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# The Blood-Brain Connection of Alzheimer's Disease: Another Glance after Quarter of a Century

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**ABSTRACT**

Alzheimer's disease (AD) is the most common neurodegenerative cognitive disorder. In recent years, the distinction between AD and vascular dementia has become less clear, as cardiovascular morbidity is commonly exhibited in the AD brain. Nitric oxide (NO) plays multiple roles in the brain and its relationship with AD pathogenesis has previously been explored. Aberrant functioning of the neurovascular unit (NVU) is now known to jeopardize blood-brain barrier integrity, and such abnoramality seems to appear early in AD. Studies on molecular aspects of NVU dysfunction and recent advances on neuroimaging could lead to the possibility of earlier detection of preclinical AD. This review briefly surveys the progress on deciphering the intimate neuro-cardiovascular connections associated with AD and relevant advances towards the developments of translational, neuroimaging, and electrophysiological biomarkers. The current evidence suggests accurate early diagnosis of preclinical AD could be made possible by combination uses of these markers, thereby allowing earlier meaningful therapeutic intervention.

**Keywords:** *Alzheimer's disease; Nitric oxide; Neurovascular unit; Biomarkers; Early detection*

## Background

It has been over two decades since we examined the role of nitric oxide (NO) in the pathogenesis of Alzheimer's disease (AD). NO is a potent vasodilator, a neuro-messenger associated with memory consolidation, and plays immunological roles. It was concluded that NO and its synthesizing enzymes have intricate relationships with AD [1]. Clinically, the demarcation between AD and vascular dementia has become increasingly blurry [2]. Cardiovascular and metabolic disorders appear to intimately associated with the development of cognitive impairments [3, 4]. At the cellular level, endothelial cell dysfunction is evident in hypertension, hypercholesterolemia, and diabetes, thereby leading to aberrant vascular regulation [5, 6]. Similar to the periphery, endothelial linings of brain vessels are also compromised. As neurons, neuroglia, and the endothelium form a functional unit, researchers have proposed that neurovascular dysfunction could be an important upstream culprit for dementing disorders [7]. The hypothesis has since been studied from various perspectives [8-10]. This paper aims to take a glimpse at the most recent advances on related topics.

## Neurovascular dysfunction and Alzheimer's disease

It has been well-recognized that the neurovascular unit (NVU) – comprising of neurons, neuroglia, and the endothelium – maintain the integrity of the blood-brain barrier (BBB) and regulate cerebral blood flow. Previous studies have demonstrated that NVU dysfunction contributes significantly to neurodegeneration [11]. We also hypothesized that such pathology could be an early culprit for neurodegenerative dementias [12]. Animal studies have shown that amyloid or tau pathology would cause brain vessel abnormalities and BBB breakdown [13]. These pathologies have since been shown to develop early during the disease process [14].

NO is produced by four types of nitric oxide synthases (NOS). In the brain, neurons, glial cells, and the endothelium are responsible for its synthesis. Classically, the endothelial form of NOS has been consistently associated with neuroprotection [15]. The inducible NOS - due to its high magnitude of NO release – leads to neurotoxicity as a result of oxidative stress [16]. Neuronal NOS appears to be yielding variable findings [17, 18]. In more recent animal studies, the molecular signaling effects of NO on AD pathogenesis are being elucidated. NO appears to downregulate an essential transporter in myelin-

forming oligodendrocytes, which could be contributing to AD onset [19]. NOS isoenzymes appear to possess multiple roles in the dysfunctional NVU. In a mouse model expressing mutated tau, neurovascular uncoupling secondary to the dissociation of neuronal NOS from postsynaptic densities has been observed. This phenomenon leads to reduce NO production and vasodilation during glutamatergic synapse activities [20]. Research on endothelial NOS-knockout mice showed the endothelial NOS-derived NO appears to be neuroprotective during the aging process, possibly by modulating amyloid precursor protein processing in cerebrovascular endothelium and neuronal tissue [21]. The inducible form of NOS has consistently been associated with neurotoxic effects as it is upregulated during inflammatory response, causing nitrosative stress [22, 23]. From these studies, constitutionally-produced NO by the neuronal and endothelial NOS isoforms appear to be disturbed during neurovascular decoupling – the prelude to NVU dysfunction [20, 24].

Both the astrocytes and pericytes are essential components of the NVU. We previously proposed that astrocytes being an important player in amyloid production through the interaction between S100β peptide and receptor for advanced glycation end product (RAGE) in the ischemic brain [12]. In a recent transgenic animal model of AD, a unique group of astrocytes have been identified – the "disease-associated astrocytes". These cells are found to be in close proximity to the amyloid oligomers and they appear early in the mouse brain prior to any observed cognitive decline [25]. Interestingly, similar cells are also found in the post-mortem brains of AD patients [26]. Pericyte abnormalities have also been noted in animal AD models and in human [27]. AD patients who are apolipoprotein E4 carriers appear to have accelerated pericytic damages [28]. Furthermore, pericyte loss, being assessed by its marker platelet-derived growth factor receptor-β (PDGFR-β), contributes significantly to BBB breakdown [28]. Retinal PDGFR-β decrease has been shown to be correlated to amyloid burden and severity of cognitive decline – from mild cognitive impairments to severe AD - in a human study [27]. In another recent human study, apolipoprotein E4 allele has been shown to be associated with increased hippocampal and medial temporal BBB breakdown, independent of amyloid or tau pathology. Moreover, such abnormality appears even in asymptomatic subjects and is more severe when cognitive deficits become apparent [29]. Taken together, NVU dysfunction and subsequent BBB breakdown appear to begin early during the neurodegenerating process [9, 14].

**Alzheimer's disease – one step closer to earlier detection?**

The large-scale Scandinavian study to examine vascular risk factors and cognitive performance in the elderly population published five years ago reminded us again cardiovascular risk factors are significantly correlated to AD development [30]. AD has been coined "type III diabetes" for more than a decade ago [31]. Primary and secondary preventions have been the advocated management strategies for cardiovascular diseases. For patients with milder cognitive impairments and AD, evidence also clearly suggests the benefits of early intervention [32]. A number of cerebrospinal fluid and blood biomarkers have been developed during the past decade, including those that represent AD hallmarks [33]. These markers, however, only indicate the presence and severity of disease, and their detections bear little relevance on altering the course of the illness. In order to optimize treatment outcome, early detection is therefore warranted. With the sufficient evidence that NVU derangement occurs relatively early in AD, the possibility of developing reliable early biomarkers could become a foreseeable option [34, 35].

In addition to its RAGE binding and subsequent β-site amyloid precursor protein cleaving enzyme upregulation, increases in S100β and neuron-specific enolase levels during BBB opening have been demonstrated [36]. Such findings implicate the feasibility of using these as early serum markers for NVU dysfunction and BBB breach [8, 14, 37]. Glial fibrillary acidic protein (GFAP) is an intermediate filament protein prominently expressed in astrocytes, playing a critical role in astrocytic-neuronal communication [38]. GFAP is not usually present in the periphery; its expression increased significantly during astrogliosis and has been used as a non-specific marker for brain injuries [39]. In a recent study, GFAP has been shown to be elevated in the plasma of AD subject [40]. Ubiquitin carboxyl-terminal esterase L1 is a neuron-specific cytoplasmic enzyme that could be another candidate to measure BBB breakdown [41, 42].

Advances in neuroimaging have allowed remarkable structural and functional visualizations of the ailing brain. Amyloid- and tau-imaging have been used to identify these AD markers [43, 44]. Although these peptides could be observed in preclinical stages of AD, they alone show variable accuracies in relation to the presence of disease [45, 46]. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been accepted as a non-invasive imaging modality to examine BBB integrity. It utilizes a gadolinium-based contrast with molecules small enough to cross a disrupted BBB [47]. Arterial spin labelling MRI is another in vivo tomographic technology that has been developed to quantitatively assess cerebral blood flow [36]. On functional imaging, resting state functional MRI (rs-fMRI) has been deployed to measure blood oxygenation level-dependent (BOLD) signal fluctuation in brain regions of psychiatric and medical patients [48]. Several studies have suggested that alterations in BOLD signaling measured in rs-MRI are implicated in early AD [49]. Functional near-infrared

spectroscopy (fNIRS) is a tool to measure neuronal activities - by detecting hemoglobin concentration changes - that has found its way into evaluating childhood psychiatric presentations [50, 51]. It has been proposed that fNIRS, in combination with other technologies such as dynamic retinal vessel analysis, could offer promising outcomes in predicting vascular cognitive impairments [52, 53].

Electroencephalography (EEG) has been a well-established method to measure brain electrical activities. It has been deemed accurate in differentiating non-demented and demented patients, and could be useful in determining various disease stages [33, 54]. EEG has been used in combination with fNIRS to measure cerebral hemodynamic changes in human performing cognitive tasks [55-57]. In a recent study, EEG data discovered a non-linear relationship with amyloid burden, indicating neuronal compensatory activities during the early preclinical phase of AD [58].

**Concluding remarks**

Since our previous studies twenty-five years ago in examining the complex relationship between NO and AD, vascular disturbance has been increasingly recognised as an important aetiology in AD pathogenesis, with neurovascular dysfunction being an early pathology. We proposed that astrocyte would likely be an influential "co-star in the dementia drama", research has demonstrated that the non-neuronal components of the NVU, not limiting to astrocytes, show aberrant functioning during the dementing process, from neurovascular uncoupling to BBB breakdown.

Since the discovery of AD in 1906, there has been no disease-changing therapeutic breakthrough despite decades of furious research. One possible reason for such failure is "too little too late". The notions of finding one "magical bullet" to halt the disease progress (too little) and to successfully treat the illness when patients are already exhibiting prominent cognitive and non-cognitive symptoms (too late) are unrealistic. Much earlier detection and interventions are therefore highly warranted.

Recent advances in neuroscientific research and neuroimaging techniques should make early detection, or even prediction, of preclinical AD possible. The combination uses of peripheral blood markers of brain microcirculation lesions and multiple structural, functional, and electrophysiological measures discussed here would constitute an informative panel to aid timely diagnosis. Further studies to assess efficacies of early or preventive interventions, using the obtained panel diagnostic results, could possibly revolutionize AD management strategies.

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# Prevalence of and Factors Associated with Depressive Symptoms Among Students in a Life Science Program in Northern Thailand

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## ABSTRACT

**Introduction:** Depressive symptoms is a sign of a mental health problem that causes a persistent feeling of sadness and a loss of interest in activities, and it can cause emotional, functional and physical problems and progress to severe depression. **Objectives:** This study aimed to estimate the prevalence of and identify the factors associated with depressive symptoms among students attending a life science program at a university located in Chiang Rai Province, Thailand. **Methods:** An analytic cross-sectional study was conducted from September to December 2019. A random method was used to select the participants. A validated questionnaire was used to collect socioeconomic information about the participants, and a health questionnaire (PHQ-9) was used to assess the participants' depressive symptoms. Logistic regression was applied to determine the association between the variables at a significance level of $\alpha$=0.05. **Results:** Of 270 students, 160 participants were recruited for the study; 87.5% were female, 43.8% reported that they did not have enough money to support their daily life, 10.0% had a family conflict, 30.6% had been subjected to bullying, and 15.6% reported that they did not consult anyone when facing a problem. The prevalence of depressive symptoms was 20.6%. After controlling for sex and age, two variables were found to be associated with depressive symptoms: family conflicts and having experienced being bullied by peers. Those who had a family conflict were more likely to have depressive symptoms than those who did not (AOR = 4.90, 95% CI = 1.46–16.38), and those who had been bullied were more likely to have depressive symptoms that those who had not (AOR = 3.24, 95% CI = 1.39–7.54). **Conclusion:** Improvements in family member relationships and minimizing bullying among peers at the university are urgently required interventions for preventing depressive symptoms among university students in Thailand.

**Keywords:***Depression symptoms, Prevalence, University students, Family conflict, Bullied experience*

## Introduction

Depressive symptoms is a common illness worldwide, with more than 264 million people affected [1]. Depressive symptoms is different from the usual mood fluctuations and short-lived emotional responses to the challenges in everyday life. Especially when it is long-lasting and has a moderate or severe intensity, depressive symptoms e may become a serious health condition and progress into severe depression. Depressive symptoms and depression can cause people to suffer in their daily lives, function poorly at work, and have difficulties at school and it can develop into domestic violence in the family. At its worst, depression can lead to suicide. Approximately 800,000 deaths due to suicide from depression are reported every year. Moreover, suicide is the second leading cause of death among people aged 15–29 years [2].

Nearly one-half of people living with depression are currently residing in the South-East Asia Region and Western Pacific Region [3]. The Department of Mental Health in Thailand reported that the prevalence of suicide in 2019 was 15.1% among people aged 20–29 years, which correlated with depression [4]. Depression and depression symptoms are clearly defined as a critical mental health problem in Thailand, leading to lost human capacity and lives from suicide, particularly among young adults who are placed under high stress in their daily lives. Among young adults aged 18–22 years

in Thailand, most are studying in the university with chaotic class schedules every day. Students who attend life science programs are much more likely to be faced with difficult classes while in this basic life stage, and they need to explore the world and participate in outdoor activities. However, due to the educational system of Thailand, most people aged 18–22 years are attending classes at a university. Some university students have a difficult time coping with stress due to their class schedule, and they might eventually develop depressive symptoms and/or depression.

In a study of depression among some at-risk populations in Chiang Rai Province, Thailand, a high prevalence of depressive symptoms (38.9%) was found, particularly among people aged 18–22 years [5]. Moreover, in a study of university students in northern Thailand, it was reported that the prevalence of depression was 31.0%, and some specific characteristics of the study population were detected as influencing factors of depression development such as the year of the study, having underlying diseases, and residency region [6]. Therefore, this study aimed to estimate the prevalence of and to identify factors associated with depressive symptoms among students attending life science classes in a university located in northern Thailand.

## Methods

### *Study design and study setting*

An analytic cross-sectional study design was used to obtain information from participants to estimate the prevalence and to determine the factors associated with depressive symptoms among students who were attending a life science program at a university located in northern Thailand. The duration of this study was 4 months, from September to December in 2019.

### *Study population*

The study population were all students attending one of the life science programs in the 2019 cohort at a selected university.

**Table 1** General characteristics and depression of participants

| Characteristics | n | % |
|---|---|---|
| **Total** | **160** | **100.0** |
| **Sex** | | |
| **Male** | 20 | 12.5 |
| **Female** | 140 | 87.5 |
| **Age (years)** | | |
| **≤ 19** | 42 | 26.3 |
| **≥ 20** | 118 | 73.8 |
| **Mean = 20.3, SD = 1.2, Min =17, Max =23** | | |
| **GPAX** | | |
| **≤ 1.99** | 12 | 7.5 |
| **≥ 2.00** | 148 | 92.5 |
| **Sufficiency of monthly allowance** | | |
| **Yes** | 90 | 56.3 |
| **No** | 70 | 43.8 |
| **Parents' marital status** | | |
| **Married** | 110 | 68.8 |
| **Ever married** | 50 | 31.3 |
| **Having a conflict within family** | | |
| **Yes** | 16 | 10.0 |
| **No** | 144 | 90.0 |
| **Having a conflict with friends** | | |
| **Yes** | 27 | 16.9 |
| **No** | 133 | 83.1 |
| **Being bullied from peers** | | |
| **Yes** | 49 | 30.6 |
| **No** | 111 | 69.4 |
| **Having a counselor while facing problem** | | |
| **Yes** | 135 | 84.4 |
| **No** | 25 | 15.6 |
| **Depressive symptoms (PHQ9)** | | |
| **Yes** | 33 | 20.6 |
| **No** | 127 | 79.4 |

**Table 2** Univariate analysis in identifying the factors associated with depression symptoms among the participants

| Variable | Depression present (N = 33) N (%) | Depression absent (N = 127) N (%) | Total | Crude OR ( 95% CI) | *P*-value |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Male | 5 (25.0%) | 15 (75.0%) | 20 | 1.33 (0.44-3.98) | 0.606 |
| Female | 28 (20.0%) | 112 (80.0%) | 140 | 1 | |
| **Age** | | | | | |
| ≤ 19 | 10 (23.8%) | 32 (76.2%) | 42 | 1.29 (0.55-3.00) | 0.553 |
| ≥ 20 | 23 (19.5%) | 95 (80.5%) | 118 | 1 | |
| **GPAX** | | | | | |
| ≤ 1.99 | 5 (41.7%) | 7 (58.3%) | 12 | 3.06 (0.90-10.36) | 0.072 |
| ≥ 2.00 | 28 (18.9%) | 120 (81.1%) | 148 | 1 | |
| **Income sufficiency** | | | | | |
| Not enough | 16 (22.9%) | 54 (77.1%) | 70 | 0.78 (0.36-1.69) | 0.539 |
| Enough | 17 (18.9%) | 73 (81.1%) | 90 | 1 | |
| **Parent marital status** | | | | | |
| Single/ Divorce/ Widow | 15 (30.0%) | 35 (70.0%) | 50 | 2.19 (0.99-4.81) | 0.051 |
| Married | 18 (16.4%) | 92 (83.6%) | 110 | 1 | |
| **Family conflict** | | | | | |
| Yes | 8 (50.0%) | 8 (50.0%) | 16 | 4.76 (1.63-13.88) | 0.004* |
| No | 25 (17.4%) | 119 (82.6%) | 144 | 1 | |
| **Being bullied** | | | | | |
| Yes | 17 (34.7%) | 32 (65.3%) | 49 | 3.14 (1.42-6.96) | 0.004* |
| No | 16 (14.4%) | 95 (85.6%) | 111 | 1 | |
| **Counselor** | | | | | |
| No | 10 (40.0%) | 15 (60.0%) | 25 | 0.20 (1.29-8.12) | ≤0.001* |
| Yes | 23 (17.0%) | 112 (83.0%) | 135 | 1 | |

* Significant level at $\alpha \leq 0.05$

***Study sample***

In 2019, there were 273 students attending a life sciences program at the selected university. Considering the prevalence of depression reported in a previous study to be 31.0% [6], this study attempted to collect information from at least 50.0% of the available cohort.

***Research instruments***

A questionnaire was used to collect information on sex, age, the accumulated grade point average (GPAX), sufficiency of the student's monthly allowance, parents' marital status, status of having a counselor, history of being bullied, and having a family conflict. The questionnaire was tested for reliability and validity by piloting it among 30 subjects who were similar with the study population, and the Cronbach's alpha coefficient was 0.86.

Detection of depressive symptoms among the participants was assessed by the Thai version of the patient health questionnaire (PHQ-9), which is a commonly used and well-validated nine-item screening tool for depression based on the DSM diagnostic criteria for major depression. This instrument contained 9 items and asked about the frequency of depressive symptoms over the past two weeks. Questionnaire items were scored on a 4-point scale from 0 (symptom absent) to 3 (severe symptoms). Then, those who scored ≥ 7 or higher were defined as having depression [7]. The Thai version of the PHQ-9 had satisfactory internal consistency with Cronbach's alpha = 0.79 [8].

**Results**

A total of 160 students participated in this study; 87.5% were female, and 73.8% were aged ≥ 20 years. Twelve people (7.5%) had a GPAX ≤ 1.99, 43.8% reported that their monthly allowance was not sufficient, and 31.3% reported their parents were or had been married. Sixteen persons (10.0%) had family conflicts, 30.6% had been bullied by peers, 15.6% did not consult anyone when facing a problem, and 20.6% had depressive symptoms (Table 1).

In the univariate analysis, three variables were found to be significantly associated with having depressive symptoms: family conflict (OR = 4.7; 95% CI = 1.63–13.88), being bullied (OR = 3.14; 95% CI = 1.42–6.96), and not having a counselor (OR = 0.20; 95% CI = 1.29–8.12) while the other variables did not show any association with depressive symptoms (Table 2).

After controlling for sex and age in the multivariate analysis, two variables were found to be associated with depressive symptoms: being bullied and family conflicts. Students who had family conflicts were more likely to have depressive symptoms than those who did not (AOR = 4.90, 95% CI = 1.46–16.38), and those who had been bullied by their peers were more likely to have depressive symptoms that those who had not (AOR= 3.24; 95% CI=1.39–7.54), respectively (Table 3).

**Table 3** Multivariate analysis in identifying factors associated with depressive symptoms among the participants.

| Factor | AOR (95% CI) | p-value |
|---|---|---|
| **Having a family conflict** | | |
| **Yes** | 4.90 (1.46-16.38) | 0.004* |
| **No** | 1.00 | |
| **Being bullied from peers** | | |
| **Yes** | 3.24 (1.39-7.54) | 0.006* |
| **No** | 1.00 | |

** Significant level at $\alpha$= 0.05 after controlling for sex and age.*

## Discussion

In this study, it was found that the prevalence of depressive symptoms among the students attending a life science program in northern Thailand was 20.6%. This prevalence is different from that reported in a study conducted by Ruanjai et al. [6], which was 31.0% for a similar population. This difference may be due to some new public health interventions have been implemented, particularly the new counseling system implemented for university students after completion of a previous study. Many universities in Thailand have developed a good protocol and guidelines to support mental health services among their students. In a study conducted in India, counsellor-delivered interventions were found to be suitable first-line interventions in a stepped care approach for students with diverse mental health problems [9].

In this study, it was found that family conflict was associated with depressive symptoms among students attending a life science program. Several previous studies showed a similar result: having high family conflicts was associated with depressive symptoms among people aged 22–25 years [10, 11]. In another study, it was clearly demonstrated that having family conflicts or having a poor relationship with parents can result in a child experiencing sadness, fear, guilt, shame, worry and other physiological reactions [12]. It has been reported that having a poor relationship with a parent had a more serious impact on the child than undergoing divorce or separation [13]. Therefore, the findings of this study are consistent with previous research and supports the idea that the parental relationship has a profound impact on youth depressive symptoms development under the Thai family structure and culture.

Moreover, this study also found that students who had experienced bullying by their peers were more likely to have depressive symptoms that those who did not. Obviously, many previous studies have shown a strong association between bullying and depressive symptoms and depression development among young adults, particularly those college students who have critical experiences in emotional loneliness, difficulties in maintaining friendships, lower self-esteem, more fearful attachments, lower health-related quality of life, less friendship quality, shyness, and lower levels of trust [14-17]. Bullying is a form of abuse, causing conflict and frustration [17]. One study reported that having been bullied included other relationship problems with their peers, such as experiencing traumatic events related to peer relationships, which can lead to depressive symptoms and depression development [18]. There are some limitations in this study. First, the participants were recruited from one program in a university, and the results might not be generalizable to all students at the university. Second, this study is cross-sectional, since its primary aim was to estimate the magnitude and then identify the causal relationships between variables that are not clearly explained. The findings of this study need to be validated in a study with a more robust design. In addition, some potentially significant variables, such as a family history of depression and risk-taking behavior, were not considered in this analysis and should be included in future studies.

## Conclusions

A large proportion of students attending a life science program at a university in northern Thailand is facing depressive symptoms. This problem might interfere with student functioning, particularly with their studies, and therefore, the university should develop a program of regular screening for depressive symptoms and closely monitor those who present with some major signs of depression. Minimizing or eliminating bullying behaviors among the students is one of the most important approaches for reducing depressive symptoms and depression problems among university students in Thailand. Additional health interventions should be focused on reducing the problem of having poor parental relationships in the Thai culture.

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# Ergonomic Risk Level Assessment in Building Process at An Automobile Tire Manufacturing

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## ABSTRACT

**Background:** Ergonomic problem among employees who are working in a workplace could induce the performance of employee in either positive or negative direction. Therefore, fixing ergonomic problems in a particular place could be improvement the productivity of a company. **Methods:** Ergonomic risk in the building process, automobile tire manufacturing at a plant in Rayong Province, Thailand were evaluated by using a cross-sectional study. The rapid entire body assessment (REBA) was used as a tool to detect the ergonomic risk and its levels among employees. **Results:** Five tasks or processes of work were found at risk index level 4 which were required immediate improvement or correction; i) pulling the raw cover out of the tire-forming machine, ii) peeling the tread, iii) changing the bead ring in the machine, iv) removing the raw rubber clog in the processing machine, called an extruder, and v) lifting the tread onto the tire building machine. Filling the steel grid with metal powder was found at risk level-3 which was required for further investigation and improvement. Lastly, at the department of the rubber sheet on softer steel called shin-gane was found at risk level 2 which was required to be investigated and continuously monitored. **Conclusion:** The findings of risk assessment from this study could be used for establishing the tire manufacturing safety measures or development a guideline to reduce the risk of ergonomic problems such as musculoskeletal disorders and enhance employees' performance.

**Keywords:** *Ergonomic; Tires; Building process; REBA method*

## Introduction

Ergonomics is an inevitable problem in industries especially in the section of produce parts or large and heavy products like automobile tires. Manual labor is required to lift and move large objects during the production process. This may result in adverse effects or illness. Severe impacts on the health of the workforce can lead to musculoskeletal disorders [1]. The body structure is composed of muscles, joints, ligaments, nerves, bones, and local circulatory systems [2]. Musculoskeletal disorders are a work-related disease caused by assuming the long same position such as standing or sitting for long periods, reduced or no body movement, inadequate rest periods, lifting or moving heavy objects and twisting, bending, or tilting any part of the body when assuming an awkward posture [3]. The symptoms and severity of musculoskeletal disorders depend on the duration and frequency of workload exposure [4] and are expressed from mild to extreme pain. The Labor Force Survey (LFS) reported that disruption to the economy towards the end of 2020 due to the emergence of COVID-19 as a national health issue had the potential to have impacted on workplace injury and work-related ill health. Between 2019 and 2020, a total of 480,000 cases of work-related musculoskeletal disorders were reported throughout the whole Thailand, and it accounted for 1,420 per 100,000 workers [5]. In 2018, musculoskeletal disorders among informal employees related to work behavior were experienced at 43.4% or 1.4 million people [6,7] which was greatly reported among employees working in heavy manufacture.

An automotive tire manufacturing involves several manual operations including material processing, tire building, curing, inspection and storage. Hazard and risk assessment focus on the ergonomic issues in all these operational processes. Employees use different parts of their bodies to lift and move heavy tires. In particular, the tire-building process requires various components, and each has to be moved into the tire-building machine. The tire building machine employees have experience musculoskeletal disorders symptoms (MSDs) which are involving on having ache, pain or body discomfort during and after work. Most frequent report of MSDs are found in several points of body; the shoulder (76.4%), lower back (72.6%), and wrist or hand pain (62.8%) [1].

MDS affects physical health, mental health and

work performance. The main impacts resulting from work-related musculoskeletal disorders are increased days off work, increased medical expenses and decreased productivity. The study of ergonomic risk level provides the necessary information for working process improvement through enhanced workstation design. Both proactive and passive control measures can be used to determine healthcare policies or work safety health promotions, with the ultimate goal of reducing fatigue, injury and musculoskeletal disorder by eliminating risk from improper work postures. Safety and well-being are basic human rights. Focusing on productivity or organizational profit is no longer the trend in modern industry that now recognizes the importance of the human resource. The promotion of health and safety at work will bring great benefits to any establishment, while also creating a good company image. This study assessed the ergonomic risk levels among employees working in the automobile tire-building process. The findings could be used for reducing the risk and improvement the performance of employees. Some specific guideline also could be developed to use in the similar settings.

## Methods

A cross-sectional study was used to collect information from participants who were working in a tire manufacturing plant located in Rayong Province, Thailand between March and May 2020. Employees who were working in five departments were observed and assessed the risk; material preparation, tire-building, curing, product inspection and warehouse storage. At the tire-building process, it was focused ergonomic problems caused by exertion lifting characteristics and heavy tire movement during the tire-building process. Six of 18 workers were observed and recorded a video to assess the problem in later. Body posture was analyzed using a rapid entire body assessment (REBA) [8], which is one of the sensitive and specific of observational posture analysis ergonomic tools. The tool is used to assess an articular angle, observing the force load and movements' repetitiveness and the postural changes' frequency [8]. REBA divides the body position into segments and is coded independently according to movement planes. A scoring system is assigned for muscle activity throughout the entire body, stagnantly, dynamically, fast-changing, or in an unsteady way, where manual handling may occur [8]. Neck, trunk, legs, arms and wrist postures are assembled into ranges. Each positional range, corresponding to the anatomical areas assessed, is related to a score corresponding to the values that get increasingly higher as the distance from the segment's neutral position increase.

*Measurement interpretation*

Score "A" represents the summation of the posture scores for the neck, trunk and legs. The force or load score which is determine the load or force required to perform the task is added. Score "B" is the sum of the posture scores for arms, and wrists and the coupling score for each hand. The coupling score between 0-3 is added. The score at "0" when there is a well-fitting handle with mid-range power grip, "1" when acceptable but not ideal hand hold or coupling acceptable with another body part, "2" when and hold not acceptable but possible, and "3" if no handles, awkward, and unsafe with any part of body.

The "A" and "B" scores are combined and finally, an activity score that describes any static postures held for longer than one minute and repetition at more than four times per minute, large rapid changes in postures, or an unstable base which will be either "0" or "1" is added to give the final REBA score.

Then the REBA score has been converted into action levels between "0" and "4", which is defining whether action is required and its urgency [9] (Table 1).

## Results

Employees worked in the tire-building process had different postures which could have diverse risks of injury from ergonomic problems while working in seven different tasks or processes as follows: i) pulling the raw cover out of the tire-forming machine, ii) peeling the tread, iii) changing the bead ring in the machine, iv) removing the raw rubber clog in the processing machine, called an extruder, v) lifting the

**Table 1** Rapid entire body assessment action levels.

| **Action level** | **REBA score** | **Risk level** | **Action** (Including further assessment) |
|---|---|---|---|
| 0 | 1 | Negligible | None necessary |
| 1 | 2-3 | Low | May be necessary |
| 2 | 4-7 | Medium | Necessary |
| 3 | 8-10 | High | Necessary soon |
| 4 | 11-15 | Very high | Necessary now |

**Table 2.** Rapid entire body assessment score for each of the seven tasks.

| Task | Task characteristic | Posture | REBA score | REBA action level |
|---|---|---|---|---|
| ***No.1*** Pulling the raw cover out of the tire-forming machine | Bending out the body to remove the raw cover from the tire-forming machine. |  | 11 | 4 |
| ***No.2*** Peeling the tread | Bending over and reaching out with the arms to peel the tread, which is then placed on the top of a pallet on the floor. |  | 11 | 4 |
| ***No.3*** Changing the bead ring in the machine | Bending the trunk and raising the legs as support during lifting the bead ring from the machine. |  | 10 | 4 |
| ***No.4*** Removing the raw rubber clog in the extruder | Bending the trunk to remove the raw rubber clog in the machine, which is a batch process for mixing and heating. |  | 8 | 4 |
| ***No.5*** Lifting the tread onto the tire building machine | Exerting wrist and arm to support the sheet tread onto the building machine. |  | 8 | 4 |
| ***No. 6*** Filling the steel grid with metal powder | Standing and bowing head to fill the steel grid with metal powder. |  | 4 | 3 |
| ***No.7*** Placing the rubber sheet on shin-gane | Bending and reaching out to place the rubber sheet on shin-gane. |  | 3 | 2 |

steel grid with metal powder, and vii) placing the rubber sheet on softer steel called shin-gane. The REBA score of each task or process is shown in Table 2.

Five postures of work in seven tasks or processes in tire building were dentified in the ergonomic risk at level 4; i) pulling the raw cover out of the tire-forming machine, ii) peeling the tread, iii) changing the bead ring in the machine, iv) removing the raw rubber clog in the processing machine, called an extruder which is a batch process for mixing and heating, and v) lifting the tread towards the tire building machine. These indicated that many tasks or processes of work were required to be improved immediately.

A posture of work in the task or process of filling the steel grid with metal powder was found in having an ergonomic risk level 3 which was required future investigation and improvement. While the posture in task or process on bending and reaching out to place the rubber sheet on shin-gane was needed the action level 2 which was needed more attention.

**Discussion and conclusion**

The postures of work in seven tasks or processes in the tire building process are facing an ergonomic risk due to having improper postures which are violated the nature of the body such as bowing the head and trunk, reaching out with the arms and knee bending. Many important ergonomic risk factors were reported in the previous study, and indicated to remove and lift the threats from the stack; a) awkward postures by the leaning forward and lateral bending; overreaching and forceful exertion creates tension as well as discomfort at lower back and lower legs; b) body discomfort area including hand, wrist, arms, neck, shoulder, back and legs; c) tacky surface and weight of thread contribute to force loading to the body parts especially the wrist [1].

These postures can cause an injury, illness or physical pain to the employees. Previous findings were also reported that the ergonomic problems occurred by improper and repetitive work posture over long periods, together with heavy lifting exertion. Moreover, body stress could induce back pain with resultant musculoskeletal disorder [10].

We recommend the prevention measures to reduce the ergonomic risk in the tire building process as follows: i) use lifting equipment to raise heavy objects which will reduce exertion to within the body capabilities and eliminate work postures that violate natural muscle use, especially when pulling the raw cover out of the tire-forming machine and changing the bead ring during the task; ii) redesign the workstation to be high and appropriate for staff physique to prevent the need for bending over while working, especially during peeling the tread and filling the steel grid with metal powder; iii) apply a rubber mat to reduce fatigue from standing for long periods; iv) Adequate rest time should be provided to reduce fatigue during work; v) health promotion activities should be implemented such as exercises with proper posture before starting work, focusing on body parts that may become fatigued; vi) organize a campaign or train and educate employees to have more aware of the dangers of ergonomic risks and the importance of their health.

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# Arterial Stiffness and Cardiac Autonomic Function in Severe Obstructive Sleep Apnea Patients without Continuous Positive Airway Pressure

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## ABSTRACT

**Background:** Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and contributes to increased morbidity and poor cardiovascular outcomes. It is one of the risk factors for cardiovascular disease. **Objective:** This study aimed to determine the associations between sleep apnea parameters and arterial stiffness, cardiac autonomic function, and evaluate changes in arterial stiffness and cardiac autonomic function in patients with severe OSA without continuous positive airway pressure (CPAP) treatment. **Methods:** Twenty severe OSA patients without CPAP treatment were recruited for this study. All participants underwent arterial stiffness evaluation by carotid-femoral pulse wave velocity (PWV) using a SphygmoCor device, and cardiac autonomic function by heart rate variability (HRV) measurement using LabChart-7. All participants were measured using these medical instruments at baseline on day 0, day 90, and day 180. Associations between sleep apnea parameters and HRV parameters were observed during the supine and tilt positions. The significance levels were set at $\alpha = 0.050$ and 0.001, respectively. **Results:** There was no significant association between sleep apnea parameters and PWV. HRV showed significant changes at day 90 (p-value < 0.001) and day 180 (p-value < 0.001). PWV increased significantly after day 180 without CPAP treatment. **Conclusions:** This study revealed that sleep apnea indices are associated with cardiac autonomic function. OSA patients without CPAP treatment have deteriorated cardiac autonomic function in the supine and tilt positions and increased arterial stiffness after day 180.

**Keywords:** *Obstructive sleep apnea; Arterial stiffness; Heart rate variability*

## Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and contributes to increased morbidity and poor cardiovascular outcomes [1]. OSA has been recognized as a major public health issue, as it has a significant influence on the incidence and prognosis of cardiovascular diseases [2]. Pathologic cardiovascular changes are associated with OSA along with many other factors. Repetitive obstructive events during sleep cause intermittent hypoxia (IH), resulting in the activation of oxygen free radicals and oxidative stress response. The concurrent presence of inflammation is linked to damage to the vascular endothelium, leading to atheroma formation, vascular events, [3] and increased sympathetic nervous system (SNS) [4]. Therefore, the adverse effects of OSA could develop a serious health challenge.

The cardiometabolic biomarkers commonly used to assess changes in vascular events and cardiac autonomic function, with two parameters are: i) carotid-femoral pulse wave velocity (cfPWV), and ii) heart rate variability (HRV). The cfPWV is the gold standard for assessing large artery stiffening because it reflects vessel status predominantly in the central aorta and proximal elastic arteries [5]. HRV is used for cardiac autonomic function, which is a noninvasive method [4]. However, there is limited information available on the associations between arterial stiffness, cardiac autonomic function, and sleep apnea severity.

Currently, continuous positive airway pressure (CPAP) therapy in the OSA patients is accepted as the 'gold standard' treatment for the management of OSA, globally. It can reduce symptoms and improve the quality of life of patients [6]. Although several clinical studies have demonstrated the effective outcome of CPAP on various biomarkers [7], there are still questions on the results. Regarding cfPWV and HRV, CPAP is associated with a deterioration of 1.21 m/s in cfPWV. HRV is calculated by the low-frequency power (LF), high-frequency power (HF), or the square root of the mean of the sum of the squares of the differences between adjacent NN intervals (RMSSD) and LF/HF representing SNS, and sympathovagal

balance, respectively. In patients with OSA, LF and LF/HF ratio is higher, while it is lower when compared with those of healthy subjects, and LF is greater while HF and LF/HF ratio are not different after non-CPAP treatments [8–10].

It is not clear whether there is any change in autonomic function and arterial stiffness in patients with severe OSA without CPAP treatment. This study aimed to determine the association between autonomic function and arterial stiffness and sleep apnea parameters, and to determine the changes in autonomic function and arterial stiffness in patients with severe OSA without CPAP treatment.

## Methods

### *Study participants and characteristics*

This study was a non-randomized, open-label design. Twenty patients with severe OSA were recruited into the study; nine males and 11 females, aged 30 years or older. Patients with a history of smoking, cardiovascular, neuromuscular, or pulmonary disease, severe microvascular diabetic complications, diabetes mellitus, hypertension (blood pressure ≥ 140/90 mmHg), arthritis, and patients who chose CPAP treatment were excluded from the study. The purpose, benefits, and possible risks associated with the study were explained to the participants before obtaining informed consent on a voluntary basis. The study protocol and all procedures used in the study were approved by the Khon Kaen University Ethics Committee for Human Research (IRB No. HE591202).

### *Research procedure*

All OSA patients who were newly diagnosed by medical specialists using polysomnography (PSG) within the month preceding the beginning of the study were recruited from the Sleep Disorder Clinic at Srinagarind Hospital, Khon Kaen, and Thailand. OSA patients had an apnea-hypopnea index (AHI) of at least 30 events per hour and no history of treatment for OSA with CPAP or oral devices, tracheostomy, or the use of oxygen therapy at home. The choice of being treated on a non-CPAP treatment was based on individual reasons such as financial problems. All participants were screened by a physician. Patients received a general health care treatment program for OSA, including nasal spray for nasal allergies and sleep hygiene education, which comprises a variety of methods to obtain good sleep quality, such as avoiding caffeine and strenuous work towards bedtime, preparing a good sleep environment, exposure to natural light, etc.

After recruitment, all participants were asked to provide genetic information such as age, gender, smoking, epworth sleepiness scale (ESS), and medical history. Physical examination was performed to obtain information on height, weight, and body mass index (BMI). Peripheral blood pressure and heart rate were measured using a blood pressure monitor (Omrom, Japan) at rest on the left upper arm three times consecutively, and the average value was used for the study. Participants

Arterial stiffness was assessed using the SphygmoCor device to determine the carotid-femoral pulse wave velocity (PWV). Heart rate variability (HRV) was measured using LabChart 7 to determine cardiac autonomic function. All measurements were performed at baseline and repeated at day 90 and day 180.

### *Outcome measures*

#### a) Polysomnography

OSA patients underwent full-night PSG using a digital system at the Sleep Disorder Clinic, Faculty of Medicine (Srinagarind Hospital, Khon Kaen University). PSG was performed using a previously described procedure [8]. Briefly, apnea was defined as a decrease in the amplitude of airflow of at least 90.0% for at least 10 seconds and continued respiratory effort. Similarly, hypopnea was defined as a reduction in airflow of at least 30.0%, which coincided with a decrease in oxygen desaturation of at least 3.0% [9].

#### b) Arterial stiffness measurement

Before cfPWV, participants were asked to rest until the vital signs were normal. The central arterial blood pressure and cfPWV were assessed non-invasively in all participants using the SphygmoCor device (AtCor Medical, West Ryde, and Australia). The cfPWV was performed using a procedure described previously [10] and assessed by sequential recordings of the arterial pressure waveforms at the left carotid artery and left femoral artery. The distance between the two arterial sites was measured. The pulse transit time was the average of 10 consecutive beats. The cfPWV was calculated as the ratio of the distance in meters to the transit time in seconds.

#### c) HRV measurement

Before HRV, the participants were asked to rest until the vital signs were normal. HRV was measured by an autoregressive power spectral analysis of RR electrocardiographic interval acquisition (LapChart 7, Power Lab 26TADINSTRUMENTS, and Australia). HRV was performed using a previously described procedure [11]. In summary, the test involved lying quietly on a bed (V.S. ENGINEERING, US.) for 10 min, tilted at an angle of 70° for a period of 10 min while electrocardiogram (EKG) was being monitored. HRV was analyzed during the 5-min period just before tilting during supine rest and during the 5-min period immediately after the tilt.

### *Statistical Analyses*

Statistical analyses were performed using STATA version 13.0 (StataCorp, College Station, TX, USA). Data are expressed as the mean and standard deviation (SD). The Shapiro-Wilk test was used to

screen the data. A repeated-measures analysis of variance (Repeated ANOVA) was used to compare arterial stiffness and heart rate variability parameters between days 0, 90, and 180. The Bonferroni post-hoc test was used to detect the significant pairs. Pearson correlation (r) analysis was used to assess the correlations between variables, and at a significance level of $\alpha = 0.050$.

***Results***

The mean age of the 20-OSA patients was 44.4 years (± 11.9) (Table 1); 9 males and 11 females. All patients were diagnosed with severe OSA, in which the information was supported by the AHI indexes: respiratory effort-related arousals, respiratory disturbance index, arousal index, apnea index, and lowest $SpO_2$.

In the supine position, AHI was found to be positively correlated with LF (r = 0.38; p-value < 0.050) and LF/HF ratio (r = 0.37; p-value < 0.050), but had a negative correlation with HF (r = -0.37; p-value < 0.050). The arousal index was found to be positively correlated with LF (r = 0.38; p-value < 0.050) and LF/HF ratio (r = 0.36; p-value < 0.050), but negatively correlated with HF (r = -0.40; p-value < 0.050). Apnea index was found to be positively correlated with LF (r = 0.35; p-value < 0.050) and LF/HF ratio (r = 0.32; p-value < 0.050), but had a negative correlation with HF (r = -0.38; p-value < 0.050). The lowest $SpO_2$ was found to be negatively correlated with LF (r = -0.39; p-value < 0.050) and LF/HF ratio (r = -0.33; p-value < 0.050) but showed a positive correlation with HF (r = 43; p-value < 0.010). In the tilt position, LF was found to be positively correlated with AHI, arousal index, and apnea index (r = 0.62, 0.64, and 0.61, respectively; p-value < 0.010), but had a negative correlation with the lowest $SpO_2$ (r = -0.42; p-value < 0.05). The LF/HF ratio was found to be positively correlated with AHI,

**Table 1.** Baseline demographic and polysomnographic data in OSA patients.

| **Demographic data** | **OSA patients** (n = 20) |
|---|---|
| Age (years) | 44.4 ± 11.9 |
| Gender (M/F) | 9/11 |
| Height (cm) | 165.2 ± 3.4 |
| Weight (kg) | 68.0 ± 7.8 |
| BMI ($kg/m^2$) | 25.9 ± 3.7 |
| Neck circumference (cm) | 32.9 ± 1.4 |
| Waist circumference (cm) | 86.3 ± 6.5 |
| Hip circumference (cm) | 93.9 ± 1.7 |
| Epworth sleepiness scale | 16.2 ± 1.5 |
| Heart rate (/min) | 88.7 ± 11.1 |
| Systolic BP (mm Hg) | 129.0 ± 8.7 |
| Diastolic BP (mm Hg) | 85.4 ± 11.0 |
| MAP (mm Hg) | 99.0 ± 11.6 |
| **Polysomnographic data (day-0)** | |
| Apnea hypopnea index (/h) | 38.9 ± 4.1 |
| Respiratory effort related arousals (/h) | 43.2 ± 11.4 |
| Respiratory disturbance index (/h) | 63.7 ± 13.8 |
| Arousal index (/h) | 53.6 ± 11.0 |
| Apnea index (/h) | 19.4 ± 8.5 |
| Lowest $SpO_2$ (%) | 82.7 ± 3.1 |

Data are expressed as mean ± SD. OSA: obstructive sleep apnea; airway pressure; M: male; F: female; BMI: body mass index; BP: blood pressure MAP: mean arterial pressure.

arousal index, and apnea index (r = 0.56, 0.57, and 0.54; p-value < 0.010), but showed a negative correlation with the lowest $SpO_2$ (r = -0.33; p-value < 0.050). There were no statistically significant correlations between sleep severity indices and arterial stiffness parameters (Table 2).

Among patients without CPAP therapy, the significant deterioration of the SDNN, LF, HF, LF/HF ratio, and RMSSD markers after day 90 (p-value < 0.010) and after the day 180 (p-value < 0.001), statistically significant differences were detected. Moreover, the SDNN (p-value < 0.001), HF (p-value < 0.001), RMSSD (p-value < 0.01), LF (p-value < 0.010), and LF/HF ratio (p-value < 0.001) were significantly impaired when compared with the values between day 180 and day 90 (Table 3). Nevertheless, in patients without CPAP therapy, the deterioration of SDNN (p-value < 0.010), LF (p -value < 0.010), and LF/HF ratio (p-value < 0.010) after day 180 were statistically significant differences. However, the SDNN (p-value < 0.050), LF (p-value < 0.010), and LF/HF ratio (p-value < 0.050) were significantly impaired when comparing between day 180 and at day 90 (Table 3).

## Discussion

In summary, the main findings of this study were as follows: (I) sleep apnea indices were associated with heart rate variability, (II) OSA patients without CPAP treatment had deteriorated cardiac autonomic function in the supine and tilt positions, and (III) arterial stiffness was significantly increased after the day 180 in patients with severe OSA without CPAP treatment.

According to the associations between sleep apnea indices and cardiac autonomic function, it was consistent with some previous studies [12, 13], while cardiac autonomic function was assessed by the assessment of HRV. In the analysis of HRV, the LF component was mainly correlated with sympathetic efferent activity and vagal activity or parasympathetic activity. The LF/HF ratio served as the specific index of sympathovagal balance [14, 15]. The severity of sleep apnea parameters was correlated with several directions of the makers: increases in LF, decrease in HF, and increase in LF/HF ratio. The correlation between indices of sleep apnea severity and sympathetic activity may be due to increased ventilatory effort during sleep. This is the result of obstructed breathing in apneic or hypopneas episodes, that could contribute to frequent arousals and increased sympathetic activity [16]. A previous study demonstrated that the OSA measurement of HRV in postural supine to tilt testing was a significant cause for different indexes: decreased LF, decreased LF/HF rate, increased SNS, and decreased in both HF and PNS. Furthermore, OSA patients without CPAP treatment showed deterioration of the cardiac autonomic function in the supine and tilt positions, and an increase in the arterial stiffness parameter. In this study, sympathetic activity increased, but vagal activity was reduced in OSA patients without CPAP treatment. Moreover, it seems that patients with OSA have a higher arousal index and a higher degree of hypoxemia, which triggers sympathetic overactivity. Without CPAP

**Table 2** Associations between heart rate variability, arterial stiffness parameters and sleep severity in OSA patients

| | | **OSA patients** (n=20) | **Correlation coefficient** (r) | | | |
|---|---|---|---|---|---|---|
| | | | AHI | Arousal index | Apnea index | Lowest $SpO_2$ |
| **Heart rate variability** | | | | | | |
| **Supine position** | SDNN (ms) | 49.2 (2.3) | -0.11 | -0.19 | -0.23 | 0.16 |
| | RMSSD (ms) | 37.2 (13.8) | 0.03 | 0.04 | 0.05 | -0.10 |
| | LF (n.u.) | 53.9 (15.8) | 0.38* | 0.38* | 0.35* | -0.39* |
| | HF (n.u.) | 41.2 (11.9) | -0.37 * | -0.40* | -0.38* | 0.43** |
| | LF/HF ratio | 1.6 (0.9) | 0.37* | 0.36* | 0.32* | -0.35* |
| **Tilt position** | SDNN (ms) | 41.3 (12.4) | -0.01 | -0.08 | -0.11 | 0.00 |
| | RMSSD (ms) | 27.3 (10.9) | -0.09 | -0.17 | -0.21 | 0.08 |
| | LF (n.u.) | 67.5 (14.5) | 0.62** | 0.64** | 0.61** | -0.42* |
| | HF (n.u.) | 28.2 (7.4) | -0.18 | -0.18 | -0.17 | 0.01 |
| | LF/HF ratio | 2.6 (1.0) | 0.56** | 0.57** | 0.54** | -0.33* |
| **Arterial stiffness** | | | | | | |
| | Pulse wave velocity (m/s) | 7.9 (0.6) | -0.07 | -0.01 | 0.02 | 0.22 |

Data are expressed as mean (SD). $SpO_2$: oxygen saturation; AHI: Apnea hypopnea index; SDNN: The standard deviation of NN intervals; RMSSD: Root mean square of successive differences; LF: Low frequency; HF: High frequency. * p-value < 0.050, ** p-value < 0.010.

**Table 3** Heart rate variability and arterial stiffness parameters in OSA patients

| | | Outcome at | | |
|---|---|---|---|---|
| | | Day-0 | Day-90 | Day-180 |
| **Heart rate variability** | | | | |
| **Supine position** | SDNN (ms) | 49.2 (2.3) | 59.0 (2.7)$^{§§§}$ | 64.9 (3.0)$^{ϒϒϒ, ββ}$ |
| | RMSSD (ms) | 37.2 (13.8) | 33.5 (12.5)$^{§§}$ | 26.8 (10.0)$^{ϒϒϒ, ββ}$ |
| | LF (n.u.) | 53.9 (15.8) | 64.7 (18.9)$^{§§§}$ | 71.2 (20.8)$^{ϒϒϒ, ββ}$ |
| | HF (n.u.) | 41.2 (11.9) | 37.0 (10.7)$^{§§§}$ | 29.6 (8.6)$^{ϒϒϒ, βββ}$ |
| | LF/HF ratio | 1.6 (0.9) | 2.1 (1.2)$^{§§§}$ | 2.8 (1.7)$^{ϒϒϒ, ββ}$ |
| **Tilt position** | SDNN (ms) | 41.3 (12.4) | 50.7 (17.6) | 63.4 (22.0)$^{ϒϒϒ, β}$ |
| | RMSSD (ms) | 27.3 (10.9) | 31.4 (13.9) | 28.2 (12.5) |
| | LF (n.u.) | 67.5 (14.5) | 74.1 (20.0) | 92.6 (25.0)$^{ϒϒϒ, ββ}$ |
| | HF (n.u.) | 28.2 (7.4) | 29.2 (10.0) | 26.3 (9.0) |
| | LF/HF ratio | 2.6 (1.0) | 3.0 (1.7) | 4.1 (2.3)$^{ϒϒ, β}$ |
| **Arterial stiffness** | | | | |
| Pulse wave velocity (m/s) | | 7.9 (0.6) | 8.1 (0.4) | 8.4 (0.5)$^{ϒ}$ |

Data are expressed as mean (SD): $^{§§}$ p-value < 0.010, $^{§§§}$ p-value < 0.001 day 0 vs. day 90; $^{ϒ}$ p-value < 0.050, $^{ϒϒ}$ p-value < 0.010, $^{ϒϒϒ}$ p-value < 0.001 day 0 vs. day 180; $^{β}$ p-value < 0.050, $^{ββ}$ p-value < 0.010, $^{βββ}$ p-value < 0.001, day 90 vs. day 180

treatment, it may promote severe damage caused by sympathetic overactivity in OSA patients.

In this study, the tilted position registered no statistically significant correlation between arterial stiffness and sleep apnea severity. However, it presented a significant increase in PWV after the 180 day without CPAP treatment in severe OSA patients. The study also found that the PWV was significantly higher in patients with OSA while comparing to healthy Thais [10]. The mechanism of the increase in pulse wave velocity could be explained by intermittent hypoxia resulting from activated oxygen free radicals and oxidative stress response. A concurrent study on inflammation has reported that damage to the vascular endothelium leads to atheroma formation and vascular events [3], which consequently leads to arterial stiffness. A previous study demonstrated that the LF/HF ratio was positively correlated with changes in brachial-ankle PWV [17]. The occurrence of changes in the sympathovagal balance might be correlated with the increase in arterial stiffness of the central to middle-sized arteries in patients with OSA.

This study clarified the associations among many markers in severe OSA patients without CPAP treatment: autonomic function, arterial stiffness, and sleep apnea parameters and changes in autonomic function and arterial stiffness. This study also found that OSA patients without CPAP treatment could have worsened cardiac autonomic function and increased arterial stiffness.

This study has some limitations. First, this study did not record the dietary and sleep diaries of OSA patients. Second, to ensure the associations between markers, it needs the longitudinal study particularly in assessing the changes in autonomic function and arterial stiffness in severe OSA patients without CPAP treatment. Finally, in further studies, it should determine the changes in sleep duration or dietary affect arterial stiffness, and the effect of optional OSA treatment programs such as lifestyle modification or oral devices on cardiac autonomic and arterial stiffness in OSA patients. In clinical application, this study provided information about the disadvantage of non-CPAP treatment on cardiac autonomic and arterial stiffness in OSA patients.

## Conclusions

The present study shows that sleep apnea indices are associated with cardiac autonomic function. OSA patients without CPAP treatment have a deterioration in cardiac autonomic function in the supine and tilt positions and increase arterial stiffness after day 180.

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# COVID-19 Outbreak in the Chiang Rai Border Area due to Illegal Immigration to Thailand: A Field Investigation

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## ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) is a novel serious infectious disease to humankind. The COVID-19 pandemic has led to the deaths of many people worldwide almost a year (the year of 2020). Countries are implementing several public health measures, and some, such as Thailand, have successfully controlled the spread of the disease. However, imported cases are a major threat to a country like Thailand. **Methods:** A field investigation was conducted to identify positive cases and implement control measures for COVID-19 cluster cases reported who illegally entried into Thailand in the Chiang Rai Province, Thailand, between November 28, 2020, and December 5, 2020. Moreover, public health measures were implemented to control and prevent the disease. Cases of new infections were closely monitored to assess the effectiveness of the implemented control measures for at least two incubation periods (28 days). **Results:** A total of 15 COVID-19 cases (nine cases resided in Chiang Rai Province): 14 women and one man (contacted indexed case) were reported in a clustered outbreak in the Chiang Rai Province from late November to December 5, 2020. Twelve Thai women of 14 cases who had returned from working at a hotel in Myanmar tested positive for COVID-19 in late November 2020. A 28-year-old Thai man who was in close contact with one of these women tested positive for COVID-19 on December 2, 2020. Among the 12 women, nine had illegally entered Thailand, while three had legally entered the country and were isolated and treated at the Chiang Rai Prachanukroh Central Hospital. The illegal entrants included three from Chiang Rai, three from Chiang Mai, and one each from Pha Yao, Phi Chit, Bangkok, and Rat Cha Buri Provinces. Among the imported cases, about 50.0% were asymptomatic, and the average age was 26.1 years (Min = 21, Max = 26). Five symptomatic patients were admitted to public hospitals and received standard care. Those who had no specific signs or symptoms were under close monitoring and were observed in a hospital. Several public health measures were implemented at all levels in the provinces. **Conclusion:** Illegal crossing border is one of the most significant factors of COVID-19 outbreaks in Thailand. However, immediate responses with effective public health interventions to prevent and control the spread of the disease (contact tracing), including effective communication and strong collaboration among partners, are key factors for success in halting the spread of COVID-19 in Thailand.

**Keywords:** *COVID-19; Illegal crossing border; Investigation; Public health control measure*

## Introduction

Coronavirus disease 2019 (COVID-19) is a serious infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SAR-CoV-2) [1]. The disease spreads primarily through droplets generated when an infected person coughs, sneezes or speak [1]. Since its first report in Wuhan, China, on December 31, 2019 [2], more than 78 million cases of infection and 1.7 million deaths have been reported worldwide [3]. On December 4, 2020, the World Health Organization (WHO) stated that the USA had reported the largest number of cases, followed by Europe and Southeast Asia (SEA) [3]. Among the countries in SEA, Indonesia reported the highest cumulative confirmed cases (549,508) and deaths (17,199), followed by the Philippines (434,357 confirmed cases and 8,436

deaths) and Myanmar (92,189 confirmed cases and 1,972 deaths) [4]. During the pandemic of the disease, many countries have implemented several control and prevention measures to save their citizens such as keeping social distancing, improving personal hygiene, etc. [5].

On January 13, 2020, Thailand has been reported the first case of COVID-19 which was the first case outside China [6]. By December 3, 2020, a total of 4,026 confirmed cases had been reported in Thailand, with 60 deaths. On the same day, Thailand's Ministry of Public Health reported 18 newly confirmed cases within 24 hours; all of them were imported [7]. Almost one year from the first reported case of COVID-19 in Thailand, several cases were reported throughout the country in different populations and different settings [8, 9]. Considering that Myanmar has been reported as one of the countries with the highest number of newly confirmed cases per day in the world [10], people in Thailand are at a high risk of infection due to the more than 2,400-km long border shared between countries with a large migrant population reported each year [11, 12]. Chiang Rai Province is located in the northernmost region of Thailand and has both permanent and temporary ports of entry or crossing channels [13]. More than 1.2 million people live in Chiang Rai Province; approximately 30.0% of the total population here belongs to the hill tribe and other stateless populations with poor economic and educational status [14, 15]. Poorly educated populations are highly vulnerable to infectious diseases [16, 17], including COVID-19 [18].

Imported cases of COVID-19 are common in Thailand. The epidemiologists and surveillance and rapid response team (SRRT) working at local and national levels promptly implemented appropriate prevention and control measures to stop the spread of the disease. There have been recognized by the WHO and are being used as the key success models to be applied in other countries [19]. This study demonstrates the system, implementations, and outcome of SRRT measures in COVID-19 prevention and control among those who illegally entered into Thailand in Chiang Rai Province.

## Methods

A field investigation [20] was conducted to identify positive cases and implement control measures for COVID-19 cluster cases reported in the Chiang Rai Province, which has various entry ports into Thailand from Myanmar, between November 28, 2020, and December 5, 2020. The data were collected and analyzed along the implementation time.

**Step 1 – Preparation for fieldwork:** All SRRTs at subdistrict, district, provincial, regional, and national levels in Thailand have well-developed structure and functions. During the COVID-19 outbreak, several training programs have been implemented to ensure that all team members are able to conduct their roles under the Thai regulations for disease control and prevention. Infrastructure, including essential medicines and standard care protocols, were provided at all levels. All relevant systems were tested multiple times during the reported period of the COVID-19 pandemic.

**Step 2 – Confirming the diagnosis:** On December 2, 2020, the first new cluster of COVID-19 cases was reported through the provincial COVID-19 information system. After testing positive for COVID-19 at a private hospital in Thailand, all cases were referred to the Chiang Rai Prachanukroh Central Hospital, which is one of the largest public hospitals in northern Thailand for a repeat COVID-19 test. Nasopharyngeal swab specimens were collected. The specimens were then transferred and tested for COVID-19 at the Regional Medical Sciences Center, Chiang Rai. Confirmed positive test results were reported to a medical doctor at the Chiang Rai Prachanukroh Central Hospital. Simultaneously, the information was reported to the Chief of the Chiang Rai Provincial Public Health Office.

Real-time polymerase chain reaction (RT-PCR) testing for the N-gene and ORF-1b gene was used to detect COVID-19 infection. QIAStat-Dx respiratory 2019-nCoV Panel was used as the reagent for RT-PCR for the first time. All positive test results and RT-PCR with the Logix Smart COVID-19 reagent were re-tested for confirmation before submitting the final report to the clinician. All PCR procedures were run on "Applied biosystem" version 7500 RT-PCR.

**Step 3 – Determining the existence of the outbreak:** The head of the provincial-SRRT was immediately informed of the positive test results, and the team started gathering information on the existence of an outbreak. COVID-19 is listed as a serious disease in Thailand and requires immediate investigation and control. Therefore, this instance was considered an outbreak of the disease. The next steps of disease investigation and control were required.

**Step 4 – Identifying and tallying cases:** Public health protocols and guidelines state that all confirmed cases of COVID-19 and those exposed to persons confirmed to have COVID-19 need to be indexed and instructed to follow public health control measures. All individuals exposed to persons with confirmed COVID-19 were classified as high-risk or low-risk. Those in the high-risk group were immediately tested for the disease following the standard procedure. Those with positive test results were isolated in a negative pressure room in a hospital for proper treatment and care. Those who had negative results were quarantined for at least 14 days. In addition to the individual measures, all environments, including schools, restaurants, and personal living residences, were cleaned with disinfecting solutions.

**Step 5 – Tabulation and orientation of data in terms of time, place, and person:** All data acquired from the fieldwork were presented in table form with

the information of the place, person, and time. The information was used for action, presentation, communication, monitoring, etc. The information was also used to identify the halting of the outbreak after careful observation for two COVID-19 incubation periods, i.e., 28 days after the last recorded case.

**Step 6 – Considering whether control measures could be implemented:** Several control measures have been introduced by the WHO and the Thai Ministry of Public Health. WHO recommends that all people use masks, wash hands, and maintain social distancing, which are common practices in Thailand. In this case, many effective methods of control were available and ready to be implemented.

**Step 7 – Developing and testing hypotheses or questions:** Our hypotheses were as follows: a) how could individuals enter Thailand without their COVID-19 status at the entry point being assessed? b) what was the scale of spread from the first imported cases? and c) could we control the cluster outbreak within the first-to-second generation of infection?

**Step 8 – Planning one or more systematic studies:** A concrete working plan was immediately developed according to the steps recommended by the SRRT. It particularly involved investigating and contacting all individuals exposed to the persons with confirmed COVID-19 in Thailand. This meant that all confirmed persons were interviewed on their recent travel history and the people they came into contact with after returning to Thailand. Moreover, all information were collected and reviewed.

**Step 9 – Implementing and evaluating control and prevention measures:** Public health prevention and control measures were immediately implemented for those exposed to the confirmed persons. In general, measures such as using a facemask, regular hand washing, and maintaining social distance, were continuously introduced through official and unofficial channels such as television, conference, social media. Moreover, contact tracing was immediately implemented to identify all exposed persons for testing and self-quarantine for at least 14 days.

**Step 10 – Communicating findings:** This was an important step in providing the public with validated information, particularly those who could be most impacted by the outbreak: residents of Chiang Rai Province, businesspeople, hospital staff, among others. Communication was executed through both formal government channels and other informal channels. The Chief of Chiang Rai Government Office and Public Health Office, including the director of Chiang Rai Prachanukroh Central Hospital, provided information once a day until the end of the outbreak. All lessons learned were identified and reported.

*Ethical considerations*

All participants were asked regarding their willingness to provide information on a voluntary basis, and written informed consent was obtained before the interview. All information, including medical records, were kept confidentially.

**Results**

Between December 1–5, 2020, 16 confirmed cases of individuals with COVID-19 who originated from the Chiang Rai Province were reported. These included one man and 14 women with an average age of 26.1 years (Min = 21, Max = 26) after excluding one 51-year-old woman. Nine of these cases were asymptomatic, while the others presented mild symptoms with fever, cough, and muscle pain. All positive COVID-19 cases were detected using PCR testing. By December 4, 2020, the individuals were living in different provinces: nine in the Chiang Rai Province, two in the Chiang Mai Province, and one in each of the following provinces: Pha Yao, Phi Chit, Sing Buri, Ratcha Buri, and Bangkok.

Among the nine patients who resided or were being treated at the Chiang Rai Prachanukroh Central Hospital, eight were women, and one was a man (transgendered). Four of the nine patients presented with mild signs and symptoms. An infected man was identified who had contracted the infection from a friend returning from Myanmar. No deaths were reported between December 1–5, 2020. All confirmed patients were admitted to the hospital for medical care and management in an isolated negative pressure room. The following are the details of early cohort cases who illegally immigrated to Thailand and were living in the Chiang Rai Province:

***Case No. 1*** *(Imported case)*

A 26-year-old woman worked at a hotel in Myanmar in early November 2020 before returning to Thailand. On November 25, 2020, she developed a mild fever, and some of her peers were detected positive for COVID-19. Early on November 27, 2020, she left Myanmar to travel to Thailand through an unofficial channel. On her way to her hotel in Thailand, she bought utilities at a small community store. On November 28, 2020, she went to Chiang Rai city by motorcycle and was tested for COVID-19 at a private hospital. She was referred to the Chiang Rai Prachanukroh Central Hospital. Twenty-eight exposed persons were identified; four of them were high-risk persons. Among those exposed, none tested positive for COVID-19. She was identified as an indexed case of the outbreak in Chiang Rai, Thailand.

***Case No. 2*** *(Imported case)*

A 23-year-old woman who worked at the same hotel as the woman in case no. 1 from the early days of November 2020 until November 27, 2020, decided to move back to Thailand. She crossed the border through an unofficial channel together with the woman in the first case and stayed at a hotel in Thailand overnight in a separate room from the woman in the first case. On November 28, 2020, she stayed for one more day at the

hotel and got food using the GrabFood delivery app. On November 29, 2020, she developed a cough and was contacted by the public health SRRT to be tested for COVID-19 at Chiang Rai Prachanukroh Central Hospital. Eventually, she tested positive for COVID-19 and was admitted to an isolated, negative pressure room at the hospital. Six contact persons were traced, with two in the high-risk group.

***Case No. 3*** *(Imported case)*

A 25-year-old symptomatic woman worked at the same hotel as the women in cases 1 and 2 between November 2–25, 2020, in Myanmar. On November 25, 2020, she found out that one of her friends who worked at the same hotel had tested positive for COVID-19. On November 26, 2020, she returned to Thailand using an unofficial channel. From November 26–27, 2020, after returning to Thailand, she stayed at her hotel and did not get out of her room. On November 28, 2020, a taxi was requested to transfer her to Chiang Rai, where she stayed at a hotel from November 28–29, 2020. On November 29, 2020, she was contacted to get tested for COVID-19 at the Chiang Rai Prachanukroh Central Hospital. On November 30, 2020, she tested positive for COVID-19. She was admitted and treated in an isolated negative pressure room at the hospital.

***Case No. 4*** *(Close contact with the imported case)*

This was the case of a 28-year-old man who had had contact with a COVID-19-positive woman living in Pha Yao Province between November 28 and 30, 2020. On December 1, 2020, he tested positive for COVID-19 at a private hospital before being treated and cared for at the Chiang Rai Prachanukroh Central Hospital.

***Case No. 5 and 6*** *(Imported cases)*

Both the patients in these cases were female and had illegally entered Thailand on November 26, 2020. From November 27–28, 2020, they stayed at a hotel located in the border area. On November 29, 2020, both women underwent COVID-19 testing using a rapid testing kit at a private clinic and had negative results. On December 2, 2020, both developed fever and chills. On December 3, 2020, they tested positive for COVID-19 at a public hospital in the border area. On the same day, they were transferred to a negative pressure room at Chiang Rai Prachanukroh Central Hospital.

However, three reported cases (a man from Chiang Rai, a woman from Ratcha Buri, and a woman from Sing Buri Province) were confirmed to have been infected from the Myanmar imported cases.

All confirmed cases are now being treated and cared for under the standard protocols in the hospital, including three additional patients who had used the official route to enter the country. No patient presented with severe disease, and no death was reported.

In summary, the main causes of the outbreak were as follows: I) the patients with suspected cases did not use the official route to enter Thailand, failed to be detected at the entry point, and could not be recruited into the recommended state quarantine program for 14 days; II) some cases (No.5 and No.6) might have been in the incubation period; therefore, the tests were negative for COVID-19 at the private clinic; III) all of the infected patients visited several entertainment venues in Thailand with or without strictly using face masks and a number of people visited these venues; IV) all of the illegally immigrated patients did not cooperate with the SRRT while reporting their history after returning to Thailand because of the fear of being punished by law; and V) poor personal concern about the problem particularly regarding the impact of the outbreak on people's life and economic loss because Chiang Rai province is one of the most attractive tourists in the autumn season in Thailand.

Several measures of prevention and control were introduced, such as closing schools, using face masks, maintaining social distancing, and regular hand washing. All individuals exposed to confirmed cases have now been contacted and detected for infection. All exposed persons were formally and officially informed to self-quarantine for 14 days. Individuals without clarity regarding COVID-19 status could be asked to get tested at both private and public hospitals. People who attended the big festival in Chiang Rai city between 28-29 November 2020 were advised to get tested for COVID-19 and self-quarantine for 14 days at least as well.

Since November 18, 2020, the Chiang Rai chief government has announced that no more COVID-19 cases were reported in Ching Rai Province. On December 27, 2020, a total of 71 cases were confirmed; 55 cases attended at the state quarantine, and 16 cases were reported inside Thailand from the current outbreak. A total of 3,259 cases were screened through the active case finding program, and 1,656 cases were screened through the sentinel surveillance system. Moreover, 11,490 persons were tested for COVID-19 through the private health clinics in Chiang Rai Province.

**Discussion**

Fifteen cases of COVID-19 were reported between December 2-4, 2020. Of these, 12 were infected while living in Myanmar and three were exposed to the confirmed cases. Most infected persons were young adult Thai females and had a history of working at a hotel in Myanmar located close to Thailand. The first infected cohort (nine individuals) crossed the border to return to Thailand through an illegal, unofficial channel. Half of the infected cases were asymptomatic and the other half presented with mild symptoms. Some infected cases had traveled to several places after returning to Thailand, particularly during one large festival in Chiang Rai city on November 29, 2020.

Few other confirmed cases traveled to Bangkok, the capital city of Thailand.

A screening for COVID-19 among all individuals entering Thailand is important because no positive cases have been reported within the country for a long time. This means that there is no COVID-19 positive case reported in Thailand. However, countries surrounding Thailand, such as Myanmar and Malaysia, are reporting a high number of newly infected cases. Therefore, close and serious monitoring of those who expect to enter Thailand is an essential procedure for Thai public health professionals. Unfortunately, there are long border areas between Thailand and Myanmar which are more than 2,400 km. Therefore, many individuals are crossing borders. Basically, Thailand has closed the airspace, intercountry road connections, and sea transportation from other countries. Crossing borders through unofficial channels has led to the spread of the COVID-19 epidemic in northern Thailand. Currently, several large-scale and serious measures have been implemented to address this problem under the collaboration of the Thai Ministry of Interior, Thai Ministry of Defense, and the Thai Ministry of Public Health.

Contacting all individuals exposed to confirmed cases or contact tracing is one of the standard procedures for controlling COVID-19 [21]. The main purpose of this exercise is to detect all possible individuals contracting the disease. This could significantly reduce the number of new cases. This is supported by different sources of contact tracing guidelines [22–24]. In Chiang Rai Province, they are two approaches to test the individuals who have been in contact with confirmed cases, including hospital and mobile laboratories. Both approaches are provided free for testing.

During the investigation and disease control in Chiang Rai Province, communication was defined as one of the key success factors. The validity of the content and frequency of communication was important to maintain collaboration among people in communities. The communication itself could be a tool to reduce the panic among people, which directly impacts businesses and tourist programs in the area. Normally, Chiang Rai Province is a tourist attraction area in Thailand and has a million people, including both Thai and foreign visitors. The high season of tourists is between November and March. Therefore, under the current situation, if the SRRT could not control and stop the disease, it could impact the people living in Chiang Rai Province on a large economic scale. This coincides with a study in India, which reported that effective communication from healthcare workers could significantly contribute to the decrease of COVID-19 cases in communities [25]. Moreover, a study conducted in Australia reported that during the pandemic, communication was one of the effective tools to reduce the burden of the disease, and the validity of the content could impact public trust as well [26]. Hinjoy et al. [27] reported that communication through reports for Thai and international populations under the Ministry of Public Health was still effective.

There are several lessons learned from the disease investigation and control. First, strengthening the operation in the border areas should continuously maintain serious action. Villagers who are living along the borders should be trained in all essential practices regarding disease prevention and control, including identifying immigrated people through the villages. Collaboration between all stakeholders is highly important in this situation for Thailand. Second, communication with effective methods to the people is crucial to reduce the impact of the transmission of the disease. If people are aware of the situation at an early stage, they will support the public health system to maintain a strong practice to prevent the disease through social distancing, hand washing, and regularly using a face mask. Communication should be performed continuously through information holders, such as SRRT or medical staff. The information will directly support the right decision of a person and reduce panic. Third, contact tracing of persons exposed to the confirmed cases is another key to success in halting the spread of the disease. If all individuals exposed to confirmed cases have a COVID-19 positive status and self-quarantine for 14 days, it would be crucial for disease control and prevention. Fourth, gathering information from those who illegally immigrated could be inadequate due to fear of being punished by law, and these people may not provide all the critical points of their history to SRRT. This limitation may lead to a second outbreak; thus, ensuring friendly communication with the cases is very important to gather real information. Fifth, granting authority to school-directors to close schools as well as other organizations in the area is important to control the spread of the disease. Finally, sharing validated information with all people or organizations who need to use it is very important to make decisions within the organizations, such as the university opting to use distant learning instead of physical classroom attendance for teaching.

Even the outbreak in Chiang Rai Province has been completely controlled, but a new cluster outbreaks are reported in the central of Thailand which is originated by Myanmar migrant workers. On December 27, 2020, almost 33 provinces were reported of having COVID-19 cases particularly in the central, southern, and eastern regions of Thailand.

**Conclusions**

Unexpected spread of the COVID-19 cases through illegal channel immigration into Thailand from a neighboring county is a serious worry for the SRRT in Thailand. An urgent response according to the national protocol through the system developed at the local level, which means the need for great collaboration between health officers and other local

authorities, is a crucial factor in halting the spread of the disease. The structure and function of the border guard system needs to be improved, particularly a specific design to control people who favor entering the country through the illegal channels promoted by long border areas. Communication from both public health agencies and local authorities to the people to maintain clear and valid information can reduce the panic among the people and maintain the economic system in these areas. National political agencies are also important to contribute to the implementation of public health prevention control measures, particularly in supporting the strong collaborations among the agencies. One of the lessons learned from this specific cluster outbreak is that having highly active working according to the international protocols for COVID-19 prevention and control at the port on country entry is very important while sharing long borders with countries with a high prevalence of COVD-19. Enhancing community capacity and engagement with COVID-19 prevention and control among people living along the border could be a great protective strategy to reduce the possibility of an unexpected outbreak in these areas.

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