group was comprised of 100 healthy volunteers. There were 61 nodular goiter and 41 PTC patients that had been treated with surgery. Serum Cu was measured using an atomic absorption spectrophotometer and the three groups were compared.

Results: The serum Cu levels of the PTC, nodular goiter and the reference group were 0.93 (0.85, 1.11) µg/ml, 1.03 (0.90, 1.14) µg/ml and 0.97 (0.80, 1.11) µg/ml, respectively. The results were not statistically different ($P = 0.10$). A post hoc subgroup analysis in the PTC group showed only serum Cu levels were significantly higher in the blood vessel invasion group ($P = 0.02$).

Conclusion: The serum Cu levels of patients with PTC and nodular goiter were not different and did not differ significantly from the reference group. Despite related to with only one pattern of histopathologically aggressive PTC-Blood vessel invasion, serum Cu levels cannot be used as an assistive tool for diagnosis and the prognosis of PTC.

Keywords: Serum copper (Cu); nodular goiter; papillary thyroid carcinoma; thyroid cancer; BRAF mutation (Siriraj Med J 2023; 75: 38-45)

INTRODUCTION

Serum Cu is an arbitrary marker for many types of malignancies and is more available and less expensive than genetic testing. Serum Cu levels rise significantly in many types of malignancies, such as esophageal cancer, gynecologic cancer, pancreatic cancer, and melanoma.[1-4] Why serum Cu is elevated in the presence of malignancy is not yet clear. Copper may be a key factor in tumor angiogenesis.[5,6] Ceruloplasmin, the Cu-binding protein, can increase in malignancies due to decreased metabolism

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or an inflammatory response state.[7,8] Zhu et al. found that Cu transportation in tumor cells increased as a result of elevated expressions of transporter genes.[9] Coates and coauthors reported that the sensitivity and specificity of high serum copper for the risk of developing a cancer were 40% and 80.4%, respectively, but a cutoff value was not determined.[10]

Serum copper plays a key role in thyroid hormone production.[11] This trace element controls T4 levels by regulating calcium homeostasis.[12] An inappropriate serum Cu level also stimulates the growth of transformed cell by providing energy (ATP) in cell cycle process.[13] Furthermore, Cu is an essential nutrient that be integrated in the antioxidant process as a cofactor of the enzyme superoxide dismutase, eliminating free radicals caused by various tissue damage in the body.[14] However, excessively high Cu levels can cause abnormal cell growth by creating free radicals and damaging DNA.[15,16]

Several studies have reported that the serum Cu levels of patients with thyroid carcinoma were higher than those of normal subjects.[17-20] Additionally, Baltaci et al. also found that serum Cu decreased after removal of thyroid tumors.[21] In contrast, Al-Sayer et al. did not identify a difference between the serum Cu levels of patients with thyroid cancer and healthy controls, and serum Cu increased after thyroidectomy.[22] Due to insufficient data and inconclusive evidence, the association between serum copper and thyroid cancer needs further investigation. Therefore, we aimed to compare the serum copper levels of patients with PTC, nodular goiter and healthy Thai women.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted at the Department of Otorhinolaryngology, Faculty of Medicine Siriraj Hospital, from July 2018 to June 2021. Serum Cu was measured by the Clinical Toxicology Laboratory of the Faculty of Medicine Siriraj Hospital. The laboratory has been certified to the ISO 15189 accreditation standard since 2013. This study was approved by the Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 367/2017) and was conducted in accordance with the Declaration of Helsinki.

Study population

Diseases of the thyroid gland are generally more common in females than males. In the Thai population, the female to male ratio of incidence of thyroid cancer is approximately 4.3:1, and the gender ratio of thyroid surgery was 5.2:1 during 2018-2020.[23] Because serum Cu levels can vary by gender,[24] we investigated only female patients. The sample size calculation was based on the primary assumption of differences between serum Cu in thyroid disease and the normal population. Totally, we aimed to collect data from 100 patients with thyroid disease (PTC and nodular goiter) and 100 normal controls. The thyroid disease group was consisted of Thai women aged 18 years and older who had thyroid nodules. Fine needle aspiration was performed prior to surgery. All patients with pathological reports of PTC or nodular goiter who needed surgical treatment for thyroid diseases were eligible. Patients with incidental papillary microcarcinoma, thyroid carcinoma other than PTC, or other thyroid or systemic diseases that could alter serum Cu levels (i.e., thyroiditis, Wilson's disease, pulmonary disease, cardiovascular disease, infectious disease, and other types of cancer) were excluded. Patients with current medications or supplements that would alter serum Cu levels, a history of previous thyroid surgery, or abnormal levels of FT4 or TSH were also excluded. The reference group consisted of healthy female volunteers with normal thyroid glands confirmed by ultrasonography and blood tests showing FT4, TSH, Cr, and eGFR within normal limits. All study subjects were fully informed about the treatment options and study protocol before signing informed-consent forms.

Data collection

Demographic data and ultrasonographic findings of the thyroid gland were recorded. Blood samples were tested for FT4, TSH, Cr, eGFR, and serum Cu levels. For the cancer group, a pathology-confirmed specimen was sent for detection of the BRAF^{V600E} mutation using the PCR-based Sanger sequencing technique combined with allele-specific, real-time PCR. Adverse features such as multifocality, blood vessel invasion, capsular invasion, extrathyroidal extension and evidence of transformation from coexisting nodular goiter were noted. The maximum diameter of the tumors was recorded in centimeters. The risk of recurrence was classified according to the 2015 guidelines of the American Thyroid Association.[25] Stage was classified using the 8th edition of the AJCC/TNM staging system of thyroid cancer.[26] If indicated, post-treatment I-131 total body scans and serum thyroglobulin (Tg) levels were used to detect residual diseases and distant metastases.

Serum Cu level analysis

Blood samples 5 ml were collected with the standard method in accordance with the Clinical and Laboratory Standards Institute guidelines for trace element analysis.[27]

Collection and access procedures were performed in the patient ward one day before surgery with talc-free gloves, a 21-gauge needle, and a BD Vacutainer plastic blood collection tube for trace element testing (K2EDTA). The tubes were kept upright and either immediately sent to the Clinical Toxicology Laboratory or stored in a refrigerator at 2° to 8° C for no longer than 24 hours. The samples were prepared by centrifugation process (3500 round per minute) for 10 minutes then the extracted plasma 0.5 ml was collected and diluted with deionized water 1 ml (1:2). Before analysis, internal quality assurance for trace elements was routinely performed using Clin Check Controls. Next, the sample was analyzed with a flame atomic absorption spectrophotometer to produce free atoms of Cu in the gaseous state. The absorbance of light with the specific wavelength of Cu was measured. The intensity of the absorbed light wave was proportional to the amount of copper in the sample. Subsequently, a standard calibration curve was plotted with linear regression. Serum Cu levels were reported as mg/dl and converted to µg/ml as a standard unit.

Statistical analysis

Demographic data are presented using descriptive statistics. One-way analysis of variance was used to compare the three groups (Reference, PTC, and nodular goiter). If the *P* values were less than 0.05, post hoc analysis was applied. Serum Cu levels (µg/ml) are reported as median and interquartile range. Subgroup analyses of the serum Cu levels of the PTC group were performed for histopathological aggressiveness and $BRAF^{V600E}$ mutation using the Mann-Whitney U test. Variant of PTC, risk of recurrence and the TNM staging were compared by one-way analysis of variance. Pearson's correlation was used to test the association between the size of the PTC or nodular goiter and the serum Cu level. A *P* value of < 0.05 was considered statistically significant. Statistical analyses were carried out using PASW Statistics for Windows (version 18; SPSS Inc., Chicago, IL, USA).

RESULTS

Two hundred and twenty-two subjects were enrolled and 17 were later excluded. The excluded subjects comprised 10 cases with papillary thyroid microcarcinoma, five cases with follicular thyroid carcinoma, and two cases with thyroiditis. Therefore, the study population was 205 subjects, consisting of 105 patients with thyroid disease (44 with PTC and 61 with nodular goiter), and 100 healthy controls. The unequal distribution between PTC (n=44) and nodular goiter (n=61) was due to the enrollment nature of our cross-sectional study design that aimed to recruit consecutive cases and could not preoperatively predict the pathological results of patients.

Serum Cu levels

The serum Cu levels of the PTC group, the nodular goiter group and the reference group, were 0.93 (0.85, 1.11) µg/ml, 1.03 (0.90, 1.14) µg/ml and 0.97 (0.80, 1.11) µg/ml, respectively (Fig 1). The results were not statistically different (*P* = 0.10). Age, serum creatinine and eGFR were significantly different among the PTC, nodular goiter and reference groups (Table 1). After adjustment for age, serum creatinine and eGFR, there was still no statistical difference.

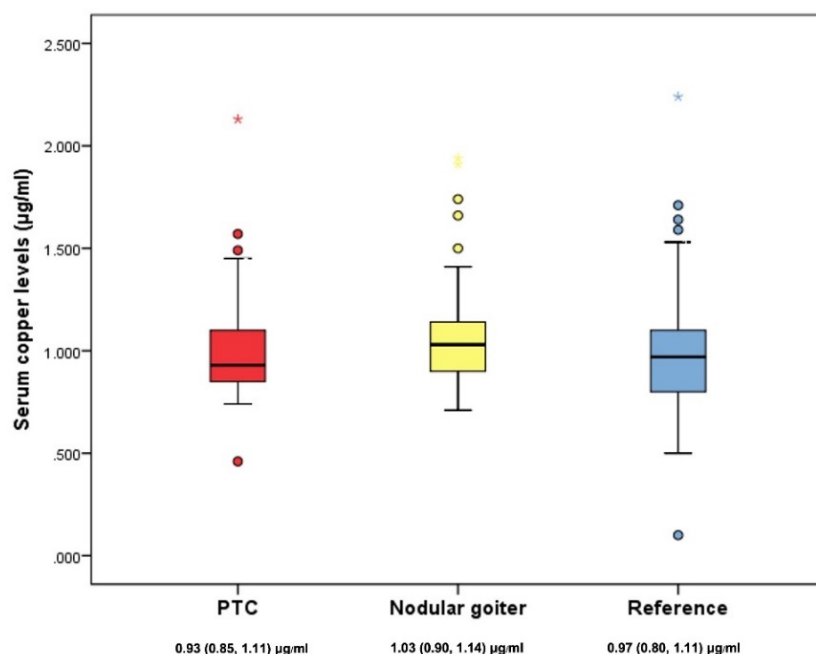

Fig 1. The serum Cu levels of the PTC group, nodular goiter group and the reference group were 0.93 (0.85, 1.11) µg/ml, 1.03 (0.90, 1.14) µg/ml and 0.97 (0.80, 1.11) µg/ml, respectively

TABLE 1. Demographic data and characteristics of PTC, nodular goiter, and the reference group.

Patient characteristics Median (IQR25,75)	PTC (n = 44)	Nodular goiter (n = 61)	Reference (n = 100)	*P* value
Age (years)	45.00 (36.25, 56.25)	48.00 (36.00, 58.00)	37.00 (29.00, 51.00)	0.001*[,a,b]
Weight (kg)	57.55 (53.20, 68.80)	58.00 (50.00, 66.00)	54.00 (50.00, 65.00)	0.47
Height (cm)	157.00 (152.00, 161.50)	155.00 (153.00, 160.00)	156.00 (153.00, 160.00)	0.83
FT4 (ng/dL)	1.21 (1.08, 1.35)	1.20 (1.10, 1.29)	1.20 (1.08, 1.29)	0.42
TSH (uIU/mL)	1.44 (0.91, 2.76)	1.28 (0.80, 1.92)	1.79 (1.28, 2.49)	0.14
Cr (mg/dL)	0.71 (0.67, 0.83)	0.68 (0.60, 0.77)	0.67 (0.60, 0.74)	< 0.001*[,a,c]
eGFR(L/min/1.73m^2)	96.54 (86.08, 108.51)	101.18 (89.74, 110.12)	109.07 (99.94, 120.34)	< 0.001*[,a,b]

* *P* values less than .05 considered statistically significant.
[a] *P* value between reference and PTC was < 0.05
[b] *P* value between reference and nodular goiter was < 0.05
[c] *P* value between PTC and nodular goiter was < 0.05
Abbreviations: PTC, papillary thyroid carcinoma; FT4, free thyroxine; TSH, thyroid stimulating hormone; Cr, creatinine; eGFR, estimated glomerular filtration rate.

PTC group

Histopathological aggressiveness

Of the 44 PTC cases, the classical variant was found in 88.6% (n = 39) and the follicular variant in 6.8% (n = 3). Two patients (4.5%) had non-invasive encapsulated follicular variant of papillary thyroid carcinoma (NIFTP). Multifocal cancers were identified in 70.5% (n = 31) of cases with no statistical difference (*P* = 0.24). The serum Cu in the blood vessel invasion group was significantly higher than those without invasion (Table 2). There were no significant differences in serum Cu levels for coexisting nodular goiter, capsular invasion, extrathyroidal extension, high- risk of recurrence and TNM staging. There was no correlation between tumor size and serum Cu levels (*r* =-0.04; *P* = 0.81). Four patients (9.1%) had distant metastases detected by I-131 total body scan. Their serum Cu levels were higher than those in the no metastasis group, but no significant difference of 1.05 (0.91, 1.38) µg/ml, and 0.93 (0.84, 1.08) µg/ml, respectively (*P* = 0.26). Meanwhile, there was also no significant difference of serum Cu levels among the subgroup of PTC histopathological aggressiveness, nodular goiter and healthy groups.

Molecular testing

The BRAF^{V600E} mutation was positive in 20 patients (45.5%) and negative in 24 (54.5%). The serum Cu levels of BRAF-positive cases were not significantly higher than in the negative groups. 1.02 (0.86, 1.17) µg/ml, and 0.92 (0.83, 0.97) µg/ml, respectively; *P* = 0.06). Nevertheless, the results from both groups remained within the reference range.

Nodular goiter group

The correlation coefficient between the diameters of the nodular goiter and serum Cu levels was (*r*= 0.02; *P* = 0.89). The median serum Cu level in cases of PTC with nodular goiter was 0.92 (0.87, 1.10) µg/ml (n = 17), while the median serum Cu level for cases with pure nodular goiter was 1.03 (0.90, 1.14) µg/ml (n = 61) (*P* = 0.76).

DISCUSSION

We compared serum Cu levels of patients with PTC, nodular goiter and normal healthy subjects. Zhang[24] and Shen[12] reported that gender and ethnicity influence serum Cu levels and so we investigated only Thai women, the

TABLE 2. Comparison of the histopathological, molecular status, risk of recurrence and staging of 44 PTC cases and their serum copper levels.

Histopathological aggressiveness		n (%)	Serum copper level (µg/ml)	*P* value
Coexisting nodular goiter	Yes	17 (38.6)	0.92 (0.87, 1.10)	0.77
	No	27 (61.4)	0.93 (0.84, 1.12)	
Multifocal (Foci > 1)	Yes	31 (70.5)	0.93 (0.85, 1.07)	0.24
	No	13 (29.5)	0.93 (0.83, 1.17)	
Blood vessel invasion	Yes	26 (59.1)	1.01 (0.87, 1.16)	0.02*
	No	18 (40.9)	0.89 (0.82, 0.96)	
Capsular invasion	Yes	25 (56.8)	0.93 (0.85, 1.16)	0.484
	No	19 (43.2)	0.92 (0.85, 1.04)	
Extrathyroidal extension	Yes	20 (45.5)	0.92 (0.84, 1.04)	0.289
	No	24 (54.5)	0.95 (0.86, 1.17)	
Variant	Classic	39 (88.6)	0.93 (0.85, 1.12)	0.50
	Follicular	3 (6.8)	0.92 (0.87, 1.17)[a]	
	NIFTP	2 (4.5)	0.84 (0.75, 0.92)[a]	
$BRAF^{V600E}$ mutation	Yes	20 (45.5)	1.02 (0.86, 1.17)	0.06
	No	24 (54.5)	0.92 (0.83, 0.97)	
Risk of recurrence	Low	11 (25)	0.92 (0.85, 1.04)	0.89
	Intermediate	23 (52.3)	0.93 (0.82, 1.15)	
	High	10 (22.7)	0.92 (0.86, 1.24)	
Tumor (T)	T1	15 (34.1)	0.92 (0.84, 1.04)	0.59
	T2	14 (31.8)	0.95 (0.86, 1.15)	
	T3	12 (27.3)	0.99 (0.83, 1.17)	
	T4	3 (6.8)	0.87 (0.86, 0.88)[a]	
Node (N)	N0	21 (47.7)	0.93 (0.86, 1.06)	0.99
	N1	23 (52.3)	0.93 (0.83, 1.14)	
Metastasis	M0	40 (90.9)	0.93 (0.84, 1.08)	0.26
	M1	4 (9.1)	1.05 (0.91, 1.38)	
Stage	1	34 (77.3)	0.92 (0.84, 1.03)	0.76
	2	7 (15.9)	1.08 (0.91, 1.15)	
	3	1 (2.3)	1.00†	
	4	2 (4.5)	1.19 (0.92, 1.45)[a]	

* *P* values less than .05 considered statistically significant.

† No min, max as there was only one data item for that category.

[a] Use min, max instead of interquartile range.

Abbreviations: NIFTP, Noninvasive follicular thyroid neoplasm with papillary-like nuclear features

gender most often affected by this disease. The median serum Cu levels of our reference group were comparable to those in diverse populations (Table 3). The most common method to measured serum Cu was the atomic absorption spectrometry, so the median serum Cu levels in healthy subjects of our study were very close to the mean value of the studies that used this technique as well as the biggest dataset in a Chinese population.[20,24,28] The results in the reference group showed reliable; However, we did not identify any statistically significant differences in the serum Cu levels among the PTC, nodular goiter, and reference groups.

The use of Cu to support the diagnosis of thyroid cancer remains inconclusive. Baltaci et al.[21] showed that serum Cu levels of women with thyroid cancer were significantly higher than those of healthy controls. Additionally, the serum Cu levels of female patients with thyroid cancer significantly decreased to levels close to those of the control group within two weeks after surgery. Vesna and colleagues[17] compared 35 cases of PTC and 13 cases of papillary thyroid microcarcinoma with 82 cases of benign thyroid tumor. The serum Cu levels of patients with PTC and microcarcinoma were significantly higher than patients with benign thyroid tumor. However, because incidental microcarcinoma was included in the PTC group, their findings are challenging to interpret and to compare with our study.

In 2015, Shen and colleagues published a meta-analysis of five case-control studies investigating serum Cu levels.[12] One study was carried out in China, three in Poland, and one in Turkey. Overall, patients with thyroid cancer had higher serum Cu levels than healthy controls. However, consistent with our results, the Polish studies did not find higher serum Cu levels in patients with thyroid cancer relative to their controls. A 2004 study from Kuwait also reported that serum Cu levels in thyroid cancer patients were not different from healthy controls and rose significantly after thyroidectomy.[22] Hence, ethnicity can influence serum Cu levels. Normally, Cu is actively recycled in the digestive tract, body fluids and tissues, and is mainly excreted from the body via bile. Copper levels are primarily controlled by recycling and resorption, and dietary Cu represents only a small proportion of total Cu resorption.[15] Therefore, dietary intake of Cu has an insignificant effect on serum Cu levels and does not need to be controlled.

In the post hoc subgroup analysis of PTC, we found significantly higher serum Cu levels in patients with blood vessel invasion. Cu is postulated to be a potent stimulator of tumor growth through its activation of angiogenic factors.[29] Nevertheless, the median serum Cu levels were not statistically significant in the presence of adverse features such as positive capsular invasion, extrathyroidal extension, lymph node involvement, distant metastases and high stage. Although, this incidental finding is less likely to demonstrate a relationship between serum Cu levels and the aggressiveness of PTC, the association between serum Cu levels and angiogenesis in thyroid cancer requires further exploration. Furthermore, the additional comparison of serum Cu in each subgroup of

TABLE 3. Serum copper levels in healthy subjects.

Studies	Year	Country	Measurement technique	N	Sex	Serum copper levels (mean ± SD; μg/ml)
Maneeprasopchoke et al.	2022	Thailand	AAS	100	Female	0.97 (0.80, 1.11) †
Zhang et al.[24]	2009	China	AAS	890	Female	1.01 ± 0.24
Baltaci et al.[21]	2017	Turkey	AES	15	Female	0.74 ± 0.24
Przybylik-Mazurek et al.[28]	2011	Poland	AAS	20	All	1.11 ± 0.19
Kosova et al.[20]	2012	Turkey	AAS	37	All	1.06 ± 0.11
Leung et al.[19]	1996	China	AES	50	All	0.74 ± 0.19
Kucharzewski et al.[18]	2003	Poland	TRXRF	50	All	0.69 ± 0.06

† Median and interquartile range

Abbreviations: AAS, atomic absorption spectrometry; AES, atomic emission spectrometry; TRXRF, total reflection fluorescence

PTC with nodular goiter to that of the healthy population showed no significant differences. Thus, we cannot infer that high serum Cu can be used to prognosticate the invasiveness of PTC.

The potential relationship between serum Cu levels and gene mutation in humans has not been studied. Since copper regulates the function of follicular cells, aberrant levels of serum Cu may be associated with molecular alterations. Currently, there are several genetic mutations reported in thyroid cancer and the $BRAF^{V600E}$ mutation is the most common biomarker for PTC. Brady et al. demonstrated that Cu is required for BRAF signaling and tumorigenesis. A reduction in serum Cu levels caused the size of $BRAF^{V600E}$-driven melanomas to decrease in laboratory animals.[30] A recent investigation by Baldari et al. also found that Cu-chelating agents reduced the proliferation, survival, and migration of human colon cancer cells carrying the $BRAF^{V600E}$ mutation.[31] We hypothesized that in thyroid cancer, the $BRAF^{V600E}$ mutation would be associated with increased serum Cu levels, as is seen in melanoma and colon cancer. Besides, no significant elevation of serum Cu levels was observed in PTC with $BRAF^{V600E}$ mutation, suggesting that serum copper does not indicate the severity of PTC.

To our knowledge, this is the first study to report serum Cu levels in terms of histopathological aggressiveness, risk of recurrence, staging, and molecular status in PTC. In addition, we screened all healthy subjects with ultrasonography of the thyroid gland to avoid unexpected thyroid nodules in the control group. This ensured that the reference serum Cu values of the healthy Thai women were reliable and could be used as a standard for further studies. On the other hand, our analyses suggest that serum Cu levels are not appropriate for diagnostic and the prognosis of PTC.

Our study has some limitations. Our subjects were Thai women with PTC and nodular goiter. We did not address the role of serum Cu levels in men, other types of thyroid cancer, and in advanced-stage thyroid cancers such as tracheal or recurrent laryngeal nerve invasion. In addition to Cu, other essential trace elements such as selenium, cadmium, zinc were likely involved in the carcinogenesis of thyroid.[32] The expand study of multiple trace element levels and their ratios would give more informative data about the relation between trace elements and thyroid cancer.

CONCLUSION

The role of serum Cu in the pathogenesis and prognosis of thyroid tumors remains unclear. Serum Cu levels in patients with PTC and nodular goiter were not different, and also were not different from the reference group. However, serum Cu was associated with only one pattern of histopathologically aggressive PTC- Blood vessel invasion. Therefore, serum Cu levels cannot be used as an assistive tool for diagnosis and the prognosis of PTC.

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Conflicts of interest: The authors declare that they do not have any conflict of interest regarding this research.

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Telehealth Service for Patients Receiving Continuous Ambulatory Peritoneal Dialysis: A Pilot Study

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ABSTRACT

Objective: This study aimed to assess the feasibility and acceptability of delivering a telehealth intervention, called PD Telehealth, for improving health outcomes among Thai patients receiving continuous ambulatory peritoneal dialysis (CAPD).

Materials and Methods: This pilot study enrolled 104 patients receiving CAPD, who were randomly classified into two groups: PD Telehealth group (PD Telehealth service plus usual care; n = 52) and usual care group (usual care only; n = 52). The 6-month telehealth service was provided to participants to deliver self-management support and telemonitoring while they received home-based treatment. Further, the repeated measures mixed analysis of variance test was used to assess health outcomes at baseline, 3 months, and 6 months. Additionally, feasibility and acceptability were assessed.

Results: Notably, the measured baseline characteristics of the two groups were not different. Regarding quality of life, a significant interaction effect was observed on two domains of the 36-Item Short Form Survey-general health (p = 0.002) and reported health transition (p = 0.018). However, self-management and clinical outcomes did not differ significantly between the two groups over 6 months. The PD Telehealth group demonstrated high acceptability and feasibility of the application.

Conclusion: The PD Telehealth service has been demonstrated to be feasible and acceptable for providing care to patients receiving CAPD. However, there were no significant differences in the main outcomes of the study. Further research studies involving a larger and more diverse sample population and conducted over a longer period are needed.

Keywords: PD Telehealth; peritoneal dialysis; telehealth (Siriraj Med J 2023; 75: 46-54)

INTRODUCTION

In 2008, the Thai government implemented the PD First policy to increase the access to dialysis treatment among Thai citizens. Under universal health coverage, people can access dialysis treatment for free in the form of continuous ambulatory peritoneal dialysis (CAPD) as the first dialysis modality unless contraindicated.[1] Notably, CAPD has fewer technical requirements and lesser need for medical staff,[2] and it is more cost-effective.[3] Therefore, the number of patients receiving CAPD in Thailand has increased. According to the Thai Renal Replacement Therapy registry, the number of patients receiving PD has increased from 5,133 in 2009 to 34,467 in 2020.[4] Of all patients receiving PD in Thailand, 97% were receiving CAPD, and only 3% were receiving automated PD.[1]

The challenges associated with CAPD care include complication management and prevention, technique failure intervention, long-term CAPD sustenance, and

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quality of life (QOL) improvement. However, currently available healthcare services for CAPD do not support patients and their families to effectively and safely perform dialysis at home. Thus, a well-designed healthcare service is required to support home-based treatment and provide effective care to this population.

Telehealth was developed to promote PD regimen adherence and ensure continuous safety and effectiveness.[5,6] Although evidence suggests improved patient outcomes by telehealth programs among those receiving PD,[7-9] in Thailand, there is a lack of tailored telehealth to support patients receiving CAPD. Therefore, PD Telehealth was developed for Thai patients receiving CAPD as well as caregivers and healthcare professionals to provide self-management support, monitor home dialysis, and enhance patient health and professional communication as required by all key stakeholders.[10] PD Telehealth aimed to transform its current care delivery model, support home-based treatment, and improve health outcomes in patients receiving CAPD. This study reports the results of a pilot study designed to assess the effects of PD Telehealth on self-management behaviors, QOL, and clinical outcomes and to evaluate the feasibility and acceptability of PD Telehealth in Thai contexts.

MATERIALS AND METHODS

Study design and participants

This two parallel-group randomized controlled pilot study was conducted at Banphaeo Dialysis Center, Bangkok, Thailand (Thai Clinical Trials Registry identification number: TCTR20221121004). Eligibility criteria were as follows: patients aged >18 years, those who had received CAPD for at least 3 months and were actively undergoing dialysis procedures, those who had no prior peritonitis in the last 3 months, and those using a smartphone or tablet with an android operating system of ≥version 6 and internet access. Patients who were bedridden or had cognitive impairment, psychiatric illness, or serious illness/condition were excluded from the study. Notably, participants who discontinued CAPD treatment or were referred to other PD clinics were withdrawn from the study sample. The sample size was calculated using power analysis. The required sample size calculation for repeated measures mixed analysis of variance (ANOVA) test indicated a sample of 104 participants (52 per group), with a power (p) of 0.80, significance level (α) of 0.05, medium effect size (f) of 0.25,[11] and attrition rate of 20%.

The study objectives, protocol, benefits, risks, privacy, and confidentiality were explained to all eligible participants. The participants were then randomly assigned to group receiving PD Telehealth plus usual care or that receiving usual care alone over 6 months after obtaining their informed consent and preforming the baseline assessment (Fig 1). They were evaluated using a questionnaire at 3 and 6 months, and their health information was obtained from medical records.

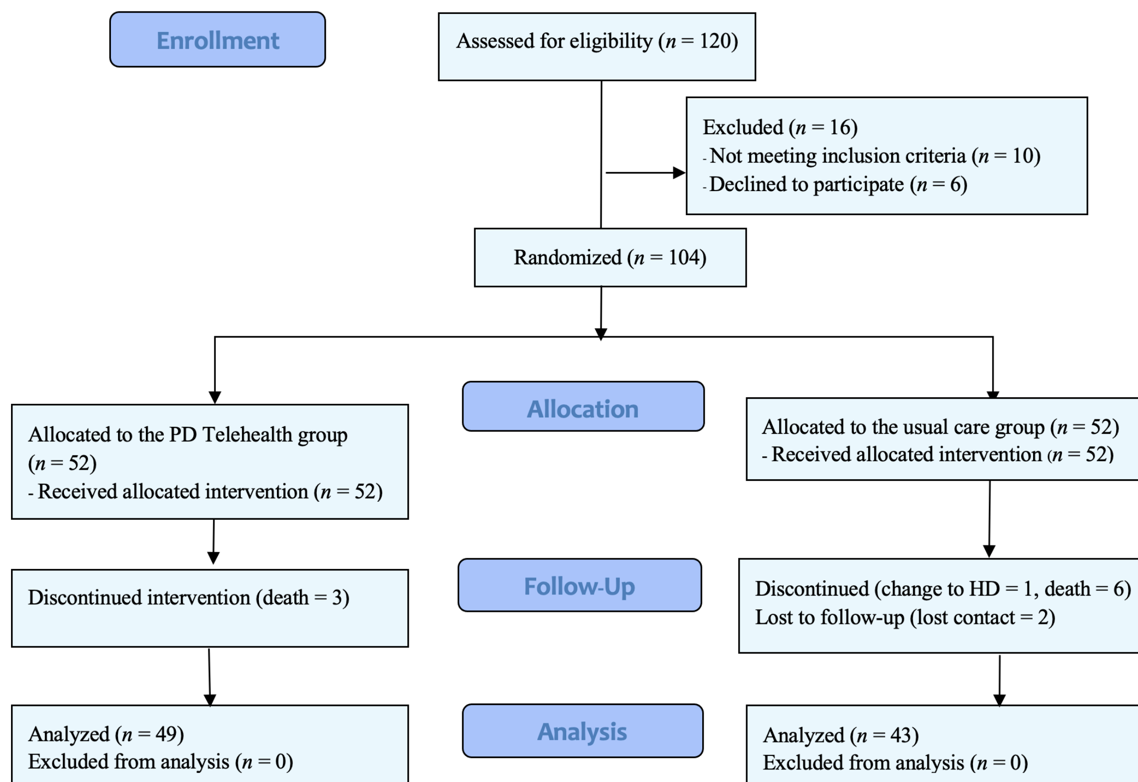

Fig 1. Flow diagram of participant eligibility and randomization process

Intervention

PD Telehealth is a service operated through a mobile application (patient side) and a web application (dialysis center side) called PD Easy. It was developed by a multidisciplinary team based on a user-centered approach. Both applications comprise multiple features to serve the needs of patients, caregivers, and healthcare professionals.[10] These features were linked using the central database and processing unit at the server.

The patient-side mobile application included eight core functions: (a) daily health and dialysis records, (b) information, (c) health advice, (d) reminders, (e) health alerts, (f) social forum, (g) news and knowledge management, and (h) contacts (Fig 2.1). The participants in the intervention group installed the application on their smartphone or tablet and were trained about its use. They were instructed to send the daily dialysis records and health-related information to the dialysis center. They were notified when the recorded data exceeded the set value. They could review PD-related resources using video clips and text-based materials. In addition, they were informed about follow-up and treatment appointments at the clinic through personal health alerts and reminders. The social forum allowed participants to share and learn from each other. Participants' contacts were used to remotely connect with healthcare providers, which potentially reduced patient visits to the clinic; moreover, participants could upload photos of, for example, exit site and dialysis fluid and contact healthcare providers for advice via the chat box. However, participants were informed that the data they sent would be checked regularly but not in real time. They had to call the healthcare providers for urgent or immediate medical assistance because PD Telehealth was not designed to support emergency services.

A web application was used to manage the PD Telehealth service at the dialysis center (Fig 2.2). Healthcare providers monitored patients by reviewing their health records through a secure password-protected web application. The clinic's health team, including a PD nurse, a dietician, and two public health technical officers, regularly reviewed alerts based on their assigned responsibilities. The team was notified via the web application when participants entered the alert zone, and the team coordinated with other healthcare providers as needed to provide care. Appropriate contacts and follow-up were established through the application, telephone call, and home or clinic visit as required.

Outcome measurement

The study outcomes included self-management (using the PD Self-Management Scale [PDSMS]),[12] QOL (using the Choice Health Experience Questionnaire [CHEQ] Thai version),[13] and clinical outcomes (obtained from patient's medical records). Furthermore, the feasibility and acceptability of PD Telehealth services among Thai patients receiving CAPD were evaluated. Notably, the feasibility was determined by application usage (obtained from Google Analytics) and retention rates, and the acceptability was assessed using the Perceived Benefits of the PD Telehealth Questionnaire developed by the research team.

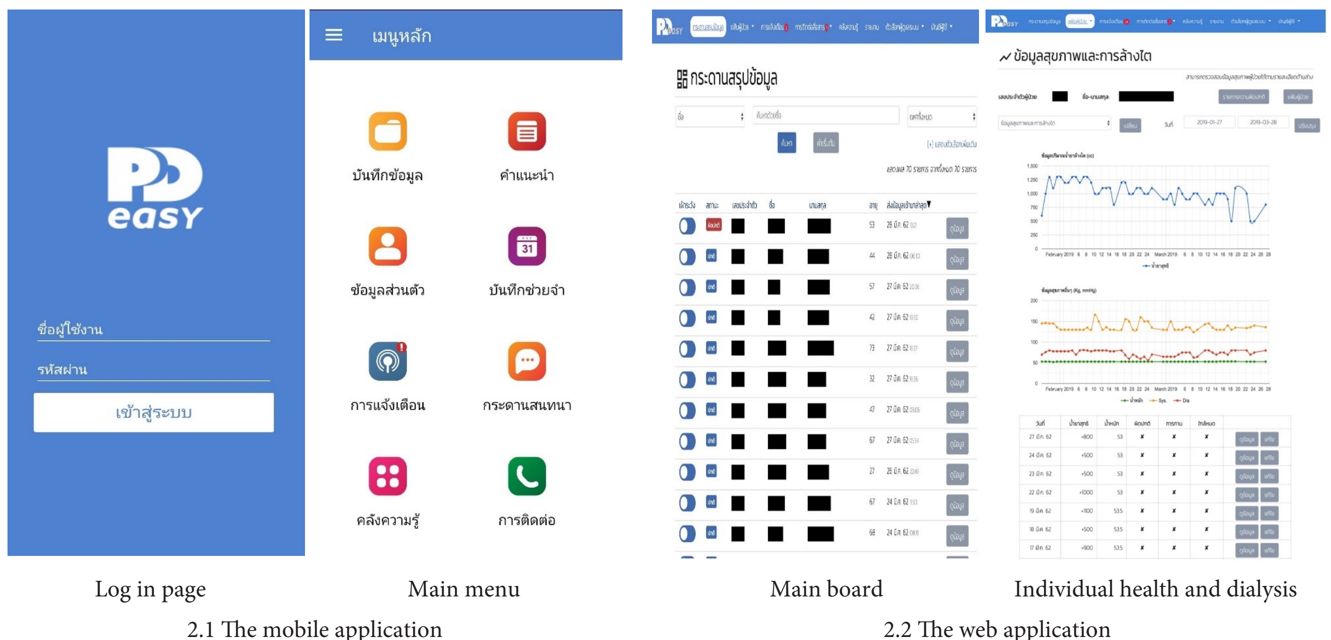

Fig 2. Sample screenshots of PD Telehealth

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL). Descriptive statistical analysis was used to summarize patient characteristics, feasibility, and acceptability. The chi-square, Fisher's exact, or independent t test was used to compare baseline characteristics between the two groups. Repeated measures mixed ANOVA test was used to compare self-management, QOL, and clinical outcomes between the two groups at baseline, 3 months, and 6 months. Furthermore, intention-to-treat analysis was used for study analysis.

RESULTS

Patient characteristics

Overall, 104 participants completed the pretest. Of these, 3 and 9 from the intervention and control groups withdrew from the study, respectively. In contrast, 92 participants completed the post-test at the end of the study (49 and 43 from the experimental and control groups, respectively). Furthermore, there was no difference between the two groups at baseline (Table 1).

Self-management

Self-management was assessed using PDSMS, and there was no difference in self-management in the overall scores or each of the five domains between the two groups at any time point (Table 2).

QOL

In this study, the QOL was determined using the CHEQ Thai version, which included the general health 36-Item Short Form Survey (SF-36) and end-stage kidney disease (ESKD)-specific domains. Notably, there was a significant interaction effect between groups and time on two domains of the 36-Item Short Form Survey—general health (p = 0.002) and reported health transition (p = 0.018). There was no significant difference between the two groups in the ESKD domains throughout the study period (Table 3).

Clinical outcomes

Clinical outcomes (i.e., hematocrit, albumin, and phosphate levels) were measured at baseline, 3 months, and 6 months. There was no significant difference at any time point in this study (Table 4). Additionally, no significant difference in other clinical outcomes, including overhydration (OH) value and peritonitis, exit site infection, and mortality rates, was found between the two groups.

Feasibility of PD Telehealth

Overall, 52 participants received the intervention (PD Telehealth); of these, 49 (94.2%) completed the study, and 3 (5.8%) did not complete the planned follow-up because of death. Notably, PD Telehealth adherence was high. In the intervention group, 70.2% participants used

TABLE 1. Participant characteristics at baseline (n = 104).

Characteristics	Experimental group (n = 52) n (%) or mean ± SD	Control group (n = 52) n (%) or mean ± SD	*P* value
Age (years)	52.8 ± 13.9	51.7 ± 11.5	0.524[c]
Gender (male)	31 (59.6)	29 (55.8)	0.691[a]
Marital status (married)	30 (57.7)	29 (55.8)	0.749[a]
Income (<15,000/month)	36 (69.2)	28 (53.8)	0.362[b]
Education (primary school)	24 (46.2)	19 (36.5)	0.714[a]
Employment status (unemployed)	30 (57.7)	26 (50.0)	0.241[a]
Healthcare scheme (universal coverage)	44 (84.6)	43 (82.7)	0.798[b]
Duration of dialysis (months)	32.5 ± 23.7	35.4 ± 25.6	0.362[c]

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

TABLE 2. Self-management at baseline, 3 months, and 6 months between the two groups.

Self-management		Intervention		Control		Repeated measures*		
		n	Mean ± SD	n	Mean ± SD	Within times, *p*	Between groups, *p*	Interaction effect, *p*
Overall score[b]	Baseline	52	80.9 ± 10.3	52	83.0 ± 8.3	0.765	0.795	0.772
	3 months	50	81.5 ± 9.0	51	82.8 ± 9.5			
	6 months	49	80.8 ± 8.9	43	81.2 ± 10.2			
Dialysis[a]	Baseline	52	36.0 ± 4.1	52	36.8 ± 3.6	0.616	0.621	0.455
	3 months	50	36.5 ± 3.7	51	36.6 ± 4.1			
	6 months	49	36.3 ± 3.7	43	36.1 ± 4.5			
Diet and fluid intake[a]	Baseline	52	12.4 ± 2.4	52	12.1 ± 2.6	0.800	0.961	0.122
	3 months	50	12.1 ± 2.3	51	12.5 ± 2.5			
	6 months	49	12.3 ± 2.0	43	11.9 ± 2.4			
Medication[b]	Baseline	52	10.1 ± 2.4	52	10.8 ± 1.5	0.837	0.794	0.820
	3 months	50	10.5 ± 1.4	51	10.6 ± 1.5			
	6 months	49	10.1 ± 2.1	43	10.7 ± 1.5			
Self-assessment[a]	Baseline	52	13.0 ± 2.1	52	12.8 ± 2.1	0.357	0.866	0.102
	3 months	50	12.5 ± 2.4	51	13.1 ± 2.0			
	6 months	49	12.7 ± 2.4	43	12.5 ± 1.9			
Complication management[a]	Baseline	52	9.3 ± 2.2	52	9.6 ± 2.2	0.463	0.709	0.903
	3 months	50	9.9 ± 2.0	51	9.8 ± 2.0			
	6 months	49	9.6 ± 2.1	43	9.7 ± 1.7			

[a]Sphericity assumed. [b]Within-group effects by Greenhouse–Geisser test.

the application more than thrice a week, 55.3% used it daily to report dialysis and health-related information, and 4.3% used it once a month. Over a 6-month period, the top three most frequently used features were personal health and dialysis records (5,788 times), social forums (1,092 times), and personal health alerts (814 times).

PD Telehealth acceptability

At the end of the study, the PD Telehealth group rated the mobile application as useful (8.73 ± 1.70). The top three advantages were health problem management (8.71 ± 1.59), health information provision (8.67 ± 1.77), and home healthcare support (8.59 ± 1.80; Table 5).

DISCUSSION

To the best of our knowledge, this is the first pilot study in Thailand to develop a telehealth service for CAPD. The efficacy of PD Telehealth demonstrated fewer opportunities to improve the measured outcomes. In this study, participants' self-management scores were good at baseline and throughout all follow-up periods. Based on the inclusion criteria, all participants were required to actively perform CAPD themselves, indicating that they were able to manage their own care. Therefore, the mobile application in CAPD care in this study did not contribute to changes in self-management.

In terms of QOL, the results showed that the SF-36 general health and reported health transition scores improved in the PD Telehealth group after 3 and 6 months, respectively, whereas these scores declined in the control group. Notably, our study results are consistent with previous systematic reviews by Cartwright et al.,[8] Yang et al.,[6] and Lunney et al.,[5] which reported that some domains of QOL were significantly improved in patients receiving PD and chronic dialysis after telehealth interventions. Our telehealth service provided remote monitoring, supported home-based treatment, and fulfilled the healthcare needs of such patients. However, the effects were small; therefore, its effects on QOL should be investigated further in Thai patients receiving CAPD.

TABLE 3. Quality of life at baseline, 3 months, and 6 months between the two groups.

QOL	Group	Treatment time Baseline	3 months	6 months	Repeated measures Within times, *p*	Between groups, *p*	Interaction effect, *p*
SF-36							
PF[a]	Intervention	51.9 ± 24.6	56.4 ± 24.1	59.1 ± 23.9	0.479	0.847	0.234
	Control	57.9 ± 28.1	52.2 ± 28.9	57.9 ± 23.8			
RP[a]	Intervention	48.1 ± 41.1	57.0 ± 41.7	47.4 ± 44.0	0.694	0.353	0.168
	Control	46.1 ± 43.0	41.7 ± 41.7	45.3 ± 43.7			
BP[a]	Intervention	67.3 ± 23.9	69.6 ± 23.3	68.3 ± 22.7	0.637	0.322	0.842
	Control	65.5 ± 25.2	65.6 ± 28.3	63.3 ± 25.6			
MH[a]	Intervention	63.8 ± 10.7	63.6 ± 11.1	62.9 ± 9.4	0.254	0.612	0.857
	Control	69.0 ± 17.3	66.0 ± 15.7	67.0 ± 16.8			
RE[a]	Intervention	61.1 ± 42.4	66.5 ± 43.6	57.1 ± 46.5	0.326	0.383	0.057
	Control	63.5 ± 41.5	48.5 ± 44.5	53.5 ± 44.5			
SF[a]	Intervention	80.0 ± 18.1	77.5 ± 19.8	79.3 ± 23.0	0.890	0.704	0.768
	Control	78.4 ± 22.6	79.0 ± 20.3	77.6 ± 19.6			
VT[a]	Intervention	59.7 ± 14.8	59.7 ± 10.7	60.8 ± 11.2	0.764	0.235	0.865
	Control	58.2 ± 18.8	58.2 ± 18.8	58.2 ± 16.9			
GH[a]	Intervention	54.1 ± 18.8	46.6 ± 18.4	50.8 ± 14.1	0.336	0.149	0.002
	Control	49.1 ± 25.1	47.1 ± 21.4	45.3 ± 20.7			
HT[a]	Intervention	69.7 ± 25.4	65.3 ± 25.9	74.0 ± 22.8	0.882	0.764	0.018
	Control	67.8 ± 22.9	70.0 ± 26.2	65.7 ± 25.6			
ESKD							
CRP[a]	Intervention	78.8 ± 25.9	74.5 ± 26.5	75.5 ± 24.2	0.463	0.240	0.791
	Control	84.6 ± 19.9	82.8 ± 26.4	80.2 ± 22.2			
CMH[a]	Intervention	74.8 ± 19.3	74.0 ± 15.3	72.6 ± 17.8	0.509	0.421	0.396
	Control	71.6 ± 20.6	74.6 ± 20.1	72.6 ± 17.2			
CGH[a]	Intervention	59.2 ± 31.7	59.6 ± 28.1	63.3 ± 24.3	0.900	0.861	0.579
	Control	66.9 ± 34.0	63.5 ± 33.8	60.9 ± 33.5			
FRE[b]	Intervention	55.6 ± 26.5	54.6 ± 29.9	58.8 ± 23.9	0.497	0.391	0.755
	Control	62.3 ± 24.0	64.6 ± 29.8	62.3 ± 25.4			
TRV[a]	Intervention	73.6 ± 25.9	71.8 ± 30.2	70.4 ± 26.4	0.453	0.747	0.280
	Control	74.5 ± 29.5	79.7 ± 23.4	73.2 ± 26.1			
CF[a]	Intervention	64.5 ± 19.7	65.8 ± 24.0	66.3 ± 21.5	0.481	0.785	0.692
	Control	67.9 ± 20.1	68.3 ± 21.8	65.7 ± 18.5			
FIN[a]	Intervention	75.0 ± 27.6	72.9 ± 28.6	71.9 ± 27.3	0.654	0.774	0.961
	Control	75.0 ± 27.6	76.0 ± 26.8	74.4 ± 31.6			
DR[a]	Intervention	61.1 ± 24.5	60.4 ± 26.7	61.7 ± 25.6	0.332	0.439	0.254
	Control	64.4 ± 31.4	62.5 ± 30.5	69.8 ± 24.1			
REC[a]	Intervention	65.4 ± 23.8	67.7 ± 25.8	64.6 ± 25.2	0.534	0.989	0.634
	Control	71.6 ± 32.5	66.1 ± 28.9	66.3 ± 25.5			

TABLE 3. Quality of life at baseline, 3 months, and 6 months between the two groups. (Continued)

QOL	Group	Treatment time			Repeated measures		
		Baseline	3 months	6 months	Within times, *p*	Between groups, *p*	Interaction effect, *p*
ESKD							
WRK[a]	Intervention	58.6 ± 38.9	55.2 ± 38.9	58.2 ± 37.6	0.264	0.018	0.627
	Control	78.8 ± 29.4	68.7 ± 37.0	66.3 ± 35.3			
BI[b]	Intervention	81.7 ± 21.6	84.0 ± 21.9	80.7 ± 23.8	0.518	0.028	0.980
	Control	88.5 ± 20.7	90.5 ± 16.7	88.4 ± 17.5			
SYM[a]	Intervention	20.3 ± 12.1	20.1 ± 13.2	18.9 ± 11.3	0.631	0.100	0.951
	Control	23.0 ± 14.3	21.5 ± 14.5	23.2 ± 13.3			
SEX[b]	Intervention	79.6 ± 29.8	80.2 ± 27.1	74.0 ± 28.3	<0.001	0.613	0.125
	Control	85.1 ± 25.0	76.8 ± 31.9	77.2 ± 26.1			
SLP[a]	Intervention	46.7 ± 16.3	46.9 ± 16.5	48.3 ± 16.4	0.482	0.366	0.307
	Control	44.1 ± 18.1	48.4 ± 21.5	49.5 ± 20.8			
DAC[a]	Intervention	80.2 ± 16.5	83.6 ± 16.0	78.7 ± 22.7	0.002	0.204	0.594
	Control	85.9 ± 19.1	88.0 ± 16.7	80.6 ± 20.6			
QOL[a]	Intervention	66.9 ± 19.9	64.6 ± 19.5	66.1 ± 18.9	0.101	0.588	0.733
	Control	64.6 ± 21.4	60.8 ± 16.4	62.9 ± 18.9			

Abbreviations: BI, body image; BP, bodily pain; CF, cognitive function; CGH, CHEQ general health; CMH, CHEQ mental health; CRP, CHEQ role physical; DAC, dialysis access-related problems; DR, dietary restrictions; FIN, finances; FRE, freedom; GH, general health; HT, reported health transition; MH, mental health; PF, physical functioning; QOL, quality of life; RE, role emotional; REC, recreation; RP, role physical; SEX, sexual functioning; SF, social functioning; SLP, sleep; SYM, symptoms; TRV, travel restrictions; VT, vitality; WRK, work.
[a]Sphericity assumed. [b]Within-group effects by Greenhouse–Geisser test.

TABLE 4. Clinical outcomes at baseline, 3 months, and 6 months between the two groups

Items	Group	Treatment time			Repeated measures		
		Baseline	3 months	6 months	Within times, *p*	Between groups, *p*	Interaction effect, *p*
Hematocrit[b]	Intervention	30.2 ± 6.2	30.1 ± 6.0	29.7 ± 6.3	0.320	0.681	0.386
	Control	31.3 ± 6.3	29.5 ± 6.6	30.6 ± 6.7			
Albumin[a]	Intervention	3.3 ± 0.5	3.4 ± 0.6	3.3 ± 0.5	0.791	0.809	0.051
	Control	3.3 ± 0.6	3.2 ± 0.6	3.3 ± 0.6			
Phosphate[b]	Intervention	4.3 ± 1.6	4.6 ± 1.6	4.5 ± 1.5	0.915	0.963	0.080
	Control	4.8 ± 2.0	4.5 ± 1.6	4.7 ± 1.7			

[a]Sphericity assumed.
[b]Within-group effects by Greenhouse–Geisser test.

TABLE 5. Perceived benefits of the PD Telehealth service (n = 49).

PD Telehealth usefulness	n	Possible range	Actual range	Mean	SD
Overall	49	0–10	2–10	8.73	1.70
Managing health problems more appropriately	49	0–10	2–10	8.71	1.59
Receiving useful health information	49	0–10	2–10	8.67	1.77
Taking care own health more appropriately	49	0–10	2–10	8.59	1.80
Motivating to take care of oneself	49	0–10	2–10	8.53	1.73
More access to health information	49	0–10	2–10	8.49	1.82
Enhancing learning	48	0–10	2–10	8.42	1.92
Reducing anxiety related to health	49	0–10	2–10	8.39	1.80
More access to healthcare services	49	0–10	2–10	8.35	1.95
Being assessed and monitored	49	0–10	2–10	8.31	1.88
Receiving more healthcare	49	0–10	2–10	8.20	1.87

Clinical results revealed no statistically significant changes in laboratory measures. Moreover, no statistically significant differences were found between the two groups, although the control group had a higher number of participants who had peritonitis and died during the study. These results were consistent with the findings of a systematic review on the impact of telehealth interventions in patients with ESKD, including PD and HD.[5] More effective strategies and a longer period may be required to determine clinical outcome changes caused by the PD Telehealth service.

The intervention group's application use and retention rates were accepted in terms of feasibility and acceptability. Only two participants, who rarely used the mobile application, rated its benefits as minor. PD Telehealth development was focused on those with low computer skill levels and vision problems because most patients receiving CAPD under universal coverage in Thailand are in their middle and late adulthood. Hence, most participants, particularly the older adults, reported no difficulties in using the application. The results of this study demonstrated that this platform is acceptable for patients receiving CAPD. All available functions were used, with high-level benefits reported. The main features of PD Telehealth were designed to meet the needs of key stakeholders to solve their problems related to health service.[10] Therefore, PD Telehealth can be used in Thai contexts. Some findings of this study are consistent with those reported in pilot studies, which revealed that telehealth programs are a viable solution for monitoring and optimizing the care of patients receiving PD.[14,15]

Our results underscore the potential of telehealth services for the delivery of CAPD care in Thailand. This platform is intended for use by healthcare providers in PD centers and eventually as part of their routine practice. The service can be used to engage patients with CAPD in their own care, as proposed by the World Kidney Day Steering Committee.[16] However, more research is needed to demonstrate the ability of PD Telehealth to improve patient outcomes and the quality of healthcare. A larger longer-term controlled study is needed to confirm the effectiveness of PD Telehealth in patients receiving CAPD.

This study has some limitations. The sample size was small and the study duration was short; thus, the differences in health outcomes could not be observed. Furthermore, this study was limited by its single-center nature and sample population size as the participants were recruited from only one dialysis center in Bangkok, Thailand.

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Ethics Statement: The present study was approved by the Institution Review Broad, Faculty of Nursing Mahidol University (COA: No. IRB-NS2018/455.1307).

Conflict of interest: All authors declare that they have no personal or professional conflict of interest.

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Recurrent Urinary Tract Infection in Women from a Urologist's Perspective

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ABSTRACT

Urinary tract infection (UTI) referred to microbial invasion of the urinary tract system, typically due to bacteria. UTI is more common in women than men, which is thought to be due to differences in lower urinary tract anatomy. Making a diagnosis of UTI begins with the presence of clinical symptoms consistent with either pyelonephritis and cystitis. When pyelonephritis symptoms are present, it is usually associated with bacterial infection, while the symptoms of clinical cystitis may or may not be caused by infection. As both urologic and non-urologic conditions can produce the clinical symptoms of cystitis, diagnosis of UTI requires both pyuria and bacteriuria on urine examination. Complicated UTI is when the infection is associated with either host or bacterial factors that increase the chance of reinfection and decrease treatment efficacy, such as altered organism virulence, immunocompromise, or urinary tract abnormalities. The urologist's primary role in UTI management is to evaluate for such urinary tract abnormalities and, if needed, resolve those conditions to prevent recurrent infection. This review will describe the urologists' evaluation and management of complicated and recurrent UTI and inform physician about the urinary tract abnormalities that can predispose to recurrent UTI.

Keywords: Cystitis; urinary tract infection; urologic condition; investigation (Siriraj Med J 2023; 75: 55-61)

INTRODUCTION

Urinary tract infection (UTI) is microbial invasion, typically bacterial, of the urinary tract. The global number of individuals with UTIs in 2019 is more than 404.6 million, with an incidence that is higher in women than in men.[1] In the United States, 10.8% of women self-reported that they had at least one presumed UTI during the past 12 months.[2] Several non-infectious genitourinary tract conditions can present with the same symptoms as UTI, so the diagnosis of UTI relies upon the combination of clinical symptoms consistent with pyelonephritis or cystitis accompanied by pyuria on urine analysis (UA) and significant bacteriuria on urine culture (UC). Importantly, in a small number of cases, recurrent episodes may suggest the presence of factors that increase the chance of reinfection or decrease treatment efficacy, factors which distinguish uncomplicated from complicated UTI. Three main factors, including organism virulence, host immune system, and urinary tract abnormality, must be considered. To prevent reinfection, these factors need to be identified and properly treated. Collaboration among health care providers, especially infectious disease specialists and urologists are needed to cure patients with complicated UTI. From the urologist's prespective, a wide range of genitourinary tract conditions can present with the clinical syndromes of UTI; as these symptoms may or may not be associated with true bacterial infection, lack

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of complete evaluation can frequently result in delayed or missed diagnoses of underlying conditions. Therefore, this review would like to guide urologists in how to evaluate and diagnose complicated UTI, particularly in the context of genitourinary tract abnormalities, as well as inform physicians about preventive strategy for patients with uncorrectable conditions.

How to diagnose UTI?

Basically, there are two clinical syndromes of UTI: pyelonephritis when the infection occurs in the upper urinary tract and cystitis for infection of the lower urinary tract. The symptoms of pyelonephritis are fever, flank pain, and/or chills, while the symptoms of cystitis are dysuria, frequency, urgency, urgency urinary incontinence, hematuria, and/or suprapubic pain. A meta-analysis examining the accuracy and precision of factors derived from the history and physical examination for UTI diagnosis in women showed that four symptoms: dysuria, frequency, hematuria, and back pain with costovertebral angle tenderness on exam significantly increased the probability of UTI. When dysuria and frequency were combined without vaginal discharge or irritation, the probability of UTI was greater than 90%.[3] However, while these clinical syndromes are most commonly linked to infections, non-infectious conditions, such as malignancy, may sometimes present with similar symptoms. To diagnose UTI correctly, urine examination including urine analysis (UA) and urine culture (UC) are essential. To be consistent with a diagnosis of UTI, UA should demonstrate pyuria, defined as the presence of ≥ 3 white blood cells per high power field of unspun urine or ≥ 10 white blood cell per cubic millimeter[4] *and* significant bacteriuria. Pyuria without bacteriuria, termed sterile pyuria, may indicate urologic malignancy, urolithiasis, or genitourinary tract tuberculosis. It is also important to note that the presence of bacteriuria on UA is not always indicative of an infection. Both colonization and contamination can present with significant bacteriuria, so symptoms are an important component of the diagnosis of UTI.

Urine culture (UC) is still considered the gold standard investigation for diagnosis of bacterial UTI; but there is substantial debate about the appropriate threshold of colony forming units (CFU) count. Previously, a cut-off value of 10^5 CFU/ml was widely accepted as significant bacteriuria consistent with infection. However, in patients with convince ing signs and symptoms of infection, a lower threshold of 10^2 CFU/ml is reasonable.[5] In addition, standard clinical urine culture does not detect all bacteria equally, preferentially detecting aerobic bacteria. If anaerobic bacterial or mycobacterial infections are suspected, special staining, culture techniques, or molecular diagnostic approaches, such as polymerase chain reaction (PCR), may be required.

In summary, a diagnosis of UTI requires the combination of the constellation of symptoms seen in UTI clinical syndromes *and* abnormal urine testing demonstrating pyuria and significant bacteriuria.

What is complicated UTI?

To determine appropriate management, UTI should be divided into uncomplicated and complicated subtypes. Complicated UTI is defined as infections associated with factors that increase the chance of reinfection and/or decrease treatment efficacy, such as atypical, highly virulent or drug-resistant organisms, host immune dysregulation, and urinary tract abnormalities.[5] The management of complicated UTI requires thorough evaluation and management of any correctable factors to break the cycle of recurrence.

Recurrent UTI is defined as ≥ 2 episodes within 6 months or ≥ 3 episodes of within 12 months of microbiologically diagnosed UTI. With these infections, symptoms should resolve between episodes prior to diagnosis of another UTI.[5,6] Risk factors for recurrent UTIs differ between age groups. In women age less than 40 years of age, risk factors typically relate to sexual behavior and spermicide use.[7-9] In postmenopausal women, a history of previous UTIs, prior urogenital surgery, symptomatic urinary incontinence, presence of cystocele on vaginal examination, maximal urine flow ≤ 15 ml/sec defined by uroflowmetry, and elevated post-void residuals were associated with a higher risk of recurrent UTI.[10] Therefore, there is a higher likelihood of functional and anatomic urinary tract abnormalities in this older population, which necessitates thorough investigation.

Conditions associated with clinical cystitis

Most episodes of clinical pyelonephritis are bacterial infections, which typically requires hospital admission for evaluation and treatment. In contrast, the clinical syndrome of cystitis is typically managed in the outpatient setting, and thus is not always thoroughly evaluated. Multiple urologic and non-urologic conditions with or without simultaneous bacterial infection can cause recurrent clinical cystitis symptoms. In addition to uncomplicated cystitis, other urologic conditions, such as malignancy, urolithiasis, neurogenic lower urinary tract dysfunction, tuberculosis of urinary tract, ketamine-induced cystitis, radiation-induced cystitis, interstitial cystitis, bladder diverticulum, urethral diverticulum, urethral stricture,

periurethral fibrosis, and functional bladder outlet obstruction, can cause cystitis-like symptoms. Non-urologic conditions can be of a gynecologic (e.g., pelvic organ prolapse, endometriosis, and uterine/cervical/vaginal tumor) or colorectal (colovesical fistula, diverticulitis, and rectal tumor) origin. (Fig 1 & 2) Other rare conditions causing clinical symptoms of cystitis are pelvic congestion syndrome and non-relaxing pelvic floor dysfunction. All conditions can initially be evaluated with careful history and physical examination. If needed, additional investigations can be considered to confirm the suspected diagnosis.

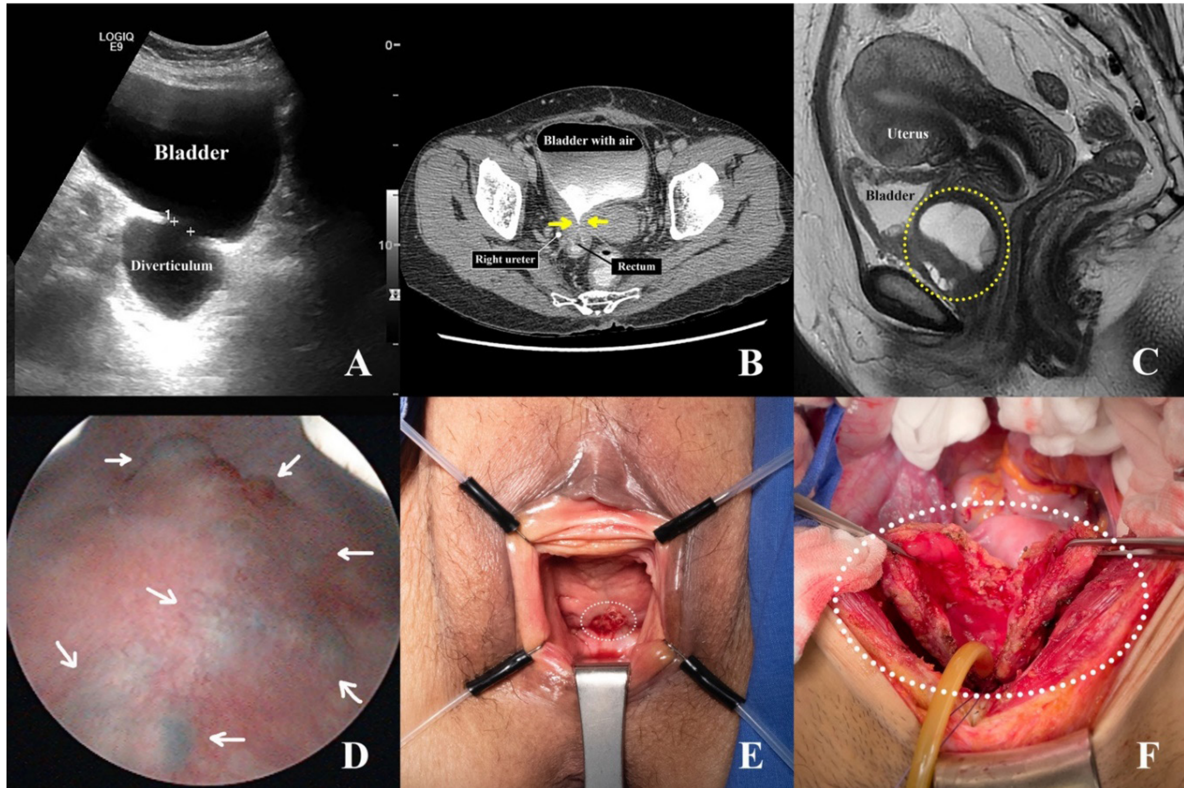


Fig 1. (A) Ultrasonography demonstrates a bladder diverticulum, an outpouching lesion arising from the posterior bladder wall. (B) Computed tomography demonstrates a rectovesical fistula, occurring after low anterior resection for rectal cancer. (Yellow arrows) (C) Magnetic resonance imaging shows a urethral diverticulum, an outpouching lesion arising from and wrapping around the urethra. (Yellow circle) (D) Cystoscopy demonstrated endometriosis, involved posterior bladder wall, seen as tortuous dark-blue lesions. (White arrows) (E) Vaginal examination demonstrated mesh extrusion (white circle) after pelvic organ prolapse repair, causing of vaginal infection and clinical cystitis-like symptoms. (F) Intraoperative findings from abdominal cystotomy demonstrated a severely contracted and inflamed bladder wall (white circle) from ketamine abuse.

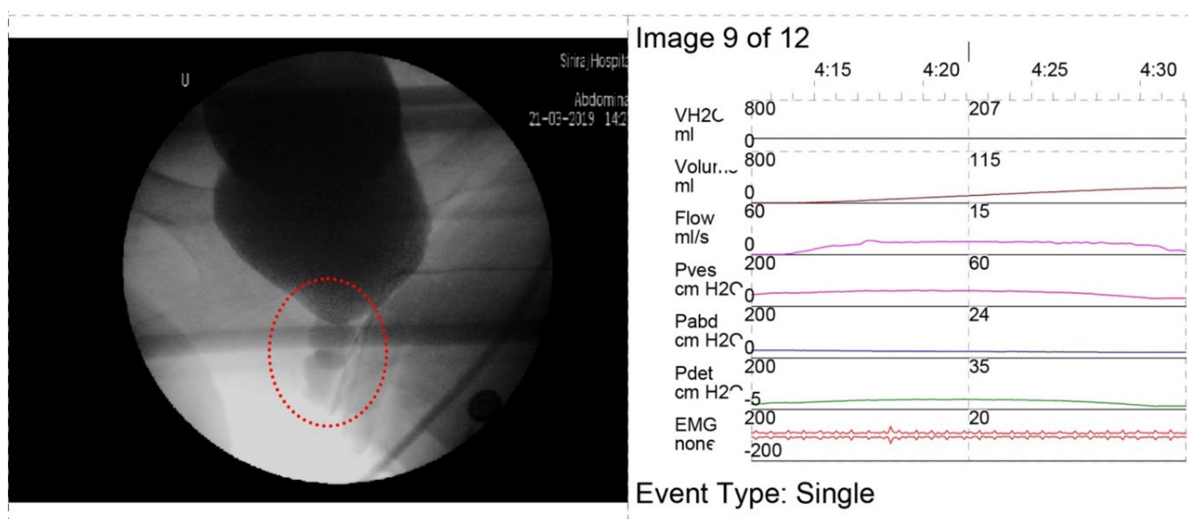
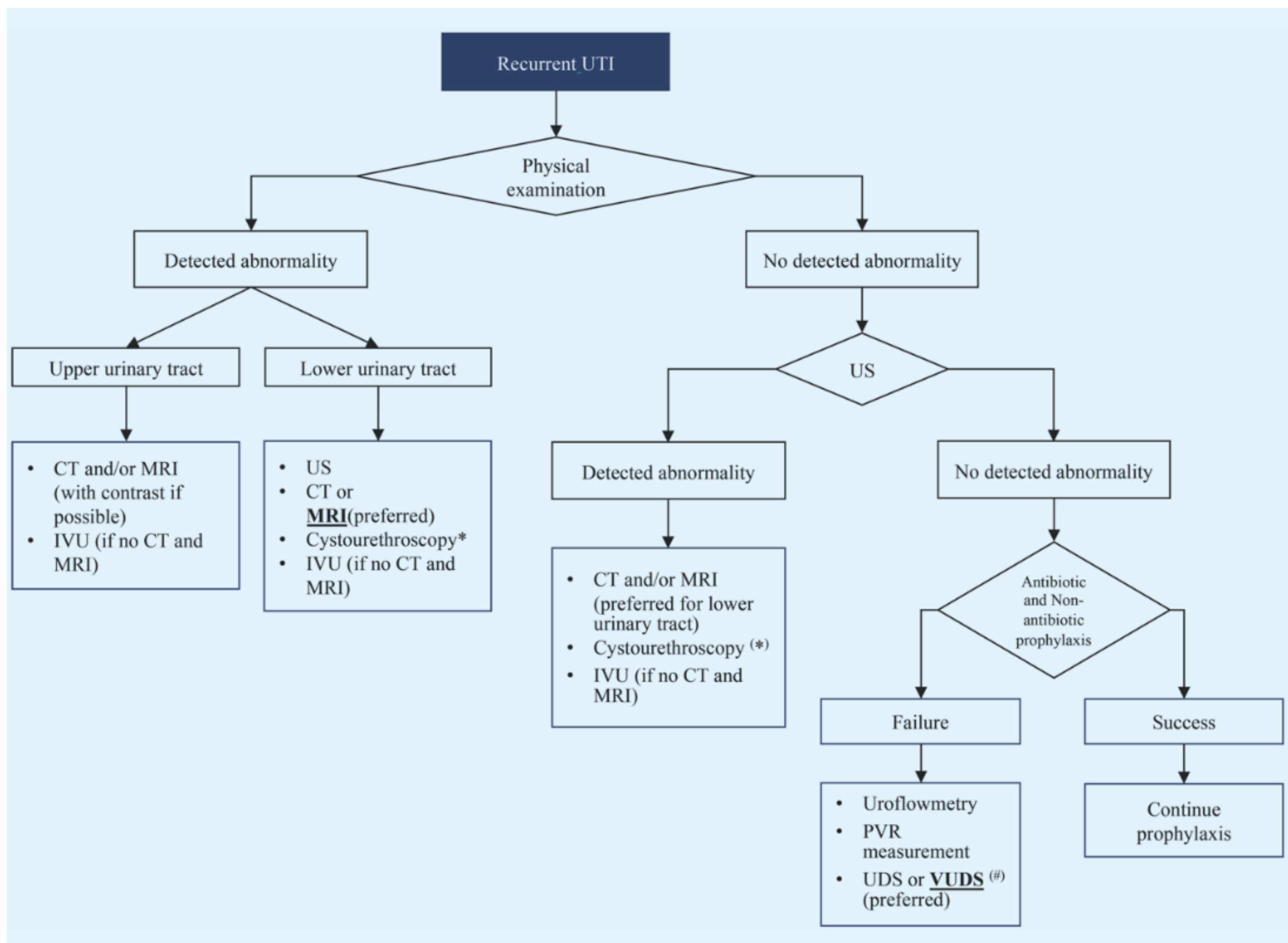


Fig 2. Voiding cystourethrography with concomitant intravesical pressure measurement on videourodynamics demonstrated urethral distortion (Red circle) and high detrusor contraction with low urine flow (Graph) consistent with bladder outlet obstruction after anterior vaginal wall repair.

Investigation for recurrent UTIs

Generally, anatomical evaluation for urinary tract abnormalities can include ultrasonography (US), intravenous urography (IVU), computed tomography (CT), and magnetic resonance imaging (MRI). Multiple studies, however, have shown little benefit for routine anatomical investigation in women with recurrent UTI.[11,12] IVU is rarely helpful; more than 80% of IVU in women with recurrent UTIs are completely normal.[13-15] As an initial investigation in women in whom there is suspicion of anatomic abnormalities, US is recommended as an initial investigation to replace IVU; US is inexpensive, non-invasive, confers no radiation exposure, and can provide guidance for further investigations.[16] CT and MRI are not routinely performed and only recommended in cases in which specific conditions, such as colovesical fistula, are suspected or abnormalities were previously detected on physical examination or US. Cystoscopy rarely provides any information that would alter management; the most common finding is mucosal inflammation.[12,14,17] If no abnormal findings are seen on US or CT, 94% of subsequent cystoscopies are normal.[17] Therefore, cystoscopy is only considered in specific conditions, such as hematuria, suspected malignancy, or suspicion for other specific clinical condition.

If anatomic investigation fails to demonstrate an abnormality, it is reasonable to consider functional investigation of the lower urinary tract.[12,18] Investigation can include non-invasive uroflowmetry (UFM), assessment of post-void residual urine (PVR), and urodynamic (UDS) assessment with or without video assessment (VUDS). In principle, functional abnormalities should be focused on incomplete bladder emptying and voiding dysfunction. VUDS showed evidence of lower urinary tract dysfunction in 67 – 90% in women with recurrent UTIs.[18,19] The most common finding was bladder outlet dysfunctions in 63% of women, with a hypocontractile detrusor seen in 16%.[19] Together, this evidence suggests an algorithmic investigation of women with recurrent UTI. (Fig 3)



(*) Cystourethroscopy when US, CT or MRI demonstrates lower urinary tract abnormality or history of lower urinary tract surgery.
(#) UDS or VUDS is indicated when uroflowmetry shows abnormality or PVR measurement is more than 20% of bladder capacity.

Fig 3. Proposed investigation flow for women with recurrent UTI

Reasons of treatment failure in urinary tract abnormality

UTIs can continue to recur due to antimicrobial resistance, biofilm formation, and immunocompromise in the host, as well as the anatomical and functional abnormalities discussed above. When the underlying cause is clearly diagnosed and appropriately treated either with surgery or medication, UTI can often be cured without recurrences. Unfortunately, majority of cases are combined between both abnormalities. Even after correcting an anatomical abnormality, UTI can still recur, frequently because of a previously co-existing or new-onset functional abnormality. Such new-onset ("de novo") abnormalities may or may not be associated with the surgical repair. It is important to consider re-evauation if UTIs continue to recur after anatomical correction, although this should only proceed after an appropriate interval for healing to avoid confounding factors occurring after surgery. Occasionally, it is not possible to correct the urinary tract abnormalities and continuous preventive strategies are necessary.

Prevention for recurrent UTIs

Prevention strategies aim to decrease UTI episodes in patients waiting for definitive treatment, those with uncorrectable conditions who have little chance of complete bacterial eradication, or those who are unable or unfit for surgical correction of their underlying condition. Strategies include antibiotic and non-antibiotic prophylaxis regimens.

Antibiotic prophylaxis regimens including continuous low-dose and post-coital antibiotics. One systematic review indicated that continuous antibiotic prophylaxis for 6 – 12 months could significantly reduce the rates of UTI in comparison to placebo.[20] Post-coital antibiotics are a reasonable option for prevention in patients whose cases of UTI are associated with sexual intercourse.[20] While continuous antibiotic prophylaxis can prevent recurrent episodes, however, this regimen potentially increases urinary and fecal antibiotic resistance. In addition, infections tend to recur once the antibiotics are stopped.[21] Given these limitations, there are many agents to use for non-antibiotic prophylaxis, including probiotics, estrogen, urine acidification agents, cranberries, and D-mannose.

Probiotics

Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) defines probiotics as live microorganisms which, when administered in adequate amounts, confer a health benefit to the host.[22] The most common probiotic used for preventing UTI in women is *Lactobacillus*. A randomized, double-blinded, non-inferiority trial comparing antibiotic prophylaxis with 480 mg of trimethoprim-sulfamethoxazole once daily to oral capsules containing Lactobacilli twice daily for 12 months demonstrated that Lactobacilli were not inferior to antibiotic prophylaxis in the prevention of UTI. Moreover, Lactobacilli did not increase antibiotic resistance.[23] However, given only a small number of equivocal studies, a lack of consistent probiotic formulations, and a high risk of bias, a recent systematic review and meta-analysis study concluded there was insufficient evidence to determine the benefit of probiotics for UTI.[24]

Estrogen

Lack of estrogen in postmenopausal women may contribute to a risk of recurrent UTI because the changing vaginal environment. Loss of the normal flora may allow pathogens to colonize and infect the lower urinary tract. A systematic review and meta-analysis showed that while oral estrogen did not significantly reduce the number of women with UTI in comparison to placebo, vaginal estrogen use significantly reduced the number of UTI when compared to both placebo and no treatment.[25] Reported adverse events were rare, but include breast tenderness, vaginal bleeding or spotting, vaginal discharge, and vaginal irritation or burning.[25] While typical vaginal estrogen doses are associated with little systemic absorption, treatment with estrogen must be used with caution in endometrial cancer, breast cancer, cardiovascular disease, deep venous thrombosis, pulmonary embolism and chronic liver disease.

Urine acidification agents

Bacterial growth is inhibited by acidified urine, so agents which can reduce urine pH may be effective treatments. Commonly used agents are Methenamine Hippurate and ascorbic acid. While the concept of urinary acidification has promoted the use of ascorbic acid, known as vitamin C, for UTI prevention, there is no strong evidence to support its use in prevention of recurrent UTI. Methenamine hippurate will also acidify the urine and has an additional bacteriostatic effect due to its peripheral metabolism into formaldehyde in the urinary tract. Dosage ranges between 1 and 4 g daily. Common adverse events are gastrointestinal irritation, abdominal cramps, anorexia, rash, stomatitis, and dysuria. While previous data had suggested a small benefit in patients without urinary tract abnormalities, a systematic review and meta-analysis demonstrated that the overall quality of the previous studies was poor, often

examining heterogenous populations.[26] As a result, this agent had not been recommended in any guidelines. A recent, randomized clinical trial, however, demonstrated non-inferiority of methenamine to continuous antibiotic prophylaxis in the prevention of recurrent UTI, suggesting this agent may have utility in UTI prophylaxis.[27]

Cranberries

A-type proanthocyanidins (PACs), found in high levels in cranberries, can prevent bacterial adhesion.[28] As a result, cranberries have been suggested as non-antibiotic prophylaxis for UTI because many studies had demonstrated that it can prevent bacterial adhesion to the urothelium in vitro.[29,30] Focusing on the outcome of women with recurrent UTI in systematic review and meta-analysis study, a meta-analysis of four studies comparing between cranberry and placebo or no treatment showed a small, non-significant reduction in risk of repeat symptomatic UTI but the analysis of two studies comparing cranberry product and antibiotic prophylaxis showed equally effective.[31] Importantly, cranberry tablets may alter urinary oxalate and uric acid excretion, so patients with a history of urolithiasis should be counselled about this risk before choosing cranberry as a preventative approach.[32] Until now, the evidence to support a role of cranberries for UTI prevention is inconclusive. Recent evidence, however, suggests that some of the conflicting evidence regarding cranberry efficacy in UTI prevention may come from differences in cranberry formulations and products; varying amounts of bioactive PACs within each product may underlie differing efficacies in UTI prevention.[33,34] As no serious adverse events have been reported, cranberries may be used in patients who desire a non-antibiotic approach.

D-mannose

D-mannose, a type of sugar, prevents bacterial adhesion to the urothelium both in vitro and in animal studies by binding to bacterial pili.[35,36] For clinical use, a recent meta-analysis of two randomized controlled trials and one prospective study showed that D-mannose treatment had similar effectiveness in preventing subsequent UTIs as antibiotic prophylaxis with minimal adverse events, but the studies were again of poor to fair quality due to allocation concealment and lack of blinding. Dosage was various from 420 to 6,000 mg daily, varying significantly between studies and formulations used. Adverse events, such as diarrhea and gastrointestinal irritation, were typically mild.[37]

CONCLUSION

Urinary tract infection (UTI) is a common problem in women. Many urologic and non-urologic conditions may present with the same clinical syndrome as UTI, including pyelonephritis and cystitis. Therefore, urine examination including urine analysis and culture is critical to confirm infection. In addition, some of these non-infectious conditions can confer an increased risk of recurrent UTI; therefore, in cases in which an anatomic abnormality is suspected from history and physical examination or recurrent episodes are refractory to treatment, further investigation should be considered. In cases of complicated UTI that are unable to be cured by definitive treatment, preventive strategies should be employed to decrease UTI episodes and prevent further consequences.

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