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The Development of Digital Elderly Health Book (DEHB) Program for Elderly Using, Thailand

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ABSTRACT

Introduction: Thailand is currently experiencing a steady increase in its elderly population, coupled with the societal shift towards digitalization in the modern era. Consequently, the utilization of digital technology to facilitate access to health services among the elderly has become crucial. This study aimed to develop a program for promoting the use of a digital elderly health book (DEHB) and evaluate its effectiveness.

Methods: A research and development approach was employed, consisting of three main steps. Firstly, basic information surveys were conducted, and a program to promote the use of DEHB was developed. The informants included stakeholders from four regions of Thailand, with a sample size of 10 people per region. Secondly, a quasi-experimental research design was implemented to assess the effectiveness of the developed program. The participants were divided into four experimental areas (158 subjects) and four control areas (157 subjects). Thirdly, the program was optimized based on the results of the effectiveness evaluation by qualified experts.

Results: The program for promoting the use of DEHB comprised three essential components: (i) enhancing the capabilities of elderly health workers; (ii) fostering demand and developing skills for utilizing health information among the elderly and their caregivers; and (iii) promoting social influence and participation. The experimental exhibited significantly higher levels of access to and utilization of DEHB compared to the control. There was a substantial level of satisfaction with DEHB.

Conclusion: The successful promotion of digital health adoption among the elderly necessitates proficiency, comprehension, and awareness of its advantages among both practitioners (i.e., public health officials) and users (i.e., elderly individuals and caregivers). It also involves creating social influence to gain more acceptance and support for digital health initiatives.

Keywords: Digital elderly health book; Digital health; Promote to use; Elderly health

Introduction

Thailand is currently experiencing a significant demographic transition, projected to reach a 20% proportion of elderly individuals in the near future, as it moves towards becoming a complete-aged society [1]. This demographic shift is occurring alongside a global digital revolution, characterized by the widespread integration of digital technologies into various aspects of daily life and interpersonal interactions [2]. Recognizing the transformative potential of digital health, the World Health Organization has established a Global Strategy on Digital Health 2020-2025, which emphasizes the importance of strengthening governance and promoting the use of digital health among individuals [3]. In the context of older adults, research has shown that digital technologies have provided them with new avenues for internet-based communication and connection with their families [4]. Additionally,

consistent adoption and use of digital technologies among the elderly have yielded several benefits. These include boosted confidence in technology, heightened self-awareness of capabilities, and reduced hesitations in utilizing digital media, thereby facilitating a broader range of digital activities [5].

The health and well-being of the elderly are crucial for active aging and significantly impact their overall quality of life. Therefore, it is essential to ensure that the elderly have access to a variety of health services, particularly in the realm of digital health, which goes beyond communication and entertainment purposes. This enables them to conveniently and expeditiously receive services from government sectors and relevant organizations, as exemplified by the increased utilization of digital health during the COVID-19 pandemic [6-7]. For example, the Mor Prom application is used by almost every Thai citizen to receive vaccine services and is a huge database for the government. Recognizing the importance of accessible health services for the elderly, the Department of Health, Ministry of Public Health of Thailand has developed the Digital Elderly Health Book (DEHB), also known as the Blue Book Application, which has been implemented in several areas since 2021 [8]. The DEHB caters to two primary user groups: 1) elderly individuals and their primary caregivers, and 2) public health officials and volunteers responsible for elderly care in their respective areas. The system encompasses functionalities for the elderly and caregivers, such as health record keeping, health risk screening, vulnerability assessment, scheduling and receiving health services and acquiring health-related knowledge. It also offers features for public health officials and volunteers, including the provision of health services, data processing of health information, and data management [9].

However, the utilization of the DEHB by users from both groups was found to be limited in 2021-2022 [7]. Studies examining digital technology usage among the elderly have revealed a lack of skills in accessing and utilizing modern communication technologies [10]. While elderly individuals may be proficient in using digital media for information searching and online shopping, they have yet to tap into its potential for self-healthcare purposes [11]. Furthermore, various barriers to digital usage have been identified, including visual impairment, memory difficulties, complexity, and technological challenges [12]. Therefore, promoting the use of digital health platforms among the elderly and relevant individuals should involve detailed and clear training programs that provide guidance and create awareness of the benefits of utilizing digital health in real-life situations. Additionally, the development of user-friendly and convenient digital health platforms is essential [13-14].

Given Thailand's aging society and the development of the DEHB to enhance healthcare accessibility for the elderly, this study aims to address two main objectives. Firstly, it seeks to develop a program specifically tailored for Thai users, including the elderly population and relevant staff, to promote the use of the DEHB. Secondly, the study aims to evaluate the effectiveness of the developed DEHB promotion program. The study's primary focus is on enhancing the elderly users' ability to effectively utilize DEHB, by drawing upon the concept of application skills as shown in Figure 1. These application skills encompass the practical use of DEHB functionalities, including data usage, tool utilization, safety precautions, and computation. [2, 16-17]. The effectiveness of the developed program will be assessed based on the improvement in these application skills among the elderly and staff users. The results of this study can provide implications for promoting the use of digital health among the target group, especially the elderly in the community and health personnel, to improve their access to data, information, and health knowledge.

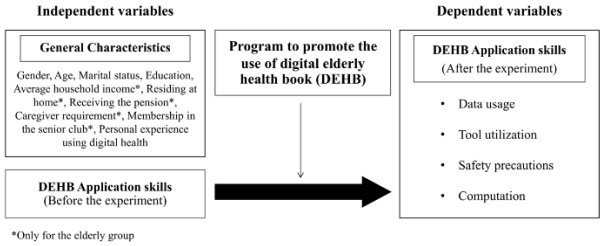

Figure 1 Conceptual framework

Methodology

The study followed a three-phase research and development approach. *Phase 1* focused on investigating and developing a program to promote the use of the DEHB. Data analysis was conducted in four regions: the northern region (Tha Thong Subdistrict, Mueang District, Phitsanulok Province), northeastern region (Tha Tum Subdistrict, Mueang District, Maha Sarakham Province), central region (Samet Tai Subdistrict, Bang Khla District, Chachoengsao Province), and southern region (Thung Takhrai Subdistrict, Thung Tako District, Chumphon Province). Data was collected through semi-structured in-depth interviews with 10 key informants in each region. The key informants comprised 3 elderly individuals, 2 family caregivers, 2 healthcare professionals, 2 village health volunteers or elderly caregivers in the long-term care system, and 1 local government official. Based on the findings, a program was developed, which involved conducting focus group discussions among stakeholders in each region. In this phase, data were analyzed using content analysis.

Phase 2 involved the evaluation of the effectiveness of the developed program through quasi-experimental research. Four areas were identified in Phase 1, four (4) were designated as experimental groups, while the remaining four areas in the same provinces served as control groups. The sample size was determined using a formula for testing the mean difference between two groups based on previous research findings [18], with a 20% increase to account for potential attrition, resulting in a minimum sample size of 75 individuals per group. The participants were divided into two groups: the elderly and the officers (healthcare workers, local government officials, or volunteers), as illustrated in Figure 2. Inclusion criteria for the elderly participants were as follows: age between 60 and 80 years, ability to perform normal activities of daily living, residence in the research area for at least one year, and possession of a personal digital device. The inclusion criteria for the officers were as follows: age of 18 years or older, a minimum of one year of experience in the field of aged care within the research area, and ownership of a personal digital device. The experimental group underwent a 3-month intervention using the developed program, while the control group did not receive the program. To assess the participants' application skills, a 3-part questionnaire was administered before and after the experiment. The questionnaire consisted of two sections: i) general characteristics; ii) self-assessment of four elements of application skills, namely data usage (e.g., platform access and knowledge), tool utilization (e.g., basic access to tools and learning), safety precautions (e.g., registering and recording personal information), and computation (e.g., viewing health reports and understanding one's health status); and iii) a satisfaction assessment used exclusively in the experimental group. Additionally, the research team evaluated the application skills across these four components using behavioral records collected from both groups. Data were gathered from the questionnaires and behavioral records and analyzed using descriptive statistical methods (mean, standard deviation) and analytical statistical methods (chi-square, independent t-test).

Phase 3 focused on refining the developed program based on the results of the effectiveness evaluation. This phase involved conducting focus group discussions with 12 key stakeholders, including elderly health professionals, community development experts, and digital health specialists. Feedback and insights gathered from these discussions were carefully considered and incorporated to enhance the program's appropriateness and effectiveness in promoting the use of DEHB.

The content validity of the semi-structured interview, questionnaire, and behavioral record form was assessed by three experts. The index of item-objective congruency for all items ranged from 0.70 to 1.00, indicating a high level of validity. Additionally, the reliability of the instruments was tested on groups similar to the sample population, and Cronbach's Alpha coefficient was found to be between 0.84 and 0.91, demonstrating good internal consistency. This study obtained ethical approval from the Department of Health on September 26, 2022 (No. 547/2565), ensuring compliance with human research ethics. Before starting the research in each area, the objectives, research process, and data collection were explained to the sample. The sample was also allowed to ask questions and to independently consider participating in the study.

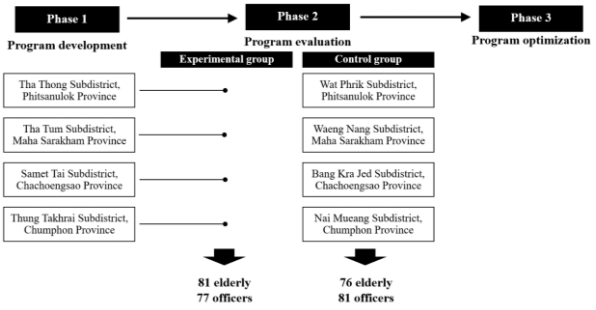

Figure 2 Research area and sample group

Results

The program to promote the use of digital elderly health books

The findings from the in-depth interviews conducted in four regions across Thailand shed light on the challenges faced by elderly individuals, volunteers, public health officials, and local government officials regarding the utilization of DEHB. The interviews revealed that elderly individuals encounter barriers related to comprehension, application skills, limited infrastructure, and awareness of DEHB. Similarly, volunteers and some officials exhibited a lack of awareness and proficiency in using DEHB, particularly in recording and processing health data. Furthermore, the impact of DEHB on elderly healthcare remains uncertain. These findings underscore the importance of targeted interventions to address these challenges, enhance awareness and skills among the elderly, and provide support to stakeholders involved in the program (Table 1).

Table 1 Findings from the in-depth interview

Informants	Findings
Elderly individuals	• Lack of understanding and still not having the skills to use DEHB, including recording data, acquiring health knowledge, and

Informants	Findings
	viewing their own health reports. • No smart phone to access DEHB. • The personal benefits of DEHB use are not known.
Family caregivers	• It is unknown whether DEHB can serve as a substitute for elderly individuals who are unable to use it independently. • They have not yet used DEHB. • They do not know the benefits of using it and are not confident in the safety of personal information.
Healthcare professionals	• They do not know how to use DEHB as a data manager. • Lack of skills in using DEHB, especially in entering data and viewing data reports. • They have not yet received benefits from its use, such as access to health information of the elderly in the area and reduced workloads.
Village health volunteers and elderly caregivers	• Lack of a smartphone and access to free internet to use DEHB. • Lack of skills in using DEHB, particularly in entering data and viewing data reports. • Preference for recording data on paper and sending reports to healthcare professionals.
Local government official	• Unaware that reports can be viewed in the areas under the responsibility of local governments. • Lack knowledge and skills to use DEHB.

The developed program aimed to promote the use of DEHB through three key components: (i) enhancing application skills for elderly health workers, public health officials, local government officials, and volunteers, focusing on usage, data management, problem-solving, and information utilization; (ii) improving the skills of elderly individuals and caregivers in recording health data, conducting health screenings, and raising awareness of DEHB's benefits, including convenient access to health services and improved health literacy; and (iii) creating social influence and participation by fostering communication, increasing awareness among the elderly, and facilitating discussions and experience sharing related to DEHB usage.

However, upon assessing the effectiveness of the program, it was observed that there were no significant differences in the computational application skills among the elderly participants. Therefore, in Phase 3 of the research, there was a focus on enhancing the skill development of the elderly and caregivers, as outlined in Figure 3. This involved increasing their understanding of how to interpret the health status information provided in the DEHB and applying it to practical scenarios. For instance, if a health screening indicates the presence of urinary incontinence, the elderly individual or their caregiver can request an assessment and be eligible to receive support in the form of adult diapers. Additionally, during this phase, the duration of each program activity was carefully determined to ensure more efficient implementation. This allowed for better utilization of the developed program and maximized its impact on the target population.

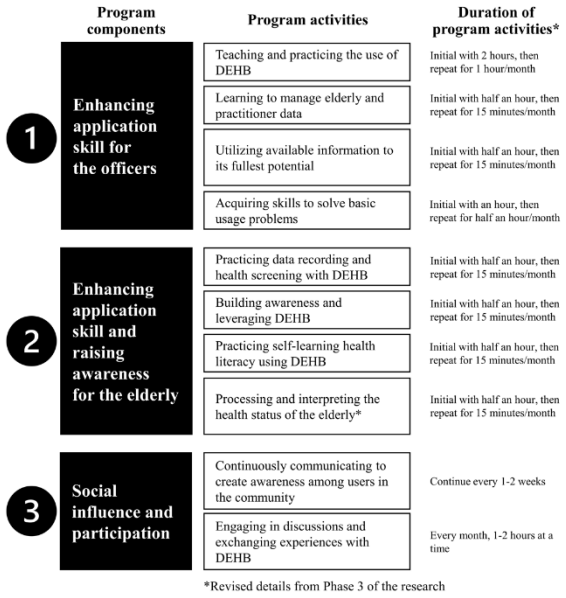

Figure 3 Revised program to promote the use of digital elderly health books in Thailand.

The effectiveness of the program to promote the use of digital elderly health books

When comparing the general characteristics of the elderly and the staff between the experimental group and the control group, no significant differences were observed. Furthermore, the mean application skills for using the DEHB were compared before the experiment, revealing no significant difference between the elderly and the staff in both the experimental and control groups (Table 2).

Table 2 General characteristics of the sample

General characteristics	The elderly			The officers		
	Experiment (n=81)	Control (n=76)	p-value	Experiment (n = 77)	Control (n = 81)	p-value
Gender						
Male	19	14	0.439	7	9	0.674
Female	62	62		70	72	
Age	$\bar{X}$ 66.55	$\bar{X}$ 67.30	0.121	$\bar{X}$ 49.29	$\bar{X}$ 50.86	0.343
	SD 5.28	SD 6.15		SD 8.62	SD 10.23	
Marital status						
Married/ living together	52	50	0.834	47	51	0.803
Unmarried/ widowed/ divorced	29	26		30	30	
Education						
No/ primary school	52	59	0.065	27	26	0.693
Secondary education and above	29	17		50	55	
Average household income	$\bar{X}$ 11071.56	$\bar{X}$ 10342.11	0.506	-	-	-
	SD 10626.69	SD 13759.42				
Residing at home				-	-	-
Living with oneself	7	13	0.157			
Living with family or someone	74	63				
Receiving the pension				-	-	-
Received	73	68	0.893			
Not received						

General characteristics	The elderly			The officers		
	Experiment (n=81)	Control (n=76)	p-value	Experiment (n = 77)	Control (n = 81)	p-value
	8	8				
Caregiver requirement				-	-	-
Require	5	11	0.086			
Do not require	76	65				
Membership in the senior club				-	-	-
Be a member	62	55	0.549			
Not be a member	19	21				
Personal experience using digital health						
Have used	38	32	0.545	71	78	0.268
Have not use	43	44		6	3	
Mean application skills for using the DEHB before the experiment	$\bar{X}$ 21.32 SD 9.56	$\bar{X}$ 19.35 SD 9.19	0.190	$\bar{X}$ 23.14 SD 9.10	$\bar{X}$ 24.26 SD 8.90	0.438

*Significant level at α=0.05

A comparative analysis of the mean application skills for using the Digital Elderly Health Book (DEHB) was conducted between the elderly participants in the experimental group and the control group, after their engagement in the developed program activity. This analysis utilized an independent t-test. The findings revealed a noteworthy disparity in the mean application skills for using DEHB between the elderly participants in the experimental and control groups. Specifically, the elderly participants in the experimental group demonstrated significantly higher mean application skills for using DEHB in comparison to those in the control group. This significant difference was evident across all application skills, including data usage, tool utilization, and adherence to safety precautions. It is important to note, however, that the experimental group only exhibited a non-significant difference in the computation element. Conversely, among the officers, the average application skills for using DEHB were significantly higher in the experimental group than in the control group, encompassing all variables examined (Table 3). Furthermore, when evaluating the satisfaction with the developed program and the use of DEHB, it was found that the elderly participants in the experimental group expressed a satisfaction rate of 91.36%, while the officers in the experimental group reported a satisfaction rate of 89.61%.

Table 3 Comparing the mean application skills for using the digital elderly health book among the elderly and the officers in the experimental and control groups

Application skills	Mean application skills for using the digital elderly health book							
	The elderly				The officers			
	Experiment	Control	t	p-value	Experiment	Control	t	p-value
All application skills	$\bar{X}$ 24.65 SD 7.32	$\bar{X}$ 18.03 SD 9.55	4.896	<0.001*	$\bar{X}$ 35.35 SD 3.81	$\bar{X}$ 28.64 SD 7.42	7.099	<0.001*
Data usage	$\bar{X}$ 5.13 SD 2.39	$\bar{X}$ 3.01 SD 2.97	4.942	<0.001*	$\bar{X}$ 8.85 SD 0.96	$\bar{X}$ 7.37 SD 1.87	6.219	<0.001*
Tool utilization	$\bar{X}$ 6.22 SD 1.91	$\bar{X}$ 4.32 SD 2.54	5.318	<0.001*	$\bar{X}$ 8.86 SD 1.00	$\bar{X}$ 6.94 SD 1.89	7.887	<0.001*

Application skills	Mean application skills for using the digital elderly health book							
	The elderly				The officers			
	Experiment	Control	t	p-value	Experiment	Control	t	p-value
Safety precautions	$\bar{X}$ 6.02 SD 2.11	$\bar{X}$ 3.75 SD 2.63	5.975	<0.001*	$\bar{X}$ 8.78 SD 1.03	$\bar{X}$ 6.67 SD 2.30	7.370	<0.001*
Computation	$\bar{X}$ 7.28 SD 2.10	$\bar{X}$ 6.94 SD 3.06	0.792	0.429	$\bar{X}$ 8.86 SD 1.06	$\bar{X}$ 7.65 SD 1.78	5.192	<0.001*

*Significant level at α=0.05

Discussion

The program designed to promote the use of DEHB in Thailand comprises three primary components that contribute to its effectiveness and reliability. The first component focuses on enhancing the application skills of elderly health workers. Previous studies have consistently highlighted the significance of regular training for health personnel to effectively utilize digital technologies, as it enhances their digital literacy [19-20]. The positive outcomes observed in this study, with health personnel demonstrating higher levels of application skills, support these findings. The development of application skills among health personnel through the program aligns with previous studies that have implemented human resource development programs aimed at cultivating competencies for more effective utilization of digital health technologies [21-22].

The second component focuses on developing the application skills of the elderly and caregivers while fostering acceptance of digital health among this group. The results of this study revealed that continuous engagement in the program for 3 months led to higher application skills among the target group. This finding is consistent with prior research that has identified higher levels of perceived usefulness and perceived ease of use as contributing factors to greater acceptance of digital health among the elderly [16, 23-25]. Moreover, the development of application skills among the elderly and their caregivers emphasizes the importance of digital competency, enabling them to use digital technologies safely [10, 16]. Significantly, the development of these application skills helps bridge the gap in digital health utilization among the elderly [26] and enhances their access to health services [16, 27-28].

The final component of the program focuses on creating social influence and fostering participation within the community. This aspect plays a crucial role in encouraging the acceptance and utilization of digital health among the elderly, caregivers, and stakeholders [24, 29]. The study findings highlight those continuous interpersonal interactions regarding digital health topics contribute to sustained usage [30]. These results align with the digital health governance proposal, which underscores the importance of involving multiple sectors in driving the implementation of digital health initiatives [28]. The inclusion of this component further enhances the reliability and effectiveness of the program in promoting the use of DEHB among the target population.

When considering program effectiveness, recipients exhibited superior application skills compared to non-recipients. This coincides with research advocating promotion strategies, including mass media utilization and digital literacy promotion on social platforms, to enhance accessibility, especially for elderly users [31]. Similarly, an instructional strategy study [32] reported that these methods bolstered older individuals' confidence, awareness, and motivation to embrace digital technologies, aligning with this study's program effectiveness.

Conclusions

The program aimed to promote the use of DEHB in Thailand by addressing challenges related to comprehension, application skills, and awareness. Three key components were developed: enhancing the application skills of stakeholders, improving the skills of elderly individuals and caregivers, and fostering social influence and participation. The first component focused on training health workers, officials, and volunteers in DEHB usage, data management, problem-solving, and information utilization. This aimed to improve their proficiency and familiarity with DEHB for effective utilization. The second component aimed to improve the skills of elderly individuals and caregivers in recording health data, conducting screenings, and raising awareness of DEHB's benefits. This empowered them to actively participate in healthcare management, enhancing access to services and health literacy. The third component emphasized creating social influence through communication, awareness campaigns, and experience sharing. It fostered acceptance and utilization of DEHB among the elderly and stakeholders, promoting sustained usage.

Efficient implementation was ensured by optimizing activity durations and maximizing program impact. Skill development and practical application were prioritized, enabling interpretation of health status information and informed decision-making. The program's effectiveness was evaluated through a comparative analysis of mean application skills and satisfaction rates. The experimental group showed significantly higher skills and expressed high satisfaction, indicating the program's positive impact.

Overall, the program addressed challenges, enhanced application skills, and fostered social influence. It empowered stakeholders and promoted healthcare access, active participation, and overall well-being of the elderly. The findings highlight the importance of targeted interventions, awareness enhancement, and skill development for effective DEHB utilization among the elderly population. The results of the research can be applied to promote the use of digital health for the elderly in the community, as well as to increase awareness and skills of public health personnel. However, it is still necessary to develop strategies to promote such use at the local level to seriously use these digital platforms in the future.

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Complementary and Alternative Medicine Combined with Symptomatic Treatment Improves Symptoms in COVID-19 Patients

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ABSTRACT

Introduction: The global population has been severely affected by the COVID-19 pandemic. The exploration of Complementary and Alternative Medicine (CAM) as a potential complement to standard management for COVID-19 is essential, but it requires conclusive evidence. This observational study aimed to investigate the association between CAM and improvements in COVID-19 symptoms, the incidence of such improvements, the utilization of complementary methods, and the stages of the disease.

Methods: This research involved a secondary data analysis that compared baseline characteristics, treatment modalities, symptoms, and vital signs before and after treatment in a randomized sample of 881 COVID-19 patients. Medical records from April to May 2021 were collected, and 273 participants were included in the study.

Results: Among the respondents, 131 (47.9%) received andrographis capsules alongside symptomatic treatment, 87 (31.9%) received Homeopathic medicine with symptomatic treatment, 33 (12.1%) received symptomatic treatment only, and 22 (8.1%) received Lianhua Qingwen alongside symptomatic treatment. When comparing the proportion of improvements after treatment, it was found that 28 (32.2%) of the 87 participants who received homeopathic medicine alongside symptomatic treatment exhibited the highest improvement in chest x-ray results. The highest proportion of patients receiving Lianhua Qingwen alongside symptomatic treatment showed favorable changes in vital signs, with 9 (41.0%) of the 22 participants demonstrating improvement. Strong evidence of improvement in symptoms was observed with andrographis capsules alongside symptomatic treatment, with 109 (83.2%) of the 131 participants experiencing improvement. Comorbidities among participants and the stage of the disease were found to significantly influence the effectiveness of these four treatment methods (p-value < 0.010).

Conclusion: This study suggests an association between CAM and improving COVID-19 symptoms. Homeopathic medicine showed considerable improvement in chest x-ray results, while andrographis capsules in the symptomatic treatment group demonstrated notable improvement in symptoms. The most remarkable improvement in vital signs was correlated with using Lianhua Qingwen.

Keywords: COVID-19, Complementary and alternative medicine (CAM), Andrographis capsule, Lianhua Qingwen, Homeopathic medicine

Introduction

The COVID-19 pandemic, originating from SARS-CoV-2 infection, first surfaced in China in December 2019. SARS-CoV-2 can afflict individuals of all age groups, manifesting with symptoms that range from asymptomatic cases to severe pneumonia, often culminating in multi-organ failure and, tragically, loss of life [1, 2]. COVID-19 impacts various dimensions of an individual's existence, encompassing not only physical and mental health but also socioeconomic well-being [3].

SARS-CoV-2 is primarily transmitted through aerosol droplets, often within a radius of six feet. Measures such as covering coughs and sneezes and adhering to social distancing guidelines have been recommended to mitigate the risk of viral transmission. Frequent hand hygiene practices remain a cornerstone in minimizing the risk of infection. The most effective approach for preventing SARS-CoV-2 infection is vaccination, a pursuit being vigorously pursued by nations worldwide. Various treatment modalities for COVID-19, including antiviral drugs, convalescent plasma therapy, vaccination, and symptomatic management, are being actively explored. Monoclonal antibodies targeting SARS-CoV-2 have gained prominence and are endorsed in the COVID-19 treatment guidelines for pre-and post-exposure prophylaxis [1, 2].

Thailand encountered its first case of COVID-19 in January 2020, with the disease rapidly disseminating throughout the nation. The initial response involved a 14-day hospital or government-supported facility-based isolation for confirmed cases. In milder and moderate cases, symptomatic treatment, featuring antipyretic, antitussive, and antiallergic medications, constituted the primary therapeutic approach. Antiviral agents were reserved for severe scenarios involving pneumonia or multiorgan failure [4]. In addition to conventional pharmaceutical interventions, there is growing interest in exploring alternative and complementary medicine (CAM) for the management of COVID-19.

Notably, a study conducted in India identified commonly employed homeopathic remedies, including arsenicum album, bryonia alba, gelsemium sempervirens, and pulsatilla nigerians, for the treatment of COVID-19 [5]. In China, Lianhua Qinwen has been employed as a treatment for COVID-19 [6], and andrographis paniculata extract is currently under scrutiny in Thailand for its potential therapeutic support [7]. This study aims to investigate whether CAM treatments, including homeopathic medicines (gelsemium sempervirens, arsenicum album, bryonia alba), andrographis paniculata extract, and Lianhua Qinwen, when combined with symptomatic treatment at Ratchaphiphat Hospital, can effectively mitigate the severity of COVID-19 symptoms.

Methodology

Study Design, Population, and Sample

This observational study collected secondary data from Ratchaphiphat Hospital of COVID-19 patients treated in April and May 2021. All study protocols were approved by the Mae Fah Luang University Ethics Committee (COA: 120/2022) and the Bangkok Metropolitan Administration Human Research Ethics Committee (COA: 110). Data were collected after receiving ethical approval. Study samples were determined using a random number table with systematic random sampling. Every third patient who met the inclusion criteria was randomly assigned among 881 asymptomatic, mild, and moderate COVID-19 patients, resulting in 294 initially selected participants. Subsequently, to meet the predetermined sample size of 273 participants, a random elimination of 21 participants was carried out from the initially selected 294 patients using a random sampling method.

Sample size calculation

Key aspects of this observational study included the incidence of symptoms, vital signs, and chest x-ray improvements, the rate of CAM treatment, the stage of disease, and the associations between CAM and COVID-19 symptom improvement. Sample size determination used the following medical and public health observational formula for estimating the proportion of COVID-19 patients showing symptom improvement, receiving Homeopathic medicine, Andrographis capsule, Lianhua Qingwen, and Symptomatic treatment based on two months of medical records:

$$n = \frac{Z_{\alpha/2}{}^2 pq}{d^2}$$

n = Sample size for this study

$Z_{\alpha/2}$ = The standard normal variate at 5% type 1 error (α= 0.050); which is 1.96

d = Absolute error or precision of 5%

p = Proportion of COVID-19 patients whose symptoms improved after treatment with homeopathic medicine in the reference study by Fujino, et al [8] was 82% or 0.82 [8].

q = 1 - p

d = Acceptable margin of error = 0.05

$$n = \frac{(1.96)^2(0.82)(1-0.82)}{(0.05)^2} = 226.8$$

Thus, n = 226.8, which was rounded up to 227 participants. After factoring in a potential 20% risk of incomplete data from participants, the final sample size was calculated as 273 participants required.

Selection criteria

Inclusion criteria were positive reverse transcription polymerase chain reaction (RT-PCR) for novel coronavirus 2019, both male and female, aged 18 years or older, and COVID-19 patients with asymptomatic and mild-to-moderate symptoms. The exclusion criteria were incomplete data.

Instruments

Data were collected from medical records, encompassing gender, age, height, weight, medical history, underlying diseases, disease severity, symptoms, vital signs, chest x-ray findings, and the treatment administered at Ratchaphiphat Hospital.

Symptoms: Severity scores on a scale of 0 to 10 were assigned to each symptom, with 0 indicating normal or no symptoms and 10 indicating the most severe symptom. Improvement, stability, or worsening of symptoms was assessed by comparing scores before and after treatment.

Vital signs: Vital signs, including temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation, were measured. The change in vital signs before and after treatment determined whether they improved, remained stable, or worsened.

Chest x-ray: Chest x-ray results before and after treatment were compared to ascertain improvement, stabilization, or worsening by specialists.

Complementary and Alternative Medicine (CAM) with Symptomatic Treatment: CAM was administered with symptomatic treatment, which prescribed medication based on the presenting symptoms. For moderate-severity patients, such as those with pneumonia, Favipiravir and steroids were also prescribed. *Andrographis paniculata* with symptomatic treatment: Patients received 3 tablets thrice daily for 5 days alongside symptomatic treatment.

Homeopathic medications with symptomatic treatment: *Gelsemium sempervirens*: 5 ml administered once daily in the morning with symptomatic treatment. *Arsenic Album*: 5 ml administered once daily at noon with symptomatic treatment. *Bryonia alba*: 5 ml administered once daily before bed with symptomatic treatment. Lianhua Qinwen with symptomatic treatment: Patients received 4 tablets thrice daily for 7 days alongside symptomatic treatment. Symptomatic treatment: This involved the administration of medications targeting distressing symptoms, including analgesics (e.g., Paracetamol), allergy medications (e.g., Cetrizine), anti-tussives (e.g., mucolytics), and expectorants.

Data collection

Data collection took place at Ratchaphiphat Hospital between April and May 2021, involving a total of 273 males and females aged 18 and above with asymptomatic, mild, or moderate COVID-19 infections. Data encompassing gender, age, weight, height, comorbidities, disease stage, pre-treatment and post-treatment outcomes related to symptoms, vital signs, chest radiographs, and treatment methods were extracted from medical records. All collected data were recorded in an Excel file for subsequent analysis.

Data analysis

Data entered into the Excel file from medical records were analyzed using descriptive statistics, which included percentages, means, and standard deviations. To explore associations, the chi-square test was employed to determine the relationship between patient factors, disease stage, treatment methods, and improvements in COVID-19 symptoms. The analysis was conducted using SPSS version 23.0 Passport Advantage Agreement Number 000020378.

Results

Between April and May 2021, Ratchaphiphat Hospital admitted a total of 881 patients with asymptomatic, mild, and moderate COVID-19 infections. This analysis focused on 273 participants: 55.3% were male and 44.7% were female, with an average age of 38.41 ± 14.22 years and an average body mass index of 24.44 ± 4.82 kg/m². 34.1% of the participants had a body mass index within the normal range, while 58.6% had a body mass index higher than the normal threshold of 23 kg/m². The 'comorbidity' variable encompassed several factors that may influence disease progression and were not mutually exclusive, as a patient could have more than one of these conditions. 35.2% had no comorbidities, while 64.8% had comorbidities (including health problems, obesity, and being over 60 years old). 78.4% of participants were classified as asymptomatic and mild. The largest proportion (47.9%) received andrographis capsules alongside symptomatic treatment (Table 1).

Table 1 Participants baseline characteristics

Characteristics	n	%
Gender		
Male	151	55.3
Female	122	44.7
Age (years)		
18-39	148	54.2
40-60	103	37.7
>60	22	8.1
Mean ± SD = 38.4 ± 14.2		
BMI		
Underweight (<18.5)	20	7.3
Normal (18.5-22.9)	93	34.1
Overweight (23-24.9)	51	18.7
Obesity (25-29.9)	74	27.1

Characteristics	n	%
Morbid obesity (>30)	35	12.8
Comorbidity presenting		
Yes, including obesity and >60	177	64.8
Hypertension	*39*	
Diabetes Mellitus	*19*	
Dyslipidemia	*17*	
Cardiac and vascular disease	*13*	
Respiratory disease	*21*	
HIV	*3*	
Smoking	*54*	
No	96	35.2
Stage of disease		
Asymptomatic and Mild	214	78.4
Moderate	59	21.6
Treatment		
Homeopathic medicine and symptomatic treatment	87	31.9
Andrographis capsule and symptomatic treatment	131	47.9
Lianhua Qingwen and symptomatic treatment	22	8.1
Symptomatic treatment	33	12.1

Symptoms

Participants were classified with 12 symptoms before and after their treatment, regardless of the treatment method used. Cough was the most prevalent symptom (48.9%) before treatment. Rhinorrhea and headache affected 37.9% and 27.8%, respectively. Following treatment, cough remained the most common symptoms (16.8%) (Table 2).

Vital Signs

The average temperature and respiratory rate did not exhibit substantial differences before and after treatment. This study reported changes in the proportion with normal blood pressure, increasing from 65.6% to 96%, and a decrease in those with abnormal blood pressure, from 34.4% to 4% (Table 2).

Table 2 Symptoms and vital signs before and after treatment

Symptoms and vital signs		Before n (%)	After n (%)
Symptoms	Fever	20 (7.3%)	2 (0.7%)
	Cough	136 (49.8%)	46 (16.8%)
	Rhinorrhea	87 (31.9%)	23 (8.4%)
	Sore throat	62 (22.7%)	13 (4.8%)
	Dyspnea	66 (24.2%)	20 (7.3%)
	Loss of smell	45 (16.5%)	23 (8.4%)
	Loss of taste	35 (12.8%)	16 (5.9%)
	Conjunctivitis	10 (3.7%)	2 (0.7%)
	Rash	13 (4.8%)	2 (0.7%)
	Diarrhea	60 (21.9%)	24 (8.8%)
	Headache	76 (27.8%)	16 (5.9%)
	Muscle pain	70 (25.6%)	24 (8.8%)
Vital signs	Temperature (Degree Celsius)	36.475 ± 0.2694	36.453 ± 0.1871
	Blood pressure: *Normal*	179 (65.6%)	262 (96%)
	Abnormal	94 (34.4%)	11 (4%)
	Pulse (Beats/min)	92.78 ± 14.061	83.68 ± 10.478
	Respiratory rate (Breaths/min)	21.35 ± 15.580	20 ± 0.171
	SpO_2 >95	268 (98.2%)	273 (100%)

Chest x-ray

Before treatment, chest x-rays indicated pneumonia (lung infiltration) in 21.6% of participants. It is important to note that chest x-ray data only reflected the 'before' condition, as pulmonary infiltration persisted despite symptom improvement.

The participants were categorized into four groups according to the treatment methods employed. Of the women, 52.9% received homeopathic medicine with symptomatic treatment, and 59.1% received Lianhua Qingwen with symptomatic treatment. Among men, 66.7% received symptomatic treatment, and 60.3% received andrographis capsules with symptomatic treatment. No significant association was found between gender and treatment methods (Table 3). Andrographis capsules with symptomatic treatment were administered to 47.98% of the sample, while 31.86% received homeopathic medicine with symptomatic treatment. A relatively low percentage of underwent symptomatic treatment, 12.08%, and Lianhua Qingwen group with symptomatic treatment, 0.08%. Average age did not demonstrate a significant association with different categories of treatment methods (Table 3).

Homeopathic medicine with symptomatic treatment exhibited the highest percentage of comorbidity, present in 78.2%. Further statistical tests indicated a significant difference in the proportion of comorbidity among treatment methods (p-value < 0.010) (Table 3).

In terms of disease stage, Lianhua Qingwen with symptomatic treatment had the highest percentage of asymptomatic and mild cases, 95.5%, while 4.5% presented with moderate cases. Moderate cases were most prevalent in the group receiving homeopathic medicine with symptomatic treatment, at 32.2%, while 67.8% were asymptomatic and mild cases (Table 3).

Table 3 Comparisons of participants' baseline characteristics and treatments

Characteristics		Homeopathic medicine with symptomatic treatment (n=87)	Andrographis capsule with symptomatic treatment (n=131)	Lianhua Qingwen with symptomatic treatment (n=22)	Symptomatic treatment (n=33)	p-value
Gender	Male	41 (47.1%)	79 (60.3%)	9 (40.9%)	22 (66.7%)	0.064
	Female	46 (52.9%)	52 (39.7%)	13 (59.1%)	11 (33.3%)	
Age		40.56 ± 14.308	38.87 ± 14.335	30.55 ± 7.269	36.15 ± 15.417	0.305
Comorbidity	Present	68 (78.2%)	80 (61.1%)	7 (31.8%)	22 (66.7%)	<0.001*
	Absent	19 (21.8%)	51 (38.9%)	15 (68.2%)	11 (33.3%)	
Stage of disease	Asymptomatic and mild	59 (67.8%)	105 (80.2%)	21 (95.5%)	29 (87.9%)	0.009*
	Moderate	28 (32.2%)	26 (19.8%)	1 (4.5%)	4 (12.1%)	

* Statistical significance at α=0.05

Andrographis capsules with symptomatic treatment demonstrated the highest rate of symptom improvement, affecting 83.2%. In contrast, the lowest rate of symptom improvement was observed in the Lianhua Qingwen with symptomatic treatment group, at 68.2%. Lianhua Qingwen with symptomatic treatment had the highest proportion of cases with stable symptoms, 27.3%, while andrographis capsules with symptomatic treatment had the lowest, at 13%. Symptomatic treatment exhibited the largest percentage of cases with worsening symptoms, at 6%, while the smallest percentage was in the andrographis capsules with the symptomatic treatment group, at 3.8%. No significant association was identified between symptom categories and the four treatment methods (Table 4).

The highest percentage of cases displaying improvement in vital signs was observed in the group that received Lianhua Qingwen with symptomatic treatment, accounting for 41% of cases. In contrast, the lowest percentage of improvement was observed in those who received symptomatic treatment, at 27.3%. Simultaneously, the group receiving symptomatic treatment exhibited the highest percentage of stable vital signs, with 72.7%, while the lowest percentage was noted in the Lianhua Qingwen with symptomatic treatment group, at 59%. Notably, only one treatment method, andrographis capsules with symptomatic treatment, had cases with worsened vital signs, at 1.5%, whereas no such cases were reported in the other three treatment groups. There was no significant association found between vital signs and treatment methods (Table 4).

Regarding chest x-ray, the highest percentage of cases with improvement was observed in the group receiving homeopathic medicine with symptomatic treatment, comprising 32.2% of cases. The smallest percentage of cases with improvement, at 4.5%, was observed who received Lianhua Qingwen with symptomatic treatment. The same group, Lianhua Qingwen with symptomatic treatment, demonstrated the most significant percentage of cases with stable chest x-ray results, at 95.5%, while the group receiving homeopathic medicines and symptomatic treatment had the lowest percentage, at 67.8%. It is worth highlighting that no cases of worsening chest radiographs were observed in any of the four treatment methods. A statistically significant difference in proportions was observed in chest x-ray results when comparing the four treatment methods (Table 4).

Table 4 Comparisons of the improvement of symptoms, vital signs, and chest x-ray between treatment methods

Characteristics		Homeopathic medicine with symptomatic treatment (n=87)	Andrographis capsule with symptomatic treatment (n=131)	Lianhua Qingwen with symptomatic treatment (n=22)	Symptomatic treatment (n=33)	p-value
Symptom	Improved	71 (81.6%)	109 (83.2%)	15 (68.2%)	25 (75.8%)	0.700
	Stable	12 (13.8%)	17 (13%)	6 (27.3%)	6 (18.2%)	
	Worsen	4 (4.6%)	5 (3.8%)	1 (4.5%)	2 (6%)	
Vital sign	Improved	34 (39.1%)	37 (28.3%)	9 (41%)	9 (27.3%)	0.440
	Stable	53 (60.9%)	92 (70.2%)	13 (59%)	24 (72.7%)	
	Worsen	0 (0.0%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	
Chest x-ray	Improved	28 (32.2%)	26 (19.8%)	1 (4.5%)	4 (12.1%)	0.009*
	Stable	59 (67.8%)	105 (80.2%)	21 (95.5%)	29 (87.9%)	
	Worsen	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

* Statistical significance at α=0.05

Discussion

In terms of symptom improvement, our study found that andrographis capsules were the most effective. This observation is in line with a study by Mahajaroensiri et al [7] which reported that andrographis capsules helped reduce inflammation by targeting the production of inflammatory substances, resulting in a reduction of COVID-19 symptoms. Similarly, Wanaratna et al [10] discovered that the use of *Andrographis paniculata* extract in the treatment of COVID-19 with mild symptoms was safe and effective. It was associated with a reduction in viral shedding time, inflammation suppression, and pneumonia prevention. However, it's important to note that some symptoms, such as cough, loss of smell, diarrhea, and muscle pain, did not improve as significantly after treatment.

Blood pressure and oxygen saturation showed significant improvements. Notably, Lianhua Qingwen with symptomatic treatment demonstrated the most significant improvement in patients' vital signs among the treatment methods. This finding is supported by Jeon et al. [11] who found that Lianhua Qingwen reduced fever symptoms, accelerated recovery time, and prevented the progression of the disease to a severe level. There is a growing body of evidence indicating that using Lianhua Qingwen with symptomatic treatment is effective in managing COVID-19 due to its antiviral, anti-inflammatory, and immune-enhancing properties [12]. Moreover, studies such as the one by Hu et al [13] have shown that Lianhua Qingwen can lead to a higher rate of symptom recovery and shorter recovery times in COVID-19 patients. However, it's worth noting that in our study, some patients' vital signs did not improve post-treatment, possibly due to underlying conditions present before treatment, such as high blood pressure.

The significant improvement in chest x-ray results, with the most pronounced improvements seen in patients treated with homeopathic medicines alongside symptomatic treatment. This observation aligns with a study by Takacs et al [14] which reported improved chest x-ray findings in COVID-19 patients following treatment with homeopathic medicines. Importantly, the results from our study could be influenced by the fact that most patients treated with homeopathic medicines were classified as moderate cases, which could lead to abnormal chest x-ray findings. Notably, none of the patients in our study exhibited worsening chest x-ray findings, irrespective of the treatment method used.

The differences between treatment methods and the stage of COVID-19 patients' disease, data indicate an association between the four treatment methods and the disease stage. As observed, a higher number of asymptomatic and mild cases were present for all four treatment methods, with moderate cases predominantly associated with homeopathic medicine treatment. This observation can be attributed to the hospital's screening protocols, which specified that moderate cases should be treated with homeopathic medicines. The differences observed between the four treatment methods and the disease stage were statistically significant.

Conclusion

This study found a statistically significant association between comorbidity, stage of diseases, and treatment methods at Ratchaphiphat Hospital in April-May 2021. Strong evidence of improvement percentage of symptoms, vital signs, and chest x-rays between treatment methods. Notably, andrographis capsules combined with symptomatic treatment showcased the most substantial improvement in symptoms, while Lianhua Qingwen, in conjunction with symptomatic treatment, revealed the most remarkable enhancement in vital signs. Homeopathic medicine, when used alongside symptomatic treatment, exhibited the most noteworthy improvements in chest x-ray findings.

Competing interests

The authors had no competing interests to declare.

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Factors Associated with COVID-19 Preventive and Control Behaviors among People in High Incidence Border Community, Thailand - Myanmar

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ABSTRACT

Introduction: The COVID-19 pandemic has posed a significant threat to global public health for over a year, affecting communities worldwide, including those residing in border areas between Thailand and Myanmar. Mae Sai District, located in the northernmost part of Chiang Rai Province in northern Thailand, serves as a prominent border crossing between the two countries, characterized by high population mobility and a substantial presence of foreign workers, thereby rendering its inhabitants susceptible to COVID-19 transmission. This study aimed to determine factors associated with the prevention and control of COVID-19 behaviors among people in Mae-Sai District, Chiang Rai Province.

Methods: An analytical cross-sectional study was conducted to collect data in Thai-Myanmar borders in Mae Sai District, Chiang Rai Province, Thailand. A validated questionnaire was used to collect the characteristics, predisposing factors, reinforcing factors, and enabling factors related to COVID-19 prevention and control behaviors. The questionnaire was assessed by three experts, and the content validity index (CVI) before use. The Kuder-Richardson coefficient (KR-20) was calculated and yielded a value of 0.73, indicating good reliability. The questionnaires were completed via face-to-face interviews. The data were summarized and analyzed by descriptive statistics and Spearman rank correlation.

Results: A total of 346 participants were recruited for the study, with a majority (59.8%) being females, and 28.3% belonging to the age group of 50 to 59 years. Most participants (53.2%) were married, and a significant proportion (76.6%) had previously experienced COVID-19 infection, with 39.0% opting for home isolation. Encouragingly, a vast majority (96.8%) had received the COVID-19 vaccine, and 52.3% had received at least two doses of vaccination. Predisposing factors, namely attitude ($r = 0.25$; p-value <0.001) demonstrated notable associations with COVID-19 prevention and control behavior. Additionally, reinforcing factors such as social support ($r = 0.39$; p-value <0.001) and participation ($r = 0.45$; p-value <0.001), along with enabling factors like service ($r = 0.35$; p-value <0.001), also positive correlations with COVID-19 prevention and control behavior.

Conclusion: The study's findings underscore the importance of targeted training programs to enhance the population's knowledge, understanding, and awareness of preventing communicable and emerging diseases, including COVID-19. As COVID-19 continues to be a major human threat, particularly in border areas with high population mobility and foreign workers, empowering the community with relevant knowledge and strategies for prevention is crucial to effectively combat the spread of the virus.

Keywords: Prevention and Control, Cross-border community, COVID-19 outbreak

Introduction

Since its emergence in Wuhan, China in December 2019, the Coronavirus Disease-2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2, has rapidly spread across the globe, becoming one of the deadliest pandemics of this decade [1, 2]. As the pandemic situation escalated, countries worldwide, including Thailand, were impacted. In response, the Thai government established a national committee to address the issue. As of the late stage of the pandemic in Thailand, the country reported 4.7 million confirmed cases, with 4.6 million patients recovered, accounting for 97.9% of all cases, and 33,935 deaths [3]. In the northernmost part of Thailand, Mae Sai District is the northernmost district of Chiang Rai Province in northern Thailand. The area is characterized by high population mobility and a substantial presence of foreign workers, making it susceptible to COVID-19 transmission. Mae Sai District has encountered the second-highest number of COVID-19 cases in Chiang Rai Province. The accumulated number of confirmed cases was 21,890, and there were 12 reported deaths [4].

The spread and severity of infectious diseases are associated with at least three main factors. The first factor is the disease pathogen, the second factor involves the behaviors and resistance of the population, and the third factor is related to societal systems and various preparedness measures, whether they are strong or weak [5]. Therefore, preventive and control behaviors against the COVID-19 virus, access to resources and healthcare services, communication of policies regarding COVID-19 prevention, and receiving support from family or community members in situations where the virus is spreading, are crucial factors.

During the COVID-19 outbreak, Chiang Rai took various preventive measures, including organizing meetings with public health agencies and establishing a center to monitor the COVID-19 situation. Some border checkpoints with neighboring countries were closed, and screenings at entry and exit points were increased. The public in Chiang Rai was repeatedly urged to work together to prevent the spread of the virus. Accurate information about the disease, effective prevention, and control measures have proven crucial during the pandemic. Guidelines from the World Health Organization (WHO) included physical distancing, mask-wearing, avoiding crowds, proper ventilation, regular handwashing, and practicing good coughing etiquette [6]. Additionally, the Thai Ministry of Public Health implemented various preventive measures such as massive lockdowns, the DMHTT (distancing, mask-wearing, hand washing, testing temperature, Thai chana application), and home isolation [7, 8]. Despite these measures and guidelines at the national and provincial levels, a lack of awareness and participation among the public could hinder the efforts to control and prevent the spread of COVID-19.

The PRECEDE model [9], which was developed in the early 1970s has been effectively applied worldwide to address a broad range of health issues. The PRECEDE model, which stands for the Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation, posits that achieving healthiness or adopting healthy behaviors is influenced by various factors. These predisposing factors encompass knowledge, attitudes, beliefs, values, and perceptions. Notably, media perception serves as a pivotal method of health communication, significantly contributing to the enhancement of knowledge and the cultivation of health protection skills, particularly in the context of the ongoing COVID-19 pandemic [10]. Reinforcing factors play a crucial role in supporting the cultivation of desired health behaviors, including elements such as warnings, commendations, and encouragement [11]. Ultimately, enabling factors, which encompass skills or physical components such as the availability and accessibility of resources or services, facilitate the correct adoption of health behaviors. The literature review found that Rojpaisarnkit's research applied the PRECEDE model [12] to identify the determinants influencing disease prevention behaviors. The study revealed a range of factors falling under individual attributes, predisposing factors, enabling factors, and reinforcing factors that impact COVID-19 disease prevention behaviors [13]. As a result, this study incorporated the following factors based on the PRECEDE model, encompassing predisposing factors (such as perception and attitude), enabling factors (accessibility service), and reinforcing factors (including social support and participation). In the literature review, there was no study on behavior in preventing and controlling COVID-19 among people in border communities in Thailand - Myanmar.

To address these challenges, this research aims to study causal factors encompassing predisposing, enabling, and reinforcing aspects that are related to COVID-19 preventive and control behaviors. Utilizing the PRECEDE framework as the conceptual framework for analysis, this research seeks to identify the underlying causes and elements contributing to the current situation, allowing for more effective planning of corrective actions and disease management, prevention, and control. Understanding the factors influencing COVID-19 prevention and control behavior in the Mae Sai border area of Chiang Rai Province is essential for developing targeted strategies and interventions to mitigate the spread of the virus effectively. By analyzing the Predisposing, Reinforcing, and Enabling aspects through the PRECEDE FRAMEWORK, this research aimed to provide valuable insights that can contribute to strengthening public health efforts in combatting the COVID-19 pandemic in this vulnerable region.

Methodology

Study Design, and Study Setting

An analytical cross-sectional study was applied. The study was conducted among a population aged more than 20 years old who lived in Mae Sai sub-district, Mae Sai district, Chiang Rai province. Data collection between the period of July, 1st 2022 December, 15th 2022.

Sample Size Calculation

The population used in this study was people aged 20 years and over, including Thai people and migrant workers. Selected by simple random sampling. The total number of population groups is 14,026 people. The sample size was calculated by the W.G. Cochran [14] formula at a confidence level of 95.0% with a tolerance of ± 5.0%

$$n = \frac{0.36(1-0.36)}{\frac{(0.05)^2}{(1.96)^2} + \frac{0.36(1-0.36)}{14{,}026}}$$

n =345.33 and abounding to 346

Inclusion and Exclusion Criteria

The study included participants who met the following criteria: aged 20 years and older, residing in the Mae Sai Subdistrict of Mae Sai District, Chiang Rai Province, for a minimum of 1 year, not employed as public health officials or volunteers involved in COVID-19 surveillance, prevention, and control, capable of speaking, listening, and communicating in the Thai language, and willing to participate in the research voluntarily. Excluded from the study were individuals who did not fully meet the specified questionnaire requirements and those with disabilities related to visual impairment, hearing impairment, communication difficulties, and mobility.

Research Instruments

A structured and validated questionnaire was utilized to collect information, comprising five parts. Part I gathered personal data, including sociodemographic information, history of COVID-19 infection, and vaccination status. Part-II focused on predisposing factors, with questions related to perception (10 items), and attitude (10 items), Part-III addressed reinforcing factors, covering social support (10 items) and participation (10 items). Part IV examined enabling factors, consisting of questions related to services (10 items). Part V focused on COVID-19 prevention and control behavior (10 items).

The questionnaire was created by the researcher, content validity was assessed by three experts, and the content validity index (CVI) method was used to improve the content validity. Reliability was also examined by administering the tool to a sample of 30 individuals in Pongpha Subdistrict, Mae Sai District, Chiang Rai Province, which was similar in characteristics to the target population. The Kuder-Richardson coefficient (KR-20) was calculated and yielded a value of 0.73, indicating good reliability.

Data Analysis

The descriptive analysis was conducted for all sections of the questionnaires using the SPSS version 23. The data were presented in the form of the frequency and percentage in all categorical data, Variables in part-II to Par-V were analyzed and interpreted in five levels [15]: low while scored < 60%, moderate while scored 60-79% and high while scored 80-100%. Spearman rank correlations were used to detect the correlation at the significant level of alpha=0.05.

Ethics Consideration

This study and its protocols had been approved for conducting research in human subjects by the Human Research Ethics Committee of Chiang Rai Provincial Public Health Office (CRPPHO No. 94/2565) and the Human Research Ethics Committee of Mae Fah Luang University (No. COA139/2022). All participants were clearly explained the research objectives and processes, confidentiality, risks, and benefits. and participants' rights before obtaining the informed consent in written form.

Results

General characteristics of participants

The majority of the participants were females (59.8%), and 28.3% were aged between 50 and 59 years (mean age = 43.67, SD = 12.55). 53.2% of the participants were married, 91.9% identified as Buddhist, and 32.9% had completed elementary school education. Regarding healthcare coverage, 67.9% were under the Universal Coverage Scheme, and 50.0% were employed. A substantial proportion of participants (76.6%) reported having experienced COVID-19 illness in the past, with 39.0% having been isolated at home. Furthermore, 96.8% of participants had received the COVID-19 vaccine, with 52.3% having received at least two doses of vaccination (Table 1).

Table 1 Characteristics of participants (n=346)

Characteristics	n	%
Total	346	100.0
Sex		
Male	139	40.2
Female	207	59.8
Age (years)		
20-29	58	16.8
30-39	76	22.0
40-49	76	22.0

Characteristics	n	%
50-59	98	28.3
≥ 60	38	11.0
Mean=43.67, SD=12.88, Min =20, Max =78		
Marital status		
Single	127	36.7
Married	184	53.2
Widowed/Divorced	35	10.1
Religion		
Buddhist	318	91.9
Christian	17	4.9
Islamic	10	2.9
Unreligious	1	0.3
Education		
Unlettered	90	26.0
Elementary School	114	32.9
Secondary School	39	11.3
High School	52	15.0
Bachelor's degree	34	9.8
Master's Degree	6	1.7
Medical treatment rights		
Universal Coverage	235	67.9
Scheme		
Social Security Fund	36	10.4
Stateless People	34	9.8
No rights	30	8.7
Civil Servant Medical	11	3.2
Benefit Scheme		
Occupation		
Employee	173	50.0
Merchant	63	18.2
Agriculturist	27	7.8
Housekeeper	24	6.9
Government Officer	13	3.8
Government Employee	4	1.2
Self-Employed.	6	1.7
State Enterprise	3	0.9
Unemployed	17	4.9
Students	13	3.8
Freelance	1	0.3
History of COVID-19		
infected		
Yes	265	76.6
No	81	23.4
Place of treatment		
Chiangrai Prachanukroh	34	12.8
Hospital		
Mae Sai Hospital	62	17.9
Kasemrad Sriburin	8	2.3
Hospital Mae Sai		
Community isolation	26	7.5
(CI)		
Home isolation (HI)	135	39.0
History of vaccination		
Yes	335	96.8
No	11	3.2
Number of vaccinations		
(Dose)		
1	4	1.2
2	181	52.3
3	140	40.5

According to predisposing found that the level of perception about COVID-19 was high (95.4%), moderate (2.9%) and low (1.7%). Level of attitude towards COVID-19 were high (93.4%), moderate (5.2%) and low (1.4%). In the aspect of reinforcing found that, the level of social support was high (88.2%), moderate (3.8%) and low (8.1%). Level of participation were high (73.7%), moderate (16.5%) and low (9.8%). Regarding enabling found that, the level of service system was high (81.8%), moderate (12.1%) and low (6.1%). Level of COVID-19 prevention and control behavior were high (84.7%), moderate (14.2%) and low (1.2%) (Table2).

Table 2 Level of predisposing, enabling, reinforcing, and COVID-19 prevention and control behaviors (n=346)

Factors	Levels					
	High		Moderate		Low	
	n	%	n	%	n	%
Independent variables						
Predisposing						
Perception	330	95.4	10	2.9	6	1.7
Attitude	323	93.4	18	5.2	5	1.4
Reinforcing						
Social support	305	88.2	13	3.8	28	8.1
Participation	255	73.7	57	16.5	34	9.8
Enabling						
Service	283	81.8	42	12.1	21	6.1
Dependent variable						
Prevention and control behavior	293	84.7	49	14.2	4	2.1

According to the correlation of predisposing, reinforcing, enabling, and COVID-19 prevention and control behaviors, it was found that predisposing (perception) showed no statistically significant correlation with COVID-19 prevention behavior (r=0.21; p-value=0.695). Predisposing (attitude) exhibited a low positive correlation with COVID-19 prevention and control behavior, which was statistically significant (r=0.25; p-value <0.001), reinforcing (social support) displayed a low positive correlation with COVID-19 prevention and control behavior, which was statistically significant (r=0.39; p-value <0.001). Reinforcing (participation) demonstrated a low positive correlation with COVID-19 prevention and control behavior, which was statistically significant (r=0.45; p-value <0.001). Enabling (service) also exhibited a low positive correlation with COVID-19 prevention and control behavior, which was statistically significant (r=0.35; p-value <0.001) (Table 3).

Table 3 Factors association with COVID-19 prevention and control behaviors

Factors	COVID-19 Preventive and Control Behaviors	
	r	p-value
Predisposing		
Perception	0.02	0.695
Attitude	0.25	<0.001**
Reinforcing		
Social support	0.39	<0.001**
Participation	0.45	<0.001**
Enabling		
Service	0.35	<0.001**

** Correlation is significant at $\alpha = 0.01$ (2-tailed)

Discussion

The majority exhibits high levels of disease prevention and control behaviors consistent with the study of it is found that behaviors related to preventing the disease caused by the COVID-19 virus align predominantly at a high level [16, 17]. This might be due to the effective dissemination of guidelines for preventing the spread of COVID-19 from the national healthcare management system in Thailand. These guidelines have been distributed to the public at various levels, spanning from central to community levels [18]. Individuals have received information from various sources about COVID-19 and its statistics. Emphasizing the severity of the disease's impact on health, potentially leading to fatal outcomes, these reports have influenced the public's correct adoption of infection prevention and control behaviors.

Predisposing factors (perception) do not correlate with COVID-19 prevention and control behaviors. The cause may be due to the area in the Thai-Myanmar border community, Mae Sai District, Chiang Rai Province, where there is a diversity of ethnicities and a limitation in communication between staff. With employers hiring foreigners and migrant workers, there is still a lack of awareness about the prevention, and control of behavior. This was supported by a previous study, which found that language and cultural differences are significant factors. The main reason that should not be overlooked is the problem of communication, stemming from language differences, where employees are unable to understand the local language, causing difficulty in communication [19].

Predisposing factors (attitude) are positively correlated with COVID-19 prevention and control behaviors. Individuals possessing sound knowledge and

positive attitudes will collectively adhere rigorously to the governmental safety protocols to safeguard themselves and those in their vicinity from contracting the infection [20]. As a result, the all-encompassing public education campaign conducted through diverse communication channels, spearheaded by the Center for COVID-19 Situation Administration (CCSA) and executed by public health professionals, has played an indispensable role in enhancing public knowledge, comprehension, and confidence in the government's endeavors to manage the pandemic. Consequently, this has fostered a positive mindset among the populace toward the instituted preventive measures and strict adherence to regulations. Witnessing the favorable outcomes stemming from these initiatives, individuals are cultivating a sense of personal responsibility in contributing to the containment of COVID-19 spread in Thailand [21].

Reinforcing (social support) is positively correlated with COVID-19 prevention and control behaviors. Social support from family, friends, health volunteers, and health personnel motivates people to change their behavior [22, 23]. Therefore, in the situation of the COVID-19 epidemic, government officials, including local government and public health officials, along with network partners in the community, village health volunteers, and related networks, should be involved in helping to encourage self-sustaining healthy practices.

In addition, reinforcing (participation) showed a positive correlation with COVID-19 prevention and control behaviors. Citizen participation and involvement of local governments are essential for performing or providing any public service. Local people in communities have played a vital role in the success of DMHTT policies during the COVID-19 pandemic. Their active participation in distancing, mask-wearing, handwashing, temperature checks, testing, and the Thai Chana application, along with collaborative efforts to raise awareness, has been instrumental in controlling the spread of the virus and safeguarding public health [24]. When people feel that they not only receive services but also belong to and have ownership of their locality [25], they are more likely to take part in relevant work or matters. People's involvement contributes to successfully managing problems and carrying out various operations. Findings from China revealed that nearly one-third of community members proactively sought information on COVID-19 [26]. Establishing partnerships with communities can help dispel COVID-19-related rumors and fallacies and alleviate unnecessary fear in community settings. If community stakeholders are not equipped with evidence-based knowledge of COVID-19, they will not be able to disseminate this critical information to residents of their communities [27-29].

Enabling (service) positive correlation with COVID-19 prevention and control behaviors. One potential explanation is that the pandemic's impact on the healthcare system has led to necessary adaptations due to various limitations in service delivery aimed at curbing the pandemic's spread. For instance, many public hospitals were compelled to suspend outpatient medical services and implement strategies to regulate local and external travel for a specific duration. Consequently, individuals faced restricted access to hospital facilities, despite their ongoing need for health services to preserve their well-being [30]. A report highlighted a shift in people's approach to healthcare during the COVID-19 crisis, guided by the Ministry of Public Health, Thailand. This transformation involved transitioning from a hospital-based reactive approach to a proactive community-based approach within primary healthcare settings [31].

Conclusion

In conclusion, the complex interplay of different factors influencing COVID-19 prevention, and control, including, attitudes towards COVID-19 preventive and control measures, social support, participation, and access to health services are related to behaviors for COVID-19 prevention and control. Policymakers and public health authorities should take into account the importance of addressing communication barriers, fostering a positive attitude, encouraging appropriate behaviors, promoting social support, and involving the community to effectively combat the pandemic. Perception's influence on COVID-19 prevention and control behavior is not consistent. It can be influenced by a range of factors, including individual variation in perception, the presence of misinformation, cultural and social influences, resource limitations, and pandemic fatigue. Understanding these factors is crucial for public health efforts to effectively promote and sustain preventive behaviors. It highlights the importance of comprehensive and tailored communication strategies that consider the diverse perceptions and challenges individuals may face during the ongoing pandemic. By leveraging these findings, we can enhance our collective efforts to manage and prevent the spread of infectious diseases like COVID-19 in the future.

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Associations between Knowledge, Attitudes, and Practices Regarding Hepatitis B Virus Infection and HBV Infection among Blood Donors in Mogadishu, Somalia: A Hospital-based Cross-sectional Study

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ABSTRACT

Introduction: Globally, more than 81 million blood units are donated annually, and blood transfusion stands as a crucial medical procedure with no viable substitute. Unsafe blood transfusion contributes to 8 to 16 million new hepatitis B virus (HBV) infections, particularly in sub-Saharan Africa. Somalia faces a high demand for blood transfusions with a prevalent HBV infection rate, driven by various factors, yet no similar previous study exists. The objective of this study was to determine the associations between the knowledge, attitudes, and practices of blood donors concerning HBV infection and their infection status in Mogadishu, Somalia.

Methods: A cross-sectional study was conducted in data collection between February and April 2023, using a 5ml blood sample and a well-structured questionnaire. A rapid test was utilized to indicate HBV positivity. Univariable and multivariable logistic regressions were employed to determine the associations, considering at $\alpha = 0.050$ as statistically significant.

Results: Out of the 420 blood donors who participated in this study, 34 (8.1%) tested positive for HBV infection. The majority of the participants (94.2%) were males with an average age of 30.4 (SD±7.2). In multivariable logistic regression, the study revealed that blood donors with poor knowledge (AOR=5.80, 95% CI=1.69-19.89), those with moderate knowledge (AOR=4.41, 95% CI=1.09-17.90), and those with poor practices (AOR=3.52, 95% CI=1.09-11.34) toward HBV infection were more likely to become infected compared to their counterparts.

Conclusion: Blood donors in Mogadishu, Somalia, face a high burden of HBV infection. To effectively address this issue and ensure a safer blood supply, prioritizing initiatives aimed at enhancing the knowledge of blood donors regarding HBV infection is crucial. This involves educating donors about the various modes of transmission, emphasizing preventive measures, and stressing the importance of regular screenings. Additionally, encouraging better practices related to HBV infection among blood donors is essential in this endeavor.

Keywords: Knowledge, Attitudes, Practice, Blood donors, HBV infection, Somalia

Introduction

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV) that triggers liver inflammation and can potentially result in severe complications such as liver cirrhosis, failure, and cancer [1]. Classified as a well-known hepadnavirus, HBV harbors a double-stranded circular DNA genome. Globally, an estimated 296 million individuals suffer from chronic HBV infection, with approximately 1.5 million new infections annually. HBV is responsible for about 57.0% of liver cirrhosis cases and 78.0% of liver cancer incidences [2-4]. Globally, more than 81 million blood units are donated annually, and blood transfusion stands as an indispensable therapeutic procedure lacking a viable substitute [5]. Unfortunately, unsafe blood transfusion practices contribute to 8 to 16 million new HBV infections [4, 5]. The World Health Organization (WHO) has projected around 45,000 new HBV and

HCV infections linked to unsafe transfusion practices in Sub-Saharan African countries [6]. HBV prevalence varies significantly, ranging from 2.1% to 25.9% across different regions [7-9].

Remarkably, viral hepatitis, predominantly driven by HBV, constitutes a pressing public health challenge in Africa. Studies reveal a high prevalence of HBV among African blood donors, recording rates of 4.2% in Rwanda [10], 4.1% in Calabar Nigeria [11], 14.9% in Burkina Faso [12], 5.6% in Kenya [13], 10.9% in Jijiga Ethiopia [14], and 2.0% in Eritrea [15]. While Somalia faces a high demand for blood transfusions with a high prevalence of HBV infection [16]. A meta-analysis conducted in Somalia revealed an overall pooled HBV prevalence of 18.9% [17]. The rates were even higher in specific demographics, with a prevalence of 20.5% among pregnant women, 39.2% among chronic liver disease patients, and 60% among individuals suffering from acute hepatitis [17]. Moreover, hemodialysis patients in Somalia were reported to have an HBV prevalence of 7.3% [18]. The demand for blood transfusions in clinical facilities across Somalia is notably high, driven by various factors including frequent terrorist incidents, road traffic accidents, endemic malaria resulting in anemia among children and pregnant women, as well as blood loss from surgical and obstetric procedures [19]. It is hypothesized that inadequate knowledge, lack of awareness, negative attitudes, and neglected practices among potential blood donors toward HBV infection contribute significantly to the burden of this disease in Somalia.

Insufficient understanding of HBV transmission and prevention often leads to high-risk behaviors, delaying testing and treatment efforts. This lack of awareness may neglect basic precautions and cultural practices that could otherwise mitigate disease transmission. A secure blood supply requires Up-to-date information about the association between blood donors' knowledge, attitudes, practices, and their HBV infection status. This knowledge is crucial for prevention strategies, guiding educational campaigns, ensuring a safe blood supply, limiting disease transmission, and significantly supporting eradication programs. Hence, the primary aim of this study is to investigate the association between the knowledge, attitudes, and practices of blood donors concerning HBV infection and their infection status in Mogadishu, Somalia.

Methodology

Study Design

A cross-sectional study was conducted at Banadir Public Hospital in Mogadishu, Somalia, spanning between February and April 2023.

Study Area

Mogadishu, the capital, and most densely populated city of Somalia served as the study city. Banadir hospitals, our focal point, play a pivotal role in the healthcare landscape by functioning as teaching and referral facilities. Established in 1976, these hospitals have been fundamental in providing medical and surgical care to over 3 million individuals. With a capacity exceeding 700 beds and a workforce of 400 healthcare professionals, Banadir Hospital consistently admits between 2,500 to 3,000 patients every month [20-22]. Given its substantial patient volume and significant contribution to community blood donation efforts, Banadir Hospital was selected as the ideal setting for our study.

Study Population and Eligibility Criteria

The study included all individuals over 18 years old who presented themselves at the blood donation unit of the hospital during the study period with the intent to donate blood or blood components. Exclusion criteria involved mentally unfit individuals, those unwilling to participate in the study, individuals with communication impairments or hearing deficiencies, and those who had received a dose of the HB vaccine within the last 30 days. The Centers for Disease Control and Prevention (CDC) guideline regarding HB marker interpretation suggests that individuals who received the HBV vaccine within the last 30 days might exhibit transiently positive HBsAg without being infected [23]. Hence, they were excluded from the study to ensure the accuracy of the HBV infection status assessment.

Sample Size and Sampling Technique

The study sample size was determined using a standardized formula for cross-sectional studies [24]. The formula, $n=Z^2_{\alpha/2}\ P(1-P)/d^2$, where $Z_{\alpha/2}$ represents 1.96, P denotes the prevalence proportion (18.6% obtained from a similar study in Nigeria [25]), and d signifies the desired precision level of 0.05. Therefore, this study initially aimed for a total sample size of 256 respondents, accounting for a 10% non-response rate. A total of 420 participants were recruited. The selection of participants was conducted using a systematic sampling technique.

Research Instruments and Measurements

The research used a 5ml blood sample and a well-structured developed, validated, and reliable questionnaire derived from existing literature, vetted by three external experts.

The questionnaire included: i) socio-demographic characteristics; ii) twelve true or false simple dichotomy knowledge statements; iii) twelve Likert 5 scale attitude statements; and iv) ten practice statements based on frequency (always, occasionally,

never). For the knowledge section, a correct response was scored "1", and an incorrect response received "0". The maximum expected knowledge score was "12", categorized as poor knowledge (<60%), moderate knowledge (60-79%), and good knowledge (≥80%), following Bloom's cut-off point classification [26-28]. Likewise, the attitude section used a scoring system ranging from strongly disagree (1 score) to strongly agree (5 score) or vice versa for negative statements with a maximum score of 60. Responses were categorized as negative attitude (<60%), neutral attitude (60-79%), and positive attitude (≥80%) based on Bloom's cut-off point classification [28-31]. The practice section scored "1" for correct responses (always) and "0" for incorrect responses (never and occasionally), with a maximum expected score of 10. Categories were designated as poor practice (<60%), moderate practice (60-79%), and good practice (≥80%) based on Bloom's cut-off point classification [26-31].

The questionnaire was initially developed in English, and then verbally translated during data collection interviews. The questionnaire was validated using the Item Objective Congruence method and involved three external experts (an infectious disease specialist, a public health researcher, and a clinical epidemiologist) [32]. A pilot study with 30 participants was conducted to ensure the questionnaire content reliability and respondents' understanding, achieving an acceptable Cronbach's alpha of 0.81.

Definition of Outcome Variable

HBV infection status was determined using a rapid test on blood samples obtained at the study hospital. Positivity for HBsAg and/or anti-HBs indicated HBV infection, excluding individuals showing anti-HBc negativity, indicating an absence of HBV exposure or evidence of recent, past, resolved, or chronic HBV [23]. The HBV marker's sensitivity and specificity were as follows: HBsAg (99.85% sensitivity, 99.90% specificity), HBsAb (99.70% sensitivity, 99.41% specificity), HBeAg (100% sensitivity, 100% specificity), HBeAb (99.34% sensitivity, 90.93% specificity), and HBcAb (99.78% sensitivity, 99.74% specificity) [33]. Interpretation followed the CDC's standardized HB serological guideline [23].

Data Collection Procedure

Five qualified licensed nurses underwent a three-day training session covering research procedures, eligibility criteria, blood sample collection techniques, and questionnaire content. Eligible participants were briefed about the study's objectives and invited to participate. Those who agreed signed a written consent form or provided a fingerprint for illiterate participants. Data collectors obtained a 5ml blood sample and conducted face-to-face interviews using the research tool, averaging 20 minutes per participant.

Data Processing and Analysis

The collected data was cleaned, coded, and entered into a spreadsheet. Subsequently, imported into SPSS version 20 (SPSS, Chicago, IL) for comprehensive analysis. Descriptive statistics were used to present a clear overview of the general characteristics. Categorical data were expressed as frequencies with percentages, while continuous data were presented as means with standard deviations (SD). Knowledge scores were based on correct (1) or incorrect (0) answers, the maximum expected score was 12. They were then grouped as poor knowledge (<60%), moderate knowledge (60-79%), and good knowledge (≥80%) following Bloom's cutoff point classification [26-28].

Attitude scores ranged from strongly disagree (1) to strongly agree (5), or their opposites for negative statements, with a maximum score of 60. Responses were categorized as negative attitude (<60%), neutral attitude (60-79%), or positive attitude (≥80%) according to Bloom's cutoff point classification [28-31]. Practice scores assigned 'always' as correct (1) and 'never'/'occasionally' as incorrect (0), leading to a maximum score of 10. These were grouped as poor practice (<60%), moderate practice (60-79%), and good practice (≥80%) aligning with Bloom's cutoff point classification [26-31].

Univariable and multivariable models of logistic regression were used to explore the potential associations between the outcome and independent variables. Variables demonstrating a p-value of ≤0.25 were selected as candidates for inclusion in the multivariate logistic regression analysis following suggestions of Bursac et al. [34], indicating that variables with a p-value ≤0.25 in univariate logistic regression might hold a reasonable association with the final model's outcome due possibility of having a potential confounding variable. The Hosmer-Lemeshow goodness-of-fit test was used to indicate the goodness of fit for the final model. In the multivariable logistic regression analysis, variables exhibiting a p-value of ≤0.05 were considered statistically significant.

Results

Hepatitis B Virus Infection Status

A total of 420 blood donors participated in this study, 34 (8.1%) tested positive for HBV infection, while 386 (91.9%) tested negative.

Socio-Demographic Characteristics

The study comprised that the majority (94.2%) of the respondents are male with an average age of 30.4 (SD±7.2). Most respondents 67.1% were single, 32.6% were illiterate, and 41.2% were employers with an average monthly income of 427.20 USD. In addition, there is a statistical association between demographical variables and HBV infection (Table 1).

Table 1 Socio-demographical characteristics between HBV-infected and non-infected

Characteristics	HBV infection		p-value
	No n (%)	Yes N (%)	
Sex			0.965
Male	364 (91.9%)	32(8.1%)	
Female	22 (91.7%)	2(8.3%)	
Age (years)			0.124
18-28	154 (90.6%)	16(9.4%)	
29-39	190 (91.3%)	18(8.7%)	
≥40	42(100.0%)	0(0.0%)	
	Mean=30.4 (SD±7.2)		
Marital status			0.112
Single	255(90.4%)	27(9.6%)	
Ever Married	131 (94.9%)	7 (5.1%)	
Education			0.874
Illiterate	124(90.5%)	13(9.5%)	
Read or write	92(92.0%)	8(8.0%)	
Primary level	110(92.4%)	9(7.6%)	
Post-primary	60(93.8%)	4(6.2%)	
Occupation			0.856
Employee	158(91.3%)	15(8.7%)	
Business	103(92.0%)	9(8.0%)	
Healthcare	54(94.7%)	3(5.3%)	
Jobless	71(91.0%)	7(9.0%)	
Residential area			0.089
Rural	81(96.4%)	3(3.6%)	
Urban	305(90.8%)	31(9.2%)	
Income $USD			0.437
<200	105 (91.3%)	10 (8.7%)	
200-400	126 (90.0%)	14 (10.0%)	
>400	155 (93.9%)	10 (6.1%)	

*Significant level at α=0.05

KAP of Blood Donors Regarding HBV Infection

The results reveal a substantial association between the HBV infection status of blood donors and their knowledge (p-value = 0.007), attitude (p-value = 0.047), and practices (p-value = 0.057), all significant at a level of ≤0.25 (Table 2).

Table 2 Knowledge, attitudes, and practices of blood donors regarding HBV Infection

Characteristics	HBV infection		p- value
	No n (%)	Yes n (%)	
Level of knowledge			
Poor	180 (88.2%)	24 (11.8%)	0.007*
Moderate	75 (91.5%)	7 (8.5%)	
Good	131 (97.8%)	3 (2.2%)	
Level of Attitude			
Negative	56 (84.8%)	10 (15.2%)	0.047*
Neutral	295 (92.8%)	23 (7.2%)	
Positive	35 (97.2%)	1 (2.8%)	
Level of Practice			
Poor	91 (86.7%)	14 (13.3%)	0.057*
Moderate	210 (92.9%)	16 (7.1%)	
Good	85 (95.5%)	4 (4.5%)	

* Significant at α=0.25

Factors associated with HBV infection

In the univariable logistic regression model, several factors including blood donors' age, marital status, resident area, knowledge, attitude, and practice showed significant associations with HBV infection at a significance level of α=0.25. These variables were selected as potential candidates for inclusion in the multivariable logistic regression model. Subsequently, variables with α=0.05 were considered statistically significant and presented in Table 3.

In multivariable logistic regression, the study found that blood donors with poor knowledge regarding HBV infection were 5.80 times more likely (95% CI = 1.69-19.89) to contract HBV compared to those with good knowledge. Similarly, individuals with moderate knowledge displayed 4.41 times higher odds (95%CI=1.09-17.90) of HBV infection compared to those with good knowledge. Furthermore, participants demonstrating poor practices concerning HBV infection showed 3.52 times higher odds (95% CI=1.09-11.34) of acquiring HBV compared to individuals who practice good habits.

Table 3 Associations between KAP and HBV Infection in univariable and multivariable models

Characteristics	OR (95%CI)	p- value	AOR (95%CI)	p-value
Age (years)				
18-28	1.33 (0.66-2.70)	0.416		
≥ 29	1.00			
Marital status				
Single	1.98 (0.84-4.67)	0.118		
Ever Married	1.00			
Residential area				
Rural	1.00			
Urban	2.74 (0.81-9.20)	0.102		
Knowledge				
Poor	5.82 (1.71-19.74)	0.005	5.80 (1.69-19.89)	0.005*
Moderate	4.07 (1.02-16.23)	0.046	4.41 (1.09-17.90)	0.037*
Good	1		1	
Attitude				
Negative attitude	6.25 (0.76-50.96)	0.087		
Neutral attitude	2.72 (0.35-20.83)	0.333		
Positive attitude	1.00			
Practice				
Poor	3.26 (1.03-10.32)	0.043	3.52 (1.09-11.34)	0.035*
Moderate	1.61 (0.52-4.98)	0.401	1.93 (0.61-6.05)	0.256
Good	1.00		1	

* Significant at p-value <0.05

Discussion

This study involved 420 blood donors, nearly half of whom exhibited inadequate knowledge about the HBV. Such gaps significantly impact disease transmission rates and individual HBV infection statuses. These knowledge deficiencies often lead individuals to unknowingly engage in behaviors contributing to increased transmission. This finding aligns with a similar study in Pakistan, underscoring a rise in HBV cases due to insufficient awareness or misconceptions about HBV transmission [35].

Furthermore, limited knowledge about the HBV vaccine has resulted in low vaccination rates, thereby increasing the risk of infection. Surprisingly, investigations into HBV vaccination rates in our specific area revealed an alarmingly low rate of complete vaccination, with only 16.0% of participants having received full vaccination. Reasons cited for non-vaccination included vaccine unavailability and high costs [36], consistent with findings from various other studies [37-39]. These results highlight the urgent need to improve vaccine uptake by addressing obstacles such as enhancing vaccine availability and reducing costs. Moreover, implementing educational campaigns is crucial in mitigating HBV transmission, advocating vaccination, limiting viral spread, and facilitating early diagnosis and treatment.

The reported HBV infection rate of 8.1% among collected samples in this study is lower than in similar studies in Burkina Faso [12], Kenya [13], Jijiga, Ethiopia [14], Eritrea [15], Nigeria [25], Ghana [40], Equatorial Guinea [41]. Conversely, this prevalence is higher than in comparative studies conducted in Tanzania [42], and other regions of Ethiopia [43]. These disparities might arise from various factors, including diverse risk factors among blood donors, variations in population and geographical locations, differences in vaccine accessibility and availability, varied exposure to infections, dissimilar risk factors, individual beliefs, and cultural influences, as well as demographic and economic disparities. Furthermore, differences in immunity statuses and sample sizes among the studies might have contributed to these variations.

This study revealed that three-fourths of the participating blood donors held a neutral attitude toward HBV infection, while a small number of them had a positive attitude. Attitudes toward HBV infection significantly influence individual and community responses. A negative or neutral stance often leads to limited awareness, hindering healthcare-seeking behavior and reducing community-wide efforts in prevention and support. This can lead to increased transmission rates, delayed diagnosis, and reduced access to necessary resources, perpetuating the cycle of infection and impeding effective control measures. A similar study reported that cultural and religious beliefs, coupled with a lack of knowledge and awareness about HBV, act as barriers to HBV screening and care [44]. Conversely, a positive attitude encourages education, proactive health-seeking behavior, and increased community support, ultimately aiding in prevention, early diagnosis, and improved access to care. Another similar study highlighted how inadequate knowledge or beliefs about HBV and its transmission can contribute to low vaccination rates within certain communities [45]. Addressing these attitudes and beliefs through targeted education and awareness campaigns, as recommended in previous studies, is crucial in increasing HBV screening, vaccination, and overall prevention efforts [46, 47].

This study found that blood donors with poor or moderate knowledge regarding HBV infection were over five and four times more likely, respectively, to become HBV infected compared to those with good knowledge. The association between a lack of knowledge about HBV infection and a higher likelihood of becoming infected is well-established. Lack of knowledge or inadequate awareness about how the virus spreads preventive measures and the availability of vaccination can contribute to an increased risk of HBV infection. Other factors such as misconceptions about transmission routes, inadequate knowledge about safe sex practices, needle sharing, or improper handling of contaminated blood or body fluids can exacerbate the situation. A previous study conducted in the same area reported inadequate knowledge of HBV and recommended tailored health education programs for this vulnerable population [48]. Furthermore, a similar study from Ghana highlighted the significant association between poor HBV knowledge and a high prevalence of HBV infection [49]. However, our study emphasizes the importance of implementing educational campaigns, and public health initiatives, and providing accurate information about HBV transmission and prevention to reduce the risk of infection.

Finally, this study revealed that individuals with poor practices toward HBV infection were over three times more likely to become HBV-infected compared to those with good practices. Poor practices toward HBV can lead to exposure to various risky behaviors or practices, as HBV primarily spreads through contact with infectious bodily fluids or blood, posing a considerable risk to individuals engaging in certain activities. Reducing these risks involves adopting safe practices, such as practicing safe sex, avoiding needle sharing, ensuring sterilized medical environments, and getting vaccinated against HBV. A similar study highlighted how stigmatizing attitudes can directly influence the HBV infection status in the community and suggested that having accurate knowledge of disease processes and being sufficiently educated may not be enough to prevent the disease without adequate practice [50]. One more study reported a low correlation between knowledge and attitudes toward HBV infection [51]. Moreover, African studies

reported a high prevalence of HBV infection attributed to poor practices toward the disease and its transmission, recommending high-quality tailored education programs targeting young students to combat disease transmission [51-53]. Therefore, our study reiterates the importance of maintaining proper hygiene, refraining from sharing personal items, particularly those contaminated with blood, and exercising caution in occupational settings as crucial preventive measures against HBV transmission.

However, the nature of this study being cross-sectional implies that it is unable to establish a definitive cause-and-effect relationship between the factors examined and the observed outcomes.

Conclusion

Blood donors in Mogadishu, Somalia, face a significant challenge of HBV infection. To effectively combat this issue and ensure a safer blood supply, it is crucial to prioritize initiatives aimed at enhancing the knowledge and practices of blood donors regarding HBV infection. Specifically, interventions should focus on educating donors about the various modes of transmission, emphasizing preventive measures, and stressing the importance of regular screenings. Encouraging better practices related to HBV infection among blood donors is essential in this endeavor. Moreover, it is highly recommended to implement collaborative efforts involving governmental health agencies, non-governmental organizations, and community leaders. These partnerships can play a pivotal role in nurturing a culture of awareness, prevention, and responsible behavior concerning HBV infection. By concentrating on education, improving practices, and fostering collaborative initiatives, we can make significant strides in reducing the burden of HBV infection among blood donors in Mogadishu, Somalia, thereby ensuring a safer and healthier blood supply for the community.

Ethical Approval and Study Considerations

This study rigorously followed the guidelines outlined in the World Medical Association's declaration of Helsinki. Ethical clearance was granted by the Ethical Committee on Human Research at Mae Fah Luang University, Muang, Chiang Rai, Thailand, with protocol number (22205-18). Before joining, all eligible participants received detailed information about the study's objectives and were invited to take part. People who could read provided written consent by signing a form. For those who couldn't read, their legal representatives helped them understand the consent form, and they agreed to participate by providing their fingerprints instead of a signature. This ensured that their involvement was voluntary and free from pressure. Additionally, participants were informed that they could choose to participate or stop the interview at any time. The study strictly maintained confidentiality by anonymizing questionnaires and presenting data only in collective form without disclosing individual identities.

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Physical and Psychological Factors Associated with Non-specific Low Back Pain among Female Cleaners in Academic Settings

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ABSTRACT

Introduction: Low back pain (LBP) is the most common musculoskeletal disorder (MSD). Cleaning professions are strenuous and physically demanding jobs that often require cleaners to perform awkward movements during cleaning tasks. Although several studies have reported a high prevalence of LBP in cleaners, few studies have identified the physical and psychological factors associated with non-specific LBP (NSLBP) in this population. The study aimed to determine the associations between physical and psychological variables and the presence of NSLBP in female cleaners working in an academic setting.

Methods: One hundred and ninety-nine female cleaners aged 18 to 60 years old with and without LBP were asked to complete a set of self-reported questionnaires to determine individual and work-related variables and quality of life and a Nordic body map to identify NSLBP. Binomial logistic regression analyses were used to determine associations between physical and psychological factors and the presence or absence of NSLBP.

Results: The overall prevalence of MSDs among cleaners was 66.92% in the last 3 months and 43.23% time at present. NSLBP accounted for the majority of MSDs, with a prevalence of 30.24% in the last 3 months and 18.08% time at present. There was a significant association between NSLBP and the WHOQOL physical health domain (AOR= 0.78; 95% CI= 0.69–0.88), the frequency of bending forward during work (AOR= 0.33; 95% CI= 0.13–0.81), the frequency of squatting or kneeling during work (AOR=3.29; 95% CI= 1.06–10.19), feeling exhausted after work (AOR= 4.51; 95% CI= 1.03–19.69), and job dissatisfaction (AOR=0.64; 95%CI= 0.01–0.22).

Conclusion: NSLBP was the most commonly reported work-related MSD among cleaners in an academic setting. Physical factors, including good or bad working postures, and psychological factors, including mental exhaustion, were significantly associated with the existence of NSLBP in cleaners.

Keywords: Prevalence, Back pain, Cleaners, Physical factors, Psychological factors, Musculoskeletal disorders

Introduction

Musculoskeletal disorders (MSDs) are defined as health conditions that are related to injury or dysfunction of the locomotor system and include compressed nerves, herniated discs, meniscus tears, sprains, strains, pain, swelling, numbness, degenerative joint disease, and connective tissue disorders [1, 2]. Approximately 1.71 billion individuals of all ages worldwide are affected by an MSD, causing MSDs to carry a high burden in terms of economic costs, healthcare needs, and social challenges due to their associated functional disability [3]. MSDs can be caused by the mechanical workload applied when performing daily tasks (e.g., sports, and housework) [1]. According to the World Health Organization (WHO), work and the circumstance of its

performance are causes of MSDs [1], an assertion supported by several studies that have indicated a relationship between physical exertion at work and work-related MSDs (WMSDs).

WMSDs have been defined as MSDs that are caused and aggravated by an individual's workload and work environment [1, 2]. MSDs among workers are impacted by several factors, including work-related, physical, and psychosocial factors. Work-related factors include physical exertion during work and work organization, which may involve repetitive movements, prolonged working postures with static and dynamic muscular activities, and awkward movements [4].

Low back pain (LBP) is the most common MSD. A diagnosis of LBP of unidentified pathoanatomical cause with no sign of serious medical conditions is termed non-specific LBP (NSLBP) [5-7]. NSLBP is the most common form of LBP, with only approximately 10% of patients having a specific LBP diagnosis [8]. In 2012, an epidemiological review of 165 studies from 54 countries reported a mean point prevalence of LBP of 18.30% and a 1-month prevalence of 30.80% [9]. Several risk factors have been associated with NSLBP and can be categorized into two primary categories: individual factors and activity-related (work and leisure) factors [10]. Individual factors involve demographic, anthropometric, physical, and psychosocial characteristics [11-13] while activity-related factors include occupational and workplace attributes such as inadequate leisure time [14], performance of heavy work tasks requiring lifting, bending, and twisting [15], and job dissatisfaction [16].

According to a review of the literature, the tasks required for cleaning are strenuous, physically demanding, and often performed in awkward positions. A few studies have investigated the prevalence and factors associated with MSDs among workers employed in cleaning professions in academic settings. Melese et al evaluated the prevalence and factors associated with MSDs among 270 cleaners at Mekelle University, Ethiopia, and reported a prevalence of MSDs during the last month of 52.30%. Of nine possible body regions, the low back was the most common painful region reported by the cleaners (34.80%), followed by the wrist and upper back (17.00%), elbow and shoulder (14.00%), knee (12.50%), neck and ankle/foot (9.50%), and hip/thigh (3.80%). MSDs were found to be significantly associated with time pressure, work experience ≥ 6 months, feeling exhausted, working ≥ 8 hours per day, work tasks requiring awkward postures, and spending > 2 hours in a sustained position [17]. Jaidee et al similarly studied the prevalence and factors associated with MSDs among 220 cleaners at Thammasat University, Thailand. Their results showed a prevalence of MSDs during the last month of 88.64%, with participants reporting neck pain (15.91%), shoulder pain (13.64%), elbow pain (0.91%), wrist/hand pain (5.91%), upper back pain (12.73%), LBP (24.09%), hip/thigh pain (17.73%), knee pain (36.36%), and ankle/foot pain (14.09%). MSDs were shown to be significantly associated with work experience, grip strength, and stress. Although several studies have identified a high prevalence of LBP and have clarified factors associated with MSDs in cleaners, the evidence thus far has focused solely on activity-related factors affecting WMSDs [18], and there is a lack of knowledge regarding the physical and psychological factors affecting LBP among cleaners. This study therefore aimed to investigate the physical and psychological factors associated with NSLBP in cleaners.

Methodology

Study Design

This study employed a cross-sectional survey research design. The study population included all female cleaners working at Chulalongkorn University from August 1, 2022, to November 30, 2022. The study protocol was approved by the Research Ethic Review Committee for Research Involving Human Research Participants, Group 1, Chulalongkorn University, Thailand (No.113/65).

Participants

All female cleaners working in the housekeeping units of 20 faculties and 23 colleges and research institutes at Chulalongkorn University were invited to participate in the study by the primary researcher. A convenience sampling method was used for subject selection. The criteria for inclusion in the study were female cleaners aged 18–60 years [3] who had worked in the same department for at least 6 months with a work schedule of at least 6 hours/day [17] and could listen, speak, read, and write in the Thai language without difficulty. Potential participants were excluded from the study if any of the following criteria were present: 1) history of specific LBP, 2) history of sciatica with lower limb numbness and weakness, and 3) history of kidney disease, tumor, or cancer [10].

The sample size was calculated based on the previous study by Jaidee et al, who investigated the prevalence and factors associated with MSDs among cleaners at Thammasat University [18]. Using their result of a 24.09% LBP prevalence, a 95% CI, and a precision of 0.05, the calculated sample size was 180. After a 10% participant dropout rate was added, the sample size of this study was set at a total of 198 cleaners.

Instruments

A screening questionnaire was used to determine eligibility to participate in the study. The questionnaire gathered data on gender, age, work schedule, ability to communicate in the Thai language, memory function, and history of specific LBP over the last 3 months.

A set of self-reported questionnaires was completed by all participating cleaners and consisted of three parts. The first part collected general information (e.g., height, body weight, education level), work-related factors (e.g., work experience, work duration, types of tasks or physical activities performed during work, frequency of performing each work posture), other activities of daily living, frequency of rest breaks at work, feelings of exhaustion and job dissatisfaction, and performance of repetitive work activities [19]. The second part collected information on quality of life using the Thai version of the WHOQOL-BREF. The WHOQOL-BREF has a total of 26 questions, which are divided into four domains—physical health (seven items), psychological (six items), social relationship (three items), and environment (eight items)—plus two independent items related to overall quality of life and health status [20]. Each item is scored on a scale of 1 to 5, with higher scores indicating better quality of life. Total scores range from 26 to 130. Total score ranges within each domain are 7–35 for the physical health domain, 6–30 for the psychological domain, 3–15 for the social relationship domain, and 8–40 for the environment domain. The third part of the questionnaire gathered information on the history of MSDs over the last 3 months, the location of the painful area on the Nordic body map, and pain intensity based on the Numeric Rating Scale (NRS) [21]. Participants rated their pain on a defined scale of NRS. Scores range from 0-10, with higher scores indicating higher pain intensity [22]. The questionnaire additionally gathered information regarding the duration and onset of the current LBP episode, any treatment being currently received, and time lost from work due to LBP. All instruments were pretested on a pilot group of 10 female cleaners prior to the initiation of the data collection phase to ensure the suitability of the questionnaires. When evaluating inter-rater agreement, an intraclass correlation coefficient of 0.96–1.00 indicated excellent reliability for continuous data [23], while a Kappa statistic (K-value) of 0.64–1.00 indicated good to excellent reliability for ordinal and categorical data [24].

Research Procedure

To recruit study participants, the primary researcher visited each workplace and asked the chief of the housekeeper unit for permission to collect data from the unit's cleaners. After obtaining permission, the researcher approached individual cleaners and explained the study's objectives and methods. Cleaners who agreed to participate in the study signed the consent form and completed the screening questionnaire. Any cleaners who met the eligibility criteria were subsequently asked to complete the set of self-reported questionnaires. The data collection process for each participant took approximately 30 minutes.

Statistical Analysis

After completing the self-reported questionnaires, the participants were divided into two sample groups, the LBP group, and the non-LBP group, for statistical analysis. Participants' self-reported pain intensity per the NRS was used to delineate the two groups. Participants who reported a current pain intensity equal to or greater than 3/10 on the NRS were placed in the LBP group, and participants with a current pain intensity equal to or less than 2/10 on the NRS were placed in the non-LBP group [10].

After all data were edited, SPSS software version 22.0 was used for quantitative data analysis. Descriptive statistics were used to describe participants' demographic characteristics, which were expressed as means and standard deviation (SD) for numerical data and percentages for categorical data. Binomial logistic regression analyses were performed to determine the association between physical and psychological factors and the presence or absence of NSLBP. The researcher adjusted some independent factors from continuous data to categorical data before calculating the univariate associations between factors. The factors with bivariate associations ($p < 0.05$) were entered into the binomial logistic regression, and the Wald backward stepwise method was employed to select variables for the model. The stepwise method employed an entry threshold of 0.05 and a removal threshold of 0.10 to explore associations between multiple variables. Crude odds ratios with 95% CI were reported. The level of significance was set at $\alpha = 0.05$ for all statistical analyses.

Results

A total of 43 academic settings comprising 20 faculties and 23 colleges and research institutes at Chulalongkorn University employ cleaners. Fourteen of the 43 workplaces participated in the study, and a total of 210 cleaners currently working in the 14 workplaces completed the screening questionnaire. Eleven potential participants were excluded from the study due to not being between 18 and 60 years of age (n = 5) and having a specific LBP diagnosis (n = 6), giving a response rate of 94%. Thus, 199 female cleaners with and without LBP were included in this study (Table 1).

The participants were divided into LBP and non-LBP groups. The LBP group included 52 (26.12%) participants with LBP and 4 (2.02%) participants with LBP and other MSDs, while the non-LBP group included 106 (53.27%) healthy participants and 37 (18.59%) participants with MSDs other than LBP. The participants with LBP reported moderate pain intensity, with a mean NRS score of 5.12 (SD: 2.09; range: 3–10), while those without LBP reported a mean NRS score of 0.51 (SD: 0.71; range: 0–2). The mean age, height, and weight of the participants were 49 years, 155.20 centimeters, and 60.60 kilograms, respectively. The participants had a workload of 5.60 days per week and 8.60 hours per day and reported spending an average of 5.40 hours per workday standing and sitting with rest breaks and 2.90 hours without rest breaks (Table 2).

Characteristics	Mean	±SD	Range
Age (years)	49.4	9.6	20-60
Height (cm.)	155.2	5.9	140-173
Weight (kg.)	60.6	12.4	32-104
Work Experience (years)	6.1	5.9	1-49
Working days per week (days per week)	5.6	0.5	5-6
Working hours per day (hours per day)	8.6	1.3	2-13
Standing and walking hours per day with rest breaks (hours per day)	5.4	2.2	1-10
Standing and walking hours per day without rest breaks (hours per day)			
Pain intensity (Numerical Pain Scale)	2.9	1.74	0.17-10
LBP (n=56)	5.12	2.09	3-10
Without LBP (n=143)	0.51	0.71	0-2

Table 1 Characteristics of study population (n=199)

The overall prevalence of MSDs was divided by body region to include the neck, shoulders, elbows, wrists/hands, upper back, lower back, hips, knees, and ankles/feet. The prevalence of MSDs among the female cleaners in the last 3 months was 30.24% in the lower back, 14.57% in the knees, 5.02% in the shoulders, 4.52% in the hips, 4.02% in the neck, 3.52% in the ankles/feet, 2.01% in the elbows, 2.01% in the wrists/hands, and 1.01% in the upper back. The prevalence of MSDs among the female cleaners at the present time was 18.08% in the lower back, 11.06% in the knees, 4.02% in the shoulders, 3.52% in the hips, 2.01% in the upper back, 1.51% in the elbows, 1.01% in the neck, 1.01% in the ankles/feet, and 1.01% in the wrists/hands (Table 2).

Table 2 Prevalence of self-reported musculoskeletal disorders in female cleaners during previous 3 month and at the present time

Body region	**MSDs previous last 3 months**	**MSD at the present time**
	n (%)	n (%)
Neck	8 (4.02)	2 (1.01)
Shoulders	10 (5.02)	8 (4.02)
Elbows	4 (2.01)	3 (1.51)
Wrist/hands	4 (2.01)	2 (1.01)
Upper back	2 (1.01)	4 (2.01)
Low back	62 (30.24)	36 (18.08)
Hips	9 (4.52)	7 (3.52)
Knees	29 (14.57)	22 (11.06)
Ankle/feet	7 (3.52)	2 (1.01)

**Include NSLBP and LBP with radicular symptoms*

Univariable analysis was used to evaluate the effect of each biopsychosocial factor on LBP. Significance results were found for the following biopsychosocial factors: standing and walking hours per day with and without rest breaks, WHOQOL physical health domain, WHOQOL psychological health domain, WHOQOL social relationship domain, WHOQOL environment domain, WHOQOL total score, WHOQOL general health, WHOQOL quality of life, frequency of forward bending during work, frequency of backward bending during work, frequency of squatting or kneeling during work, frequency of lifting moderate to heavy objects from the floor during work, frequency of maintaining static postures during work, frequency of using heavy tools during work, feeling exhausted, and job dissatisfaction. Factors that were significant in univariate analysis were added to a binomial logistic regression model (Wald backward stepwise method) to eliminate confounding variables (Table 3).

Table 3 Univariate analysis of participants with and without LBP according to biopsychosocial factors (n=199)

Factors	OR	95% CI	p-value
Work experience	0.98	0.92-1.05	0.636
Working days per week	1.20	0.73-1.98	0.463
Working hours per day	1.28	0.99-1.65	0.057
Standing and walking hours per day with rest breaks	1.25	1.08-1.45	0.003*
Standing and walking hours per day without rest breaks	1.27	1.06-1.151	0.007*
Sweeping/mopping	1.00	0.99-1.00	0.190
Bathroom cleaning	1.00	0.99-1.01	0.095
Wiping glass	0.99	0.99-1.00	0.871
Cleaning tools	1.00	0.99-1.00	0.189
Walking time apart from work	1.00	0.99-1.00	0.569
Sitting time apart from work	1.00	0.99-1.01	0.245
WHOQOL physical health domain	0.80	0.72-0.87	<0.001*
WHOQOL psychological health domain	0.88	0.81-0.95	0.003*
WHOQOL social relationship domain	0.86	0.80-0.92	<0.001*
WHOQOL environment health domain	0.74	0.63-0.87	<0.001*
WHOQOL All	0.94	0.91-0.96	<0.001*
WHOQOL general health	0.36	0.24-0.56	<0.001*
WHOQOL quality of life	0.53	0.36-0.78	0.001*
Frequency of forward bending during work	0.11	0.03-0.38	<0.001*
Frequency of pushing or pulling heavy object during work	0.57	0.18-1.76	0.327
Frequency of twisting body in a narrow space during work	0.50	0.20-1.24	0.136
Frequency of backward bending during work	0.12	0.02-0.62	0.011*
Frequency of squat sitting or kneeling during work	0.23	0.07-0.73	<0.001*
Frequency of lifting moderate to heavy objects from floor during work	0.40	0.10-1.58	0.012*
Frequency of static posture during work	0.06	0.00-0.50	0.004*
Frequency of using heavy tools during work	0.35	0.13-0.98	0.05*
Frequency of walking up/downstairs during work	0.74	0.33-1.49	0.134
Frequency of rest breaks during work	0.92	0.15-5.50	0.532
Feeling exhausted	0.25	0.11-0.54	<0.001*
Job dissatisfaction	0.09	0.04-0.20	<0.001*
Repetitive work	0.39	0.111-1.39	0.148

According to the binomial regression analysis, NSLBP was significantly associated with various physical and psychological factors, including the WHOQOL physical health domain, the frequency of forward bending during work, the frequency of squatting or kneeling during work, feeling exhausted, and having job dissatisfaction. The final logistic regression model was statistically significant, with a chi-square value of 82.12 (p-value< 0.001). All of the significant factors explained 48.60% (Nagelkerke R^2) of the variance in the presence of NSLBP and correctly classified 84.00% of cases. Every 1-point increase in the WHOQOL physical health domain decreased the odds of having LBP by 0.79 (95% CI= 0.69–0.89). Regarding the frequency of forward bending during work, sometimes performing forward bending during work decreased the odds of having LBP by 0.34 (95% CI= 0.14–0.82) compared to usually working in a forward-bent position. On the other hand, sometimes performing squatting or kneeling during work increased the odds of having LBP by 3.29 (95% CI= 1.07–10.18) compared to usually working in a squatting or kneeling position. Concerning psychological factors, having mental exhaustion increased the probability of having LBP (OR= 4.52; 95% CI= 1.04–19.69) while having job dissatisfaction decreased the odds of having LBP (OR= 0.063; 95% CI= 0.02–0.23) (Table 4).

Table 4 Multivariable logistic regression model for the association of variables attributed low back pain

Factor	AOR	95% CI	p-value
WHOQOL physical health domain	0.78	0.69-0.88	<0.001*
Frequency of forward bending during work			
Usually	1.00	1.00	
Sometimes	0.33	0.13-0.81	0.016*
Almost never	0.32	0.07-1.45	0.141
Frequency of squat sitting or kneeling during work			
Usually	1.00	1.00	
Sometimes	3.29	1.06-10.18	0.038*
Almost never	0.58	0.12-2.67	0.487
Feeling exhausted	4.51	1.03-19.69	0.045*
Job dissatisfaction	0.06	0.01-0.22	<0.001*

** Significance level at P < 0.05.*

[a] Model chi-square test, $\chi 2 = 82.125$ (P < 0.001).

Overall percentage of correctly predicted = 83.9%. Nagelkerke $R^2 = 0.486$.

Discussion

Cleaning professions are labor-intensive and require high cardiopulmonary and musculoskeletal loads as well as both dynamic and static muscular work with the aid of various cleaning tools, which altogether contribute to MSDs. In many countries, cleaning work is predominantly performed by females, particularly older women [4]. This study aimed to determine the prevalence of NSLBP among other MSDs and investigate the association between NSLBP and physical and psychological factors in female cleaners working in academic settings at Chulalongkorn University, Thailand.

The findings revealed NSLBP to be the most prevalent MSD in the last 3 months (30.14%) and at the present time (18.08%) in female cleaners in an academic setting. In previous studies, the prevalence of NSLBP among cleaners has ranged from 19.70% to 63.00% [11, 14, 17, 18, 25-28]. The results of the present study are comparable to the LBP prevalence findings of studies conducted in India (26.50%), Denmark (34.20%), and Taiwan (37.80%) (14, 26, 28). However, this study's findings are higher than the results of other studies conducted in Ethiopia (19.70%) and Denmark (21.00%) while lower than the studies by Krause et al in the United States (63%) and Chuppawa and Aungudornpukdee in Thailand (44.10%) [11, 17].

The variability in prevalence values reported in the existing literature may be due to differences in individual pain levels, outcomes, sample size, occupational setting, culture, and participants' comprehension and response to questionnaires. Occupational settings may affect the prevalence of MSDs and LBP among cleaners due to differences in the work environment and tools available to assist in cleaning tasks. Alie et al revealed a high rate of MSDs among street cleaners, with cleaners who covered greater than 2 kilometers per day having 2.5 times the risk of reporting an MSD compared to those who covered a smaller distance [29]. Street cleaners may be required to work over a larger area than workers in other cleaning professions. Another previous study showed a similarly high prevalence of MSDs and LBP among hotel cleaners, who primarily performed mirror/glass polishing and sink/tub cleaning tasks [27]. Differences in setting thus cause differences in required cleaning tasks, which may affect the prevalence of MSDs and LBP. Cleaners in the United Kingdom were found to use different tools during their cleaning tasks, with their primary tasks being vacuuming and buffing [27], and the weight of the tools employed during cleaning tasks may further affect the prevalence of MSDs and LBP. Other possible reasons for the variability across studies in LBP prevalence are differences in participant age and the time period used to assess the history of NSLBP. For instance, the mean age of participants in the study by Melese et al was 21.94 ± 56 years while the mean age of participants in the present study was 49.40 ± 56 years [17]. In the present study, the last 3 months and the present time were used to investigate the prevalence of NSLBP among female cleaners, while most previous studies used the last 12 months, last 1 month, and last week to determine the frequency of NSLBP [11, 14, 17, 25, 26, 28].

LBP is one of the most common MSDs and constitutes a prevalent and multifactorial health care challenge. Our results revealed significant associations between NSLBP and the WHOQOL physical domain, the frequency of forward bending and squatting during work, feeling exhausted, and having job dissatisfaction. Chronic LBP can affect quality of life due to its associated pain, functional disability, and psychological distress [30, 31]. A few studies have investigated the quality of life of patients with LBP using the WHOQOL

and found patients with LBP to have a lower WHOQOL score than patients without LBP [30, 31]. In the present study, binomial regression analysis showed protective effects (AOR= 0.79; 95% CI= 0.69–0.89) of higher scores on the WHOQOL physical domain. An increase in quality of life, particularly physical quality of life, including increased physical well-being, improved physical function, decreased physical pain, and enhanced access to health care services, may reduce the occurrence of LBP in cleaners.

Cleaners frequently work in awkward positions that can increase the risk of MSDs, particularly LBP [28, 32]. When comparing cleaners who often worked in forward-bent positions with those who were less frequently required to perform forward bending, the study's results indicated that the cleaners in the latter group had a lower likelihood of experiencing LBP. These results are consistent with the findings of studies conducted among hospital cleaners in Thailand (AOR= 2.81; 95% CI= 1.43–5.50) and university cleaners in Ethiopia (AOR= 15.7; 95% CI= 6.47–38.176) [17, 20] and support the importance of reducing prolonged or repetitive forward bending at work in preventing low back injuries in cleaners. The occurrence of NSLBP in cleaners may depend on the repetitive performance of various cleaning tasks, including those that require twisting, forward bending, and lifting objects, as well as the work environment, equipment used, and workload [4, 17].

In contrast, to forward bending, the current study showed that the risk of experiencing NSLBP was elevated for cleaners who reported a lower frequency of working in squatting or kneeling positions compared to those who frequently worked in these positions. Performing squatting or kneeling, which develops greater hip and knee flexion mobility while maintaining a neutral spinal position, may constitute a strategy to avoid working in improper spinal positions such as forward bending and reduce the risk of low back injuries. Though the cleaners performed cleaning tasks that were located close to the floor, such as lifting heavy objects from the floor and cleaning the bathroom, those who less often worked in squatting or kneeling positions presented with a greater likelihood of experiencing NSLBP.

Previous studies have reported that awkward positions during cleaning tasks are associated with the presence of MSDs. Woods and Buckle investigated task and postural requirements in cleaners in the United Kingdom and found mopping, vacuuming, and buffing to be cleaners' primary cleaning tasks, which usually require prolonged trunk rotation and flexion, neck flexion, arm abduction, and excessive wrist deviation [33]. Krause et al evaluated cleaners in the United States who predominantly performed the tasks of mirror/glass polishing and sink/tub cleaning, which require back extension as well as squatting and kneeling [27]. Moreover, a previous study used the Ovako Working Posture Assessment System to identify awkward positions in cleaners and revealed forward bending and trunk twisting to be major adverse movements. Although previous studies have shown awkward positions to be associated with MSDs, evidence on the frequency of cleaners with NSLBP required to perform these movements is still limited. The present study could be used as a model for future research on the frequency of performing various movements during cleaning tasks.

In the present study, cleaners who felt exhausted after work were found to be 4.3 times more likely to develop NSLBP than those who did not feel exhausted. This finding is supported by a study conducted in Ethiopia (AOR= 2.70; 95% CI= 1.16–6.20), though our study focused more specifically on NSLBP rather than MSDs in general. The demanding workload and fatigue associated with performing intensive and repetitive movements in awkward positions during cleaning tasks can lead to NSLBP and significantly impact cleaners' capacity to complete these tasks [17].

The association between job dissatisfaction and NSLBP found in this study differed from the results of previous studies [26, 29]. Chang et al [26] did not find a relationship between job dissatisfaction and low back discomfort among the cleaners included in their study, while Alie et al reported a significant association between job dissatisfaction and the prevalence of MSDs in street cleaners. However, our results showed an odds ratio value (AOR= 0.64; 95% CI= 0.018–0.228) that was lower than that reported by Alie et al (AOR= 2.66; 95% CI= 1.05–6.75). Different cleaning settings may be the reason for the differing values, as the present study included cleaners working at a university while Alie et al recruited street cleaners, whose occupational characteristics may involve cleaning tasks requiring a greater physical workload than that required in an academic setting. Work-related stress and a lack of influence over work conditions may result in job dissatisfaction and contribute to the occurrence of NSLBP among cleaners [4, 26]. Interestingly, cleaners in the present study who reported job dissatisfaction were less likely to suffer from NSLBP compared to those who did not have job dissatisfaction. This might be explained by cleaners who are satisfied with their work and income working harder, leading to a heightened risk of LBP, while those with job dissatisfaction may have a lower work ethic or divert attention to searching for a new job.

This study had several limitations to note. First, this study only investigated associations between NSLBP and physical and psychological factors among female cleaners working in different sectors at Chulalongkorn University. The results can thus only be generalized to the cleaners of this single public university. To ensure generalizability to all cleaners,

future studies should recruit cleaners from other private companies and small enterprises. Additionally, participants' level of physical activity was not assessed, which might confound the occurrence of NSLBP. As this study collected data solely through self-reported questionnaires, an objective examination should be added as a prediction factor in future studies. Feeling exhausted was evaluated as a single variable, though it comprises several aspects, including physical, mental, and emotional exhaustion; further study should thus delineate the various components of exhaustion to improve the understanding of this risk factor. The associations between NSLBP and other physical, psychological, and work-related factors, such as age, body mass index, task duration, distance covered while cleaning per day, leisure time, and stress level, should be explored in future studies, as should the population of male cleaners.

The findings of this study present several implications for clinical practice. First, the results may help physical therapists and health care providers to design clinical decision-making models to prevent and treat cleaners with NSLBP through early identification of the causes of LBP and education on proper lifting techniques and appropriate ergonomics during work. Second, the results highlight the importance of workers properly managing their work schedules, as the appropriation of work and leisure time may reduce the presence of LBP. Finally, the findings of this study may help work organizations raise awareness regarding mental health to increase the quality of life of people in the cleaning profession.

Conclusion

This study revealed a high prevalence of NSLBP compared to other MSDs in female cleaners working at Chulalongkorn University. Associations between NSLBP and physical and psychological factors involving postures at work, quality of life, and job satisfaction were investigated. Decreasing forward bending, having higher physical quality of life scores, and proposing better strategies for performing tasks to ensure job satisfaction were identified as protective factors while performing less squatting and kneeling during work and experiencing mental exhaustion were identified as risk factors for NSLBP in female cleaners. It is thus recommended that female cleaners undergo ergonomic training and exercise prescriptions to prevent NSLBP.

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Cross-cultural Adaptation of the Roland-Morris Disability Questionnaire for Individuals with Low Back Pain in Myanmar: Psychometric Validation Study

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ABSTRACT

Introduction: Self-reported subjective measures are important for the assessment and treatment of low back pain (LBP) individuals. The Roland-Morris Disability Questionnaire is a widely used and validated questionnaire for measuring disability due to LBP. This study aimed to develop a cross-culturally adapted Myanmar version of the Roland-Morris Disability Questionnaire (M-RMDQ) and examine its reliability and validity in individuals with LBP.

Methods: The M-RMDQ was developed based on the established guidelines and underwent prefinal testing on 20 individuals with LBP resulting in minor adaptations. The adapted M-RMDQ was conducted on 99 individuals with LBP for internal consistency, test-retest reliability, ceiling and floor effects, and concurrent and construct validity. Reliability was evaluated with Cronbach's alpha and intraclass correlation coefficient (ICC), while concurrent and construct validity were determined through correlations with the Myanmar version of the Oswestry Disability Questionnaire (M-ODQ), visual analogue scale (VAS), back performance scale (BPS), and the Stark Quality of Life (QoL) questionnaire.

Results: The M-RMDQ had good internal consistency (Cronbach's alpha = 0.70, n=99) and test-retest reliability ($ICC_{2,1}$ = 0.868; n=83). The M-RMDQ was moderately positive correlated with the M-ODQ (rho = 0.525; n=99) and showed a fair positive correlation with VAS (rho = 0.252; n=99) and BPS (rho = 0.265; n=99), and fair negative correlation with the physical component of the Stark QoL questionnaire (rho = - 0.323; n=99). No correlation was demonstrated with the mental component of the Stark QoL questionnaire (rho = - 0.179; n=99).

Conclusion: The M-RMDQ exhibited favorable psychometric properties, establishing it as a reliable and valid measure for assessing LBP-related disability in the Myanmar population. It is recommended for use in both clinical settings and research studies among Myanmar individuals with LBP.

Keywords: Low back pain, Roland-Morris Disability Questionnaire, Reliability, Validity, Myanmar

Introduction

Low back pain (LBP) is a major health problem and the highest burden of disability worldwide, affecting 60 to 90% of the global population [1]. It is the primary cause of disability, with a lifetime prevalence of up to 84% [2]. LBP has a profound impact on physical activity and consequently on productivity loss and quality of life [3-5]. The prevalence of high disability due to low back pain is 10.5%, so it has been considered a major cause of the global burden of disability and a leading cause of many years of living with disability [6, 7]. Condition-specific health status measures are commonly used as outcome measures in clinical trials and are important to assess patient progress in routine clinical practice [8]. Restoring normal function in LBP patients is a primary goal in physical therapy management; therefore,

outcomes to measure functional limitations associated with LBP are essential [8, 9]. The functional status of many daily activities may not be directly observed by objective measurements, so subjective evaluation is important to integrate information on disability [10]. Many back-specific questionnaires are available to measure disability in people with LBP, among them the Roland-Morris Disability Questionnaire (RMDQ), which is one of the most widely used and validated questionnaires to assess disability in the LBP [11].

The RMDQ was developed by Roland and Morris in 1983 and consisted of 24 items assessing disability related to LBP [12]. It is short, simple, and takes less time to complete the questionnaire [13]. According to a systematic review, the RMDQ has been translated and culturally adapted into over 30 languages, including Polish [14], Spanish [15], Brazilian-Portuguese [16], Hausa [17], Japanese [18], Hungarian [19], Turkish [20], Amharic [21], and reported an ICC ranging from 0.79 to 0.91 and a Cronbach's alpha value from 0.7 to 0.9, demonstrating acceptable psychometric properties [22]. Nowadays, when using outcomes in different cultures, cultural adaptation is needed to ensure the validity of the outcome at a conceptual level [23]. Reliable and valid measurement tools play an essential role in research studies, clinical settings, and health status assessment [24]. Assessing psychometric properties helps determine the properties of measurement, aids in selecting appropriate tools for clinical practice and research, and ensures research and treatment quality [24, 25]. Currently, there are 2-3 million migrants from neighboring countries living in Thailand, with 80% of them being from Myanmar [26]. The prevalence of LBP among migrant workers is high in Thailand. In the healthcare sector, the treatment of LBP has become an important social concern, and it is crucial to have appropriate measurements to evaluate and monitor when treating LBP patients [27].

Accordingly, relevant cross-cultural adaptation and psychometric testing studies need to be conducted to focus on many of the issues between multinational and multicultural groups within many countries [23, 28, 29]. Nowadays, it is recognized that if the measures are to be applied in different cultures, not only the outcome be well translated but also culturally adapted to maintain the reliability and validity of the outcome at a conceptual level [23]. Currently, there is no established reliable and valid Myanmar version of the RMDQ (M-RMDQ) for assessing disability in patients with LBP. Therefore, this study aimed to develop a cross-cultural adaptation of the M-RMDQ and examine its reliability and validity in the Myanmar population with LBP.

Methodology

This cross-cultural adaptation and cross-sectional study were conducted on the Myanmar population. The ethical approval was obtained from the Research Ethics Review Committee for Research Involving Human Research Participants, Group I, Chulalongkorn University, No. 102/65. This study consisted of two stages: translation and cultural adaptation of the RMDQ into Myanmar, and evaluation of internal consistency, test-retest reliability, ceiling and floor effects, concurrent validity, and construct validity. The correlation between the M-RMDQ and other validity criteria measures such as the Myanmar version of the Oswestry Disability Questionnaire (M-ODQ), visual analogue scale (VAS), back performance scale (BPS), and the Stark Quality of Life (QoL) questionnaire.

Translation and cultural adaptation

Permission was obtained from the developer of RMDQ to adapt it into a Myanmar version by the guidelines proposed by Beaton et al [19]. The procedure consisted of five stages: initial translation, translation synthesis, backward translation, expert committee review, and testing the prefinal version. Two forward translators, whose mother tongue was Myanmar and who had different backgrounds, obtained two independent translations. Next, two translation versions of M-RMDQ from each forward translator were obtained. These two translation versions of M-RMDQ were synthesized into one version. A synthesized version of M-RMDQ was produced by having discussions between translators, and inappropriate word choices were identified and resolved. Two blinded bilingual translators whose native language was English and who had no background concepts of RMDQ as well as medial backgrounds were involved in producing backward translations of M-RMDQ into English. Finally, the committee, which consisted of two physical therapists and four translators, discussed all translation versions and decided to achieve equivalence between the original and the translated version. Some minor adaptations were made in item 16 of the RMDQ to adjust to the Myanmar lifestyle. After expert committee discussion, the prefinal version of M-RMDQ was produced. Pilot testing was conducted with 20 participants experiencing LBP, during which they were asked to provide feedback on any difficulties encountered while completing the questionnaires. All participant comments were carefully considered, and it was found that no major difficulties were reported. Subsequently, the M-RMDQ was produced. The translation and cross-cultural adaptation process are depicted in Figure 1.

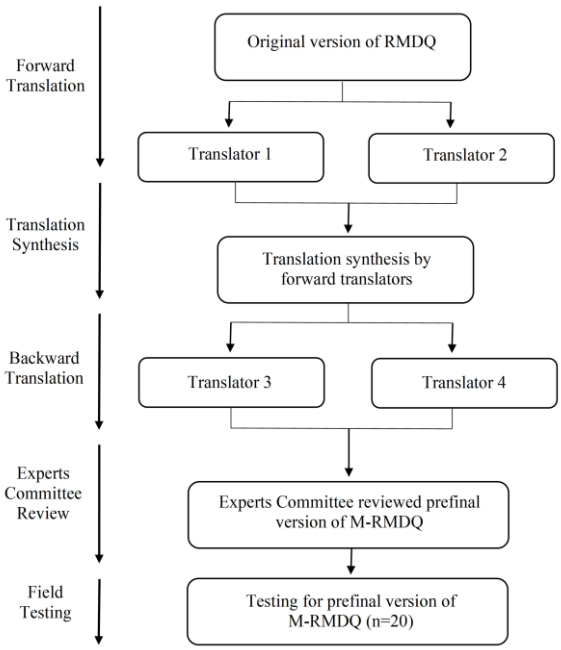

Figure 1 Translation and cross-cultural adaptation process of M-RMDQ

Participants

This study recruited the Myanmar population who were staying in Bangkok, Thailand. To be eligible, participants must be aged between 18 and 55 years old, present with subacute and chronic LBP, and be literate in Myanmar. The location of pain must be the area between the margins of the lower ribs and the inferior gluteal folds. The exclusion criteria were pregnant women, neurological pathologies, and mental disorders such as depression, anxiety, and insomnia.

Sample size estimation

According to the "Quality criteria for measurement properties of health status questionnaires", a sample size of ≥ 50 participants was considered adequate for reliability, validity, and ceiling and floor effect analyses [30]. Based on sample size ranges in previous studies, a sample range of between 55 and 81 was observed [22]. Thus, a sample size estimate of 100 participants was considered as adequate for this study.

Outcomes

(i) M-RMDQ

The M-RMDQ comprised 24 items that assessed various daily functional and physical activities, including tasks related to personal care, sleeping, mobility, work, and pain severity associated with LBP. Each item was scored as 1 if the patient answered "YES" and 0 if the patient answered "NO". The scores for each item were then summed to obtain the total score, which ranged from 0 (indicating no disability) to 24 (representing maximum disability) points [12].

(ii) M-ODQ

The M-ODQ comprised 10 sections assessing various aspects related to LBP, including pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling. Each section was scored on a scale of 0 to 5, with 5 indicating the highest level of disability. The scores for all sections were summed together, resulting in a possible total score of 50. The total score was then doubled and expressed as a percentage. In cases where responses to certain sections were omitted, the score was adjusted accordingly to maintain consistency [31].

(iii) VAS

The Myanmar version of the VAS was employed to evaluate the severity of pain. It features a 100 mm long horizontal line, with one end indicating no pain and the other end representing the worst possible pain. The patient's pain intensity is measured and recorded in millimeters along the line. Higher scores on the VAS correspond to higher levels of pain intensity [32].

(iv) Stark QoL Questionnaire

The Myanmar version of the Stark QoL questionnaire was used to measure health-related QoL by using only images including mood, energy, social contact, and physical functioning of an individual. The mood item consists of five smileys; the score for a very happy face is 100 and a very sad one is 0. The energy item consists of three pictures presenting their energy level. The total possible score is 100, the score for being full of energy is 100, and the score for the participants who seem to be depressed is 0. The social contact item measures the social contact of an individual and displays three pictures. The person who has good social contact with others is scored as 100, and the person who has no social contact is scored as 0. The total possible score to measure social contact is 100. These three items constitute the mental component. The last item consists of six pictures measuring the physical functioning of an individual. Activities like shopping, moving a table, tying shoes, taking a glass, sweeping rubbish, and lifting a heavy box are included in this item. The score for each picture ranges from 0 to 100, 0 means a person can do the activity very poorly, and 100 means very well. These six items constitute a physical component [33].

(v) BPS

The BPS was developed to assess mobility-related activity limitations in patients with LBP. It consists of five tests: the sock test, pick-up test, roll-up test, fingertip-to-floor test, and lift test. Each of the five tests has scores ranging from 0 to 3, depending on the difficulty or ease with which they are performed. The BPS is the sum of scores from all five tests and ranges from 0 (no disability) to 15 (maximum disability) [34].

(vi)7-point Global Perceived Effect (GPE) Scale

The Myanmar version of the 7-point GPE scale was used to detect any alteration in LBP symptoms between the two assessments. It included 7 responses: very much improved, much improved, a little improved, not changed, a little deterioration, much deterioration, and very much deterioration. This scale was used to identify the participants with stable symptoms that required data analysis [35].

Procedure

The screening and data collection processes were performed at the physical therapy clinic at the Faculty of Allied Health Science, Chulalongkorn University, Bangkok, Thailand. The participants who passed the screening process were considered eligible to participate in this study. All eligible participants were invited and explained the objective and process of the study, and those who agreed to participate in the study signed the informed consent form. Then, the participants had to complete the demographic questionnaire first.

A total of 143 participants with subacute and chronic LBP were contacted and invited for this study. However, 99 participants with subacute and chronic LBP were enrolled in this study, as 44 participants were excluded due to having psychological problems, having a duration of LBP of less than six weeks, and being unable to read the Myanmar language. Ninety-nine participants with subacute and chronic LBP participated and completed the M-RMDQ on two occasions at the baseline and 7 days apart to evaluate test-retest reliability. After 7 days, patients answered the 7-point GPE scale to detect any big alternation in LBP symptoms between the two assessments. Respondents who answered, "a little improved," "not changed," or "a little deterioration" were classified as stable [35]. Patients with stable symptoms were evaluated for test-retest reliability. The participants who improved or worsened were excluded from the test-retest reliability data analysis. Among these 99 participants, 16 participants with subacute and chronic LBP were excluded from this study due to the change in their clinical symptoms during the study period and lost to follow-up for reassessment. Therefore, the remaining 83 participants with subacute and chronic LBP were included in evaluating the test-retest reliability of M-RMDQ.

The validity study of the M-RMDQ was conducted together with the internal consistency study in 99 participants with LBP. The demographic questionnaire and M-RMDQ, which were completed in the test-retest reliability study, were used in this study. Moreover, the M-ODQ, Stark QoL questionnaire, and VAS were administered by the participants. The researcher also assessed the BPS at the baseline assessment to evaluate concurrent and construct validity. The data collection procedure for this study is shown in Figure 2.

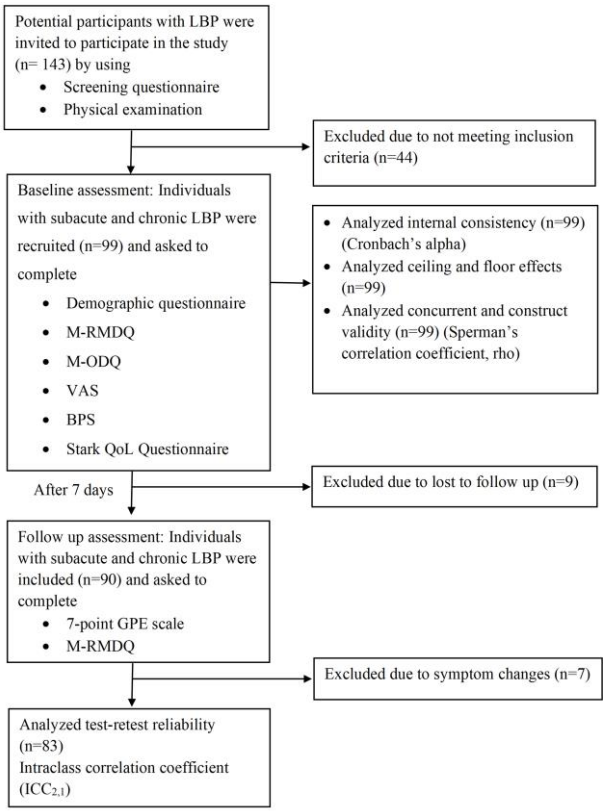

Figure 2 Data collection procedure for this study

Statistical analysis

The data analysis was conducted by using SPSS (v.22 for Windows). The significance level was set at α=0.05. The Shapiro-Wilk test was used to evaluate the normal distribution of the data for all variables. Demographic characteristics of participants were analyzed using descriptive statistics [36].

Test-retest reliability of the M-RMDQ was evaluated by using the absolute agreement, 2-way mixed-effects model of intraclass correlation coefficient ($ICC_{2,1}$). ICC values of < 0.50 represented poor, 0.50-0.75, > 0.75–0.90, and > 0.90 represented moderate, good, and excellent reliability, respectively [37]. Cronbach's alpha coefficient was used to assess the internal consistency of the M-RMDQ. An acceptable Cronbach's alpha value was at least 0.70. However, the Cronbach's alpha value over 0.9 was considered as redundancy [30].

Ceiling and floor effects were determined if more than 15% of respondents obtained the maximum or minimum possible scores. The ceiling and floor effects of M-RMDQ were determined by calculating the number of participants obtaining the highest status (24) or the lowest status (0) of M-RMDQ scores [30].

Spearman's rank correlation coefficient was calculated to examine the concurrent and construct validity of M-RMDQ. Correlations were conducted between the M-ODQ and VAS with the M-RMDQ to examine the concurrent validity. Correlations were also

conducted between the BPS and Stark QoL with the M-RMDQ to examine the construct validity. Correlation coefficient values were interpreted as follows: <0.25 (little or no relationship), 0.25-0.50 (fair), > 0.50-0.75 (moderate), and > 0.75 (excellent) [30].

Results

The translation and cross-cultural adaptation of the M-RMDQ were done successfully, with minor changes in item 16 by adding the familiar word to Myanmar people “longyi" in terms of "putting socks or stockings”. During the pilot testing phase of the M-RMDQ, there were no difficulties or misunderstandings in completing the questionnaire. Thus, the final version of the M-RMDQ was obtained. Then ninety-nine participants with subacute and chronic LBP were recruited to assess the psychometric properties of the M-RMDQ.

Test-retest reliability

Ninety-nine participants with subacute and chronic LBP were enrolled in this study, as 16 participants were excluded due to symptom changes and lost to follow-up assessments. A total of 83 subacute and chronic LBP participants, with a mean age of 32.16 years, were recruited for this study. The majority of the participants were women (59%), and the majority of LBP cases were chronic (79.5%) (Table 1). The average duration of LBP was 40 months, and the mean BMI value was 23.14 kg/m2. A summary of the demographic characteristics of the participants included in this study is shown in Table 1. A total of 83 participants with subacute and chronic LBP participated and completed the M-RMDQ at the baseline assessment. A reassessment was conducted 7 days after the baseline assessment. The test-retest reliability was calculated with $ICC_{2,1}$, and the results showed that M-RMDQ has good test-retest reliability with an ICC value of 0.86 (Table 3).

Table 1 Demographic characteristics of participants for test-retest reliability of M-RMDQ (n=83)

Variables	n (%)	Mean (SD)
Gender		
Male	34 (41)	-
Female	49 (59)	-
Age (years)	-	32.16 ± 8.83
Weight (kg)	-	62.25 ± 13.47
Height (m)	-	1.74 ± 1.10
Body mass index (kg/m^2)	-	23.14 ± 5.01
Duration of LBP (months)		40.29 ± 46.35
Subacute (6-12 weeks)	17 (20.5)	
Chronic (> 12 weeks)	66 (79.5)	
7-point GPE scale		
A little improved	35 (42.2)	-
Not changed	37 (44.6)	-
A little deterioration	11 (13.3)	-

SD = Standard deviation, LBP = Low back pain, 7-point GPE scale = 7-point global perceived effect scale

Internal consistency

A total of 99 subacute and chronic LBP participants participated in this study. The demographic characteristics of the participants for the internal consistency analysis of the M-RMDQ are presented in Table 2. The RMDQ demonstrated a satisfactory internal consistency, with a Cronbach’s alpha value of 0.70 (Table 3).

Table 2 Demographic characteristics of participants for internal consistency, validity, ceiling and floor effects of M-RMDQ (n=99)

Variables	n (%)	Mean (SD)
Gender		
Male	41 (41.4)	-
Female	58 (58.6)	-
Age (years)	-	32.43 ± 9
Weight (kg)	-	62.84 ± 14.39
Height (m)	-	1.73 ± 1.01
Body mass index (kg/m^2)	-	23.25 ± 5.07
Duration of LBP (months)		38.29 ± 43.31
Subacute (6-12 weeks)	17 (17.2)	-
Chronic (> 12 weeks)	82 (82.8)	-

SD = Standard deviation, LBP = Low back pain

Table 3 Test-retest reliability (n=83) and internal consistency of M-RMDQ (n=99)

Questionnaire	Baseline		Follow-up		ICC $_{2,1}$ (95%)	Cronbach's alpha	p- value
	Mean	SD	Mean	SD			
M-RMDQ	4.29	2.95	4.19	2.75	0.868	0.70	< 0.001

M-RMDQ = Myanmar version of Roland-Morris Disability Questionnaire, ICC= Intraclass correlation coefficient

Ceiling and floor effects

No ceiling or floor effects of the M-RMDQ were found in this study. None of the respondents obtained the highest score, while one respondent obtained the lowest score, accounting for 1.01% of the sample (Table 4).

Table 4 Ceiling and floor effects of M-RMDQ (n=99)

Questionnaire	Ceiling effect N (%)	Floor effect N (%)
M- RMDQ	0 (0)	1 (1.01)

M-RMDQ= Myanmar version of Roland-Morris Disability Questionnaire

Validity

Table 2 summarizes the demographic characteristics of participants, including those included in the validity study of the M-RMDQ. A total of 99 participants with subacute and chronic LBP measured the M-RMDQ, M-ODQ, VAS, Stark QoL Questionnaire, and BPS to calculate the concurrent and construct validity of the M-RMDQ. The Spearman correlation coefficient between the M-RMDQ, and other validity criteria measures is presented in Table 5. The results showed that the M-RMDQ has a significant positive moderate correlation with the M-ODQ (rho = 0.525) and a fair correlation with the VAS (rho = 0.252), respectively. For construct validity, there was a significant negative and positive fair correlation between M-RMDQ, and the physical component of the Stark QoL Questionnaire (rho = - 0.323) and BPS (rho = 0.265), respectively. Little or no correlation was shown between the M-RMDQ and the mental component of the Stark QoL Questionnaire (rho = - 0.179).

Table 5. Concurrent and construct validity of M-RMDQ (n=99)

	M-ODQ (rho)	VAS (rho)	Stark QoL Questionnaire (rho)		BPS (rho)
			Mental component	Physical component	
M-RMDQ	0.525*	0.252*	- 0.179	- 0.323*	0.265*

*Rho= Spearman's correlation coefficient, *Significant correlation; p<0.05 (2-tailed)*

Discussion

According to the author's knowledge, this was the first study in which the RMDQ was translated and culturally adapted from its original language into Myanmar, following the guidelines proposed by Beaton et al [19]. Additionally, the reliability and validity of the M-RMDQ were examined. The only notable change was made to item 16, where the word "longyi" was added to familiarize it with Myanmar culture. This change was necessary because most Myanmar people do not wear socks and stockings in their daily lives, but rather "longyi", which is one of the traditional garments worn in Myanmar. The results of the study indicated that the M-RMDQ was easy to administer and understand for patients with LBP. The findings also demonstrated that the M-RMDQ is an acceptable, reliable, and valid outcome measure suitable for assessing and determining treatment plans for individuals with LBP in the Myanmar population. The sample size included in this study was comparable to other RMDQ adaptation studies [14, 38].

Test-retest reliability means the consistency of results and the stability of the questionnaire on two different occasions [24]. The test-retest reliability in this study was high, with an ICC value of 0.868, and showed good test-retest reliability. Previous validation studies stated that the ICC value ranged from 0.79 to 0.91 and that the interval used for test-retest assessment was between 1 and 14 days [15, 17, 21, 39]. The ICC values of this study were comparable to previous validation studies of the RMDQ. Due to variations in the interval used to assess test-retest reliability, the values of test-retest may vary. In this study, the 7 days were chosen to avoid memory recall effects and not be too long to change the nature of pain. The time interval of 1 to 2 weeks is considered adequate to measure the reproducibility of outcomes [30].

In the present study, internal consistency was measured by calculating the value of Cronbach's alpha. The indicated values to determine adequate Cronbach's alpha range from 0.7 to 0.9 [30]. The Cronbach alpha of M-RMDQ showed 0.70, indicating that it has adequate internal consistency. The alpha value obtained in this study was found to be comparable to the Hausa and Arabic versions of the RMDQ, which had values of 0.70 and 0.72, respectively [17, 40]. However, the values obtained from this study were lower compared to other validation studies of the RMDQ, which may be attributed to the inclusion of a diverse sample population encompassing all types of LBP (acute, subacute, chronic) [16, 21]. In the present study, only subacute and chronic LBP patients were included. Furthermore, the Cronbach's alpha value of each item in the M-RMDQ did not exceed the total value, indicating the homogeneity of the M-RMDQ. A Cronbach's alpha value higher than 0.9 suggests redundancy in the questionnaire, while a value lower than 0.7 indicates that not all items in the questionnaire measure the same construct, which is related to disability in the LBP [30].

The ceiling and floor effects of the M-RMDQ were analyzed on the total score. The percentage of respondents who achieved the lowest M-RMDQ score (floor effect) was 1.01% (1 patient), and none of the respondents achieved the highest M-RMDQ score (ceiling effect). There were no ceiling and floor effects, as less than 15% of patients had either the lowest or highest M-RMDQ scores. These results are consistent with the previous reports [16, 17, 21].

To assess the concurrent validity, Spearman's rank correlation coefficient between M-RMDQ, M-ODQ, and VAS was calculated. Although M-RMDQ has a moderately positive correlation (rho = 0.525) with M-ODQ, there is a fair correlation between M-RMDQ and VAS. These results of correlation are in line with the previous studies [30, 37, 38]. The inclusion of the diverse sample population with various types of LBP might be the reason for fair correlation with the VAS.

Construct validity was assessed by evaluating Spearman's rank correlation coefficient between the M-RMDQ, the Stark QoL questionnaire, and the BPS. In most of the validation studies, the authors used the Short Form 36 (SF-36), which is a tool used for measuring health-related quality of life, to make a correlation with the RMDQ. In this present study, we used the Stark QoL questionnaire, which has good psychometric properties and measures the health-related QoL of an individual using images because there is no validated Myanmar version of the subjective questionnaire measuring QoL. Our results showed that there was a significant correlation between the M-RMDQ and the physical component of the Stark QoL questionnaire (rho = -0.323) which is in line with the Polish version of the RMDQ, in which there is a fair correlation with the physical component of the SF-36 [14]. According to our results, the Stark QoL questionnaire can be applicable as a validity measure for assessing the QoL of an individual, as it was easier to use because it included fewer words. Moreover, there was no correlation between the M-RMDQ and the mental component of the Stark QoL questionnaire found in this study (rho = -0.179) but the result is in contrast to a previous study in which they conducted a correlation between the RMDQ and the mental component of the SF-36. [14] The possible reason might be that the components included in the SF-36 questionnaire were more detailed and specific for measuring health-related QoL. The correlation of M-RMDQ with BPS showed a fair correlation (rho = 0.265) which contrasts with the results of the Moroccan version of the RMDQ (rho = - 0.211). In the study of the Moroccan version of the RMDQ, they used Schober's test to test correlation with the RMDQ [38].

There are a few limitations related to this study. Firstly, in the evaluation of test-retest reliability, we did not restrict any interventions that patients may have received during the test-retest interval, which could have influenced changes in symptoms. Secondly, we only recruited literate individuals, which may impact the broader applicability of this questionnaire. Another potential limitation is that exploratory factor analysis to assess scale dimensionality and responsiveness analysis were not conducted in this study. On the other hand, the strengths of this study include the translation and cross-cultural adaptation process adhering to recommended guidelines, as well as the use of a 7-day interval to determine test-retest reliability, which helps minimize memory recall effects.

Conclusion

In conclusion, the translation and cross-cultural adaptation of the M-RMDQ was successfully produced, and the results of this study demonstrated that the M-RMDQ exhibits acceptable levels of reliability and validity. Therefore, it can be considered a reliable and valid outcome measure for individuals with LBP in the Myanmar population. This may help in choosing the M-RMDQ as an outcome to assess disability-related LBP and assist in providing more accurate information to physical therapists and researchers. Moreover, the M-RMDQ is recommended for use in both clinical settings and research studies among the Myanmar population. We also recommend finding out the responsiveness of the M-RMDQ to detect the clinical change after the intervention of the LBP population in Myanmar for future research.

Conflict of interests

The authors declare that there were no conflicts of interest in this study.

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Stability of Hybridoma Cell Line Clone 4C91F9 Secreting Anti-E Monoclonal Antibody

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ABSTRACT

Introduction: Since 2018, the Antiserum and Standard Cell Preparation Section, National Blood Center, Thai Red Cross Society (NBC) have succeeded in producing a hybridoma cell line secreted anti-E with a good antibody titer and suitable for blood grouping reagent anti-E production. At first, we established 4 different human monoclonal hybridoma IgM cell lines stably expressing anti-E, namely 4C91A2, 4C91B9, 4C91F9, and 4C91G5, respectively. After that, 4 different cell lines were selected only the perfect one with good growth rate and high titer antibody character. Finally, a clone namely 4C91F9 was selected for culture on a large scale and its supernatant was collected for blood grouping reagent anti-E production. So, we must ensure the 4C91F9 cell line has good antibody titer production stability in the long run. The study aimed to detect the stability of hybridoma cell line clone 4C91F9 secreting anti-E monoclonal antibody from 1st to 3rd generation.

Methods: The cell line clone 4C91F9 secreting 1st generation anti-E was thawed from liquid nitrogen and selected to be the best single cell line with a good growth rate and high titer antibody secretion tested by limiting dilution method. Afterward, the selected cell line will be frozen in liquid nitrogen for 7 days. In addition, the 1st generation cell line that separated from freezing was cultured to harvest supernatant subjected to further serologic testing. The 2nd generation cell line was thawed after being frozen for 7 days for the limit dilution method again until 3rd generation. Serological testing for supernatant from all generation cell lines consisted of antibody identification with panel cells and antibody titration (potency) with R1R2, R1Rz, and r"r red blood cell group O. Also, a specificity test with antigen E positive and antigen E negative red blood cells was performed.

Results: Anti-E antibodies from all three generations of clone 4C91F9 showed perfect stability with high titer. Titers of 512, 1024, and 1024 were obtained at room temperature, and 512, 512, and 512 were obtained at the indirect antiglobulin test (IAT), respectively.

Conclusion: The characteristics of all generations of anti-E production are comparable to the American Association of Blood Banks (AABB) standard. This result confirms the quality of the anti-E monoclonal antibody suitable for being a blood typing reagent produced by Nation Blood Center, Thai Red Cross Society to ensure the safety of the blood donation and transfer process.

Keywords: Anti-E, Human monoclonal, Hybridoma cell, Limiting dilution

Introduction

Since, 1975 when monoclonal antibody was successfully developed by using the mouse monoclonal hybridoma technique continuous development of monoclonal antibody production technique has been ongoing until now [1, 2]. In Thailand the production of murine monoclonal blood grouping reagent succeeded around 2001, the first blood grouping reagent that succeeded in producing from murine monoclonal antibody is anti-A and anti-B by Antiserum, and standard cell preparation section, National Blood Center, Thai Red Cross Society (NBC) [3, 4].

Afterward, the production of monoclonal for blood grouping reagent production in Thailand has

continuously developed until the present we use both murine and human monoclonal techniques. According to some types of cell lines in the Rh system establishing can only use human monoclonal techniques such as anti-E, anti-C, anti-e, anti-c, etc. Because mice cannot be immunized with all types of antigens. In addition, mice must respond only to nontoxic antigens and especially, only antigen that has protein which involved with the evolutionary sequence of mice can immunize its immune system [5]. However, some cell lines can use both murine and human monoclonal techniques such as anti-A, anti-B, anti-M [6, 7], etc.

After Antiserum and standard cell preparation section staff back from human monoclonal training at the Japanese Red Cross Society in 2012-2014, we succeeded in establishing many antibodies secreting cell lines, especially human monoclonal anti-E. In the past anti-E supernatant was imported from abroad with high cost. Including anti-E is crucial for blood grouping regent used in red blood cell antigen testing before a blood transfusion to ensure safety. This is particularly significant due to variation in the frequency of E antigen with Caucasians having a frequency of 29%, Blacks is 22% and Asians is 39% [8, 9]. Therefore, a stable antibody-secreting cell line is one requirement because if the cell line is not stable that means the quality of the blood grouping reagent was not good, either. This study aimed to search for 3 generations of stable expressing anti-E clone 4C91F9 cell lines by using the limiting dilution method.

Methodology

Limiting dilution and cell culture [10]

The 1st generation single cell line, name 4C91F9 was limited dilution and culture in 96 well plates (1 cell per well) with RPMI 1640 medium and incubated in CO_2 incubate (37°C, 5% CO_2) until 7-14 days cell line was grown as a single colony. When the colony area was about 2 out of 3 parts of the well bottom, the supernatant was collected for the serological test (specificity test with E antigen-positive cell) and 10 of good growth rate, high antibody titer was selected to culture in 24 well plates. Then, supernatant from 24 well plates was collected for the serological test again (specificity, titration, and identification) but in this step, only one stable cell line was selected for transfer to a 25 cm^2 tissue culture flask. Finally, the cell line in a 25 cm^2 tissue culture flask was divided into 2 parts, part 1 was re-frozen in liquid nitrogen for 7 days and it was called 2nd generation, name 4C91F93F9. In part 2 cell line was continuously cultured in the same 25 cm^2 tissue culture flask which the first cell concentration was adjusted to 2.5 x 10^5 cells/ml approximately and cultured till death. Then, the supernatant was harvested for serological test (identification, potency test or antibody titration, specificity test, and specificity test by using enzyme technique) The 2nd generation cell line namely 4C91F93F9 was thawed after being frozen for 7 days and selected a good cell line by limiting dilution method again until supernatant of 3rd generation (4C91F93F93D3) was harvested and 4th generation cell line was got.

Serological test

(i) Antibody Identification [11, 7]

All 3 generations of supernatant were identified with panel cell of NBC Lot.62060 Exp. 15 JUL 2019 by using the tube technique method 100 µl of supernatant and 100 µl of panel cell were dropped into the test tube and incubated at room temperature for 5 minutes. Then, centrifuged at 3000 rpm for 15 seconds, and grading (w,0-4) agglutination was observed and recorded. Next step, incubated at 37oC for 30 minutes centrifuged at 3000 rpm for 15 seconds and grading (w,0-4) agglutination was observed and recorded. Finally, washed 3 times with 0.9% normal saline solution and 100 µl of anti-human globulin serum was dropped and centrifuged at 3000 rpm for 15 seconds and grading (w,0-4) agglutination was observed and recorded. Also, blood grouping anti-E reagent of NBC was used as a positive control.

(ii) Potency test (antibody titration)

3 generations of supernatant were tested with 3% group O red blood cell R1R2 (genotype DCcEe), R1Rz (genotype DCEe) and r"r (genotype dcEe) phenotype suspension with two-fold serial dilution method by using tube technique method that 100 µl of supernatant and 100 µl of 3% red blood cell suspension were dropped into the test tube and incubated at room temperature for 5 minutes. Then, centrifuged at 3000 rpm for 15 seconds, and the score (w,0-12) agglutination was observed and recorded. Next step, incubated at 37°C for 30 minutes centrifuged at 3000 rpm for 15 seconds, and score (w,0-12) agglutination was read and recorded. Finally, washed 3 times with 0.9% normal saline solution and 100 µl of anti-human globulin serum was dropped and centrifuged at 3000 rpm for 15 seconds and score (w,0-12) agglutination was observed and recorded. Blood grouping anti-E reagent of NBC was used as a positive control.

(iii) Specificity test

The 3 generations of supernatant were tested with 100 samples group O red blood cell that has E antigen positive, phenotype R1R2 (genotype DCcEe), R1Rz (genotype DCEe), R2R2 (genotype DcE), R2r (genotype DdcEe) and r"r (genotype dcEe). Also, tested with 100 samples group O red blood cell that has E antigen negative, phenotype R1R1 (genotype DCe), R1r(genotype DdCce), rr (genotype dce) and r'r (genotype dCce). This step was incubated at room temperature for 5 minutes, centrifuged at 3000 rpm for 15 seconds and results were interpreted by grading (w,0-4) agglutination. Also, blood grouping anti-E reagent of NBC was used as a positive control.

(iv) Specificity test by using enzyme technique [12, 13]

Papain enzyme was used with a two-stage enzyme technique for the specificity test with group A, B, O, and AB red blood cells, 182 known antigen samples which have Ee, EE, and ee antigen and 195 unknown antigen samples compared with blood grouping regent anti-E of NBC.

In addition, bromelain enzyme was used with a one-stage enzyme technique for the specificity test with group A, B, O, and AB red blood cells, 182 known antigen samples that have Ee, EE, and ee antigens, and 195 unknown antigen samples compared with blood grouping regent anti-E of NBC.

Results

Cell line expression anti-E clone name 4C91F9 representative of 1st generation was thawed from liquid nitrogen with good condition, does not have any dead cell, and have good morphology (round shape). Also, they can produce 2 good generations of clone names 4C91F93F9 and 4C91F93F93D3 with perfect characters like a mother cell.

For serological testing results, antibody identification with panel cell Lot.62060 (product of NBC) compared with blood grouping reagent anti-E (product of NBC) shows that all 3 generation cell lines perfectly secrete anti-E (Table 1).

Table 1 Antibody identification of supernatant from 3 generations of human monoclonal hybridoma anti-E, compared with anti-E from National Blood Center, Thai Red Cross Society (NBC) (Lot.61020 Exp. 23 JAN 20)

		Antibodies Identification Results											
Anti-E	**Temp.**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Specificity**
4C91F9	RT	0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F93F9		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F93F93D3		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
Anti-E of NBC		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F9	37°C	0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F93F9		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F93F93D3		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
Anti-E of NBC		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F9	IAT	0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F93F9		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
4C91F93F93D3		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E
Anti-E of NBC		0	0	0	0	0	4+	4+	4+	0	0	4+	anti-E

Remark: This table use grading agglutination test while 4+ is agglutination suggested the perfectly secretion anti-E
4 is one solid agglutinate background is clear.
3 is several large agglutinates; background is clear.
2 is medium sized agglutinates; background is clear.
1 is many small agglutinates; background is turbid.
0 is no agglutination or hemolysis of red cells. Cells float freely.

The potency test (antibody titer) of 3 generations with R1R2 phenotype red blood cells compared with blood grouping reagent anti-E (product of NBC) at room temperature are 512, 1024, 1024, and 128. At 37°C step antibody titer are 1024, 1024, 1024, and 256. Also, antibody titer at IAT is 512, 512, 512, and 256, respectively (Table 2). In addition, potency tests with cell R1Rz and r"r phenotype of all 3 generations of the cell line are according to the standard of anti-E titer (Tables 3 and 4). In conclusion the potency test, 3 generation cell lines of the 4C91F9 clone are anti-E(IgM) antibodies and have a strong reaction at room temperature, 37°C, and IAT step.

Table 2 Comparison of anti-E titer from 3 generation stable cell lines supernatant and anti-E reagent of National Blood Center, Thai Red Cross Society (NBC) (Lot. 61020 Exp. 23 JAN 20) with R1R2 (genotype DCcEe) cell

		Agglutination strength of each dilution											**Titer**
	Anti-E	N	2	4	8	16	32	64	128	256	512	1024	
RT 5	4C91F9	12	12	12	12	12	12	12	10	8	5	3	512
minutes	4C91F93F9	12	12	12	12	12	12	12	10	8	5	5	1024
plus spin	4C91F93F93D3	12	12	12	12	12	12	12	10	8	8	5	1024
	Anti-E of NBC	12	12	12	12	10	8	5	5	3	0	0	128
37°C 30	4C91F9	12	12	12	12	12	12	12	10	8	5	5	1024
minutes	4C91F93F9	12	12	12	12	12	12	12	10	8	8	5	1024
plus spin	4C91F93F93D3	12	12	12	12	12	12	12	10	8	8	5	1024

		Agglutination strength of each dilution											Titer
IAT	Anti-E of NBC	12	12	12	10	10	8	8	5	5	3	1	256
	4C91F9	12	12	12	12	10	8	8	5	5	5	3	512
	4C91F93F9	12	12	12	12	12	10	8	8	5	5	3	512
	4C91F93F93D3	12	12	12	12	12	10	8	8	5	5	3	512
	Anti-E of NBC	12	12	12	12	12	10	8	5	5	3	3	256

Remark: *This table use score 1-12 agglutination while 12 is one solid agglutinate background is clear. 10 is several large agglutinates; background is clear. 8 is medium sized agglutinates; background is clear. 3-5 is many small agglutinates; background is turbid. 0 is no agglutination or hemolysis of red cells. Cells float freely.*

Table 3 Comparison of anti-E titer from 3 generation stable cell lines supernatant and anti-E reagent of NBC, TRCS (Lot. 61020 Exp. 23 JAN 20) with R1Rz (genotype DDEe) cell

		Agglutination strength of each dilution											Titer
	Anti-E	N	2	4	8	16	32	64	128	256	512	1024	
RT 5 minutes plus spin	4C91F9	12	12	12	12	12	12	10	8	5	5	3	512
	4C91F93F9	12	12	12	12	12	12	10	8	8	5	3	512
	4C91F93F93D3	12	12	12	12	12	12	10	8	8	5	3	512
	Anti-E of NBC	12	12	12	12	10	10	5	5	1	0	0	128
37°C 30 minutes plus spin	4C91F9	12	12	12	12	12	12	12	10	8	8	5	1024
	4C91F93F9	12	12	12	12	12	12	12	10	8	8	5	1024
	4C91F93F93D3	12	12	12	12	12	12	12	10	8	8	5	1024
	Anti-E of NBC	12	12	12	12	10	8	5	5	3	3	1	128
IAT	4C91F9	12	12	12	12	10	10	8	5	5	3	3	256
	4C91F93F9	12	12	12	12	12	10	10	8	8	5	3	512
	4C91F93F93D3	12	12	12	12	12	10	10	8	8	5	3	512
	Anti-E of NBC	12	12	12	12	10	10	8	8	5	3	3	256

Remark: *This table use score 1-12 agglutination while 12 is one solid agglutinate background is clear. 10 is several large agglutinates; background is clear. 8 is medium sized agglutinates; background is clear. 3-5 is many small agglutinates; background is turbid. 0 is no agglutination or hemolysis of red cells. Cells float freely.*

Table 4 Comparison of anti-E titer from 3 generation stable cell lines supernatant and anti-E reagent of National Blood Center, Thai Red Cross Society (NBC) (Lot. 61020 Exp. 23 JAN 20) with r"r (genotype dcEe) cell

		Agglutination strength of each dilution											Titer
	Anti-E	N	2	4	8	16	32	64	128	256	512	1024	
RT 5 minutes plus spin	4C91F9	12	12	12	12	12	12	12	10	10	8	5	1024
	4C91F93F9	12	12	12	12	12	12	12	10	10	8	5	1024
	4C91F93F93D3	12	12	12	12	12	12	12	10	10	8	5	1024
	Anti-E of NBC	12	12	12	12	12	10	8	8	5	3	1	256
37°C 30 minutes plus spin	4C91F9	12	12	12	12	12	12	12	10	8	8	5	1024
	4C91F93F9	12	12	12	12	12	12	12	10	8	5	5	1024
	4C91F93F93D3	12	12	12	12	12	12	12	10	8	5	5	1024
	Anti-E of NBC	12	12	12	12	12	10	8	5	5	3	3	256
IAT	4C91F9	12	12	12	12	12	12	10	8	8	5	5	1024
	4C91F93F9	12	12	12	12	12	12	10	8	8	5	5	1024
	4C91F93F93D3	12	12	12	12	12	12	10	8	8	5	5	1024
	Anti-E of NBC	12	12	12	12	12	10	8	5	5	3	3	256

Remark*: This table use score 1-12 agglutination while 12 is one solid agglutinate background is clear. 10 is several large agglutinates; background is clear. 8 is medium sized agglutinates; background is clear. 3-5 is many small agglutinates; background is turbid. 0 is no agglutination or hemolysis of red cells. Cells float freely.*

Specificity testing results, all 3 generations of supernatant reacted with 100 samples antigen E positive group O red blood cell phenotype R1R2 (genotype DCcEe), R1Rz (genotype DCEe), R2R2 (genotype DcE), R2r (genotype DdcEe) and r"r (genotype dcEe) and did not react with 100 samples antigen E negative group O red blood cell phenotype R1R1 (genotype DCe), R1r (genotype DdCce), rr (genotype dce) and r'r (genotype dCce) (Table 5).

Table 5 Specificity from 3 generation stable cell lines supernatant and anti-E reagent of National Blood Center, Thai Red Cross Society (NBC) (Lot. 61020 Exp. 23 JAN 20) with antigen E positive red blood cell which have phenotype R1R2, R1Rz, R2R2, R2r and r"r phenotype and E negative red blood cell which have phenotype R1R1, R1r, rr and r'r

Antigen E positive cells							**Antigen E negative cells**			
Anti-E	Phenotype	R1R2	R1Rz	R2R2	R2r	r"r	R1R1	R1r	Rr	r'r
4C91F9		58	6	24	8	4	0	0	0	0
4C91F93F9	Number of	58	6	24	8	4	0	0	0	0
4C91F93F93D3	positive	58	6	24	8	4	0	0	0	0
Anti-E of NBC	results	58	6	24	8	4	0	0	0	0
4C91F9		0	0	0	0	0	68	18	8	6
4C91F93F9	Number of	0	0	0	0	0	68	18	8	6
4C91F93F93D3	negative	0	0	0	0	0	68	18	8	6
Anti-E of NBC	results	0	0	0	0	0	68	18	8	6

Remark: *phenotype R1R2 (genotype DCcEe), R1Rz (genotype DCEe), R2R2 (genotype DcE), R2r (genotype DdcEe) and r"r (genotype dcEe) phenotype and E negative red blood cell which have phenotype R1R1 (genotype DCe), R1r (genotype DdCce), rr (genotype dce) and r'r (genotype dCce)*

For specificity test by using two-stage and one-stage enzyme technique, papain and bromelain were used with two-stage and one-stage enzyme technique, respectively. Both papain and bromelain were tested for 3 generations supernatant compared with blood grouping reagent anti-E of NBC, they are 100% accuracy reacted with known samples which have antigen E positive red blood cell. In the same way, they are also 100% accuracy reacted with unknown samples that is antigen E positive red blood cells. On the other hand, they do not react with both known and unknown antigen E-negative red blood cells (Tables 6-9).

Table 6 Specificity from 3 generation stable cell lines supernatant and anti-E reagent of National Blood Center, Thai Red Cross Society (NBC) (Lot. 61020 Exp. 23 JAN 20) by using two-stage enzyme technique (papain) with known antigen E positive red blood cell and E negative red blood cell samples

Cell	**Number of**	**Anti-E 4C91F9**			**Anti-E 4C91F93F93D3**			**Anti-E4C91F93F93D3**			**Anti-E of NBC**		
		Ee	EE	ee	Ee	EE	ee	Ee	EE	ee	Ee	EE	ee
A	Positive results	10	11	0	10	11	0	10	11	0	10	11	0
	Negative results	0	0	28	0	0	28	0	0	28	0	0	28
B	Positive results	12	10	0	12	10	0	12	10	0	12	10	0
	Negative results	0	0	23	0	0	23	0	0	23	0	0	23
O	Positive results	17	8	0	17	8	0	17	8	0	17	8	0
	Negative results	0	0	25	0	0	25	0	0	25	0	0	25
AB	Positive results	5	8	0	4	8	0	4	8	0	4	8	0
	Negative results	0	0	25	0	0	25	0	0	25	0	0	25

Table 7 Specificity from 3 generation stable cell lines supernatant and anti-E reagent of National Blood Center, Thai Red Cross Society (NBC) (Lot. 61020 Exp. 23 JAN 20) by using two-stage enzyme technique (papain) with unknown antigen E positive red blood cell and E negative red blood cell samples

Cell	Number	Anti-E 4C91F9		Anti-E 4C91F93F93D3		Anti-E 4C91F93F93D3		Anti-E of NBC	
		E (+)	E (-)	E (+)	E (-)	E (+)	E (-)	E (+)	E (-)
A	50	12	38	12	38	12	38	12	38
B	50	19	31	19	31	19	31	19	31
O	50	8	42	8	42	8	42	8	42
AB	45	15	30	15	30	15	30	15	30

Table 8 Specificity from 3 generation stable cell lines supernatant and anti-E reagent of National Blood Center, Thai Red Cross Society (NBC) (Lot. 61020 Exp. 23 JAN 20) by using one-stage enzyme technique (bromelain) with unknown antigen E positive red blood cell and E negative red blood cell samples

Cell	Number	Anti-E 4C91F9		Anti-E 4C91F93F93D3		Anti-E 4C91F93F93D3		Anti-E of NBC	
		E (+)	E (-)	E (+)	E (-)	E (+)	E (-)	E (+)	E (-)
A	50	12	38	12	38	12	38	12	38
B	50	19	31	19	31	19	31	19	31
O	50	8	42	8	42	8	42	8	42
AB	45	15	30	15	30	15	30	15	30

Table 9 Specificity from 3 generation stable cell lines supernatant and anti-E reagent of National Blood Center, Thai Red Cross Society (NBC) (Lot. 61020 Exp. 23 JAN 20) by using one-stage enzyme technique (bromelain) with unknown antigen E positive red blood cell and E negative red blood cell samples

Cell	Number	Anti-E 4C91F9		Anti-E 4C91F93F93D3		Anti-E 4C91F93F93D3		Anti-E of NBC	
		E (+)	E (-)	E (+)	E (-)	E (+)	E (-)	E (+)	E (-)
A	50	12	38	12	38	12	38	12	38
B	50	19	31	19	31	19	31	19	31
O	50	8	42	8	42	8	42	8	42
AB	45	15	30	15	30	15	30	15	30

A total of 266 individuals were recruited into the analysis; there were 103 males and 163 females; aged 30-90 years, with an average age of (62.27±9.63) years. A large proportion of family history and comorbidities were hypertension. BMI within 18.5–24.9 (Normal weight) and 25.0–29.9 (Pre-obesity). A large proportion of blood lipids; 40.60% were TC <200 mg/dL, 36.84% were TG<150 mg/dL, 33.83% were LDL-C<100 mg/dL and 49.62% were HDL-C 40-59 mg/dL (Table 1).

Discussion

Cell line anti-E clone 4C91F9 is appropriate to use as a master cell for the large-scale culture that is about 10 liters per year or more depending on blood bank and hospital demand because they have stable antibody titer till 3rd generation. The serological testing results of supernatants of all 3 generations are according to the American Association of Blood Banks (AABB) standard [14] Wherefore, they are suitable for use to be a raw material of blood grouping reagent anti-E production when compared with related anti-E human monoclonal research [15].

Nowadays cell line 4C91F9 has been used as a master cell of blood grouping reagent anti-E production for a while. The main reason why we must do a limiting dilution method to select some perfect cell line before large-scale culture is hybridoma cell is a hybrid of B lymphocyte and myeloma cell fusion that can mutate all the time. The effect of mutation is cell line may have an antibody titer-secreting decrease or loss of antibody-secreting ability. Sometimes, the secreting and non-secreting antibody cell lines were mixed and nobody was known by the naked eye.

When the mix of secreting and non-secreting antibody cell lines were cultured on a large scale, normally non-secreting antibody cell lines will grow rapidly and use all nutrients. Finally, when insufficient nutrients all cell lines must die but secreting cell lines do not grow enough to secrete antibodies, and the direct effect is low antibody titer and inability to detect all weak antigens leading to false negative results. Production staff will resolve low titer antibody problem by concentration which means high-cost production

occurs. On the other hand, a high antibody titer has more benefits such as can be diluted with 0.9% normal saline solution to an antibody titer according to the standard of each antibody in the production process. In addition, blood grouping reagent which is high titer antibody can be diluted with 0.9% normal saline solution or phosphate buffered saline (PBS) to be applied on an Automated Pretransfusion Blood Testing Analyzer (PK7300/PK7400) for donor screening [16]. Therefore, limiting dilution must be done every time after the cell line is thawed from liquid nitrogen or a 6-month check once in a while using the cell line.

Conclusion

The anti-E clone name 4C91F9 is appropriate to use as a master cell for producing supernatant as raw material for blood grouping reagent anti-E and good quality of them will reduce financial cost in medical services because supernatant transportation or commercial anti-E blood grouping reagent cost from aboard is expensive. Sometimes, may take a long time to wait. But at present, we have our cell line so we can immediately produce as much as desired.

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Evaluative Discourse on Noseclip Utilization in Spirometric Assessments: An Extensive Review

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ABSTRACT

This review critically examines the use of noseclips in spirometry, a key diagnostic tool in respiratory medicine. While noseclips are commonly employed to prevent nasal breathing and theoretically enhance the accuracy of spirometric measurements such as Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1), their actual efficacy is debated. Analyzing a range of studies, the review reveals that the impact of noseclips varies across populations, with no significant changes observed in spirometric values in many cases, while others note an improvement in detecting conditions like exercise-induced bronchoconstriction, particularly in children. The review also highlights patient comfort concerns. Discomfort from noseclips can potentially influence patient cooperation and test accuracy. Technical considerations further complicate the picture; improper fitting of noseclips may alter natural breathing patterns, affecting results. In summary, this article presents a divided consensus on the effectiveness of noseclips. While some studies advocate their use, especially in specific clinical or research settings, others question their necessity, citing the negligible impact on spirometric outcomes and potential patient discomfort. The evidence suggests the need for further nuanced research, including exploring non-invasive spirometric techniques, to establish a more standardized approach to spirometry. Understanding the specific scenarios where noseclips are beneficial is crucial for improving respiratory diagnostics and patient care.

Keywords: Spirometry, Noseclip Usage, Respiratory Assessment, Measurement Accuracy

Introduction

Spirometry is a fundamental diagnostic tool in respiratory medicine, quantifying lung function by measuring inhaled and exhaled air volumes. Key parameters such as Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) are derived, aiding the diagnosis and management of respiratory conditions like Chronic Obstructive Pulmonary Disease (COPD) and asthma.

Employing nose clips during spirometry to prevent nasal breathing is standard practice [1, 2], as it purportedly enhances the accuracy of measured pulmonary parameters through oral airflow [3]. However, the empirical necessity of nose clips has been questioned. Some studies indicate that nose clips improve the detection rate of exercise-induced bronchoconstriction during Exercise Challenge Tests (ECT)[4], while others found no significant variance in spirometric values with or without nose clips [5-8]. The disparities in findings may be attributed to individual anthropometric factors, the severity of the respiratory ailment, comfort and compliance with nose clips, technical aspects of the spirometric procedure, and practitioner experience [5, 7-9]. Moreover, altering breathing patterns via nose clips can potentially affect spirometric accuracy [10-12].

This review meticulously analyzed the influence of nose clips in spirometry and respiratory evaluations, focusing on empirical studies from authoritative respiratory medicine journals. Utilizing databases like PubMed and Google Scholar, research was selected based on keywords such as ‘body position’,

'pulmonary function', and 'gas exchange'. Emphasis was placed on original articles from distinguished journals like the American Journal of Respiratory and Critical Care Medicine and the European Respiratory Journal. The criteria prioritized studies that examined the effects of nose clips on spirometry measurements, comfort, and breathing patterns. Non-empirical or irrelevant studies were excluded from this review. This selection process ensured a comprehensive and focused examination of the subject matter, highlighting the critical role of nose clips in accurate respiratory assessments.

Accurate spirometric measurements are essential for the precise diagnosis and management of respiratory diseases. However, the ongoing debate regarding the necessity of using nose clips in spirometry highlights a significant gap in our understanding. This debate emphasizes the need for uniform procedures in spirometry to guarantee dependable and repeatable results, which are critical for effective patient care and the progression of respiratory health care. Clarifying the role and impact of nose clips in spirometric accuracy is crucial. This unresolved issue presents a clear research gap, underscoring the need for further studies. These investigations are essential to determine whether standardizing the use of nose clips can enhance the reliability of spirometric tests, ultimately leading to improvements in diagnostic methods within respiratory medicine.

Noseclip Effectiveness?

The application of noseclips in spirometry and other respiratory measurements has been extensively investigated to ascertain their impact on the precision and accuracy of the tests. This review encapsulates findings from various studies on the effectiveness and implications of noseclip usage during respiratory assessments.

Table 1 Impact of Noseclip Usage on Spirometric Measurements in Diverse Populations

Population	Noseclip Usage Impact	Key Findings
Healthy Adults [13]	Varied	EMGpara increased significantly with mouthpiece, noseclip, and pneumotachograph in situ.
Healthy Adults [5]	Negligible	Technical details like noseclip usage during MVV had no relevant variation in spirometric variables.
Diseased Adults [9]	Negligible	Spirometric measurements were similar with and without noseclips.
Children [6]	Negligible	No clear benefit of using noseclips in children performing open-circuit spirometry.
Children [14]	Negligible	No systematic differences in FEV1 or FVC measured with and without noseclips.
Healthy Children [15]	Minor Decrease	Use of a noseclip caused a small decrease in exhaled nitric oxide (NO) values.
Healthy Adults [16]	Significant	Notable changes in diaphragm kinetics were observed.
Healthy Adults [17]	Varied	Changes in breathing pattern and FRC were noted with different apparatus.
COPD Patients [18]	Limiting	Noseclip/mouthpiece use was found to limit exercise tolerance in COPD patients.
Industrial Workers [3]	Negligible	No significant effect on FVC and FEV1 measurements.
Healthy Adults [10]	Altered Breathing	Alteration in majority of the volume and time indexes of breathing pattern was noted.
Healthy Naive Subjects [11]	Route Dependent	Breathing pattern changes were dependent on the breathing route.
Naive Patients [12]	Route Dependent	Soft palate directed airflow during breathing, impacting oronasal breathing flow.
Healthy Subjects [19]	Noncontact Method	Introduced a noncontact method for spirometry, mitigating the need for noseclips.
Healthy Adults [7]	Negligible	No statistical significance in static and dynamic lung volumes with or without noseclip.
Adolescents [4]	Increased Detection	Noseclip use during ECT increased detection rate of exercise induced bronchoconstriction.
Pediatric Patients [20]	Clinically Relevant	Clinically relevant increases in spirometry measurements were noted while wearing a noseclip in a proportion of patients tested.
COPD Patients [8]	Negligible	No added advantage of noseclip was observed, suggesting its usage may be reserved for research purposes only.

The impact of noseclips on spirometric precision appears to be population-specific. In healthy adults and industrial workers, the influence ranges from negligible to significant [3, 5, 13]. For patients with chronic conditions like COPD, the effect varies from negligible to potentially limiting [8, 9, 18]. In pediatric populations, the impact is generally minimal, though certain studies indicate notable differences [4, 6, 14, 20].

The studies present a spectrum of effects when comparing spirometric measurements taken with and without nose clips. While some report negligible differences [3, 5-9, 14], others highlight significant changes in respiratory parameters or patterns [4, 10-13, 16-18, 20]. This suggests that the decision to use noseclips should be tailored to individual patient characteristics and the specific requirements of the respiratory assessment.

Insignificant Variances

A multitude of studies including Verrall, et al [3], Sipoli, et al [5], Carter [6], Agarwal, et al [8], Newall, et al [9], and Chavasse, et al [14] reported that no significant differences in spirometric measurements with the use of noseclips. Moreover, Newall, et al [9] presented similar spirometric measurements in patients with varying diseases, with or without noseclips.

Noteworthy Differences

Contrastingly, some studies like Spivak, et al [4], Perez and Tobin [10], Rodenstein and Stănescu [11], Morrison, et al [18], and Larcombe, et al [20] demonstrated significant alterations in measurements or breathing patterns with noseclip use. Moreover, Morrison, et al [18] unveiled that the use of a noseclip and low-resistance mouthpiece significantly limited exercise tolerance in patients with advanced COPD. Similarly, Spivak et al [4] indicated an increased detection rate of exercise-induced bronchoconstriction with noseclip usage during exercise challenge tests in the pediatric population.

Alternative Approaches

Liu, et al [19] proposed a noncontact spirometric method, illustrating a potential avenue for achieving accurate spirometric assessments without the conventional encumbrances like noseclips, thereby enhancing accessibility for patients.

The compiled evidence elucidates a divided consensus on the necessity and effectiveness of noseclips in enhancing spirometric precision. While some studies affirm a discernible impact, especially in certain patient cohorts or test conditions, others negate any significant advantage. These findings beckon further nuanced investigations, possibly leading toward more personalized or technologically advanced approaches to spirometric assessments.

Noseclip Usage in Spirometric Measurements

The utilization of noseclips during spirometric assessments has been scrutinized to understand their influence on the accuracy and reproducibility of important pulmonary function parameters. This analysis delineates the differences observed in spirometric measurements when conducted with and without noseclips, grounded on an extensive review of empirical studies.

Table 2. Comparative Analysis of Spirometric Measurements with and without Noseclips

Parameter	Noseclip Utilization	Without Noseclip	Significant Variation
FVC [3-5, 7, 8, 20]	Varied	Varied	Mixed
FEV1 [3-5, 7, 8, 20]	Varied	Varied	Mixed
Exercise-Induced Bronchoconstriction [4]	Increased Detection	Decreased Detection	Yes
Exhaled NO [15]	Decreased	Not Affected	Yes
Discomfort Level [18, 3, 10, 11, 12, 19, 7, 8]	Increased	Decreased	Yes

The utilization of noseclips is theorized to prevent nasal leaks, potentially leading to more precise spirometric readings. However, empirical evidence presents a spectrum of outcomes. Some studies affirm the positive impact of noseclips on FVC and FEV1 measurements [3, 8, 20], while others report no significant variations in these parameters [4, 5, 7]. Additionally, the impact on exercise-induced bronchoconstriction in adolescents was noted to be significant with noseclip usage, as it amplified the detection rate of exercise-induced bronchoconstriction [4]. In contrast, a segment of studies showcased that noseclip use could be discomforting to subjects and may not significantly alter the spirometric outcomes, thus questioning the necessity of its routine application [3, 7, 8, 10-12, 18, 19].

Furthermore, the influence of noseclips on exhaled nitric oxide measurements, another pivotal respiratory parameter, was examined. One study

elucidated a slight decrease in exhaled nitric oxide (NO) values with noseclip utilization [15].

Patient Tolerability and Comfort

Spirometric evaluations, crucial for diagnosing and monitoring respiratory disorders, often employ nose clips to ensure mouth-only breathing, aiming at accurate measurements. However, patient comfort during these assessments is equally critical, as discomfort might impact the accuracy of spirometric results.

Patient Comfort

Several studies have explored the effect of nose clips on patient comfort during spirometric evaluations. Patients have reported varying levels of discomfort when nose clips were employed, with some expressing a preference for spirometry without nose clips due to the physical discomfort experienced during the procedure [3, 8].

Spirometry Accuracy

The accuracy of spirometry largely hinges on the correct technique and cooperation from the patients. Studies have shown no significant difference in spirometric values like FEV1 and FVC with or without the use of nose clips [7, 8].

Interplay of Comfort and Accuracy

The interplay between patient comfort and spirometry accuracy is a nuanced one. Discomfort caused by nose clips might affect patient cooperation, potentially compromising the quality of spirometric data. On the other hand, nose clips aim to enhance measurement accuracy by preventing nasal breathing [3, 7, 8].

Patient comfort is integral for accurate and reliable spirometry data. While nose clips are designed to improve measurement accuracy, their use can cause discomfort which may, in turn, affect the accuracy and reliability of spirometric measurements. The dichotomy poses a significant challenge, necessitating a balance between ensuring patient comfort and obtaining accurate spirometric data.

Technical Considerations

Spirometry, a pivotal test for lung function assessment, often incorporates the use of nose clips to ensure oral airflow. While this method is traditionally employed, the technical implications and guidelines surrounding nose clip usage demand a comprehensive evaluation.

Technical Aspects

Nose clips, when applied, necessitate a precise fit to prevent nasal airflow. Inadequate fitting could lead to erroneous results due to potential nasal expiration or inspiration. This encompasses one of the primary technical aspects that demand meticulous attention. Further, the implementation of nose clips has been observed to influence breathing patterns, often altering the natural respiratory route [10, 11]. The ensuing modification in breathing dynamics could potentially sway spirometric outcomes, hence needing precise acknowledgment in the interpretative process.

The use of nose clips has also been associated with changes in certain respiratory parameters. During specific respiratory assessments, the presence of nose clips showed a notable increase in some spirometric values [20], while others reported no significant impact [3, 7]. These fluctuations emphasize the necessity for a standardized protocol to minimize variances and ensure reproducible results.

Guideline Evaluation

Various professional bodies have set forth guidelines regarding nose clip utilization in spirometry. The inconsistency in recommendations reflects a lack of consensus within the scientific community. Some studies aligned with these guidelines, showcasing the importance of nose clips in obtaining accurate spirometric measurements [4], while others demonstrated no significant benefit, thus challenging the mandates [8].

American Thoracic Society (ATS) [1] and European Respiratory Society (ERS) [2]. two of the eminent bodies suggest nose clip usage for accurate spirometric assessments, albeit, the empirical evidence supporting this guideline appears to diverge. The juxtaposition of guidelines against practical findings unveils a gap that necessitates further exploration.

The technical considerations surrounding nose clip usage in spirometry are multifaceted, encompassing fitting precision, influence on breathing patterns, and potential sources of error. The evaluation of existing professional guidelines juxtaposed with empirical findings reveals a nuanced landscape. It beckons a thorough re-evaluation of current guidelines to ascertain the true merit of nose clip usage in spirometric assessments, ensuring accurate, consistent, and reproducible results.

Recommendations and Future Directions

The utilization of nose clips during spirometric evaluations has been delineated through a myriad of studies, encompassing an array of demographic cohorts and clinical settings. This essay elucidates the existing recommendations regarding nose clip usage in spirometry and proffers suggestions for impending research to bridge the lacunae in the present understanding.

Current Recommendations

The current body of literature presents a mixed view on the necessity and efficacy of nose clip usage during spirometry. While some studies endorse the use

of nose clips for more accurate spirometric measurements [4, 18, 20], others find no significant difference or even suggest a discomfort or altered breathing pattern induced by nose clips [3,7,8]. The nose clips, as depicted in various studies, seem to have a minor effect on the outcomes of FVC) and FEV1 [8, 11, 14].

The evidence suggests a lack of consensus on a universal guideline regarding nose clip usage, with some studies advocating for its use, particularly in certain clinical or research settings, while others negating any significant advantage [3, 18]. Moreover, the employment of nose clips appears to be contingent on the specifics of the cohort under investigation, such as age, health status, or the particularities of the respiratory assessment [4, 6].

Suggestions for Future Research

Expanding Cohort Diversity: Future studies should aim to encompass a more diverse range of subjects, including varying age groups, health statuses, and different ethnic backgrounds to derive more generalizable conclusions [5, 9, 13].

Longitudinal Assessments: Employing longitudinal designs can elucidate the long-term impacts and the consistency of the spirometric measurements with and without nose clips [3, 18].

Technological Advancements: Investigating the efficacy of nose clip usage in tandem with emerging respiratory assessment technologies may be insightful [7, 19].

Standardization of Protocols: There is a pressing need for standardizing the protocols regarding nose clip usage, ensuring consistency across different settings and studies [11, 14, 20].

Educational Interventions: Evaluating the impact of educating the subjects on the importance and proper usage of nose clips during spirometry can also be an area worth exploring [4, 8].

Individualized Assessment: Research should also focus on individualized assessments to determine the necessity and efficacy of nose clip usage on a case-by-case basis [11, 14].

The diverse recommendations underscored in various studies reflect the nuanced nature of nose clip utility in spirometric evaluations. The table succinctly summarizes the disparate recommendations, underscoring the need for more comprehensive and diverse research endeavors to foster a more nuanced understanding and potentially uniform guidelines regarding nose clip usage in spirometry.

Conclusion

The exploration of noseclip application in respiratory evaluations, especially in spirometric assessments, unveils a multifaceted understanding of their utility and implications. The key findings from the surveyed studies predominantly articulate that the utilization of noseclips does not markedly alter spirometric variables such as FEV1 and FVC among both healthy individuals and those with respiratory conditions like COPD [3, 5-9, 11]. However, a divergence is noted in certain scenarios. For instance, a notable enhancement in the detection rate of exercise-induced bronchoconstriction during Exercise Challenge Tests (ECT) in pediatric populations was observed with noseclip application [4]. Similarly, a study elucidated a clinically significant increase in spirometry measurements among a subset of cystic fibrosis patients with noseclip usage [20].

Moreover, the technical intricacies inherent in spirometry, such as the deployment of mouthpieces and pneumotachographs, were found to impact diaphragm kinetics and other respiratory metrics [10, 16]. The alteration in the respiratory route due to noseclip application emerged as a pivotal factor in modulating the breathing pattern, consequently affecting the spirometric outcomes [10-12]. This aspect accentuates the need for meticulous consideration in clinical practice.

The proposition of non-invasive alternatives to conventional spirometry, like non-contact spirometry, aims to mitigate potential discomfort and inconsistencies in measurements associated with noseclip use and other apparatuses [19]. While these innovative approaches portend a more amicable and accessible patient experience, the comparative accuracy and clinical relevance of such methods necessitate further rigorous evaluation.

In summation, the nuanced application of noseclips in spirometry and other respiratory evaluations is warranted, contingent on the specific patient demographics and clinical circumstances. The disparate impact of noseclip usage across varied studies underscores the imperative for more comprehensive, methodologically sound investigations to ascertain the precise conditions under which noseclips either augment or impede the accuracy and reliability of respiratory measurements. Concurrently, the exploration of emerging non-invasive technologies and their potential to augment patient comfort without compromising on measurement accuracy is a pertinent avenue for future research. These endeavors are instrumental in refining contemporary respiratory assessment protocols, thereby engendering more precise diagnosis and monitoring of respiratory ailment

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The Impacts of Body Position on Respiratory Function and Lung Measurements: A Comprehensive Review

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ABSTRACT

Pulmonary function is a critical determinant of respiratory health, governing the exchange of oxygen and carbon dioxide in the human body. This review explores the intricate relationship between body position and pulmonary function, drawing insights from various studies. Alterations in body position can have a profound impact on pulmonary parameters. Transitioning from sitting to supine positions leads to decreased forced expiratory volume in 1 second (FEV1) and reduced vital capacity (VC). Similarly, the prone position shifts tidal ventilation towards specific lung regions, highlighting the influence of body position on ventilation distribution. In healthy individuals, sitting positions generally result in better pulmonary function, with higher FVC, FEV1, PEF, VC, PImax, and PEmax values. However, this effect varies in individuals with specific medical conditions. For example, patients with chronic heart failure experience worsened lung function in lateral decubitus positions. Understanding these position-related changes in pulmonary function is essential for optimizing patient care, particularly in clinical settings. These findings underscore the need for further research to elucidate the nuanced interactions between body position and lung mechanics, ultimately enhancing diagnostic and therapeutic strategies for respiratory disorders.

Keywords: Pulmonary Function, Body Position, Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), Peak Expiratory Flow (PEF)

Introduction

Pulmonary function is paramount in assessing and monitoring respiratory health, serving as a vital indicator of the efficiency of the respiratory system in maintaining adequate oxygenation and eliminating carbon dioxide [1, 2]. The study of pulmonary function holds great significance not only in clinical practice but also in advancing our understanding of respiratory physiology. Recent research endeavors have increasingly scrutinized the intricate relationship between body position and pulmonary function, revealing that posture plays a pivotal role in modulating various aspects of respiratory performance [3, 4]. It is within this context that this comprehensive review aims to explore the multifaceted impact of body position on pulmonary function.

Despite the growing body of literature on the influence of body position on pulmonary function, a comprehensive synthesis of existing research remains conspicuously absent [1]. The majority of prior investigations have been compartmentalized, often concentrating on specific aspects of pulmonary function or particular patient populations. While these focused studies have yielded valuable insights [5], there exists a discernable need for a holistic review that assembles and interprets this scattered body of knowledge [6]. This review, therefore, addresses the existing gap by offering an inclusive analysis that integrates diverse original research articles, allowing for a comprehensive understanding of the intricate interplay between body position and respiratory health [5]. By amalgamating these scattered pieces of the puzzle, we aim to provide a holistic view of the subject matter, thus contributing to a more profound comprehension of the topic.

To conduct this comprehensive review, a systematic search of the existing literature was performed using various academic databases, including PubMed, Google Scholar, and relevant medical journals. The search terms included ‘body position’, ‘pulmonary function"’, ‘lung volumes, ‘ventilation’, and ‘gas exchange’. Only original research articles were considered for inclusion in this review. A total of 36 original texts that directly addressed the impact of body position on pulmonary function were selected for analysis.

Table 1 Impact of Body Position on Respiratory Function and Lung Measurements

Body Position	Key Findings	Author
Sitting	In healthy men with BMI < 30 kg/m2, changing from sitting to supine or prone resulted in a statistically significant change in respiratory pattern. Spirometry values were normal.	Vilke et al.[7]
Sitting	Maximum inspiratory and expiratory mouth pressures were higher in the sitting position compared to supine or semi-upright sitting positions.	Costa et al., 2015 [2]
Sitting, Supine	Changes in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV(1)), and other spirometric measurements in spinal cord injury individuals depended on injury level and posture.	Baydur et al., 2001[8]
Sitting, Supine	Body position influenced lung volumes and ventilation distribution in children with cystic fibrosis.	Ramsey et al., 2017[9]
Sitting, Supine	Sitting position provides greater improvement in chest-wall diameter changes and volume related to rib-cage function. Supine position results in superior enhancement in the abdomen.	Sonpeayung et al., 2018[10]
Sitting, Supine, Prone	Peak expiratory flow was higher when seated compared to prone or supine positions. No difference observed between prone and supine positions.	Antunes et al., 2016[11]
Supine	Lateral decubitus position in chronic heart failure patients resulted in discomfort and worsened lung function.	Palermo et al., 2005[12]
Supine	Supine reduction in functional residual capacity (FRC) was observed after weight loss in morbidly obese individuals.	Sebbane et al., 2015[3]
Supine	Supine FVC is an excellent predictor of diaphragmatic weakness in patients with amyotrophic lateral sclerosis. Accessory muscle use and abdominal paradox are associated with diaphragmatic weakness.	Lechtzin et al., 2002[13]
Standing	Mean PEF in the standing position was significantly higher than in the lying back and sitting positions. Clinicians should ensure PEF is obtained with patients out of bed and in the standing position.	Wallace et al., 2013[14]
Prone	Change from supine to prone position improves gas-tissue distribution, lung stress and strain, and oxygenation. Main reason for implementing prone position in ARDS is improved ventilation-perfusion matching.	Guérin et al., 2020[15]
Airflow distribution in healthy subjects	Posture changes lead to significant changes in regional lung ventilation. Volume and airflow distribution are affected by posture.	Ides et al., 2022[16]
Asthmatic children	Sitting FEV1/FVC is lower in overweight/obese asthmatic children compared to normal weight asthmatic children. Weight negatively correlates with asthma control.	Emil et al., 2020[17]
COVID-19 patients	Prone position increases ventilation distribution and oxygenation in invasive and non-invasive ventilation. Differences in severity may affect results.	Dos Santos Rocha et al., 2022[18]
Dorsal and Lateral Decubitus	Peak expiratory flow decreased in dorsal and lateral decubitus positions compared to sitting.	Gianinis et al., 2013[4]
Forward head posture in neck pain	Forward head posture is associated with expiratory muscle weakness in chronic neck pain patients. Neck disability is correlated with weakness and respiratory dysfunction.	Solakoğlu et al., 2020[19]
Head-up tilt and standing	Passive tilting increases ventilation in healthy subjects. Standing increases minute ventilation, tidal volume, and V(E)/VCO2. Increased muscle activity in standing affects V(E).	Chang et al., 2005[20]
Laboratory vs. habitual sleeping position	Polysomnography in laboratory and home settings results in more time spent in the supine position compared to habitual sleep. This overestimates OSA severity in supine-predominant OSA patients.	Yo et al., 2022[21]
Left lateral body position	Left lateral body position increases pulmonary vein stress during atrial relaxation phase. Implications for posture-triggered AF.	Gottlieb et al., 2021[22]
Orthostasis to Recumbent	Recumbent positions increased vital capacity in patients after upper abdominal surgery.	Martinez et al., 2015[1]
Swimming body position	Swimmers experience symptoms during competition speed swimming. Transition from land to water decreases FEV1/FVC ratio. VE exceeds target ventilations during intense swimming.	Päivinen et al., 2021[23]

Body Position	Key Findings	Author
Thoracic surgery	Mechanical power and lung elastance are increased in lateral position with one-lung ventilation. Prone recruitment maneuvers improve lung aeration and oxygenation after cardiac surgery.	Emil et al., 2020[24]; Martinsson et al., 2021[36]
Transition from invasive to noninvasive	Transitioning from invasive to noninvasive respiratory support increased EELV and shifted tidal ventilation to the ventral lung regions in preterm infants.	van der Burg et al., 2015[25]
Upine position	Supine position increases vital capacity and forced expiratory volume in the first second. Phase shift between thorax and abdomen during breathing increases.	Miccinilli et al., 2016[26]
Upright CT vs. supine CT	Lung and lobe volumes are significantly greater in the standing position compared to the supine position. Right middle lobe volume remains similar between positions.	Yamada et al., 2020[27]
Upright posture in highlanders	In highlanders, SpO2 is higher in the upright-seated compared to the supine posture, especially with older age. Posture may contribute to hypoxemic burden during sleep.	Arias et al., 2019[28]
Upright, Supine, Prone	In healthy individuals, DL(CO) improved from upright to supine and prone positions. No significant changes in DL(CO) observed in COPD patients.	Terzano et al., 2009[29]
Upright vs. supine position during exercise	Oxygen uptake kinetics are slower in the supine position during exercise. Muscle deoxygenation remains elevated after priming in supine.	Goulding et al., 2020[30]
Various	Body position influences chest wall volumes, lung function, and respiratory muscle strength in individuals with abdominal obesity.	Sonpeayung et al., 2019[5]
Various	Ventilatory muscle strength and endurance were reduced in patients with generalized myasthenia gravis, with no change in those with isolated ocular involvement.	Keenan et al., 1995[31]
Various	Postural disorders in adults with asthma correlated with pulmonary function and body composition.	Almeida et al., 2013[32]
Various	Forward head posture was associated with lower respiratory functions in young adults.	Kim et al., 2017[33]
Various	Body position did not significantly affect pulmonary circulation during exercise testing, but semirecumbent position decreased maximum workload.	Forton et al., 2016[6]
Various	Physiotherapist-led physical activity interventions increased physical activity levels in adults at risk of NCDs.	Kunstler et al., 2018[34]
Various	Recumbent positions led to diminished pulmonary functions and discomfort in young, healthy volunteers.	Naitoh et al., 2014[35]

Effect of Body Position on Pulmonary Function

The study of how body position influences pulmonary function is a critical area of research in the field of respiratory physiology. While factors like age, gender, and health status are well-known influencers of lung function [2], the role of body posture remains underexplored yet significant [1, 3-5, 34]. Understanding this influence is vital for several reasons. Firstly, it unveils the intricate biomechanics of breathing, showing how postural changes can affect airflow distribution in the lungs. Secondly, it has practical implications in clinical settings, where patients' posture can change due to illness or immobilization [5, 14]. Lastly, it informs the optimization of pulmonary function in healthy individuals, athletes, and those engaged in physical activities [7, 11]. Body position significantly affects lung volumes, including vital capacity (VC), functional residual capacity (FRC), and total lung capacity (TLC) [1, 7, 9, 13, 26]. This happens because chest wall mechanics and diaphragm position change, impacting lung volume [26]. For instance, FRC is lower in the supine position than in sitting [9]. This decrease in FRC in the supine position is due to the weight of the abdominal contents pressing against the diaphragm, reducing the available space for lung expansion [1].

Forced vital capacity (FVC) and Forced Expiratory Volume in 1 second (FEV1) are crucial parameters in assessing lung function. Body position has been shown to influence these measurements as well. In some studies, changing from a sitting to a recumbent position resulted in a statistically significant decline in FVC and FEV1 values [7]. These changes in FVC and FEV1 could be attributed to alterations in respiratory mechanics, as chest wall motion and lung volumes are modified with changes in posture [35].

Respiratory muscle strength is also influenced by body position, with maximal inspiratory and expiratory mouth pressures (PImax and PEmax) varying based on posture [2]. For example, these pressures tend to be higher when sitting compared to supine positions [2].

Furthermore, gas exchange and oxygen transport are affected by body position. Transitioning from sitting to supine, for instance, affects alveolar-to-arterial oxygen partial pressure difference and pulmonary gas exchange [3]. This is relevant for conditions like obesity, where postural changes can impact pulmonary gas exchange [3]. Peak expiratory flow (PEF), an important parameter in respiratory function assessment, also varies with body position. PEF values are higher when seated compared to prone or supine positions [4, 11]. This suggests that the choice of body position can affect PEF testing outcomes, impacting the diagnosis and management of respiratory conditions.

In summary, body position's impact on pulmonary function is a crucial area of study. It affects lung volumes, respiratory muscle strength, gas exchange, PEF, FVC, and FEV1. The following sections will delve into a detailed analysis of these effects using data from various original studies, shedding light on the intricate relationship between body position and pulmonary function.

Sitting VS. Supine Position

The effect of body position on pulmonary function has been a subject of interest in the field of respiratory physiology. Researchers have conducted various studies to investigate how different body positions, specifically sitting and supine, influence pulmonary function in both healthy individuals and patients with various medical conditions. This essay aims to provide a detailed analysis of the studies comparing pulmonary function measurements in sitting and supine positions, with a focus on key parameters such as FVC, FEV1, FRC, PEF, VC, PImax, and PEmax, Alveolar-to-Arterial Oxygen Partial Pressure Difference, and Total and Compartmental Chest Wall Volumes. The analysis will be presented separately for healthy individuals and patients with various medical conditions.

Pulmonary Function in Healthy Individuals

FVC and FEV1: Studies have consistently shown that sitting posture generally results in higher FVC and FEV1 values compared to the supine position in healthy individuals [6, 18, 33]. The upright position facilitates greater lung expansion, leading to increased FVC and improved expiratory flow rates [33]. However, it is essential to consider that these differences, while statistically significant, may not always be clinically relevant in healthy individuals [6].

FRC: The supine position tends to reduce FRC in healthy individuals compared to the sitting position [9]. This decrease is primarily attributed to changes in chest wall mechanics and diaphragmatic function when transitioning from an upright to a supine posture.

PEF: PEF values also exhibit variability depending on body position. Studies have shown that PEF is higher in the standing or sitting positions compared to the supine position in healthy individuals [14]. This is likely due to the increased thoracic and abdominal pressure generated in the upright posture, enhancing expiratory flow.

VC: Vital Capacity, a crucial parameter reflecting lung function, generally follows a similar trend as FVC in healthy individuals. It tends to be higher in the sitting or standing position compared to the supine position [6]. This is indicative of increased lung volume attainable in the upright posture.

PImax and PEmax: Maximum Inspiratory and Expiratory Mouth Pressures, measures of respiratory muscle strength, may exhibit variations with body position. Studies have reported changes in these parameters when transitioning from supine to upright positions [1, 35]. However, the clinical significance of these changes in healthy individuals remains a subject of further investigation.

Alveolar- to- Arterial Oxygen Partial Pressure Difference: The Alveolar-to-Arterial Oxygen Partial Pressure Difference is influenced by changes in pulmonary ventilation and perfusion that accompany alterations in body position. Studies have observed variations in this parameter, especially during positional changes in patients with lung disease [22].

Total and Compartmental Chest Wall Volumes: Body position can affect chest wall volumes, with supine positions often leading to alterations in the distribution of ventilation within the lungs [16]. These changes can have implications for lung mechanics and gas exchange.

Pulmonary Function in Patients with Medical Conditions

Patients with specific medical conditions may exhibit different responses to changes in body position. For instance

Asthma: Patients with asthma may experience specific postural disorders that correlate with pulmonary function and body composition [32]. These correlations suggest that assessing postural variables could be valuable in tailoring pulmonary rehabilitation approaches for these patients.

Chronic Neck Pain: Forward Head Posture (FHP) in patients with chronic neck pain has been shown to impact expiratory muscle strength [19]. Such findings emphasize the relevance of posture-related

interventions in patients with musculoskeletal conditions.

Chronic Obstructive Pulmonary Disease (COPD): In patients with COPD, postural variations may not lead to significant changes in the Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) [29]. This indicates that lung capillary rigidity could play a role in modulating the effect of body position in this patient population.

Spinal Cord Injury: Patients with spinal cord injury exhibit reduced lung volumes and flow rates, especially when transitioning from sitting to supine positions [8]. This suggests that individuals with spinal cord injury are particularly sensitive to changes in body position concerning pulmonary function.

Myasthenia Gravis: Patients with myasthenia gravis may have associated ventilatory muscle involvement. Measures of ventilatory muscle endurance appear to be more sensitive indicators of ventilatory muscle involvement than strength measures. Body position-related changes in pulmonary function may be less pronounced in isolated ocular myasthenia gravis [31].

In summary, body position has a significant impact on pulmonary function in both healthy individuals and patients with various medical conditions. Key parameters, including FVC, FEV1, FRC, PEF, VC, PImax, PEmax, Alveolar-to-Arterial Oxygen Partial Pressure Difference, and Total and Compartmental Chest Wall Volumes, are influenced by body position. In general, sitting positions tend to result in better pulmonary function measurements compared to supine positions in healthy individuals. However, the effect of body position can vary depending on the underlying medical condition, with some conditions, such as chronic heart failure and spinal cord injury, leading to discomfort and worsened lung function in specific positions. These findings underscore the importance of considering body position when assessing and managing pulmonary function in both clinical and research settings.

Other Body Positions

Body position plays a crucial role in influencing pulmonary function, with various positions such as standing, prone, lateral decubitus, and more potentially affecting lung mechanics and gas exchange. Understanding the impact of these positions is essential, particularly for individuals with various medical conditions. This essay explores the research findings related to different body positions and their effects on pulmonary function, focusing on specific groups of individuals with different diseases.

Standing Position

Standing is the most common body position in daily life. Research has shown that pulmonary function remains relatively stable in the standing position [32]. In a study of patients with asthma, no significant changes in FEV1/ FVC were observed when transitioning to a standing posture [32]. This suggests that standing does not have a pronounced effect on pulmonary function in healthy individuals.

Prone Position

The prone position, in which individuals lie face down, has been studied extensively in various clinical contexts. It is known to improve oxygenation in patients with acute respiratory distress syndrome (ARDS) [15]. In healthy subjects, transitioning to the prone position can lead to enhanced ventilation in dorsal lung zones [18]. The improved ventilation-perfusion matching and distribution of lung regional aeration suggest that prone positioning may be beneficial in optimizing pulmonary function in specific clinical situations.

Lateral Decubitus Position

Lying on one's side, known as the lateral decubitus position, can generate discomfort and worsen lung function in chronic heart failure patients [12]. Research has shown that airway obstruction and lung diffusion impairment become more pronounced in this position, particularly as heart dimensions increase [12]. In contrast, healthy individuals tend to experience a decrease in peak expiratory flow (PEF) in lateral decubitus positions [4]. These findings highlight the importance of considering body position in the assessment and management of patients with cardiopulmonary conditions.

Upright Position

Upright posture has been shown to increase oxyhemoglobin saturation in individuals living at high altitudes. In this population, transitioning from a supine to an upright seated posture led to a significant improvement in oxygen saturation [28]. This effect may be particularly relevant in high-altitude regions, where hypoxia amplifies oxyhemoglobin saturation fluctuations with changes in respiratory mechanics.

Forward Head Posture (FHP)

FHP, a common posture-related issue, has been associated with expiratory muscle weakness in chronic neck pain patients. The negative correlation between FHP and Pemax suggests that correcting posture may have a positive impact on respiratory muscle function [28].

Body position plays a significant role in modulating pulmonary function, and its impact varies across different postures and clinical contexts. While standing and supine positions generally have limited

effects on pulmonary function in healthy individuals, positions like prone, lateral decubitus, and upright may significantly influence respiratory parameters. Understanding these effects is essential for optimizing patient care, especially in conditions like ARDS, chronic heart failure, and high- altitude living. Moreover, recognizing the association between posture-related issues such as FHP and respiratory muscle weakness underscores the importance of posture assessment and correction in clinical practice.

Percentage difference in pulmonary function parameters

Sitting VS Supine Position

FEV1/FVC: Almeida et al. and Naitoh et al. reported a significant decrease in FEV1/FVC in the supine position compared to sitting, with a percentage difference of approximately 10%.

TLC: Almeida et al. indicated an increase in TLC (around 5%) in the supine posture, while Forton et al. found no significant difference between sitting and supine positions.

RV: Almeida et al. reported an increase in RV (approximately 5%) in the supine position, suggesting reduced expiratory reserve volume.

VC: Martinez et al. observed higher VC values in orthostasis compared to the supine position, with a notable percentage difference of up to 15%.

PEF: Wallace et al. showed that PEF was significantly higher in the standing position compared to lying down, with a percentage difference of approximately 8%.

Other Body Positions

Right Lateral Position: Ides et al. highlighted increased regional ventilation in the right lung compared to the left lung in the right lateral position.

Prone Position: Guérin et al. and Martinsson et al. emphasized the benefits of the prone position in improving oxygenation and lung recruitment.

Upright Position: Yamada et al. found that total lung volume increased by approximately 10.9% in the standing position compared to supine.

Body position plays a substantial role in altering pulmonary function parameters. The supine position generally results in decreased FEV1/ FVC, increased TLC and RV, and decreased VC compared to sitting or standing. Other positions, such as the prone position, have been shown to improve oxygenation and lung recruitment. These findings emphasize the importance of considering body posture in clinical assessments and pulmonary rehabilitation programs, particularly for individuals with respiratory conditions. Further research is needed to explore the specific mechanisms underlying these changes and to tailor interventions accordingly.

Conclusion

The plethora of studies reviewed underscores the critical nexus between body position and pulmonary function, a salient knowledge domain for both clinical and rehabilitation settings. This synthesis unveils key insights into how body positioning intricately modulates lung mechanics, lung volumes, and muscle distribution, thereby influencing pulmonary functionality.

Lung Mechanics: The seminal correlation between pulmonary function and posture in asthmatic patients delineates how the horizontal alignment of the head significantly correlates with pivotal indices like FEV1/FVC, TLC, and RV, hinting at posture-induced modulation of lung mechanics [32]. A study showcasing the effect of different head-neck postures on respiratory function in healthy males further elucidates how Forward Head Posture (FHP) can potentially attenuate respiratory functions, hence accentuating the importance of correct head posture [33]. The intricate relationship between body position and lung mechanics is further manifested in a study on young healthy participants, where transitioning from a sitting to a recumbent position significantly dwindled FEV1 values, albeit without affecting MIP or MEP [35].

Lung Volumes: Ventilation distribution, a quintessential aspect of lung volume, is markedly influenced by body posture as seen in children with Cystic Fibrosis (CF) where Functional Residual Capacity (FRC) and Lung Clearance Index (LCI) showed significant variances between seated and supine postures [9]. Similarly, a study on postoperative upper abdominal surgery patients revealed notable increments in vital capacity values when transitioning to more vertical postures, thereby underlining the posture-induced modulation of lung volumes [1] . The investigation on the effect of posture on lung ventilation distribution in children with CF further corroborates how body posture critically impacts lung volumes and their distribution [9].

Muscle Distribution: The distribution of respiratory muscles and their functionality is pivotal in mediating pulmonary function across different body positions. For instance, the study on the effect of different head-neck postures elucidates how varying craniovertebral and cervical retroversions can modulate Sternocleidomastoid muscle activity, thereby affecting respiratory function [33]. The effect of posture on breathing kinematics in spinal cord injury patients as analyzed through optoelectronic plethysmography also unveils how supine position enhances vital capacity and FEV1, possibly due to a more favorable diaphragmatic length, albeit at the expense of respiratory kinematics of the chest wall [26]. The astute observation that the sitting position improves rib-cage function while the supine position augments the abdominal part, as

reviewed in a meta-analysis, further accentuates the quintessential role body position plays in modulating respiratory muscle distribution and function [10].

The importance of understanding the impact of body position on pulmonary function cannot be overstated. It not only forms a crucible for optimal clinical and rehabilitative strategies but also furnishes a deeper understanding of the physiological interplay between posture and respiratory mechanics, volumes, and muscle distribution. The nuanced understanding of these dynamics is instrumental in devising more effective therapeutic and rehabilitative interventions, particularly for individuals with respiratory or postural challenges. The meticulous scrutiny of the data and the resultant insights thereof, furnish an invaluable scaffold upon which more targeted research and clinical strategies can be developed. This narrative, enriched by the plethora of empirical evidence, epitomizes the quintessence of interdisciplinary understanding necessary for advancing both clinical and academic pursuits in the realm of pulmonary physiology and rehabilitation science.

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Assessing the Accuracy of the Figure-of-Eight Walk Test in Distinguishing Between Household and Community Ambulation in Post-Stroke Individuals

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ABSTRACT

Introduction: Traditional post-stroke walking assessments often prioritize linear trajectories, failing to capture the complexity of everyday ambulation. Navigating the intricacies of everyday life requires adaptability that extends beyond the confines of linear paths. It involves addressing dynamic challenges, such as turns, varied terrains, and unexpected obstacles, which are often not adequately captured by traditional post-stroke walking assessments. The Figure-of-Eight Walk Test (F8WT) compensates for this limitation by assessing walking ability in varied scenarios. However, investigations into its accuracy for differentiating walking capabilities post-stroke are notably lacking. This study aimed to investigate the precision of the F8WT in distinguishing between household and community walkers among individuals post-stroke.

Methods: Sixty-two stroke participants, capable of walking independently or with minimal assistance (one assistant at most), were categorized into household and community walkers based on gait speed measurements. The F8WT was then administered, with its discriminative accuracy assessed using the area under the receiver operating characteristic (ROC) curve. Additionally, an optimal cutoff value distinguishing the two categories was calculated.

Results: The F8WT demonstrated robust discriminative potential, achieving the area under the curve (AUC) of 0.96 (95% CI = 0.91–1.00) on the ROC curve analysis. It registered a sensitivity of 97.60% and a specificity of 84.20%. A critical cutoff point was established at >11.20 seconds for effective categorization.

Conclusions: The F8WT is a potent assessment tool, successfully differentiating between household and community walking abilities among stroke survivors. This precise demarcation underscores its applicability in individualized post-stroke rehabilitative planning.

Keywords: Figure-of-Eight Walk Test, post-stroke assessment, Walking ability, Gait categorization, Rehabilitation

Introduction

Impaired walking function post-stroke significantly hinders individuals' independence both within their homes and the broader community [1, 2]. Coupled with this impairment is a heightened risk of falls, making the recovery of autonomous ambulation a critical rehabilitation target [3]. While approximately 60-80% of stroke survivors regain independent walking abilities within six months, many continue to face limitations in autonomous ambulation and community mobility [4, 5]. A substantial percentage, ranging from 20.7% to 82.3%, find themselves restricted to walking independently and ambulating in a community setting [4, 5]. Hence, comprehensive assessments of walking capabilities, encompassing both home-based and community environments, are essential for these individuals.

Community ambulation refers to the ability and confidence required to navigate various environments, from indoor and outdoor public spaces to more challenging terrains [6]. This form of mobility is not merely a physical action but a key determinant of participation in meaningful activities, self-perceived health status, mental well-being, social engagement, and

overall quality of life [7-9]. Factors influencing community ambulation include gait speed, balance, and endurance, with gait speed often serving as a primary indicator [10].

Traditional assessment tools focus predominantly on linear walking activities, neglecting the more nuanced aspects of daily mobility such as turning, maneuvering through confined spaces, and safely navigating various obstacles and terrains [11, 12]. Real-world ambulation, particularly in home and community settings, requires not only straightforward walking but also the ability to navigate turns and curved paths [13]. Navigating these complex pathways requires specific gait characteristics and body adjustments [14], with any asymmetry in posture or movement particularly impacting stroke survivors' ability to execute precise turns or coordinate movements effectively, thereby increasing their fall risk [15, 16].

The Figure-of-Eight Walk Test (F8WT) has been designed to address these complexities by assessing walking function over straight and curved paths, requiring directional changes [17, 18]. The F8WT entails walking a figure-eight pattern between two cones spaced five feet apart [17, 18]. It precisely measures dynamic aspects of walking, including agility, balance, and adaptability [17-19]. Unique to the F8WT is its emulation of everyday walking challenges, providing a more comprehensive picture of an individual's functional walking capacity than straight-path assessments [19]. Although widely used in various populations, including older adults, individuals with Parkinson's disease, and stroke survivors [17-19], the F8WT's applicability for differentiating walking abilities among stroke patients in home and community settings has not been explored. This study aimed to fill the existing research gap by examining the accuracy of the Figure-of-Eight Walk Test (F8WT) in classifying the walking capacities of post-stroke individuals, specifically focusing on distinguishing between household and community walkers. The methodology involved analyzing the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve. This analysis was complemented by assessing walking ability using the 10-Meter Walk Test (10MWT), a reference standard in this field. It was hypothesized that the F8WT would prove to be a reliable and precise tool in differentiating walking capacities, reflecting the true functional mobility levels in individuals post-stroke.

Methodology

Study Design

A cross-sectional study was conducted to evaluate the efficacy of the Figure-of-Eight Walk Test (F8WT) in accurately assessing the walking abilities of stroke. This research initiative was sanctioned by the Institutional Research Ethics Review Committee for Research Involving Human Subjects, conforming to the standards outlined in COA No. 227/65. The study was centered on validating the F8WT's precision in differentiating functional mobility levels among post-stroke individuals, contributing critical insights for enhancing rehabilitation methodologies.

Participants

Individuals who had experienced a stroke were recruited for the study through a combination of advertisements and community outreach initiatives in Kanchanaburi, Thailand. The recruitment period spanned two months, from February to March 2023. The required sample size was established based on statistical calculations using MedCalc software (version 20.110), setting the parameters for a type I error at 0.05 and a type II error at 0.20 [20]. These thresholds were chosen to maintain a balance between statistical rigor and practical feasibility. The anticipated area under the receiver operating characteristic (ROC) curve (AUC) was projected at 0.7, with a null hypothesis value of 0.5. These considerations necessitated a sample size of 62 participants for the study.

Out of 66 individuals screened, 62 met the study's inclusion criteria and were subsequently enrolled. Informed written consent was obtained from each participant, ensuring they understood the study's scope, procedures, and their rights within the research context.

The study established several benchmarks for inclusion criteria for participation selection: (i) diagnosis of the individual's first stroke, either ischemic or hemorrhagic, by a clinician, with accompanying hemiparesis; (ii) participants aged between 18 and 80 years; (iii) the capability to walk independently or with minimal assistance (one assistant at most); and (iv) adequate cognitive function to understand and respond to simple commands.

Those Individuals were excluded from participation if they: 1) Presented with other neurological impairments that could interfere with stroke-related outcomes; 2) Had severe orthopedic conditions impacting their ability to walk, unrelated to their stroke history; 3) Were dealing with visual or vestibular disorders that could affect balance or navigation; 4) the Thai Mental State Examination (TMSE) < 23 scores; 5) Were managing serious concurrent medical issues like unstable angina or uncontrolled hypertension, which could pose health risks during testing procedures.

Procedures

Upon enrollment in the study, individuals underwent an initial interview and screening process. During this phase, baseline demographic and clinical data were meticulously recorded. The collected variables included age, sex, height, weight, type of stroke, duration since the stroke occurred, the affected

side of the body, the use of any walking aids, and scores on the Modified Rankin Scale (mRS), which evaluates the degree of disability or dependence in daily activities.

This study was constructed as a single-blind experiment to ensure an unbiased outcome. The first stage of practical assessment involved an assessor, uninformed about the participants' subsequent evaluations, administering the 10-Meter Walk Test (10MWT). Performance on this test was employed to categorize participants into two distinct groups: community walkers and household walkers. This categorization was based on their demonstrated walking ability over a short distance. After the 10MWT, participants' walking skills were further assessed using the Figure-of-Eight Walk Test (F8WT). A different assessor, blinded to the groups established by the 10MWT, conducted these tests. This method ensured that preconceived notions did not influence objective assessment. The F8WT requires the participant to walk in a straight line and then along a figure-of-eight trajectory, testing not only the straight-line walking ability but also the capacity to navigate turns and directional changes [17, 18].

Both the 10MWT and F8WT were conducted across three trials to account for variability in performance and ensure consistency in the results. After each trial, a rest period of one minute was instituted, and following each full test, a longer break of five minutes was observed. Additional resting time was provided as required, based on each participant's fatigue levels and personal needs, to prevent any test-induced strain. To optimize performance and ensure safety, participants were instructed to wear attire and footwear that provided comfort and did not restrict movement.

Measurements

(i) 10-Meter Walk Test

The 10MWT, a standardized assessment of gait speed, required participants to walk 14 meters at a comfortable pace upon a verbal cue. The total distance included 2 meters each for acceleration and deceleration, ensuring that the actual timed 10-meter distance was free from these variables' influence [21]. Each participant performed three trials, with the average time recorded. Gait speed was calculated by dividing the distance by the time taken to walk the middle 10 meters. The results of the 10MWT led to the classification of participants into two groups: those with a walking speed of less than 0.8 m/s were categorized as home walkers, and those achieving speeds above 0.8 m/s were identified as community walkers [22].

(ii) Figure-of-Eight Walk Test

The F8WT evaluated the ability to navigate straight and curved paths. Participants initiated the test from a standing position between two cones set 5 feet apart and were instructed to walk around the cones in a figure-eight pattern until they returned to the start [18]. The test comprised three trials with rest periods in between. The primary outcome measure was the time taken to complete the course, measured from the first step until the participant returned to the starting position [17].

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism version 9.5.1 (GraphPad Software, La Jolla, CA, USA). The D'Agostino–Pearson test verified demographic data normality. To describe participant characteristics, descriptive statistics were employed. The participant characteristics were presented as means compared between groups using the independent t-test for continuous data and the Chi-squared test for non-continuous data. For all analyses, a p-value of less than 0.05 was considered statistically significant.

The accuracy of the tests was evaluated using the Receiver Operating Characteristic (ROC) curve, illustrating the trade-off between sensitivity (true positive rate) and specificity (false positive rate). The area under the ROC curve (AUC) values were employed for categorizing the accuracy of the tests into the following: high accuracy (AUC >0.9), moderate accuracy (0.7–0.9), low accuracy (0.5–0.69), or non-informative (AUC <0.5) [23].

Additionally, Youden's index was utilized to determine the optimal cutoff score for each test, calculated as the maximum sensitivity plus specificity minus one [24]. This study also scrutinized the sensitivity, specificity, positive likelihood ratios (LR+), and negative likelihood ratios (LR-) at the determined cutoff points. Sensitivity reflected the ability of the test to correctly identify true positives (household walkers at risk), while specificity represented the accurate detection of true negatives (community walkers not at risk) [25].

Further, LR+ and LR- were calculated to assess the probability of positive and negative test results in household walkers relative to community walkers. LR+ was derived by dividing sensitivity by the complement of specificity (1-specificity), while LR- involved dividing the complement of sensitivity (1-sensitivity) by specificity. Test results were considered more indicative of household walkers when LR+ was greater than 1.0 and LR- was less than 1.0 [26]. The effectiveness of the tests in confirming or ruling out a diagnosis was evaluated based on LR+ and LR-. Specifically, ratios greater than 10 for LR+ or less than 0.1 for LR- were considered highly effective. The impact of the LRs on diagnostic probability was interpreted as follows: Large and often conclusive shift in diagnosis probability: LR+ >10 or LR- <0.1; Moderate shift: LR+ = 5–10 or LR- = 0.1–0.2; Small but potentially important shift: LR+ = 2–5 or LR- = 0.2–0.5; Minor change in diagnosis probability: LR+ = 1–2 or LR- = 0.5–1; No change in

probability: LR+ and LR- values not meeting the above criteria [27, 28].

Results

The study evaluated 62 participants post-stroke, categorizing them into two distinct groups based on their walking abilities: household walkers (n=43, ranging from 23 to 80 years old) and community walkers (n=19, aged between 33 and 75 years) (Table 1). A comprehensive comparison of demographic and clinical characteristics between the groups is detailed in Table 1. While most attributes were consistent across both categories, notable differences were observed in the mRS scores and the prevalence of walking aid usage (Figure 1).

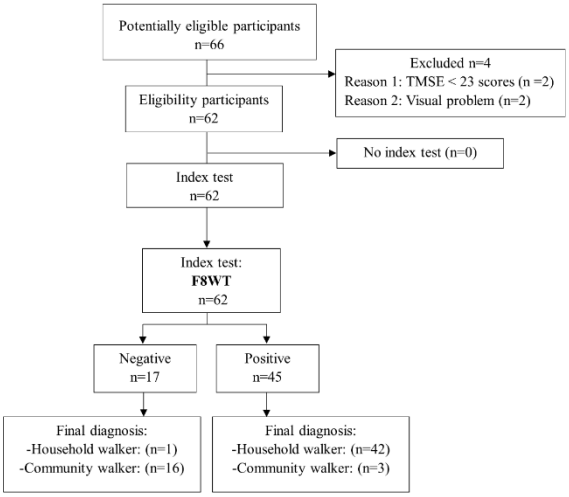

Figure 1 The flow of participants through the study

Table 1 Comparison of demographics characteristics and clinical characteristics among household and community walkers

Characteristics	Household walker (n=43)	Community walker (n=19)	p-value
Age (years) [mean (SD)]	62.42 (10.484)	59.74 (11.66)	0.373
Sex [n (%)]			0.469 [b]
Male	29 (67.4%)	11 (57.9%)	
female	14 (32.6%)	8 (42.1%)	
Height (cm) [mean (SD)]	162.16 (6.229)	161.58 (8.846)	0.767
Weight (kg) [mean (SD)]	66.28 (13.267)	64.24 (9.010)	0.544
Body mass index (kg/m^2) [mean (SD)]	25.19 (4.781)	24.73 (3.956)	0.715
Etiology [n (%)]			0.356 [b]
Infraction	36 (83.7%)	14 (73.7%)	
Hemorrhage	7 (16.3%)	5 (26.3%)	
Hemiplegic side [n (%)]			0.351 [b]
Left	24 (55.8%)	19 (100%)	
Right	19 (44.2%)	0 (0%)	
Stroke duration (months) [mean (SD)]	30.19 (38.668)	25.63 (32.833)	0.657
Modified Rankin Scale [n (%)]			< 0.001 [b]*
Grade 1	5 (11.6%)	18 (94.7%)	
Grade 2	24 (55.81%)	1 (5.3%)	
Grade 3	7 (16.3%)	0 (0%)	
Grade 4	7 (16.3%)	0 (0%)	
Grade 5	0 (0%)	0 (0%)	
Use of a walking aid [n (%)]			< 0.001 [b]*
No	15 (34.9%)	18 (94.7%)	
One-point cane	4 (9.3%)	1 (5.3%)	
Tripod cane	22 (51.2%)	0 (0%)	
Quad cane	2 (4.7 %)	0 (0%)	
Use of an orthosis [n (%)]			0.503 [b]
No	42 (97.7)	19 (100%)	
Yes	1 (2.3%)	0 (0%)	

*[a] T-test; [b] Chi-square test. *Statistical significance at $\alpha = 0.05$.*

A crucial aspect of the evaluation involved the F8WT, the results of which are quantified in Table 2. Utilizing the Mann-Whitney U test for comparison, data revealed a significant disparity in the time taken to complete the F8WT between household and community walkers. Specifically, household walkers exhibited a prolonged completion time, indicative of diminished walking capabilities.

Table 2 The score of F8WT in household and community walkers

Test	Household walker (n=43) Median (IQR)	Community walker (n=19) Median (IQR)	p-value
F8W time (s)	22.30 (15.28 - 45.78)	9.15 (7.43 - 10.63)	< 0.001*

*Mann-Whitney test. IQR: interquartile range; F8W: the figure of eight walk test. *Statistical significance at α= 0.05.*

Subsequent analysis emphasized the diagnostic power of the F8WT in distinguishing between household and community walking statuses. The ROC curve analysis demonstrated that the F8WT was a highly accurate classifier with an AUC of 0.96 (95% CI= 0.91–1.00) (Figure 2). This impressive accuracy was further evidenced by a sensitivity of 97.60% and specificity of 84.20%, established at an optimal cutoff point of >11.20 seconds for the test duration. These metrics signify an excellent ability of the F8WT to differentiate participants' walking abilities accurately.

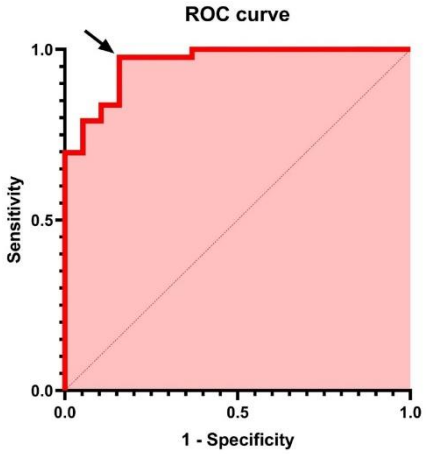

Figure 2 The receiver operating curve for comparing the accuracy of the Figure-of-Eight Walk Test (F8WT) to predict the walking classification of individuals with stroke between household and community walkers.

In further support of these findings, the likelihood ratios associated with the F8WT results underscored the test's effectiveness. Both LR+ and LR- confirmed the substantial evidential weight of the F8WT in correctly identifying participants as either household or community walkers, as detailed in Table 3.

Table 3 AUC, cut-off score, sensitivity, specificity, LR+, and LR- of F8WT for discriminating household and community walker

Indicator	F8W time (s)
AUC	0.96
SE	0.02
95%CI	0.91 - 1.00
p-value	<0.001*
Youden's index	0.82
Cut-off score	>11.2
Sensitivity	97.67
Specificity	84.21
LR+	6.19
LR-	0.03

*F8W: the figure of eight walk test; AUC: area under the ROC curve; SE: standard error; LR+: positive likelihood ratio; LR-: negative likelihood ratio. *Statistical significance (null hypothesis: AUC = 0.5) at α = 0.05.*

The demonstrated high diagnostic accuracy of the F8WT in our study suggests its utility as an effective screening tool for walking impairments in post-stroke individuals. Early and accurate identification of walking difficulties using the F8WT can guide clinicians in making informed decisions about initiating appropriate rehabilitative interventions, potentially improving recovery trajectories.

Discussion

This study illuminated the critical role of the F8WT in differentiating walking abilities among post-stroke individuals, categorizing them into household or community walkers. The results underscore the test's substantial accuracy, with a notable AUC of 0.96, an impressive sensitivity of 97.60%, and a specificity of 84.20%. These metrics not only affirm the test's precision but also highlight its potential as a reliable tool in clinical and rehabilitative settings.

Contextualizing F8WT within Post-Stroke Recovery

Walking, a complex motor task, demands the integration of physical strength, balance, coordination, and cognitive function. For stroke survivors, these components often become disjointed, impeding efficient walking [11]. Particularly, the ability to navigate curved paths, essential for household and community ambulation, becomes compromised, leading to increased fall risk and limited functional independence [17, 18]. The F8WT's high sensitivity and specificity in this study accentuate its effectiveness in capturing these nuanced deficits, empowering clinicians with a precise tool for evaluating walking abilities in post-stroke individuals. The test, by incorporating straight and curved walking, challenges the individual's dynamic balance, weight shifting, and cognitive-motor interface, offering deeper insights into their walking proficiency and underlying neurological recovery [17].

Interpreting the Cutoff Point

The introduction of a cutoff point of >11.20 seconds in the F8WT is a pivotal finding of this study. This threshold is practical, helping to distinguish between household and community walkers. In a clinical context, this cutoff point simplifies decision-making for practitioners. It acts as an indicator necessitating more intensive, targeted rehabilitation strategies for individuals struggling with ambulation post-stroke, particularly those surpassing this time limit.

It is important to recognize that this cutoff is not just a number but a significant demarcation guiding patient categorization. It aids in identifying stroke survivors who are in a transitional phase of recovery, indicating a potential readiness to navigate more complex environments beyond the household. This distinction is crucial, as it helps in tailoring therapy, setting realistic goals, and providing motivation for patients undergoing rehabilitation.

Moreover, this cutoff can facilitate consistent monitoring of progress, enabling therapists to objectively measure improvements in walking ability over time and adjust interventions accordingly. It standardizes a component of stroke recovery, ensuring that individuals receive appropriate, evidence-based care aligned with their recovery trajectory.

F8WT and Cognitive Function

Walking, especially on curved paths, is not purely a motor task but involves significant cognitive input, requiring attention, planning, and visuospatial awareness [29]. Post-stroke deficits often blur this cognitive-motor interface, making tasks like the F8WT more challenging and thereby more revealing of a person’s functional and cognitive recovery scope. The relationship between F8WT scores and cognitive function underscores the need for comprehensive post-stroke care, integrating cognitive rehabilitation and physical therapy.

Biomechanics of Curved Walking

Curved walking post-stroke is biomechanically demanding, requiring asymmetrical adjustments, inner leg loading, and continual rebalancing [30]. These requirements, disrupted by stroke-induced motor and balance impairments, prolong the F8WT completion time, reflecting the individual's struggle to maintain stability [31]. Rehabilitation programs, thus, need to address these specific biomechanical demands, possibly through targeted interventions like weight-shift training, strength building, and neuromuscular re-education. Numerous investigations have explored the efficacy of curved-path gait training. Kim et al. (2012) discovered that eight-way curved-path gait training significantly improves balance and ambulation in stroke patients [32]. Richard (2010) further noted that altering the center of gravity and pelvis rotation during training enhances adaptability in motor control on the affected side, improving curved-path gait performance and the ability to provide sensory information and support during walking [33]. In addition, Jin et al. (2023) found that curved-path gait training significantly improves gait ability, resulting in a more balanced walking pattern compared to general gait training. This highlights the potential of curved-path gait training as a meaningful intervention for improving the asymmetrical gait ability of stroke patients with hemiplegia [34].

Strengths and Limitations

While the study heralds new understanding, certain limitations temper its implications. Its cross-sectional design precludes observing longitudinal recovery, necessary for understanding how walking abilities evolve post-stroke. Additionally, focusing on command-compliant participants excludes insights from those with cognitive impairments, a significant post-stroke cohort.

Future Directions

Given the F8WT's demonstrated efficacy, future studies should explore its predictive validity over longer-term recovery and its applicability across diverse stroke populations, including varying stroke severities, and cognitive statuses. Additionally, integrating technological advancements like motion analysis systems could offer objective insight into the biomechanical aspects of curved walking post-stroke.

Conclusion

In conclusion, the F8WT emerges as a potent tool for discerning walking capabilities in individuals recovering from a stroke, with profound implications for targeted rehabilitation strategies. This aspect of the study is particularly important because it provides new information that can inform clinical practice and rehabilitation programs for individuals with stroke. Its robust association with both the physical and cognitive facets of post-stroke recovery necessitates its consideration in future research and clinical practice, ultimately contributing to enhanced quality of care and life for stroke survivors.

Declarations of interest

The authors report no conflicts of interest.

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Comparative Effects of Vojta Therapy and Standard Physical Therapy on Pain Level and Functional Ability in Working-Age Patients with Non-Specific Low Back Pain

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ABSTRACT

Introduction: The standard physical therapy plays a role in reducing low back pain and increasing functional ability. Vojta therapy helps strengthen the deep muscles of the trunk, beneficial effect on patients with back pain. However, there is a lack of studies on vojta therapy in working-age back pain patients. The study aimed to compare the effects of vojta therapy combined with standard physical therapy and standard physical therapy alone on pain and the functional ability in working-age patients with non-specific low back pain.

Methods: The participants were 50 working-age patients with low back pain and were divided into 2 groups: the experimental group received vojta therapy combined with standard physical therapy (n=25), and the standard physical therapy alone group (n=25). The vojta therapy is 30 minutes and standard physical therapy treatment is 45 minutes, 2-3 times per week, for 4 weeks. Assessment of pain levels and functional ability before and after 4 weeks of treatment or 10 complete treatments. Descriptive statistics include mean, percentage, and standard deviation to describe characteristics, and inferential statistics was an independent t-test to compare pain level and functional ability between the experimental group and the control group. The statistical significance level was set at the 0.05 level.

Results: Within both the experimental and control groups, a significant reduction in pain scores (mean=1.00±0.00) and an improvement in functional ability (mean=1.92±1.45) were observed between pre-test and post-test assessments. When comparing the groups, the experiment exhibited significantly reduced pain scores (mean=1.00±0.00; 95% CI= -1.52 - 0.32) and improved functional ability (mean=4.72±3.62; 95% CI=-8.1-1.74) compared to the control.

Conclusion: Both groups are effective in managing pain and improving the functional ability of low back pain patients. However, vojta therapy combined with standard physical therapy has had better results than the standard physical therapy alone group.

Keywords: Standard Physical Therapy, Working-Age Patients, Pain level, Rehabilitation Non-Specific low-back pain, Vojta therapy

Introduction

Low back pain is a common musculoskeletal disorder and has an impact on both physical and mental health, affecting the ability to work in daily life. Approximately 60–80% of the world's population suffers from low back pain. Currently, approximately 619 million people suffer from low back pain; most of them have non-specific low back pain. It is expected that this number will increase to 843 million in 2050 [1-4]. The cause is due to increasing age, hard work, improper movement, obesity, smoking, and a lack of exercise. In particular, increasing age increases the risk of low back pain, which is caused by deterioration of the spinal structures [1-2, 4-5]. In Thailand, it was found that lower back pain is most commonly found in illnesses of the musculoskeletal system. The majority, 50.5%, had low back pain from their occupation, and 90% were of a non-specific type [5-6]. Low back pain is a major health problem. It is the cause of absenteeism, decreased work

performance, and physical ability. In cases of chronic back pain, it often affects mental health and social interaction, creating a burden on health services and causing economic loss [4-7]. In summary, there is no known reason for the illness known as low back pain. All ages and genders are susceptible to it, affecting day-to-day living; in extreme situations, it could result in a loss of mental and physical health as well as society.

There are many approaches to treating low back pain, such as using drugs to reduce pain and inflammation and not using drugs such as physical therapy, alternative medicine, exercise, and surgical treatment is used in cases when the disease is severe or other treatments are ineffective [5, 8-9].

Physical therapy is the standard treatment for patients with low back pain. Its main purpose is to reduce pain and increase the ability to do daily activities. It consists of main methods such as using electrical tools (electrotherapy modalities), the use of manual therapy techniques such as mobilization or massage, and the provision of therapeutic exercise programs to increase the strength and flexibility of muscles and joints, including counseling, advice, and knowledge about the disease. In addition, appropriate postures for daily living, working, and exercising prevent disease and reduce the occurrence of recurring low back pain [9-10]. The theory of reflex locomotion stimulation of the neurophysiological system underlies the physical therapy method known as 'vojta therapy'. Reflex locomotion can be used therapeutically to help patients whose central nervous systems and locomotor systems have been compromised regain some of their basic movement patterns, or at least make them more accessible. The reason for the beginning (starting position) and stimulation of pressure in a specific direction and according to specific spots or zones, which results in the muscle's ability to relax the motor and sensory nerves. The supporting point of the muscles used for sucking and excretory system management is crucial, resulting in movement. The work of various muscles and automatic balance control work better and promote more correct movement of the body, such reactions are caused by movements that are not produced by the patient. The initial posture consists of two main postures: reflex rolling, which involves lying on the back and sides; and reflex creeping, which involves lying on the stomach or in a position with the back on top, such as the crawling position. The 10 key stimulating points or zones are breast zone, trunk zone, acromial zone, ASIS (anterior superior iliac spine) zone, medial epicondyle of femur zone, radial epicondyle zone, gluteal zone, medial border of scapular zone, medial epicondyle of the humerus. Selecting a starting position and the location of the trigger point are chosen according to the purpose of treatment. Multiple zones can be stimulated at the same time; this should be done regularly; the duration is at least 1 minute per zone, and it should be stimulated four times a day because the effects of vojta therapy will last for about 2–3 hours after treatment [11-12]. During the initial stage, vojta therapy is used for treatment and to stimulate locomotion activity in cerebral palsy pediatric patients [11-14]. Later, it was used for treatment in various disease groups of all ages, such as neurological patients with stroke, spinal cord injury, shoulder pain, low back pain, and scoliosis. The fundamental idea behind vojta reflex locomotion is the preservation of postures by isometric muscle contractions during point (breast zone) stimulation. This approach ensures consistent patterns of muscle contraction and stimulates muscles, joints, ligaments, and tendons. Additionally, it is known that the exteroceptors and exteroceptors are connected to the vojta reflex movement, which serves as a source of afferent stimulation for the brain [8, 16-20]. The vojta reflex locomotion has been shown to stimulate the deep muscles of the spine and the trunk muscles to control spinal rotation force and regulate trunk stability, improving postural control capacity [1, 21-23]. The ability of the core, which is at the body's center of gravity, to maintain or modify internal conditions in response to changes in the external environment is referred to as trunk stability. Particularly, the trunk muscles are crucial for maintaining postures since they function as a corset to anchor the body and spine regardless of whether the extremities move or not. The trunk muscles also keep the body aligned while in the sitting and standing positions and serve as supports for carrying out tasks. Additionally, during whole-body activity, the trunk muscles function as tonic or postural muscles and are crucial for the segmental stability of the lumbar spine and postural control [3-6]. A recent study indicated that vojta therapy helped limbo-sciatica patients experience less discomfort and impairment as well as improved muscle flexibility and weakness. Patients with low back pain have abnormal transverse abdominal muscle contraction patterns or timing, as well as a reduced cross-sectional area. The diaphragm and transverse abdominis are crucial muscles for supporting the trunk and they have an impact on spinal stiffness either directly through muscle contraction or indirectly through increased internal abdominal pressure. Recent studies on the effectiveness of physical therapy for patients with disc herniations have greatly improved our knowledge of these treatments; nevertheless, data on the advantages of vojta therapy for patients with non-specific low back pain are scant. Since low back pain is the most typical symptom of worker age, vojta therapy and conservative physical therapy are frequently utilized to reduce pain and disability in patients. The vojta approach involves applying goal-directed pressure to certain areas of the patient's body by the therapist. Reflex rolling and reflex creeping are two movement complexes that are spontaneously and involuntarily triggered by such stimuli, regardless of the age of the patient.

However, there hasn't been research that puts these two treatments side by side [2], and there is a lack of research focusing on the effects of vojta therapy on a wide range of measures of variables relevant to non-specific low back pain. The present study aims to test the hypothesis that the combination of vojta therapy and standard physical therapy will result in a statistically significant reduction in pain levels and improved functional ability compared to standard physical therapy alone in working-age patients with low back pain.

Methodology

Participants

Randomized controlled trials (RCT) in 50 working-age patients with low back pain were divided into 2 groups: the experimental group received vojta therapy combined with standard physical therapy (25 patients), and the control group received standard physical therapy treatment (25 patients) by simple random sampling and lottery methods. The patient had non-specific low back pain that was diagnosed by modern medicine between March and August 2022 at the Physical Therapy Department, Rehabilitation Medicine Center, Udon Thani Hospital. Patients were aged between 20 and 60 years old, and non-specific low back pain lasting more than 2 weeks was used as a criterion for inclusion. Patients who have undergone spinal surgery, congenital heart disease, osteopenia, osteogenesis imperfecta, cancer, pregnancy, spinal tumors, spinal fractures, epilepsy, hemophilia, and patients who did not complete the treatment according to the prescribed program were all considered exclusion criteria. Sample size calculation, according to previous study found that the average ODI values were 39.09 and 32.15. Standard deviation= 8.83, 7.89, error value= 0.05, r = 1 [12]. Using the t-two dependent means formula of the N4 studies 17 application, the sample size was 46. Set the significance level, statistically, at alpha (α) = 0.05. To prevent dropouts, the researcher increased the sample size by another 10 percent, resulting in a sample size of 50 people. This study was approved by the Institutional Review Board of Udon Thani Hospital (REC No. 8/2565) on February 18, 2022, in Thailand and was conducted following the Declaration of Helsinki.

Intervention

All patients will be evaluated on a personal characteristic assessment form and assessed on their functional ability before and after week 4 treatment. After that, both groups will receive advice on proper behavior and posture in daily life. Each group will receive the treatment program 2-3 times per week, 1-3 days apart, for 4 weeks, or a total of 10 treatments.

The standard physical therapy is 45 minutes; pelvic traction is 20 minutes; and the formula for calculating traction weight is 10-25% of a patient's body weight. Transcutaneous electrical nerve stimulation (TENS); conventional high-frequency TENS was applied using two electrodes (5x8 cm) on the lower back with a pulse duration of 60 µsec x a frequency of 60 Hz and a total treatment time of 20 min. Ultrasound diathermy involves the therapeutic application of low-radiofrequency 1-MHz continuous ultrasound with a half-value depth of approximately 1.3 watt/m^1 on the paravertebral muscle in the low back area or gluteal muscle for a total treatment time of 5 minutes [7].

Vojta therapy (consisting of 3 positions, stimulating both sides alternately for 10 minutes on each position, sustained pressure for 2–5 minutes for each point, reflex rolling, and the first position stimulating two points at the same time, total time 30 minutes). While receiving vojta therapy, the patient will have involuntary muscle reactions such as abdominal contractions, chest expansion, and pelvic tilting. The patient may feel abdominal muscle spasms, twitching of the corners of the mouth, and feeling tired (mild to moderate) after therapy [31, 32].

Reflex rolling (side lying). Starting in the side-lying position, lie on your side with shoulder flexion 90 degrees, the lower arm bent at the elbow 90 degrees, and the other arm placed at the side of the body. Hands placed on the same side of the hip. The upper legs on the floor, hips and knees, are bent 90 degrees, and the lower legs are slightly bent. Stimulate location at the gluteal area (gluteal zone) and trunk zone; the area is in line with the lower edge of the scapula bone (Figure 1).

Reflex creeping (prone) [6, 27]. Starting in the prone position. The head and neck are the same as the spine; the head and neck are aligned with the spine; the arm is on the facial side, raised at an angle of 120 degrees to the body; the hand facing down; the other arm on the side; shoulder blade rotated; hand facing up (forearm pronation); leg on the same side as the facial side; rest comfortably. The leg opposite the face (occipital leg) has hip joint flexion of 40–45 degrees with external rotation and knee flexion of 45 degrees. Stimulation location: calcaneus bone, lower outer edge (heel zone) (Figure 2).

First position. Starting in the crawl position. The coccyx between the feet places the forehead on the floor, and the head and neck rotate 30 degrees. Turn your head to the same side as the raised arm (facial arm), lift the facial arm, and place it at a 120-degree angle to the body, hands facing down on the floor. The opposite arm (occipital arm) is placed at the side of the body, the hand is placed at the side of the body, and the hand is facing up (forearm pronation). Stimulation locations are the calcaneus bone, outer lower edge (heel zone), and the anterior superior iliac spine (ASIS) zone (Figure 3).

Figure 1 Reflex rolling

Figure 2 Reflex creeping

Figure 3 First position

Outcome measurements

Personal characteristic assessment forms conclude: gender, age, body mass index, occupation, working hours per day, period of back pain, and underlying disease.

The visual analog scale (VAS) is a self-reported scale consisting of a horizontal or vertical line, usually 10 cm long (100 mm). For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and pain as bad as it or worst imaginable pain (score of 10.) [22].

Modified Oswestry low back pain disability index (ODI). The functional state was evaluated using the ODI, which also showed any limitations in daily activities. The ODI is a 10-item questionnaire with values ranging from 0 to 5 [7]. The final result is a ranking of 50 no to mild disability (0-40 %; score 0-20), 41-100%; score: 21-50) is a severe disability). A more (bedridden) is indicated by higher scores [7, 22] (0-20%=minimal disability, 21-40%=moderate disability, 41-60=severe disability, 61-80%=crippled disability, 81-100% = bed-bound disability).

Statistical analysis

The s-wilk test was used to test the normal distribution of values. Descriptive statistics were frequency, percentage, mean, and standard deviation (SD) to express personal characteristics. Inferential statistics were a chi-square test used to compare personal characteristics between the experimental and control group, a dependent t-test used to compare pain level and functional ability within the group, and an independent t-test used to compare pain level and functional ability after the trial (post-test) in the experimental group and control group at 95% confidence interval. We used $\alpha = 0.05$ as the cut-off point of statistical significance.

Results

Personal characteristics

Comparing the personal information of the two groups, it was found that there was a difference in gender, age, body mass index, working hours per day, period of low back pain, and underlying disease that was not statistically significant (Table 1).

Table 1 Participants' characteristics

Characteristics	**Experiment** (n=25)	**Control** (n=25)	p-value
Sex			
Male	11 (44.00)	5 (20.00)	0.06
Female	14 (56.00)	20 (80.00)	
Age (years)			
20-49	17 (68.00)	15 (60.00)	0.64
50-60	8 (32.00)	10 (40.00)	
Mean/SD	40±12.39	43.44±11.21	
Min-max	20-59	21-60	
Body mass index (kg/m^2)			
Standard	14 (56.00)	9 (36.00)	0.08

Characteristics	Experiment (n=25)	Control (n=25)	p-value
Overweight	11 (44.00)	16 (64.00)	
Mean/SD	22.41±3.56	24.37±3.46	
Min-max	17.67-33.60	18.70-30.8	
Work hour per day (hrs)			
8	18 (71.00)	13 (52.00)	0.34
> 8	7 (28.00)	12 (48.00)	
Period of low back pain (month)			
≤ 6	17 (68.00)	16 (64.00)	0.68
> 6	8 (32.00)	9 (36.00)	
Underlying disease			
No	12 (48.00)	9 (36.00)	0.39
Yes	13 (52.00)	16 (64.00)	
NCD (HT, DM, DLP)	*8 (61.53)*	*10 (62.50)*	
SLE	*1 (7.69)*	*0*	
MPs (neck, upper back)	*2 (15.38)*	*2 (12.50)*	
PU	*1 (7.69)*	*0*	
GERD	*0*	*1 (6.25)*	
Asthma	*0*	*2 (12.50)*	
Hyperthyroid	*1 (7.69)*	*1 (6.25)*	

Chi-square test; NCD=non communicative disease; HT=hyper tension; DM=diabetes mellitus; DLP=dyslipidemia; SLE= systemic lupus erythematosus (SLE); MPs=myofasial pain syndrome; PU=peptic ulcer; GERD= gastroesophageal reflux disease

The pain level and functional ability

The pain score and the functional ability before and after treatment: comparing before and after treatment, the results showed that, both groups' pain scores and functional ability decreased statistically significantly (Table 2).

Table 2 Comparing the pain score (VAS) and the Oswestry disability index (ODI) before and after treatment

Indicator	Experiment (n=25)			Control (n=25)		
	Pre-test	Post-test	p-value	Pre-test	Post-test	p-value
Pain score	6.12±1.30	1.00±0.00	<0.001	6.40±1.65	1.92±1.45	<0.001
Oswestry disability index	14.04±7.01	4.7±3.62	<0.001	22.48±20.69	9.68±7.13	0.005

Comparing the pain score and functional ability between groups before treatment

The results showed that comparing the mean pain scores between the experimental group (6.12±1.30) and the control group (6.4±1.65) and the mean score of functional ability between the experimental group (14.04±7.01) and the control group (22.48±20.69), they were not significantly different (p-value = 0.51 and p-value = 0.059, respectively) (Table 3).

Table 3 Comparing the pain score and Oswestry disability index between groups before treatment

Indicator	Two-sample t test with equal variances					t	df	p-value
	Mean	SD	SE	95% CI				
				Lower	Upper			
Visual analog scale								
Experiment (n=25)	6.12	1.30	0.28	-1.13	0.57	-1.93	48	0.51
Control (n=25)	6.40	6.40	-8.44	-17.23	0.49			
Oswestry disability index								
Experiment (n=25)	10.04	7.01	4.37	-17.23	0.49	-3.10	48	0.59
Control (n=25)	22.48	20.69	-4.96	-8.12	-1.74			

Comparing the pain score and functional ability between groups after treatment

The results showed that, comparing the mean pain scores between the experimental group (1.00±0.00) and the control group (1.92±1.49) and the mean score of functional ability between the experimental group (4.72±3.62) and the control group (9.68±7.18), they were significantly different (p-value = 0.005 and p-value = 0.004, respectively) (Table 4).

Table 4 Comparing the pain score (VAS) and Oswestry disability index (ODI) between groups after treatment

Variables	Two-sample t test with equal variances					t	df	p-value
	Mean	SD	SE	95% CI				
				Lower	Upper			
Visual analog scale								
Experiment (n=25)	1.00	0.00	-9.20	-1.52	0.32	-3.07	48	0.005
Control (n=25)	1.92	1.49	-0.29	-1.53	-0.30			
Oswestry disability index								
Experiment (n=25)	4.72	3.62	-4.96	-8.18	-1.74	-3.10	48	0.004
Control (n=25)	9.68	7.18	1.60	-8.21	-1.71			

Discussion

The present results found that both treatments reduced low back pain and improved functional ability. This is due to the effect of pelvic traction on the stretching of the joints and other structures, which reduces the force exerted on the sprained spinal disc and helps increase blood flow, resulting in improved flexibility and movement of the lumbar spine [32]. Transcutaneous electrical nerve stimulation (TENS) can reduce pain because, based on the principles of gate control theory, it increases the peripheral sensory system's ability to access the central nervous system. It has to go through a "gate" in the spinal cord to reach the brain. As a result, the pulse that arrives first will prevent the door from permitting the pulse that enters later. Even if another pulse arrives at this gate sooner, it reduces muscle spasticity and increases the flexibility of muscles, tendons, and joints [33]. The results of ultrasound diathermy are deep heat, which can increase tolerance to pain (pain threshold), improve circulation, reduce spasticity, reduce inflammation, and increase flexibility [34]. The vojta therapy effect results in the automatic and regular functioning of the body's muscles. The vojta therapy effect results in the automatic and regular functioning of the body's muscles; the core muscles, leg muscles, and hip muscles are stronger. After being stimulated, it causes the muscles in almost every part of the body to work, especially the core muscles, legs, and hips, which helps the spine to stretch (elongation) and increases the twisting and rotation of the spine, helping to increase the angle of movement of the spine. It has a positive effect on patients with low back pain [5, 10, 11, 13, 18, 29]. Therefore, vojta therapy is like exercising, but the patient does not do it himself. In addition, the effects of stimulation, which also contribute to the muscle work of the core muscles, legs, and hips muscles, especially the muscle group that rotates the legs and spreads them out (Abduction with external rotation muscle), working in unison and being stronger [9, 11], affecting low back pain patients to be able to function, reduce pain, and have a normal gait [2,19]. Based on these results, patients in vojta therapy combined with standard physical therapy had lower pain levels and were able to perform more functions when compared to the standard physical therapy group. According to the study of Iosub, et al. [26] conducted a comparative study of vojta therapy and standard physical therapy treatment in 17 patients with disc herniation, aged 30-79 years. It was found that both groups had decreased pain scores and improved ability to perform activities of daily living (ODI).

The study of Hamed et al. [12] conducted a study comparing vojta therapy combined with TENS therapy and a hot pack and another group receiving TENS combined with a hot pack in 40 patients with non-specific low back pain, with an average age of 26 years. It was found that the vojta therapy combined with TENS and a hot pack had a significantly better quality of life (ODI) than another group. Vojta therapy consists of starting postures and applying pressure to stimulation points in predetermined positions and directions based on vojta therapy's principles, and the motor centers are stimulated in the appropriate sequence to control the muscles of both the upper and lower limbs via the 12 propriospinal neurons in the spinal cord. This causes the transmission of nerve impulses to control the motor system and sensory processing, resulting in brain stimulation, reflex movement, and body movement according to the developmental patterns of normal humans [6, 15] This is consistent with a study by Łozińska [2] that compared the effects of vojta therapy and standard physical therapy in low back pain patients on gait patterns in 17 adults with non-specific low back pain patients. It was found that the vojta therapy group had a rhythmic step and elongated both the left and right feet, increasing walking speed significantly more than the physical therapy group. There is also a study by Juárez-Albuixech et al. [29], who studied to compare the

effects of voyta therapy with transcutaneous electrical stimulation (TENS) in 12 back pain patients aged 31–74 years. The results of voyta therapy show positive results in terms of reducing pain, increasing functional ability, and increasing flexibility more than using TENS with statistical significance, which is consistent with the study of Żurawski et al. (2019) [13], who studied the effects of vojta on low back pain in teenagers with discopathy-associated syndromes for 2 weeks and found that the pain score decreased with statistical significance. Vojta Therapy is a program that promotes muscle strength and increases movement efficiency. Patients do not have to exert themselves, which is different from normal training in general programs. Therefore, it is beneficial for back pain patients, patients who have difficulty moving, or patients who do not like to exercise. They can also advise patients with back pain to practice basic postures by themselves at home or instruct the caregiver to stimulate the patient under guidance. However, only physical therapists who have been trained and have obtained a certificate can provide treatment. At present, treatment with vojta therapy is still limited. Lack of personnel It is seen that physical therapists should be encouraged to study and train to become experts in vojta. To be used in the treatment of this group of patients and other groups of patients in the future to continue to become more widespread. Results for long-term vojta therapy for back pain patients should be monitored in the future. Additionally, vojta therapy should be studied in disease groups related to the skeletal and musculoskeletal systems that are commonly observed, such as individuals with neck pain. The results of the Oswestry Indicator score (ODI) before treatment showed that the experimental group had a moderate disability of 28.08% (ODI=21-40%; 14.04±7.01), and the control group had a low ability of 44.96% (severe disability) (ODI= 41-60%; 22.48±20.69). After treatment showed that both groups had a high ability to perform daily activities (minimal disability: 9.4% for the experimental group (ODI= 0-20%; 4.72±3.62) and 19.36% for the control group (ODI= 0-20%; 9.68±7.18).

In the present study, there was no restriction on the exercise of the sample group before or during the study, which may affect the current results. The long-term effects of vojta therapy on patients should be studied, and the results must be measurable by physical therapy devices to confirm the correct intervention, such as back-leg strength and range of motion of the lumbar spines, hips, knees, and ankles.

Conclusion

In summary, combining vojta therapy with standard physical therapy has had beneficial effects on patients with non-specific low back pain. Both reduce pain and increase their functional ability and work when compared with standard physical therapy alone. After treatment, the vojta Therapy group combined with standard physical therapy experienced a 13–14% greater reduction in back pain compared to the standard program group alone. Treatment results of vojta therapy combined with physical therapy according to standards result in reduced back pain. Increase the ability to do daily activities and increase the work efficiency of patients with back pain, such as sitting and working longer when the pain decreases and the core muscles are stronger.

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Health Impacts from Air Pollution in Border Community of Thailand-Myanmar

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ABSTRACT

Introduction: Health impacts from air pollution are a major health challenge for people living in border areas in northern Thailand particularly those who live in Mae Sai District, Chiang Rai. The study aimed to assess the health impacts of air pollution among people living in the border community of Thailand–Myanmar.

Methods: The mixed-method study was applied to collect data from selected people living in Wiang Phang Kham sub-district, Mae Sai District, Chiang Rai Province. Data were collected by a validated questionnaire, in-depth interview, and group discussion between August 2022 to March 2023.

Results: A total of 404 participants were randomly selected for the study in the quantitative phase. At the individual level, difficulty in breathing, chest tightness, and conjunctivitis, especially in the elderly were reported. Stress and anxiety from lack of income were detected. Moreover, being unable to work was the majority of issues reported among the working-age. A large number of people who had health problems related to poor air pollution were reported. Finally, non-effective policies implemented indirectly affect people's health. Avoiding outdoor activities, trade, and agriculture were immediately effective measures.

Conclusion: Poor air pollution impacts directly on those people suffering from health, especially among patients related to respiratory diseases including children and the elderly. It urgently needs national and international collaboration to improve poor air quality in northern Thailand.

Keywords: Health Impacts, Air pollution, Border Community, PM2.5

Introduction

Air pollution is not only caused by smog but also by the contamination of indoor or outdoor environmental burnings, leading to the poor quality of the atmosphere [1]. Almost all people who are living in countries related to agricultural sectors are facing poor air quality or air pollution. After exposure for a long time, people develop health issues due to air pollution problems. The particle matter of 2.5 microns is a major source of health problems in humans especially exceeding the standard level [1]. There are four major health problems caused by PM 2.5: (i) cardiovascular disease; (ii) respiratory system diseases; (iii) dermatitis, and (iv) conjunctivitis [2].

The major high-risk populations are young children, the elderly, pregnant women, congenital diseases such as heart disease, stroke, pulmonary diseases, asthma, allergies, etc [1]. For those people who have some medical conditions, exposure the PM2.5 could develop a severe stage and require intensive medical care [1]. Air pollution across borders is one of the significant issues for people who live in border areas which means that if an open burning in neighboring countries, people living in Thailand could get a serious impact [3].

The Department of Air Pollutions Control, Thailand reported that March 2023 was the month that had severe air pollution in northern Thailand compared to previous years [4], particularly the 24-hour PM2.5 level which was higher than the standard at 170 micrograms per cubic meter. In 2023, the PM2.5 value of

Wiang Phang Kham Subdistrict, Mae Sai District, Chiang Rai Province which is the border areas of Thailand and Myanmar, had reached the highest PM2.5 level at 586 micrograms per cubic meter which was the highest area in Thailand and is considered to have a significant impact on health [4, 5]. The problem has been detected and concerned for many years without

any effective implementation implemented to address the problem, and a large number of people have been observed in their health from the consequence of poor air quality in the areas [5]. Wiang Phang Kham Sub-district is a special area surrounded by mountains and located on the border of Thailand and Myanmar a large of people live in the area. Moreover, the area is a favorite with people from outside Thailand to stay and work [3]. The majority of people living in this area are working in farming. Then the study aimed to assess the health impacts of poor air quality or air pollution on those who were living in border areas of Thailand- Myanmar particularly while people faced a long period of the problem from open burning from both internal and external countries.

Methodology

Study Design and Study Setting

A mixed-method design was applied. The study setting was the Wiang Phang Kham Sub-district border community area. Data were collected data between August 2022 and March 2023.

Sample Size Calculation

The sample size was calculated according Krejcie & Morgan (1970) formula [6]; $n = X^2 NP(1-P)/e^2(N-1) + X^2 P(1-P)$ where $X^2 = 3.841$ for 95%CI; P is proportion of the population (P = 0.5); e is acceptable tolerance level (0.05). A total of 365 samples were needed for the study. However, adding 10% for any error, 404 samples were required for the analysis.

Research Instruments

A questionnaire was developed and tested for its validity and reliability before use based on the literature review and application of the Department of Haze-related Health Behavior Assessment form [1]. The questionnaire was used to collect general information about the participants, illness information, awareness, and self-protection behaviors. The questionnaire was improved its quality by the item-objective congruence (IOC) method by three experts. The pilot test was carried out among 30 selected participants who had similar characteristics as the study population, and the alpha coefficient was found at 0.80,

Data Collection

Access to the villages and participants was granted by the district government officer. Health officers who were working at Mae Sai District and Mae Sai Hospital were further contacted for data collection. Villagers who met the inclusion and exclusion criteria were contacted for an interview five (5) days ahead. Before starting of data collection, all participants were explained the study objectives and the content required on a questionnaire. All participants signed on a written consent voluntary basis before the commencement of data collection. The in-depth interview lasted 20 minutes, and the focus group discussion took 45 minutes each.

Data Analysis

Descriptive statistics were used to describe the characteristics of the participants in the form of percentages and mean values. Thematic analysis was applied to analyze the qualitative based on the ecological and social concepts [7].

Ethical Considerations

The study protocols were approved by the Mae Fah Luang University Ethics Committee (No. EC 21250-18).

Results

The majority were Thai (96.29%), 57.92% were females, 39.60% were aged 40-49 years, and 47.03% were working as daily wage employees. Most of the participants graduated from primary school (35.40%), 48.02% had monthly income between 10,001-15,000 baht, and 59.16% lived in urban areas (Table 1).

Table 1 General characteristics of participants

Characteristics	n (404)	%
Sex		
Male	170	42.08
Female	234	57.92
Age (years)		
20 – 29	37	9.16
30 – 39	73	18.07
40 – 49	160	39.60
50 – 59	103	25.50
≥ 60	31	7.67
Occupation		
Farmer	163	40.35
Daily wage employee	190	47.03
Traders	28	6.93
Government officer	19	4.70
Private employees	4	0.99
Education		
No schooling	10	2.48
Primary school	143	35.40
Junior high school	117	28.96
High school	84	20.79
Diploma/university degree	50	12.38
Nationality		
Thai	389	96.29
Burmese	3	0.74
Laotian	3	0.74
Chinese	9	2.23
Monthly income (bath)		
<5,000	42	10.40
5,000 – 10,000	96	23.76
10,001 – 15,000	194	48.02
15,001 – 20,000	50	12.38

Characteristics	n (404)	%
>20,000	22	5.45
Residential area		
Forest areas	7	1.73
Agricultural areas	158	39.11
Urban community	239	59.16

The major health problem was difficulty breathing (62.87%) during facing poor air quality, and wearing mask (66.09%) was the key measure (Table 2).

Table 2 Health problems and preventive measures during having air pollution

Disease and preventive measures	n (404)	%
Symptoms during air pollution		
No symptom	37	9.16
Asthma	55	13.61
Itchy or burning skin	35	8.66
Difficulty breathing	254	62.87
Pneumonia	23	5.69
Preventive measures		
No prevention	95	23.51
Wearing mask	267	66.09
Avoid leaving the building	42	10.40

The findings from the thematic analysis, it was found that the impacts of poor quality of air or air pollution on the population in five (5) levels namely individual, interpersonal, organization, community, and public policy. (i) At the individual level, it was found that individuals were suffering from server illness and disease progression from air pollution. Most of the participants reported that several respiratory and eye-related diseases presented during the severe air pollution season including difficulty breathing, sore nose, sore throat, shortness of breath, chest tightness, and red eyes. Those with chronic obstructive pulmonary disease (COPD) reported having been more frequently to be hospitalized in the season. Those children and the elderly were the most vulnerable populations from exposure to poor air quality for illness development. (ii) On the interpersonal level, families with children and the elderly had more concern and impacted the air pollution in the season. The family had stress during the air pollution from concerning their family member getting an illness. (iii) At an organization level, the problem of poor air quality or air pollution led community leaders including people working in an organization to get stressed concerning their employees' health. Most people had been informed to avoid any outdoor activities to prevent the impacts. (iv) People living in a particular area had a high possibility of getting health problems during the peak of air pollution. Several patients related to poor air quality were presented in health institutes significantly. And (v) public policy level, several public policies were developed and implemented during the high season of air pollution, however, many of the implementations had small positive effects on reducing the problem due to the origin of the problem was not properly addressed.

Discussion

Results of a study on health and social impacts from air pollution in villages along the Thai-Myanmar border which study based on the ecological model, categorized the impact into five (5) levels: individual, interpersonal, organization, community, and public policy. Several health impacts had been detected particularly respiratory and dermatology systems. The children and the elderly were the major vulnerable populations. Those who had medical conditions, particularly COPD patients had a higher frequency of being hospitalized during the peak of PM2.5. Several public policies and implementations were implemented, but they needed collaboration from people and organizations at local, national, and international levels to mitigate the problem for the people who lived in the border areas of Thailand and Myanmar.

The group of people who have underlying diseases related to the cardiovascular system, such as various types of heart disease and cerebrovascular disease, and people with underlying diseases related to respiratory diseases and allergies were at a greater risk of developing health problems from exposure to poor air quality or air pollution [8]. The problem also led to individuals and family member's stress and anxiety about getting illness to their family members [9]. The numbers of seeking medical care were related to the severity of the PM2.5 especially to those who had health problems related respiratory system [10].

At the community and policy levels, the health system of Thailand had spent a large amount of finance to support treatment and acre during the high PM2.5 significantly [5]. In 2016, more than 800 cases of severe illness related to PM2.5 were admitted to Chiang Rai Hospital [5]. More than 74,799 cases were reported in Chiang Mai Province which was one of the highest impacts on air pollution in Thailand in 2016 [5]. According to satellite surveys, it was found that Myanmar had the highest hotspots in the region, with 41% [10], and currently used as the major source of monitoring system between countries air pollution situation [11]. The problem has been clearly defined and it needs collaboration among countries' people and organizations to address the problem [12] including the participants of the people who live in the areas [13] to get the optimal effect of any measures.

One of the important that had been pointed oy from the study was the impact on the family income due to the inability to work outdoors [9]. A large amount of income is lost from the air population in the northern region of Thailand [14]. People who live in border areas

could be impacted by their family income from air pollution due to being unable to farm and reduce the number of tourists where are tourist destinations [18, 2], particularly in Songkran festival [15]. It was clear that the high PM2.5 impacted the income from tourist businesses by 25% reduced in 2007 compared to 2022 [2, 15].

Since this is a small study conducted in villages located in the border areas of Thailand and Myanmar, the findings could not completely generalize to other populations. The study should also cover the whole year cycle to see the impact in the whole five (5) dimensions. Extending the study to people who are living in Myanmar could help in understanding the context completely.

Conclusion

Farming and other outdoor burnings are major sources of poor air quality or air pollution in the border areas of Thailand and Myanmar. Several health impacts are identified from the air pollution including poor quality of life to those who have underlying diseases including stress and anxiety and lack of family income during the pollution presented. Collaborations between organizations at local, national, and international levels are urgently required to address this great problem in the areas.

Competing interests

The authors had no competing interests to declare.

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In vitro Effect of Lipophilic and Hydrophilic Rice Strain Extracts in Sa Kaeo Province on the Prevention of Calcium Oxalate Crystal Formation and Aggregation

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ABSTRACT

Introduction: Kidney stone is a worldwide urological problem affecting human health, with a recurrence rate of up to 50%. It contains a multi-process involving crystal nucleation, growth, and aggregation. Using substances to interfere with these processes may be useful in reducing recurrent stone formation. The study aimed to investigate the inhibition effect of local colored rice strain extracts from Sa Kaeo Province on the formation and aggregation of calcium oxalate (CaOx) crystals *in vitro*

Methods: Black rice, black glutinous rice, and red rice strains were extracted using hexane and ethanol, called lipophilic and hydrophilic rice extracts, respectively. Rice extracts at different concentrations (10–400 µg/ml) were incubated with the CaOx crystal solution overnight. The number of CaOx crystals was counted and the percentage inhibition of CaOx crystal formation and aggregation was calculated. Statistical analysis with a significant difference was considered at $\alpha = 0.05$.

Results: All three rice extracts significantly decreased the number of CaOx crystal formation and aggregation. Using hexane extract, the red rice showed the highest inhibition of CaOx crystal formation, whereas the black glutinous rice showed the highest inhibition of CaOx crystal formation among the three rice strains' ethanol extracts. In addition, black glutinous rice had the strongest inhibition of the crystal aggregation among the three rice strains' hexane extracts, whereas black rice showed the highest inhibition among the three rice strains' ethanol extracts.

Conclusion: Black glutinous rice containing lipophilic and hydrophilic molecules was most effective in inhibiting the formation and aggregation of CaOx crystals. This study can be applied to the development of a supplemental product to prevent kidney stone formation.

Keywords: Lipophilic rice extract, Hydrophilic rice extract, Calcium oxalate, Crystal formation, Crystal aggregation

Introduction

Calcium stone is a cause of urolithiasis worldwide including in Thailand, especially in the Northeast region. The incidence of urinary stones in the 3 villages of Kon Kean Province detected by ultrasound was 16.9% and 2 times more abundant in males than females [1]. Most of this disease was affected by the deposition of calcium oxalate (CaOx) in parts of the uriniferous tubule [2, 3]. The internalization of calcium oxalate crystal by tubular epithelium resulted in the production of oxidative stress and led to the induction of renal inflammation process and fibrosis [4].

The calcium oxalate crystallization process is composed of nucleation, growth, and aggregation which are regulated by various factors. The hypercalciuria (>200mg/d) and hyperoxaluria (>40 mg/dl) [5] conditions resulted in the formation of calcium oxalate monohydrate (COM), calcium oxalate dihydrate (COD), and calcium oxalate trihydrate (COT). Moreover, kidney stone formation was modulated by urine acidity/alkalinity [6], concentration of citrate molecules [7], magnesium molecules, potassium molecules [8], and polyanion molecules [9].

Urolithiasis therapy by using herbal medicine is more promising than the limited-used pharmacological agents or the high recurrent rate extracorporeal shock wave lithotripsy or ureteroscopy treatments. The antilithiatic activity was proposed by using aqueous-extracted green tea [10], 70% ethanol-extracted avocado leaves [11], aqueous-extracted raspberry root [12], 99% ethanol-extracted roselle leaves, 70% methanol-extracted oregano [13] and aqueous-extracted *Herniaria hirsute* L. [14]. The 100% ethanol-extraction of *Acalypha indica* leaves expressed the highest inhibition effect on CaOx nucleation, growth, and aggregation over the chloroform-, ethyl acetate- and acetone-extraction [15].

Black rice and red rice were nourished with gamma oryzanol, alpha-tocopherol, tocotrienol [16], and anthocyanin [17], which contained powerful antioxidant capacity. Therefore, various strains of rice extracts were suggested for multiple health impacts using, such as antiaging [18], antiinflammation [19], anticholesterolemia [20, 21], anticancer [22], and antilithiasis [23, 24, 25]. The unpolished Rice Berry rice and local purple sticky rice bran extracted with 75% ethanol were shown to be the candidate agents by preventing the growth and aggregation of CaOx crystal *in vitro* [23, 25]. Moreover, unpolished Sungyod sticky rice, a local rice strain of Songkhla province, extracted with 75% ethanol could reduce the CaOx-induced kidney pathology by reducing free radical molecules and increasing antioxidant enzyme (SOD and catalase) expressions [24].

Purple rice bran was extracted with hexane and anhydrous methanol to obtain lipophilic and hydrophilic fractions. The majority of the lipophilic fraction was tocotrienol, tocopherol, and oryzanol, whereas cyanidine-3-glucoside was identified as a major constituent in the hydrophilic fraction. Moreover, the free radical scavenging capacity and total phenolic content of hydrophilic extract were higher than hydrophobic extract [26]. These studies demonstrated that the different solvents used in the rice research strategy resulted in diverse activities of the extracts.
Recently, the collection of various local colored rice strains from the Thailand-Cambodia border in Sa Kaeo Province was identified as the higher capacity free radical scavengers and high potential in cultivation promotion [27]. However, these colored rice strains are under agricultural farming research and cosmetic or pharmaceutical applications. Therefore, this study aimed to examine the inhibition effect of lipophilic and hydrophilic extracts of local colored rice strains collected from Sa Kaeo Province on the formation and aggregation of CaOx crystals *in vitro*.

Methodology

Preparation of rice samples

Three rice strains, namely black rice, black glutinous rice, and red rice were cultured on the organic farm at the Faculty of Agricultural Technology, Burapha University, Sa Kaeo Campus. 800 grams of each rough rice sample was milled at 2500 r/min for 5 min. The milled rice samples were then dried at 60 ^{o}C for 48 hr. The milled rice powder was stored at 4 ^{o}C until use.

Preparation of lipophilic extract

800 grams of each milled rice powder was extracted with hexane at a ratio of 1:5 and incubated in the dark for 24 hours. The extracted solution was filtered and collected in the test tube. The extract solution was then evaporated at 60°C and dried in a freeze dryer. The dried extract was weighted and calculated its lipophilic extraction yield.

Preparation of hydrophilic extract

800 grams of each rice powder were performed by the previous hexane extraction protocol. The residue was then dried and mixed with 75% ethanol at a ratio of 1:5 and incubated for 24 hours in the dark. The extracted solution was filtered and collected in the test tube. The residue was re-extracted once. The combined extract solution was then evaporated at 60°C and dried in a freeze dryer. The dried extract was weighted and calculated its hydrophilic extraction yield.

In vitro studies

(i) CaOx crystal formation assay

The CaOx crystal formation was prepared using the method of Thongboonkerd et al [28]. Briefly, the final concentration of 5 mM calcium chloride and 0.5 mM sodium oxalate solution was added in a 10 mM Tris and 90 mM sodium chloride buffer at pH 7.3. The extracts at the various concentrations including 10, 20, 50, 100, 200, and 400 µg/ml were prepared and then added to the CaOx crystal solution. As a control, the solution without any extract was performed. The reaction was incubated at room temperature overnight. The CaOx crystal formation was observed using a phase contrast microscope in a high-power field (40X) area. Ten areas/samples were used to calculate the number of CaOx crystals. The inhibition of CaOx crystal formation was analyzed as [(number of $CaOx_{control}$ - number of $CaOx_{extract}$)/number of $CaOx_{control}$] x 100.

(ii) CaOx crystal aggregation assay

The CaOx crystal aggregation was performed by the method of the Thongboonkerd et al. protocol [28]. In Brief, the mixture of calcium chloride and sodium oxalate solutions was prepared at the final concentration of 1 mM and 5 mM, respectively. The mixture solution was added into a buffer containing 10 mM Tris and 90 mM sodium chloride at pH 7.3. The extracts at the various concentrations including 10, 20, 50, 100, 200, and 400 µg/ml were prepared and then added to the CaOx crystal solution. The solution with no extract was used as the control. The reaction was then

incubated at room temperature overnight. The COM crystal aggregation was observed by a phase contrast microscope in a high-power field (40X) area. Ten areas/samples were used to calculate the number of CaOx crystal aggregations. The inhibition of CaOx crystal aggregation was determined using a formula: [(number of CaOx aggregated $_{control}$ - number of CaOx aggregated $_{extract}$)/number of CaOx aggregated $_{control}$] x 100.

Statistical analysis

The data was expressed as the mean and standard error of the mean (SEM). For multiple comparisons, the results were analyzed by one-way ANOVA, followed by Turkey-HSD's test. The significant difference was considered if P <0.05.

Results

Rice extraction yield

The yield of lipid content in red rice was slightly higher than that of black rice and black glutinous rice, whereas the yield of hydrophilic extract was the highest in black glutinous rice and the lowest in red rice (Table 1).

Table 1 Yields of the lipophilic and hydrophilic extracts from black rice, black glutinous rice and red rice

Rice extracts	Lipophilic extract	Hydrophilic extract
	(%)	(%)
Black rice	3.41	0.91
Black glutinous rice	3.53	1.96
Red rice	3.66	0.55

CaOx crystal formation after incubation with lipophilic and hydrophilic rice extracts

After incubation with lipophilic rice extracts at concentrations of 10, 20, 50, 100, 200, and 400 µg/ml. CaOx crystal formation was observed in all groups (Figure 1A). Black rice and red rice extracts tend to decrease the number of CaOx crystals with increased extract concentration, whereas high concentrations of black glutinous rice extract tend to increase the number of CaOx crystals (Figure 1B). The maximum percentage inhibition of CaOx crystal formation was 57.05±6.05, which was observed in red rice lipophilic extract at a concentration of 400 µg/ml.

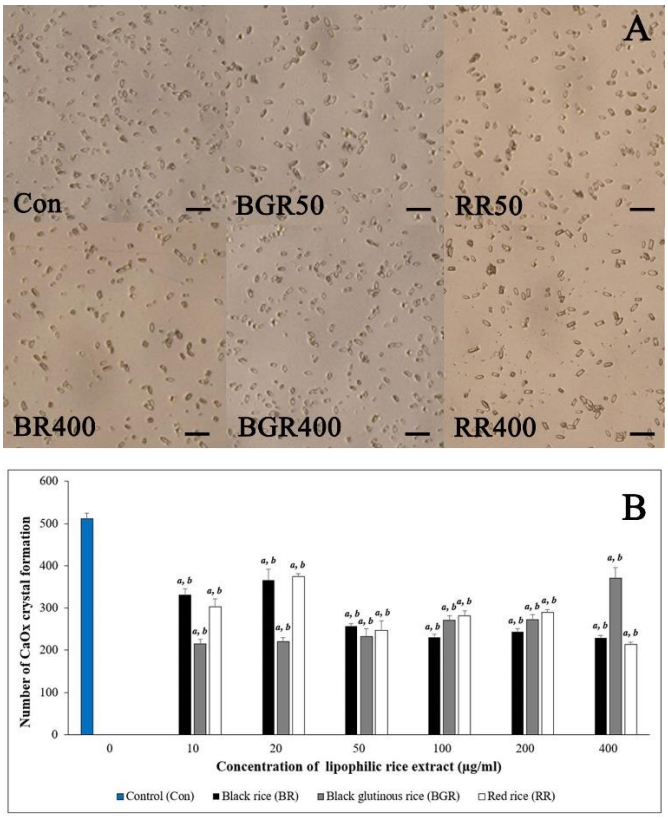

Figure 1 (A) The photograph showing CaOx crystal formation in the control group (Con) and lipophilic rice extract treated group at the concentration of 50 and 400 µg/ml (BR: Black rice; BGR: Black glutinous rice; RR: Red rice; scale bar = 10 µm). (B) The number of CaOx crystal formations in the control group (0 µg/ml) and lipophilic rice extract treated group (10-400 µg/ml). a and b indicate significant differences at p-value<0.05 and p-value<0.001, respectively compared

After incubation with hydrophilic rice extracts at concentrations of 10, 20, 50, 100, 200, and 400 µg/ml, all groups showed CaOx crystal formation (Figure 2A). Black rice extract tends to decrease the number of CaOx crystals with increased extract concentration. While black glutinous rice and red rice extracts at concentrations of 10 – 100 µg/ml significantly decrease the number of CaOx crystals. The number of CaOx crystals was increased when increasing the concentration to 200 and 400 µg/ml (Figure 2B). The maximum percentage inhibition of CaOx crystal formation was 71.37±9.18, which was observed in black glutinous hydrophilic rice extract at a concentration of 100 µg/ml.

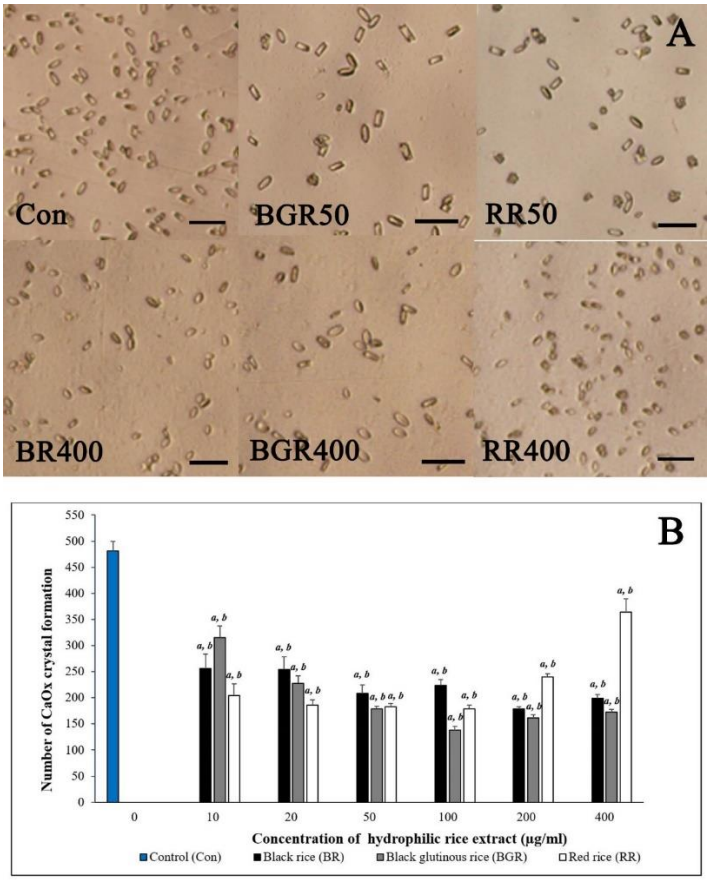

Figure 2 (A) The photograph showing CaOx crystal formation in the control group (Con) and hydrophilic rice extract treated group at the concentration of 50 and 400 µg/ml (BR: Black rice; BGR: Black glutinous rice; RR: Red rice; scale bar = 10 µm). (B) The number of CaOx crystal formations in the control group (0 µg/ml) and hydrophilic rice extract treated group (10-400 µg/ml). *a* and *b* indicate significant differences at p-value<0.05 and p-value<0.001, respectively compared to the control.

CaOx crystal aggregation after incubation with lipophilic and hydrophilic rice extracts

The CaOx crystal aggregation was identified in lipophilic and hydrophilic rice extracts (Figures 3A and 4A). The number of CaOx crystal aggregates was significantly decreased when increasing the concentration of all lipophilic rice extracts (Figure 3B). In addition, the highest percentage inhibition of CaOx crystal aggregation was 57.05±6.0, which was observed in black glutinous lipophilic rice extract at doses of 200 µg/ml. Following incubation with hydrophilic rice extracts, all rice extracts at concentrations of 10 – 100 µg/ml significantly decrease the number of CaOx crystal aggregations. The number of CaOx crystal aggregation was increased when the concentration increased to 200 and 400 µg/ml (Figure 4B). The highest percentage inhibition of CaOx crystal aggregation was 72.40±3.69, which was observed in black rice hydrophilic extract at a concentration of 100 µg/ml.

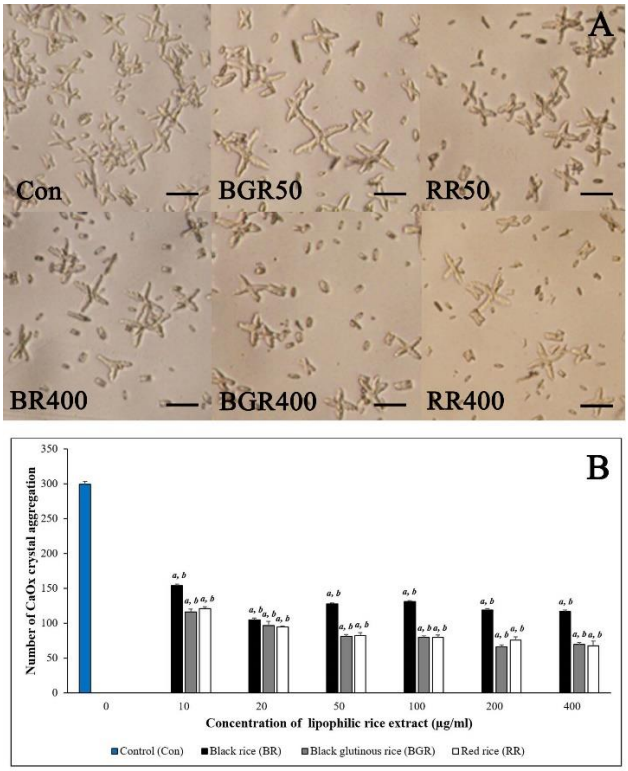

Figure 3 (A) The photograph showing CaOx crystal aggregation in the control group (Con) and lipophilic rice extract treated group at the concentration of 50 and 400 µg/ml (BR: Black rice; BGR: Black glutinous rice; RR: Red rice; scale bar = 10 µm). (B) The number of CaOx crystal aggregates in the control group (0 µg/ml) and lipophilic rice extract treated group (10-400 µg/ml). *a* and *b* indicate significant differences at p-value<0.05 and p-value<0.001, respectively compared to the control.

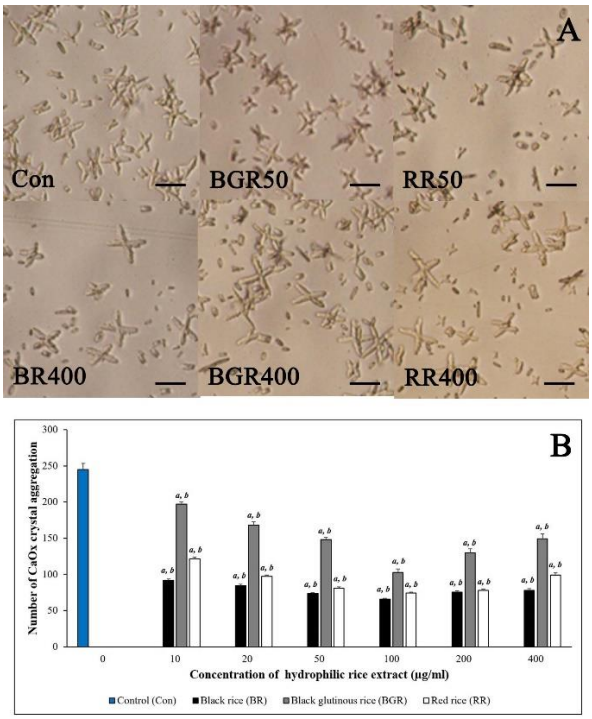

Figure 4 (A) The photograph showing CaOx crystal aggregation in the control group (Con) and hydrpophilic rice extract treated group at the concentration of 50 and 400 µg/ml (BR: Black rice; BGR: Black glutinous rice; RR: Red rice; scale bar = 10 µm). (B) The number of CaOx crystal aggregates in the control group (0 µg/ml) and hydrophilic rice extract treated group (10-400 µg/ml). *a* and *b* indicate significant differences at p-value<0.05 and p-value<0.001, respectively compared to the control.

Discussion

In this study, two solvents were used to extract three rice strains: black rice (non-glutinous rice), black glutinous rice, and red rice (non-glutinous rice). We also evaluated the percentage inhibition of CaOx crystal formation and aggregation compared to the control. These results showed that both extraction systems were able to detect the prevention of crystal formation and aggregation in all rice extracts with different degrees depending on the extraction solvent used. In this study, ethanol extracted tends to increase the percentage inhibition of CaOx crystal formation. In contrast, hexane extracted tends to increase the percentage inhibition of CaOx crystal aggregation. The result indicated that three rice extracts may contain different types and amounts of bioactive compounds that could differently affect crystal formation and aggregation.

Previous studies on the bioactive compounds in colored rice showed that purple rice bran contains lipophilic chemicals such as oryzanol, tocopherol, and tocotrienol, which could have antioxidant properties. Additionally, compared to the lipophilic extract, the hydrophilic extract of purple rice bran contained higher total phenolic components [26]. It was also comparable to the Peanparkdee et al. [29] showing that ethanol extract contained high amounts of phenolic acids, flavonoids, and anthocyanins. Previous studies also showed that pigmented rice such as red rice, black glutinous rice, and black rice contained a high amount of phenolic compounds and might be used as a natural antioxidant [25, 30].

Kidney stone formation is a multi-physiochemical process that involves crystal nucleation, growth, aggregation, adhesion to renal tubular cells, and internalization into renal epithelial cells [4]. The induction of CaOx crystal formation is a necessary step for subsequent crystal aggregation [31]. Previous studies have demonstrated that natural compounds like antioxidants and vitamins can interfere with the formation and aggregation of CaOx crystals. This interference may be useful in reducing recurrent stone formation [10, 32-36]. This study showed that black glutinous rice hydrophilic extract had a potential effect on the inhibition of calcium oxalate crystal formation in a low dose-dependent manner, while black glutinous rice and red rice lipophilic extracts had a potential effect on the inhibition of calcium oxalate crystal aggregation in a dose-dependent manner. These results correspond with a previous study on the local purple sticky rice bran extract. It showed that the extract at high concentration can induce CaOx crystal formation, especially COD crystals [25]. A previous study on *Herniaria hirsuta* extract showed that it can promote CaOx crystal nucleation, particularly COD crystals, by increasing their number while decreasing their size [14]. In this study, the morphology CaOx crystal was primarily present in the COM which appeared to be more harmful than COD due to their higher affinity for renal tubular cell damage [34]. It has been shown in a previous study that the formation of CaOx crystals depends on the charges of the ions in the solution. For example, proteins having acidic amino acid residues like Asp, Glu, and Gla will be deprotonated and negatively charged. They could interact with the positively charged Ca ions and inhibit the growth of CaOx crystals [37]. In addition, highly negatively charged proteins with Asp or Glu residues, like osteopontin, strongly bind to CaOx crystals and inhibit CaOx crystal formation, whereas weakly positively charged proteins, like Tamm−Horsfall protein, prothrombin fragment 1, albumin and bikunin, appear to primarily inhibit crystal aggregation and crystal adhesion to renal epithelial cells [38]. Accumulating studies suggest that several negatively charged macromolecules can interact throughout the crystallization process by modifying the shape or altering the electrostatic charge equilibrium of the CaOx crystals. [35, 38]. However, the exact molecule in natural substances including rice extract that affects the formation of CaOx crystals needs to be investigated further.

Conclusion

The potential for inhibition of crystal formation and aggregation in descending order was black glutinous rice, black rice, and red rice. The high content of lipophilic and hydrophilic active molecules in black glutinous rice could inhibit the formation of CaOx crystals as well as their aggregation. These findings suggest that colored rice may be used as a supplement to prevent the formation and aggregation of CaOx crystals. However, further studies are needed to determine how these extracts play a role in the prevention of kidney stone formation.

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Thalassemia and Hemoglobinopathies in Thailand: A Systematic Review

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ABSTRACT

Thalassemia and hemoglobinopathies are inherited autosomal recessive blood diseases, that have been the major health problem in Thailand. The study on the prevalence of thalassemia and hemoglobinopathies is important for the prevention and control of thalassemia diseases. The object of this article is to provide the current prevalence of thalassemia mutations in Thailand, focusing on common α- and β-thalassemia mutations. The prevalence of α-thalassemia mutations and the data reveal that the frequency of α0-thalassemia (SEA type) is the most common throughout the country. Meanwhile, α+-thalassemia (3.7 kb deletion) is also high, followed by 4.2 kb deletion. While codon 41/42 (-TCTT) and codon 17 (A>T) make up the majority of β-thalassemia mutations, the frequency of these two types is high, accounting for more than 50% in the North, Northeast, and Central Thailand. While it is lower in southern Thailand, averaging about 22-32% because codon 19 (A>G) is widely distributed after codon 41/42. However, Hb E is the major β-hemoglobinopathy owing to its high prevalence in all regions.

Keywords: Thalassemia, Hemoglobinopathies, Thailand

Introduction

Thalassemia is an inherited autosomal recessive blood disease caused by genetic defects through mutation, deletion of genes, or insertion of bases, characterized by reduced or absent synthesis of the essential globin chains of hemoglobin. A recessive condition is one where both genes of the pair associated with a condition must be changed or mutated. A carrier state can exist in which a person carries one normal and one mutated gene. There are two categories of thalassemia disease: these are thalassemia and hemoglobinopathies. Thalassemia is the term applied to the quantitative problem of having decreased or absent globin chain synthesis. At the same time, hemoglobinopathies describe the qualitative problem of having structurally abnormal globin chains or abnormal forms of hemoglobin. Thalassemia and hemoglobinopathies are the most prevalent in the Mediterranean (Greece, Italy, and Cyprus), Middle East, parts of Africa, India, and Asia regions, especially Southeast Asia [1].

Thalassemia and hemoglobinopathies are major health problems in Thailand. Approximately 1% (620,000 people) of the Thai population has thalassemia disease and around 30-40% (18-24 million people) are carriers of thalassemia genes. Each year, almost 50,000 pregnancies are at risk of having babies with thalassemia disease, of which approximately 12,000 results in thalassemic newborns. Among the 12,000 affected children each year, around 5,000 of them are affected by thalassemia major [2]. Thalassemia disease affects not only thalassemia health but also the socio-economic situation and mental health of their families. The Thai government spends over 5,000 million bath annually for the prevention and treatment of thalassemia disease. Thus, the disease burden for the country is huge [3]. The study on the prevalence of thalassemia and hemoglobinopathies is important for the prevention and control of thalassemia diseases. Therefore, this article aims to describe the prevalence of thalassemia mutations in Thailand that were studied from 2002 to 2022. These include common α- and β-thalassemia mutations, severe thalassemia diseases, and strategies for the prevention and control of thalassemia.

Hemoglobin synthesis

The hemoglobin molecule within red blood cells transports oxygen from the lungs to all parts of the body. Hemoglobin is a tetrameric-structured protein that is made up of 2 α-like and 2 β-like globin chains. Each

subunit of hemoglobin has a heme group made up of iron and porphyrin rings. At various developmental stages, β-like globin chains are combined with α-like globin chains to form a variety of hemoglobin tetramers [4]. Hemoglobin synthesis is controlled by two multiple-gene clusters, one on chromosome 11p.15.5 encodes β-like globin chains including ε, G_{γ}, A_{γ}, δ and β-globin chains and another on chromosome 16p.13.3 encoding α-like globin chains including ζ and α-globin chains. In normal adults, 95-97% of total hemoglobin is HbA ($\alpha_2\beta_2$), while 2-3% is HbA_2 ($\alpha_2\delta_2$) and less than 1% is HbF ($\alpha_2\gamma_2$) [4]. Thalassemia syndrome can be caused by variations in the genes encoding α-and β-globin chains, which can lead to improper hemoglobin function.

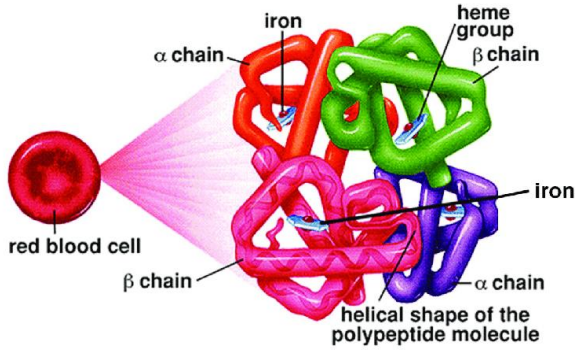

Figure 1 Tetrameric structure of hemoglobin that contains 2α-like and 2β-like globin chains [5]

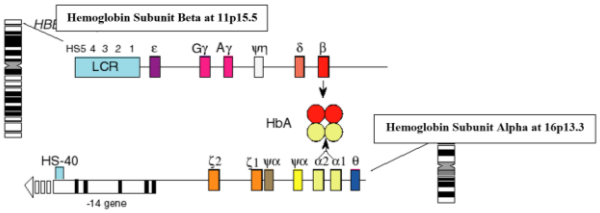

Figure 2 Schematic representation of the human β-globin gene cluster on chromosome 11p15.5 and the α-globin gene cluster on 16p13.3 [6]

Classification of thalassemia

Thalassemia syndrome can be classified according to the particular globin chains responsible for α, β, δβ, and εγβ thalassemia's inefficient synthesis. However, the most frequently found thalassemia worldwide are α- and β-thalassemia.

α-thalassemias and α-hemoglobinopathies

α-thalassemia results in reduced or absent production of the α-globin chain. Anemia is caused by decreasing levels of α-globin chains that contain hemoglobins, HbA ($\alpha_2\beta_2$), HbA_2 ($\alpha_2\delta_2$), and HbF ($\alpha_2\gamma_2$). Under-production of α-globin chains leads to excess production of γ-globin chains resulting in the formation of γ_4-tetramers (Hb Bart's) and β_4-tetramers (HbH). Therefore, the diagnostic marker for α-thalassemia is the presence of Hb Bart's and Hb H in the blood [7].

α-thalassemia is caused by either deletion or non-deletion of the α-globin gene such as a point mutation. The deletional type is the major form of α-thalassemia, which involves the deletion of one or two α-globin genes on the cis chromosome and gives rise to two types of deletional α-thalassemia. The first type is α-thalassemia 2 (α^+-thalassemia) in which one cis α-globin gene is deleted leaving the other cis α-globin gene intact. α^+-thalassemias consists of two forms, α^+-thalassemia caused by the rightward deletion (3.7 kb deletion) and leftward deletion (4.2 kb deletion), etc. The other non-deletional types are caused by mutations i.e., Hb Constant Spring (Hb CS) and Hb Pakse, that are included in α-hemoglobinopathies. The second type is α-thalassemia 1 (α^0-thalassemia), in which both cis α-globin genes are deleted. Homozygotes for α^0-thalassemia can lead to Hb Bart's hydrops fetalis [1, 8-10].

β-thalassemias and β-hemoglobinopathies

β-thalassemias are a group of blood disorders characterized by reduced or absent synthesis of β-globin chains. The major molecular defect in most cases of β-thalassemia is a point, whereas few cases are caused by deletion. The two types of β-thalassemia are β^0 which shows a complete absence of the β-globin chain, and β^+-thalassemia where reduced levels of the β-globin chain are found [11-12].

At present, there are more than 150 mutations in β-globin genes that cause β^0 and β^+-thalassemia [13]. In Thailand, the 4bp (-TCTT) deletion at codon 41/42 ($\beta^{41/42}$) and A>T substitution at codon 17 of the β-globin genes are the predominant mutations observed in β^0-thalassemia patients. In β^+-thalassemia, the A>G substitution at nucleotide -28 in the promoter region of the β-globin gene (β^{-28}) is the major molecular defect found in Thailand. Within the group of β-hemoglobinopathies in Thailand, Hb E is the most important hemoglobin variant due to its high prevalence across the country [14]. Hb E is caused by G>A substitution at codon 26 of the β-globin gene and is named the β^E-allele. This mutation changes the triplet codon for glutamic acid to that for lysine. In addition, this G>A mutation activates a cryptic slice site at codon 25, which results in reduced synthesis of the β^E-globin chain and leads to the β^+-thalassemia phenotype [9, 14-20].

Prevalence of thalassemia and hemoglobinopathies in Thailand

Globally, the carrier frequency of β-thalassemia falls between 1% and 20%, whereas that of α-thalassemia is much higher, with a range of 10-20%, or maybe as high as 40% in some Middle Eastern and Indian populations. The distribution of α^0-thalassemia is restricted; it is more common in regions of Southeast Asia. In Thailand, α and β thalassemias are the most common types of thalassemias. As previously reported,

before 2000, approximately 20-30% of the Thai population had α-thalassemia genes, while 3-9% had β-thalassemia genes. Hb Constant Spring (Hb CS) was the major α-hemoglobinopathy found in Thailand, (1-8%) and Hb E was the major β-hemoglobinopathy (8-60%). These vary depending on each region [8, 21-25].

From 2002 to 2022, in Thailand, there was modest regional variation in the prevalence of common thalassemia mutations. In the north, the frequencies were 5.2-21.0% for α^0-thalassemia (SEA type), α^+-thalassemia (3.7 kb deletion and 4.2 kb deletion) 19.9%, and 4.5%, 14.9-37.3% for Hb E, 0.3-4.2% for Hb CS and 0.5% for Hb Pakse, respectively [26-32]. In the northeast, α^0-thalassemia (SEA type) was 3.1-13.6%, α^+-thalassemia (3.7 kb deletion and 4.2 kb deletion) were 25.1 and 0.8%, Hb CS was 5.4%, Hb Pakse was 1.4% and Hb E was 39.1-(50-60)%, respectively [33-34]. While in the Central region, we found 4.6% of α^0-thalassemia (SEA type), α^+-thalassemia (3.7 kb deletion plus 4.2 kb deletion) was 17.2%, Hb CS 5.6%, Hb Pakse 0.5% and 22.7% of Hb E respectively [35]. Finally, in the South region, frequencies were 4.8% of α^0-thalassemia (uncharacterized) and 16% of Hb E [36-38].

At present, there are more than 20 α-thalassemia mutations in Thailand. The predominant genotype of α^0-thalassemia among Thai people is SEA type. Whereas with the α^+-thalassemia gene, the 3.7-kb deletion ($-\alpha^{3.7}$) is the major genotype, and the 4.2-kb deletion ($-\alpha^{4.2}$) is the major one [26-29,32,34,36-38]. There are approximately 30 types of β-thalassemia that have been identified in Thailand. The frequency of β-thalassemia varies modestly. The 4 bp deletion at codon 41/42 (-TCTT) or $\beta^{41/42}$ is the most common, followed by nonsense A>T mutation at codon 17 (A>T). Hb E is the major β-hemoglobinopathy due to its widespread throughout the country [26-31, 36-37, 39-40].

Severe thalassemia diseases in Thailand

Severe thalassemia diseases in Thailand comprise homozygous α^0-thalassemia (Hb Bart's hydrops fetalis), homozygous β-thalassemia, and β-thal/Hb E. In Thailand, the most common type of α-thalassemia 1 is the Southeast Asian type ($--^{SEA}$), which involves the deletion of approximately 20 kb of DNA, removing ψα2, ψα1,α2, α1, θ globin genes [23]. 5.2% to 21% of the Thai population carry this deletion [26-28,33-34]. Homozygosity of α-thalassemia 1 (SEA type) can cause Hb Bart's hydrops fetalis. The other α-thalassemia 1 deletion that can result in hydrops fetalis is the compound heterozygosity of $--^{SEA}/--^{THAI}$. In 2019, new cases of Hb Bart's hydrops fetalis in lower northern Thailand were found to be caused by the compound heterozygous mutations Southeast Asian type and Chiang Rai deletion type ($--^{SEA}/--^{CR}$). THAI deletion is caused by the deletion of approximately 34.5 kb, resulting in the removal of the entire α-globin gene family. The most recently described cause of severe thalassemia, the Chiang Rai deletion type, was found in 2019 and causes an approximately 44.6 kb α^0-thalassemia deletion on chromosome 16 [41-42].

Hb Bart's hydrops fetalis is the most severe form of α-thalassemia, a lethal form of thalassemia. Most of the affected fetuses died before labor began, during labor and delivery, or shortly after delivery. The prevalence of this disease varies from 1:200 to 1:2,000 in Southeast Asia [43]. Fetuses with Hb Bart's hydrops fetalis, where all 4 α-genes were deleted, had non-functional hemoglobin homotetramers (γ_4 and β_4). γ_4 homotetramers have a high affinity for oxygen, living only a small amount of embryonic Hb Portland ($\delta_2\gamma_2$) to deliver and liberate oxygen to the tissues of the fetus. Fetuses with this disease suffered severe anemia in utero, resulting in severe tissue hypoxia, heart failure, and abnormalities such as hepatosplenomegaly and urogenital overload, resulting in edema over the entire body, leading to the designation hydrops fetalis. Risks for the mother include preeclampsia, polyhydramnios or oligohydramnios, antepartum hemorrhage, and premature delivery. Pregnant women and carrier couples are at risk of having a fetus with Hb Bart's fetalis and because of fetal and maternal complications, termination is usually advised [44]. Other severe forms consist of β-thalassemia major including homozygous β-thalassemia and some cases of β-thal/Hb E. These two forms affected children, presenting symptoms within the first 2 years of birth, often 3 to 6 months after birth and hemoglobin levels in untreated patients were 3-6 g/dL. People with β-thalassemia major require life-long blood transfusions and need monitoring for complications and treatment for iron overload. The child with these severe forms can be pale, have a poor appetite, and present with many infections during the first 1-2 years of life. Without treatment, it can cause an enlarged liver and spleen and the bones become thin and brittle, with the presence of a prominent forehead, frontal bossing, full cheekbones, and a depressed bridge of the nose. In teenagers and adults, complications with iron overload commonly occur, which may result in heart failure, liver cirrhosis, hypoparathyroidism, hypogonadism, etc. [45].

Thalassemia and hemoglobinopathies in northern Thailand

A study in 2004 [29] among 516 pregnant women who attended the Antenatal Clinic of Maharaj Nakorn Chiangmai Hospital. Most of these women resided in Chiangmai, while others resided in other northern provinces. The percentage of pregnant women who were carriers of α-thal 1 (SEA type) was 6.6%, β-thalassemia heterozygote 3.7%, Hb E heterozygote 11.6%, combination of α-thal 1 (SEA type) and β-thal heterozygote 1.2%, combination of α-thal 1 (SEA type) and Hb E heterozygote 1.5%, homozygous Hb E 0.8% and β-thal/Hb E disease 0.2% [29].

A study in 2005 [26] among 500 people from Uttaradit, Phetchabun, and Phitsanulok provinces in northern Thailand found that 40.4% of the population

carried a thalassemia gene with the following distribution,7.8% heterozygous α-thalassemia 1 (SEA type), 2.2% β-thalassemia trait, 26.6% Hb E heterozygous, and 3.8% homozygous Hb E. A study of pregnant women and their partners [27] who attended Buddachinnaraj provincial hospital and 8 community hospitals in Phitsanulok between 2002 and 2003, found that 4.8% were heterozygous for α-thalassemia 1, 1.6% for the β-thalassemia trait, 12.4% were heterozygous for Hb E, 2.7% were homozygous for Hb E and 0.25% for Hb CS [27]. A study in 2013 [30] among 50 persons who attended hospitals in Phitsanulok province and were diagnosed with β-thalassemia. The distribution of codon 41/42 (-TCTT) was highest at 48%, followed by codon 17 (A>T) at 30%, nt-28 (A>G) at 6%, IVS-I-1 (G>T) 6%, -87 (C>A) at 4%, codon 35 (C>A) at 2%, codon 71/72 (+A) at 2% and IVS-II-654 (C>T) at 2% [30].

Parameeyong, et al [32] reported that people who attended 7 hospitals in Phayao province and found that the percentage of carriers with α-thalassemia 1 (SEA type) was 9.6% [32]. Pharephan, et al [28] reported that α-thalassemias in 638 pregnant women who attended the Antenatal Clinic at Maharaj Nakorn Chiangmai Hospital, came from 15 provinces in northern Thailand, such as Chiangmai, Chiangrai, Kamphaung Phet, Lampang, Lamphun, Mae Hong Son, Nan, Nakorn Sawan, Phayao, Phitsanusalok, Phrae, Sukhothai, Tak, Utthai Thani and Uttaradit. They noted that thalassemia distribution of heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$) was high, about 15.52%, followed by heterozygous α^{0}-thalassemia (SEA type) 12.23%, heterozygous Hb CS 4.23%, deletional disease ($--^{SEA}/-\alpha^{3.7}$) 2.82%, homozygous α^{+}-thalassemia ($-\alpha^{3.7}$) 0.78% and heterozygous α^{+}-thalassemia ($-\alpha^{4.2}$) about 0.31%.

The prevalence of thalassemia genes was also studied by Limveeraprajak [31], who investigated at-risk couples who attended the Antenatal Care clinic, Sawanpracharak Hospital, Nakorn Sawan province, between 2012 to 2017. He found the percentage of Hb E heterozygote was high, about 17.5%, followed by β-thalassemia heterozygote (15.7%), SEA α-thal 1 heterozygote (13.9%), double heterozygote SEA/E (6.3%), homozygous Hb E (4.4%), Hb E/β-thalassemia (2.1%) and Hb H disease (1.3%).

Thalassemia and hemoglobinopathies in northeastern Thailand

A large study in Northeastern Thailand looking at the prevalence of thalassemia genes amongst a population was done by Vimolsarte, et al. [34]. They studied 18,461 subjects in patients, pregnant women, and their partners, who attended Health Service Area 7 of Thailand during 2011-2012. The distribution was as follows: α-thalassemia 1 (SEA type) was 13.6%, while THAI deletion type was 0.11%. Hb E was the most common for β-hemoglobinopathies about 50-60%; the β-thalassemia mutation found codon 41/42 (-TCTT) at 43.1%, codon 17 (A>T) at 21.5%, nt-28 (A>G) at 21.5%, codon 71/72 (+A) at 7.6%, IVS-II-654 (C>T) at 1.5%.

Chaibunruang, et al. [33] reported that among 350 newborns delivered at Maternal and Child Hospital, Regional Health Promotion Center 7, Khon Kaen, Northeastern Thailand. The distribution of thalassemia genes showed that heterozygous Hb E was highest at about 17.1%, followed by heterozygous α^{+}-thalassemia (3.7 kb deletion) at 11.4%, a combination of 3.7 kb deletion and Hb E at 5.7%, heterozygous Hb CS at 3.4%, homozygous Hb E at 2.9%, combination of α^{0}-thalassemia (SEA type) and Hb E at 1.4%, homozygous α^{+}-thalassemia (3.7 kb deletion) and heterozygous α^{0}-thalassemia (SEA type) at 1.1%.

Thalassemia and hemoglobinopathies in central Thailand

Studies from central Thailand found that the prevalence of Hb E was highest at about 22.7%, followed by α^{+}-thalassemia (3.7 kb deletion) plus (4.2 kb deletion) at about 17.2%, Hb CS at 5.6%, α^{0}-thalassemia (SEA type) at 4.6%, Hb Pakse at 0.5% and β-thalassemia at 0.7% [33].

A study conducted 80 pediatric patients who were followed in the Phramongkutkhao Hospital, Central Thailand [38] and were carrying β-thalassemia mutations. Most patients resided in Bangkok while some resided in other provinces in central Thailand. The genotypes of β-thalassemia encountered were alleles of codon 41/42 (-TCTT) 37.5%, followed by codon 17 (A>T) 26.1%, IVS-I-5 (G>C) 8%, IVS-II-654 (C>T) 6.8%, IVS-I-1 (G>T) 4.5% and codon 71/72 (+A) 2.3% and codon 19 (A>G) 1.1%. Panichchob, et al [40] reported that the distribution of β-thalassemia mutations in eastern Thailand. The data showed that six common β-thalassemia mutations were identified as codon 41/42 (-TCTT) at 35.6%, codon 17 (A>T) at 18.9%, nt-28 (A>G) at 15.7%, IVS-II-654 (C>T) at 6.3%, IVS-I-1 (G>T) at 5.8% and codon 19 (A>G) at 4.7%.

Thalassemia and hemoglobinopathies in southern Thailand

In southern Thailand, α-thalassemia mutations were rarely reported. A 2006 study by Tienthavorn V et al. investigated [35] the prevalence of thalassemia carriers in Nakorn Si Thammarat and found that carriers for α^{0}-thalassemia were 4.8%. Panyasai, et al [37] found the frequency of Hb Pakse in Nakorn Si Thammarat to be 0.4%. Nopparatana, et al. [36] studied at-risk couples who resided in 14 provinces in southern Thailand and found heterozygosity for β-thalassemia was 5.6%, α^{0}-thalassemia was 4.5% and Hb E mutation was 16.0%. The proportion of α^{0}-thalassemia (SEA type) was 98% while the THAI type was 2%. The seven most common mutations causing β-thalassemia were, codon 19 (A>G) 18.6%, followed by codon 41/42 (-TCTT) 14.4%, IVS-I-5 (G>C) 13.2%, 3.5 kb deletion 9.2%, codon 17 (A>T)

7.7%, nt-28 (A>G) 7.3% and IVS-I-1 (G>T) 7.1% [36]. Additionally, Nuinoon, et al. [39] studied the frequency of β-thalassemia mutations in 181 β-thalassemia patients and found that codon 41/42 (-TCTT) was 23.9%, codon 17 (A>T) was 14.1%, codon 19 (A>G) was 6.3%, nt-28 (A>G) was 4.4% and IVS II-654 (C>T) was 4.4%.

Prevalence of common thalassemia mutations in Thailand

Table 1 Prevalence of common α-thalassemia mutations in the North, Northeast, Central and South of Thailand, studied from 2002 to 2022.

α-thalassemia mutations	**North** **%** [26-29,31-32]	**Northeast** **%** [33-34]	**Central** **%** [33]	**South** **%** [35,37]
SEA type	5.2-21.0	3.1-13.6	4.6	
α^0-thalassemia uncharacterized				4.8
3.7 kb deletion	19.9	25.1	17.2	ND
4.2 kb deletion	4.5	0.8		
Hb CS	0.3-4.2	5.4	5.6	ND
Hb Pakse	0.5	1.4	0.5	0.4

Note that there was rarely reported in the South

** ND; not determined*

Table 2 Prevalence of common β-thalassemia mutation in the North, Northeast, Central and South of Thailand, studied from 2002 to 2022.

β-thalassemia mutations	**North** **%** [26-27, 29-31]	**Northeast** **%** [34]	**Central** **%** [33, 38, 40]	**South** **%** [36, 39]
Codon 41/42 (-TCTT)	48.0	43.1	35.6-37.5	14.4-23.9
Codon 17 (A>T)	30.0	21.5	18.9-26.1	7.7
Codon 19 (A>G)	-	-	1.1-4.7	6.3-18.6
nt-28 (A>G)	6.0	21.5	15.7	4.4-7.3
IVS-II-654 (C>T)	2.0	1.5	6.3-6.8	2.7-4.4
Hb E	14.9-37.3	39.1-(50-60)	22.7	16

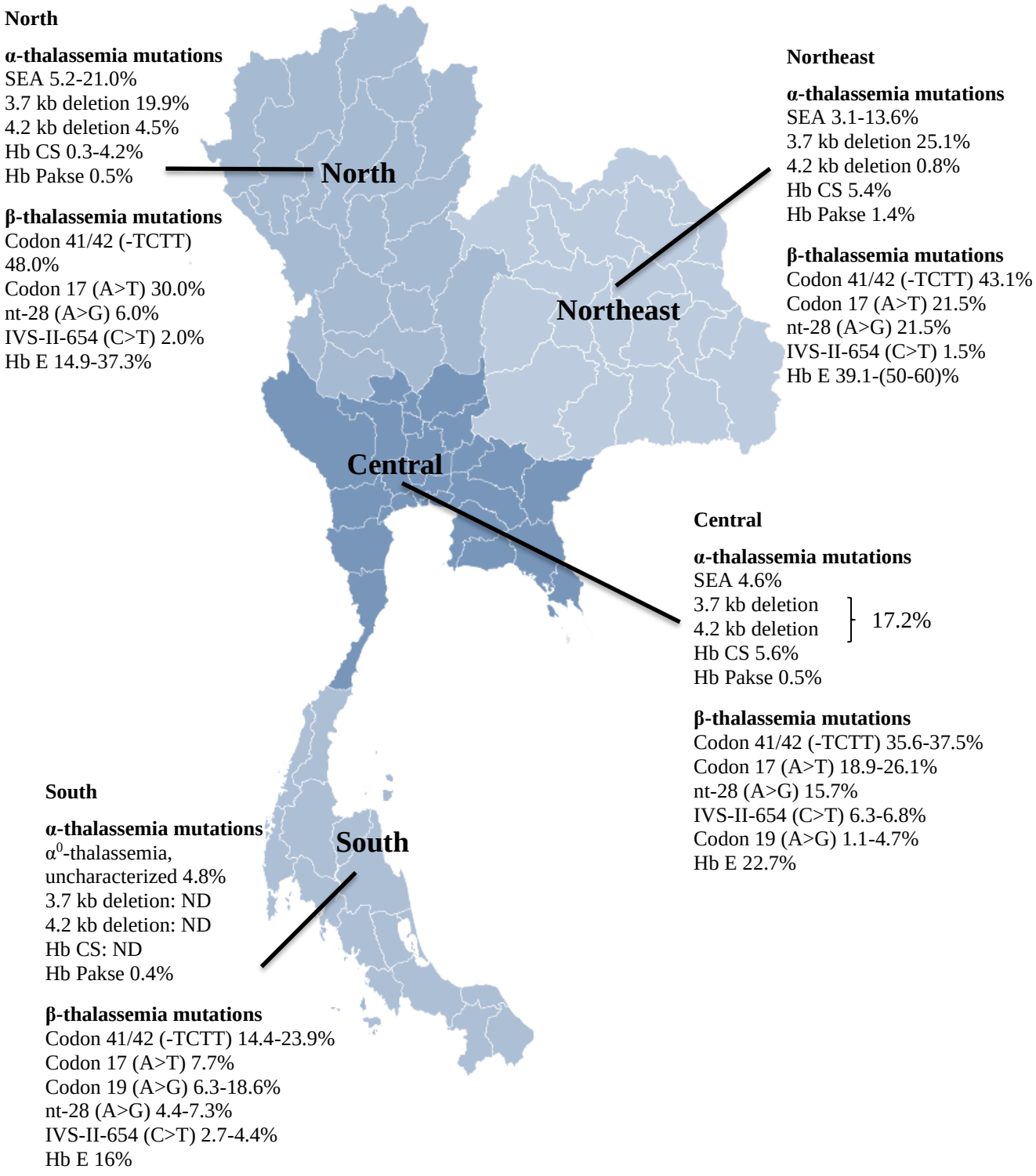

Figure 3 Map representation for common thalassemia mutations in Thailand, studied from 2002 to 2022. ND; not determined

Clinical symptoms of thalassemia and hemoglobinopathies

The clinical symptoms of thalassemia can range from asymptomatic carriers to severe anemia with these complications. When left with adequate treatment, thalassemia can cause severe anemia, extramedullary hematopoiesis, growth deficits, and iron overload, all of which can substantially reduce life expectancy. The quantity of lost globin chains is correlated with the severity of clinical symptoms. In clinics, three types of thalassemia syndrome are typically seen, including i) thalassemia major: is the most severe group of thalassemia, consisting of Hb Bart's hydrops fetalis in those who are homozygous for α-thalassemia 1 and β-thalassemia major, who are homozygous or a compound heterozygote of severe types of β-globin gene mutation. People with thalassemia major manifest clinically between the ages of 6 and 12 months. Hemoglobin levels in untreated patients are as low as 3 to 4 g/dL, which makes the patient transfusion dependent, ii) thalassemia intermediate: this group of thalassemia is clinically milder than the major form of the disease. This type of thalassemia includes Hb H disease which refers to a compound heterozygote form of α-thalassemia 1 and α-thalassemia 2 and some cases of homozygous β-thalassemia or compound heterozygous of Hb E and β-thalassemia. When compared to patients with thalassemia major, patients with intermediate thalassemia typically develop clinical symptoms later in life. With hemoglobin levels between 7-9 g/dL and late disease onset, patients with intermediate types thalassemia typically require only infrequent or no blood transfusion; and iii) thalassemia minor: this type of thalassemia is seen in a carrier, heterozygote trait states. No obvious clinical symptoms are seen for this type. Hemoglobin level is usually equal to or more than 9 g/dL [45-48].

Strategies for the prevention and control of thalassemia diseases in Thailand

Thailand's national-wide program for the prevention and control of severe thalassemia which includes Hb Bart's hydrops fetalis, homozygous β-thalassemia, and β-thalassemia/Hb E was established by the Ministry of Public Health in 1997. The two main principles of this program were: 1) to offer the best treatments and improve patients' quality of life 2) prevent or minimize new births affected by severe thalassemia through screening, counseling and prenatal diagnosis under the policy (choose partner, select pregnancy, select delivery) [49]. In addition, laboratory staff members received varying degrees of training on how to identify high-risk couples and thalassemia carriers. The first simple screening included the osmotic fragility test (OF test) and dichlorophenol-indophenol precipitation test (DCIP test), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin). Secondly, if a couple had positive screening such as reduced MCV (<80 fL cutoff value) and MCH (<27 pg cutoff value) or positive OF/DCIP will be further investigated by a confirmatory test such as high-performance liquid chromatography (HPLC), low performance liquid chromatography (LPLC), capillary electrophoresis or using DNA analysis that is an important technique for the diagnosis of α-thalassemias [50]. The national policy to promote the prevention and control of severe thalassemia in Thailand was established in 2005 as follows [49]; (i)Every pregnant woman should receive genetic counseling for thalassemia; (ii) Every pregnant woman should receive thalassemia screening by consent. If the result of the pregnant woman is found to be positive for thalassemia or hemoglobinopathies, then the husband will also be screen; (iii) If the pregnant woman and her husband both have a positive thalassemia screen, they should undergo confirmatory tests to be sure that they are appropriately categorized as a couple at high-risk of having an offspring with severe thalassemia; (iv) If the pregnant woman and her husband are found to be a high-risk couple, they should be offered a prenatal diagnosis; (v) Every health care unit should establish a quality service system to promote/prevention/control of thalassemia. If any service exceeds the capacity of the unit, the case should be referred to a service network.; and (vi) Students, women of child bearing age and married couples will be extensively informed about thalassemia.

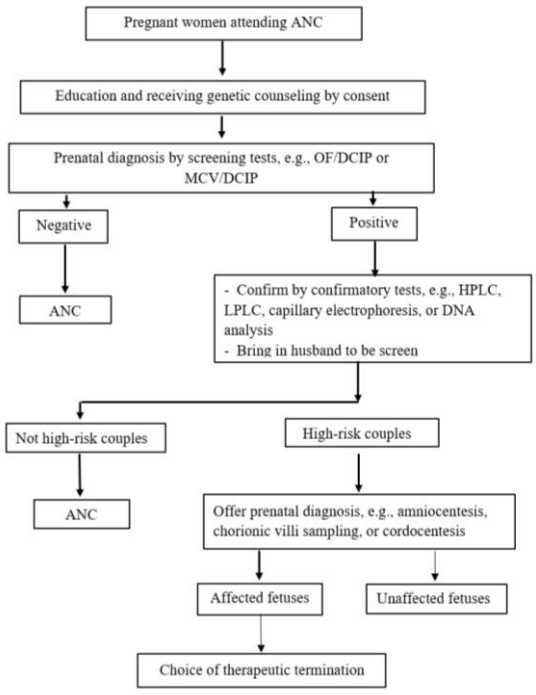

Figure 4 The schematic of the prenatal prevention program for severe thalassemia in Thailand: ANC; Antenatal Care Clinic, OF; osmotic fragility test, DCIP; dichlorophenol-indophenol precipitation test, MCV; mean corpuscular volume, HPLC; high performance liquid chromatography, LPLC; low performance liquid chromatography

Conclusion

This article described the current prevalence of α- and β-thalassemia mutations and focused on common mutations in the North, Northeast, Central and South of Thailand. For the prevalence of α-thalassemia mutations, the data reveals that the frequency of α0-thalassemia (SEA type) is highest throughout the country, while, α+-thalassemia (3.7 kb deletion) is also high, followed by 4.2 kb deletion. For the prevalence of β-thalassemia mutations, the frequency of codon 41/42 (-TCTT) is the most frequent mutation and codon 17 (A>T) is the major one. These two types accounted for more than 50% in North, Northeast and Central Thailand, while in the South, the frequency is lower, averaging about 22-32%, because of codon 19 (A>G) which is widely distributed after codon 41/42. However, Hb E is the major β-hemoglobinopathies owing to its high prevalence in all regions.

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