IJPHS
International Journal of Public Health and Health Sciences

2019

# International Journal of Public Health and Health Sciences

Vol.1 No.1 January-April, 2019

ISSN 2672-9148 (print)
ISSN 2651-1711 (online)

ISSN 2672-9148 (print) ISSN 2651-1711 (online)

# International Journal of Public Health and Health Sciences (IJPHS)

## Aims and Scope of IJPHS

The International Journal of Public Health and Health Sciences (IJPHS) aims to publish original articles and contributions relevant to public health and medical sciences. IJPHS is published by the Praboromajchanok Institute for Health Workforce Development (PBRI), Ministry of Public Health, Thailand. It is a non-profit, peer-reviewed, open-access, international, scientific journal that publishes articles in areas of health sciences disciplines. The scope of the IJPHS is broad, covering the following categories: original articles, reviewed articles, special articles, case reports, correspondence, and others in the fields of public health, medical sciences and related allied health, especially the following areas:

-Health policy and management, health care and services
-Health promotion, health education and behavioral health
-Environmental and occupational health
-Health technology and data management
-Global health and Sustainable Development Goals (SDGs)
-Nursing and nursing sciences
-Community health, dental public health, community pharmacy, toxicology, and other relevant health issues of health and medical sciences.

Three issues will be published annually: January - April, May - August, and September - December. Authors from all areas of health and medical sciences are invited to submit scientific papers and contribute in this journal.

ISSN 2672-9148 (print) ISSN 2651-1711 (online)

## Editorial Board

eISSN 2673-0251 (Online)
ISSN 2673-0200 (Print)

ISSN 2672-9148 (print) ISSN 2651-1711 (online)

# Editorial Statement

*Inaugural Issue of the IJPHS*

It is with much pleasure that we celebrate the inaugural issue of the International Journal of Public Health and Health Sciences (IJPHS). For the inaugural issue of IJPHS, I on behalf of editorial board would like to express our gratitude to all supporters and sponsors for such a first international journal for the Praboromajchanok Institute for Health Workforce Development (PBRI). We would like to dedicate and hardworking, together with PBRI leaders for kindly financial support to envision to become one of leading health sciences institutions in Southeast Asia focusing on public health and community health.

PBRI is only one higher institution under Ministry of Public Health, Thailand and one of leading universities producing public health professions, registered nurses and allied health professions. It's also known as His Royal Highness Prince Mahidol of Songkla or Father of Modern Public Health and Medicine in Thailand. It former name was Institute of Health Manpower Development in 1993, combined with all public health, allied health and nursing colleges into PBRI. Until recently, PBRI has been endorsed under His Majesty the King Maha Vajiralongkorn Bodindradebayavarangkun (King Rama X) on April 4, 2019. Originally, the nursing colleges and public health colleges have been inaugurated back long to the history for more than 70 years. The aims of PBRI are to strengthen the efficiency and management of health workforce development for health personnel for serving throughout all regions of Thailand, especially in rural areas.

IJPHS aims to publish original articles and contributions relevant to public health and medical sciences. It is a non-profit, peer-reviewed, open-access, international, scientific journal that publishes articles in areas of health sciences disciplines. The scope of the IJPHS is broad, covering the following categories: original articles, reviewed articles, special articles, case reports, correspondence, and others in the fields of public health, medical sciences and related allied health. Three issues will be published annually. Authors from all areas of health and medical sciences are invited to submit scientific papers and contribute in this journal. First inauguration issue is consisting of interesting variety topics covering public health and medical sciences which you can download articles in the journal at the website https://www.tci-thaijo.org/index.php/ijphs

The editorial board of IJPHS sincerely hope that the members, faculty members, students, medical, nursing and public health personnel as well as alumni who are interested in obtaining more detail from original articles, reviews, and other to use or transform research information into teaching and research fields.

ISSN 2672-9148 (print) ISSN 2651-1711 (online)

**Content**

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

*Original article*

**Article history**
*Received: Sept 4, 2018;*
*Accepted: Apr 27,2019;*
*Published: Apr 30,2019*

# Lifestyle-Appropriate Peer Supports for Glycemic Control among Type 2 Diabetes Patients in Thailand

Boosaba Sanguanprasit[1], Pimsurang Taechaboonsermsak[2], Kanonkarn Mekanantachai[1], and Sirinun Charoenphol[1]

[1]Boromarajonani College of Nursing Nopparat Vajira[1] Mahidol [2]University Faculty of Public Health

## Abstract

Diabetes, a worldwide health problem, is a chronic, lifelong condition which requires continuous self-care management to keep glycemic level under control. More often than not, self-care management is short-lived if not appropriately supported. This quasi-experimental study, three-group pre-post-test was carried out to assess the effects of context and lifestyle appropriate peer support models in an agricultural and non-agricultural communities. A total of 58 and 30 type 2 diabetes patients were recruited into the intervention and comparison groups, respectively. Out of 58 patients in the intervention group, 29 patients each were selected from an agricultural community and from non-agricultural community to observe different peer support models and glycemic levels between these two groups and in the comparison group. The inclusion criteria included aged 35 – 75 years, fasting blood sugar (FBS) lied between 30 – 300 mg/dl, and systolic blood pressure did not exceed 200 mmHg. Trans-theoretical Model, participatory learning, inclusive planning, and social support were used to guide the intervention activities to increase knowledge and self-care management behaviors. Twenty village health volunteers in the experimental areas were recruited and trained to function as peer supporters. The intervention lasted six months from July to December 2011. After the intervention, patients in both experimental groups significantly improved their self-care management and reduced HbA1C from 8.02 to 7.5% (p-value<0.05) in agricultural and from 8.54 to 7.60% in non-agricultural group (p-value<0.01), while those of the comparison group slightly increased. Two different peer support models were identified in the agricultural and non-agricultural communities. Results from this study showed that peer supports appropriately tailored to the context and lifestyle of diabetes patients could significantly increase knowledge, improve self-care management, reduce BMI and blood sugar levels of the patients. It is suggested that peer support using context and lifestyle appropriate strategies be integrated into country health care system to make self-care management among chronically ill patients sustainable.

**Key words**: glycemic control, lifestyle-appropriate peer supports, self-care management

***Corresponding author***: Boosaba Sanguanprasit Email: boosaba@bcnnv.ac.th

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Introduction

Diabetes mellitus (DM) is a worldwide health problem and has been increasing in numbers. It was estimated that 629 million adults of the world population would have diabetes in 2045 and over 60% of which lived in Asia. Thailand is no exception. The prevalence of diabetes in the country rose from 7.7% in 2009 to 9.9% in 2014 and caused 30,000 DM related deaths annually (Aekplakorn et. al, 2018). Only about 30% and 41% of diabetes patients in urban and in rural areas, respectively, were able to control their blood glucose within normal blood levels (Pethchit, 2015; Worawongprapa, 2008; Mayurasakorn et. al, 2009). Uncontrolled glycemic level can lead to complications, and the severity of which is well documented (ADA, 2008; WHO, 2007; Sanguanprasit et. al, 2016).

Self-care management which includes healthy eating, proper exercise, stress management, and foot care, mostly affected by individuals' gender, age, education and sufficiency of household income (Henderson et. al, 2011), is essential for type 2 diabetes patients to effectively control their glycemic levels and reduce the risks of acquiring associated complications. However, such self-care management is often short-lived and faded soon after the end of an education program (Becker, 1974).

Evidences from previous studies showed that the majority of diabetes patients in Thailand had inappropriate self-care management in controlling eating and exercise behaviors (Aekplakorn et. al, 2018; Mayurasakorn et. al, 2009; Sanguanprasit et. al, 2016). Healthy behaviors can be promoted by raising persons' perceived threat of developing serious complications and developing their self-efficacy in diabetes self-care management through learning processes (Bandura, 1977; Lerman& Glanz, 1997; Henderson et. al, 2011; Brownson & Heisler, 2009). Since diabetes self-care management is a life-long practice, the patients need suitable, context appropriate supports to maintain their health behaviors (Brownson & Heisler, 2009; Fisher et. al, 2015; Fisher et. al, 2010; Sanguanprasit et., al, 2011; Fisher et. al, 2012). To this end, the concept of peer supports will be an effective strategy in helping the patients to develop and sustain their self-care management.

Peer support, defined as the provision of support from an individual with experiential knowledge based on a sharing of similar life experiences, is broadly feasible and sustainable, usually provided within a volunteering framework and can be delivered in many ways, including group or individual support or through more remote formats such as telephone or internet-based support that are appropriate for patients' lifestyle and context. Peers can be family members, friends, community people, volunteers, or peer patients. Supports provided by peer include assistance in daily management of diabetes, social and emotional support and linkage between community and health system. Nonprofessionals could well contribute to supporting patients' self-care management and glycemic control (Sanguanprasit et. al, 2011; Dale et. al, 2009; Sacco et. al, 2009). The approach has been widely implemented using different methods of support. However, most peer support programs previously carried out, the activities of which were predominately determined and designed by researchers and the sustainability of the programs was questionable (Fisher et al, 2015).

Village health volunteers (VHVs) which is part of Thailand's primary health care were chosen to function as peer supporters in this study because they have been trained to help local health staffs in various health promotion and disease prevention programs as well as to undertake simple tasks as taking temperature, measuring blood pressure, wound dressing, and first aid. Therefore, they could be a good choice for peer support to promote self-care management among DM type 2 patients (Sanguanprasit et. al, 2016).

Currently, there are few health promotion programs for diabetes patients in Thailand that yield sustainable benefits. To make behavior modification sustainable requires innovative approaches that are suitable for context and lifestyle of the subjects. Take agricultural and non-agricultural communities as an example, these two communities differ in terms of structure, lifestyle, daily activities, and

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

facilities such that no one health promotion program can fit both. Therefore, the aim of this study was to assess the effectiveness of the context and lifestyle appropriate peer support models in agricultural and non-agricultural communities using VHVs as peer supporters to develop and sustain self-care management among diabetes type 2 patients. Inclusive planning, team learning, and social supports would be used to empower the patients in designing and implementing activities as well as monitoring and evaluation of their health behaviors.

It was hypothesized that type 2 diabetes patients who participated in the program in both agricultural and non-agricultural communities, compared with their base-line information and with the comparison group, would have higher mean scores of diabetes knowledge, self-care management, reduced body mass index (BMI) and HbA1C level by the end of the program. Glycemic control in this study was defined as patients' ability to reduce their glycemic levels as measured by HbA1C. Non-agricultural community is defined as the community where more than 50% of income generation is associated with wage work or self-employment including agro-processing and setting up a small or adaptive (switching from cash crop cultivation to commodity trading) business (Davis and Pearce, 2001).

## Research Methodology

The study was a quasi-experimental design, three-group, pre-post-test.

*Study Population and Sample*

Two provinces, Suphan Buri in the central, and Nakhon Ratchasima in the northeast region, were selected based on high prevalence of type 2 DM and the willingness of the provincial chief medical officer to participate in the study. An agricultural and a non-agricultural community were selected from Suphan Buri province as an experimental and comparison group, respectively. A non-agricultural community was selected from Nakhon Ratchasima province. All groups were selected from comparable settings in terms of age, gender, and sufficiency of household income.

*Sample size*

The number of the patients included in the study was calculated by using the mean HbA1C of diabetes patients before the intervention which was 8.2 and the mean reduction in HbA1C level from baseline among patients without an intervention which was 0.2% with standard deviation of 1.5% (Howteerakul et. al, 2007). We believed that the intervention would further decrease patient's HbA1C level by 2% with the smallest change of HbA1C level was 0.15. A total of 84 patients (28 patients in each group) are needed to achieve 80% power at two-sided 5% significance level (Lwanga &Lemeshow, 1991).

The inclusion criteria were having type 2 diabetes, age between 35 – 75 years; and blood glucose not exceed 300 mg/dl. The patients were excluded if being treated with insulin; having severe complications such as renal failure, gangrene, or psychologically ill; and resting systolic blood pressure over 200 mmHg. A total of 58 and 30 patients were recruited into the experimental and comparison groups, respectively.

*Steps of the study*

The study was carried out in three phases: preparation, implementation and evaluation.

1. Preparation phase

Intervention mapping (Bartholomew et. al, 2001), a theoretical and evidence-based intervention, was used to guide the development of the intervention project. A structured questionnaire was developed to collect the data from the patients which included socio-demographic information, height, body weight, HbA1C, knowledge about diabetes mellitus, and diabetes self-care management. The questionnaire was validated by experts in health behaviors, nutrition, and exercise; field tests for reliability were carried out in these two provinces but not in the study areas. The Cronbach alpha of self-care management was 0.84 and KR-20 for knowledge was 0.79.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

A preliminary survey was carried out using face-to-face interview. Six focus group discussions were carried out among patients, volunteers and health staffs to identify problems and determinants related to patients' self-care management and the volunteers' ability to support diabetes patients. The results were used to develop a training curriculum for the village health volunteers to enhance their capacities in encouraging and supporting diabetes patients to develop and maintain their self-care management.

The researchers met with VHVs in the respective experimental and comparison communities to inform them about the project and their roles. Ten VHVs each were recruited in the experimental groups to act as peer supporters. The criteria for selection included having at least two participating diabetes patients under his/her own care, being able to read and write Thai language, and willing to participate until the end of the study. Those who agreed to participate in the project signed the consent form. Twenty VHVs in the experimental groups were trained to enhance their knowledge and skills in diabetes management, inclusive planning, and context and lifestyle appropriate supports.

2. Implementation

After the training, VHVs and respective local health staffs met with diabetes patients to inform them about the study and asked them to join on voluntary basis and signed consent form. Medical records of those who agreed to join were reviewed to ensure their eligibility to join the study. They were then interviewed to assess health behaviors and lifestyle, and physically examined (height, weight, and blood pressure) and blood checked for HbA1C.

In each experimental group, discussions among the participating patients, VHVs, and local health staffs, who provided technical supports was carried out to set behavior and glycemic control goals, map out activities plan including monitoring and evaluation, and support strategies and schedule, as agreed by the patients and the VHVs. The researchers and responsible health staffs met with VHVs and patients in each group once a month to discuss activities, problems and obstacles; advice and moral supports were then provided accordingly. The intervention lasted six months.

In the comparison group, the patients and VHVs were invited to participate in the pre and post intervention surveys. These patients received usual care and supports provided by public health personnel and VHVs which included health education on diabetes mellitus, self-care management, and conventional home visit by health staffs and VHVs.

3. Evaluation

Face-to-face interview using structured questionnaire was used to evaluate the intervention; focus group discussions were used to identify the participants' satisfaction. The indicators used in the evaluation were:

Process measures included knowledge about diabetes mellitus and self-care management (eating and exercise behaviors, foot care, and stress management).

Output measures or physiologic endpoints included HbA1C and body mass index(BMI).

***Data Management and analysis***

Field supervision was carried out during data collection by the research team to ensure the quality of the data. The mean scores of knowledge, self-care management behaviors, BMI, and HbA1C levels between the two intervention and comparison groups were compared before and after the intervention, both within and between groups. Dependent t-tests was used to test the differences of the mean scores of the indicators within group and One-way ANOVA was used to test the differences between the experimental groups against the comparison group. Due to unequal mean scores of the indicators among the three groups prior to the intervention, the mean changes of these variables were used to compare between groups.

***Ethical Approval***

The ethical clearance of this study No. MUPH2009-112 was issued by the Research Ethic Committee of the Faculty of Public Health, Mahidol University, Thailand.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

**Results**

1. Peer Support Models

Non-agricultural group

The approaches used in this group were more formal and individualistic. A half-day diabetes camp was organized by the VHVs and local health staffs to provide the participants knowledge about diabetes and enhance their self-care management skills. Methods used in the diabetes camp included group discussions and sharing information among participants, demonstration and practice.

The patients were divided into three zones according to the distribution of VHVs. Each zone consisted of 9 – 11 patients with 3-4 VHVs who collaboratively worked with the patients to identify self-care problems and determinants, set appropriate goals, identify means to achieve these goals, methods and tools used to assess their actions. VHVs in each group took turn to visit the patients at home once every two weeks, as agreed upon by the patients. During the visit, VHVs observed and discussed the patients' self-care management and provided advice and support accordingly. Most patients chose to exercise individually by brisk walking and bicycling. There was no formal gathering among the patients in the zone, but they occasionally met to share their experiences and provided each other moral support.

Local health staffs functioned as technical supporters for the VHVs as needed.

Agricultural group

The approaches used by this group were predominantly non-formal and team-based. All VHVs and participants worked inclusively, from sharing information and experiences about diabetes, problems in glycemic control, planning for actions to be taken, implementing and monitoring the activities. Team learning was the main stream of all activities and the patients took active roles in proposing and leading the activities. Exercise, done in group, led by the patients using appropriate technology such as stick (Mai Plong) exercise and hoo-la-hoop, was carried out daily at a VHV's house. A community organic garden was founded, a stationary bicycle was installed and used as an electricity generator for a water pump. The patients cycled the bike as a mean for exercise and at the same time watered the plants.

Every two weeks all VHVs and the patients met at the health center to discuss their progress and obstacles. Local health staffs were also present to provide additional information or advice if needed. After discussions, everyone would exercise and then cook a healthy meal which was served for lunch.

Regular home visits were undertaken at least twice a month, on days agreed upon by VHVs and their patients. Patient folder was used to track patient's progress and to provide guidance during home visits. VHVs in near-by villages worked as a team (usually 3-4 members per team) to visit patients under their care. During home visit the VHVs discussed the progress or any obstacles in diabetes management. Any problems beyond their capacity, the VHVs would call the local health staff for help and advice.

2. Characteristics of the patients

The three groups had comparable characteristics in terms of age, gender, education, and duration of having diabetes mellitus. About 55% of the participants in the agricultural group engaged in agricultural activities, while only 31% of those in the non-agricultural group did and the comparison group fell in between. Results of the pre-test revealed that all groups were not statistically significant difference in terms of duration of having DM, knowledge about DM, self-care management, and HbA1C (tables 1 and 2).

3. Within group comparison

Table 3 presents within group comparison of knowledge, selfcare management, BMI, and HbA1C levels of all groups.

Knowledge about DM

After the intervention, out of the total score of 28, the knowledge about diabetes mellitus of the experimental-agricultural group significantly increased from 18.5 to 24.6 (p-value <0.001). This was the only group that the mean score of the knowledge has significantly increased. While the knowledge of the non-agricultural group reduced but not statistically significant; likewise, though the knowledge of the comparison group increased from 16.8 to 17.6, this was not statistically significant.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

**Table 1**. Socio-demographic characteristics of experimental and comparison groups before intervention

| Factors | Agricultural (n=29) | | Non-agricultural (n=29) | | Comparison (n=30) | | *p-value* |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Age (Mean) | 60.69 | | 61.72 | | 59.43 | | NS |
| (SD) | 9.11 | | 11.30 | | 8.47 | | |
| Sex (% female) | 23.00 | 79.30 | 20.00 | 69.00 | 24.00 | 80.00 | NS |
| Education level | | | | | | | NS |
| - No formal education | - | - | - | - | 2 | 6.70 | |
| - Primary | 29 | 100.00 | 25 | 86.20 | 25 | 83.30 | |
| - Secondary or higher | - | - | 4 | 13.80 | 3 | 10.00 | |
| Occupation | | | | | | | NS |
| - Agriculture | 16 | 55.17 | 9 | 31.03 | 14 | 46.70 | |
| - Unskilled worker | 4 | 13.89 | 7 | 24.14 | 9 | 30.00 | |
| - Others | 2 | 6.89 | 8 | 27.58 | - | - | |
| - Unemployed/housewives | 7 | 24.13 | 5 | 17.24 | 7 | 23.39 | |
| Household income | | | | | | | NS |
| - Sufficient | 12 | 41.30 | 13 | 44.82 | 15 | 50.00 | |
| - Insufficient | 17 | 58.70 | 16 | 55.18 | 15 | 50.00 | |

**Table 2**. Mean scores of diabetes related information of experimental and comparison groups before intervention

| Factors | Agricultural (n=29) | | Non-agricultural (n=29) | | Comparison (n=30) | | *p-value* |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | |
| Duration of DM (Years) | 6.07 | 4.79 | 8.80 | 5.60 | 6.00 | 3.80 | NS |
| Knowledge | 18.06 | 5.09 | 18.55 | 4.19 | 16.83 | 5.18 | NS |
| Self-care management | 77.00 | 7.13 | 76.18 | 7.10 | 76.60 | 8.67 | NS |
| BMI | 25.89 | 4.17 | 25.82 | 3.26 | 26.64 | 4.12 | NS |
| HbA1C | 8.02 | 1.88 | 8.54 | 2.34 | 7.57 | 1.68 | NS |

Self-care management and BMI

After the intervention, out of the total score of 100, the mean score of self-care management of the agricultural experimental group significantly increased from 77.00 before the intervention to 82.52 (p-value <0.01); while those of the non-agricultural group and the comparison group were not significantly increased. The BMI among the agricultural and non-agricultural experimental groups significantly decreased from 25.8 to 24.53 (p-value<0.05) and from 25.82 to 25.10 (p-value<0.05), respectively; while that of the comparison group stayed almost the same.

Glycemic control

Despite the non-significant knowledge, and behavioral changes among the non-agricultural experimental group, the reduction of HbA1C in this group was more prominent and significant, from 8.54 to 7.6% (p-value<0.01) than that of the agricultural group, from 8.02 to 7.50% (p-value<0.05). While that of the comparison group non-statistically increased from 7.57 to 7.99%.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

**Table 3**. Within group comparison of mean scores of factors, before and after intervention

| Factors | Before | After | *p-value* |
|---|---|---|---|
| **Knowledge** | | | |
| Agricultural (n=29) | 18.06 (5.09) | 24.62 (2.42) | <0.01 |
| Non-agricultural (n=29) | 18.55(4.19) | 18.34(3.89) | 0.16 |
| Comparison (n=30) | 16.83(5.18) | 17.63(4.20) | 0.52 |
| **Self-care Management** | | | |
| Agricultural | 77.00(7.13) | 82.52(5.38) | <0.01 |
| Non-agricultural | 76.18(7.10) | 76.20(6.14) | 0.42 |
| Comparison | 76.60 (8.67) | 77.13 (7.39) | 0.20 |
| **BMI** | | | |
| Agricultural | 25.89 (4.17) | 24.53 (4.00) | 0.05 |
| Non-agricultural | 25.82 (3.26) | 25.20(3.05) | 0.05 |
| Comparison | 26.64(4.12) | 26.84 (4.78) | 0.30 |
| **HbA1C** | | | |
| Agricultural | 8.02(1.88) | 7.50 (1.50) | 0.03 |
| Non-agricultural | 8.54 (2.34) | 7.60(1.81) | <0.01 |
| Comparison | 7.57 (1.68) | 7.99 (2.00) | 0.32 |

**Note**: Numbers in brackets are standard deviations

**Table 4**. Comparison of mean score changes of knowledge, self-care management, BMI, and HbA1C after the intervention of the two experimental groups as compared against comparison group

| Factors | Mean difference | Standard error | p-value |
|---|---|---|---|
| **Knowledge** | | | |
| Agricultural | -5.80 | 1.46 | <0.01 |
| Non-agricultural | 2.10 | 1.49 | 0.17 |
| **Self-care Management** | | | |
| Agricultural | -4.86 | 0.21 | 0.02 |
| Non-agricultural | 0.76 | 0.21 | 0.72 |
| **BMI** | | | |
| Agricultural | -0.95 | 0.41 | 0.02 |
| Non-agricultural | -0.94 | 0.41 | 0.02 |
| **HbA1C** | | | |
| Agricultural | -0.87 | 0.37 | 0.02 |
| Non-agricultural | -1.29 | 0.37 | <0.01 |

4. Between groups comparison

Results from One-way ANOVA and Bonferroni test showed that after the intervention the agricultural experimental group significantly out-performed the comparison group in all aspects, knowledge, self-care management, BMI, and HbA1C (the significant levels ranged from p = 0.02 to p-value<0.01). The non-agricultural group, however, had significantly out-performed the comparison group only in the reduction of BMI (p-value <0.05) and HbA1C (p-value<0.01).

**Discussion and Conclusions**

Results from this study showed that trained VHVs could be an effective tool in supporting type 2 diabetes patients to significantly gain more knowledge, improve self-care management, reduce BMI and blood sugar levels; and that patient-centered, context and lifestyle appropriate methods remarkably effective in engaging and retaining the participants in the activities. The results of this study were consistent with previous studies

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

which found peer supports could help the patients to significantly reduce HbA1C levels and increase self-care management mean score of the participants in the intervention group (Sanguanprasit et. al, 2011; Thom et. al, 2013; Long et. al, 2012; Lorig et. al, 2009; Bauman & Dang, 2012).

Different approaches used by agricultural and non-agricultural were in accord with patients' contexts and lifestyles. In the non-agricultural community, most houses located along the main road due to the tenants' livelihood that they needed to commute to the main business district for their work. As such the approaches used in this group were more formal and individualistic; the participants did their own exercise and diet with the supports of respective VHVs. Whereas in the agricultural community the majority of the participants engaged in agricultural and labor activities, most people lived close by, such that they could conveniently do activities together. Group activities such as traditional exercise and cooking that fit their lifestyle effectively inspired each individual to do better and adhere to healthy behaviors. The activities at the community organic garden, which was both fun and economically productive, provided them the opportunity to exercise and to have organic produce for household consumption. This effectively made the participants perceived the benefits of and adhered to the activities which is an essential element in sustaining people's behaviors (Sanguanprasit et. al, 2016; Long et. al, 2012; Lorig et. al, 2009; Bauman & Dang, 2012).

In the focus group discussions, the participants indicated that they enjoyed the supports provided by VHVs, sharing experiences and supporting each other among themselves. This had lifted up their spirits and inspired them to do better. Setting goals for diet control really helps them to manage their diets. The personal record helped them discern positive changes after joining the activities and kept them adhered to the activities (Becker, 1974; Bandura, 1977). Members in the agricultural group said that by allowing them to have a free-hand in designing their own activities, supported by VHVs and local health staffs, they could design the activities that were consistent with their daily life and made them adhere to the activities. Such comments supported previous studies which found people-centered health promotion program with minimum competing interests could yield better and sustainable health behaviors (Brownson & Heisler, 2009, Fisher et. al, 2015; Sanguanprasit et. al, 2011).

The intervention could significantly reduce BMI and HbA1C, but not significantly increase the knowledge and self-care management among the participants of non-agricultural group. This could be explained, as mentioned above, that the peer supports in the non-agricultural group was mostly done individually. As a result, the patients had less chance to share and reinforce their knowledge and experiences regularly. However, knowledge by itself may not have much effects on health behaviors (Becker, 1974; Bandura, 1977; Henderson et. al, 2011). Although their overall self-care management was not significantly increased, their eating behavior significantly increased from 38.11 to 40.10 (p-value = 0.02). Detailed information on self-care management suggested that the agricultural group needed to improve their eating behavior. Manyof them ate more rice than what is recommended. This could be due to the fact that about 69.00% of the participants engaged in labor-intensive work such that they needed more energy to carry out daily hard work. These can become a major barrier to achieving behavioral goals (Bauman & Dang, 2012).

*Strengths of the study*

The intervention of this study was carefully designed by using the concept of intervention mapping (as explained above). Preliminary quantitative and qualitative study was conducted and the results of which were used to design a training program for VHVs and peer supports to ensure that the activities were suitable for and attractive to the participants, thus the results were expected to be sustainable.

Training of data collector and field supervision were carried out to ensure the quality of the data. Both quantitative and qualitative data were used to ensure the accuracy and usefulness of the study.

*Limitations of the study*

Seasonal variation had great impacts on patients' self-care management, especially among the agricultural community. Their daily routine including eating and sleeping schedules had changed and reduced during planting and harvesting seasons and made it difficult for them to maintain self-care behaviors. The

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

intervention did not take into account for the seasonal variation, the harvest season, which may affect the daily routines and livelihood and health behaviors of the participants in the agricultural community.

*Conclusions*

This study has demonstrated that village health volunteers, if properly trained, can be an effective tool in supporting type 2 diabetes patients to gain more knowledge and improve their self-care management, reduce BMI and blood sugar levels.

**Research Implications and Recommendations**

VHVs should be trained to enhance their competencies in providing direct and indirect supports as appropriate to build self-confidence and self-efficacy among the patients. To make glycemic control sustainable, the patients should take an active role in setting appropriate goals, identify means to achieve these goals, and regularly assess the results of their actions. Tools for self-monitoring should be made available to the patients to reinforce their self-care management. Peer support by using context and lifestyle appropriate strategies for sustainable self-care management among chronically ill patients should be integrated into health care system of Thailand since the model is culturally, socially and economically appropriate.

More research is needed to determine whether the effects of peer support can be sustained beyond six months. Family members should be involved in supporting self-care of the patients, especially in agricultural community where seasonal variations affect patients' behaviors. More study is also needed to understand how to best prepare and support peer leaders so that they can be more effective in supporting the patients to maintain their behaviors over a long period of time.

**Acknowledgement**

We are thankful for Peer for Progress, A program of the American Academy of Family Physician Foundation which financially supported this study; Professor Edwin B Fisher, the global director of Peer for Progress who tirelessly provided technical supports and opportunities to learn from each other; our local research assistants who actively did all they could to help us carry out all activities in the field; local administrators in both provinces who facilitated us during the course of the project; last but not least, all the participants in our project both experiment and comparison groups, without whom, this study would not be completed.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## References


Aekplakorn, W., Chariyalertsak, S., Kessomboon, P., Assanangkornchai, S., Taneepanichskul, S.,&Putwatana P. (2018). Prevalence of Diabetes and Relationship with Socioeconomic Status in the Thai Population: National Health Examination Survey, 2004–2014.*Journal of Diabetes Research.*Article ID 1654530, 8 pages.Retrieved March 22, 2019, from https://doi.org/10.1155/2018/1654530.

American Diabetes Association. *Diabetes Learning Center for the Recently Diagnose.*Retrieved 20th August 2008 from: http://www.diabetes.org/all-about-diabetes/diabetes-learning-center.jsp.

Bandura, A. (1977). *Social Learning Theory***.**Englewood Cliffs: Prentice Hall.

Bartholomew, LK., Parcel, G.S., Kok, G., & Gottlieb, N.H. (2001). *Intervention Mapping:designing theory-and evidence-based health promotion program*. Mountain View, California: Mayfield Publishing Company.

Baumann, LC., Dang, Thanh, & Ngoc, Tran. (2012).Helping patients with chronic conditions: overcome barriers to self-care. *The Nurse Practitioner***,** 37(3):32-8.

Becker M.H. The Health Belief Model and personal health behavior**.**(1974). New Jersy: Slack. Thorofare.

Brownson, CA., & Heisler, M. (2009).The role of peer support in diabetes care and self-management. The Patient-Centered Outcomes Research. Retrieved 11th December 2011 from: http://adisonline.com/the patient/Abstract/2009/02010/The_Role_ of_Peer_Support_in_Diabetes_Care_and. 2.aspx.

Bureau of Policy and Strategy, Ministry of Public Health. (2007).*Thailand Health Profile Report.Bangkok*.Express Transportation Organization Printing Press.

Dale, J., Caramlau, I., Sturt, J., Friede, T., & Walker, R. (2009). Telephone peer-delivered intervention for diabetes motivation and support: the telecare exploratory RCT. *Patient Educ Couns*, 75(1):91–8.

Fisher, EB., Ayala, GX., Ibarra, L., Cherrington, AL., Elder, JP., Tang, TS., et al,.(2015). Contributions of Peer Support to Health, Health Care, and Prevention: Papers from Peers for Progress. *Annals of Family Medicine,* 13(Suppl 1): s2-s8.

Fisher, EB., Earp, JA., Maman, S., &Zoloter, A. (2010). Cross-cultural and international adaptation of peer support for diabetes management. *Fam Pract*, 27(Suppl 1):i6-i16.

Fisher, EB., Boothroyd, RI., Coufal, MM., Bauman, LC., Mbanya, JC., Rotheram-Borus, MJ., Sanguanprasit, B., &Tanasukarn, C. (2012). Peer Support For Self-Management of Diabetes Improved Outcomes in International Settings. *Health Affairs*, 31(1):130-139.

Heisler, M., Vijan, S., Makki, F., &Piette, JD. (2010). Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. *Ann Intern Med*, 153(8):507–15.

Henderson, S., Kendall, E., & See, L. (2011). The effectiveness of culturally appropriate interventions to manage or prevent chronic disease in culturally and linguistically diverse communities: a systematic literature review. *Health and Social Care in the Community*, 19(3):225-249.

Howteerakul, N., Suwannapong, N., Rittichu, C., &Rawdaree, P. (2007).Adherence to Regimens and Glycemic Control of Patients with Type2 Diabetes Attending a Tertiary Hospital Clinic**.***Asia Pac J Public Health*,19(1): 43-49.

Junior Davis and Douglas Pearce (2001). The Non-Agricultural Rural Sector inCentral and Eastern Europein 'The Challenge of Rural Development inthe EU Accession Process'. Lerman, Z and Csaki, C. (editors).World Bank Technical Publication.

Lerman, C., & Glanz, K. (1997). Stress, Coping and Health Behavior. In Glanz, K., Lew's, F.M., &Rimer, B.K. (Eds.) Health Behavior and Health Education: Theory, Research, and Practice. 2nd Edition(pp. 211-230).San Francisco:Jossy-Bass Publishers.

Long ECJ, JA., Richardson., DM., Loewenstein, G., &Volpp, KG. (2012).Peer mentoring and financial

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

incentives to improve glucose control in African American veterans. *Ann Intern Med*,156:416–24.

Lorig, K., Ritter, PL., Villa, FJ., &Armas, J. (2009). Community-based peer-led diabetes self-management: a randomized trial. *Diabetes Educ*, 35(4):641–51.

Lwanga, SK., &Lemeshow, K. (1991). *Sample size determination in health studies: A practical manual*.World Health Organization, Geneva.

Mayurasakorn K, Sornthip N, Caengow S, Chulkarat N, Wanichsuwan M. (2009). Glycemic control and microvascular complications among type 2 diabetes at primary care units. *J Med Assoc. Thai*, 92(8):1094-1101.

Pethchit R. (2015). Self-Care Behaviors and Blood Sugar Control among Patients with Diabetes Mellitus at Khiensa Hospital, Suratthani Province. *The Southern College Network Journal of Nursing and Public Health*, 6(2):15-28

Sacco,WP., Malone, JI., Morrison, AD., & Friedman, A., & Wells, K. (2009). Effect of a brief, regular telephone intervention by paraprofessionals for type 2 diabetes. *J Behav Med*, 32(4):349–59.

Sanguanprasit, B., Leelaphan, P., Techaboonsermsak, P., &Jongsuwat, R. (2016).Village health volunteers as peer supports for glycemic control among type2 diabetes patients in Thailand. *Journal of Public Health and Development*, 14(2): 49-60.

Sanguanprasit, B., Leelaphan, P., Techaboonsermsak, P., &Jongsuwat, R. (2011). Community volunteers help control diabetes in Thailand.*Health in South-east Asia*, 4(2): 7-10.

Thom, DH., Ghorob, A., Hessler, D., De Vore ,D., Chen, E., & Bodenheimer, TA. (2013). Impact of peer health coaching on glycemic control in low-income patients with diabetes: a randomized controlled trial. *Ann Fam Med*,11(2):137-144.

Toobert, DJ., Hampson, SE., &Glasgow, RE. (2002). *Diabetes Care*, 23(7): 943 – 950.

Worawongprapa O (2008). Glycemic control in diabetes with metabolic syndrome in community hospital. *J Med Assoc. Thai*,21(5):641-647.

World Health Organization, Department of Noncommunicable Disease Surveillance. (1999). *Definition, Diagnosis and Classification of Diabetes Mellitus and its complications*. WHO, Geneva.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

*Original article*

*Received: Mar 25, 2019;*
*Accepted: Apr 26 2019;*
*Published: Apr 30, 2019*

# Analytical Method Validation for Testing of Limit of High Molecular Weight Proteins in Filgrastim Biopharmaceutical Products

Soraya Surasarang*, Chanida Karnpracha, Boontarika Boonyapiwat

Bureau of Drug and Narcotics, Department of Medical Sciences, Ministry of Public Health, Thailand

## Abstract

Filgrastim is a biopharmaceutical drug used for treatment chemotherapy-induced neutropenia in cancer patients. High molecular weight proteins (HMWP) of filgrastim can lead to loss of efficacy and immunogenicity. Limit of HMWP is one of the test items showing quality of filgrastim products. However, a compendial method used for determination of these impurities in pharmaceutical products has not yet been available. In this study, a size-exclusion chromatographic (SEC-HPLC) method was validated for determination of HMWP of filgrastim. Method validation conducted parameters including specificity, limit of quantitation (LOQ) and precision. The results showed that the analysis of HMWP of filgrastim was not interfered by the excipients and other reagents in the analytical system. The method was sensitive with the lowest limit of quantitation of 0.0002 mg/mL. In addition, the percent relative standard deviation of repeatability and intermediate precision was in a range of 1.9-3.5% and 1.9-7.3%, respectively. These values were within the limits calculated from Horwitz's equation. Thus, the size-exclusion chromatography (SEC) method was specific, sensitive, precise and valid for determination of HMWP of filgrastim in pharmaceutical products. This validated method has been utilized as a standard method to quantify the HMWP of filgrastim in biopharmaceutical products collected from all over nation by the Thai FDA.

**Keywords**: filgrastim, high molecular weight proteins, aggregation, method validation, size exclusion chromatography

***Corresponding author***: Soraya Surasarang ; soraya.h@dmsc.mail.go.th

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Introduction

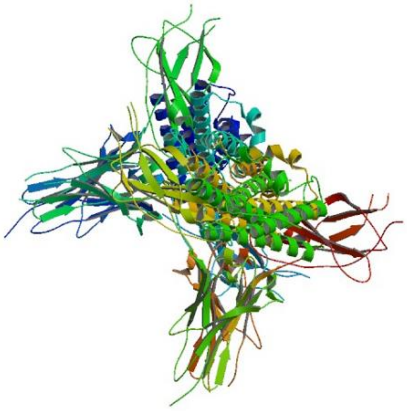
Biological products are used for diagnosis, prevention, and treatment of the diseases or medical conditions. Vaccines, blood and blood components, allergenics, tissues, monoclonal antibodies, and recombinant therapeutic proteins are some examples of the biological products (Pedersen-Bjergaard et al, 2019). Recently, the development of biological products has been greatly increasing. In the United States, biological products are growing fastest as compared with other therapeutic products (FDA, 20111). Top three largest segments of the biologics market are monoclonal antibodies, recombinant therapeutic proteins, and vaccines, respectively. These three segments are growing at an annual rate greater than 9%. However, their prices are notably more expensive than most of the small molecules (TBR, 2018). In most cases of the small molecule drugs, prices of the pharmaceutical products reduced by 50-80% after their original patent protection has expired due to the competition between multiple generic copies (Mulcahy et al, 2014). Unlike chemical drugs, molecular structure identity of biological products cannot generally be established due to the complexity of the production and minor natural variations in the molecular structure (Gámez-Belmonte et al, 2018). Generic products of the biologics launch after the patent of the originators have expired could be 'stand-alone biologicals' or 'biosimilars' (FDA, 2011; Calam PD, 2006). In general, stand-alone biologicals refer to the novel products with full clinical studies, which share the same international nonproprietary names. Whereas biosimilars are pharmaceutical products that are developed to have similar properties to an existing approved product and has no clinically significant differences (FDA, 2019). The amount of clinical data of the biosimilars needed are generally less than that required for a stand-alone products (Calam PD, 2006). This results in cost reduction of biosimilars as compared with that of the innovator products (Mulcahy et al, 2014). Biosimilars have been encouraged from the governments around the world to reduce the healthcare costs (TBR, 2018).

Both biological products and their biosimilars are inherently produced through biotechnology in a living system, such as a microorganism, plant or animal cells Jeske et al, 2013). They are generally large and more complex than small molecule drugs; therefore, characterizations of these drugs are more difficult. This leads to the challenging questions for the development and regulatory evaluation of the biosimilar products (Berkowitz et al, 2012). Regulatory agencies in several countries, starting with the European Medicines Agency, adopted the guidelines focusing on comparison issues and assurance quality, efficacy, and safety of the biosimilar products (Bennett et al, 2014). To monitor the critical quality attributes of drug substances and drug products, including biosimilars, a set of various analytical techniques are required to provide the complex information of the proteins (Driver et al, 2007; Boschetti et al, 2000). One of the characteristics according to the guidelines from the regulatory agency is the quantitative determination of the aggregation, including dimers and higher order aggregate of the active protein. There are number of analytical techniques used to characterize the aggregate such as light scattering techniques, analytical ultracentrifugation (AUC), filed-flow fractionation (FFF), gel electrophoresis, and size-exclusion chromatography (SEC) method (Hong et al, 2012; Philo et al, 2009). SEC has been a dominant favored method for aggregation analysis by far due to its speed, good sensitivity and reproducibility (Philo et al, 2009; Yu et al, 2008; Brange et al, 1992; Oliva etal, 2000). Moreover, SEC is able to separate both covalent and non-covalent dimers from the monomers (Watson et al, 1988).

Recombinant human granulocyte colony-stimulating factor (G-CSF) is a biopharmaceutical drug produced through genetic recombination (Souza et al, 1986; Lu et al, 1992). There are two types of G-CSF; glycosylated (lenograstim) and non-glycosylated (filgrastim) form produced by using the expression in mammalian cells and in *E. coli*, respectively (Vanz et al, 2008). Filgrastim, molecular weight of 18,800 daltons,

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

consists of 175 amino acids with an extra N-terminal methionine (Figure 1) (Vanz et al, 2008; FDA, 2012). A well-known and well-characterized biopharmaceutical drug as filgrastim has been approved for use in treatment of chemotherapy-induced neutropenia in cancer patients (Wang W, 1999; Beveridge et al, 1998). Pharmacodynamic of filgrastim is that the drug binds to G-CSF receptor and stimulates the production of neutrophils in bone marrow. G-CSF and its receptor are necessary for basal and stress-induced granulopoiesis, which forms neutrophils (Panopoulos & Watowich, 2008). The patents on Neupogen®, an originator product, expired in Europe and the US in 2006 and 2013, respectively (ICH, 2005). A number of filgrastim biosimilars have entered the market. In 2018, filgrastim products have been launched in Thai market under 10 brand names (18 registration numbers), which include 2 biosimilar products (Thai FDA, 2018). Analytical procedures are required to evaluate quality of the different products. Besides the potency assay, determination of high molecular weight proteins (HMWP) is the other significant test method to assess the characteristics of filgrastim (British Pharmacopeia, 2018; USP, 2017) since the HMWP of filgrastim may lead to multiple adverse effects, such as loss of efficacy and enhancement of immune responses to the monomeric form (Rosenberg AS, 2006). However, a compendial method for evaluating the HMWP of filgrastim in pharmaceutical products has not yet been available in any international pharmacopeias. The objective of this study is to validate the analytical method for determination of the HMWP of filgrastim in the pharmaceutical products. The size-based separation by SEC for separation of the different HMWP of filgrastim is studied.



MTPLGPASSLPQSFLLKCLEQVRKIQGDGAALQEKLCATYKLCHPEELVLLGHSLGIPWA
PLSSCPSQALQLAGCLSQLHSGLFLYQGLLQALEGISPELGPTLDTLQLDVADFATTIWQ
QMEELGMAPALQPTQGAMPAFASAFQRRAGGVLVASHLQSFLEVSYRVLRHLAQP

**Figure 1**. Structure (a) and amino acid sequence (b) of filgrastim (Filgrastim – DrugBank,2019)

## Materials and Methods

### *Materials*

USP high molecular weight filgrastim RS was purchased from the US Pharmacopeia, MD, USA. Ammonium hydrogen carbonate, sodium hydroxide, and acetic acid were acquired from Carlo Erba reagents, Italy. D-mannitol and sodium acetate were purchased from Sigma-Aldrich, MO, USA. Sorbitol, tween 80, and L-glutamic acid were purchased from TCI, Japan, Scharlau, Spain and Acros Organics, Belgium, respectively. Orthophosphoric acid was obtained from Merck, Germany. Water type I was produced from the Milli-Q® type I ultrapure water systems (Merck Ltd., Germany). All other chemicals and solvents used were American Chemical Society (ACS) reagent or high-performance liquid chromatography (HPLC) grade.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

### *Reagent preparation*

*Mobile phase*

Ammonium hydrogen carbonate (7.9 g) was dissolved in 1000 ml of ultrapure water. The pH of the solution was adjusted by phosphoric acid to 7.0. The final volume was made up to 2,000 mL with ultrapure water (final concentration of 0.05 M). The solution was filtered by 0.2 µm of nylon membrane filter (National Scientific Supply Company, Inc., CA, USA).

Dissolve 7.9 g of ammonium hydrogen carbonate in 1,000 mL of water, and adjust with phosphoric acid to a pH of 7.0; dilute to 2,000 mL with ultrapure water, then filter with a nylon membrane filter, pore size 0.2 µm (National Scientific Supply Company, Inc.CA, USA)

*Matrix solution*

A mixed matrix solution contained all of the excipients often filgrastim brand names marketed in Thailand. The 100-mL of matrix solution contains 4 mg of tween 80, 60 mg of acetic acid, 6 mg of sodium hydroxide, 12.3 mg of sodium acetate, 500 mg of sorbitol, 500 mg of mannitol, and 147.2 mg of L-glutamic acid. The excipients were weighed and dissolved in water until a clear solution was obtained. The solution was sterile using membrane filtration technique ( 0. 2 µm cellulose acetate syringe filter, sterile Minisart® single use filter unit, Sartorius Stedim Biotech S.A., Germany).

*Stock solution of high molecular weight (HMW) filgrastim (0.5 mg/mL)*

USP HMW filgrastim RS is a mixture of filgrastim HMW including dimer, oligomer 1, oligomer 2, aggregate and filgrastim monomer. The contents of an entire vial of USP HMW filgrastim RS was reconstituted with the matrix solution to obtain a stock solution of HMW filgrastim (0.5 mg/mL).

*Resolution solution*

For system suitability testing, the resolution solution was prepared. The stock solution of HMW filgrastim was diluted with water to obtain a clear solution of the resolution solution (0.3 mg/mL).

*Resolution solution in matrix solution*

To determine the interferences from the excipients in all marketed products, the mixture of filgrastim and its HMWP in matrix solution was prepared. The stock solution of HMW filgrastim was diluted with matrix solution to obtain a clear solution of the resolution solution (0.3 mg/mL). This solution was used as a 'reference solution' for comparing the relative peak area of each impurity as well.

### *HPLC chromatographic condition*

A Thermo Scientific high-performance liquid chromatography (HPLC), Ultimate 3000 module ( Thermo Scientific, MA, USA) equipped with the PDA detector and Chromeleon 7 software was used for the analysis. The experiments were performed on a TSK gel SWxL G3000 (300 mm x 7.8 mm I.D.) size- exclusion column ( Tosho Corporation, Japan). A security guard column with the same packing materials ( Tosho Corporation, Japan) was used to protect the analytical column. The flow rate and column temperature were set at 0.5 mL/min and 30°C, respectively. A twenty µL of the solution was injected onto the column and chromatograms were acquired at a detection wavelength of 215 nm.

*System suitability*

To ensure the suitability of the analytical system, the resolution solution was firstly injected to the HPLC. Resolution between the peaks due to the filgrastim dimer and the monomer should be greater than 3 (British Pharmacopeia, 2018).

### *Method validation*

The analytical method was adapted from the methods of the United States Pharmacopeia 40 National Formulary 35 (USP 40 NF 35) and the British Pharmacopoeia (British Pharmacopeia, 2018; USP, 2017). The validation procedures followed the International Conference of Harmonization (ICH) guidelines

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

Q2(R1) validation of analytical procedures: text and methodology (ICH, 2005). This study evaluated the parameters beyond the guidelines to confirm that the method was sensitive and precise. Thus, the following parameters, specificity, limit of quantitation (LOQ), precision, and intermediate precision (inter-day precision and different analysts), were demonstrated.

*Specificity*

The specificity of the method for the filgrastim and its HMWP was established through the determination of interference of the excipients in matrix solution, diluent (water) and mobile phase. Peaks of any excipients and reagents used in the analytical method do not co-elute at the retention time of the interested peaks of the HMWP and filgrastim monomer.

*Limit of quantitation (LOQ)*

The predicted LOQ of each impurity was calculated based on the standard deviation of the response and slope. Firstly, a regression line of each impurity was generated by plotting peak area of the impurity as a function of concentration. The stock solution of HMW filgrastim (0.5 mg/mL) was diluted with water to obtain a series of solutions ( concentrations 0.001-0.5 mg/mL). Then the mean peak area of each impurity from the triplicate determinations was plot against the concentration. The standard error of the predicted y-value for each x in the regression and slope of the regression line was evaluated. The predicted LOQ value of each impurity was calculated. Then the LOQ values were confirmed in the experimental test by preparing the triplicate LOQ solutions as calculated and injecting to the HPLC. The signal to noise ratio (S/N) of each HMWP of filgrastim at LOQ level was considered as not less than 10:1 (Shrivastava & Gipta, 2011). In case the 10:1 S/N of the predicted LOQ of any impurity did not reach, the LOQ value was obtained by diluting the solution until the S/N at least 10:1 was achieved.

*Precision*

The precision of the method was determined by repeatability and intermediate precision. Owing to the very small amount of impurity, Horwitz' s equation and Horwitz' s ratio ( HORRAT) ( Horwitz W, 2006) were applied to set the limit of the relative standard deviation (RSD) as the following equation;

$$RSD = 0.66 \times 2C^{-0.1505}$$

where $C$ is the concentration ratio (no unit)

While the limit of HORRAT would not be more than 2. Calculation of the HORRAT was presented as follows;

$$HORRAT = \frac{RSD\ obs}{RSD\ expected}$$

where $RSD\ obs$ is the RSD calculated from the experiment
$RSD\ expected$ is the RSD calculated from Horwitz's equation

*Repeatability (Intra-day precision)*

Repeatability was examined by performing of 6 replicate injections of 6 determinations of HMW filgrastim solution at LOQ level. Percent relative area of any interested impurity (from the solution at LOQ level) was normalized as compared with the total peak area of the filgrastim and the other HMWP from the chromatogram of the reference solution of 0.3 mg/mL, excluding the peak area of that interested impurity (see the equation below). The RSD of % relative area of the HMW filgrastim from the replicate determinations expressed repeatability parameter.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

*Intermediate precision*

Intermediate precision of the method was assessed by inter-day precision and different analysts. Intermediate precision was also expressed as RSD. Limit of the RSD was also specified by the value obtained from Horwitz's equation and HORRAT.

*Inter-day precision*

The intra-day precision was repeatedly carried out on three non-consecutive days. The RSD of the data from 3-day experiments was calculated.

*Different analysts*

Two analysts were separately performed the experiments in the same manner. The RSD of the data from both analysts was calculated.

## Results and Discussion

### *Method optimization*

Two major concerns of the chromatographic method are stationary and mobile phases. Since the method needed to separate the molecular weight of filgrastim and its HMWP of approximately 18,800 Daltons and greater, the silicon-based size exclusion column was used as the stationary phase. The neutral buffer (pH 7.0, ammonium hydrogen carbonate solution) was selected as the mobile phase to separate the aggregates from the intact filgrastim since the neutral pH buffer trended to have lesser effect on breaking up the non-covalent aggregates than the acidic running buffer. The pH 7.0 was much closer to the isoelectric point of the filgrastim (pI = 5.65) [34] resulting in lacking of the formation of any potential components (USP, 2013). Besides, it seemed to be clearer from the interferences of the excipients, tween 80 in particular.

### *Method validation*

*Specificity*

As reference standard of each filgrastim impurity is not available, the USP HMW filgrastim RS containing all major HMWP (dimer, oligomer 1, oligomer 2 and aggregate) and the monomer was used for method validation. Moreover, it was found that the smallest peak of HMWP X was also detected. Figure 2 shows chromatograms of diluent (water), mobile phase, resolution solution in matrix solution and matrix solution. The relative retention time (RRT) of aggregate, HMWP X, oligomer 1, oligomer 2, dimer and filgrastim monomer were 0.61, 0.78, 0.81, 0.84, 0.89, and 1.00, respectively. Resolution of the filgrastim dimer and monomer was not less than 3, which exhibited suitability of the system. There was no co-eluting peak from any excipients, diluent or mobile phase at the retention times of filgrastim and its HMWP peaks. According to the peak shape, it was noted that aggregate formed a broad and irregular shape while the other peaks were narrower and more symmetric.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

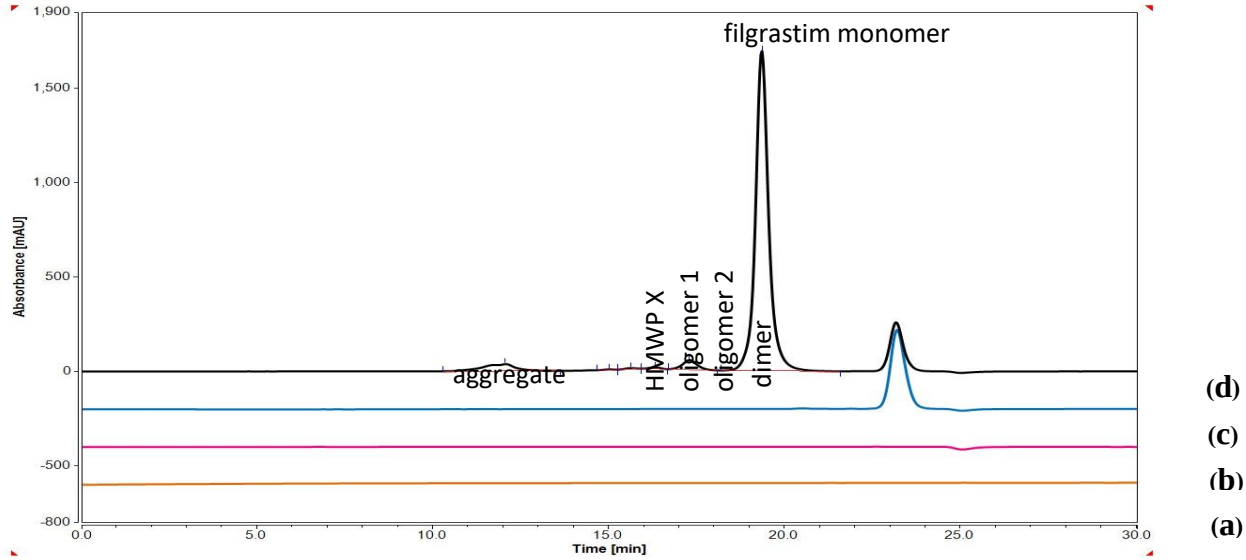



**Figure 2**. Chromatograms of mobile phase (a), diluent (water) (b), matrix solution (c), and resolution solution in matrix solution (d)

*LOQ*

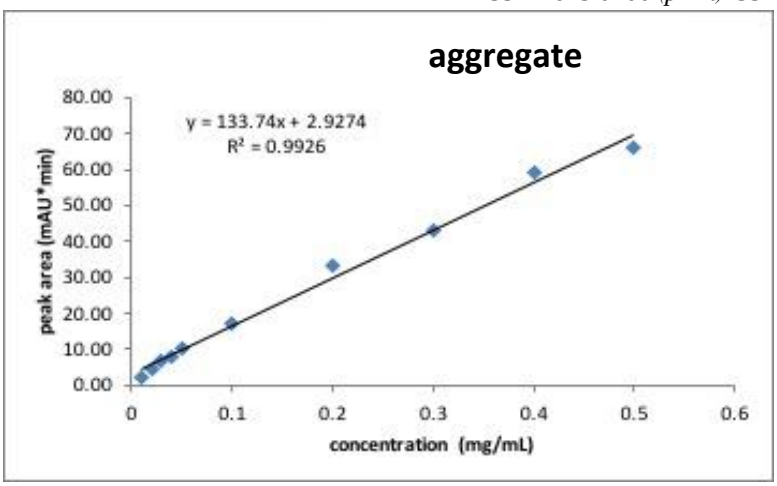
The LOQ value shows how low the analyte compound can be reliably quantified [32]. There are various methods to obtain LOQ value. The mathematical calculation from the relationship between the standard deviation of the calibration curve and its slope using the multiplier suggested by the ICH guidelines was followed to determine the LOQ in this study [36]. As the USP HMW filgrastim RS used was the mixture of filgrastim and its HMWP, the initially calculated values were the concentrations of the USP HMW filgrastim RS solution, not the LOQ concentration of each HMWP.

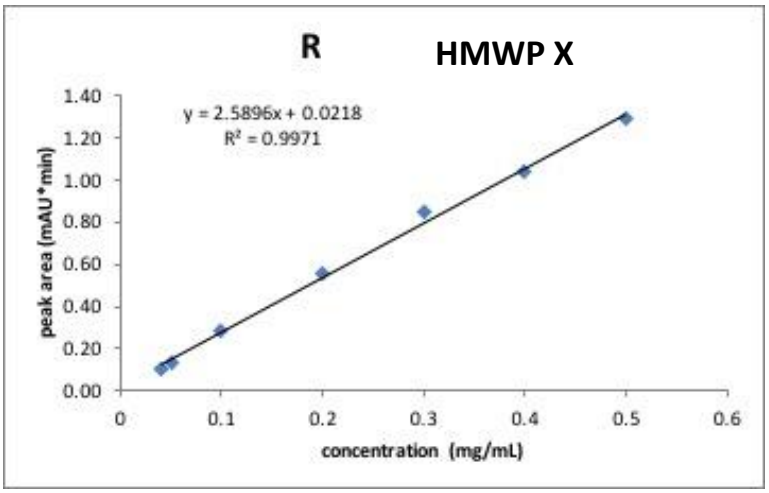
A standard curve of each impurity was built from a series of the concentration of the USP HMW filgrastim RS solution varied from 0.001-0.5 mg/mL. Peak areas of each HMWP were plotted against the concentrations (Figure 2). All curves including oligomer 1 and oligomer 2 (data not shown) achieved the $R^2$ of ≥ 0.99, which indicated good linear relationship for analysis of impurity (Yin H, 2011). Slopes obtained from the regression lines and the STEYX calculated from the peak areas and concentrations were applied to determine the concentrations of the USP HMW filgrastim RS solutions as per the following equation;

$$concentration\ of\ the\ USP\ HMW\ filgrastim\ \ RS\ at\ LOQ\ level = \frac{10\ x\ (STEYX)}{Slope}$$

where $STEYX$ is the standard error of the predicted y-value for each x in the regression and $Slope$ is the slope of the regression line

ISSN 2673-0200 (print) ISSN 2673-0251 (online)



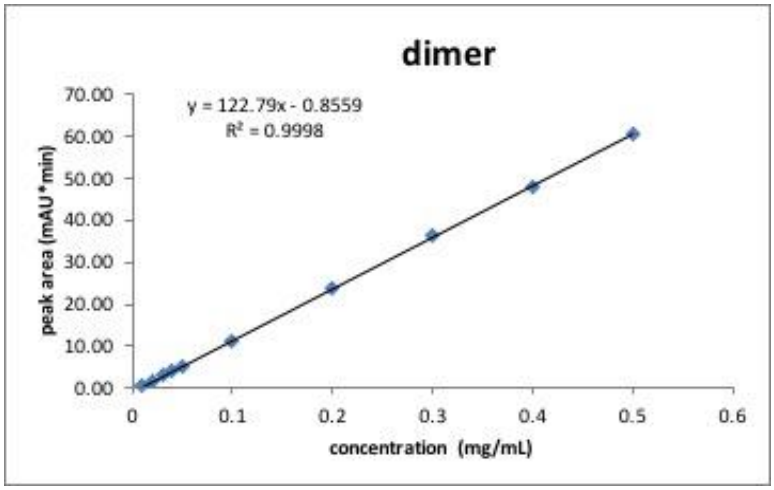




**Figure 3**. Linear curves between peak areas of HMWP of filgrastim and concentrations of the USP HMW filgrastim RS solutions

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

**Table 2**. The concentration of the USP HMW filgrastim RS solution calculated based on standard deviation of the response (STEYX) and slope of each curve, experimental concentration, and S/N

| Component | RRT | STEYX | Slope | Calculated concentration (mg/mL) | S/N | % relative area | LOQ (mg/mL) |
|---|---|---|---|---|---|---|---|
| aggregate | 0.61 | 2.18 | 133.74 | 0.16 | 2,000:1 | 0.21 | 0.0006 |
| HMWP X | 0.78 | 0.03 | 2.5896 | 0.12 | 10:1 | 0.05 | 0.0002 |
| dimer | 0.89 | 0.29 | 122.79 | 0.02 | 10:1 | 0.28 | 0.0008 |

Table 2 shows the concentrations of the USP HMW filgrastim RS solutions calculated based on standard deviation of the response (STEYX) and its slope. The S/N ratio of each peak was verified and confirmed by the experiment. As mentioned earlier, S/N ratio of about 10:1 was expected to be obtained from the solution with concentration calculated based on the linear curve method. The peak of HMWP X was the smallest one adjacent to the peaks of oligomer 1 and 2. Thus, this peak was a representative in the evaluation of S/N ratio, % relative area and LOQ of these small peaks. The experimental results indicated that S/N ratios of HMWP X and dimer with the calculated concentrations were about 10:1 as predicted. However, S/N ratio of the aggregate peak (2000:1) was much greater than 10:1. The poor prediction accuracy of S/N ratio of the aggregate peak was because this peak composed of different sizes of groups of a number of filgrastim monomers leading to the irregular, broad peak shape (as shown in Figure 2). Particularly at low concentrations, the broad peaks resulted in lower accuracy of the prediction. This reflected on the $R^2$ of its regression line (0.9926) as compared with the other impurities (range of the $R^2$ from 0.9938 (oligomer 1) to 0.9998). To acquire S/N ratio of about 10:1 of the aggregate peak, the USP HMW filgrastim RS solutions were diluted and injected until the expected value was achieved. In summary, the 0.01, 0.12 and 0.02 mg/mL of USP HMW filgrastim RS solutions provided the acquired S/N ratio (10:1) of the aggregate, HMWP X and dimer peaks, respectively.

Then, % relative area of each peak was evaluated and used for calculation of LOQ. The USP HMW filgrastim RS solution of 0.3 mg/mL was used as the reference solution. The solution was appropriate for calculation of % relative area since this is the concentration of most filgrastim products and would be used as concentration of the test solution for this validated method. The peaks with S/N ratio of 10:1 obtaining from the USP HMW filgrastim RS solutions from the above were used for calculation of LOQ as 'Peak area A'. Peak area of the interested impurity on the chromatogram of the reference solution (0.3 mg/mL) was subtracted from total peak area of the same chromatogram. The 'Peak area A' was replaced by the subtracted area (Peak area B) and relative calculated as follows;

$$\%\ relative\ area = \frac{Peak\ area\ A}{(Total\ peak\ area\ from\ the\ ref.solution - Peak\ area\ B) + Peak\ area\ A}\ x\ 100$$

where $Peak\ area\ A$ is peak area of the interested impurity obtaining from the chromatogram of the USP HMW filgrastim RS solution providing peak with S/N of 10:1

$Total\ peak\ area\ from\ the\ ref.solution$ is total peak area of all peaks obtaining from the chromatogram of the 0.3 mg/mL reference solution

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

$Peak\ area\ B$ is peak area of the interested impurity obtaining from the chromatogram of the 0.3 mg/mL reference solution

To calculate the LOQ of each HMWP of filgrastim, the following equation was applied.

$$LOQ\ of\ the\ imp.(mg/mL) = \frac{relative\ area\ (\%)\ x\ C_{ref.solution}(mg/mL)}{100}$$

where $relative\ area\ (\%)$ calculated from the above equation

$C_{ref.solution}$ = concentration of the reference solution = 0.3 mg/mL

The LOQ of aggregate, HMWP X, and dimer as 0.0006, 0.0002, and 0.0008 mg/mL, respectively (Table 2).

*Precision and Intermediate Precision*

The precision of the method was demonstrated in terms of repeatability and intermediate precision. A total of 36 injections (6 determinations x 6 injections) for each LOQ were analyzed per day for the repeatability study. The repeated experiments were carried out in three non-consecutive days to evaluate the inter-day precision. The intermediate precision was also demonstrated by two analysts, using the same HPLC system, performing in the same manner as for the first analyst. The RSD calculated from the Horwitz's equation and HORRAT of each impurity was presented in Table 3. The RSD between of the within-day replicate measurements was reported as 1.9-3.5%. Intermediate precision is the outcomes of the within-laboratory variations resulting from random situations, such as inter-day precision and different analysts [26]. Also, RSD of the inter-day precision were reported as and 3.3-6.1%. The RSD of the results of both analysts had to be lower than the RSD calculated from the Horwitz's equation. Table 3 shows the RSD of each impurity met the criteria. The RSD of 1.9-7.3% was also below the acceptance values (10.9-13.5%). This illustrated the good within-lab reproducibility of the analytical method. Therefore, this proposed SEC method was precise for analysis of HMWP of filgrastim.

**Table 3**. RSD, the acceptance criteria of RSD and HORRAT

| **Impurity** | **RSD observed** | | | **Acceptance criteria** | |
|---|---|---|---|---|---|
| | repeatability | inter-day precision | different analysts | of RSD (RSD expected) | HORRAT (repeatability) |
| **aggregate** | 1.9 | 6.1 | 7.3 | 11.4 | 0.2 |
| **HMWP X** | 2.2 | 3.3 | 1.9 | 13.5 | 0.2 |
| **dimer** | 3.5 | 4.1 | 5.3 | 10.9 | 0.3 |

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Conclusion

The results show the validation of SEC method was successful. The proposed method was specific, precise, and possesses excellent reproducibility attribute. Hence, this validated method was appropriate to use as a standard method to quantify the HMWP of filgrastim in various brands of biopharmaceutical products collected from multiple manufacturers by the Thai FDA.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## References


Bennett CL, Chen B, Hermanson T, Wyatt MD, Schulz RM, Georgantopoulos P, et al. Regulatory and clinical considerations for biosimilar oncology drugs. Lancet Oncol 2014;15: p. e594–605. doi:10.1016/S1470-2045(14)70365-1.

Berkowitz SA, Engen JR, Mazzeo JR, Jones GB. Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nat Rev Drug Discov 2012;11: p. 527–40. doi:10.1038/nrd3746.

Beveridge RA, Miller JA, Kales AN, Binder RA, Robert NJ, Harvey JH, et al. A Comparison of Efficacy of Sargramostim (Yeast-Derived RhuGM-CSF) and Filgrastim (Bacteria-Derived RhuG-CSF) in the Therapeutic Setting of Chemotherapy-Induced Myelosuppression. Cancer Invest 1998;16: p. 366–73. doi:10.3109/07357909809115775.

Biosimilars > Biosimilar and Interchangeable Products https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapEUticBiologicApplications/Biosimilars/ucm580419.htm (accessed January 16, 2019).

Boschetti E, Jungbauer A. 15 Separation of antibodies by liquid chromatography. In: Ahuja S, editor. Sep. Sci. Technol., vol. 2, Academic Press; 2000: p. 535–632. doi:10.1016/S0149-6395(00)80062-8.

Brange J, Langkjaer L, Havelund S, Vølund A. Chemical stability of insulin. 1. Hydrolytic degradation during storage of pharmaceutical preparations. Pharm Res 1992;9: p. 715–26.

British Pharmacopoeia 2018. Filgrastim Concentrated Solution. British Pharmacopoeia 2018, vol. I, London: Stationery Office. p. I-1024–7.

Calam PD. WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products: p. 11.

Commentary Second Supplement USP 36-NF 31 https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/2013-10-25_usp36-nf31_2s_commentary_updated.pdf (accessed September 21, 2018).

Company TBR. Faster Drug Approval Process Will Boost the Biologics Market. Mark Res Blog 2018. https://blog.marketresearch.com/faster-drug-approval-process-will-boost-biologics-market (accessed March 9, 2019).

Driver JL, Raynie DE. 15 Method development for biomolecules. In: Ahuja S, Rasmussen H, editors. Sep. Sci. Technol., vol. 8, Academic Press; 2007: p. 425–39. doi:10.1016/S0149-6395(07)80021-3.

FDA. Biologics regulated products. Rockville, MD: FDA; 2009a. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123205.htm. (accessed July 20, 2011).

Filgrastim. U.S. Pharmacopeia-National Formulary [USP 40 NF35], vol. 1, Rockville, MD: United States Pharmacopeial Convention, Inc.; 2017, p. 4196–202.

Filgrastim - DrugBank. https://www.drugbank.ca/drugs/DB00099 (accessed June 12, 2019).

Gámez-Belmonte R, Hernández-Chirlaque C, Arredondo-Amador M, Aranda CJ, González R, Martínez-Augustin O, et al. Biosimilars: Concepts and controversies. Pharmacol Res 2018;133:251–64. doi:10.1016/j.phrs.2018.01.024.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

Hong P, Koza S, Bouvier ESP. Size-Exclusion Chromatography for the Analysis of Protein Biotherapeutics and their Aggregates. J Liq Chromatogr Relat Technol 2012;35: p. 2923–50. doi:10.1080/10826076.2012.743724.

Horwitz W, Albert R. The Horwitz ratio (HorRat): A useful index of method performance with respect to precision. J AOAC Int. 2006;89: p. 1095–109.

International Conference on Harmonization (ICH). Analytical Procedure Development and Revision of Q2(R1) Analytical Validation 2005.

International Conference on Harmonization (ICH). International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, Validation of analytical procedures: Text and Methodology. ICH-Q2B 1996.

Jeske W, Walenga JM, Hoppensteadt D, Fareed J. Update on the safety and bioequivalence of biosimilars – focus on enoxaparin. Drug Healthc Patient Saf 2013;5: p. 133–41. doi:10.2147/DHPS.S28813.

Lu HS, Clogston CL, Narhi LO, Merewether LA, Pearl WR, Boone TC. Folding and oxidation of recombinant human granulocyte colony stimulating factor produced in Escherichia coli. Characterization of the disulfide-reduced intermediates and cysteine-serine analogs. J Biol Chem 1992;267: p. 8770–7.

Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States. Perspectives (Montclair) 2014.

Oliva A, Fariña J, Llabrés M. Development of two high-performance liquid chromatographic methods for the analysis and characterization of insulin and its degradation products in pharmaceutical preparations. J Chromatogr B Biomed Sci App 2000;749: p. 25–34. doi:10.1016/S0378-4347(00)00374-1.

Panopoulos AD, Watowich SS. Granulocyte Colony-Stimulating Factor: Molecular Mechanisms of Action During Steady State And 'Emergency' Hematopoiesis. Cytokine 2008;42: p. 277–88. doi:10.1016/j.cyto.2008.03.002.

Pedersen-Bjergaard S, Gammelgaard B, Halvorsen TG. Introduction to Pharmaceutical Analytical Chemistry. John Wiley & Sons; 2019: p. 460.

Philo JS. A critical review of methods for size characterization of non-particulate protein aggregates. Curr Pharm Biotechnol 2009;10: p. 359–72.

Rosenberg AS. Effects of protein aggregates: an immunologic perspective. The AAPS Journal 2006;8: p. E501–E507.

Shrivastava A, Gupta VB. Methods for the determination of limit of detection and limit of quantitation of the analytical methods. Chronicles of Young Scientists 2011;2: p. 21. doi:10.4103/2229-5186.79345.

Souza LM, Boone TC, Gabrilove J, Lai PH, Zsebo KM, Murdock DC, et al. Recombinant human granulocyte colony-stimulating factor: effects on normal and leukemic myeloid cells. Science 1986;232: p. 61–5. doi:10.1126/science.232.4746.61.

Tange M, Matsumoto A, Yoshida M, Kojima H, Haraguchi T, Uchida T. Comparison of the Adsorption of Original and Biosimilar Preparations of Filgrastim on Infusion Sets and the Inhibition of Adsorption by Polysorbate 80. Chem Pharm Bull 2017;65: p. 36–41. doi:10.1248/cpb.c16-00478.

Thai Food and Drug Administration, Bureau of Drug Control. Searching and Statistic Information; Filgrastim. http://www.fda.moph.go.th/sites/Drug/ (accessed July 22, 2018).

U.S Food & Drug Administration. Neupogen® Filgrastim. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103353s5147lbl.pdf

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

Vanz AL, Renard G, Palma MS, Chies JM, Dalmora SL, Basso LA, et al. Human granulocyte colony stimulating factor (hG-CSF): cloning, overexpression, purification and characterization. Microb Cell Factories 2008;7: p. 13. doi:10.1186/1475-2859-7-13.

Wang W. Instability, stabilization, and formulation of liquid protein pharmaceuticals. Int J Pharm 1999;185: p. 129–88. doi:10.1016/S0378-5173(99)00152-0.

Watson E, Kenney WC. High-performance size-exclusion chromatography of recombinant derived proteins and aggregated species. J Chromatogr A 1988;436: p. 289–98. doi:10.1016/S0021-9673(00)94586-2.

Yin H. Method and Validation basics-HPLC case study 2011.

Yu C-M, Mun S, Wang N-HL. Phenomena of insulin peak fronting in size exclusion chromatography and strategies to reduce fronting. J Chromatogr A 2008;1192: p. 121–9. doi:10.1016/j.chroma.2008.03.055.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

*Original article*

*Received: Mar 30, 2019;*
*Accepted: Apr 28, 2019;*
*Published Apr 30,2019*

# Prescribing Aspirin for Primary Prevention and Risk Factors of Cardiovascular Events in Diabetic Patients at Huaiyot Hospital, Trang Province

Parinda Kongprasom [1], Chattima Ongpalakorn [1], Tapanan Prateepko[2], Rosmalin Thotham[1], Jarumon Lukkanawiwat[1], Mayuree Lakkanasirorat[1], Supreeya Tirapat[1], Panitsara Thongrit[1]

[1]Huaiyot Hospital, Trang, Thailand
[2]Faculty of Education, Prince of Songkla University, Pattani, Thailand

## Abstract

**Background**: Cardiovascular diseases (CVDs), including coronary heart disease and stroke, are a major cause of death in many countries. Currently, using aspirin, an antiplatelet, is recommended to prevent CVDs in diabetic patients but there are still no clear benefits for primary prevention. **Objectives**: To compare the incidence of cardiovascular diseases between received aspirin and non-received aspirin groups among diabetic patients without prior CVDs, to identify risk factors for CVD outcomes and to find out the adherence to the American Diabetic Association (ADA) guidelines for aspirin therapy in primary prevention among diabetic patients. **Materials and methods**: Retrospective data review was conducted by assessing electrical medical records from January 2012 to 2017. The main interesting risk factors and aspirin used and non-used data were extracted. The outcomes were the new event of CVDs. The processes of data collection and validation following the inclusion and exclusion criteria were performed by the diabetic patient care team. Data analyses were performed by t-test, chi-square test, and multiple logistic regressions. **Results**: 1,671 diabetic patients were finally enrolled in the study. There was no statistically significant difference of CVDs between aspirin and non-aspirin user with adjusted OR of 1.16 (95% CI,0.80-1.69). Albuminuria, duration of DM more than 10 years and comorbidity with hypertension and dyslipidemia increased the risk of CVDs with adjusted OR of 1.88(95%CI,1.31-2.71), 1.48(95%CI, 1.01-2.25), 3.34 (95%CI,1.75-6.38), 3.89(95%CI,2.00-7.35), respectively. Eighteen point six percent of the subjects were overused aspirin following the ADA recommendation. **Conclusions**: The use of low-dose aspirin was not associated with new CVDs events in diabetic patients without prior CVDs because no statistical significance. There is some overuse of aspirin for primary prevention. Doctors should pay attention to other comorbidities such as hypertension and dyslipidemia, especially in a patient with albuminuria and long duration of DM more than 10 years.

**Keywords**: Aspirin, Cardiovascular disease, Primary prevention, Diabetic patient

***Corresponding author***: Parinda Kongprasom, Huaiyot Hospital, Trang 92130, Thailand. Phone: +66-87-8824341, Fax: +66-75-272064, Email: Parinda.kong47@gmail.com

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Introduction

Cardiovascular diseases (CVDs) become the major cause of death, in which the World Health Organization (WHO) estimated that 17 million people died from CVDs, particularly heart attacks and strokes every year and it will increase to 25 million people per year in 2030 (WHO,2015). The number of deaths from CVDs was mainly in the developing countries because of the increasing incidence of high blood pressure, dyslipidemia, diabetes mellitus(DM), smoking, inactivity lifestyle and obesity that are considered as the major risk factors of CVDs (Lim et al, 2012). Whereby, in Thailand, as of 2012, there were 501,000 people (29%) died with CVDs of all 66,785,000 people and it was the first cause of death in both sexes and all age groups (WHO,2014).

One of the major risk factors of CVD is diabetes. The data of the American Heart Association in 2015 reported that at least 68%and 16%of more than 65 years old diabetic patients have died from coronary heart disease and stroke, respectively (Pignone et al, 2010). In diabetic patients, a chance of having CVDs was 2-4 folds more than non-diabetic ones because major CVD risk factors such as dyslipidemia, hypertension, and obesity were frequently founded in the patients (Pignone et al, 2010). In addition, diabetes is associated with an increased platelet activity, inflammatory and pro-thrombotic environment, exacerbating the development of atherothrombosis (Pignone et al, 2010; Guirguis-Blake et al, 2015). Therefore, antiplatelet treatment strategies were developed and used in many diabetic patient treatment guidelines, especially low dose aspirin that has been playing a role to prevent CVDs in DM patients for many years (Pignone et al, 2010; Guirguis-Blake et al, 2015). Currently, the American Diabetic Association (ADA) has recommended indication of low dose aspirin (75–162 mg/day) to prevent CVDs by considered from Atherosclerotic Cardiovascular Disease risk (ASCVD risk) that is calculated from age, sex, co-morbidities, smoking, blood pressure and level of cholesterol that predicted chance to occur CVDs in 10 years (American Diabetes Association, 2014). Meanwhile, in 2013, the European Society of Cardiology suggested that low dose aspirin should be considered only in high CVD risk patients and it has benefited more than the risk of bleeding complication (Fifth Joint Task Force of the European Society, 2012).

From the previous fourteen studies, using aspirin for primary prevention was associated with reducing 10% of CVD events but increased 6% of hemorrhagic stroke and there are now no clear pieces of evidence on the benefits of low dose aspirin for primary prevention in DM patients and the adverse events with continuous aspirin use (Ogawa et al, 2008; Xie et al, 2014). In the past five years, 43% of DM patients have prescribed aspirin for primary prevention in Huaiyot Hospital and there was no data about the incidence of CVDs in both groups (aspirin and non-aspirin). As a result, this study aimed to compare the incidence of CVDs between received aspirin and non-received aspirin groups of DM patients without prior CVDs, to identify risk factors for CVD outcomes and to find out the adherence to the ADA guidelines for aspirin therapy in primary prevention among diabetic patients.

## Methods.

The study was conducted in January 2017. The secondary data from the database of the HOSxP program of Huaiyot Hospital, Trang Province, South of Thailand, were used through reviewing electrical medical records (EMRs). The hospital numbers (patient's identifications) of all patients diagnosed with DM before January 2012 following the ICD 10 codes (E10-E14) and have had no prior CVDs (cerebrovascular disease and ischemic heart disease I20-I25, I60-I69) were extracted. The data were then entered into the designed recording forms. The processes of data collection and validation were performed by diabetic patient care team consisted of doctor, nurses, pharmacist, and information technology (IT) staff.

The diabetic patients were excluded from the study if, i) age less than 18 years, ii) false diagnosis to DM, iii) died before the date

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

of study, iv) lost follow up and uncompleted data after the date of study and v) received anticoagulant drugs.

In the study, aspirin users defined as patients who received aspirin less than 162 mg per day before the date of study (January 2012) until January 2017.The needed aspirin patients defined as patients who were recommended for aspirin use following the ADA guideline 2014. The main interested risk factors were age, sex, duration of disease, aspirin received data, body mass index (BMI), blood pressure, dyslipidemia (total cholesterol > 200 mg/dl, LDL > 100 mg/dl,TG > 150 mg/dl, HDL < 40 mg/dl), smoking, albuminuria (albumin creatinine ratio from spot urine > 30 µg/mg creatinine) , blood glucose, HbA1C, cholesterol, and ASCVD risk score calculated from the start date of data collection, January 2012.

The outcomes of the study were new CVD cases onset after the date of study (January 2012) and non- CVD cases. A CVD group was patients who were diagnosed with CVDs following ICD-10 codes of stroke and ischemic heart disease from January 2012 to January 2017. Any patient who died from all causes after the date of the study was also included into the study.

**Statistical analysis**

All analyses were undertaken by R-program version 3.3.3. In data analysis processes, continuous data were firstly tested for normal distribution by Shapiro test. Univariate analyses were performed to compare means of the baseline characteristics by t-test and presented the results as mean (standard deviation, SD). For categorical baseline characteristics, chi-square tests were performed. To identify interested risk factors for CVD outcomes among diabetic patients, multiple logistic regressions were finally performed and the results were displayed as odds ratio (OR) with 95% confidence interval (CI). The adjusted odd ratios were done by adjusted with the main interested risk factor of CVDs, and the appropriately fitted model as finally selected for presenting as the results.

**Results**

A total of 1,671 patients were enrolled to the study after excluded those who had uncompleted data (159 patients), a false diagnosis of DM (66 patients), died before the date of study (35 patients) and patients received other anticoagulants (warfarin) (5 patients) (Figure 1). For baseline characteristics of the study subjects, CVD patients were more likely to be men, smokers, aspirin users, presented with albuminuria, hypertension, and dyslipidemia (Table1). Mean age was higher in CVD group. The longer duration of DM was observed in CVD group. There were no significant differences of both groups in means of BMI, SBP, blood glucose, HbA1C, cholesterol, HDL and LDL levels, but there was a higher triglyceride level in CVD group(Table2). There were 35.6% in needed aspirin group that have received aspirin properly. Eighteen point six percent of the diabetic patients were prescribed aspirin in unneeded aspirin group or overuse (Chart1).

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

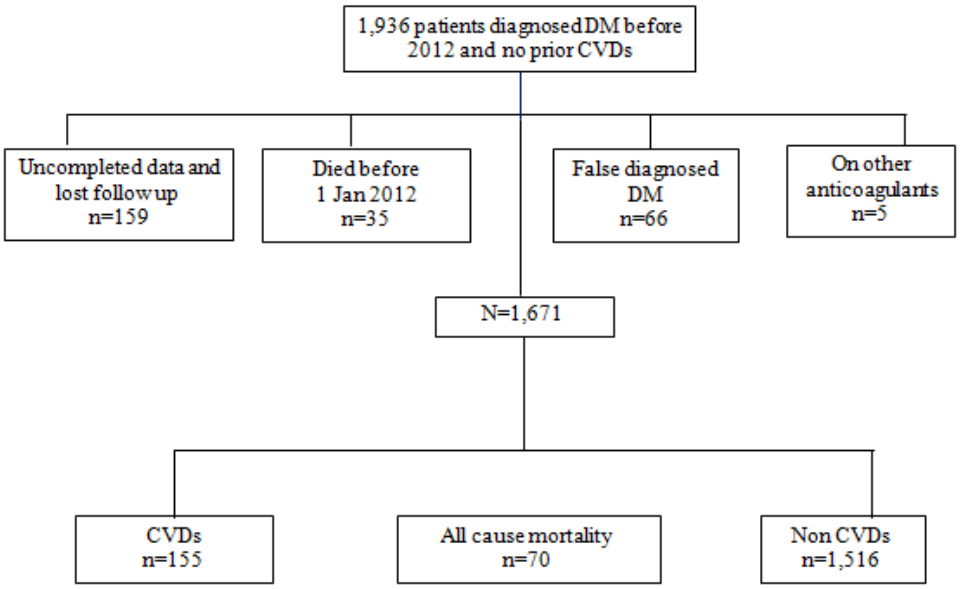



**Figure 1**. Flow chart of extracting the study subjects

**Table 1**. Baseline characteristics of the study subjects

| Characteristic | All patients n =1,671 (%) | Non CVDs n = 1,516 (%) | CVDs n =155 (%) | *p-value* |
|---|---|---|---|---|
| Sex | | | | 0.001 |
| Female | 1108(66.3) | 1024(67.5) | 84(54.2) | |
| Male | 563(33.7) | 492 (32.5) | 71(45.8) | |
| Aspirin user | | | | 0.050 |
| Non Aspirin | 803(48.1) | 740(48.8) | 63(40.6) | |
| Aspirin | 868(51.9) | 776(51.2) | 92(59.4) | |
| Smoke | | | | 0.010 |
| Non smoke | 1,465(87.7) | 1,339(88.3) | 126(81.3) | |
| Smoke | 206(12.3) | 1,77(11.7) | 29(18.7) | |
| Hypertension | | | | < 0.001 |
| Non hypertension | 404(24.2) | 390(25.7) | 14(9.0) | |
| Hypertension | 1,267(75.8) | 1,126(74.3) | 141(91.0) | |
| ASCVD score | | | | < 0.001 |
| <10% | 859(51.4) | 807(53.2) | 52(33.5) | |
| 10-<20% | 550(32.9) | 485(32.0) | 65(41.9) | |
| 20-<30% | 171(10.2) | 146(9.6) | 25(16.1) | |
| 30-<40% | 79(4.7) | 68(4.5) | 11(7.1) | |
| >40% | 12(0.7) | 10(0.7) | 2(1.3) | |

ASCVD = Atherosclerotic cardiovascular disease
BMI = Body mass index
*NA = Not available

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

**Table 1**. Baseline characteristics of the study subjects (cont.)

| Characteristic | All patients n =1,671 (%) | Non CVDs n = 1,516 (%) | CVDs n =155 (%) | *p-value* |
|---|---|---|---|---|
| Dyslipidemia | | | | |
| No | 444(26.6) | 431(28.4) | 13(8.4) | < 0.001 |
| Dyslipidemia | 1,227(73.4) | 1,085(71.6) | 142(91.6) | |
| Albuminuria | | | | |
| No | 994(59.5) | 928(61.2) | 66(42.6) | < 0.001 |
| Albuminuria | 659(39.4) | 570(37.6) | 89(57.4) | |
| NA* | 18(1.1) | 18(100) | 0(0) | |
| BMI level | | | | 0.350 |
| Underweight | 59(3.6) | 56(3.7) | 3(1.9) | |
| Normal | 376(22.6) | 336(22.3) | 40(10.6) | |
| Overweight | 316(19.0) | 292(19.4) | 24(15.5) | |
| Obesity | 911(54.8) | 823(54.6) | 88(56.8) | |

ASCVD = Atherosclerotic cardiovascular disease
BMI = Body mass index
*NA = Not available

**Table 2**. Means and standard deviations of baseline characteristics of the study subjects

| Characteristic | All patients mean (SD) | Non CVDs mean (SD) | CVDs mean (SD) | *p-value* |
|---|---|---|---|---|
| Age(years) | 59.3(13.3) | 58.9(13.4) | 63.0(11.8) | < 0.01 |
| BMI($kg/m^2$) | 25.9(4.7) | 25.9(4.7) | 25.9(4.5) | 0.89 |
| SBP(mmHg) | 137(21) | 137(20) | 140(20) | 0.05 |
| Duration of disease ( | 6.4(4.8) | 6.3 (4.7) | 7.2(5.1) | 0.02 |
| FBS(mg/dl) | 172.0(69) | 172.5 (70.2) | 164.6(59.2) | 0.18 |
| HbA1C(%) | 8.4(2.3) | 8.5(2.3) | 8.3(2.2) | 0.53 |
| Cholesterol(mg/dl) | 194.6(44.8) | 194.3(44.2) | 197.4(44.8) | 0.41 |
| LDL(mg/dl) | 105.6(38.8) | 105.5(38.6) | 106.6(40.3) | 0.73 |
| TG(mg/dl) | 183.9(102.8) | 182.1(103.4) | 200.9(95.2) | 0.03 |
| HDL(mg/dl) | 52.0(14.2) | 52.1(14.1) | 49.9(14.39) | 0.07 |

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

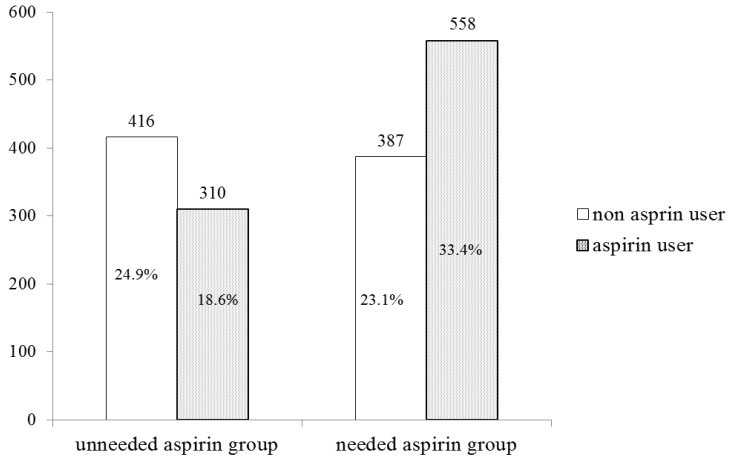



**Chart 1** Prescribing aspirin adhered to the ADA recommendation for primary prevention in DM patients

Comparison of individuals who have not been used and used aspirin, aspirin users were more likely to have CVDs (cOR=1.48, 95% CI,1.04-2.11); however, after adjusted by age, sex, hypertension, smoking, BMI, ASCVD score, there was no statistically significant difference. Having hypertension, dyslipidemia, albuminuria, long duration of DM (> 10 years) were significantly increased the risk of CVDs with adjusted OR of 3.34(95%CI,1.75-6.38), 3.89(95%CI, 2.00-7.35), 1.88(95%CI, 1.31-2.71) and 1.48(95%CI, 1.01-2.25), respectively. Other risk factors liked age more than 60 years, male sex, smoking, high HbA1C seemed to be somewhat higher risk of CVDs, but not statistical significance (Table 3).

**Table 3**. Risk factors for CVDs among diabetic patients

| Risk factor | Total CVDs (n =155)n(%) | Crude OR(95%CI) | Adjusted OR (95%CI) |
|---|---|---|---|
| Aspirin user | 92(10.6) | 1.48 (1.04, 2.11) | 1.16 (0.80, 1.69) |
| Male | 71(45.8) | 1.62 (1.14, 2.30) | 1.45 (0.96, 2.18) |
| ASCVD risk | | | |
| < 10% | 52(33.5) | 1 | 1 |
| 10-20% | 65(41.9) | 2.12 (1.42, 3.14) | 1.65 (0.94, 2.89) |
| 20-30% | 25(16.1) | 2.59 (1.53, 4.4) | 1.60 (0.71, 3.62) |
| 30-40% | 11(7.1) | 2.02 (0.92, 4.47) | 1.04 (0.36, 3.01) |
| > 40% | 2(1.3) | 3.43 (0.72, 16.32) | 1.60 (0.27, 9.50) |
| Age> 60 years | 88(11.9) | 1.72 (1.21, 2.44) | 1.13 (0.64,1.99) |
| Smoking | 29(14.1) | 1.59 (0.99, 2.54) | 1.40 (0.82, 2.40) |
| HbA1C > 7% | 99(9.4) | 1.03 (0.71, 1.49) | 1.19 (0.81, 1.74) |
| SBP >140 mmHg | 76(11.5) | 1.49 (1.06, 2.11) | 1.13 (0.74, 1.71) |
| LDL >100 mg/dl | 76(9.2) | 0.96 (0.68, 1.36) | 1.04 (0.73, 1.49) |
| Hypertension | 141(9.3) | 3.83 (2.05, 7.17) | 3.34 (1.75, 6.38) |
| Dyslipidemia | 1,227(73.4) | 4.44(2.37, 8.33) | 3.89(2.00, 7.35) |
| Albuminuria | 659(39.4) | 2.17(1.53, 3.07) | 1.88(1.31, 2.71) |
| Duration of disease | 1,371(82.1) | 1.81(1.22, 2.68) | 1.48(1.01, 2.25) |
| > 10 years | | | |

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Discussion

The present study showed that an incidence of CVDs between aspirin and non-aspirin users was not significantly associated with the CVDs outcome among diabetic patients. Even though this result was different from some other previous studies that have reduced the incidence of CVDs in the aspirin user group,15.4 % versus (VS) 13.8% for all CVD event rates, RR = 0.9 (95%CI, 0.20-0.89) from the TPT study (Pignone et la, 2010). A study in Japan in 2008, all CVD events in aspirin and non-aspirin group was 5.4% and 6.7% with HR of 0.80 (95%CI, 0.58-1.10) (Ogawa et al, 2008). However, the above two mentioned studies, there were only small differences between both groups and no statistically significant benefits. The reasons that might explain the difference of this result from the previous studies that, in fact, there were many factors not only aspirin user but also other risk factors played a role for the CVD outcomes, in which in the study after adjusted with the other factors, the estimated risk was decreased (adjusted OR = 1.16, 95%CI, 0.80-1.69).

For the other risk factors that affected CVD outcomes, the authors found that hypertension was significantly increased risk of CVDs that was similar to the previous studies, a study among Chinese population showed significantly higher average or mean SBP in coronary heart disease, stroke VS non-CVDs as 130 mmHg (95% CI 127.1–134.4), 140.6 (95% CI 137.1–144.1) VS 121.6 (95% CI 121.3–122.0) (p<0.001) (Yang et al, 2012).

Dyslipidemia as a comorbidity of DM was one of the most significant risks of CVDs (OR=3.89, (95%CI2.0-7.35), even the mean LDL level was a bit over the therapeutic goal (103 mg/dl) but not different between CVD and non-CVD groups. The previous study showed that the diabetic patients over 40 years with estimated 10 years' risk, over 7.5 % should be treated with high intensity of statin and less than 7.5% with a moderate statin (Stone et al, 2008). The clinicians, therefore, should consider more on medication to treat with the proper intensity of statin rather than LDL level only.

Moreover, the authors found some risk factors such as albuminuria, long duration of DM (> 10 years) were statistically significant differences between CVD and non-CVD groups. Albuminuria is a microvascular complication of DM and there is a strong association of proteinuria and cardiovascular morbidity and mortality in both type-2 DM patients with and without nephropathy. Also, there was supported data from the Multinational Study of Vascular Disease in Diabetics for evidence of proteinuria and ischemic heart disease in type 2 diabetes (Morrish et al, 1991).

In the study, aspirin was prescribed for primary prevention about 51.9% in the diabetic clinic. There were 18.6 % received aspirin without indication following the recommendation of the ADA guidelines 2014 or overuse. All of the overused cases were among young patients in both sexes (male □ 50 years, female ≤ 60 years) and low ASCVD risk score that has had no benefit and might be increased risk of bleeding complication. The study in the United States from 2010 to 2012 was also evidenced aspirin overutilization without CVDs that older age, more frequently visiting providers and obesity, were the significant factors for inappropriate aspirin use (Van et al, 2014).

There were some limitations of the study that could affect the results, such as unknown compliance of aspirin users and statins using. We used secondary data from the local hospital database, so it could miss the diagnosis of CVDs from ICD-10 codes owing to the doctors were not recorded the diagnosis in the database; however, the team has reviewed EMRs manually by the clinical team for reducing under diagnosis.

## Conclusions

The use of low-dose aspirin was not significantly associated with CVD events in diabetic patients without prior CVDs. Overall there is some overuse of aspirin for primary prevention. Consequently, the doctor should re-evaluate on prescribing aspirin only in high-risk patients because the study shows no benefit for primary prevention. Further study about the adverse effect of aspirin should be conducted.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

Even aspirin has not decreased the risk of CVDs, but doctors should pay attention to other comorbidities such as hypertension and dyslipidemia, especially in a patient with albuminuria and long duration of DM more than 10 years.

**What is already known on this topic?**

There is no clear benefit of aspirin for primary prevention of CVDs in DM patients.

**What this study adds?**

The present study indicated that there is some overuse of aspirin for primary prevention in clinical practice. Using low-dose aspirin was not associated with CVD outcome. Hypertension, dyslipidemia, albuminuria and long duration of DM more than 10 years increased the risk of CVDs more than using or non-using aspirin.

**Acknowledgments**

The authors would like to sincerely acknowledge to Huaiyot Hospital for the database that was used in the study. Many thanks to Professor Dr. Virasakdi Chongsuviwatwong for initiating this research project. Our special thanks are extended to the Thai Health Promotion Foundation and the Institute of Research and Development for Health of Southern Thailand for supporting research funds.

**Potential conflicts of interest**

The authors declare no conflict of interest.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## References


American Diabetes Association. Standard of medical care in diabetes-2014. Diabetes Care[Internet]. 2014 [cited 2018 Feb 4];37(Supplement 1):S14-80. Available fromhttps://doi.org/10.2337/dc14-S014

de Jong PE, Gansevoort RT, Bakker SJ. Macroalbuminuria and microalbuminuria: do both predict renal and cardiovascular events with similar strength? Journal of Nephrology. 2007;20(4):375-80.

de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004;110(8):921-7.

Fifth Joint Task Force of the European Society of C, European Association of E, European Association of Percutaneous Cardiovascular I, European Heart Rhythm A, Heart Failure A, European Association for Cardiovascular P, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). European journal of preventive cardiology. 2012;19(4):585-667.

Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Sep. (Evidence Syntheses, No. 131.) References [cited 2018 Feb3].Available from:https://www.ncbi.nlm.nih.gov/books/NBK321630/

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.

Morrish NJ, Stevens LK, Fuller JH, Jarrett RJ, Keen H. Risk factors for macrovascular disease in diabetes mellitus: the London follow-up to the WHO Multinational Study of Vascular Disease in Diabetics. Diabetologia. 1991;34(8):590-4.

Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. Jama. 2008;300(18):2134-41.

Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Circulation. 2010;121(24):2694-701.

Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 years observational follow up study. BMJ. 1996;313(7060):779-84.

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;63(25 Pt B):2889-934.

VanWormer JJ, Miller AW, Rezkalla SH. Aspirin overutilization for the primary prevention of cardiovascular disease. Clinical epidemiology. 2014; 6:433-40.

World Health Organization. Atlas of heart disease and stroke[Internet]. 2015[cited 2018 Apr 15]. Available from:http://www.who.int/cardiovascular_diseases/resources/atlas/en/

World Health Organization. Non communicable diseases (NCD) country profiles [Internet]. 2014 [cited 2018 Feb 2].Available fromhttp://www.who.int/nmh/countries/tha_en.pdf

Xie M, Shan Z, Zhang Y, Chen S, Yang W, Bao W, et al. Aspirin for primary prevention of cardiovascular events: meta-analysis of randomized controlled trials and subgroup analysis by sex and diabetes status. PloS one. 2014;9(10):e90286.

Yang ZJ, Liu J, Ge JP, Chen L, Zhao ZG, Yang WY, et al. Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007-2008 China National Diabetes and Metabolic Disorders Study. European heart journal. 2012;33(2):213-20.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

*Original article*

# Development and Validation of the RCC Ventilator Weaning Assessment Checklist in Patients Who Are Ventilator-Dependent

*Received: Feb 27, 2019;*
*Accepted: April 28, 2019;*
*Published Apr 30,2019*

Jung-Chen Lee[1], Hsing-Mei Chen[2,*]

[1]Department of Nursing, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan
[2]College of Medicine, National Cheng Kung University, Taiwan

## Abstract

**Background**: Although a number of clinical weaning profiles have been developed, they are not completely suitable since some items in the profiles are out of date and not used in our practice. Developing a weaning checklist that is applicable and suitable in our practice can help achieve better weaning outcomes. **Purpose**: The purpose of this study was to develop and validate a 26-item respiratory care unit (RCC) ventilator weaning assessment checklist for predicting successful weaning from ventilators in patients with respiratory failure. **Methods**: A retrospective descriptive research design was employed, including two steps. In step 1, a heterogeneous focus group was held with five experts to discuss and finalize the RCC ventilator weaning assessment checklist, which has three domains: physiological function, electrolyte balance, and respiratory function. The content validity index of the new checklist was then assessed. In step 2, a chart review was employed to collect data and test the criterion validity using the RCC ventilator weaning assessment checklist. A total of 180 medical records were reviewed. The patients were those with acute respiratory failure who were admitted to the RCC of a medical center in southern Taiwan between January 2011 and December 2012. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off point for predicting weaning success using the checklist. Sensitivity, specificity, and positive and negative predictive values were calculated. **Results**: The content validity index of the five experts was 74% to 97% for the 26 items and 90% for the total scale. The mean age of the 180 participants was 74.28 ± 13.29 years old. Of the 180 participants, 80 (44.4%) were successfully weaned. The ROC curve analysis showed that the cut-off point for the checklist score was 67%, and the area under the curve (AUC) was 0.874 ± 0.026 ($p < .001$), with a sensitivity of 88%, a specificity of 79%, a positive predictive value of 77%, and a negative predictive value of 89%. Patients who had a score of 67% or above were 4.1 times more likely to wean successfully than those with a score lower than 67%. **Conclusions**: The 26-item RCC ventilator weaning assessment checklist is a useful tool for predicting successful weaning from ventilators for patients with acute respiratory failure. Further validation of this tool with prospective studies is needed.

**Keywords**: Ventilator weaning assessment checklist, ventilator-dependent, ventilator weaning, mechanical ventilation, respiratory failure.

***Corresponding author***: Hsing-Mei Chen, PhD, RN Tel: +886-6-2353535 ext. 6272
Email address: hsingmei@mail.ncku.edu.tw

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Introduction

Clinically, patients with acute respiratory failure undergoing mechanical ventilation should be taken off ventilator support within seven days. However, approximately 20% to 30% of such patients experience repeated ventilator weaning failure and prolonged mechanical ventilation and then need to be transferred to a respiratory care center (RCC) for respiratory training (Lone & Walsh, 2011). Ventilator dependency can cause complications such as ventilator-associated pneumonia (prevalence of 9%-27%; Chastre, Luyt, & Fagon, 2013) and sinusitis (prevalence of approximately 27%; Agrafiotis, Vardakas, Gkegkes, Kapaskelis & Falagas, 2012), increasing the difficulties for ventilator weaning. Ventilator dependency also promotes additional stresses and burden on the patients' families (Pai et al., 2007). The medical costs for this population are gradually increasing annually (Lone & Walsh, 2011). In Taiwan, the number of patients requiring mechanical ventilation was approximately 16,902 in 2016. The annual medical costs for patients using a ventilator for more than 21 days were up to 26 billion Taiwan dollars, which ranked third in total medical expenditures for critical illnesses (Wu & Yang, 2012). Early weaning from mechanical ventilation, therefore, is vital to help patients and their families return to normal life, decrease stress, and reduce medical burden.

Failure to help successfully wean patients from mechanical ventilation may be due to failure to assess the readiness of the patients; therefore, the weaning process is initiated either too early or too late (Liu et al., 2008). Previous studies have found that using key weaning indices, as suggested by the American Chest Task Force group (Macintyre, 2012), or structured assessment tools, such as the Burns Wean Assessment Program (BWAP; Burns, Fahey, Barton, & Slack, 1991), can help practitioners assess the readiness of patients. These indices and assessment tools, however, are not completely suitable since some parameters in the existing profiles are out of date and no longer used in our practice. Therefore, the development of a new weaning checklist that is applicable in our practice in Taiwan is imperative to improve weaning outcomes.

Weaning success refers to patients being able to maintain spontaneous breathing for at least 5 days after extubation, while weaning failure is defined as patients failing to pass a spontaneous breathing trial or needing to be reintubated within 48 hours following extubation (Hayat, Khan, Khalil, & Asghar, 2017).

Ventilator weaning is a complicated process; therefore, using a structured checklist can make it possible to conduct a comprehensive assessment of the spontaneous breathing trial. Among the current existing weaning assessment tools, the BWAP developed by Burns et al. (1991) is the most commonly used. The BWAP comprises 12 items related to general physiological measurements and 14 items related to respiratory function (Burns et al., 1991). A percentage score is calculated by summing up the positive answers and dividing by the 26 items. A BWAP score of 65% or higher indicates being ready for weaning (Burns, Ryan, & Burns, 2010). During a 5-year period, Burns et al. assessed a total of 1,889 weaning attempts and found that 1,669 of these attempts were successful (Burns et al., 2010). The authors concluded that the BWAP is effective in determining weaning outcomes.

However, the BWAP has some limitations, especially with regard to its application among elderly patients. In an Epstein and Peerless (2006) study with BWAP, the authors suggested that maintaining fluid balance might be useful in weaning elderly patients from mechanical ventilation. Assessment of fluid balance, however, is not one of the items in the BWAP (Epstein, & Peerless, 2006). Likewise, some BWAP factors may lack sensitivity in cases with a longer duration of ventilator use, for example, maximal inspiratory pressure (Pimax) and maximal expiratory pressure (Pemax) in Liu et al.'s study (2008) of 319 elderly patients. In their study, these two factors were significantly different between the weaning success and

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

failure groups, which had a mean duration of 41.5 days of ventilator use (Macintyre, 2012). However, no significant between-group differences were found after ventilator use for over 60 days.

On the other hand, other clinical factors should be taken into consideration based on the evidence from previous studies showing a significant association with successful weaning outcomes. These factors are minute ventilation ($V_E$) (Baptistella et al., 2018; El-Khatib & Bou-Khalil, 2008), heart rate, blood pressure, peripheral capillary oxygen saturation ($SpO_2$), arterial blood gas, the rapid shallow breathing index (RSBI), and a high partial pressure of oxygen ($PaO_2$)/fraction of inspired oxygen ($FiO_2$) ratio (Agarwal, Kachhwah, Thakur, & Narang, 2018).

The purpose of this study was to develop and validate a new weaning assessment checklist to fit the current needs of our practice. By using the BWAP as a starting point, we developed a new RCC weaning assessment checklist. We hypothesized that this checklist could adequately assess the weaning readiness of the patients. Therefore, the predictability of this new checklist was examined with ventilator-dependent patients who had experienced respiratory failure.

## Methods.

### *Research Design*

A retrospective descriptive research design was employed, including two steps. In step 1, a heterogeneous focus group discussion was held to develop and test the content validity of the new checklist. In step 2, a chart review was conducted to test the criterion validity (in terms of the prediction ability) of the checklist.

### *Sample and Setting*

Step 1. Five experts in the respiratory care unit were invited: two physicians, one head nurse, one nurse practitioner, and one respiratory therapist.

Step 2. A convenience sample of 180 medical records was used. Participants were patients who were admitted to the respiratory care center of a medical center in southern Taiwan during the period of January 2011 to December 2012. A total of 280 medical records were reviewed. Of them, 180 patients met the inclusion and exclusion criteria and entered this study. The inclusion criteria were as follows: (1) aged 20 years or older, (2) had a diagnosis of respiratory failure due to pulmonary diseases and transfer from the medical intensive care unit (MICU), and (3) had undergone weaning trials for mechanical ventilation. Exclusion criteria included surgical and terminally ill patients (e.g., cancer, severe/decompensated cardiopulmonary failure).

### *Demographic Data and Disease Characteristics*

Demographic data included sex, age, and body mass index (BMI). Disease characteristics consisted of the Glasgow Coma Scale [GCS], APACHE II disease severity score, and the duration of time on the ventilator prior to transfer into the RCC.

### *The RCC Ventilator Weaning Assessment Checklist*

The RCC ventilator weaning assessment checklist was developed based on the BWAP (Hayat et al., 2017) and the literature review. Considering that several items in the BWAP had not been used as weaning indicators in our practice, the five experts suggested that some items, including Pemax, vital capacity (not used clinically), adequate sleep/rest (subjective determination), anxiety and nervousness (subjective determination), should be removed and that items that are commonly used in real practice, including RSBI, the daily routine general pain score, and chest X-ray findings, should be added.

The RCC checklist has three domains: a 7-item physiological function assessment, a 7-item electrolyte balance assessment, and a 12-item respiratory function assessment. The physiological functions are (1) a heart rate of 60-100 beats/min and absence of arrhythmia prior to weaning; (2) a systolic blood pressure of 90-160 mmHg, a diastolic blood pressure 60-100 mmHg, and an absence of vasopressor use prior to weaning; (3) a tympanic temperature of 36-

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

37.5 °C and absence of fever prior to weaning; (4) systemic hydration: intake/output > 1500 ml for the past 3 days; (5) the daily routine general pain score: measured with a visual analogue scale (VAS) ranges between 0 (no pain) and 10 (possible worse pain); (6) absence of bowel problems (diarrhea, constipation); and (7) a chest X-ray indicating no improvement, improvement, or normal.

The 7 items of the electrolyte balance domain are (1) hematocrit > 25%; (2) albumin > 2.5 g/dl; (3) Na: 135~145 meq/L; (4) K: 3.5~5.5 meq/L; (5) Ca: 4.5~5.5 meq/L; (6) Mg: 1.7~2.8 meq/L; and (7) P: 2.5~4.5 meq/L.

The 12-item respiratory function domain consists of (1) the spontaneous respiratory rate (＜30 breaths/min); (2) absence of adventitious breathing sounds (rhonchi, wheezing); (3) sputum (amount, color, character): little, moderate, or a significant amount; color: white, yellow white, or yellow; character: thick or thin; (4) presence of tracheostomy; (5) coughing ability; (6) Pimax □ -20 - -25 $cmH_2O$; (7) tidal volume ($V_T$) > 5 ml/kg; (8) RSBI＜105 min/L; (9) $V_E$＜10 L/min; (10) pH: 7.35-7.45; (11) $PaCO_2$: 35~45 mmHg; and (12) $PaO_2$□60 mmHg.

Each item is rated on a 2-point scale (1 = yes, 0 = no). The total score ranges from 0 to 26. A percentage score is calculated by summing the number of "yes" responses and then dividing by 26 and multiplying by 100, with a higher score indicating better readiness for ventilator weaning.

### *Procedures for Data Collection*

This study was reviewed by the Institutional Review Board of the study hospital (KMUH-IRB-20120276). We were granted permission to use the BWAP and received permission from the administrators of the hospital to conduct this study. After the checklist development, we explained the purposes and methods of this study to the RCC attending physicians. We also requested permission to access medical records from the medical records department. Then, the primary researcher screened the database for eligible cases based on the inclusion and exclusion criteria and collected data according to the checklist. The data collection period was from March 1, 2013 to July 31, 2013.

### Data Analysis

Data were analyzed using SPSS for Windows (SPSS Inc., Chicago, IL), release 18.0. In step 1, the content validity index was calculated. In step 2, descriptive statistics, including the frequency distribution, percentage, mean, and standard deviation, were used to describe the data for all variables. For the criterion validity test, the criterion index was the participants' weaning outcomes. The 180 participants were grouped into either success or failure groups based on their real weaning outcomes. As a result, 80 patients were in the success group, and 100 patients were in the failure group. The differences between the groups were examined with chi-square tests for categorical variables and independent-t tests for continuous factors. The receiver operating characteristic (ROC) curve analysis was utilized to determine the characteristics of different RCC ventilator weaning assessment checklist intervals or cut-off points as a function of the weaning outcomes (success vs. failure). Test characteristics, including sensitivity, specificity, and positive and negative predictive values, were calculated for the cut-off point score.

## Results

### *Content Validity of the RCC Ventilator Weaning Assessment Checklist*

In the content validity test, the five experts were invited to evaluate three qualities of each item: importance, clarity, and usefulness. The scale options for each quality were 1 (not relevant), 2 (unable to assess relevance without item revision), 3 (relevant but needs minor alteration), or 4 (very relevant and succinct). By taking the number of items > or = 3, the content validity index (CVI) ranged from

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

74% to 97% for the 26 items and was 90% for the total scale.

***The Predictability Analysis of the Checklist Assessed by Weaning Outcomes***

The mean age of the 180 participants was 74.28 (SD=13.29) years. Table 1 shows the comparisons of the demographic and disease characteristics between the success group (n = 80) and the failure group (n = 100). The success group had significantly higher GCS scores (9.73 ± 4.23 vs. 7.85 ± 4.26, t = 2.94, p <0 .01) and lower APACHE II scores (15.14 ± 4.92 vs. 19.94 ± 5.84, t = 5.87, p <0 .001) than those of the failure group. The mean percentage score of the 180 participants was 66% (SD = 15%). The success group had significantly higher percentage scores prior to the weaning trials than the failure group (76% ± 9% vs. 57% ± 14%, p <0.001).

**Table 1**. Differences in Demographic and Disease Characteristics between the Success Group and the Failure Group

| | Overall (*N*=200) | Success (*n*=80) | Failure (*n*=100) | *t* /$\chi^2$ | *p* |
|---|---|---|---|---|---|
| Variables | *M* ± SD | *M* ± SD | *M* ± SD | | |
| Sex[a] | | | | 3.68 | 0.055 |
| Male, *n* (%) | 102 (57) | 39 (49) | 63 (63) | | |
| Female, *n* (%) | 78 (43) | 41 (51) | 37 (37) | | |
| Age | 74.28 ± 13.29 | 74.89 ± 13.87 | 73.79 ± 12.85 | 0.55 | 0.583 |
| BMI | 22.94 ± 5.91 | 23.10 ± 6.62 | 22.80 ± 5.29 | 0.34 | 0.740 |
| GCS | 8.68 ± 4.34 | 9.73 ± 4.23 | 7.85 ± 4.26 | 2.94 | 0.004 |
| APACHE II | 17.81 ± 5.94 | 15.14 ± 4.92 | 19.94 ± 5.84 | 5.87 | <0.001 |
| Duration on ventilator | 19.56 ± 8.72 | 19.56 ± 8.82 | 20.01 ± 8.66 | -0.77 | 0.440 |

Note. [a]$\chi^2$ tests; BMI: body mass index; GCS: Glasgow coma scale; APACHE II: acute physiology and chronic health evaluation II.

Among the 26 items of the checklist (Table 2), significant between-group differences were found in 3 physiological functions, 2 electrolytes, and 8 respiratory variables. In the physiological function domain, the success group had significantly lower heart rates (83.54 ± 13.92 vs. 91.23 ± 18.97, *t* = -3.14, *p* < 0.01), systemic hydration (404.13 ± 616.31 vs. 716.00 ± 741.56, *t* = -3.02, *p* <0.01), and normal or improving chest X-rays (98% vs. 37%, $\chi^2$ = 70.83, *p* < 0.001) than the failure group. They also had higher hematocrit (29.81 ± 5.09 vs. 28.01 ± 4.16, *t* = 2.61, *p* < 0.05) and albumin levels (2.72 ± 0.36 vs. 2.46 ± 0.48, *t* = 4.14, *p* < 0.001) than the failure group in the electrolyte balance domain.

In terms of the respiratory function domain, the success group had significantly lower spontaneous respiratory rates (20.54 ± 4.48 vs. 29.24 ± 6.61, t = -10.49, p <0.001), Pimax (-24.10 ± 8.87 vs. -12.80 ± 9.89, t = -7.96, p < 0.001), RSBI (61.19 ± 25.61 vs. 117.53 ± 42.20, t = -11.05, p < 0.001), and VE (7.76 ± 2.16 vs. 13.29 ± 2.82, t = -14.91, p <0.001) but higher use of tracheostomies (58% vs. 35%, $\chi$2 = 9.09, p <0 .010), coughing ability (82% vs. 47%, $\chi$2 = 22.18, p < 0.001), VT (372.54 ± 124.81 vs. 283.07 ± 105.29, t = 5.12, p < 0.001), and PaO2 (115.92 ± 30.03 vs. 95.80 ± 31.67, t = 4.33, p < 0.001) than the failure group.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

**Table 2**. RCC Ventilator Weaning Assessment Checklist between the Success Group and the Failure Group

| Variables | Success (*n*=80) *M* ± SD | Failure (*n*=100) *M* ± SD | $\chi^2/t$ | *p* |
|---|---|---|---|---|
| Physiological function | | | | |
| Heart rate | 83.54 ± 13.92 | 91.23±18.97 | -3.14 | 0.002 |
| Systolic blood pressure | 135.85 ± 19.78 | 130.86 ± 21.30 | 1.61 | 0.109 |
| Diastolic blood pressure | 71.75 ± 14.36 | 70.64 ± 14.58 | 0.51 | 0.610 |
| Tympanic temperature | 36.80 ± 0.54 | 36.85 ± 0.72 | -0.51 | 0.611 |
| Intake/output balance | 404.13 ± 616.31 | 716.00 ± 741.56 | -3.02 | 0.003 |
| Pain score change | 0.38 ± 1.28 | 0.51 ± 1.51 | -0.64 | 0.524 |
| Absence of bowel problems[a], *n* (%) | 68 (85) | 75 (75) | 5.07 | 0.226 |
| Chest X-rays improved or normal[a], *n* (%) | 78 (98) | 37 (37) | 70.83 | 0.001 |
| Electrolytes | | | | |
| Hematocrit | 29.81 ± 5.09 | 28.01 ± 4.16 | 2.61 | 0.010 |
| Albumin | 2.72 ± 0.36 | 2.46 ± 0.48 | 4.14 | 0.000 |
| Na | 139.53 ± 6.34 | 141.79 ± 7.01 | -2.25 | 0.056 |
| K | 4.00 ± 0.60 | 4.09 ± 0.69 | -0.85 | 0.394 |
| Ca | 4.97 ± 0.51 | 5.10 ± 0.56 | -1.58 | 0.116 |
| Mg | 2.40 ± 0.46 | 2.33 ± 0.50 | 0.98 | 0.327 |
| P | 3.39 ± 1.18 | 3.53 ± 1.03 | -0.84 | 0.402 |
| Respiratory function | | | | |
| Spontaneous respiratory rate | 20.54 ± 4.48 | 29.24 ± 6.61 | -10.49 | <0.001 |
| Absence of adventitious breath sounds[a], *n* (%) | 6 (8) | 2(28) | 3.17 | 0.075 |
| Sputum (amount, color, character)[a] | | | 10.96 | 0.054 |
| Small, whitish, sticky, *n* (%) | 26 (33) | 14 (14) | | |
| Moderate, whitish, sticky, *n* (%) | 48 (60) | 68 (68) | | |
| Significant, yellowish/whitish, sticky, *n* (%) | 6 (8) | 18 (18) | | |
| With tracheostomy[a], *n* (%) | 46 (58) | 33 (35) | 9.09 | 0.003 |
| Cough ability[a], *n* (%) | 65(82) | 47(47) | 22.18 | <0.001 |
| Pimax | -24.10 ± 8.87 | -12.80 ± 9.89 | -7.96 | <0.001 |
| Tidal volume ($V_T$) | 372.54 ± 124.81 | 283.07 ± 105.29 | 5.12 | <0.001 |
| Rapid shallow breathing index | 61.19 ± 25.61 | 117.53 ± 42.20 | -11.05 | <0.001 |
| Minute ventilation ($V_E$) | 7.76 ± 2.16 | 13.29 ± 2.82 | -14.91 | <0.001 |
| PH | 7.43 ± 0.04 | 7.39 ± 0.08 | 3.11 | 0.125 |
| $PaCO_2$ | 39.55 ± 7.31 | 40.07 ± 11.85 | -0.37 | 0.713 |
| $PaO_2$ | 115.92 ± 30.03 | 95.80 ± 31.67 | 4.33 | <0.001 |

[a] Analyzed with chi-square tests.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

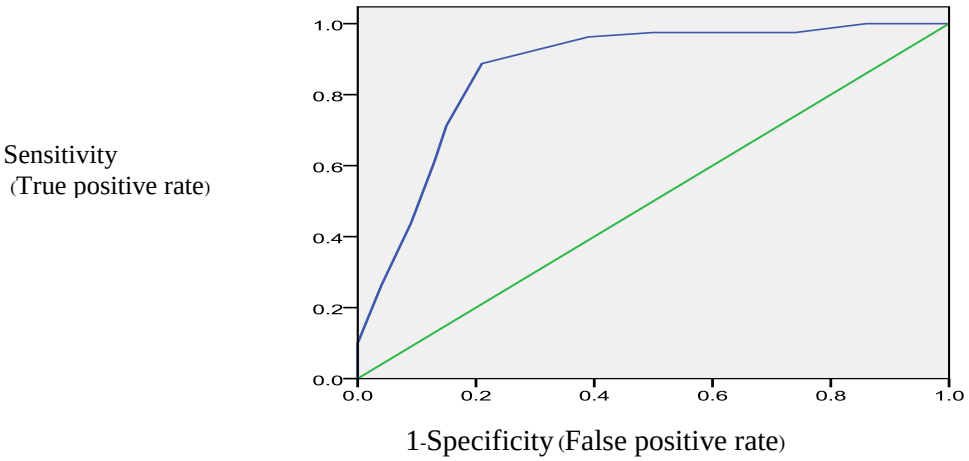



**Figure 1**. ROC curve of the total score of the RCC Ventilator Weaning Assessment Checklist (n=180); the cut-off point was 67.3%

**The ROC results**

There were 80 participants who successfully weaned and 100 who failed to wean. As shown in Figure 1, the ROC curve analysis showed that the area under the curve (AUC) was 0.874 ± 0.026 ($p < .01$). The most acceptable cut-off point of the percentage score was 67.3%, with a sensitivity of 88.8% and a 1-specificity of 21%. Table 3 presents a detailed examination of the operating characteristics of different cut-off points from percentage scores of 65% to 70%. The results indicated that scores in the range of 66% to 69% had the same sensitivity, specificity, and likelihood values for predicting weaning outcomes.

**Table 3**. Operating Characteristics of Different RCC Ventilator Weaning Assessment Checklist Cut points for Diagnosing Weaning Success (N=180)

| Checklist score | Sensitivity (%) | Specificity (%) | Likelihood ratio (%) |
|---|---|---|---|
| ≧65% | 93 | 66 | 2.7 |
| ≧66% | 88 | 79 | 4.1 |
| ≧67% | 88 | 79 | 4.1 |
| ≧68% | 88 | 79 | 4.1 |
| ≧69% | 88 | 79 | 4.1 |
| ≧70% | 71 | 84 | 4.4 |

**Table 4**. Diagnostic test results of the RCC Ventilator Weaning Assessment Checklist for Weaning Success

| Weaning outcomes | ≧67% | < 67% | Total |
|---|---|---|---|
| Success | 71 | 9 | 80 |
| Failure | 21 | 79 | 100 |

Sensitivity：88 %（71/80）; Specificity：79%（79/100）;Predictive value（+）：77%（71/92）
Predictive value（-）：89%（79/88）; Positive Likelihood ratio（+）：4.1（0.88/1-0.79）
Negative Likelihood ratio（-）：0.15（1-0.88/0.79）; Overall, correct rate：83%（71+79/180）

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Discussion

Overall, the results supported the use of this RCC ventilator weaning assessment checklist for determining weaning outcomes. The success group had significantly higher percentage scores prior to the weaning trials than the failure group (76% vs. 57%). The ROC analysis revealed that patients with a percentage score greater than 67% were more likely to be weaned successfully. With a cut-off point of 67%, this checklist demonstrated a sensitivity of 88% and a specificity of 79%.

Although percentage scores of 66% to 69% had the same predictability for weaning success, a percentage score of 67% was identified as the successful weaning score based on the ROC curve analysis result. Likewise, the mean score of the current study was 66%. Previously, the BWAP score was 65% (Boles et al., 2007). The sensitivity, specificity, positive predictive value, and negative predictive value of the RCC ventilator weaning assessment checklist were 88%, 79%, 77%, and 89%, respectively, whereas those of the BWAP were 77%, 60%, 20%, and 95%, respectively. The greatest difference between the BWAP and this RCC checklist was the positive predictive value (20% vs. 77%). This may be because we merely used cross-sectional retrospective data, whereas Burns, Burns, and Truwit (1994) used prospective data to analyze the predictability of the tools.

Regarding the 26 items on the RCC weaning assessment checklist, 13 items showed significant between-group differences. The success group had significantly lower heart rates, better intake and output balance and improved or normal CXR in the physiological function domain and higher hematocrit and albumin levels in the electrolyte balance domain than those of the failure group. These findings support previous studies showing that stable hemodynamics (Boles et al., 2007; Twibell, Siela, & Mahmoodi, 2003), sufficient nutritional status (Macintyre, 2012), and control of pulmonary infection (Boles et al., 2007) are important for improving oxygen delivery and reducing respiratory muscle fatigue, thus increasing the probability of weaning success. Likewise, the success group had higher GCS scores and lower APACHE II scores than those of the failure group, indicating that patients who had a stable condition were more likely to achieve favorable weaning outcomes than those who did not (Islam, 2013), suggesting the need to stablize the patient's condition before iniating the weaning process.

Participants in the weaning success group also had significantly more stable pulmonary function, including spontaneous respiratory rate, spontaneous $V_T$, higher $PaO_2$, better coughing ability, lower Pimax, lower RSBI, lower $V_E$, and fewer endotracheal intubations in the respiratory function domain. The RSBI can be used as an indicator of the tolerance of respiratory muscle (Blumhof, Wheeler, Thomas, McCool, & Mora, 2016), while $V_E$ < 10 L/min can prevent respiratory muscle fatigue (Silva, & Rocco, 2018). When patients have stable and spontaneous respiratory rates, they can reach optimal $V_T$, retain coughing ability, and maintain a patent airway (Terzi et al., 2018).

The finding that the success group had fewer endotracheal intubations is congruent with the findings of a study by Lee, Lin, and Weng (2008). The participants in the current study were mainly elderly patients who had experienced problems such as ineffective airway protection, poor coughing ability, and ineffective airway clearance. These problems can precipate difficulties in weaning attempts. Therefore, a tracheostomy was recommended to, but commonly refused by, patients and their families the first time. We suggest that in the future, healthcare providers should put more effort into encouraging such patients to undergo a tracheostomy early to improve the success rate of weaning.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

*Limitations*

This study only involved patients with pulmonary diseases from a respiratory care center located in southern Taiwan, which limits the generalizability of the study. Future research should include more participants with respiratory failure owing to different causes, such as neurological disorders. Likewise, prospective studies should be conducted to test

The usefulness of our RCC ventilator weaning assessment checklist.

**Conclusions**

The results supported the prediction ability of the RCC ventilator weaning assessment checklist. A percentage score of ≥ 67% could predict successful weaning with a sensitivity of 88%, a specificity of 79%, a positive predictive value of 77%, and a negative predictive value of 89%. Future studies, however, should be conducted to confirm the applicability and usefulness of the checklist.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## References


Agarwal, D., Kachhwah, V., Thakur, K. K., & Narang, N. (2018). To assess rapid shallow breathing index as a predictor for weaning in intensive care unit patients. *International Journal of Scientific Study*, *6*(6), 121-130.

Agrafiotis, M., Vardakas, K. Z., Gkegkes, I. D., Kapaskelis, A., & Falagas, M. E. (2012). Ventilator-associated sinusitis in adults: Systematic review and meta-analysis. *Respiratory Medicine*, *106*(8), 1082-1095. doi: https://doi.org/10.1016/j.rmed.2012.03.009

Baptistella, A. R., Sarmento, F. J., da Silva, K. R., Baptistella, S. F., Taglietti, M., Zuquello, R. Á., & Nunes Filho, J. R. (2018). Predictive factors of weaning from mechanical ventilation and extubation outcome: A systematic review. *Journal of Critical Care*, *48*, 56-62.

Blumhof, S., Wheeler, D., Thomas, K., McCool, F.D., & Mora, J. (2016). Change in diaphragmatic thickness during the respiratory cycle predicts extubation success at various levels of pressure support ventilation. *Lung*, *194*(4), 519-525.

Boles, J.M., Bion, J., Connors, A., Herridge, M., Marsh, B., Melot, C., ... Welte, T. (2007). Weaning from mechanical ventilation. *European Respiratory Journal*, *29*(5), 1033-1056. doi: 10.1183/09031936.00010206

Burns, S. M., Ryan, B., & Burns, J. E. (2000). The weaning continuum use of Acute Physiology and Chronic Health Evaluation III, Burns Wean Assessment Program, Therapeutic Intervention Scoring System, and Wean Index scores to establish stages of weaning. *Critical Care Medicine*, *28*(7), 2259-2267.

Burns, S.M., Burns, J. E., & Truwit, J. D. (1994). Comparison of five clinical weaning indices. *American Journal Critical Care*, *3*(5), 342-352.

Burns, S.M., Fahey, S. A., Barton, D. M., & Slack, D. (1991). Weaning from mechanical ventilation: A method for assessment and planning. *Advanced Practice in Acute and Critical Care Nurses Clinical Issues*, *2*(3), 372-389.

Burns, S.M., Fisher, C., Tribble, S. S., Lewis, R., Merrel, P., Conaway, M. R., & Bleck, T. P. (2010). Multifactor clinical score and outcome of mechanical ventilation weaning trials: Burns Wean Assessment Program. *American Journal of Critical Care*, *19*(5), 431-439. doi: 10.4037/ajcc2010273

Chastre J, E., Luyt, C. E., & Fagon, J. Y. (2013). Chapter 46. Pneumonia in the ventilator-dependent patient. In M. J. Tobin, Principles and practice of mechanical ventilation (3rd ed.). New York, NY: McGraw-Hill Companies. Retrieved from https://accessmedicine.mhmedical.com/content.aspx?bookid=520&sectionid=41692291

El-Khatib, M. F., & Bou-Khalil, P. (2008). Clinical review: Liberation from mechanical ventilation. *Critical Care*, *12*(4), 221. doi: 10.1186/cc6959

Epstein, C. D, & Peerless, J.R. (2006). Weaning readiness and fluid balance in older critically ill surgical patients. *American Journal of Critical Care*, *15*(1), 54-64.

Hayat, A., Khan, A., Khalil, A., & Asghar, A. (2017). Diaphragmatic excursion: Does it predict successful weaning from mechanical ventilation? *Journal of the College of Physicians and Surgeons Pakistan*, *27*(12), 743-746.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

Islam, M. S. (2013). APACHE score as a predictive indices for weanability from mechanical ventilation. *Bangladesh Critical Care Journal*, *1*(1), 18-22.

Lee, C. Y., Lin, Y. J., &Weng, M. H. (2008). The outcome of early tracheostomy versus late trachostomy patients in a respiratory care center. *Taiwan Critical Care Medicine*, *9*(2), 100-109.

Liu, C. J., Chu, C. C., Liang, W.M., Chen, W., Cheng, W. W., & Shih, C. M. (2008). Serial measurements of weaning index as a predictor of weaning outcome in respiratory care center patients. *Journal of Respiratory Therapy*, *7*(2), 82.

Lone, N. I., & Walsh, T. S. (2011). Prolonged mechanical ventilation in critically ill patients: Epidemiology, outcomes and modelling the potential cost consequences of establishing a regional weaning unit. *Critical Care*, *15*(2), R102. doi: 10.1186/cc10117

Macintyre, N. R. (2012). Evidence-based assessments in the ventilator discontinuation process. *Respiratory Care*, *57*(10), 1611-1618. doi: 10.4187/respcare.02055

Pai, Y. C., Tung, C. L., Hang, S.P., Tsou, Y. C., Yang, H. C., & Huang, C. P. (2007). A study of mobility training program and the weaning off ventilators. *Yuan-Yuan Nursing*, *1*(2), 42-51.

Silva, P. L., & Rocco, P. R. (2018). The basics of respiratory mechanics: ventilator-derived parameters. *Annals of Translational Medicine*, *6*(19), 1-11.

Terzi, N., Lofaso, F., Masson, R., Beuret, P., Normand, H., Dumanowski, E., ... Orlikowski, D. (2018). Physiological predictors of respiratory and cough assistance needs after extubation. *Annals of Intensive Care*, *8*(1), 1-10. doi: 10.1186/s13613-018-0360-3

Twibell, R., Siela, D., & Mahmoodi, M. (2003). Subjective perceptions and physiological variables during weaning from mechanical ventilation. *American Journal of Critical Care*, *12*(2), 101-112.

Wu, C.P., & Yang, S. H. (2012). Prolonged mechanical ventilation in Taiwan.*National Health Insurance Dispute Medication Report*, *51*, 1-8.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

# Factors Influencing Innovative Management of In-Patient Departments among Community Hospitals, Ministry of Public Health

Kanyawee Mokekhaow[1]

[1]Community Health and Psychiatric Nursing Department,
Boromarajonani College of Nursing Chon Buri, Chon Buri, Thailand

***Original article***

*Received: Dec 15, 2018;*
*Accepted: Apr 28, 2019;*
*Published Apr 30,2019*

**Abstract**

**Background:** Innovative management of in-patient department has played a crucial role in developing quality nursing services and outcomes as well as enhancing patient safety. Consequently, factors affecting innovative management should be determined. **Objectives:** This descriptive study aimed to examine outcomes and analyze factors influencing the innovative management of in-patient departments. **Methods:** Head nurse who have at least three-year experience in the management of in-patient departments in community hospitals were selected using stratified sampling and simple random sampling techniques. Data were conducted using questionnaires regarding the topics of knowledge creation and innovative management performance with reliability at 0.87 and 0.91 respectively, as well as personal information. The data were analyzed using percentage, mean, standard deviation, and Pearson correlation coefficient as well as stepwise multiple regression analysis. **Results:** The study revealed that the mean of knowledge creation, overall of innovative management performance, the compositions of knowledge creation as well as innovative management's performance of in-patient departments were high. Factors including knowledge creation, experiencing the training of knowledge management and experiencing research related to innovation were statistically significant with outcomes of innovative management (p-value < 0.01). In addition, these factors could collaboratively predict 48.7 percent of innovative management performance. **Conclusion:** Nursing administrators should impose policy and create action plans to enhance the skills of head nurses of In-Patient Departments such as creating new knowledge in wards and encouraging head nurses to conduct innovative research and training regarding knowledge management. Consequently, these will result in effective and efficient innovative management of In-Patient Departments.

**Keywords;** Innovative management performance, knowledge creation, In-patient departments, Community hospital

***Corresponding author*** Kanyawee Mokekhaow, Community Health and Psychiatric Nursing Department, Boromarajonani College of Nursing Chon Buri, Chon Buri, Thailand, Email: kanyawee2509@bnc.ac.th

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## Introduction

Rapid changes in advanced sciences and technologies have created societies with knowledge and innovation (Drucker, 1993). Currently, the Thai government has realized the importance of this issue and has announced a policy focusing on producing innovative products, encouraging people to develop innovative services, developing organization by using technologies, creativity, and innovation (Chanocha, 2015) as well as implementing this policy to all government agencies.

Bureau of Nursing has imposed this policy by encouraging hospitals to create and develop a variety of innovation since this will enhance quality-nursing services in their organizations (Bureau of Nursing, 2012). In addition, community hospitals have implemented the policy regarding creativity of innovation because this can assist hospitals to develop quality nursing services more effectively (Jirapaet, 2012), improve nursing outcomes (Oecon, 2006) as well as ensure clients safer (Klangtamnian, 2012). Hence, innovation is a key factor, which results in the development of nursing quality services in nursing organizations (McGregor, 2015). However, an assessment of innovative management among in- patient departments revealed that hospitals could not implement innovation in every unit and it could partly use in nursing services (Nursing organization, 2015).

Factor influencing a success of innovative management performance among in-patient departments consisted of knowledge creation, which could create relevant information and knowledge. Ultimately, these led to potentially enhance practical innovation and were useful in organizations (Nonaka, & Takeuchi, 1995; Berraies, et al, 2014; Tidd & Bessant, 2014). As a reviewed literature regarding personal factors (age), a study reported that younger people had a more creative idea in creating innovation (Amabile, 2013). Due to experiencing research related to innovation, this age is the crucial factor influencing a success innovative management performance in organizations. Integrating between research methodology and make of innovation could solve problems resulted from routine work, developed outcomes of innovation more valuable and useful for organizations (Jirapaet, 2010; Hughes, 2006). In addition, experiencing a training of innovation and knowledge management helped officers to be more knowledgeable in this area. This assisted organizations in achieving their ultimate goals. Furthermore, a result of training programs resulted in exploring new knowledge faster and potentially enhanced the skills of innovative creation (Smith et al, 2008).

Currently, knowledge about factors influencing innovative management performance among nurses is still limited. Consequently, the researcher would like to examine factors that affect innovative management performance of in- patient departments since this will enhance the skills of knowledge management and can be applied in creating an innovation of in-patient departments in the future.

### *Objectives*

1. To examine knowledge creation and innovation management performance of in-patient departments.
2. To analyze the factors regarding establishing of knowledge, age, experiences of innovative research, experiences of trainings of innovation as well as knowledge management that affect innovation management performance of in-patient departments.

### *Conceptual Framework*

The conceptual framework was based on the concept of innovative management (Tidd & Bessant, 2014). This resulted from resources management and knowledge creation supported innovation management performance. This framework concerned innovative management performance that could be used in nursing practice which three component included input to the innovation process, organizations with focused on innovation can be described as requiring necessary and sufficient input resources, process as an organization structure consistent with innovation creation, flexible structures, distributed power, teamwork

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

supporting innovation such as allowing personnel to express opinions and participate in decision- making leading to learning and innovation creation and output that assess capabilities or success of organizations in creating innovations. The four knowledge creation were applied consisting of crucial and included socialization, externalization, combination, and internalization ( Nonaka & Takeuchi, 1995) since knowledge cycles these were believed to be a very factor that could affect innovative management performance of in- patient departments support as shown in figure 1.

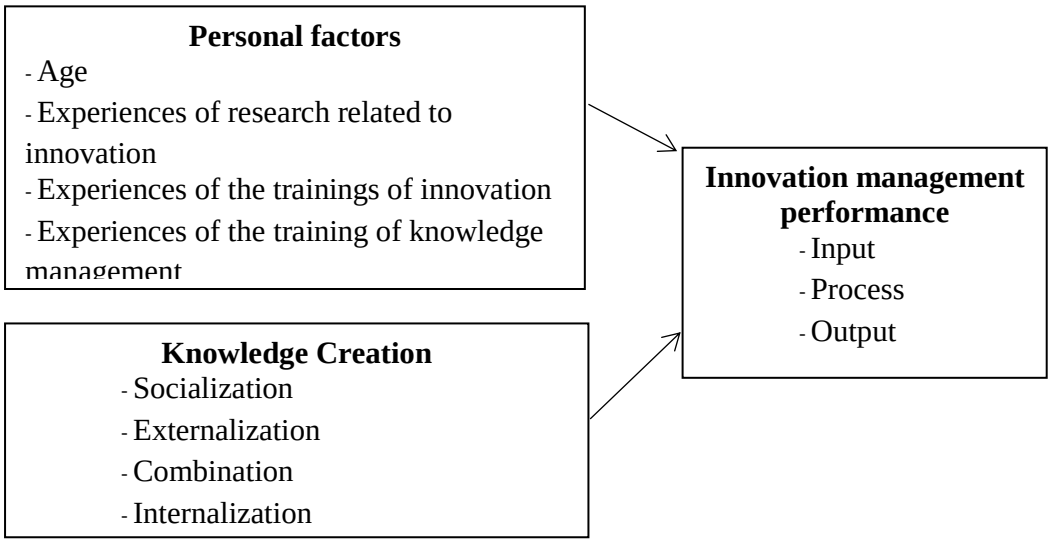



**Figure 1** Conceptual Framework

## Material and Method

The study was prediction research.

### *Population and Sample*

Populations were 454 head nurses in 88 community hospitals in health region 12. The samples included three hundred head nurses who have at least three- year experience in the management of in- patient departments in community hospitals. This study used stratified sampling and simple random sampling without replacement technique to select hospital and nurse samples. The study was conducted from September to November 2016.

### *Research instrument*

The research tool for data collection was a questionnaire composed of 3 parts;

Part 1 personal data: the question were developed by the researcher. This consisted of age, experiences of conducting innovative research as well as experiences of training regarding innovation and knowledge management.

Part 2 knowledge creation: the researcher applied the tool from of Schulz and Huagel( 2008) with a content validity at 0.84 and used cross- cultural translation. The questions consisted of the perception of nursing directors regarding behavior of nursing staffs in creating new knowledge. The four- knowledge transformations were socialization, externalization, combination, and internalization. Sixteen questions were applied using Rating Scale including strongly agree (5), quite agree (4), neutral agree (3), less agree (2), and least agree ( 1) . Due to reliability, the researcher tried out the questionnaires with 30 head nurses who have at least three years' experience in the management of in- patient departments in community hospitals and the Cronbach's alpha coefficient was at 0.87.

Part 3 innovative management performance: the questionnaire was created by the researcher based on the theory of an innovative management by Tidd and Bessant ( 2014) . Questions aimed to examine of the perception of head nurses of in- patient departments. In order to measure this part, the

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

researcher used three components including input, process and output. Twenty- three questions were applied using the Likert Scale regarding strongly agree (5) agree (4) neutral (3) disagree (2) and strongly disagree (1). In term of validity, the questionnaire of this part was approved by nine experts and the content validity index was calculated at 0.84. To enhance reliability, the researcher tried out the questionnaires with 30 head nurses who have at least three-year experience in the management of nurse units in community hospitals and the Cronbach's alpha coefficient was at 0.91. Defining the criteria, interpreting the mean of knowledge creation and innovative management performance of in- patient departments were classified using the scores as the highest mean (4.51 – 5.00), the high mean (3.51 – 4.50), the moderate mean (2.51 – 3.50), the less mean (1.51 – 2.50) and the lest mean (1.00 – 1.50) (Sristhitnarakul, 2012).

***Data Collection***

The researchers made a letter of permission in collecting data to the directors of community hospitals and requested the ethical approval of human research from community hospitals. Before the data collection, there was a process to clarify the purposes of this study and details of methodology with head nurses. After this process, the researcher sent out the questionnaires to either head nurses or research coordinators and asked them for their participation. The information obtained in this study was kept confidentially and finally, 294 complete questionnaires were collected, presenting 98 percent of the sample.

***Data Analysis***

This study used computer programs to analyze the data as the followings.

1. Used descriptive statistics regarding frequency and percentage to analyze the personal information.

2. Applied mean and standard deviation in analyzing the scales of the opinion, knowledge creation as well as innovative management performance.

3. Analyzed the associations among personal factors, knowledge creation and innovative management performance using the Pearson's Correlation Coefficient.

4. Analyzed the prediction of personal information, knowledge creation affecting innovative management performance in in-patient departments using Multiple Regression Analysis.

**Results**

**Part 1** Personal information of two hundred nighties four participants. The results showed that approximately sixty percent of participants were 41 – 50 years old. The average of aged was 48.66 years. More than half of participants (58.8 percent) had experienced research related to innovation. Of those 30.6 percent and 22.1 percent once and twice, respectively. Around sixty-two percent of participants had experienced the training of innovation 40.5 present of those attended a training for one time and 12.9 percent for two times two times. Approximately 80 percent of participants had experienced the training of knowledge management. Those people participated in the training one time (24.5 percent) and followed by two (19.4 percent) and five times (13.9 percent) respectively.

**Part 2** Mean ( $\overline{X}$ ), standard deviation ( SD) of knowledge creation as well as innovative management performance of in-patient departments among community hospitals were presented in the table 1.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

**Table 1** Mean ( $\overline{X}$ ), standard deviation (SD) and interpretation of knowledge creation and innovative management performance.

| Variables | $\overline{x}$ | S.D | Level |
|---|---|---|---|
| **Knowledge creation** | 3.81 | 0.39 | High |
| Socialization | 3.88 | 0.42 | High |
| Externalization | 3.83 | 0.49 | High |
| Combination | 3.81 | 0.41 | High |
| Internalization | 3.73 | 0.47 | High |
| **Innovative management performance** | 3.87 | 0.41 | High |
| At the period of process | 4.14 | 0.47 | High |
| At the period of output | 3.78 | 0.54 | High |
| At the period of input | 3.70 | 0.47 | High |

**Part 3** Analytical results of the association among variables

The table 2 Analytical results of the association among variables including age, experiencing research related to innovation, experiencing the training of innovation, experiencing the training of knowledge management, knowledge creation as well as innovative management performance.

**Table 2** The results of the associations among variables including age, experiencing research related to innovation, experiencing the training of innovation, etc.

| Variables | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ |
|---|---|---|---|---|---|
| Age ($X_1$) | 1.000 | | | | |
| Experiencing research related to innovation ($X_2$) | -.106* | 1.000 | | | |
| Experiencing the training of innovation ($X_3$) | -.144** | .172** | 1.000 | | |
| Experiencing the training of knowledge management ($X_4$) | .031 | .275** | .440** | 1.000 | |
| Knowledge creation ($X_5$) | -.227** | .446** | .265** | .374** | 1.000 |
| Outcomes of innovative management (Y) | -.195** | .421** | .233** | .414** | .665** |

*p< 0.05, **p< 0.01

The table 2 revealed that knowledge creation, experiencing research related to innovation, experiencing the training of knowledge management as well as experiencing the training of innovation were found to be positively correlated with innovation management performance at r= 0.665, p-value< 0.01; r= 0.421, p-value< 0.01; r= 0.414, p-value< 0. 01; r= . 233, p- value< 0. 01 respectively. However, age was found to be negatively correlated with innovative management performance at r= -0.195, p value< 0.01, while, all variables were found to be multicollinearity.

**Part 4** Analytical results of the prediction regarding personal information and

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

knowledge management, resulting in outcomes of innovative management.

Table 3 Analytical results of the prediction regarding personal information and knowledge management, resulting in outcomes of innovative management of in- patient departments (n=294)

**Table 3** Analytical results of the prediction regarding personal information and knowledge management, resulting in outcomes of innovative management of in-patient departments (n=294)

| Variables | b | SE b | $\beta$ | t | p-value |
|---|---|---|---|---|---|
| Constant | 1.604 | 0.187 | | 8.594 | <0.001 |
| Knowledge creation ($X_5$) | 0.567 | 0.052 | 0.540 | 10.997 | <0.001 |
| Experiencing the training of knowledge management ($X_4$) | 0.067 | 0.007 | 0.175 | 3.837 | <0.001 |
| Experiencing research related to innovation ($X_2$) | 0.050 | 0.018 | 0.132 | 2.784 | <0.001 |

R= 0.698, $R^2$= 0.487, F= 91.877**, Durbin- Watson= 1.784

The table 3 showed that knowledge creation, experiencing research related to innovation and experiencing the training of knowledge management predicted innovative management performance at 48.7 percent. In addition to the prediction, knowledge creation predicted innovative management performance most using a formulation as the following.

$$Y = 0.540 (X_5) + 0.175 (X_4) + 0.132 (X_2) + e$$

## Discussion

The study revealed that the factors influencing innovative management performance included knowledge creation, experiencing the training of knowledge management and experiencing research related to innovation of head nurses and these could be explained as the followings.

### *Knowledge creation*

This study found that knowledge creation has the most impact on the innovation management of in- patient departments. This implies that knowledge creation is a significant factor in creating innovation. Setting a goal to create new knowledge by head nurses and apply this strategy with a routine work leads to a success of innovation management. Sharing knowledge from experiences among nurses (Tacit Knowledge) and developing to be explicit knowledge can create new knowledge and apply to establish innovation of nursing practice. This is consistent with a study by Schulze and Hoegl, [16] reviewing the prediction of innovation management performance. Knowledge creation predicted innovation management performance ($R^2$=0.60). In addition, a study conducted by Berraies, Chaher and Yahia (2014) revealed that knowledge creation influenced innovation management performance ($\beta$ = 0.79). This is also consistent with a knowledge creation theory by Nonaka and Takeuchi (1995). New knowledge resulted from knowledge creation could potentially enhance innovation and application in organizations.

### *Experiencing the training of knowledge management*

As a result, experiencing the training of knowledge management has influenced innovation management performance. This implies that head nurses with knowledge management skills are knowledgeable. This results in creating new knowledge, disseminating knowledge to nursing staffs as well as creating innovation of in- patient departments regularly. This is also consistent with a study conducted by Smith, Busi, Ball, and Meer (2008). Participants with experience in knowledge management influenced innovative

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

management with $\beta$ = 0.195. In addition, a study by Li, Zhou, and Liu (2006) supported that leaderships who experienced a training related to knowledge management was found to be positively associated with a innovation management performance (r= 0. 41, p- value< 0.01).

**Experiencing research related to innovation**.

The study showed that experiencing the training of innovative management is one of the crucial factors influencing innovative management. This affirms that head nurses with three years' experience in innovation management could apply research skills to solve the problems resulted from their routine work( Jirapaet, 2010) [4]. Research related to innovation is a new concept test using the empirical findings and it can be usable (Hughes, 2006). Hence, head nurses with experiences are more understandable and manageable in this field and this result in effective innovation which can be used in health care units. The study is consistent with a study by Prajogo, and Ahmed (2006) which found that the leaders with experience in research was found to be positively associated with the development of innovation (r = .534 and p-value < 0.01).

***Recommendations***

1. In order to enhance knowledge about innovation, advance nursing science and management for head nurses, it is crucial to impose a relevant knowledge management and innovation management policy and action plan which should be applied with in- patient departments since these can create innovation management and result in an application among patients.

2. Human resource development plan regarding knowledge management and research skill are needed for head nurses because this can be applied to develop effective and efficient innovation management performance.

**3.** Head nurse should be taken training about creation of innovation and knowledge management with other organization about innovation management.

**Acknowledgement**

The researcher would like to thank the head nurses of the in- patient departments of community hospitals affiliated to the Ministry of Public Health who provided beneficial data for this study.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

## References


Amabile, T. M. Componential theory of creativity; Retrieved February 5, 2016, from http://www.hbs.edu/faculty/Publication.pdf;2013.

Bureau of Nursing, Ministry of Public Health. National nursing service strategy. Nonthaburi: Veterans Affairs Organization; 2012. (in Thai).

Drucker, P.F. Post-capitalist Society. New York: Harper Business; 1993.

Chanocha, P. Policy statement of the Council of Ministers. Bangkok: Cabinet and Royal Gazette Publishing office; 2015. (in Thai).

Hair, J. F., Black, W. C., Babin, B. J., Anderson, R. E& ham Ronald L. Multivariate Data analysis. 7th ed. New Jersy: Prentice Hall; 2010.

Hughes, F. Nurses at the Forefront of Innovation. International Council of Nurses, Int Nurs Rev J. 2006; 53: 94-101.

Jirapaet, V. Guidelines for the development and design of nursing innovations. Proceeding of the National Conference on nursing innovation for sustainable quality development; 2010 May 15- 16; Bangkok: SD Avenue Hotel, 2010. (in Thai).

Klangtamniam, K. Nursing Service Innovations. J. of Phrapokklao Nursing College, Chanthaburi. 2012; 22 (2): 71-9. (in Thai).

Li, Y., Zhou, Y., & Liu. The Relationship between HRM, Technology innovation and performance in China. International Journal of Manpower. 2006; 27(7): 679-96.

McGregor, J. The world's most innovative companies; Retrieved December 10, 2015, from http://www.bloomberg.com/bw/stories/2007-05-04.

Nonaka, I. & Takeuchi, H. The Knowledge-Creating Company: How Japanese Companies Create the Dynamics of Innovation? New York: Oxford University Press; 1995.

Berraies, S., Chaher, M., & Yahia, K.B. Knowledge Management Enablers, Knowledge Creation Process and Innovation Performance: An Empirical Study in Tunisian Information and Communication Technologies Sector. Business Management and Strategy. 2014; 5(1): 1-26.

Nursing Organization. Report of Nursing Indicators. Community Hospitals, district 6 (Unpublished); 2015. (in Thai)

Oecon, B. W. A. Employee innovation behaviour in health care: The influence from management and colleagues. Int Nurs Rev. 2006; 53: 231-7.

Prajogo, D.I., & Ahmed, P.K. Relationships between innovation stimulus, innovation capacity, and innovation performance. R & D Management. 2006; 36(5): 499- 515.

Smith, M., Busi, M., Ball, P., & Meer, R. Factors Influencing an Organizations ability to Manage Innovation: a Structured Literature Review and Conceptual Model. International Journal of Innovation Management. 2008; 12: 655-76.

Schulze, A. & Hoegl, M. Organizational knowledge creation and the generation of new Product ideas: A behavioral approach. Res Policy. 2008; 37: 1742–50.

Sristhitnarakul, B. Development and Quality Assurance of Research Instruments: Psychological Measurement Qualities. Bangkok: Chulalongkorn University Press; 2012 (in Thai).

Tidd, J and Bessant, J. Management innovation. (5th ed). West Sussex: Wiley; 2014.

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

*Author Guideline and Instruction*

**International Journal of Public Health and Health Sciences (IJPHS)**

*Instruction for Authors & Guidelines (Revised March 18, 2019)*

1. About the Journal

1.1. The International Journal of Public Health and Health Sciences(IJPHS) is published by Praboromajchanok Institute for Health Workforce Development (PBRI), a higher educational institute of Ministry of Public Health, Thailand. PBRI is consisting of 39 Sirindhorn Colleges of Public Health, Kanchanabhishek Institute of Medical and Public Health Technology and Abhaibhubejhr College of Thai Traditional Medicine Prachinburi, 30 Boromarajonani College of Nursing and Nursing Colleges under Praboromarajchanok Institute for Health Workforce Development, Ministry of Public Health, Thailand.

1.2 The aim of publishing original articles and contributions is relevant to public health and medical sciences. The scope of the journal is broad, covering health policy and management, health care and services, health promotion/health education/behavioral health, environmental and occupational health, health technology and data management, global health, nursing and nursing sciences, community health, dental public health, community pharmacy, toxicology, and other relevant health issues of health and medical sciences. The IJPHS publishes original papers, systematic review articles, brief reports, case studies, field studies, and letters to the editor.

2. Policies

2.1. The Editorial Board decides whether a contribution will be sent for peer review, and if so, it will consider the peer reviewers' reports and make the final decision to accept or reject the manuscript for publication. The Editorial Board reserves the final right to decide the section (manuscript type) in which the paper will be published if it is found to be acceptable for publication.

2.2. Submission of a manuscript to the IJPHS implies that it has not been published elsewhere, that it does not duplicate material already published in any language elsewhere, and that it is not in submission elsewhere.

3. Ethical issues

3.1. Human studies are expected to conducted in accordance with the recommendations outlined in the Declaration of Helsinki (1964, revised 1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008 and 2013).

3.2. Authors should state in their Subjects (Materials) and Methods section that their institution's review board (ethics review committee) has approved the study proposal, as well as the manner in which informed consent was obtained from the subjects (if applicable).

4. Manuscript categories

The following types of contributions will be considered for publication.

4.1. Reviews: Review, evaluation or commentary of a number of research reports on a specific theme.

4.2. Originals: Articles with new findings and original research results, research methodologies, research materials and interpretations of the authors own or of other research results and articles of a similar nature.

4.3. Brief Reports: Articles with limited but original data and having the same format as originals.

4.4. Case Studies: Reports on cases of interest in the field of public health and related fields.

4.5. Field Studies: Reports on investigation into the status of public health with relevant data.

4.6. Opinions: Short articles conveying authors' own opinions or comments on various aspects of public health.

4.7. Letters to the Editor: Letters to the Editor on material published in the IJPHS are

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

welcome. Authors can submit Letters to the Editor by e-mail to the editorial office (ijph-editor@scphtrang.ac.th). The length must not exceed 500 words, only one table or figure is permitted, and there should be no more than five references. When appropriate, the journal may invite replies.

5. Copyright

If the manuscript is accepted for publication, copyright of the article shall be assigned to the IJPHS. After acceptance of a manuscript, the authors will be requested to complete a copyright transfer agreement form.

6. Manuscript format and style

Manuscripts should be prepared in the following manner. Submissions that do not conform to the instructions will be returned unread. The Editorial Office holds the right not to publish an article at any stage of the submission, review, and copyediting if the manuscript does not follow the required format and style.

6.1. Manuscripts should be written in English. Non-native English authors are encouraged to seek the assistance of an English-proficient colleague or commercial English editing services before submission of manuscripts to the journal.

6.2. Manuscripts should be typed in MS Word 97/03 for Windows or higher version, size 12-point type with margins of 2.5 centimeters on A4 (ca.22 × 28 cm) paper. Double spacing should be used throughout, and the right margin should be unjustified.

6.3. All papers should be organized to include the following: a title page, abstract, text, acknowledgments, references, figure legends, tables and figures. Each of the elements should begin on a separate page.

6.4. Pages should be numbered consecutively, beginning with the abstract. Line numbers should be put in the left margin of each page of the text.

6.5. Title page. The title page should include the following: a concise and descriptive title, name of each author, departmental and institutional affiliation of each author, the telephone and fax numbers as well as the e-mail address of the corresponding author, type of contribution, running title (not more than 60 letters including spaces), the number of words in the abstract and the text and the number of tables and figures.

6.6. Abstract. For all submissions except Letters to the Editor, structured abstracts should not exceed 250 words and should normally be organized under the following headings: Objectives, Methods, Results, and Conclusions. Abstracts are necessary for Opinions; however, abstracts for Opinions can be unstructured if appropriate.

6.7. Word count. Originals and Field Studies should be limited to 4,000 words, and Reviews should be limited to 6,000 words, excluding the abstract, acknowledgments, references, tables and figure legends. Brief Reports should not exceed 3,000 words and should contain no more than a total of 2 short tables or figures.

6.8. Format. Originals should generally use the following format: Introduction, Subjects (or Materials) and Methods, Results, and Discussion. Subheadings are paragraph titles should be used whenever possible. Brief Reports and Case Studies should be limited to four printed pages (normally, 800–1,000 words (text base) per page) including references, tables and figures.

6.9. Key words. For all submissions, give a list of 3-5 key words in alphabetical order. The authors are recommended to refer to Medical Subject Headings (MeSH) selected from main headings listed in Medical Subject Headings in Index Medicus, published by the National Library of Medicine (http://www.nlm.nih.gov/mesh/MBrowser.html). Key words will be placed after the abstract for Reviews, Originals, Case Studies and Field Studies.

6.10. Tables and figures. Tables and figures should be of adequate quality to withstand reduction in size. Each table and figure should be submitted on a separate A4 sheet. Their locations in the text should be

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

indicated in the right margin of the text. Only 6 or fewer tables and figures are permitted in total. Each table and figure should constitute a single unit of communications; that is, it should be completely informative in itself without reading the body of the text.

6.11. References. The style of references should follow the Uniform Requirements for Manuscripts Submitted to APA Formatted References, 6th Edition (http://lumenjournals.com/wp-content/uploads/2017/08/APA6thEdition.pdf).

Please refer to the examples of references listed below. List all authors when there are six or fewer; when there are seven or more authors, list the first three authors, followed by "et al." References should be numbered according to the order in which they appear in the text and should be listed at the end of the text. References should be limited to 30 original papers. Please ensure that the references include the most current articles and information.

*Originals*

Yuychim, P., Niratharadorn, M., Siriumpunkul, P., Buaboon, N. (2018). Effects of a Family Participation Program in Managing Drug Managing Drug Use Behaviors among Older Adults with Chronic Disease in Phun Phin Community. *Journal of Public Health*, *48*(1): 44-53.

Thepaksorn, P., Fadrilan-Camacho, V. & Siriwong, W. (2017). Respiratory symptoms and ventilatory function defects among Para rubber wood sawmill workers in the South of Thailand. *Human and Ecological Risk Assessment: An International*, *23*(4):788-797.

Fraenkel, R. J., Wallen, E. N. & Hyun, H. H. (2012). *How to Design and Evaluate Research in Education*. (8th ed.). New York: McGraw-Hill.

Praboromarajchanok Institute of Heath Workforce Development. (2013) Collection of Academic Performance in Humanized Service Mind. Nontaburi: Ministry of Public Health.

*Citation in book chapter*

Waite, J. (2011). "Information and Documentation. In Potter, A.P., Perry, G.A., Stockert, A.P. & Hall, A." *Basic Nursing Challenge*. (pp. 142-164). Missouri: Mosby/Elsevier.

*Internet*

Chen, M.W., Santos, H.M., Que, D.E., Gou, Y.Y., Tayo, L.L., Hsu, Y.C. (2018). Association between Organochlorine Pesticide Levels in Breast Milk and Their Effects on Female Reproduction in a Taiwanese Population. *International Journal of Environmental Research and Public Health*. Retrieved June 3, 2018 from http://www.mdpi.com/1660-4601/15/5/931.

*Thesis/dissertation*

Hom, K. E. (2018). *Association of Air Pollution with Longitudinal Changes in Arterial Stiffness and Correlated of Longitudinal Changes in Arterial Stiffness in the Multi-Ethnic Study of Atherosclerosis (MESA)*. A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctoral of Philosophy, University of Washington.

7. Charges

7.1. Page charges. No charge will be imposed on the authors of papers comprising up to ten printed pages with exemption for 200 $ in 2019-2020. However, charges for papers comprising more than ten pages will be levied on the authors at a rate of $50 per page.

7.2. Color figure charges. Color figures will incur a charge of $50 per each page.

8. Submitting a manuscript

Manuscripts should be submitted online through the web site at https://www.tci-thaijo.org/index.php/ijphs Authors can suggest preferred / non-preferred reviewers for their manuscript, but the editors are not obliged to use/not to use author suggested reviewers. In the IJPHS editorial process, six filed editors and

ISSN 2673-0200 (print) ISSN 2673-0251 (online)

their associate editors will handle submitted papers according to their relevant areas of expertise. Please choose 2 appropriate fields in the order you prefer, as this will help ensure a prompt and efficient editorial process. The editorial board may allocate papers to fields other than those chosen by the authors when appropriate, but authors should endeavor to select the appropriate fields. Selection of inappropriate fields will delay the editorial process.

9. Accepted manuscripts

9.1. Research articles accepted for publication in the IJPHS will appear initially as author-supplied unedited files online in the IJPHS -in-Press section on the website (https://www.tci-thaijo.org/index.php/ijphs) shortly after acceptance. The date the articles was included on the website will be considered the publication date. Any substantive changes at this stage will require an erratum to be published. Articles will be published in the print version in order of acceptance as journal space permits.

9.2. Copyediting

Accepted manuscripts will undergo copyediting. The authors of the accepted manuscript are asked to make appropriate changes requested by the Editorial Office. The authors will be asked to submit the corrected manuscript to the Editorial Office as a Microsoft Word file(s).

9.3. Page proofs will be made available once to the submitting author.

9.4. Accepted manuscripts can also be accessed from the journal's page on the website free of charge. Authors can download the PDFs of their accepted articles and send then to colleagues for noncommercial use.

10. Editorial Office contact information

Questions regarding the instructions for authors should be addressed to the journal office via e-mail (ijphs@scphtrang.ac.th) or Tel. 66-88-7531547.