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Seeking the Solution to COVID-19 in Border Areas of Thailand: Experts' Perspectives

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ABSTRACT

This summarized article is taken from information provided during a panel seminar focused on seeking the solution to coronavirus disease-19 (COVID-19) in the border areas of northern Thailand, on 29 March 2021. World-class health professionals and academics who are working in the field were invited to deliver both information and their perspectives on different aspects of the pandemic. The information is divided into three levels, namely, the global situation and challenges, including further recommendations; the local lessons learned in Thailand and further action and collaborations required of society; and the cutting age research developing COVID-19 vaccines and their implementation and practical recommendations. In conclusion, vaccines are just one of the tools that can be used against the disease, and these vaccines need to be considered as a whole picture, including the prioritization of the administration of vaccines under limited supply, the equity of availability to all people in the world, and the negotiation of affordable prices. Moreover, our traditional prevention and control measures, such as social distancing, face-mask use, and maintenance of personal hygiene, are still strictly recommended.

Keywords: *COVID-19; Solution; Vaccine; Prevention and control measures; Lessons learned; Thailand*

Background

The information in this article is presented by three international experts (a WHO representative in Thailand; a member of the advisory board of the Department of Disease Control, Ministry of Thailand; and an international expert in medical virology and vaccinology from Chulalongkorn University, Thailand) who give their perspectives on COVID-19 by using the current scenario in Thailand; the information is summarized from a seminar panel that occurred on 29 March 2021 at Mae Fah Luang University, Thailand. All information presented herein is based on the knowledge and personal experts' ideas as of the date of the seminar. Three topics are critically presented in the article: COVID-19: global challenges and a sustainable future; lessons learned and how to better prevent and control future serious epidemics in Thailand; and pathogenesis, clinical management, and the COVID-19 vaccine. The article is summarized by the team from the Center of Excellence for Hill Tribe Health Research, Mae Fah Luang University, Thailand.

A. COVID-19: Global challenges and a sustainable future

Global situation

More than 126 million cases and 2.8 million deaths attributable to COVID-19 have been reported globally. A million new infected cases were reported every 2-3 weeks with an 8.0% increase over the previous weeks (up to March 14, 2021), while deaths plateaued, slowing to 100,000 new deaths every 11-13 days. According to regional epidemic curves, there were increases in the epidemic severity, which could be due to new severe variants of the virus, while the effectiveness of global vaccines is not yet known.

Thailand has demonstrated effectiveness in the prevention and control of the disease in recent months, as evidenced by fewer reported cases. Almost the entire Thai population has complied with prevention and control measures, including case tracing and case isolation, which has resulted in a low number of new cases (29,127 cumulative confirmed cases) and a low number of cumulative deaths (below 100 deaths). However, several clustered outbreaks in Thailand have

been reported in Samut Prakan Province (the index case was a migrant construction worker that was symptomatic, and 15 out of 17 cases were identified as symptomatic), the Suan Plu and Bang Khen immigration detention centers (98 out of 1,888 detainees (5.2%) were positive for COVID-19), the Rama II cluster (the index cases were 2 migrant workers that were symptomatic, and 30 out of 71 screened individuals were positive for COVID-19), and the Bang Khae market, where a market vendor was the index case (the vendor experienced the onset of symptoms on 1 March 2021 and tested positive on 5 March 2021).

Thailand's achievements

Several effective approaches have been used in Thailand to minimize the risk of COVID-19 in the past months: a) a timely effective response to minimize the risk of widespread transmission; b) excellent laboratory capabilities to confidentially confirm a timely diagnosis; c) a highly visible risk communication platform to encourage broad public awareness and engagement; and d) a sound vaccination plan to deliver safe and effective vaccines to Thai citizens. However, vaccination is just one of the several tools used to address the problem.

Globally, more than 459 million doses of vaccine have been administered in 178 countries, but 42 countries have not yet commenced vaccination (30 countries of which are low-income countries (LICs) or low-middle-income countries (LMICs)). Currently, the efficacy and resulting immunity of all vaccines are well documented; however, some points are not clearly answered, such as the efficacy in some age categories (children and other special groups of populations), duration, required booster, and impact on transmissibility.

On 5 March 2021, seventy-nine COVID-19 candidate vaccines were in the stage of clinical development, of which 12 vaccines were in phase III trials and 4 vaccines were in phase IV trails. There are another 182 candidate vaccines in preclinical development. More than 90.0% of all the top candidate vaccines will be delivered through intramuscular injection. A study of the Pfizer vaccine effectiveness in Israel found that that the vaccine could prevent infection by 94.0% (87.0-98.0%), could reduce hospitalization by 87.0% (55.0-100.0%), and could reduce progression to the severe stage of disease by 92.0% (75.0-100.0%) [1]. A retrospective cohort study on the effectiveness of the Pfizer and Moderna vaccines in the United States reported their effectiveness to be 89.0% (68.0-97.0%) and documented a 3.7% hospitalization rate in individuals vaccinated with two doses [2]. According to data from a prospective cohort study in Scotland on the effectiveness of the Pfizer and AstraZeneca vaccines, the effectiveness rates on days 28-34 after vaccination were reported to be 85.0% (76.0-91.0%) and 94.0% (73.0-99.0%), respectively [3].

Since the vaccine demand outweighs the supply, the World Health Organization (WHO) recommends first providing the vaccine to prioritized groups, such as older adults, persons with underlying conditions, and health care workers. This method aims to reduce the severe cases among those populations, to relieve congestion in health care settings, to provide easy access for the entire population in need of health care that is not related to COVID-19, and to reduce mortality. Moreover, the WHO suggests that vaccines are just one of the tools for use against COVID-19; maintaining social distance, using face masks and regularly washing hands are still required.

Thailand started administering vaccines on 28 February 2021 using the SINOVAC vaccine (CoronaVac) in 13 priority (high-risk) provinces. This plan is aligned with the WHO COVID-19 vaccine road map. Three objectives have been preliminarily considered from the implementation: a) to reduce the severity and fatality rate, especially in those aged over 60 years; b) to protect the public health system from being overwhelmed; and c) to ensure that the economy and society can move forward.

Under the Thailand national vaccine plan, two vaccines have been used: SINOVAC and AstraZeneca. SINOVAC recommends two doses with an interval of 2-3 weeks between doses, and this vaccine is mainly used to prevent progression to the severe stage of disease after infection. AstraZeneca recommends two doses with an 8-12 week time interval between doses. This vaccine has been demonstrated to have no severe side effects and to produce a strong immune system response. The WHO is concerned about the side effects of the various vaccines and the acute effects following immunization (AEFI). Today, the WHO is working closely with all national authorities to monitor the quality, safety, and efficacy of vaccines to ensure they meet the global standard. Several concerns arising from the WHO on vaccine monitoring are as follows: a) a billion people will be vaccinated, which means that some side effects are possible; b) are there any side effects other than those that are expected?; c) is there a plausible biological mechanism for these side effects? and d) how can authorities understand the difference between association and causation with regard to vaccines and side effects? Regarding thromboembolic problems and AstraZeneca, the WHO reported that there was no strong evidence to make a conclusion because the proportion of vaccinated persons and general persons with thromboembolisms was not significantly different. Thus, the WHO recommends continuing to implement this vaccine.

Challenges

a) Mutations of the virus increase its transmission ability, increase the severity of the infection, and reduce the efficacy of vaccines.

b) There is currently unequal to access vaccines, especially by those who truly need to receive them. This is one of the greatest challenges of the limited supply of the vaccine and a large subgroup of the population who are in need of the vaccine. Having a hundred percent vaccination in a certain country, while other countries are not able to access the vaccine might not be a good strategy as a whole. Rather, providing access to the vaccine without economic barriers to those who truly need it, i.e., both those who need it due to underlying conditions and those who are working in high-risk circumstances, would be economically beneficial for the global population.

c) Proof of vaccination or immunity for international travel is not recommended by the International Health Regulation (IHR) Emergency Committee due to critical knowledge regarding the efficacy of vaccination in reducing transmission and the limited availability of vaccines.

What next?

Given the current information about COVID-19, the pandemic will not end soon, and an infection risk in one place is equivalent to an infection risk everywhere. It is clearly known that the vaccine is not the only sufficient tool used to combat the virus. For Thailand, many things need to be considered, such as a) the introduction of new variants with increased severity in a community, including B-1.1.7, b) cross-border introductions from national political conflicts in neighboring countries, and c) the challenges of vaccine supply to first-priority populations. Two major patterns of transmission are closely monitored: a) high-density population areas, particularly in migrant worker residences, and b) community markets, which are common places for people to gather in a community.

B. Lessons learned and how to better prevent and control future serious epidemics in Thailand

Introduction

This section aims to review the lessons learned from previous public health emergencies of regional and global concern that Thailand has experienced during the past years. The presentation is focused on the current good COVID-19 pandemic responses and the remaining challenges.

Key lessons learned

1) Since 1980, Thailand has experienced HIV/AIDS, SARS, avian influenza both in animals and humans, imported cases of MERS, the 2009 H1N1 pandemic, and the current COVID-19 pandemic. The crucial lessons learned include the need for transparent alerts and unified emergency responses.
2) Thailand has made major improvements by implementing the 1st-4th National Strategic Plans for Emerging Infectious Diseases, especially in the areas of establishing surveillance and rapid response teams (SRRTs) in every district, increasing laboratory capacity in every regional center, collaborating closely between human and animal health worker sectors and passing a new infectious disease control act that delegates the control of decisions to the provincial level.
3) Thailand was the first country outside of mainland China to report a case of COVID-19. There were two major waves of COVID-19 in March and December 2020 (lasting until 29 March 2021). Except at the beginning of the first wave, thus far, the country has contained its COVID-19 outbreaks.
4) Good practices in regard to COVID-19 responses are as follows: a) appropriate reporting for surveillance; b) laboratory surge capacity to test RT-PCR in every province; c) investigations with extensive contact tracing and the containment of many important clusters of COVID-19 outbreaks; d) systematic and reliable quarantine at state and local levels; e) field hospitals for mild cases; f) social distancing, hand washing, universal face-mask wearing in public areas; g) rapid and transparent risk communication; h) vaccine procurement and research; i) existence of a Provincial Infectious Control Committee; and j) whole government responses coordinated by National COVID-19 Administrative Centers.
5) The vaccine is a new important tool used to control COVID-19 and will be made available widely. This strategy is focused on the transition from strict containment to long-term stability with the hope of resuming domestic and international travel and trading in the last quarter of 2021.

Suggestions for future actions

Thailand will become increasingly stronger by addressing both the public health system and social determinants of health. We should maintain and increase public health capabilities by investing in an epidemiological workforce and robust surveillance tools, laboratory networking and vaccine research. We should also do our best to reduce at least the following three vulnerable conditions. The first condition is reducing noncommunicable diseases by controlling risk factors, which will help reduce mortality and intensive care needs in the next pandemic. Second, vulnerable settings should be reduced, especially migrant working and living conditions, inmate and prisoner conditions, and crowded slums in large cities. This area needs strong policies to be effective. Third, risk behaviors should be reduced by promoting safe social behaviors, for instance, by encouraging people to have small and meaningful events instead of large events, which will save the environment and responsibly promote social justice.

Conclusion

Each of us can make a difference in preparing our country for future serious epidemics or pandemics by practicing, advocating and enabling our own community.

C. COVID-19 Impact, Management, and Vaccine

Presently, one major problem posed by the going COVID-19 globally is the emergence of virus variants of concern (VOC). A large number of new confirmed cases were reported a week ago (between 20 March 2021 and 27 March 2021) in Europe despite ongoing vaccination [4]. For Thailand, the national health system records showed several positive impacts of COVID-19. Increased awareness of better personal hygiene has reduced the incidence of the flu and other infectious respiratory infection [5]. Limitation in movements resulted in a marked decrease in traffic accidents [6]. However, COVID-19 seems to have little impact on mosquito-borne diseases such as dengue fever, which are more influenced by environmental management than personal hygiene [4].

Today, the development of COVID-19 vaccines offer new hope for the global population. Thailand had three options for vaccination: developing its vaccine, cooperating with other international companies in vaccine development, or buying the vaccines. To be widely accepted by the general population, an ideal vaccine (preferably offered as a single dose) should have minimal side effects, be relatively effective and affordable, and be easily shipped and stored at room temperature. Since coronavirus can mutate and re-infect humans, it makes vaccine development challenging.

There are currently ten platforms or types of COVID-19 vaccine. 1) inactivated SARS-CoV-2 grown in cell culture and then chemically inactivated, 2) live attenuated but genetically weakened SARS-CoV-2 grown in cell culture, 3) recombinant whole spike protein, 4) recombinant receptor-binding domain of spike protein, 5) genome-devoid virus-like particles displaying surface spike protein, 6) replication-incompetent vector capable of expressing the spike protein, 7) replication-competent vector capable of expressing the spike protein, 8) chemically inactivated virus vector with spike protein on the surface, 9) plasmid DNA encoding the spike gene under a mammalian promoter, and 10) messenger RNA encoding the spike protein packaged in lipid nanoparticles [7].

There are more than 300 research institutes involved in vaccine development. Thirteen vaccines in four platforms have been approved under emergency use [8]. They are inactivated virus (SINOVAC and Bharat Biotech), virus vector (AstraZeneca, Sputnik V, Johnson&Johnson, CanSino Biologics), RNA-based (Pfizer and Moderna), and recombinant protein (Novavax). More vaccines are expected to be approved in the future.

Messenger RNA vaccine

Naked RNA is intrinsically unstable. It is typically present with 5' and 3' non-coding region with 5' cap and 3' poly-A tail and is often associated with membrane proteins. RNA encoding the spike protein is made stable by combining with lipid nanoparticles in glycerol to make a vaccine. When injected into the muscle, the spike-encoding RNA molecules which made it to the cellular ribosomes are translated. The presence of the spike protein eventually stimulates an antibody response. This mechanism is the basis of the Pfizer and Moderna vaccines, which have never been used in a human vaccine. A study reports a very high efficacy (95.0%) after two doses of such vaccine [9]. This technology has the potential for other vaccine development in the future.

Virus vector vaccine

The Ebola vaccine is an example of a virus vector vaccine. Virus vectors often utilize adenovirus (36,000 base-pairs) to induce foreign protein expression in host cells. Wild-type adenovirus typically causes acute respiratory tract infection and diarrhea in humans. Coronavirus spike gene is large (approximately 4 kilobases or more than 1,000 amino acids), which in comparison is larger than the hepatitis B virus spike glycoprotein (226 amino acids). In order to include the spike gene into the adenovirus vector, the adenovirus E1 gene, which has a viral replication function, is deleted. As such, the adenovirus vector can express the spike protein but cannot replicate itself. Expression of the coronavirus spike from the adenovirus-encoded DNA in the cellular cytoplasm eventually stimulates antibody production. This platform is the basis for COVID-19 vaccines by Astra Zeneca, Sputnik, Johnson & Johnson, and CanSino. In particular, the Sputnik vaccine developed by Russia uses two different adenoviruses, Ad26 for the first dose and Ad5 for the second dose. The purpose is to avoid the host antibody to Ad26 from the first dose and improves the booster effect to the spike proteins (92.0% efficacy). For the Johnson &Johnson vaccine, only Ad26 is used in a single dose, while CanSino Biologics of China uses Ad5.

Inactivated vaccine

For over 50 years, this traditional method has been used to produce vaccines for polio, hepatitis A, and rabies. Cultured virus stock is inactivated with beta-propiolactone, which is easily disintegrated. After purification by centrifugation, the inactivated virus is absorbed with aluminum salt as the adjuvant.

SARS-CoV-2 Recombinant Protein

This process is used for the hepatitis B vaccine, in which virus-like particles are produced from yeast

cells. Novavax uses a baculoviral vector encoding the spike genes and a novel "Matrix-M adjuvant" extracted from the Quillaja sapoaria from Molina tree to make its COVID-19 vaccine. This adjuvant can effectively stimulate the human antibody response.

In conclusion, almost all COVID-19 vaccines developed thus far have sufficient efficacy and meet the WHO criteria in preventing mortality from COVID-19. Most vaccines cannot prevent infection but can alleviate COVID-19 severity. Some vaccines have been shown to elicit cross-protection against the South Africa variant (B.1.351).

Final recommendations

There are several recommendations for vaccination and clinical practice: 1) Vaccination can prevent severe COVID-19 requiring hospitalization; 2) Vaccination should be done soon as possible on a voluntary basis. More than 530 million doses (as of 29 March 2021) have been administered worldwide, and 15 million doses are administered every day. High immunization coverage can reduce the number of new cases and deaths, which should help the economy recover; 3) Any vaccine is good to use under emergency use authorization at the moment, given the limited supply; 4) Price of vaccine is one of the considerations for real-world implementation; 5) Acceptance is important in vaccine implementation given the 10% vaccine hesitancy rate among Thais surveyed; 6) Risks and benefits of a COVID-19 vaccine have to be compared. Vaccination is a much more positive impact on social and economic dimensions. A small proportion of vaccination side effects will require medical attention; 7) Antibodies to the coronavirus nucleocapsid result from either natural infection or vaccination with an inactivated vaccine, while antibodies to the spike protein will result from vaccination. Nucleocapsid antibody is detectable earlier than spike antibody, and the IgM and IgG are detectable in the same period. In practice, IgG is detected in routine work. Detection of IgG for nucleocapsid will be more practical to identify natural infection since titers are higher than for the spike protein; 8) Rapid COVID-19 test could be used. The highest antibody is detected in the third week of the infection. The detection rate by using the rapid test in week-1 and 2 is around 50%. Patients who progressed to severe pneumonia are associated with higher antibody titer. Nevertheless, antibody detection depends on the method and the target antigen; 9) After vaccination, it is not necessary to detect the antibody. Antibody to spike from vaccination is generally higher than from natural infection. A very high title of antibody to spike and a very low antibody to nucleocapsid suggest an infected individual who was vaccinated; 10) AstraZeneca confirms that the wide gap between the first dose and the second dose would yield a better antibody response; 10-12 weeks is recommended; 11) If anyone has been infected and lives in an epidemic area, they should be vaccinated 6 months after recovery; 12) The significance of a booster vaccination after the second dose has not been reported, but it is a possibility if the antibody titer decreases to a level lower than the protective level; and 13) COVID-19 vaccination is not recommended for pregnant women, but there is no need to test women for pregnancy before vaccination. In most cases, the benefits outweigh the risk from the vaccination.

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Roles and Challenges of Mathematical Modellers in the Era of Coronavirus Disease 2019 (COVID-19) Pandemic

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ABSTRACT

The emergence of Coronavirus Disease 2019 (COVID-19) creates huge opportunity for mathematical modellers to play a pivotal role in policy decision making towards pandemic suppression and containment. Modelling studies can serve as a tool to measure the impact of policies and identify leverage point where the policies will be most effective. Economic evaluation studies combined with epidemic modelling help gauge the economic impact of COVID-19 as well as the monetary benefit and payoff given various COVID-19 measures. The models can also project future end-game scenarios of the pandemic. The academic modellers mostly work with theory-driven research questions, while the service-oriented modellers usually deal with day-to-day operational questions and need to validate the findings against policy direction in equal importance with scientific validation. A platform to finetune diverse understandings and interests between policy-makers and modellers should be established.

Keywords: *Coronavirus disease 2019; Pandemic; Mathematical modellers; Challenges*

Contribution of modelling study in pandemic response

Since the advent of Coronavirus Disease 2019 (COVID-19), a number of mathematical modellers have used diverse techniques to assess the dynamics of disease transmission [1]. The modelling studies of COVID-19 pandemic gain much more substantial attention from the wider society (including, government, media and general population) than for any previous pandemic. This may be attributed to the dramatic impact of COVID-19 on almost all walks of life, and the world had little knowledge on the disease at the very beginning of the pandemic. At the same time, it means that the world is in dire need of research in all angles of COVID-19. This is the first time since the H1N1 influenza pandemic in 2009 when there is an unprecedented advancement in global communication and technical support in modelling studies on emerging diseases [2]. Novel model frameworks, improved computational techniques, public data sharing, improved code availability, better visualisation methods and integration of models across scientific paradigms are observed in the current scientific arena.

Policy-makers involve modellers in various steps of the policy process, though some models face considerable criticism and their limitations require serious acknowledgement [3,4]. A clear example can be noticed in the case of China where border-closure policy was strongly influenced by the modelling. Imai et al and De Salazar et al suggest that, during the early phase of the pandemic, the incidence rates were significantly under-reported both in and outside China [5] . China then imposed an internal travel lockdown on Wuhan in late January 2020 and many countries enacted the same mobility restrictions in the following months [6]. The modelling studies on COVID-19 appear in numerous forms. A systematic review on 242 peer-review articles related to COVID-19 demonstrate that about 46% of the papers used compartmental models, and 32% used time-series and growth models [1]. Few used novel analysis techniques, such as artificial intelligence (7%), Bayesian approach (5%) and agent-based models (1%) [1].

With respect to model application, the model projections based on viral infectiousness help demonstrate the pandemic potential, which can be used as a guidance for healthcare resource planning [7,8]. The models may serve as a tool to assess the impact of policies and address optimization problems like which policy is effective in which sub-population by what approaches.

The economic evaluation studies combined with epidemic modelling help gauge the economic consequences of COVID-19 and the monetary benefit

(or payoff) for each measure. Ultimately, the models can project future end-game scenarios and address certain key policy questions, for instance, whether, how, and when suppression can be achieved [9,10].

Platform where modellers interact with policy-makers

The interaction between policy-makers and modellers is highly dynamic. At one end, some mathematical modellers who are not part of the state authorities start a direct communication with the wider public through academic publications or media campaign. Once their findings are 'bought-in' by the public then they become a key input for policy decision.

The majority of these 'academic modellers' work in educational institutes which, literally, are not always part of the bureaucracy. Often, these modellers worked with theory-driven research questions via a relatively 'clean' secondary dataset. A scientific validation is the foremost concern of the analyses. A prominent example of academic modellers is a team by Imperial College London, which heralded the widespread of disease across UK and US if a suppression strategy to hammer reproduction number down to below one was not pursued [8].

Some renowned academic institutes commissioned groups of modelling experts to address a vast range of questions, and sometimes these questions lie beyond a single country concern. Another obvious example is 'The Lancet COVID-19 Commission' [11] and 'COVID-19 International Modelling Consortium [CoMo Consortium] by University of Oxford and Cornell University' [12]. The function of these initiatives is greatly diverse, from descriptive monitoring of the global progress to addressing complicated multi-faceted issues (such as genomic epidemiology, health-systems preparedness and political economy of the pandemic) [12].

At the other end, there are mathematical modellers who are part of the bureaucracy, namely, 'service-oriented modeller'. Oftentimes, the state authorities, like the Ministry of Public Health, or even the Cabinet itself, set up groups of experienced technocrats and official public health specialists to work on mathematical models to respond to the pandemic.

Some key differences between service-oriented modellers and academic modellers are presented in Table 1. While academic modellers are mostly engaged with theory-driven questions, service-oriented modellers are basically influenced by policy directions and field implementation in practicality. Additionally, service-oriented modellers may have more advantages than academic modellers in terms of data accessibility in a timelier manner despite the fact that these data are not often well organised and sometimes subject to measurement error. However, the distinction between academic modellers and service-oriented modellers is just a fine line and some modellers play a dual role from time to time.

Challenges of how modelling studies can be injected in policy decision making

The inconvenient truths faced by all modellers are 'no model is perfect' and 'no model can address all policy questions.' In addition, not all the time, policy-makers make a decision based on evidence generated by the models. This situation happens partly because

Table 1 Key differences between academic modellers and service-oriented modellers

Characteristics	Academic modellers	Service-oriented modellers
Institution of modellers	- Mostly academic institutes (universities or research entities)	- Mostly government authorities (such as the Cabinet and the Ministry of Public Health)
Data involved	- Clean and structured but less timely - Accessed via public domains	- Timely but not well organized and often with higher inaccuracy - Accessed via internal database of the authorities
Model questions	Theory driven	Operation driven or policy driven
Model validation	Focusing on more complete scientific validation, based on external reliable data and less relying on expert opinion	Focusing on policy validation based on expert opinion and available data while keeping acceptable scientific rigour
Finding dissemination	-Research reports or academic journal -Direct communication with media	-Internal reports of the authorities -Direct communication with high-level officials or policy-makers

there are numerous contextual environments affecting policy decision, which cannot be captured by conventional mathematical parameters. The challenge herewith is how the modellers translate those influences into mathematical parameters and plug them into the model. This approach makes the model more comprehensive but the modellers need to spend a payoff with enhanced computational burden and risk of losing interpretation power.

Another key challenge is the policy question is not always well set from the outset, but policy-makers demand for mathematical models to initiate the policy direction. Such a situation contradicts conventional approach of the modellers where the work is usually commenced only once the research question is well-established.

Therefore, it is crucial to have a platform or process to finetune diverse understanding and interest of between policy-makers and the modellers. This process should be able to translate and tailor policy-makers' need while accounting for model feasibility; and the scientists (or the modellers) may contribute to the process by providing input or proposing better-specified objectives or modified interventions (raised previously by policy-makers) to the platform. To do so, a method for harnessing the collective knowledge of all concerned parties beyond policy-makers' and modellers' sphere is demanded [13]. This era, when the COVID-19 pandemic is still ongoing, is an opportune period to establish the aforementioned work platform; and if it is successful, the world will be better prepared for any emerging diseases or future unexpected health threats.

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Burden and Factors Associated with Hypertension Among the Adult Population of the Lisu Hill Tribe, Northern Thailand

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ABSTRACT

Introduction: Hypertension (HT) is a serious silent disease that can lead to difficult complications, particularly in individuals living with unhealthy behaviors and those with poor socioeconomic status. The Lisu hill tribe in Thailand is vulnerable to HT due to their poor socioeconomic status. **Objective:** This study aimed to estimate the magnitude of HT and identify the factors associated with HT among the Lahu hill tribe population aged 30 years and over in Thailand. **Methods:** A cross-sectional study was conducted with the aim of assessing several factors relevant to the sociodemographic and health behaviors of participants, including the assessment of HT using a validated questionnaire and a manual sphygmomanometer. Five of the 35 Lisu hill tribe villages in the Chiang Rai province were randomly selected. All the individuals in selected villages aged 30 years and over were invited to provide the information after obtaining a written informed consent on voluntary basis. A 5 mL blood specimen was collected for testing lipid profiles. Logistic regression was used to detect the associations at a significance level of α=0.05. **Results:** A total of 282 participants were recruited in the study; 61.3% were women and 69.5% were aged between 40 and 69 years. Most participants were married (78.4%), and never attended a school (74.0%), and Buddhist (72.7%). A large proportion of participants was working as farmers (57.4%); 70.9% had an income of less than 50,000 baht (1,515 USD) per year per family, and 22.0% reported having family debt. The overall prevalence of HT was 31.6%. After controlling for age, sex, marital status, and religion in the multivariable model, two factors were found to be associated with HT among the Lisu adult population in Thailand. Participants who reported using a low volume of monosodium glutamate were more likely to have HT than those who reported a high volume (AOR=2.87; 95%CI=1.35–6.12) and those who had normal levels of triglycerides were more likely to have HT than those who had high triglycerides (AOR=2.05; 95%CI=1.18–3.54). **Conclusion:** The Lisu people in Thailand are living in a poor economic situation, have low education level, and mainly work in the agricultural sector. A large proportion of people suffer from HT; therefore, an effective public health program to improve health behaviors and adjusting their cooking practices could lead to a reduction in the burden of HT particularly in providing them a valid medical advice to use appropriate volume of monosodium glutamate and cooking oil in their daily life.

Keywords: *Burden; Factors associated; Hypertension; Lisu; Hill tribe*

Introduction

Hypertension (HT) is one of the greatest health problems and is considered as a major threat for non-communicable diseases (NCD) for people worldwide. It could lead to several health problems, such as heart, brain, and kidney diseases [1]. The major critical points of HT effective care and treatment are early detection among people who are in the asymptomatic stage and maintaining the blood pressure at an acceptable level after treatment [2]. These points will directly support the reduction of complications from the disease [3], which could reduce the quality of life among people with severe complications from the pathogenesis [4]. Therefore, early detection and treatment would be a better recommendation, particularly for people who belong to a vulnerable or risk population, such as those

aged 30 years and over [5]. However, identifying the risk factors or influencing factors of HT in a certain population and designing a proper public health intervention should be the advanced measures to minimize utilizing resources including live and economic loss, and to improve well-being eventually [6].

In 2019, the World Health Organization (WHO) estimated that 1.13 billion people worldwide had HT, and two-thirds lived in low-and middle-income countries [1]. HT has been recognized as a major cause of premature death worldwide and is attributed to 25.0% of all NCDs among the adult population [1]. In 2019, the Ministry of Public Health Thailand reported that a population of approximately 6 million Thai developed HT, and only half of them were properly diagnosed [7]. Thailand needs all medication expenses of 80,000 baht for 10 million individuals with HT, which is a large burden for the national health system [8]. The definition of HT is clearly defined by the WHO, as a measure of blood pressure in individuals for 2 days and having a systolic blood pressure reading on both days equal to or greater than 140 mmHg, and/or the diastolic blood pressure reading on both days equal to or more than 90 mmHg [1]. Several risk factors have been clearly identified in different populations, such as older age [9], high BMI [10], salty dietary intake including monosodium glutamte [11], serum lipid [12], smoking [13], and living in a rural area [14]. People who are living in poor socioeconomic status are much more vulnerable to HT [15].

Lisu is one of the hill tribes in Thailand with a population of approximately 30,000 living in 35 villages in the Chiang Rai province, Thailand [16]. The Lisu have their own language and practices according to their culture, including cooking practices. The majority of the Lisu in Thailand are living in low socioeconomic status and working in the agricultural sector. More than half of the Lisu are unable to use Thai fluently, which is the main barrier to receiving essential health information from government agencies in Thailand, which uses Thai for all communications. Moreover, a large proportion of the Lisu people are living in a very rural area of northern Thailand, particularly in the border areas of Thailand and Myanmar.

Therefore, this study aimed to estimate the magnitude and determine the factors associated with HT among the Lisu adult population aged 30 years and over living in Thailand.

Methods

A cross-sectional study design was used to collect essential information from participants from the Lisu hill tribe living in the Chiang Rai province, Thailand. The study settings were the Lisu villages which were randomly selected for five of 35 Lisu villages in the Chiang Rai province. Individuals living in five Lisu villages and aged 30 years and over were invited to participate in the study between November 2018 and June 2019.

The sample size was calculated using the standard method [17] for a cross-sectional design, with p=0.22 [18], q=0.78, and e=0.05; therefore, 265 participants were required for the analysis.

A questionnaire was developed by reviewing the literature on different sources of information. All questions developed detected its validity and reliability in a small group of people (20 people) who had similar characteristics with the targeted population of the study in Mae Fah Laung District, Chiang Rai province, Thailand, with the overall Cronbach's alpha of 0.73. Eventually, a set of questions was ready for data collection, which consisted of four sections. In Section No.1, seven questions were used to collect the demographic characteristics of the participants. In Section No.2, sixteen questions were used to analyze the daily health behaviors that were relevant to HT. In Section No.3, 20 questions were used to assess the knowledge and attitude toward HT prevention and control. In Section No.4, four blank open questions were provided for filling laboratory information, such as lipid profiles, HbA1c levels, and blood pressure.

In this study, stress was assessed by the standard tool, the stress test-5 questions. It was developed by the Department of Mental Health, Thailand, composed of five questions, with four ranked response options for each item (0–3) [19]. The body mass index (BMI) was classified into three categories: underweight (≤18.5 kg/m2), normal (18.51–22.99 kg/m2), and overweight (≥23.0 kg/m2) [20]. The waistline for men was classified into two groups; normal (<90 cm) and over standard (≥90 cm); and two groups were classified in women, normal (<80 cm) and over standard (≥80 cm) [21]. With respect to the male-waist-to-hip ratio, two groups were categorized as: normal (≤0.90) and obese (>0.90), while in among the women, two groups were classified: normal (≤0.85) and obese (>0.85) [21]. Two groups were categorized for values of total cholesterol: normal (≤199 mg/dL) and high (≥200 mg/dL) [22]. With respect to high-density lipoprotein (HDL) cholesterol, two groups were categorized for men: low (<40 mg/dL) and normal (≥40 mg/dL). Additionally, two groups were categorized for females: low (< 50 mg/dL) and normal (≥50 mg/dL) [22]. With respect to the low-density lipoprotein (LDL) cholesterol, two groups were categorized: normal (<100 mg/dL) and high (≥100 mg/dL) [22]. Two groups for triglycerides level were classified: normal (≤149 mg/dL) and high (≥150 mg/dL) [22]. Glycated hemoglobin (HbA1c) values were classified into three categories: normal (<6.0), prediabetes (6.0–6.4), and diabetes (≥6.5) [23]. The identification of HT followed the definition of the WHO guideline, as mentioned earlier [1].

All selected village headmen were contacted after obtaining permission from the local government. They were informed of all essential information regarding

the study and the inclusion and exclusion criteria for the eligible population for the study. Those who met the eligibility criteria for the study were requested to not consume food and drink for at least 12 h before the collection of the 5 mL blood specimen. On the day of data collection, all participants were double-checked to ensure that everyone was eligible for the study. Written informed consent was obtained after given the details regarding the study. The interview lasted for 20 min each.

The questionnaires were converted into a code and entered into an Excel sheet before being transferred into the R program for analysis. A descriptive analysis was performed to present the characteristics of participants in terms of mean and SD for continuous data, while percentages were presented for categorical data. Logistic regression was used to identify the factors associated with HT with different levels of significance for the univariable (α=0.20) and multivariable (α=0.05) analyses.

Ethical consideration

All the study protocols were by the Mae Fah Luang University Research Ethic Committee on Human Research (No. REH-6100). Before starting interview, all participants were provided all relevant and essential information, and a written inform consent form was obtained in all participants before starting interview.

Results

A total of 282 participants were recruited in the study; 61.3% were women, 78.4% were married, and 69.5% were aged between 40 and 69 years. Most participants were uneducated (74.0%), Buddhist (72.7%), and farmers (57.4%) and had a family income

Table 1 Univariable and multivariable analyses in identifying factors associated with HT among Lisu adult populations

Factor	Total (%)	HT		OR	95%CI	p-value	AOR	95%CI	p-value
		Yes (%)	No (%)						
Total	**282 (100.0)**	**89 (31.6)**	**193 (68.4)**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Sex									
Male	109 (38.7)	33 (30.3)	76 (69.7)	1.00					
Female	173 (61.3)	56 (32.4)	117 (67.6)	1.10	0.66-1.85	0.712			
Age (years)									
30-39	46 (16.3)	14 (30.4)	32 (69.6)	1.00					
40-49	61 (21.6)	21 (34.4)	40 (65.6)	1.20	0.53-2.73	0.663			
50-59	69 (24.5)	22 (31.9)	47 (68.1)	1.07	0.48-2.40	0.870			
60-69	66 (23.4)	21 (31.8)	45 (68.2)	1.07	0.47-2.41	0.877			
70-79	33 (11.7)	9 (27.3)	24 (72.7)	0.86	0.32-2.31	0.760			
≥ 80	7 (2.5)	2 (28.6)	5 (71.4)	0.91	0.16-5.29	0.920			
Marital status									
Single	9 (3.2)	2 (22.2)	7 (77.8)	1.00					
Married	221 (78.4)	68 (30.8)	153 (69.2)	1.56	0.32-7.68	0.588			
Other	52 (18.4)	19 (36.5)	33 (63.5)	2.02	0.38-10.70	0.411			
Education									
No	209 (74.0)	66 (31.6)	143 (68.4)	1.00	0.57-1.78	0.991			
Yes	73 (26.0)	23 (31.5)	50 (68.5)	1.00					
Religion									
Buddhism	205 (72.7)	61 (29.8)	144 (70.2)	1.00					
Other (Christianity and Islam)	77 (27.3)	28 (36.4)	49 (63.6)	1.35	0.78-2.34	0.288			
Occupation									
Unemployed	70 (24.8)	19 (27.1)	51 (72.9)	1.00					
Agriculturalist	162 (57.4)	57 (35.2)	105 (64.8)	1.46	0.79-2.70	0.232			
Other	50 (17.7)	13 (26.0)	37 (74.0)	0.94	0.41-2.15	0.889			
Income per family per year (baht)									
≤ 50,000	200 (70.9)	60 (30.0)	140 (70.0)	1.00					
50,001-100,000	68 (24.1)	24 (35.3)	44 (64.7)	1.27	0.71-2.28	0.417			
≥ 100,001	14 (5.0)	5 (35.7)	9 (64.3)	1.30	0.42-4.03	0.654			
Family debt									
No	220 (78.0)	72 (32.7)	148 (67.3)	1.29	0.69-2.41	0.428			
Yes	62 (22.0)	17 (27.4)	45 (72.6)	1.00					
Family member (person)									
0-4	149 (52.8)	53 (35.6)	96 (64.4)	4.97	1.11-22.24	0.036*			
5-8	113 (40.1)	34 (30.1)	79 (69.9)	3.87	0.85-17.63	0.080*			
≤ 9	20 (7.1)	2 (10.0)	18 (90.0)	1.00					

Table 1 Univariable and multivariable analyses in identifying factors associated with HT among Lisu adult populations (cont.)

Factor	Total (%)	HT		OR	95%CI	p-value	AOR	95%CI	p-value
		Yes (%)	No (%)						
Father's history of HT									
No	161 (59.2)	55 (34.2)	106 (65.8)	1.32	0.77-2.26	0.306			
Yes	14 (5.0)	3 (21.4)	11 (78.6)	0.71	0.22-2.35	0.579			
Unknown	107 (37.9)	31 (29.0)	76 (71.0)	1.00					
Mother's history of HT									
No	167 (59.2)	56 (33.5)	111 (66.5)	1.18	0.69-2.04	0.549			
Yes	12 (4.3)	3 (25.0)	9 (75.0)	2.32	0.89-6.05	0.085*			
Unknown	103 (36.5)	30 (29.1)	73 (70.9)	1.00					
Stress (ST-5)									
Low	238 (84.4)	72 (30.3)	166 (68.7)	1.00					
Moderate	38 (13.5)	13 (34.2)	25 (65.8)	1.20	0.58-2.48	0.624			
High	6 (2.1)	4 (66.7)	2 (33.3)	4.61	0.83-25.75	0.082*			
Exercise									
No	152 (53.9)	47 (30.9)	105 (69.1)	0.97	0.45-2.09	0.938			
Sometimes	92 (32.6)	30 (32.6)	62 (67.4)	1.05	0.47-2.36	0.909			
Everyday	38 (13.5)	12 (31.6)	26 (68.4)	1.00					
Smoking									
No	195 (69.1)	66 (33.8)	129 (66.2)	1.00					
Yes	87 (30.9)	23 (26.4)	64 (73.6)	0.70	0.40-1.23	0.217			
Alcohol use									
No	208 (73.8)	68 (32.7)	140 (67.3)	1.00					
Yes	74 (26.2)	21 (28.4)	53 (71.6)	0.82	0.46-1.46	0.493			
Salt in daily cooking									
Low	40 (14.2)	18 (45.0)	22 (55.0)	2.16	1.00-4.69	0.051*			
Moderate	151 (53.5)	46 (30.5)	105 (69.5)	1.16	0.65-2.06	0.621			
High	91 (32.3)	25 (27.5)	66 (72.5)	1.00					
Monosodium glutamate in daily cooking									
Low	44 (15.6)	24 (54.5)	20 (45.5)	3.10	1.49-6.45	0.002*	2.87	1.35-6.12	0.006**
Moderate	134 (47.5)	36 (26.9)	98 (73.1)	0.95	0.54-1.69	0.861	0.86	0.47-1.58	0.631
High	104 (36.9)	29 (27.9)	75 (72.1)	1.00			1.00		
Cooking oil									
Low	49 (17.4)	24 (49.0)	25 (51.0)	2.45	1.14-5.25	0.021*			
Moderate	162 (57.4)	45 (27.8)	117 (72.2)	0.98	0.53-1.83	0.951			
High	71 (25.2)	20 (28.2)	15 (71.8)	1.00					
Knowledge of HT prevention and control									
Low	154 (54.6)	42 (27.3)	112 (72.7)	1.00					
Moderate	61 (21.6)	21 (34.4)	40 (65.6)	1.40	0.74-2.65	0.300			
High	67 (23.8)	26 (38.8)	41 (61.2)	1.69	0.92-3.10	0.089*			
Attitudes toward HT prevention and control									
Negative	210 (74.5)	65 (31.0)	145 (69.0)	1.00					
Neutral	56 (19.9)	19 (33.9)	37 (66.1)	1.15	0.62-2.14	0.670			
Positive	16 (5.7)	5 (31.3)	11 (68.8)	1.01	0.34-3.04	0.980			
Body mass index (BMI)									
Normal	94 (33.3)	31 (33.0)	63 (67.0)	1.00					
Underweight	20 (7.1)	3 (15.0)	17 (85.0)	0.36	0.10-1.32	0.122*			
Overweight	168 (59.7)	55 (32.7)	113 (67.3)	0.99	0.58-1.69	0.968			
Waistline									
Normal	138 (48.9)	41 (29.7)	97 (70.3)	1.00					
Risk for metabolic complication	144 (51.1)	48 (33.3)	96 (66.7)	1.18	0.72-1.96	0.513			
Waist-to-hip ratio									
Normal	157 (55.7)	47 (29.9)	110 (70.1)	1.00					
Risk	125 (44.3)	42 (33.6)	83 (66.4)	1.18	0.72-1.96	0.511			
Total cholesterol									
Normal	176 (62.4)	58 (33.0)	118 (67.0)	1.00					
High	106 (37.6)	31 (29.2)	75 (70.8)	0.84	0.50-1.42	0.516			
Triglycerides									
Normal	162 (57.4)	61 (37.7)	101 (62.3)	1.98	1.17-3.37	0.011*	2.05	1.18-3.54	0.010**
High	120 (42.6)	28 (23.3)	92 (76.7)	1.00			1.00		
HDL cholesterol									
Low	154 (54.6)	47 (30.5)	107 (69.5)	0.90	0.54-1.49	0.680			
Normal	128 (45.4)	42 (32.8)	86 (67.2)	1.00					
LDL cholesterol									
Normal	92 (32.6)	27 (29.3)	65 (70.7)	1.00					
High	190 (67.4)	62 (32.6)	128 (67.4)	1.17	0.68-2.00	0.578			

*Significant level at α=0.20, and **Significant level at α=0.05

equal to or less than 50,000 baht per year (70.9%) (Table 1).

The prevalence of HT among the participants was 31.6% (89 of 282). Among 89 HT cases, 82 (92.1%) were on treatment at the date of data collection, and 7 (7.9%) cases were newly identified. Women (32.4%) had a higher prevalence than males (30.3%). The prevalence was observed to decrease with the increase of age; however, it was not different between those who had attended a school and those did not (Table 1).

A large proportion reported alcohol use (26.2%), smoking (30.9%), moderate to high salt use in their daily cooking practice (85.8%), moderate-to-high monosodium glutamate use in their daily cooking practice (84.4%), and moderate-to-high use of cooking oil in their daily cooking practice (82.6%) (Table 1).

Using ST-5 to assess the stress, 15.6% participants had moderate to high stress, 54.6% participants had a low level of knowledge of HT prevention and control, and 74.5% participants had negative attitude on HT prevention and control (Table 1).

More than half of the participants were overweight based on BMI assessment (59.7%), 44.3% participants were categorized into the risk group based on the waist-to-hip ratio, and 51.1% participants were observed to be at risk for metabolic complications based on the waistline assessment (Table 1).

High total cholesterol was detected in 106 participants (37.6%); 42.6% had high triglycerides, and 67.4% had high LDL cholesterol (Table 1).

In the univariable analysis, eight factors were found to be associated with HT: number of family members, mother's history of HT, BMI, salt use in daily cooking practice, monosodium use in daily cooking practice, stress, knowledge of HT prevention and control, and triglyceride level (Table 1). However, after controlling for age, sex, marital status, and religion in the multivariable model, two factors were found to be associated with HT among the Lisu adult population in Thailand. Those who reported using a low volume of monosodium glutamate were more likely to have HT than those who reported a high volume (AOR=2.87; 95%CI=1.35–6.12), and those who had normal levels of triglycerides were more likely to have HT than those who had high triglycerides (AOR=2.05; 95%CI=1.18–3.54).

Discussion

Under the living circumstances of the Lisu hill tribe people in Thailand, a large proportion of individuals were suffering from HT. More than half of the people aged 30 years and over never attended a school and worked on traditional farms with low incomes. Smoking and alcohol use were common, particularly in men. The heavy use of salt, monosodium glutamate, and cooking oil for their daily cooking practice, including having low knowledge and negative attitude toward HT prevention and control were observed. More than half of the participants had overweight and high lipid levels. However, it was notable that those who reported using low levels of monosodium glutamate and normal triglyceride levels were more likely to have HT than those who reported using a high volume of monosodium glutamate and high triglyceride, respectively.

In our study, it was found that the prevalence of HT was 31.6% (89 of 282 participants); 82 (92.1%) cases were on treatment at the date of data collection, and 7 (7.9%) cases were newly identified. The prevalence of HT between sex and different age groups was not statistically different. The prevalence among the adult multi-ethnic population in China was also closely reported as in this study, which was 29.5 [24]. However, the report of the prevalence of HT among the people aged 35 years and over in Nepal from the national survey reported it to be between 20.8–41.7%; additionally, the prevalence increased with an increase in age [15], in contrast to our study where the prevalence decreased with an increase in age. A study among the hill tribe elderly aged 60 years and over in Thailand reported that the prevalence of HT was 45.5% [25], while in our study, 27.3–31.8% were found among the Lisu aged 60 years and above. This might be the impact of a large proportion of the Lisu people who intended to check their HT status from health professionals and know their HT status. However, the prevalence among Thai adult populations has been reported to be 22.1% [18], which is significantly lower than the hill tribe adult population.

Some factors were found to be associated with HT among the Lisu hill tribe adult population in the univariable analysis at a significance level of α=0.20, such as number of family members, mother's history of HT, BMI, salt use in daily cooking practice, monosodium use in daily cooking practice, stress, knowledge of HT prevention and control, and triglyceride level. However, these factors were not found to be significantly associated with HT in the multivariable analysis. It may be necessary to increase the sample size and also requires stronger study design to assess the associations such as case-control or cohort study.

In our study, it was found that those people who reported using a low volume of monosodium glutamate for cooking were more likely to have HT than those who reported use of a high volume of monosodium glutamate. This might be the negative impact of conducting a cross-sectional study, in which most of the HT among the Lisu had been diagnosed and treated. Subsequently, the association could be found in the opposite relationship because the majority of HT patients used a low volume of monosodium glutamate after receiving medical advice for reducing the risk factor from health professionals. However, the relationships between using a high volume of monosodium glutamate and HT development has been reported in several studies [26–28].

Only triglycerides among serum lipids were found to be associated with HT among the hill tribe adult population in Thailand. However, the association was found in the opposite association; those who had normal triglyceride levels were more likely to have HT than those with high TG levels. This might be the negative impact of a cross-sectional study, particularly among the Lisu people in Thailand. The majority of Lisu adults who have HT have known their HT status and treatment. Therefore, it is highly possible that those who know their HT statuses are under control of their dietary habits and are having normal levels of triglycerides. Normally, several studies have reported the association between high serum triglyceride levels and HT in different populations and countries [29–31].

There are several limitations in this study. First, some questions, particularly asking about the volume use of sodium, monosodium glutamate, and cooking oil, were impractical because most of the participants' responses were based on their perception. This might have interfered with the analysis in the final step. Second, it was difficult to make the participants understand the questions with respect to knowledge and attitude in a clear manner and obtain valid responses due to the poor education level of the participants. However, in this study, researchers optimized the way to obtain the most validated answers by repeating their understanding on the certain question before providing the answer. A few people reported that they did not clearly follow the instructions of no food and drink 12 h before collecting blood specimens. However, during the analysis, those specimens showed inappropriate for laboratory work and were excluded from the analysis. Finally, with the limitations of a cross-sectional study, some associations did not follow expectations, such as a low use of monosodium glutamate was found to be associated with HT, which might be because participants who obtained a diagnosis of HT previously (92.1%) were using low monosodium glutamate after receiving advice from health professionals.

Conclusions

The population of the Lisu hill tribe in Thailand lives in an illiterate manner and in a poor economic status. Substance use is common. A large proportion of them use high volumes of salt, monosodium glutamate, and cooking oil in their daily cooking practices. The majority of the Lisu people have BMI above the normal range and high serum lipid levels. One-third of the population was observed to have HT, and high levels of monosodium glutamate and triglycerides are factors associated with HT among the adult Lisu population in Thailand. However, further strong study design is suggested to perform to confirm the associations such as a case-control study.

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Burden and Factors Associated with Hypertension Among the Adult Population of the Lisu Hill Tribe, Northern Thailand

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ABSTRACT

Introduction: Hypertension (HT) is a serious silent disease that can lead to difficult complications, particularly in individuals living with unhealthy behaviors and those with poor socioeconomic status. The Lisu hill tribe in Thailand is vulnerable to HT due to their poor socioeconomic status. **Objective:** This study aimed to estimate the magnitude of HT and identify the factors associated with HT among the Lahu hill tribe population aged 30 years and over in Thailand. **Methods:** A cross-sectional study was conducted with the aim of assessing several factors relevant to the sociodemographic and health behaviors of participants, including the assessment of HT using a validated questionnaire and a manual sphygmomanometer. Five of the 35 Lisu hill tribe villages in the Chiang Rai province were randomly selected. All the individuals in selected villages aged 30 years and over were invited to provide the information after obtaining a written informed consent on voluntary basis. A 5 mL blood specimen was collected for testing lipid profiles. Logistic regression was used to detect the associations at a significance level of α=0.05. **Results:** A total of 282 participants were recruited in the study; 61.3% were women and 69.5% were aged between 40 and 69 years. Most participants were married (78.4%), and never attended a school (74.0%), and Buddhist (72.7%). A large proportion of participants was working as farmers (57.4%); 70.9% had an income of less than 50,000 baht (1,515 USD) per year per family, and 22.0% reported having family debt. The overall prevalence of HT was 31.6%. After controlling for age, sex, marital status, and religion in the multivariable model, two factors were found to be associated with HT among the Lisu adult population in Thailand. Participants who reported using a low volume of monosodium glutamate were more likely to have HT than those who reported a high volume (AOR=2.87; 95%CI=1.35–6.12) and those who had normal levels of triglycerides were more likely to have HT than those who had high triglycerides (AOR=2.05; 95%CI=1.18–3.54). **Conclusion:** The Lisu people in Thailand are living in a poor economic situation, have low education level, and mainly work in the agricultural sector. A large proportion of people suffer from HT; therefore, an effective public health program to improve health behaviors and adjusting their cooking practices could lead to a reduction in the burden of HT particularly in providing them a valid medical advice to use appropriate volume of monosodium glutamate and cooking oil in their daily life.

Keywords: *Burden; Factors associated; Hypertension; Lisu; Hill tribe*

Introduction

Hypertension (HT) is one of the greatest health problems and is considered as a major threat for non-communicable diseases (NCD) for people worldwide. It could lead to several health problems, such as heart, brain, and kidney diseases [1]. The major critical points of HT effective care and treatment are early detection among people who are in the asymptomatic stage and maintaining the blood pressure at an acceptable level after treatment [2]. These points will directly support the reduction of complications from the disease [3], which could reduce the quality of life among people with severe complications from the pathogenesis [4]. Therefore, early detection and treatment would be a better recommendation, particularly for people who belong to a vulnerable or risk population, such as those

aged 30 years and over [5]. However, identifying the risk factors or influencing factors of HT in a certain population and designing a proper public health intervention should be the advanced measures to minimize utilizing resources including live and economic loss, and to improve well-being eventually [6].

In 2019, the World Health Organization (WHO) estimated that 1.13 billion people worldwide had HT, and two-thirds lived in low-and middle-income countries [1]. HT has been recognized as a major cause of premature death worldwide and is attributed to 25.0% of all NCDs among the adult population [1]. In 2019, the Ministry of Public Health Thailand reported that a population of approximately 6 million Thai developed HT, and only half of them were properly diagnosed [7]. Thailand needs all medication expenses of 80,000 baht for 10 million individuals with HT, which is a large burden for the national health system [8]. The definition of HT is clearly defined by the WHO, as a measure of blood pressure in individuals for 2 days and having a systolic blood pressure reading on both days equal to or greater than 140 mmHg, and/or the diastolic blood pressure reading on both days equal to or more than 90 mmHg [1]. Several risk factors have been clearly identified in different populations, such as older age [9], high BMI [10], salty dietary intake including monosodium glutamte [11], serum lipid [12], smoking [13], and living in a rural area [14]. People who are living in poor socioeconomic status are much more vulnerable to HT [15].

Lisu is one of the hill tribes in Thailand with a population of approximately 30,000 living in 35 villages in the Chiang Rai province, Thailand [16]. The Lisu have their own language and practices according to their culture, including cooking practices. The majority of the Lisu in Thailand are living in low socioeconomic status and working in the agricultural sector. More than half of the Lisu are unable to use Thai fluently, which is the main barrier to receiving essential health information from government agencies in Thailand, which uses Thai for all communications. Moreover, a large proportion of the Lisu people are living in a very rural area of northern Thailand, particularly in the border areas of Thailand and Myanmar.

Therefore, this study aimed to estimate the magnitude and determine the factors associated with HT among the Lisu adult population aged 30 years and over living in Thailand.

Methods

A cross-sectional study design was used to collect essential information from participants from the Lisu hill tribe living in the Chiang Rai province, Thailand. The study settings were the Lisu villages which were randomly selected for five of 35 Lisu villages in the Chiang Rai province. Individuals living in five Lisu villages and aged 30 years and over were invited to participate in the study between November 2018 and June 2019.

The sample size was calculated using the standard method [17] for a cross-sectional design, with p=0.22 [18], q=0.78, and e=0.05; therefore, 265 participants were required for the analysis.

A questionnaire was developed by reviewing the literature on different sources of information. All questions developed detected its validity and reliability in a small group of people (20 people) who had similar characteristics with the targeted population of the study in Mae Fah Laung District, Chiang Rai province, Thailand, with the overall Cronbach's alpha of 0.73. Eventually, a set of questions was ready for data collection, which consisted of four sections. In Section No.1, seven questions were used to collect the demographic characteristics of the participants. In Section No.2, sixteen questions were used to analyze the daily health behaviors that were relevant to HT. In Section No.3, 20 questions were used to assess the knowledge and attitude toward HT prevention and control. In Section No.4, four blank open questions were provided for filling laboratory information, such as lipid profiles, HbA1c levels, and blood pressure.

In this study, stress was assessed by the standard tool, the stress test-5 questions. It was developed by the Department of Mental Health, Thailand, composed of five questions, with four ranked response options for each item (0–3) [19]. The body mass index (BMI) was classified into three categories: underweight (≤18.5 kg/m2), normal (18.51–22.99 kg/m2), and overweight (≥23.0 kg/m2) [20]. The waistline for men was classified into two groups; normal (<90 cm) and over standard (≥90 cm); and two groups were classified in women, normal (<80 cm) and over standard (≥80 cm) [21]. With respect to the male-waist-to-hip ratio, two groups were categorized as: normal (≤0.90) and obese (>0.90), while in among the women, two groups were classified: normal (≤0.85) and obese (>0.85) [21]. Two groups were categorized for values of total cholesterol: normal (≤199 mg/dL) and high (≥200 mg/dL) [22]. With respect to high-density lipoprotein (HDL) cholesterol, two groups were categorized for men: low (<40 mg/dL) and normal (≥40 mg/dL). Additionally, two groups were categorized for females: low (< 50 mg/dL) and normal (≥50 mg/dL) [22]. With respect to the low-density lipoprotein (LDL) cholesterol, two groups were categorized: normal (<100 mg/dL) and high (≥100 mg/dL) [22]. Two groups for triglycerides level were classified: normal (≤149 mg/dL) and high (≥150 mg/dL) [22]. Glycated hemoglobin (HbA1c) values were classified into three categories: normal (<6.0), prediabetes (6.0–6.4), and diabetes (≥6.5) [23]. The identification of HT followed the definition of the WHO guideline, as mentioned earlier [1].

All selected village headmen were contacted after obtaining permission from the local government. They were informed of all essential information regarding

the study and the inclusion and exclusion criteria for the eligible population for the study. Those who met the eligibility criteria for the study were requested to not consume food and drink for at least 12 h before the collection of the 5 mL blood specimen. On the day of data collection, all participants were double-checked to ensure that everyone was eligible for the study. Written informed consent was obtained after given the details regarding the study. The interview lasted for 20 min each.

The questionnaires were converted into a code and entered into an Excel sheet before being transferred into the R program for analysis. A descriptive analysis was performed to present the characteristics of participants in terms of mean and SD for continuous data, while percentages were presented for categorical data. Logistic regression was used to identify the factors associated with HT with different levels of significance for the univariable (α=0.20) and multivariable (α=0.05) analyses.

Ethical consideration

All the study protocols were by the Mae Fah Luang University Research Ethic Committee on Human Research (No. REH-6100). Before starting interview, all participants were provided all relevant and essential information, and a written inform consent form was obtained in all participants before starting interview.

Results

A total of 282 participants were recruited in the study; 61.3% were women, 78.4% were married, and 69.5% were aged between 40 and 69 years. Most participants were uneducated (74.0%), Buddhist (72.7%), and farmers (57.4%) and had a family income

Table 1 Univariable and multivariable analyses in identifying factors associated with HT among Lisu adult populations

Factor	Total (%)	HT		OR	95%CI	p-value	AOR	95%CI	p-value
		Yes (%)	No (%)						
Total	**282 (100.0)**	**89 (31.6)**	**193 (68.4)**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Sex									
Male	109 (38.7)	33 (30.3)	76 (69.7)	1.00					
Female	173 (61.3)	56 (32.4)	117 (67.6)	1.10	0.66-1.85	0.712			
Age (years)									
30-39	46 (16.3)	14 (30.4)	32 (69.6)	1.00					
40-49	61 (21.6)	21 (34.4)	40 (65.6)	1.20	0.53-2.73	0.663			
50-59	69 (24.5)	22 (31.9)	47 (68.1)	1.07	0.48-2.40	0.870			
60-69	66 (23.4)	21 (31.8)	45 (68.2)	1.07	0.47-2.41	0.877			
70-79	33 (11.7)	9 (27.3)	24 (72.7)	0.86	0.32-2.31	0.760			
≥ 80	7 (2.5)	2 (28.6)	5 (71.4)	0.91	0.16-5.29	0.920			
Marital status									
Single	9 (3.2)	2 (22.2)	7 (77.8)	1.00					
Married	221 (78.4)	68 (30.8)	153 (69.2)	1.56	0.32-7.68	0.588			
Other	52 (18.4)	19 (36.5)	33 (63.5)	2.02	0.38-10.70	0.411			
Education									
No	209 (74.0)	66 (31.6)	143 (68.4)	1.00	0.57-1.78	0.991			
Yes	73 (26.0)	23 (31.5)	50 (68.5)	1.00					
Religion									
Buddhism	205 (72.7)	61 (29.8)	144 (70.2)	1.00					
Other (Christianity and Islam)	77 (27.3)	28 (36.4)	49 (63.6)	1.35	0.78-2.34	0.288			
Occupation									
Unemployed	70 (24.8)	19 (27.1)	51 (72.9)	1.00					
Agriculturalist	162 (57.4)	57 (35.2)	105 (64.8)	1.46	0.79-2.70	0.232			
Other	50 (17.7)	13 (26.0)	37 (74.0)	0.94	0.41-2.15	0.889			
Income per family per year (baht)									
≤ 50,000	200 (70.9)	60 (30.0)	140 (70.0)	1.00					
50,001-100,000	68 (24.1)	24 (35.3)	44 (64.7)	1.27	0.71-2.28	0.417			
≥ 100,001	14 (5.0)	5 (35.7)	9 (64.3)	1.30	0.42-4.03	0.654			
Family debt									
No	220 (78.0)	72 (32.7)	148 (67.3)	1.29	0.69-2.41	0.428			
Yes	62 (22.0)	17 (27.4)	45 (72.6)	1.00					
Family member (person)									
0-4	149 (52.8)	53 (35.6)	96 (64.4)	4.97	1.11-22.24	0.036*			
5-8	113 (40.1)	34 (30.1)	79 (69.9)	3.87	0.85-17.63	0.080*			
≤ 9	20 (7.1)	2 (10.0)	18 (90.0)	1.00					

Table 1 Univariable and multivariable analyses in identifying factors associated with HT among Lisu adult populations (cont.)

Factor	Total (%)	HT		OR	95%CI	p-value	AOR	95%CI	p-value
		Yes (%)	No (%)						
Father's history of HT									
No	161 (59.2)	55 (34.2)	106 (65.8)	1.32	0.77-2.26	0.306			
Yes	14 (5.0)	3 (21.4)	11 (78.6)	0.71	0.22-2.35	0.579			
Unknown	107 (37.9)	31 (29.0)	76 (71.0)	1.00					
Mother's history of HT									
No	167 (59.2)	56 (33.5)	111 (66.5)	1.18	0.69-2.04	0.549			
Yes	12 (4.3)	3 (25.0)	9 (75.0)	2.32	0.89-6.05	0.085*			
Unknown	103 (36.5)	30 (29.1)	73 (70.9)	1.00					
Stress (ST-5)									
Low	238 (84.4)	72 (30.3)	166 (68.7)	1.00					
Moderate	38 (13.5)	13 (34.2)	25 (65.8)	1.20	0.58-2.48	0.624			
High	6 (2.1)	4 (66.7)	2 (33.3)	4.61	0.83-25.75	0.082*			
Exercise									
No	152 (53.9)	47 (30.9)	105 (69.1)	0.97	0.45-2.09	0.938			
Sometimes	92 (32.6)	30 (32.6)	62 (67.4)	1.05	0.47-2.36	0.909			
Everyday	38 (13.5)	12 (31.6)	26 (68.4)	1.00					
Smoking									
No	195 (69.1)	66 (33.8)	129 (66.2)	1.00					
Yes	87 (30.9)	23 (26.4)	64 (73.6)	0.70	0.40-1.23	0.217			
Alcohol use									
No	208 (73.8)	68 (32.7)	140 (67.3)	1.00					
Yes	74 (26.2)	21 (28.4)	53 (71.6)	0.82	0.46-1.46	0.493			
Salt in daily cooking									
Low	40 (14.2)	18 (45.0)	22 (55.0)	2.16	1.00-4.69	0.051*			
Moderate	151 (53.5)	46 (30.5)	105 (69.5)	1.16	0.65-2.06	0.621			
High	91 (32.3)	25 (27.5)	66 (72.5)	1.00					
Monosodium glutamate in daily cooking									
Low	44 (15.6)	24 (54.5)	20 (45.5)	3.10	1.49-6.45	0.002*	2.87	1.35-6.12	0.006**
Moderate	134 (47.5)	36 (26.9)	98 (73.1)	0.95	0.54-1.69	0.861	0.86	0.47-1.58	0.631
High	104 (36.9)	29 (27.9)	75 (72.1)	1.00			1.00		
Cooking oil									
Low	49 (17.4)	24 (49.0)	25 (51.0)	2.45	1.14-5.25	0.021*			
Moderate	162 (57.4)	45 (27.8)	117 (72.2)	0.98	0.53-1.83	0.951			
High	71 (25.2)	20 (28.2)	15 (71.8)	1.00					
Knowledge of HT prevention and control									
Low	154 (54.6)	42 (27.3)	112 (72.7)	1.00					
Moderate	61 (21.6)	21 (34.4)	40 (65.6)	1.40	0.74-2.65	0.300			
High	67 (23.8)	26 (38.8)	41 (61.2)	1.69	0.92-3.10	0.089*			
Attitudes toward HT prevention and control									
Negative	210 (74.5)	65 (31.0)	145 (69.0)	1.00					
Neutral	56 (19.9)	19 (33.9)	37 (66.1)	1.15	0.62-2.14	0.670			
Positive	16 (5.7)	5 (31.3)	11 (68.8)	1.01	0.34-3.04	0.980			
Body mass index (BMI)									
Normal	94 (33.3)	31 (33.0)	63 (67.0)	1.00					
Underweight	20 (7.1)	3 (15.0)	17 (85.0)	0.36	0.10-1.32	0.122*			
Overweight	168 (59.7)	55 (32.7)	113 (67.3)	0.99	0.58-1.69	0.968			
Waistline									
Normal	138 (48.9)	41 (29.7)	97 (70.3)	1.00					
Risk for metabolic complication	144 (51.1)	48 (33.3)	96 (66.7)	1.18	0.72-1.96	0.513			
Waist-to-hip ratio									
Normal	157 (55.7)	47 (29.9)	110 (70.1)	1.00					
Risk	125 (44.3)	42 (33.6)	83 (66.4)	1.18	0.72-1.96	0.511			
Total cholesterol									
Normal	176 (62.4)	58 (33.0)	118 (67.0)	1.00					
High	106 (37.6)	31 (29.2)	75 (70.8)	0.84	0.50-1.42	0.516			
Triglycerides									
Normal	162 (57.4)	61 (37.7)	101 (62.3)	1.98	1.17-3.37	0.011*	2.05	1.18-3.54	0.010**
High	120 (42.6)	28 (23.3)	92 (76.7)	1.00			1.00		
HDL cholesterol									
Low	154 (54.6)	47 (30.5)	107 (69.5)	0.90	0.54-1.49	0.680			
Normal	128 (45.4)	42 (32.8)	86 (67.2)	1.00					
LDL cholesterol									
Normal	92 (32.6)	27 (29.3)	65 (70.7)	1.00					
High	190 (67.4)	62 (32.6)	128 (67.4)	1.17	0.68-2.00	0.578			

*Significant level at α=0.20, and **Significant level at α=0.05

equal to or less than 50,000 baht per year (70.9%) (Table 1).

The prevalence of HT among the participants was 31.6% (89 of 282). Among 89 HT cases, 82 (92.1%) were on treatment at the date of data collection, and 7 (7.9%) cases were newly identified. Women (32.4%) had a higher prevalence than males (30.3%). The prevalence was observed to decrease with the increase of age; however, it was not different between those who had attended a school and those did not (Table 1).

A large proportion reported alcohol use (26.2%), smoking (30.9%), moderate to high salt use in their daily cooking practice (85.8%), moderate-to-high monosodium glutamate use in their daily cooking practice (84.4%), and moderate-to-high use of cooking oil in their daily cooking practice (82.6%) (Table 1).

Using ST-5 to assess the stress, 15.6% participants had moderate to high stress, 54.6% participants had a low level of knowledge of HT prevention and control, and 74.5% participants had negative attitude on HT prevention and control (Table 1).

More than half of the participants were overweight based on BMI assessment (59.7%), 44.3% participants were categorized into the risk group based on the waist-to-hip ratio, and 51.1% participants were observed to be at risk for metabolic complications based on the waistline assessment (Table 1).

High total cholesterol was detected in 106 participants (37.6%); 42.6% had high triglycerides, and 67.4% had high LDL cholesterol (Table 1).

In the univariable analysis, eight factors were found to be associated with HT: number of family members, mother's history of HT, BMI, salt use in daily cooking practice, monosodium use in daily cooking practice, stress, knowledge of HT prevention and control, and triglyceride level (Table 1). However, after controlling for age, sex, marital status, and religion in the multivariable model, two factors were found to be associated with HT among the Lisu adult population in Thailand. Those who reported using a low volume of monosodium glutamate were more likely to have HT than those who reported a high volume (AOR=2.87; 95%CI=1.35–6.12), and those who had normal levels of triglycerides were more likely to have HT than those who had high triglycerides (AOR=2.05; 95%CI=1.18–3.54).

Discussion

Under the living circumstances of the Lisu hill tribe people in Thailand, a large proportion of individuals were suffering from HT. More than half of the people aged 30 years and over never attended a school and worked on traditional farms with low incomes. Smoking and alcohol use were common, particularly in men. The heavy use of salt, monosodium glutamate, and cooking oil for their daily cooking practice, including having low knowledge and negative attitude toward HT prevention and control were observed. More than half of the participants had overweight and high lipid levels. However, it was notable that those who reported using low levels of monosodium glutamate and normal triglyceride levels were more likely to have HT than those who reported using a high volume of monosodium glutamate and high triglyceride, respectively.

In our study, it was found that the prevalence of HT was 31.6% (89 of 282 participants); 82 (92.1%) cases were on treatment at the date of data collection, and 7 (7.9%) cases were newly identified. The prevalence of HT between sex and different age groups was not statistically different. The prevalence among the adult multi-ethnic population in China was also closely reported as in this study, which was 29.5 [24]. However, the report of the prevalence of HT among the people aged 35 years and over in Nepal from the national survey reported it to be between 20.8–41.7%; additionally, the prevalence increased with an increase in age [15], in contrast to our study where the prevalence decreased with an increase in age. A study among the hill tribe elderly aged 60 years and over in Thailand reported that the prevalence of HT was 45.5% [25], while in our study, 27.3–31.8% were found among the Lisu aged 60 years and above. This might be the impact of a large proportion of the Lisu people who intended to check their HT status from health professionals and know their HT status. However, the prevalence among Thai adult populations has been reported to be 22.1% [18], which is significantly lower than the hill tribe adult population.

Some factors were found to be associated with HT among the Lisu hill tribe adult population in the univariable analysis at a significance level of α=0.20, such as number of family members, mother's history of HT, BMI, salt use in daily cooking practice, monosodium use in daily cooking practice, stress, knowledge of HT prevention and control, and triglyceride level. However, these factors were not found to be significantly associated with HT in the multivariable analysis. It may be necessary to increase the sample size and also requires stronger study design to assess the associations such as case-control or cohort study.

In our study, it was found that those people who reported using a low volume of monosodium glutamate for cooking were more likely to have HT than those who reported use of a high volume of monosodium glutamate. This might be the negative impact of conducting a cross-sectional study, in which most of the HT among the Lisu had been diagnosed and treated. Subsequently, the association could be found in the opposite relationship because the majority of HT patients used a low volume of monosodium glutamate after receiving medical advice for reducing the risk factor from health professionals. However, the relationships between using a high volume of monosodium glutamate and HT development has been reported in several studies [26–28].

Only triglycerides among serum lipids were found to be associated with HT among the hill tribe adult population in Thailand. However, the association was found in the opposite association; those who had normal triglyceride levels were more likely to have HT than those with high TG levels. This might be the negative impact of a cross-sectional study, particularly among the Lisu people in Thailand. The majority of Lisu adults who have HT have known their HT status and treatment. Therefore, it is highly possible that those who know their HT statuses are under control of their dietary habits and are having normal levels of triglycerides. Normally, several studies have reported the association between high serum triglyceride levels and HT in different populations and countries [29–31].

There are several limitations in this study. First, some questions, particularly asking about the volume use of sodium, monosodium glutamate, and cooking oil, were impractical because most of the participants' responses were based on their perception. This might have interfered with the analysis in the final step. Second, it was difficult to make the participants understand the questions with respect to knowledge and attitude in a clear manner and obtain valid responses due to the poor education level of the participants. However, in this study, researchers optimized the way to obtain the most validated answers by repeating their understanding on the certain question before providing the answer. A few people reported that they did not clearly follow the instructions of no food and drink 12 h before collecting blood specimens. However, during the analysis, those specimens showed inappropriate for laboratory work and were excluded from the analysis. Finally, with the limitations of a cross-sectional study, some associations did not follow expectations, such as a low use of monosodium glutamate was found to be associated with HT, which might be because participants who obtained a diagnosis of HT previously (92.1%) were using low monosodium glutamate after receiving advice from health professionals.

Conclusions

The population of the Lisu hill tribe in Thailand lives in an illiterate manner and in a poor economic status. Substance use is common. A large proportion of them use high volumes of salt, monosodium glutamate, and cooking oil in their daily cooking practices. The majority of the Lisu people have BMI above the normal range and high serum lipid levels. One-third of the population was observed to have HT, and high levels of monosodium glutamate and triglycerides are factors associated with HT among the adult Lisu population in Thailand. However, further strong study design is suggested to perform to confirm the associations such as a case-control study.

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COVID-19 State Quarantine Operation at a Local Setting: Implementation Evaluation

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ABSTRACT

Purpose and objectives: This study aimed to evaluate the effectiveness of the coronavirus disease 2019 (COVID-19) state quarantine implemented at the local border between Thailand and Myanmar in the aspects of the satisfactions of people involving the operation and new infected cases from the people attending the quarantine. **Intervention approach:** A state quarantine in a local border of Thailand and Myanmar setting, which was a community intervention approach, was implemented. **Evaluation methods:** A qualitative method was used to assess the effectiveness of the state quarantine operation. Selected participants were invited to provide information through in-depth interviews. Questionnaires were developed and tested for their validity before commencement of the interviews. Mobile phone and face-to-face interviews were conducted, which lasted 45 minutes each. **Results:** Seventeen participants were interviewed. The attendees were highly satisfied with the infrastructure and process of the operation. The community where the quarantine facility was built needed essential information about the state quarantine operation. Two challenges were detected during the quarantine operation: public health officers who were insufficiently trained for working in the quarantine facility and some workers working in the quarantine facility were highly vulnerable to COVID-19. **Implications for public health:** A state quarantine in the local area, particularly in Chiang Rai Province, Thailand, is highly effective as confirmed by 55 participants who were free of COVID-19 after completing the 14-day quarantine period in the facility.

Keywords: *State quarantine; Local setting; Implementation evaluation; Border area*

Introduction

Coronavirus disease 2019 (COVID-19) has been recognized as a major threat to humans, with a millions of individuals infected and dead worldwide, since its detection in December 2019. Since March 4, 2021, more than 114 million people have been infected with COVID-19, and 2.5 million people have already died. In Southeast Asia, more than 13 million people are infected with COVID-19, with 26,108 infected cases reported in Thailand [1]. Considering the specific characteristics of the disease, which spreads rapidly through people mobilization, people living in one country can be infected by people traveling from another country. Therefore, state quarantine is recommended by the World Health Organization (WHO) to control the COVID-19 pandemic [2].

State quarantine has been used as one of the major prevention and control measures to minimize the impact of COVID-19 globally, including in Thailand. Thailand has a long border area with three different countries: Myanmar, Laos, and Cambodia. Since late August 2020, Myanmar has experienced severe COVID-19 epidemic, with more than 144,000 infected cases and 3,199 deaths [3]. With the severe epidemic in Myanmar, numerous people crossed the border to Thailand. Subsequently, state quarantine has been introduced to control the disease at the border areas, particularly in Chiang Rai Province, Thailand, which has more than two official ports and a long unofficial port along the border.

In late November 2020, a large cohort of COVID-19 cases was reported along the border between Thailand and Myanmar [4]. The Chiang Rai Public Health Office had decided to implement state quarantine at Num Jum Village, Pong Pha Subdistrict, Mae Sai District, Chiang Rai Province, Thailand. The

facility was operated by various healthcare professionals from five districts in Chiang Rai Province.

Purpose and objectives

This study primarily aimed to evaluate the effectiveness of the COVID-19 state quarantine in a local setting in the border area of Chiang Rai, Thailand, and Tachileik District, Myanmar, in the aspects of the satisfactions of people involving the operation and new infected cases from the people attending the quarantine which was operated between December 16, 2020, and January 31, 2021.

Intervention approach

State quarantine in a local setting having three components: input, process, and output.

Input

Several factors were required to be used as criteria in selecting the facility used in the present study. The facility should be located in an area where electricity and communications infrastructures are easily accessible, including the presence of transportation facilities in case of an emergency. The standard infrastructure of the facility was strictly required for the management of COVID-19 patients. Inside the facility, a one-way walking facility was required for case management, including during specimen collection. Air-conditioners were not allowed, and only electric fans were used inside the rooms. Moreover, drinking water and disinfectants were sufficiently provided inside the room for 14 days. Communication with relatives was allowed; however, posting any information on social media platforms was not allowed.

All participants had a mobile phone and were required to report through the central medical number for essential information, including reports on their health status such as body temperature and signs and symptoms related to the disease. Individual body temperature was obtained daily to regularly monitor each participant's temperature. Food and drinks were provided to all participants.

The facility that could be used for the state quarantine operation required emergency rooms, standard infrastructures, electricity, and communications infrastructure. An appropriate safeguard system and waste management were also required.

Medical staff

Several healthcare professionals, such as medical doctors, nurses, pharmacists, epidemiologists, and psychiatric nurses, were required for the quarantine operation. A manager was appointed for the quarantine operation under the law and regulations for disease control in Thailand. The manager was the focal point of contact when managing and monitoring all work systems in the local setting. Initially, the organizational structure was developed, including several role and job descriptions. The workflow was developed and deployed for all the relevant individuals. The communication system was specifically developed for use during work.

Medicines

General medicines for urgent treatment were provided. However, medicines for respiratory tract infection were not available in the facility. Participants who had signs and symptoms of the disease were assessed by a medical doctor before receiving proper treatment and management.

Environmental management

Ventilation was the primary concern in the quarantine facility. Only electric fans were allowed in all rooms. Wastes from a room were properly managed by the developed waste management system. Several disinfectants were provided, such as sodium hypochlorite, alcohol gel, and soap. Facemasks were required on the day of the specimen collection. The nasopharyngeal swab collection was conducted outside the facility. Chlorine was added into the wastewater before it passed through the public area.

Process

Quarantine setting and facility

The facility was chosen based on the standard requirements of the COVID-19 quarantine. Ventilation, spaces, standard wastewater, and solid waste management were used as the basic criteria for setting the state quarantine. Transportation facility and communications infrastructure availability were also used as the standard criteria for setting the state quarantine. Regarding the rooms inside the facility for the participants, the toilet availability inside the room was a must. Community acceptance was also one of the selection and operation criteria for the quarantine operation.

Community preparation

Mutual understanding with community leaders was a critical point of concern. The manager discussed with community leaders regarding the COVID-19 pandemic. Information regarding several immigrants crossing the border to Thailand daily, which has a significant effect on economy and society, was also discussed by the manager and community leaders. Establishing an agreement with community members and leaders before starting the project was an important point.

Workflow system development

The specific workflow system was developed among hospital leaders, district public health officers, and community leaders. The workflow had been cleared, especially according to the hierarchical order and role of each position and team. Thus, the three sections of the workflow were medical and epidemiological, safety, and environmental management.

Staff recruitment and orientation

Medical staff from five district hospitals and district public health offices in Chiang Rai Province worked in this setting. The Chiang Rai Public Health Officer acted as a leader in working with the local quarantine manager. All medical staff were instructed to voluntarily work in this setting.

Daily monitoring system development

The manager monitored the working staff daily, especially in coping with urgent problems and system-related problems they encountered. The manager was also responsible for the management of the facility, including waste management. Each participant's health status was assessed daily by an assigned medical staff using a specific designed form. However, participants experiencing the major signs and symptoms of COVID-19 could directly contact the medical staff any time.

Client entry

Individuals who crossed Thailand at the official border and unofficial ports were invited to attend the state quarantine. All relevant information were provided to the participants and informed consent form was obtained from them before their entry into the quarantine facility, including the channel of communication for 14 days. At the state quarantine, all individuals were identified by the Thai identification card. Individuals' general health status was assessed, including the first polymerase chain reaction test for COVID-19 on the 0th–1st day, the second test that was performed on the 5th day, and the last test that was performed on the 13th day. The specimens were sent and tested at the Chiang Rai Medical Laboratory Center. Laboratory results were obtained 2–3 days after the test.

Medical requirement flow

Along with staying at the state quarantine, all participants were regularly assessed to obtain essential information, while supporting their mental health. Participants were able to communicate with their friends and family members; however, they were not allowed to post any information in social media. The participants measured and recorded their body temperature twice a day by themselves, and they were requested to report this information to the communication channel provided.

Food and water

Food and drinking water were provided to everyone who were quarantined. The quality and quantity of food and drinking water were controlled and monitored by the public health staff. Personal things for daily use were also sufficiently provided during the quarantine.

End of quarantine

In the early morning on the 15th day of the quarantine, individuals who met the criteria for leaving the quarantine were finally assessed for general health, that is, physical examination and body temperature assessment. Moreover, individuals who finished their 14-day quarantine and left the facility were advised to continue wearing face mask and observe social distancing.

Waste management and disinfection management

Daily wastes from the participants were carefully packed and managed by only one person who had been sufficiently trained for managing infectious waste. All wastes were treated at Mae Fah Luang University Medical Center with advanced technology for waste management.

Final report

Final reports were provided by the public health staff members working at the quarantine facility, whereas daily reports were provided by the team leaders. The following two forms were used in this study: general information form at the beginning of recruitment (general information) and daily health monitoring and assessment form. Subsequently, the information was reported directly to the provincial committee weekly.

Output

A total of 55 individuals attended the state quarantine between December 16, 2020, and January 31, 2021, of which 50.9% were male, 67.3% were aged 20–44 years (mean=25.7, standard deviation=12.4), 49.1% resided in Chiang Rai Province, and 10.9% resided in Chiang Mai Province (Table 1).

Table 1 General characteristic of attendees at the state quarantine, Mae Sai District, Chiang Rai Province between 16 December 2020 and 31 January 2021

Characteristics	n	%
Sex		
Male	28	50.9
Female	27	49.1
Age (years)		
3-19	12	21.8
20-44	37	67.3
45-74	6	10.9
Mean = 25.7, SD= 12.3		
Hometown		
Chiang Rai	27	49.1
Chiang Mai	6	10.9
Bangkok	4	7.3
Other	18	32.7
Region		
Northern	36	65.5
Central	10	18.2
North East	8	14.5
Southern	1	1.8

Evaluation methods

A qualitative method was used to evaluate the effectiveness of the state quarantine operation.

A questionnaire was developed that included different items for different key performances. The following five questions were asked to gather information from the Chief of Chiang Rai Public Health Office, district public health officer, and manager: (1) What do you think is the significance of state quarantine to public health? (2) In the state quarantine, how did you allocate health resources? (3) Did you have any trouble managing the state quarantine? How did you address these problems? (4) What were your expectations? Were your expectations achieved at the end of the project? (5) Do you have any specific policy in disease control and prevention along the border areas?

The following five questions were asked to gather information from public health and medical staff: (1) Were you ready to work at the state quarantine before it started? (2) Did you have any worry before entering into work at the state quarantine? (3) How did you adapt while working at the state quarantine (4) Did you have any problems? If yes, how did you cope with those problems? (5) In this state quarantine operation, were there aspects that need to be improved? The following six questions were asked to gather information from participants who attended the state quarantine: (1) Did you have any worry before participating in the state quarantine (2) Did you have any problems during the 14-day state quarantine, (3) What were the aspects that allowed you to be satisfied in this state quarantine? Why? (4) What were the aspects that you are dissatisfied with in this state quarantine? Why? (5) Could you please provide an example of a situation observed during the state quarantine that really needs improvement? (6) Could you please provide the advantages of a state quarantine?

The following three questions were asked to gather information from the participants' relatives: (1) Did you worry about your relative attending the state quarantine? Why? (2) How did you help your relative who attended the state quarantine? (3) What is your opinion on the procedure performed by the medical staff during the state quarantine? The following five questions were asked to gather information from community leaders: (1) Did you worry that your community was possibly assigned as a state quarantine facility? (2) How did your fellow community members feel about setting up the state quarantine facility in your community? (3) Did you face any problems during the state quarantine? If yes, how did you solve these problems? (4) In what way do you think that the government has supported the operation? (5) What are the points that need improvement?

Finally, the following four questions were asked to gather information from community health volunteers: (1) How did you help the state quarantine operation? (2) How did you help community leaders operate the system? (3) How did you help the participants? (4) Please provide the advantages and disadvantages of running a state quarantine in your community.

All questions were validated before use by three experts according to the item congruence techniques (IOC); public health professional, epidemiologist, hospital director. Each question was scored in three options; -1 refers to the question did not reflect the context of the study, 0 refers to the question was reflected to the study context but it's required some improvement before use, and +1 refers to the question was completely reflected to the context of the study. Finally, a sum score from three experts were pooled and interpreted; if the sum score was less than 0.5, the question did not suitable to use in the study; the sum scores equal 0.51-0.70, the question was required improvement before use; if the sum score more than 0.7, the question was ready to use.

All selected key informants were invited to the interview. The interviews were conducted 3 days in advance. The interviews were conducted via phone calls, which means that the interviewer and interviewee were blinded each other. The interviewer was an expert in conducting qualitative studies and was knowledgeable in the entire process of the state quarantine operation. However, the interviewer was not involved in any section or stage of the operation. All interviews were recorded and complemented with field notes.

All records were typed and corrected before the analysis. Data were analyzed using the NVivo program (NVivo, qualitative data analysis software; QSR International Pty Ltd., version 11, 2015).

Ethical consideration

All study concepts and protocols were approved by the Chiang Rai Provincial Public Health Research Ethics Committee on Human Research (CRPPHO No.32/2564). All participants were provided information regarding the study before obtaining their informed consent. All participants were interviewed in a private and confidential setting. The interviews lasted 45 minutes each.

Results

Seventeen (3 [project leaders], 5 [public healthcare professionals], 3 [community members], 6 [attendees of the quarantine and their respective relatives]) participants were interviewed. The participants were of Thai and other nationalities, but all the participants were able to speak the Thai language. Two participants had no mobile phone and subsequently encountered several challenges with communication during their stay.

Infrastructure and communication

Readiness and satisfaction with the infrastructure, including building, room, and sanitary materials, were reported at a significant level by participants and medical staff. The facility where the state quarantine was implemented was new and located in a quiet area.

Participants were highly satisfied with communications infrastructure and transportation facilities in the state quarantine facility. Moreover, communications infrastructure and transportation facilities were considered effective.

Procedure of the operation

The command and communication chain among the public health staff and participants were considered effective in this study. Two-way communication and regular meetings were properly implemented throughout the entire process. A decision was made based on this evidence. The procedures performed during the state quarantine operation were found to be challenging considering that the quarantine facility was constructed in a limited amount of time. Major challenges were observed during the state quarantine operation: time constraints in the preparation of medical staff working in the quarantine facility and inadequate essential documents in the state quarantine operation. There was no standard public health training program provided to improve the knowledge and skills of medical staff working in the quarantine facility in Thailand. Further, some young insufficiently trained medical professionals were assigned to work in the quarantine facility. Changing of medical staff who worked in the quarantine facility over time had a significant effect on communication and effective care in the quarantine facility.

Another challenge was that the documents used for the operation were incomplete. Due to the urgent requirement of performing this state quarantine operation in the border area where a cluster of COVID-19 cases was reported, some documents and guidelines were not completely developed and effectively used at the initial steps.

Medical care and support

Medical care and support for both physical and mental health problems, which were provided in the state quarantine facility, were considered effective. The quarantine was operated in an area close to two large hospitals: Mae Sai Hospital and Mae Chan Hospital. Subsequently, participants in the state quarantine operation received sufficient physical and mental care and support from medical professionals and public health staff who worked in the quarantine facility. Mental health care was not directly to support attendees but also to public health staff.

Food and daily support

Food, drinking water, and other personal things were sufficiently provided. Different food and drink items were provided during the whole quarantine generation, which greatly satisfied the participants. However, three food and drink providers were at the highest risk of COVID-19 infection because of their access to the quarantine facility.

Communication

There were communication channels between the public health staff and participants in the quarantine facility. First an online application, was used as the major communication channel to communicate on daily temperature reports, laboratory specimen collection appointments, feedback of the results, and daily personal requests. This channel was created and used by those who had smartphones. The second channel was a common mobile phone and post-it notes (small piece of paper), which were used to communicate needs.

Community agreement

The project public health leaders were responsible for allowing the community members to understand and trust the state quarantine operation. The community leaders discussed to villagers the essential information on performing state quarantine operation, including the safety precautions undertaken to prevent viral transmission. During the discussion, public health leaders from the provincial level joined in the discussion so that villagers further understand the state quarantine operation.

Outcomes

Positive COVID-19 cases were not observed among the participants, and secondary infections were not noted in those who attended the state quarantine in Mae Sai District. Participants' information was not released to the public to avoid social stigma. None of the public health staff working in the state quarantine facility was COVID-19 positive. Villagers were significantly satisfied with the state quarantine operation. In early February 2021, the leader of Chiang Rai Province announced that the province was free of COVID-19.

Implications for public health

This study showed that state quarantine can be effectively implemented in a local setting. It is essential to control and prevent diseases at the port and in the border areas. Establishing a state quarantine facility in a local setting could reduce the disease management cost and risk of spreading the disease. State quarantine is one of the best procedures performed to reduce all public health and medical expenses from disease control implementation and case management at a hospital. A strong collaboration between community and health institutes throughout the integrative work on state quarantine could have a tremendous impact on the health and economy of a country.

Discussion

There was an urgent need to establish a state quarantine facility at Mae Sai District, the border areas of Thailand and Myanmar in early December 2020, considering a number of COVID-19 cases reported among individuals crossing the border back to Thailand during the severe COVID-19 epidemic in Myanmar. It was an urgent policy that needed to be immediately implemented to prevent disease transmission along the border areas. Several key

success factors were detected, such as the central government's significant commitment to prevent the spread of COVID-19 and the provincial team's quick response to the COVID-19 pandemic. Communication between stakeholders in both the vertical and horizontal lines was excellent and effective. Allowing villagers to understand the importance of state quarantine operation before the actual operation was one significant point addressed in this study. Eventually, the villagers were able to understand the clinical importance of a quarantine facility, and they accepted and cooperated in the state quarantine operation. Finally, the local public health team was able to demonstrate their leadership ability in managing a significantly difficult task of operating the quarantine facility. Teamwork observed from public health staff working in the quarantine facility was one of the outstanding capacities detected; however, other departments did not fully cooperate in the state quarantine operation.

A few challenges were detected during the state quarantine operation. First, several of the public health staff who participated in the quarantine operation were insufficiently trained in managing severe COVID-19 patients. Only a short guideline and limited information were provided in the quarantine operation, with only one mentor in the quarantine facility to guide the quarantine operation. Some documents were not developed and designed properly, which led to confusion during the quarantine operation. Some staff, particularly those who provided food and drink to the participants, were at the greatest risk of infection. This problem should be considered in future quarantine operations. In addition, mental health issue in both attendees and staff were detected. This coincides with a study Brooks, et al [5] which reported that the psychological impact was an important challenge in implementing a state quarantine.

The state quarantine operation has been accepted by the WHO [6] and Centers for Disease Control and Prevention when managing the COVID-19 pandemic [7]. The Ministry of Public Health, Thailand, has also recommended and implemented state quarantine operations at the national and local levels, particularly in areas or provinces with port entries [8]. Moreover, the guidelines and protocols of these operations met the criteria and requirements for the standard hotel quarantine, which was developed by the National Review of Hotel Quarantine, Australia Government [9]. The process of the quarantine operation has also met the international standard of quarantine operation, which was reported by Tognotti [10].

In our study, the state quarantine operation at a local setting in Chiang Rai Province has been found to be highly effective, although this is the first quarantine operation performed in Chiang Rai Province bordered with Myanmar at Tachileik District, with both official and unofficial ports or crossing borders. In this study, the effectiveness of the quarantine operation was confirmed considering that COVID-19 cases were not detected in the quarantine facility in the present study. This concurs with the report from China [11], which showed that state quarantine was a key factor in eliminating COVID-19 in China.

This study has a few limitations. Some of the primary participants were not interviewed. Some information provided by the participants was relatively inaccurate considering that they could not clearly and appropriately answer the questions asked since the study was conducted from late March to early April 2021.

Conclusion

State quarantine is one of the most effective prevention and control measures to prevent the spread of COVID-19 in border areas. However, several factors need to be considered while managing the state quarantine operation. Community agreement is a crucial factor. Before starting a state quarantine operation in a community, an agreement should be obtained from community members, particularly community leaders. Designing an organizational structure is of crucial importance when managing the state quarantine operation. The effective structure includes having public health staff in all relevant fields and creating a well-established workflow daily, especially when assessing the health status of all participants in the state quarantine. Monitoring participants' health and specimen collection requires a specific procedure, including the availability of a specific medical technician. Mental support to participants participating in the quarantine operation is an important factor that all medical staff should consider both during the quarantine and after being discharge from the quarantine facility.

Based on the state quarantine operation in Mae Sai District, Chiang Rai Province, we recommend some points. First, at the national level, there should be an effective training program to handle crises or severe conditions so that public health staff can effectively respond to the crisis. The standard guidelines used to respond to a crisis should be developed and provided to all concerned individuals.

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Dyslipidemia Treatment by Traditional Chinese Medicine: A Systematic Review

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ABSTRACT

Dyslipidemia is a significant non-communicable disease among adult populations globally. This systematic review focused on understanding current case management using traditional Chinese medicine (TCM) internal and external treatments, integrated TCM, and Western medicine, including other genomic research related to dyslipidemia. This could be used to understand the effectiveness of the care and management of patients with dyslipidemia based on different medical principles. Finally, the information can be used to support clinical decisions to choose the best approach for the care and management of patients.

Keywords: *Dyslipidemia; Traditional Chinese medicine treatment; Gene and protein expression*

Introduction

Dyslipidemia generally refers to the levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) higher than normal or the levels of high-density lipoprotein cholesterol (HDL-C) being lower than normal. Dyslipidemia is a common metabolic disease that is an important risk factor for atherosclerotic cardiovascular disease. The high-incidence group consists of middle-aged and elderly people. The modern Chinese medicine believes that dyslipidemia is mainly caused by phlegm, blood stagnation and heat, which is closely related to the dysfunction of liver, spleen, and kidneys, and mostly belongs to the deficiency in origin and excess in superficiality [1–3]. According to its clinical manifestations, it is classified as "phlegm," "blood stasis," "vertigo," "stroke," and other diseases.

With the improvement of living standards, the level of blood lipids in the Thai population is gradually rising. This leads to a significant increase in the number of patients with dyslipidemia. A cross-sectional study by the Medical Research Network of the Consortium of Thai Medical Schools between 2010 and 2014 showed that 88.9% of patients with diabetes had dyslipidemia [4]. Additionally, dyslipidemia has been associated with chronic kidney disease [5], hypertension [6], erectile dysfunction [7], preterm birth [8], and others.

In this review, we aimed to present the comparisons of several research findings in understanding dyslipidemia with respect to the treatment of internal and external traditional Chinese medicine (TCM), integrated TCM, western medicine treatment, and related genes and proteins with the regulation mechanism of lipid metabolism.

Dyslipidemia case management by internal TCM

Several studies have demonstrated the effectiveness of internal TCM in the management of dyslipidemia. A study conducted among 50 dyslipidemia patients with carotid atherosclerosis plaque treated using Erchen and Siwu decoctions for 8 weeks showed that the total effective rate was 88.0%, while that of the Diao zhibituo tablets treatment group was 82.0% ($p < 0.05$) [9]. An 8-week treatment course on Jiangya Tiaozhi decoction among 30 patients with hypertension and dyslipidemia with phlegm-turbidity stagnation demonstrated that the total effective rate was 90.0% in the treatment group and 70.0% in the western medicine treatment group (nifedipine controlled release, irbesartan and hydrochlorothiazide, and atorvastatin calcium tablets), with a significant difference ($p < 0.05$) [10].

The combination of Banxia baizhu tianma decoction and Xuefuzhuyu decoction to 45 patients who had hypertension and dyslipidemia with 8 months course, it was found that the total effective rate of blood lipid was 88.9%, while that of the western medicine treatment group (amlodipine besylate tablets, nifedipine, valsartan, betaloc, rosuvastatin, and atorvastatin) was 85.0% ($p < 0.05$) [11]. Ke [12] used Tongyu huazhuo decoction to treat 64 cases of dyslipidemia for 4 weeks, and the results showed that the Tongyu huazhuo decoction and atorvastatin groups had equivalent curative effects, and the total effective rates were 90.6% and 82.3%, respectively. There was

no significant difference between the two groups ($p > 0.05$); however, the improvement in TC, TG, and HDL-C in the Tongyu huazhuo decoction group was more obvious than the atorvastatin group, and the differences were statistically significant ($p < 0.05$).

A study on 30 dyslipidemia patients with spleen deficiency and phlegm stasis treated using Sanshen tiaozhi decoction for 8 weeks showed that the total effective rate was 93.3%, while that using atorvastatin calcium tablets was 80.0%, and the difference was statistically significant ($p<0.05$) [13]. A study using Huatan jiangzhi decoction to treat 48 patients with dyslipidemia for a 1-month showed that it could reduce TC, TG, and LDL-C, increase HDL-C, and was significantly better than the simvastatin tablets in reducing TG ($p < 0.05$) [14].

These clinical trials using the TCM approach have shown that several drugs or herbs are effectively used to reduce lipids in patients with dyslipidemia.

Dyslipidemia case management by external TCM

The following are the studies on the effectiveness of external TCM in reducing lipid levels among patients with dyslipidemia.

The acupoint catgut embedding therapy (Ganshu [BL18], Pishu [BL20], Shenshu [BL23], Danzhong [RN17], Guanyuan [RN04], Zhongwan [RN12], Tianshu [ST25]) combined with acupuncture (Fenglong [ST40], Zusanli [ST36], Sanyinjiao [SP06], Neiguan [PC06]) was used to treat 35 cases of dyslipidemia with phlegm dampness obstruction, while the control group was only treated using acupuncture for 8 weeks, and the results showed that TC, TG, LDL-C, and HDL-C were improved, and the curative effect of the combined group was significantly better than that of the control group ($p<0.05$) [15]. A clinical study among 29 obese female patients with dyslipidemia, after 3 months of treatment, the TC, TG, LDL-C, and HDL-C of ear acupuncture (Sanjiao [CO17], Jiaogan [AH6a], Pi [CO13], Shen [CO10], Shenshangxian [TG2p], Neifenmi [CO18], pizhixia AT4]) combined with warming needle moxibustion (Fenglong [ST40], Taixi [KI03], Shenshu [BL23], Pishu [BL20], Zhongwan [RN12], Guanyuan [RN04], Taibai [SP03], Yinlingquan [SP09], and Zhongji [RN03]) groups were significantly improved compared to those who were treated only by warming needle moxibustion, and the difference was statistically significant ($p < 0.05$) [16].

Tao et al. [17] used acupoint catgut embedding (Xinshu [BL15], Geshu [BL17], Ganshu [BL18], Pishu [BL20], Shenshu [BL23], Zusanli [ST36], Zhongwan [RN12], and Guanyuan [RN04]) combined with thunder-fire moxibustion to treat 30 patients with the spleen and kidney yang deficiency type dyslipidemia. The course of the treatment was 8 weeks. The results showed that the curative effect of acupoint catgut embedding combined with thunder fire moxibustion was equivalent to that of atorvastatin calcium tablets, and the total effective rate of blood lipid index was 90.0% vs. 93.3%. There was no significant difference between the two groups ($p > 0.05$); however, the acupoint catgut embedding combined with thunder fire moxibustion improved the mental status, abdominal distension, anorexia, stool, and other TCM symptoms more significantly ($p < 0.05$) than the atorvastatin calcium tablets.

A study on a 49 patients with dyslipidemia who received mild moxibustion using moxa stick (Zusanli [ST36], Shenque [RN08], Sanyinjiao [SP06]) as the main acupoints for 8 weeks showed that the moxibustion and fenofibrate groups had equivalent curative effects, and the total clinical effective rates were 71.4% and 66.7%, respectively [18]. There was no significant difference between the two groups ($p > 0.05$); however, the alanine transferase in the moxibustion group decreased significantly after treatment, and the differences were statistically significant ($p < 0.05$).

A study on electroacupuncture (Quchi [LI11], Zusanli [ST36], Xiajushu [ST39], Shangjushu [ST37], Neiting [ST44], Qiangu [SI02], Erjian [LI02], Tianshu [ST25], Fenglong [ST40]) combined with ear-acupuncture (Waibi [TG1.2i], Pi [CO13], Wei [CO4], Xin [CO15], Xiaochang [CO6], Fei [CO14], Dachang [CO7], Sanjiao [CO17], Neifenmi [CO18]) treated 65 cases with obesity of stomach-intestine excessive heat type complicated with dyslipidemia [19], and the control group treated using only electroacupuncture for 3 months, the results showed that TG, TC, LDL-C, and HDL-C were significantly better than those in the control group ($p < 0.05$).

Based on the above information, many external TCM approaches could significantly reduce lipid levels among patients with dyslipidemia.

Dyslipidemia case management by integrated TCM and western medicine

Many studies have demonstrated the effectiveness of controlling and reducing lipid levels in patients with dyslipidemia.

The study on Jianpi Huashi therapy combined with simvastatin tablets was used to treat 53 patients with dyslipidemia in spleen deficiency with phlegm-dampness type [20] for 3 months. The results showed that the total effective rate was 90.6%, while that of the simvastatin tablets treatment group was 75.5%, and the difference was statistically significant ($p < 0.05$). An interesting study was conducted using the Banxia Baizhu Tianma decoction combined with amlodipine besylate and atorvastatin calcium tablets in 58 patients with hypertension combined with dyslipidemia of phlegm-dampness stagnation type [21]. The course of treatment was 2 months, and the total effective rate was 91.4%, while that of the amlodipine besylate and atorvastatin calcium tablets treatment group was 75.9%. Systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, TC, LDL-C, and HDL-C were

improved, and the difference was statistically significant ($p < 0.05$).

In a study among 37 patients with dyslipidemia, Qutan huazhuo decoction combined with atorvastatin tablets and atorvastatin tablets alone were used for 8 weeks, with the total effective rate of 91.2% and 69.1%, respectively and the difference was statistically significant ($p < 0.05$) [22]. Another study was conducted in China [23] by using resolving phlegm and promoting blood circulation methods with simvastatin dispersible tablets to treat 40 patients with dyslipidemia for 8 weeks. The results showed that TC, TG, LDL-C, apolipoprotein B (Apo-B), endothelin, and nitric oxide were improved, and the difference was statistically significant ($p < 0.05$).

Huoxue huayu jiangzhi decoction combined with simvastatin capsules was used to treat 48 patients with dyslipidemia; after treatment, the total effective rate was 93.8%, which was significantly better than that using simvastatin capsules (81.3%) ($p < 0.05$) [24]. A study among 48 patients with spleen deficiency and phlegm stasis type dyslipidemia by using Dantian Shenzhu decoction combined with atorvastatin calcium dispersible tablets demonstrated that TG, TC, LDL-C, and HDL-C were improved, and the effective rate was 93.8%, which was significantly better than that using atorvastatin calcium dispersible tablets (77.8%) ($p<0.05$) [25]. Additionally, Hedan zhaze decoction combined with atorvastatin calcium tablets was used to treat 30 patients with dyslipidemia for 4 weeks showed that the total effective rate was 93.3% in the treatment group and 73.3% in the atorvastatin calcium tablets treatment group ($p < 0.01$). The levels of HDL-C, LDL-C, TG, and TC decreased significantly [26].

Many studies have shown that integrative TCM and Western medicine can effectively control lipid levels in dyskinesia.

Correlation between the expression of related genes and proteins with the regulation mechanism of lipid metabolism

In this study, we presented the mechanism of lipid metabolism based on several studies.

Danhong injection could inhibit the activation of the nucleotide-binding domain-like receptor protein 3 inflammatory complex pathway, reduce the expression of Caspase-1, interleukin (IL)-1β, and IL-18, and regulate the levels of TC and TG in hyperlipidemic rats with cerebral ischemia-reperfusion injury [27]. Thirty patients with hyperlipidemic pancreatitis were treated using oral liquid of Rosa roxburghii Tratt and Crataegus pinnatifida based on routine pancreatitis treatment [28]. The results showed that the levels of TC, TG, LDL-C, and HDL-C were improved, and the expression of LPL mRNA and protein in liver tissue was significantly increased. The mRNA expression of nuclear factor erythroid 2–related factor 2 (Nrf2) and gamma-glutamylcysteine synthetase (γ-GCS) in the liver tissue of hyperlipidemic rats was determined using quantitative real-time polymerse chain reaction, and it was found that Hedan Sanqi Jiangzhi tablet could regulate the levels of TC, TG, and LDL-C in serum and significantly increase the expression of Nrf2 and γ-GCS mRNA in liver tissue [29].

Gypenoside granules could promote the protein expression of ABCA1, increasingly regulate the gene expression of ABCA1, CYP7A1, and SR-BI, and regulate the level of blood lipids [30]. Combined with atorvastatin, Gypenoside granules could synergistically reduce blood lipids. Moreover, modified rhizoma alismatis decoction can reduce serum TG, TC, and LDL-C, significantly increase the content of HDL-C, and regulate the expression of AQP3 gene protein in colon tissue [31]. Additionally, Sini powder can prevent the increase in serum TG and LDL-C levels, increase HDL-C and ApoA-I levels, and significantly increase ApoA-I mRNA expression in the liver [32].

Conclusion

According to many factors that cause these effects, the incidence rate of dyslipidemia is continuously increasing, which affects our health and quality of life. Statins are commonly used in clinical practice. It significantly helps to regulate blood lipid levels. It reduces LDL and TC levels. Statins appear to have a fast-healing efficacy and reduce mortality owing to cardiovascular diseases. Therefore, statins are widely used in clinical practice; however, researchers have also found that using statins alone or in combination with other drugs can cause adverse reactions in patients. It effects the treatment and overall results, namely statin-associated muscle symptoms [33], new-onset diabetes [34], and drug-drug interactions [35].

The role of modern Chinese medicine in regulating blood lipids has become increasingly prominent, with fewer adverse reactions and a high effective rate [36]. TCM believes that dyslipidemia is mainly caused by external factors such as inappropriate diet, excessive consumption of fatty and sweet foods, emotional stress, and exhaustion. The accumulation of phlegm and blood stasis is an internal cause of dyslipidemia. The deposition in the blood vessels after the transformation of lipids appears to be the main factor that causes dyslipidemia to develop into cardiovascular disease. Dyslipidemia is closely related to liver, spleen, and kidney dysfunction. In clinical practice, the treatment of dyslipidemia mainly involves invigorating the spleen to eliminate dampness, promoting qi and resolving phlegm, promoting blood circulation by removing blood stasis, and tonifying the liver and kidney [37].

The treatment of TCM is individualized. TCM choose the appropriate treatment according to the different patients' conditions, such as those with spleen deficiency and excess dampness should be treated by

invigorating the spleen to eliminate dampness. The method of promoting blood circulation by removing blood stasis should be used in patients with phlegm and blood stasis. The treatment methods can change during the disease progression, and dyslipidemia has its own characteristics from mild to severe conditions. Therefore, different treatment methods should be used during dyslipidemia treatment at different stages.

The speed of disintegration and absorption for various TCM dosage forms differ. The time and interval of medication use are also different. The absorption of the pill is slow; therefore, the effect is mild, and the action can last longer. Decoction, liquor, and syrup have faster absorption, and rapid effect. The time of Chinese prescription or the number of times of acupuncture and moxibustion treatment was determined according to the patient's condition, drugs, and other specific conditions. In patients with adverse reactions [38, 39], treatment should be discontinued immediately, and other treatment methods should be used with caution after the symptoms are relieved.

The existing literature is limited, often focusing on the treatment of dyslipidemia using Chinese medicine; the curative effect of Chinese herbal medicine, acupuncture, moxibustion, and acupoint catgut embedding; and only a few studies have integrated treatment of TCM and western medicine using modern scientific methods. TCM treatment of dyslipidemia has the highest degree of development, and there are still many effective reports in the literature to be studied.

Additionally, some challenges persist in treatment using Chinese medicine, such as international nomenclature, body and auricular acupuncture point location in the body area appear to be generally well-defined, quality and safety of Chinese herbal medicines, and lack of standards and specifications that reduce the credibility of TCM. Therefore, a standard treatment for dyslipidemia in TCM must be established to develop and grow globally.

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Dyslipidemia Treatment by Traditional Chinese Medicine: A Systematic Review

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ABSTRACT

Dyslipidemia is a significant non-communicable disease among adult populations globally. This systematic review focused on understanding current case management using traditional Chinese medicine (TCM) internal and external treatments, integrated TCM, and Western medicine, including other genomic research related to dyslipidemia. This could be used to understand the effectiveness of the care and management of patients with dyslipidemia based on different medical principles. Finally, the information can be used to support clinical decisions to choose the best approach for the care and management of patients.

Keywords: *Dyslipidemia; Traditional Chinese medicine treatment; Gene and protein expression*

Introduction

Dyslipidemia generally refers to the levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) higher than normal or the levels of high-density lipoprotein cholesterol (HDL-C) being lower than normal. Dyslipidemia is a common metabolic disease that is an important risk factor for atherosclerotic cardiovascular disease. The high-incidence group consists of middle-aged and elderly people. The modern Chinese medicine believes that dyslipidemia is mainly caused by phlegm, blood stagnation and heat, which is closely related to the dysfunction of liver, spleen, and kidneys, and mostly belongs to the deficiency in origin and excess in superficiality [1–3]. According to its clinical manifestations, it is classified as "phlegm," "blood stasis," "vertigo," "stroke," and other diseases.

With the improvement of living standards, the level of blood lipids in the Thai population is gradually rising. This leads to a significant increase in the number of patients with dyslipidemia. A cross-sectional study by the Medical Research Network of the Consortium of Thai Medical Schools between 2010 and 2014 showed that 88.9% of patients with diabetes had dyslipidemia [4]. Additionally, dyslipidemia has been associated with chronic kidney disease [5], hypertension [6], erectile dysfunction [7], preterm birth [8], and others.

In this review, we aimed to present the comparisons of several research findings in understanding dyslipidemia with respect to the treatment of internal and external traditional Chinese medicine (TCM), integrated TCM, western medicine treatment, and related genes and proteins with the regulation mechanism of lipid metabolism.

Dyslipidemia case management by internal TCM

Several studies have demonstrated the effectiveness of internal TCM in the management of dyslipidemia. A study conducted among 50 dyslipidemia patients with carotid atherosclerosis plaque treated using Erchen and Siwu decoctions for 8 weeks showed that the total effective rate was 88.0%, while that of the Diao zhibituo tablets treatment group was 82.0% ($p < 0.05$) [9]. An 8-week treatment course on Jiangya Tiaozhi decoction among 30 patients with hypertension and dyslipidemia with phlegm-turbidity stagnation demonstrated that the total effective rate was 90.0% in the treatment group and 70.0% in the western medicine treatment group (nifedipine controlled release, irbesartan and hydrochlorothiazide, and atorvastatin calcium tablets), with a significant difference ($p < 0.05$) [10].

The combination of Banxia baizhu tianma decoction and Xuefuzhuyu decoction to 45 patients who had hypertension and dyslipidemia with 8 months course, it was found that the total effective rate of blood lipid was 88.9%, while that of the western medicine treatment group (amlodipine besylate tablets, nifedipine, valsartan, betaloc, rosuvastatin, and atorvastatin) was 85.0% ($p < 0.05$) [11]. Ke [12] used Tongyu huazhuo decoction to treat 64 cases of dyslipidemia for 4 weeks, and the results showed that the Tongyu huazhuo decoction and atorvastatin groups had equivalent curative effects, and the total effective rates were 90.6% and 82.3%, respectively. There was

no significant difference between the two groups ($p > 0.05$); however, the improvement in TC, TG, and HDL-C in the Tongyu huazhuo decoction group was more obvious than the atorvastatin group, and the differences were statistically significant ($p < 0.05$).

A study on 30 dyslipidemia patients with spleen deficiency and phlegm stasis treated using Sanshen tiaozhi decoction for 8 weeks showed that the total effective rate was 93.3%, while that using atorvastatin calcium tablets was 80.0%, and the difference was statistically significant ($p<0.05$) [13]. A study using Huatan jiangzhi decoction to treat 48 patients with dyslipidemia for a 1-month showed that it could reduce TC, TG, and LDL-C, increase HDL-C, and was significantly better than the simvastatin tablets in reducing TG ($p < 0.05$) [14].

These clinical trials using the TCM approach have shown that several drugs or herbs are effectively used to reduce lipids in patients with dyslipidemia.

Dyslipidemia case management by external TCM

The following are the studies on the effectiveness of external TCM in reducing lipid levels among patients with dyslipidemia.

The acupoint catgut embedding therapy (Ganshu [BL18], Pishu [BL20], Shenshu [BL23], Danzhong [RN17], Guanyuan [RN04], Zhongwan [RN12], Tianshu [ST25]) combined with acupuncture (Fenglong [ST40], Zusanli [ST36], Sanyinjiao [SP06], Neiguan [PC06]) was used to treat 35 cases of dyslipidemia with phlegm dampness obstruction, while the control group was only treated using acupuncture for 8 weeks, and the results showed that TC, TG, LDL-C, and HDL-C were improved, and the curative effect of the combined group was significantly better than that of the control group ($p<0.05$) [15]. A clinical study among 29 obese female patients with dyslipidemia, after 3 months of treatment, the TC, TG, LDL-C, and HDL-C of ear acupuncture (Sanjiao [CO17], Jiaogan [AH6a], Pi [CO13], Shen [CO10], Shenshangxian [TG2p], Neifenmi [CO18], pizhixia AT4]) combined with warming needle moxibustion (Fenglong [ST40], Taixi [KI03], Shenshu [BL23], Pishu [BL20], Zhongwan [RN12], Guanyuan [RN04], Taibai [SP03], Yinlingquan [SP09], and Zhongji [RN03]) groups were significantly improved compared to those who were treated only by warming needle moxibustion, and the difference was statistically significant ($p < 0.05$) [16].

Tao et al. [17] used acupoint catgut embedding (Xinshu [BL15], Geshu [BL17], Ganshu [BL18], Pishu [BL20], Shenshu [BL23], Zusanli [ST36], Zhongwan [RN12], and Guanyuan [RN04]) combined with thunder-fire moxibustion to treat 30 patients with the spleen and kidney yang deficiency type dyslipidemia. The course of the treatment was 8 weeks. The results showed that the curative effect of acupoint catgut embedding combined with thunder fire moxibustion was equivalent to that of atorvastatin calcium tablets, and the total effective rate of blood lipid index was 90.0% vs. 93.3%. There was no significant difference between the two groups ($p > 0.05$); however, the acupoint catgut embedding combined with thunder fire moxibustion improved the mental status, abdominal distension, anorexia, stool, and other TCM symptoms more significantly ($p < 0.05$) than the atorvastatin calcium tablets.

A study on a 49 patients with dyslipidemia who received mild moxibustion using moxa stick (Zusanli [ST36], Shenque [RN08], Sanyinjiao [SP06]) as the main acupoints for 8 weeks showed that the moxibustion and fenofibrate groups had equivalent curative effects, and the total clinical effective rates were 71.4% and 66.7%, respectively [18]. There was no significant difference between the two groups ($p > 0.05$); however, the alanine transferase in the moxibustion group decreased significantly after treatment, and the differences were statistically significant ($p < 0.05$).

A study on electroacupuncture (Quchi [LI11], Zusanli [ST36], Xiajushu [ST39], Shangjushu [ST37], Neiting [ST44], Qiangu [SI02], Erjian [LI02], Tianshu [ST25], Fenglong [ST40]) combined with ear-acupuncture (Waibi [TG1.2i], Pi [CO13], Wei [CO4], Xin [CO15], Xiaochang [CO6], Fei [CO14], Dachang [CO7], Sanjiao [CO17], Neifenmi [CO18]) treated 65 cases with obesity of stomach-intestine excessive heat type complicated with dyslipidemia [19], and the control group treated using only electroacupuncture for 3 months, the results showed that TG, TC, LDL-C, and HDL-C were significantly better than those in the control group ($p < 0.05$).

Based on the above information, many external TCM approaches could significantly reduce lipid levels among patients with dyslipidemia.

Dyslipidemia case management by integrated TCM and western medicine

Many studies have demonstrated the effectiveness of controlling and reducing lipid levels in patients with dyslipidemia.

The study on Jianpi Huashi therapy combined with simvastatin tablets was used to treat 53 patients with dyslipidemia in spleen deficiency with phlegm-dampness type [20] for 3 months. The results showed that the total effective rate was 90.6%, while that of the simvastatin tablets treatment group was 75.5%, and the difference was statistically significant ($p < 0.05$). An interesting study was conducted using the Banxia Baizhu Tianma decoction combined with amlodipine besylate and atorvastatin calcium tablets in 58 patients with hypertension combined with dyslipidemia of phlegm-dampness stagnation type [21]. The course of treatment was 2 months, and the total effective rate was 91.4%, while that of the amlodipine besylate and atorvastatin calcium tablets treatment group was 75.9%. Systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, TC, LDL-C, and HDL-C were

improved, and the difference was statistically significant ($p < 0.05$).

In a study among 37 patients with dyslipidemia, Qutan huazhuo decoction combined with atorvastatin tablets and atorvastatin tablets alone were used for 8 weeks, with the total effective rate of 91.2% and 69.1%, respectively and the difference was statistically significant ($p < 0.05$) [22]. Another study was conducted in China [23] by using resolving phlegm and promoting blood circulation methods with simvastatin dispersible tablets to treat 40 patients with dyslipidemia for 8 weeks. The results showed that TC, TG, LDL-C, apolipoprotein B (Apo-B), endothelin, and nitric oxide were improved, and the difference was statistically significant ($p < 0.05$).

Huoxue huayu jiangzhi decoction combined with simvastatin capsules was used to treat 48 patients with dyslipidemia; after treatment, the total effective rate was 93.8%, which was significantly better than that using simvastatin capsules (81.3%) ($p < 0.05$) [24]. A study among 48 patients with spleen deficiency and phlegm stasis type dyslipidemia by using Dantian Shenzhu decoction combined with atorvastatin calcium dispersible tablets demonstrated that TG, TC, LDL-C, and HDL-C were improved, and the effective rate was 93.8%, which was significantly better than that using atorvastatin calcium dispersible tablets (77.8%) ($p<0.05$) [25]. Additionally, Hedan zhaze decoction combined with atorvastatin calcium tablets was used to treat 30 patients with dyslipidemia for 4 weeks showed that the total effective rate was 93.3% in the treatment group and 73.3% in the atorvastatin calcium tablets treatment group ($p < 0.01$). The levels of HDL-C, LDL-C, TG, and TC decreased significantly [26].

Many studies have shown that integrative TCM and Western medicine can effectively control lipid levels in dyskinesia.

Correlation between the expression of related genes and proteins with the regulation mechanism of lipid metabolism

In this study, we presented the mechanism of lipid metabolism based on several studies.

Danhong injection could inhibit the activation of the nucleotide-binding domain-like receptor protein 3 inflammatory complex pathway, reduce the expression of Caspase-1, interleukin (IL)-1β, and IL-18, and regulate the levels of TC and TG in hyperlipidemic rats with cerebral ischemia-reperfusion injury [27]. Thirty patients with hyperlipidemic pancreatitis were treated using oral liquid of Rosa roxburghii Tratt and Crataegus pinnatifida based on routine pancreatitis treatment [28]. The results showed that the levels of TC, TG, LDL-C, and HDL-C were improved, and the expression of LPL mRNA and protein in liver tissue was significantly increased. The mRNA expression of nuclear factor erythroid 2–related factor 2 (Nrf2) and gamma-glutamylcysteine synthetase (γ-GCS) in the liver tissue of hyperlipidemic rats was determined using quantitative real-time polymerse chain reaction, and it was found that Hedan Sanqi Jiangzhi tablet could regulate the levels of TC, TG, and LDL-C in serum and significantly increase the expression of Nrf2 and γ-GCS mRNA in liver tissue [29].

Gypenoside granules could promote the protein expression of ABCA1, increasingly regulate the gene expression of ABCA1, CYP7A1, and SR-BI, and regulate the level of blood lipids [30]. Combined with atorvastatin, Gypenoside granules could synergistically reduce blood lipids. Moreover, modified rhizoma alismatis decoction can reduce serum TG, TC, and LDL-C, significantly increase the content of HDL-C, and regulate the expression of AQP3 gene protein in colon tissue [31]. Additionally, Sini powder can prevent the increase in serum TG and LDL-C levels, increase HDL-C and ApoA-I levels, and significantly increase ApoA-I mRNA expression in the liver [32].

Conclusion

According to many factors that cause these effects, the incidence rate of dyslipidemia is continuously increasing, which affects our health and quality of life. Statins are commonly used in clinical practice. It significantly helps to regulate blood lipid levels. It reduces LDL and TC levels. Statins appear to have a fast-healing efficacy and reduce mortality owing to cardiovascular diseases. Therefore, statins are widely used in clinical practice; however, researchers have also found that using statins alone or in combination with other drugs can cause adverse reactions in patients. It effects the treatment and overall results, namely statin-associated muscle symptoms [33], new-onset diabetes [34], and drug-drug interactions [35].

The role of modern Chinese medicine in regulating blood lipids has become increasingly prominent, with fewer adverse reactions and a high effective rate [36]. TCM believes that dyslipidemia is mainly caused by external factors such as inappropriate diet, excessive consumption of fatty and sweet foods, emotional stress, and exhaustion. The accumulation of phlegm and blood stasis is an internal cause of dyslipidemia. The deposition in the blood vessels after the transformation of lipids appears to be the main factor that causes dyslipidemia to develop into cardiovascular disease. Dyslipidemia is closely related to liver, spleen, and kidney dysfunction. In clinical practice, the treatment of dyslipidemia mainly involves invigorating the spleen to eliminate dampness, promoting qi and resolving phlegm, promoting blood circulation by removing blood stasis, and tonifying the liver and kidney [37].

The treatment of TCM is individualized. TCM choose the appropriate treatment according to the different patients' conditions, such as those with spleen deficiency and excess dampness should be treated by

invigorating the spleen to eliminate dampness. The method of promoting blood circulation by removing blood stasis should be used in patients with phlegm and blood stasis. The treatment methods can change during the disease progression, and dyslipidemia has its own characteristics from mild to severe conditions. Therefore, different treatment methods should be used during dyslipidemia treatment at different stages.

The speed of disintegration and absorption for various TCM dosage forms differ. The time and interval of medication use are also different. The absorption of the pill is slow; therefore, the effect is mild, and the action can last longer. Decoction, liquor, and syrup have faster absorption, and rapid effect. The time of Chinese prescription or the number of times of acupuncture and moxibustion treatment was determined according to the patient's condition, drugs, and other specific conditions. In patients with adverse reactions [38, 39], treatment should be discontinued immediately, and other treatment methods should be used with caution after the symptoms are relieved.

The existing literature is limited, often focusing on the treatment of dyslipidemia using Chinese medicine; the curative effect of Chinese herbal medicine, acupuncture, moxibustion, and acupoint catgut embedding; and only a few studies have integrated treatment of TCM and western medicine using modern scientific methods. TCM treatment of dyslipidemia has the highest degree of development, and there are still many effective reports in the literature to be studied.

Additionally, some challenges persist in treatment using Chinese medicine, such as international nomenclature, body and auricular acupuncture point location in the body area appear to be generally well-defined, quality and safety of Chinese herbal medicines, and lack of standards and specifications that reduce the credibility of TCM. Therefore, a standard treatment for dyslipidemia in TCM must be established to develop and grow globally.

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