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*I don't want you to be only
a doctor but I also want you
to be a man*

A quotation by His Royal Highness Prince Mahidol of Songkla



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message from the editor

Dear readers,

I hope this message finds you well and welcome you all to the last issue of volume 43. In this issue, you will have a chance to read the academic article about cloud computing assisting learning. The system that is now growing dramatically in medical education and other disciplines. Moreover, there are also two interesting articles about the advancement of laboratory techniques and palliative care. We wish you enjoy reading our journal as usual.

Enjoy!

Thammasorn Jeeraaumponwat, M.D., Ph.D.
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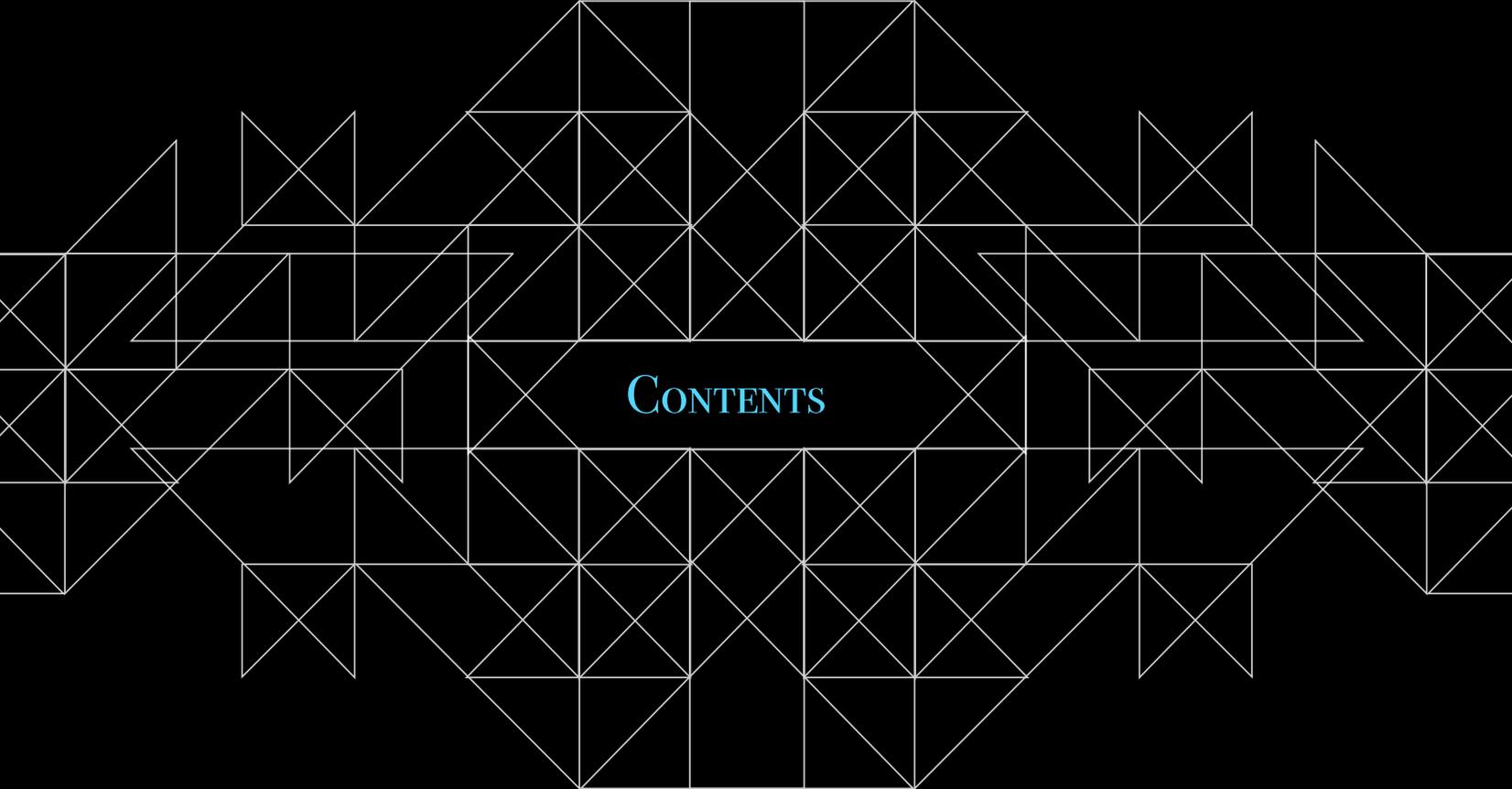
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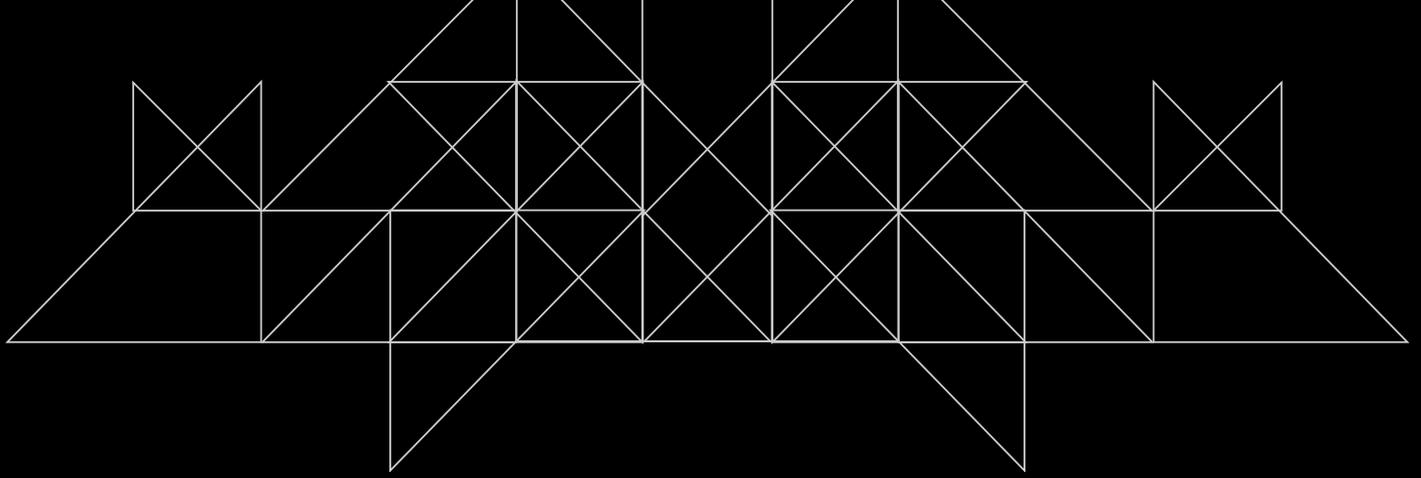
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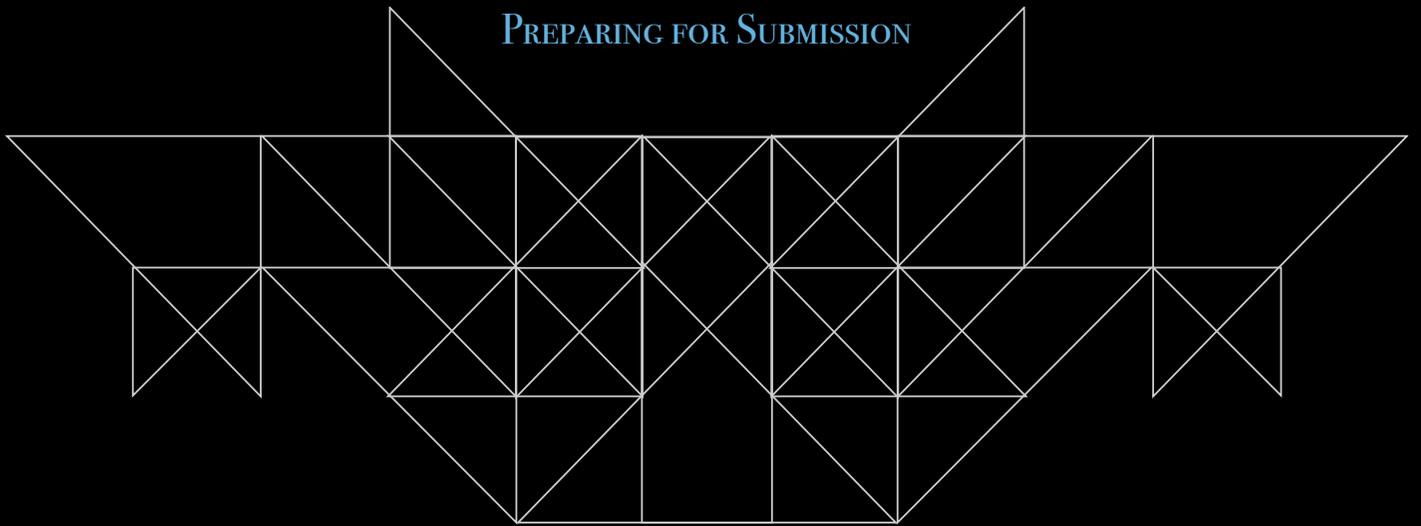
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INTERNATIONAL COMMITTEE OF MEDICAL
JOURNAL EDITORS
(ICMJE)

RECOMMENDATION FOR
PREPARING FOR SUBMISSION



1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT for randomized trials, STROBE for observational studies, PRISMA for systematic reviews and meta-analyses, and STARD for studies of diagnostic accuracy. Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, selecting, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network and the NLM's Research Reporting Guidelines and Initiatives.

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

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Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

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b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not over-interpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential. Funding sources should be listed separately after the Abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

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Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

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iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

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if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.”

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Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

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ii. Reference Style and Format

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Development of documentation system using cloud computing for clinical clerkship

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To develop a documentation system for clinical clerkship using cloud computing.

METHODS

This study was conducted using the design thinking process. There were five steps in this process; analyze the needs, define the problems, generating ideas, implement the prototypes, and test the complete system. The impacts of the developed documentation system on the needs in clinical clerkship were evaluated at the initial phase (in 2014) and the maintenance phase (in 2019).

RESULTS

The documentation system was developed using cloud computing comprising three components; online documents, real-time collaborated feedback systems, and remote repository. After implementation, the majority of sixth-year pharmacy students perceived the benefits of the cloud documentation system on cost-saving of paper, feasibility, and experiential learning in clerkship rotations. All students relied on the cloud documentation system and recommended this system to others.

CONCLUSION

With the design thinking process approach and using cloud computing services, the developed documentation system can benefit cost-saving, and foster efficient information clerkship management during clerkship based on ubiquitous and enlighten experiential learning. To scale up this system, technology acceptance should be evaluated.

INTRODUCTION

The Basel Statements on the future of hospital pharmacy practices have been revised and released by the International Pharmaceutical Federation (FIP) since 2015.¹ Hospital pharmacists take responsibility for many aspects including procurement, preparation and delivery, monitoring medication used, training, and conducting research that promotes patient safety. Pharmacy student training is also one of the Basel Statements of hospital pharmacy practices. Undergraduate pharmacy curricula should include hospital-relevant contents and experiences of hospital pharmacy practice.²

All pharmacy students involved in medication use processes must be able to demonstrate the competency in their clerkships. The augmentation of their quality assignment is a great increase in paperwork, additionally, a system of documentation should be done in any clerkships.^{3,4} Therefore, good documentation should be an essential part to ensure the standards of practice are met. Facing huge documents, time-consuming, and delayed response, however, are the main problems for pharmacy students. Similarly, pharmacy educators from both hospitals and universities may have time constraints on giving feedback and on tracing students back to their activities.

Cloud computing is a technology design and a model that provides convenient, ubiquitous, and on-demand network access to a shared pool of services, applications, storages, and resources.⁵ National Institute of Standards and Technology (NIST) defines, three service models of cloud computing including Software as a Service (SaaS),

Platform as a Service (PaaS), and Infrastructure as a Service (IaaS).⁵ Based on network technology, SaaS is an application delivery model that enables users to utilize a software solution over cloud computing. As a result, the user can use such applications without downloading and installation their computer. These characteristics of SaaS can reduce the cost of hardware and software development, maintenance, and operations.^{6,7}

During a decade, cloud computing has been shown as a milestone and challenged to achievement in medical and nonmedical informatics development.⁸⁻¹⁴ Regarding cloud computing, users can access shared resources directly through the internet, from anywhere at any time by using any devices, and without any technical or physical concerns.

Surprisingly, despite cloud computing is a much more efficient and cost-effective way to deal with information management, it is rarely used for clinical clerkships in Thailand. The reasons or problems with this point are unknown. To adopt cloud computing effectively, real and complex problems should be defined. Design thinking has emerged as a solution-based approach and has been utilized to develop better products and services which are related not only to technology but also to medical education.¹⁵⁻²¹

As a consequence, the Meta-data of Information Drilled Access System (MIDAS), a SaaS-based application has been designed, developed, and implemented. In our knowledge, MIDAS is the first project designed for Thai pharmacy students who have been trained and pharmacists who have supervised, coached, and evaluated such performance of those. This article has shown the design thinking process of MIDAS development.

METHODS

STUDY DESIGN

This study has been conducted using the Design Thinking model, since January 2013.^{15,20-21} There are five stages in the Design Thinking methods including empathizing, defining, ideating, prototyping, and testing. Empathizing is the first stage to understand the collaborators and their needs deeply. Defining is the second stage to analyze, synthesize, and re-frame the problem in a human-centered manner. Ideating, the third stage, is to identify new solutions by creating many ideas in brainstorming sessions. The fourth stage, Prototyping, is an experimental phase to identify the best possible solution for each of the problems identified and then maybe shared and tested within the research team. Testing is the final stage to alter and refine to rule out problem solutions and derive an understanding of the application and its users.

PARTICIPANTS AND STUDY SITES

The main collaborators consisted of hospital pharmacists, pharmacy students, and faculty members. The study site was mainly conducted in a regional and medical teaching hospital, Khon Kaen Hospital (KKH), where the pharmacy students were trained. At the initial stage, there were two universities involved in this study including Khon Kaen University (KKU) and Mahasarakham University (MSU). Additionally, during the testing phase, other universities also participated including Ubonratchathani University, Chulalongkorn University, Silpakorn University, Siam University, and Burapha University.

Hospital pharmacists who responsible for pharmacy students' training, preceptors, and those provided pharmacy services in ambulatory care settings, inpatient care settings, or drug information service settings were eligible for participating in the present study. Faculty members from each university e.g., pharmacy educators and student service coordinators were also included. Faculty members who were responsible for the administration of clerkship training were also eligible. Eligible pharmacy students were sixth-year pharmacy students. To empathize with their insightful experiences and motivations, those students who had been trained at KKH were selected.

DATA COLLECTION

Data collection was performed with face-to-face interviews and brainstorming to evaluate their problems and needs. The first author observed and engaged with each collaborator and the data also were collected from these approaches. The findings from the first stage to the third stage were used for creating the solution-based approach using cloud computing as a SaaS model. For the fourth and fifth stages, the application was implemented and the findings generated during these stages were used to discuss the most recent problems. The application was developed and tested periodically as a cycle from 2014 to 2019. Variables regarding the users including technology experiences, perception of application, usefulness, and obstacles were gathered through online feedback forms. The perceptions of application, in the aspects related to needs assessment, were compared among trained students in the year 2014 with those in 2019.

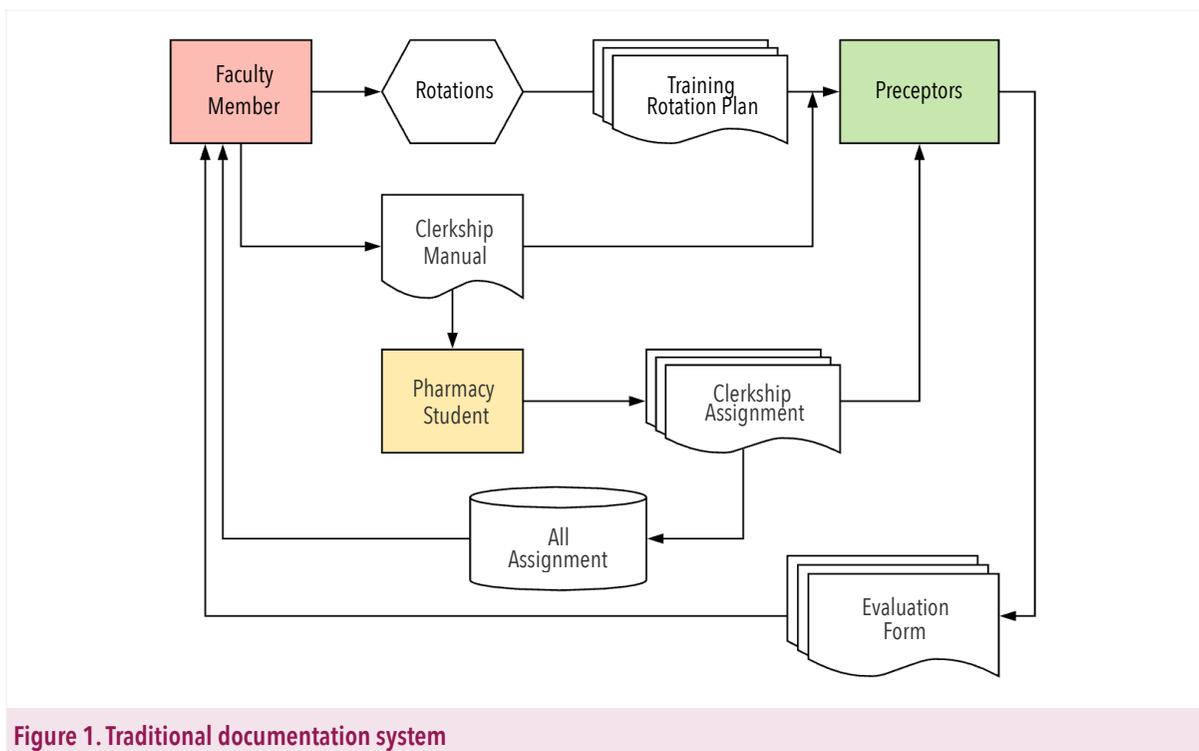


Figure 1. Traditional documentation system

STATISTICAL ANALYSIS

The quantitative data were analyzed using descriptive statistics. Regarding gathered information during each stage, qualitative data were analyzed and synthesized the main issues not only to create a problem statement but also to rule out problem solutions.

RESULTS

INTRODUCTION OF THE FRAMEWORK

At the initial stage, three preceptors from KKH and six faculty members from KKH and MSU were interviewed. Regarding activities in clinical clerkship, six pharmacy students from both universities were also interviewed and observed. In terms of a rule of six, each sixth-year pharmacy student has to be trained at least six rotations

which last for six weeks per rotation. In brief, all students have to be trained in three core clerkships (outpatient care, inpatient care, and community pharmacy) and another three elective clerkships i.e., drug information services (DIS), adverse event monitoring (AEM), chemotherapy preparation, or specific ambulatory care clinics.

The traditional documentation system began with the faculty sent the documents related to the clinical clerkship training rotation plan and guide book for training as hardcopy to the preceptors and pharmacy students. The preceptors sent the evaluation form back to the faculty and the pharmacy students also sent the clerkship assignment back to the faculty (Figure 1). The training rotation plan consisted of students' names in each rotation and their clerkships. Pharmaceutical Care Clerkship Manual (PCCM) has

Table 1. Needs and insights of collaborators

Collaborators	Needs	Insights
Pharmacy students	To use less than 2 copies of each assignment and no paper waste	They did not want to duplicate more copies for a presentation that was used only a few hours and then thrown away. It was important to save the earth.
	To receive teacher's feedback in their assignment during training in the rotation	They receive feedback after finished the rotation. Some feedback was very useful, however, they could not improve themselves because they were rotated to other clerkships.
	To secure all their documents	Most of them found malware on their computers and then they lost all the files. In some cases, they forgot to save files
Preceptors	To search for students' document and access to those within 5 minutes	They kept all documents as hardcopy and it took more than an hour to look for the document that they wanted. Sometimes, they could not find and forget all them.
	To evaluate students' assignment efficiently	Some students responded to the assignment late and might have plagiarism which is difficult to identify.
Faculty members	To calculate each student's score accurately and efficiently	All student's written scores were transcribed into the spreadsheet. There were over 100 forms per each rotation. Those forms were sent back from many hospitals at different times. They had to wait for gathering and then doubly entered the scores.

been provided as a guide book for training pharmacy students by The Pharmacy Education Consortium of Thailand (PECT). The PCCM also included the templates of activity logbook and evaluation forms (both attitude and performance). Each template is much more different, depends on prespecified clerkship. All preceptors duplicated those templates for all pharmacy students based on their clerkships. After each rotation completed, not only students have to prepare a huge document following PCCM, but preceptors also provide a lot of evaluation form and send them back to the university.

Regarding brainstorm among each group of collaborators, their problems and needs

concerned with clinical clerkship are presented in Table 1. There were three main needs that to be the points of view; cost-effective system management, efficient repository, and real-time response. To ideate the problem solutions, the questions were used during brainstorm as following; "How might we reduce the document use, so pharmacy students could reduce their cost?"; "How might we keep the important documents that we can access anywhere, at any time, with access control?"; and "How might we increase learning from immediate feedback?". Afterward, many solutions offered by collaborators included document scanning, keeping documents in CD or flash drives, scoring in the spreadsheet, and reuse one-sided paper.

Those approaches were, however able to solve some needs and the rest important needs were still unsolved. Cloud computing was considered as another solution-based approach, due to its characteristics including efficient, flexible, scalable, and reliable. These could be explained that all documents are stored in a cloud that can be reached through an internet connection. Everyone can access those documents by using a computer or smartphone. The maximum usage of resources has the potential to multiply productivity with a minimal incremental cost. Automated changes with the tracking back system can be solved. As a consequence, the best way to either solve a problem or provide the elements required to overcome emerged from cloud computing. Therefore, we carried out a model using cloud computing to be the prototype of these solutions. The service model that we chose was SaaS. In addition, the public cloud as Google Cloud was chosen to deploy.

MIDAS

The security, an issue of great importance, is the primary concern in using cloud applications. All collaborators have to be mentioned as the following: authentication, authorization, confidentiality, and integrity. Regarding the basis for access control to the cloud application, preceptors and pharmacy students were granted permission to access the application after identifying themselves as a genuine member–Authentication. All collaborators were permitted to access specific resources differently based on their roles–Authorization. Confidentiality denotes the assurance that all documents in the application are

kept secret and private and we disclosed such documents to only authorized users. Only authorized persons are permitted to create, change, and delete the document–Integrity. The Meta-data of Information Drilled Access System (MIDAS) has been designed to achieve our needs using Google application, which is an efficient tool. To follow the rule of security, all collaborators must identify themselves to access the cloud application. Therefore, all collaborators must have such a Google account as an official Gmail to identify themselves. The MIDAS composed three components, as the following: (i) online documents, (ii) real-time collaborated feedback system, and (iii) remote repository.

Online documents

The first component, the online documents consisting of a set of activity logs, case reports or SOAP notes, evaluation forms, and other online documents for pharmacy students stored in Google Drive. There were many folders in a drive. One folder was created for one rotation of one pharmacy student. Each folder contained five parts including two spreadsheet files and three folders. First, learning resources were listed in the online spreadsheet, namely Table of Content (Table 2). Pharmacy students could gain access to the link of any learning resources. Second, the students were required to do the assignments which are listed in the spreadsheet, namely Summary Activities. Third, this part was a folder of Task. The students were required to keep all assignments in this folder. Fourth, this folder included an online form and an online spreadsheet related to Activity Log. Fifth, the last folder was related to the evaluation.

Table 2. Infrastructure based on cloud computing

Folder	Pharmacy student	Hospital pharmacist	Academic staff
Student folder	View	View	View
Activity logs	Edit & View	Comment	View
Job assignment (Task)	Edit	Edit	Comment
Evaluation Form	Inaccessible	Edit	View
Learning Resources	View	Edit	View
Official documents	Inaccessible	View	View
Student profile	Inaccessible	View	View
Student registration	Inaccessible	View	View
Control room	Inaccessible	View	View

The individual folder, as described earlier, has been shared with an individual student. Such pharmacy students were able to access all their shared documents except two folders including the activity log and the evaluation. Their documents which are the job assignments can be edited but those which are the learning resources can be viewed only. All students' folders have been shared with preceptors who are their supervisors. Preceptors were able to access all documents related to their clerkships, however, they were able to edit only the documents of their trainees or those who were assigned. For the faculty, they were able to only view all shared documents related to their students. Nonetheless, faculty members can also request to participate to comment on the job assignment of their students.

Regarding the evaluation, the online evaluation forms stored in the folder of each

student and all evaluation forms have been listed in and linked to the folder of Control Room (Table 2). Preceptors were able to access and edit only their evaluation form of their assigned student. The faculty was able to view all online evaluation forms of their students but not to edit. An online evaluation form comprises the formulas that summarize and make the grade immediately when such preceptors provide scores of each issue. Therefore, those final scores have to be confirmed and then faculty members will use those scores for summative evaluation. To reassure that those scores must not change, the access level of all collaborators will be changed to view only. If they need to change the scores after the score confirmation, they have to provide a reasonable written request for the correction to the administrative team and authorized faculty member.

Real-time collaborated feedback system

Those online documents was able to easily worked on the MIDAS. Files in the MIDAS mostly match up to the format of documents, spreadsheets, and slides, according to Google application. Any updates were automatically saved and stored in Drive. Subsequently, all users was able to have the latest version of those files. Therefore, this advantage was the second component of MIDAS. A real-time collaborated feedback system provide a new style of feedback. The students were able to send their assignments to preceptors earlier than the traditional system. Both preceptors and the faculty were able to give feedback collaboratively. Then, the system sent a notification note to the shared group simultaneously. Pharmacy students also got online notifications of those comments and they were able to respond to each comment as soon as possible. After each response occurs, the system also sent the notification to the shared group as a cycle. Furthermore, students were able to work in the documents with their peers at the same time and were able to share valuable comments from their supervisor. Two-way commenting with the notification was able to reduce the gap of time lag or delayed response and, particularly, enhance student learning. On top of this, we were able to work offline and then those changes are immediately updated once online was available.

Remote repository

The need for document storage management was the last component of the MIDAS. The metadata was aggregated and managed in a central location

in Google Drive of the administration of the team. Regarding this remote repository, all files and folders were decided who can get access to such files or folders. The collaborators were granted to edit, view, or just add comments as individual persons or groups. All files were able to manage from anywhere on any device and at any time. Although we created the new files in the shared folder, we kept those private until we decided to share them. Interestingly, this component provides a powerful search, for any file, which reflects the security models of the MIDAS. That means the collaborators only see search results for documents they have access to.

IMPLEMENTATION OF MIDAS

We evaluated the capability of implementing the application and learning environments at the end of 2013. We found that the most pharmacy students lacked of experience in using Google application, although they used other online applications frequently. Moreover, some students did not have neither their computer nor smartphone. Regarding the education approach, the number of internet access points in KKH was limited. The conference room was small, and the office equipment had only a whiteboard and an LCD projector.

To implement the MIDAS effectively, therefore, the internet access points were installed. Any wireless devices were adapted to suit the system. The conference room was renovated, expanded, and upgraded (such as Digital TV), to enhance cloud-based learning. Besides, preceptors at KKH and faculty members were planned

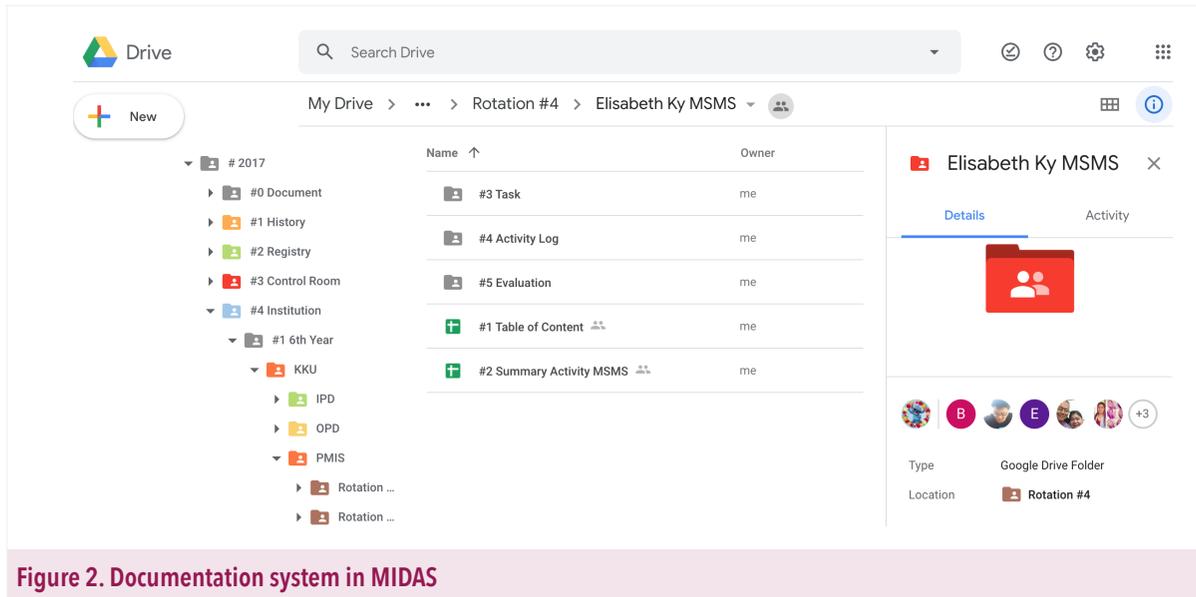


Figure 2. Documentation system in MIDAS

together to provide computer reserves for the students who have a computer problem. In terms of competency, all students who applied for training at KKH should be trained to use the MIDAS. The training program was scheduled for three hours at their universities (KKU and MSU) before starting the clerkship.

MIDAS training program consisted of three main components, including what was the MIDAS, how to manage the online documents, and how to enhanced learning with MIDAS. The first session described the advantages and disadvantages of the traditional system compared with MIDAS. The second session showed how to create, share, delete, upload, download, and set the permission of the documents using Google application. The third session presented how to notify their supervisor proof their assignments and how to respond to the notification as two-way comments. MIDAS has been launched since January 2014. Seventy-five pharmacy students applied for

training during this year. There were 147 clerkship rotations. The number of students was higher than expected, and those were from five universities (KKU, MSU, and other-three universities). The administrative team, preceptors, and the faculty discussed a strategy for creating a positive learning experience of MIDAS to their students. Therefore, we decided to provide the orientation and training program for MIDAS on the first day at the training site. The training program was rescheduled for three hours and integrated into a comprehensive orientation on the first day of each rotation.

When students arrived at the practice site on the first day of each rotation, the orientation and training program was provided to them. After the training program completed, all students were invited to create their Gmail to identify themselves. They also applied for the permission of internet access at the practice site. Later, each student was shared their folders and assessed their readiness to access the shared documents (Figure 2).

There were many core activities in each rotation. First, students had to record their activity daily. Regarding the new system, they filled the online form of activity log instead of writing on the paper. They can check their logs on the website immediately after submitting and they can also see other logs from their peers. Second, students had to provide services based on their clerkship and they were required to document their case reports or other assignments in all clinical clerkships. Third, students were also required to provide both journal club activity and academic education in all clerkships. Pharmacy students kept all files including case reports, slide presentations, and other assignments in the shared folder of MIDAS. During implementing MIDAS, some students unintentionally removed their important files from the shared drive and it might be very frustrating to lose them all. Hence, to prevent these events and to ensure the recovery of their files, they had to make the administrative team the owner of the new documents that they created. This approach has also provided the benefits of storage all files as long as the main team needed. After they completed their 6-week rotations, they had to send all documents back to the faculty. We found that some students still printed all documents as hard copy or downloaded their folder and burned those to a CD or DVD to their faculty members.

IMPACT OF MIDAS

In June 2014, six months after MIDAS implementation, forty pharmacy students were trained and sixty-four rotations were provided. A follow-up anonymous, voluntary, online survey was conducted and sent to all students via email. The

survey was to measure how the pharmacy students were using MIDAS in clinical practice, and other assignments, as well as to examine their perceptions of MIDAS and their attitudes towards the impact of cloud computing through MIDAS on their workflow. This survey was developed according to the needs and insights from the collaborators involved in the initial phase. We also obtained feedback on additional needs.

Thirty-six pharmacy students (90%) responded to the follow-up survey. All respondents owned and used a computer at the time of using MIDAS. Only one respondent (3%) had no smartphone whereas only four students (11%) had an iPad or Tablet. Twenty-five respondents (69%) were unfamiliar with Google applications prior to MIDAS implementation. Over half (55%) had been trained and used MIDAS for one clerkship rotation, whereas the rest had been trained and used MIDAS for more than two rotations. Regarding Google applications, all respondents used MIDAS most frequently related to Google Drive (94%), Documents (81%), Slides (67%), and Sheets (39%).

Five approaches to MIDAS were assessed in terms of the relationship between students and preceptors, cost-saving, feasibility, experiential learning, and trustworthiness (Figure 3). Most respondents (92%) agreed that MIDAS helped them communicate to their preceptors frequently and increased relationships between preceptors and them. In terms of cost-saving, almost all respondents (97%) agreed that MIDAS can make a big saving of paper use. Ninety-two percent reported a decrease in other resources (i.e., ink, toner, and carbon), whereas 17% perceived the problem of the cost related to wifi access. Nearly

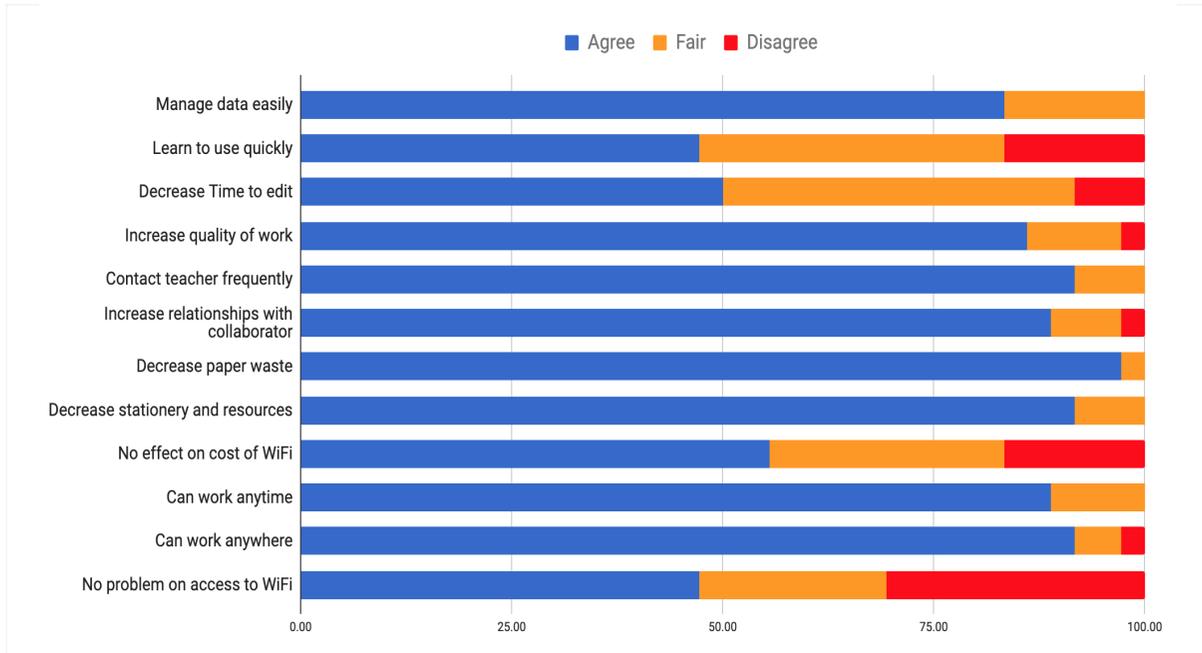


Figure 3. The percentages of perception of MIDAS in 2014

90% reported that it was feasible to access MIDAS anywhere and at any time.

Regarding experiential learnings, most respondents indicated that MIDAS increased their learning with 2-way comments and they can manage documents efficiently (69% and 83%, respectively). Over half (56%) agreed that MIDAS was beneficial not only to clerkships but also to other activities. The majority (86%) indicated that MIDAS was a trustworthy application. Most respondents perceived that autosave, quick search, collaborative work, and paperless were major advantages of MIDAS. In contrast, they mentioned font formatting in MIDAS as a big disadvantage because they were unfamiliar with limited Thai font and preferred such available traditional fonts. However, 92% reported that they recommended MIDAS to their peers and preceptors in other practice sites.

MIDAS AND SUSTAINABLE SOLUTIONS

In December 2014, after one year implementation MIDAS, the advantages and disadvantages presented to all collaborators and were discussed. Other issues had been also adjusted to manage according to the cloud computing system. Faculty members agreed with preceptors about providing online documents instead of paperwork and agreed with pharmacy students about using cloud storage documentation instead of burning a CD or DVD. Training program for MIDAS has been widely acknowledged, by all collaborators, as one of the beneficial tools for clerkship rotations.

Later clerkship rotations had started in March 2015 and ended in March 2016. There were 90 trained pharmacy students in a total of 168 clerkship rotations. Over 40% were trained only one rotation at KKH and another 40% were trained two rotations at this site. Figure 4 shows that the

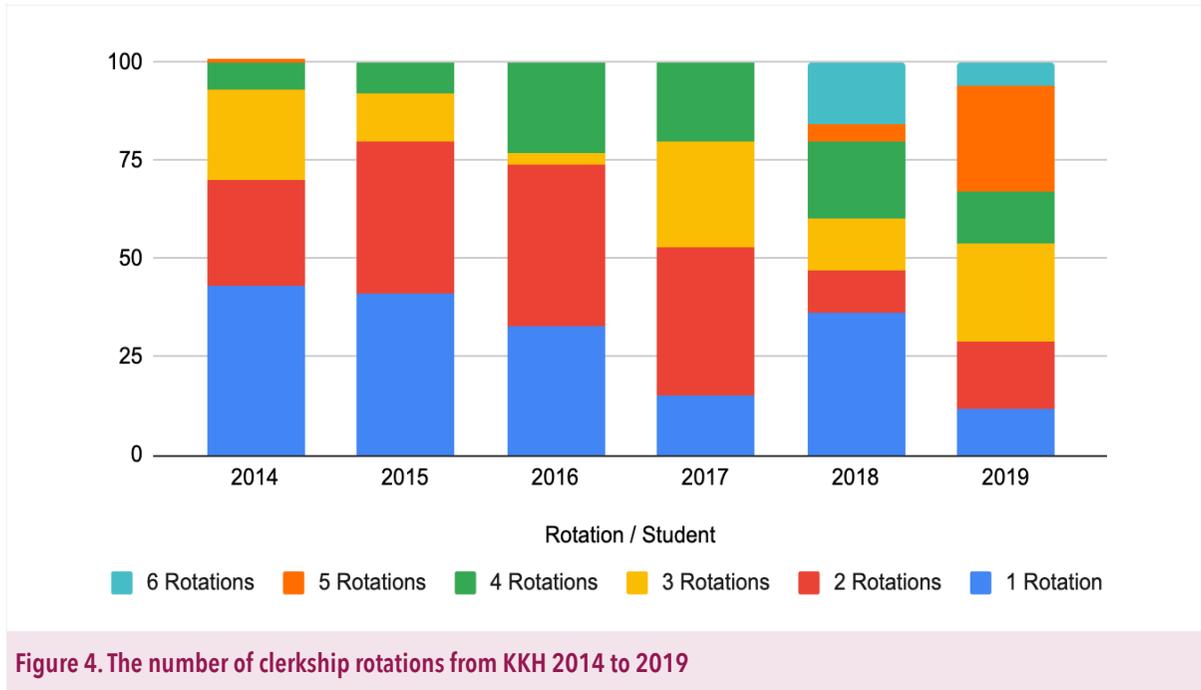


Figure 4. The number of clerkship rotations from KKH 2014 to 2019

proportion of those trained more than 4 rotations was higher in the year 2016 and 2017, whereas the number of total students was nearly the same (61 vs 60, respectively). Students who were trained at KKH more than 2 rotations reported that they were familiar with and preferred to use MIDAS, compared to the traditional system at other practice sites. On the contrary, those trained only one rotation indicated that they consumed a lot of time to learn to use MIDAS, however, they still perceived the benefits of MIDAS on cost-saving, experiential learning, and efficient documentation system.

For sixth-year students trained in the year of 2018, the Pharmacy Council of Thailand had announced a change in core clerkship rotations which added a new core clerkship related to medication safety management.^{22,23} All pharmacy students who intended to be clinical pharmacists had to be trained with three core clerkships in the hospital. These clerkships included

ambulatory clerkship, acute care clerkship, and a new one, a medication safety management system (MSMS). Many students realized that consecutive hospital clerkship rotations in one practice site provided the most benefit to them. The explanation of a long-lasting rotation was that they would be familiar with the practice site and healthcare team and they were able to manage their time wisely to accomplish their enormous tasks. Therefore, most students tended to apply for training in one hospital at least 3 rotations rather than in different practice sites.

Figure 4 presents the percentages of pharmacy students from 2014 to 2019, based on the number of trained rotation. As mentioned earlier, the percentages of those trained more than three rotations at KKH increased dramatically from 20% in 2017 to 53% in 2018 and 71% in 2019. The number of students who applied to be trained at KKH in 2019 was higher than the number of those

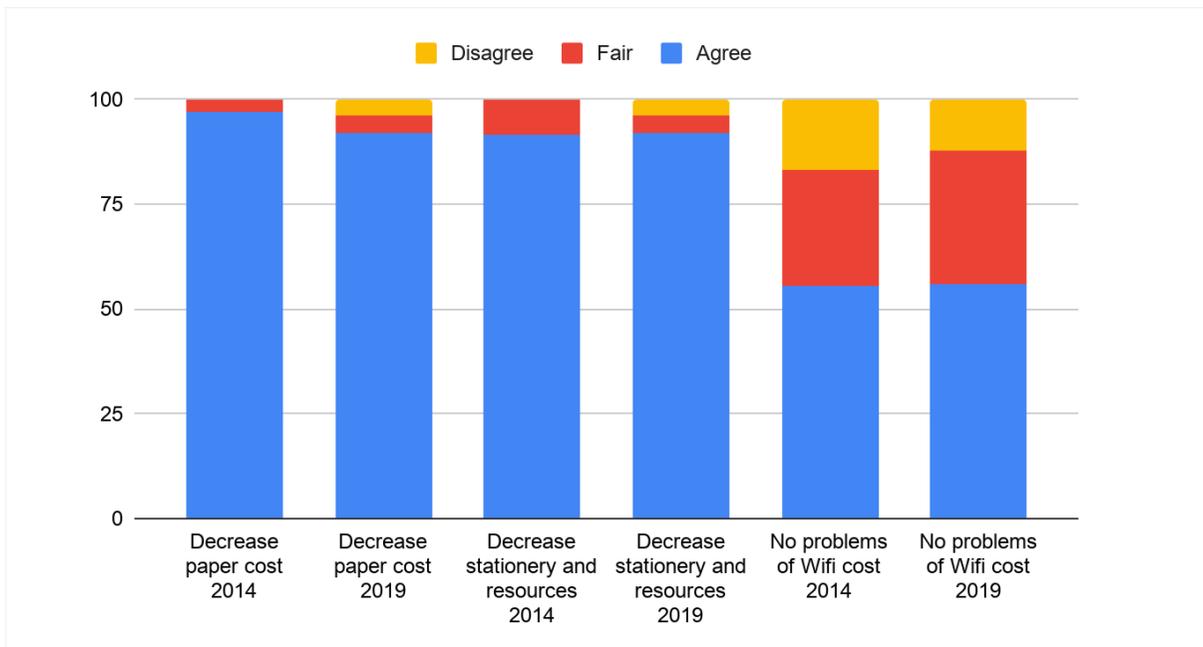


Figure 5. The perceptions of the cost related to MIDAS between 2014 and 2019

in previous years (52 students vs 45 students) and the number of all rotations was also substantially higher (179 rotations vs 132 rotations). On top of this, the students that applied to be trained for more than four consecutive clerkship rotations at KKH also increased from 20% in 2018 to 33% in 2019.

During five years of MIDAS implementation, new communications and computing technology have emerged rapidly and offered more choices to pharmacy students and preceptors. The new environment has also expanded the need to consider not only how to address students' need smarter, but also how to capture value from providing innovations, particularly MIDAS. Therefore, an online survey was also conducted to evaluate how pharmacy students, in the year 2019, perceive MIDAS as a valuable application for their clerkship. This survey included similar issues to the previous survey in 2014.

Twenty-five pharmacy students (74%) who were trained at KKH in 2019 provided their voluntary and anonymous responses to the survey. All respondents had their own computers and smartphones. There was a higher percentage of having an iPad or tablet among students trained in 2019, compared with those in 2014 (82% vs 11%; $P < 0.001$). Only one-fourth of respondents indicated that they usually used the computer for education whereas others preferred to use either iPad or tablet (41%) or smartphone (33%). Experiencing with google application prior to MIDAS was significantly higher among trained students in 2019, compared with those trained in 2014 (80% vs 28%; $P < 0.001$). In addition, the perception of easily use of MIDAS in 2019 was significantly higher than in 2014 (80% vs 47%; $P = 0.039$).

Approach to cost related to MIDAS, almost respondents both in 2014 and 2019 perceived the

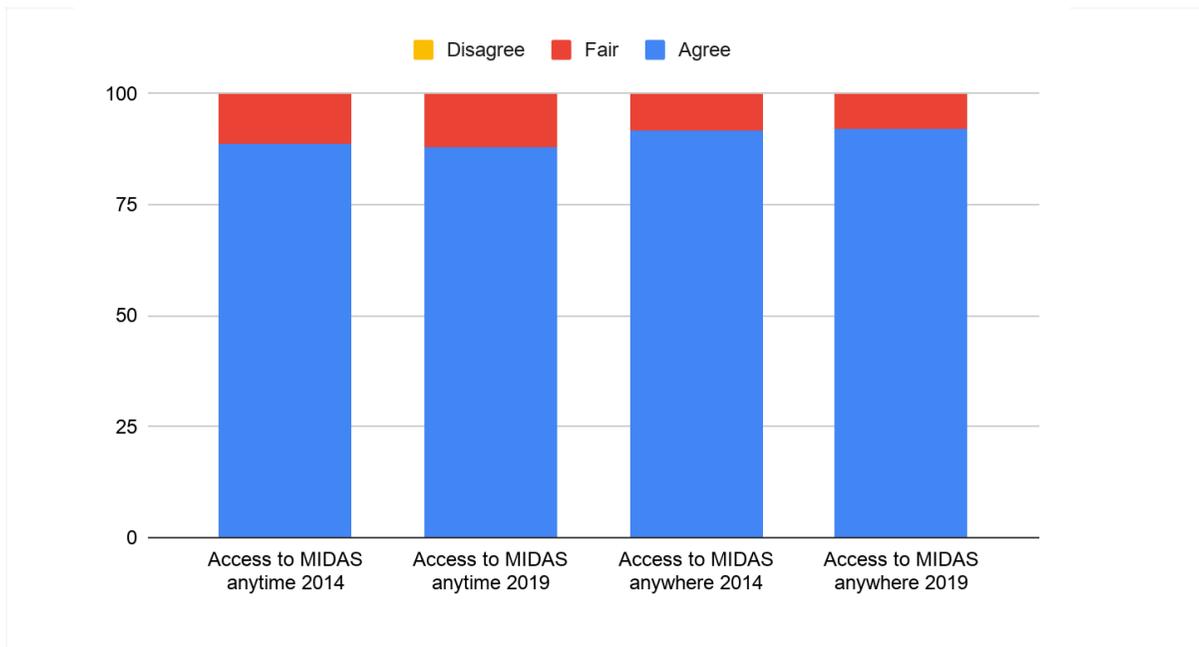


Figure 6. The perception of feasibility related to MIDAS between 2014 and 2019

benefits of MIDAS on cost reduction of paper (97% vs 92%), and stationery and other resources (93% vs 92%), as shown in Figure 5. The percentage of respondents who rated wifi cost as a problem in 2019 was higher than those in 2014 (18% vs 12%). In the viewpoints of access to MIDAS, all respondents accepted that it was more feasible to use MIDAS at any time and from anywhere (Figure 6). There were no differences in the percentages of having strong positive perceptions between trained students in 2014 and those in 2019 (92% vs 92%).

Figure 7 shows the perceptions of experiential learning from MIDAS compared to trained students in 2019 to those in 2014. The percentage of respondents who strongly agreed on increasing learning by 2-way comments, which was a specific feature of MIDAS, was increased from 70% in 2014 to 92% in 2019 ($P=0.116$). Similarly, an increase in the percentage of those who responded to the benefit of MIDAS to efficient

documentation was also found in 2019 (from 83% to 96%). The percentage of respondents in 2019 who applied MIDAS to other activities was significantly higher than that of those in 2014 (96% vs 56%, $P=0.002$). Regarding the learning environment, the percentage of respondents who reported a problem with computer use was similar between 2014 and 2019 (17% vs 16%). Those who trained in 2019 reported a problem with internet access lower than those trained in 2014 (12% vs 31%).

In 2019, 72% indicated that they easily and frequently communicated with their preceptors and 64% had a high relationship with them. These were significantly lower than the perceptions of those who trained in 2014 (92% in 2014, $P=0.046$ and 92% in 2014, $P=0.01$, respectively). In terms of the trustworthiness of MIDAS, 100% of respondents in 2019 relied on MIDAS to manage their clerkship and strongly recommended MIDAS

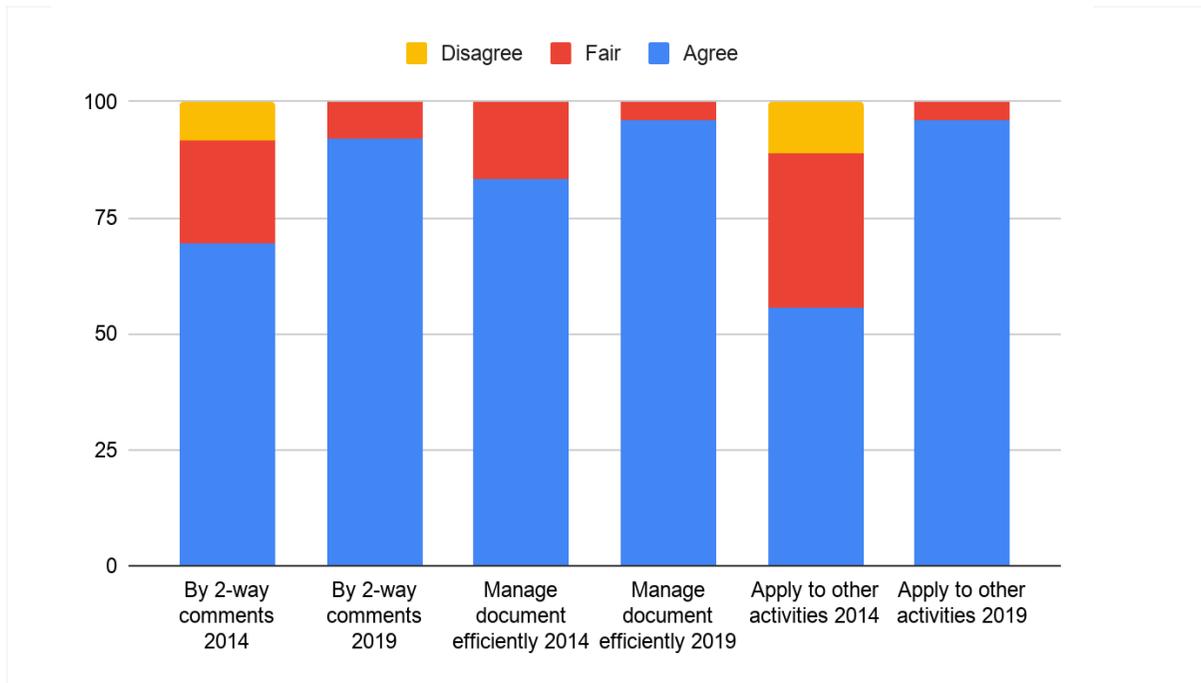


Figure 7. The perception of experiential learning related to MIDAS between 2014 and 2019

to their friends and other preceptors, compared to those in 2014 (86% and 92%, respectively). They indicated that they appreciated MIDAS for its organization's easiness, 2-way communication, ubiquitous learning, and efficient team collaboration.

DISCUSSION

Half a decade, cloud computing in clinical clerkship was a reasonably new phenomenon in Thailand. The important step was to perform a needs assessment before any implementation, particularly new technology. We utilized the five-step of the design thinking process to provide a solution-based approach.^{15,16} The collaborators in pharmacy training indicated that cost-effective system management, efficient repository, and real-time response were the main needs to improve the

documentation system. Our results reveal that the initiated online application, MIDAS, had achieved cloud computing characteristics including efficient, flexible, scalable, and reliable. MIDAS provided the benefits of cost-saving on paper and other resources, experiential learning with 2-way comments, and efficient organization. To our knowledge, MIDAS is the first and last-long application for pharmacy clinical clerkship in a hospital setting.

The majority of students in 2014 were new to cloud applications like Google. Some students disappointed the format and font of paperwork since they were already satisfied with their established approach. However, they were substantially interested in the benefits of MIDAS on cost-saving and ubiquitous learning. These points were able to overcome a fashion presentation and empowered them to take the time needed to learn

how to use MIDAS. In contrast, the young generations, nowadays, perceive more benefits of cloud computing on paperless and benefits of using the iPad or Tablet technology for recording their notes digitally with handwriting on the screen.²⁴ This advantage enhances their learning and they overwhelm a combination of electronic and paper notes. Hence, trained students in 2019 rated that it was worth using MIDAS in their clerkships.

There were significant differences in the perceptions of preceptor-student relationships between those in 2014 and 2019. One explanation of such higher relationships in 2014 is that the students had no more choice of the ways to communicate with their preceptors rather than face-to-face. E-mail and simultaneous 2-way comments, at that time, were the best choices for them to contact preceptors any time and take a fruitful source of information. Effective communication between preceptors and students can provide the most important element for success in student learning. Therefore, using MIDAS provided the opportunity to share and learn from each other without time constraints. In contrast, preceptors have been using other efficient mobile applications (i.e., Facebook messenger, LINE application) to ease their communication with the students and their peers since 2015. Nevertheless, students still benefit from an online discussion with 2-way comments in MIDAS.

Using mobile and iPad or tablet technology has been rapidly increasing in the young generations, as mentioned earlier. Many previous studies in medical education showed that these technologies resulted in increased productivity and learning challenges in the

classroom and experiential settings.²⁵⁻²⁸ Moreover, there are several key factors contributed to technology acceptance. Students who spent a minimum of 3 rotations (18 weeks) enabled them to readily adapt to new technology⁴ and their positive attitude toward using technology is the most important factor supporting continuance intention to use cloud services.²⁹ In the same manner, preceptors and faculty members who adopt these technologies and integrate them in class or students' assignments would also empower their students to be proficient in learning.³⁰

In this study, there were several limitations. First, MIDAS was implemented only one practice site. As different characteristics of preceptors could affect several aspects of MIDAS, future studies should be done on the concept of the technology acceptance model (TAM). Second, brainstorming at the initial stage was conducted with only two universities, whereas some trained students were from other universities. Nonetheless, the design thinking process allowed us to reanalyzed the problems and develop the solutions continuously as a cycle. Third, the training program for MIDAS use was served only for students. Limited training was provided to preceptors and faculty members. This may have influenced MIDAS usage, however, MIDAS was easy to use in the role of preceptors and faculty members. In a recent decade, new technology and devices have been developed and innovated rapidly, and lifestyles change of our students should be considered. In 2018, positive challenges emerged that pen-friendly application was launched to integrate with iPad or tablet technology and the Thai students can own them at a reasonable price. Consequently, the

majority of students use this technology frequently in their education. The strength of this study is that there were significant different characteristics of students in 2014 and 2019. The former, low proficient in technology, were done before high efficient devices were released and compared to the latter who were familiar with cloud computing. Our findings show that MIDAS has continued to be a robust tool in spite of generational differences. In the future, we will continue to evaluate the impacts of global change affecting MIDAS.

In summary, all collaborators participated in solving the clerkship documentation system using the design thinking process. Their needs including cost-saving, efficient documentation, and well organized were solved by using cloud computing applications, as MIDAS. MIDAS also encouraged pharmacy students to manage their clerkship efficiently and enlighten them about experiential learning in other aspects. Technology acceptance should be evaluated to scale up MIDAS use.

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Fluorescence intensity of anti–nuclear antibodies patterns on anti–extractable nuclear antigens detection

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To provide assistive information for diagnosis of patients with autoantibodies.

METHODS

This study reviewed laboratory records of patients who were suspected of autoimmune diseases by clinicians and underwent ANA and anti–ENA tests at Khon Kaen Hospital, Thailand, from January 2012 to January 2016. 543 anti–ENA results with positive ANA were analyzed. Anti–ENA test was used to identify a group of specific autoantibodies, including anti–RNP, anti–Sm, anti–SSA, anti–Ro52, anti–SSB and anti–Scl70 antibodies.

RESULTS

The detection rate of anti–ENA antibodies in ANA positive serum samples was 66.1% (95% confidence interval (CI); 62 to 70). ANA patterns of homogeneous and fine speckled types with high fluorescence intensities from 3+ to 4+ showed 23.4%–35.9% of anti–SSA and anti–Ro52 antibodies detection. Meanwhile, the coarse speckle 3+ to 4+ could detect anti–SSA and anti–Ro52 antibodies by up to 50.0%–63.6% and started to detect anti–Sm antibody by 18.8% and 33.8%. Moreover, the coarse speckle 4+ showed 66.2% of anti–RNP and 20.8% of anti–SSB antibodies detection. Nucleolar 4+ showed the highest detection rate of anti–Scl70 antibody at 77.8%. Similar tendency of anti–Scl70 antibody detection could be found from low to high intensities of fine speckled and homogeneous patterns, which usually show up in mix patterns. Centromere pattern 4+ showed 10.5%–26.3% of anti–SSA, anti–Ro52, anti–SSB and anti–Scl70 antibodies detection. At low fluorescence intensities, fine speckled 1+ and homogeneous 1+ (titer 1:100) could detect anti–SSA antibody with highest probability of 17.5% and 13.5%, respectively. The coarse speckle 1+ also showed 5.6% of anti–SSA, anti–Ro52 and anti–SSB antibodies detection, while speckle 2+ had the increasing rate of anti–SSA, anti–Ro52 and anti–RNP antibodies detection from 15.1% to 33.3%.

CONCLUSION

The tendency of detection of some specific anti–ENA antibodies can be roughly estimated as the fluorescence intensity is 3+ or above. However, low intensities 2+ or below do not rule out the expected anti–ENA antibodies related to clinical diagnosis.

INTRODUCTION

Detection of anti-nuclear antibodies (ANAs) using indirect immunofluorescence assay (IFA) is a subjective screening test for autoimmune rheumatic diseases (ARDs) or connective tissue diseases. This method is recommended by the American College of Rheumatology (ACR) as the gold standard for ANA testing.¹ The staining pattern and fluorescence intensity or ANA titer will be reported by manual reading. The test plays an important role in supporting a diagnosis of many connective tissue diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), Systemic sclerosis (SSc) or scleroderma, polymyositis (PM) or dermatomyositis, Raynaud phenomenon and rheumatoid arthritis (RA).^{2,3}

ANA by IFA showed high sensitivity and high specificity in SLE patients. However, it also gave a positive result in patients with multiple medical problems who had no symptoms of connective tissue diseases or in patients with non-autoimmune diseases.^{4,5} It has also been reported that ANA positive results could be found at low titers of 1:80 and 1:160 even in normal healthy persons.^{4,5,6} Moreover, many studies presented that healthy people had a prevalence range of ANA varying from 0.5% to 20.0% at titers no more than 1:80, and 0.1% to 3.7% at higher titers.⁷ From guidelines for the laboratory use of autoantibody tests of autoimmune rheumatic diseases, ANA detection was suggested only in patients with clinical symptoms suspected of ARD. Determination of antinuclear specific antibodies should be done only in patients with ANA positive by IFA or in ANA negative patients but exhibit clear symptoms of ARD.⁸ In addition, the international

recommendations for detection of autoantibodies also advise to find out antibodies to extractable nuclear antigens (anti-ENA antibodies) in ANA positive cases.⁹ Anti-ENA antibodies used in routine laboratories consist of seven main antibodies, namely anti-RNP, anti-Sm, anti-SSA (anti-Ro), anti-Ro52, anti-SSB (anti-La), anti-Scl70 and anti-Jo1. These specific autoantibodies could be found in and are related to many connective tissue diseases.^{10,11}

The specificity of the anti-ENA test by line-blot immunoassay (LIA) has been reported to be higher than the ANA test by IFA (84.4% and 52.5%, respectively). This performance increases when both methods are used together.¹² Nevertheless, the different types of ANA staining patterns were also reportedly associated with several connective tissue diseases, which when combined with clinical symptoms were useful for identifying the specific autoantibodies.¹³⁻¹⁵ At the screening dilution of 1:40 and 1:80 by using Hep-2 or Hep-2000 cells as substrate antigens, ANA titer and fluorescence intensity were also demonstrated to be beneficial in predicting specific antibodies against ENAs.¹⁶⁻¹⁸

However, these previous works on ANA were performed at different initial serum dilutions from what used in the laboratory of Khon Kaen Hospital and those on anti-ENA antibodies with different methods. Therefore, this study aimed to analyze ANA staining patterns from IFA at a single dilution of 1:100 which were positive with intensities 1+ to 4+, to find the frequency and probability of anti-ENA antibodies detection as found from line-blot immunoassay, to provide information for estimating the chance of more specific antibodies detection from a given ANA screening test.

METHODS

PATIENTS

This study was a retrospective descriptive study of laboratory records of patients who were clinically suspected of autoimmune diseases by clinicians' judgment. The laboratory data consist of 543 patient records with positive ANA by IFA and with anti-ENA results from January 2012 to January 2016. Ethical approval was obtained from the Khon Kaen Hospital Institute Review Board in Human Research (KIRB). The Ethical approval number is KE59047.

INDIRECT IMMUNOFLUORESCENCE ASSAY OF ANA DETERMINATION

The semi-quantitative ANA testing by IFA was performed in serum samples at a single dilution of 1:100 using phosphate buffer saline (PBS-Tween) pH 7.2 and staining on HEp-20-10 cells and primate liver cells (monkey's liver cells). Fluorescein-labeled anti-human IgG (goat) was used for monitoring the antigen and autoantibody reaction. The staining performed according to the instruction manual of the test kit (EUROIMMUN, Germany). Negative and positive controls with known ANA fluorescence pattern as homogeneous 4+ were used as internal quality control (IQC) in each slide. Fluorescence intensity was graded from 1+ to 4+ and reporting of negative and positive results performed as suggested in the guideline of the national committee for clinical laboratory standards (NCCLS).¹⁹ ANA five major patterns of the cell nucleus, namely Homogeneous, Fine speckled, Coarse speckled, Nucleolar and Centromere patterns, were classified based on the Hep-2 cells-based nomenclature proposed by Wiik, et al.²⁰

LINE-BLOT IMMUNOASSAY (LIA) OF ANTI-ENA ANTIBODIES DETECTION

Seven specific antigens of ENA were used: nRNP/Sm, Sm, SSA (Ro), Ro52, SSB (La), Scl70 and Jo1, which were coated on immunostrip of LIA commercial kit (Anti-ENA ProfilePlus 1, EUROIMMUN, Germany). As in the manufacturer's instruction, the 1:100 diluted serums was incubated with antigens on immunostrip. After washing unbound antibodies, alkaline phosphatase-labeled anti-human IgG (enzyme conjugate) was added and incubated with antigen-antibody complex. After washing steps, the substrate (NBT/BCIP) was incubated for color development on the antigen-antibody complex. The immunostrips were then scanned and analyzed using EUROLineScan software to get semi-quantitative results.

STATISTICS ANALYSIS

Data were analyzed for the probability of anti-ENA antibodies detection by line-blot immunoassay in serum samples of patients with ANA positive results. The results were presented in percentage, with a 95% confidence interval. The frequency and probability of each type of anti-ENA antibody detection were also studied for each ANA positive pattern and intensity (1+ to 4+).

RESULTS

From the review of 543 ANA by IFA positive results of patients who had symptoms suspected of autoimmune diseases, 359 cases were found anti-ENA positive by LIA, the probability was 66.1% (95% confidence interval (CI); 62 to 70). At ANA screening dilution of 1:100, fluorescence intensities from 3+ to 4+ of homogeneous and

fine speckled patterns showed 23.4%–35.9% of anti-SSA and anti-Ro52 antibodies detection. Coarse speckle 3+ to 4+ could also detect anti-SSA and anti-Ro52 antibodies by up to 50.0%–63.6%. Coarse speckle 4+ obviously showed high probability of anti-RNP antibody detection at 66.2% (95% CI; 55.4 to 77.0) and anti-SSB at 20.8% (95% CI; 11.5 to 30.1). At the intensity of 3+, a coarse speckled pattern could detect anti-Sm antibody by 18.8%, and up to 33.8% (95% CI; 23.0 to 44.6) at intensity 4+. High intensity 4+ of the nucleolar pattern showed the highest probability of anti-Scl70 antibody detection at 77.8% (95% CI; 71.3 to 84.3). Similar tendencies of anti-Scl70 antibody detection can be found from low to high intensity of fine speckled and homogeneous patterns, which usually appear in mixed patterns. Centromere pattern 4+ showed 10.5%–26.3% of anti-SSA, anti-Ro52 and anti-SSB antibodies detection, and 15.8% of anti-Scl70 antibody detection. For low fluorescence intensities, fine speckle 1+ and homogeneous 1+ could detect anti-SSA antibody with notable probability of 17.5% (95% CI; 9.0 to 26.0) and 13.5% (95% CI; 2.0 to 25.1), respectively. Coarse speckle 1+ also showed 5.6% anti-SSA, anti-Ro52, and anti-SSB antibodies detection, while speckle 2+ had an increasing rate of anti-SSA, anti-Ro52, and anti-RNP antibodies detection from 15.1% to 33.3%, as shown in Table 1 and Table 2.

DISCUSSION

This study evaluated laboratory records of 543 patients who were suspected of autoimmune diseases and had ANA positive results by IFA from January 2012 to January 2016. Of these records, 359 (66.1%) showed anti-ENA positive by LIA. The

Probabilities of detection of anti-ENA antibodies for each ANA positive pattern with different fluorescence intensities were then analyzed.

SPECKLED AND HOMOGENEOUS PATTERNS AT HIGH INTENSITIES

For high fluorescence intensities from 3+ to 4+, ANA staining of fine speckled and homogeneous patterns, which are always present in mixed patterns, could yield anti-SSA and anti-Ro52 antibodies detection rate by 23.4%–35.9%. Moreover, a coarse speckled pattern of intensities 3+ to 4+ could also detect anti-SSA and anti-Ro52 antibodies by up to 50.0%–63.6%. These results were consistent with many previous studies which reported that high titers or high intensities of ANA speckled and homogeneous types demonstrated a high detection rate of anti-ENA antibodies.^{16–18}

Since this study was retrospective, without information on clinical symptoms, it should be useful for applying the provided data to mention some related previous studies. Agustinelli et al. and Mariz et al. reported that a high titer of a fine speckled pattern ($\geq 1:1,280$) could be found in a high percentage of patients with autoimmune rheumatic diseases (ARDs).^{5,6} Recently, Rodsaward et al. also demonstrated that fine-coarse speckled patterns had a significant association with anti-SSA and anti-Ro52 antibodies in juvenile SLE patients, and mixed patterns of homogeneous-fine speckled patterns also showed high percentage in SLE patients, especially in juvenile SLE patients.¹⁵

Therefore, the high fluorescence intensity of speckled and homogeneous patterns in the ANA screening test, which has a high probability of anti-SSA and anti-Ro52 antibodies detection, might be helpful in the diagnosis of ARDs, especially SLE.

Table 1. Frequencies and probabilities of each anti-ENA antibody detection in ANA patterns with fluorescence intensity 1+ to 4+

ANA pattern and anti-ENA antibody	Frequency (Percentage) Fluorescence intensity of ANA			
	1+	2+	3+	4+
Homogeneous	37	47	55	220
anti-RNP	2 (5.4)	7 (14.9)	12 (21.8)	39 (17.7)
anti-Sm	1 (2.7)	2 (4.3)	5 (9.1)	11 (5.0)
anti-SSA	5 (13.5)	12 (25.5)	14 (25.5)	79 (35.9)
anti-Ro52	2 (5.4)	10 (21.3)	16 (29.1)	66 (30.0)
anti-SSB	1 (2.7)	1 (2.1)	4 (7.3)	20 (9.1)
anti-Scl70	2 (5.4)	3 (6.4)	13 (23.6)	134 (60.9)
Fine speckle	80	53	47	165
anti-RNP	5 (6.3)	8 (15.1)	11 (23.4)	14 (8.5)
anti-Sm	3 (3.8)	2 (3.8)	3 (6.4)	3 (1.8)
anti-SSA	14 (17.5)	10 (18.9)	11 (23.4)	46 (27.9)
anti-Ro52	6 (7.5)	11 (20.8)	13 (27.7)	39 (23.6)
anti-SSB	2 (2.5)	1 (1.9)	3 (6.4)	11 (6.7)
anti-Scl70	2 (2.5)	3 (5.7)	13 (27.7)	124 (75.2)
Coarse speckle	18	15	16	77
anti-RNP		4 (26.7)	4 (25.0)	51 (66.2)
anti-Sm			3 (18.8)	26 (33.8)
anti-SSA	1 (5.6)	5 (33.3)	8 (50.0)	49 (63.6)
anti-Ro52	1 (5.6)	3 (20.0)	8 (50.0)	44 (57.1)
anti-SSB	1 (5.6)	1 (6.7)	1 (6.3)	16 (20.8)
anti-Scl70				9 (11.7)
Nucleolar	29	25	30	162
anti-RNP		2 (8.0)	8 (26.7)	20 (12.4)
anti-Sm	2 (6.9)		2 (6.7)	3 (1.9)
anti-SSA	1 (3.5)	3 (12.0)	10 (33.3)	43 (26.5)
anti-Ro52	2 (6.9)	4 (16.0)	9 (30.0)	38 (23.5)
anti-SSB		1 (4.0)	2 (6.7)	8 (4.9)
anti-Scl70	1 (3.5)	3 (12.0)	8 (26.7)	126 (77.8)

Table 1. (continued.)

ANA pattern and anti-ENA antibody	Frequency (Percentage)			
	Fluorescence intensity of ANA			
	1+	2+	3+	4+
Centromere		1	2	19
anti-RNP				
anti-Sm				
anti-SSA		1 (100)	1 (50)	5 (26.3)
anti-Ro52			1 (50)	5 (26.3)
anti-SSB				2 (10.5)
anti-Scl70				3 (15.8)

The presence of anti-SSA and anti-Ro52 antibodies as predicted by high intensity of speckled and homogeneous patterns is also supposed to be helpful in Sjögren's syndrome (SS) diagnosis, as the latest 2016 classification criteria for primary Sjögren's syndrome states that anti-SSA is the only specific antibody that indicates this disease when considered with clinical symptoms.^{21,22} For the anti-Ro52 antibody, it was also reported to have the highest positive predictive value (100%) for primary SS.²³ Recently, the presence of anti-Ro52 antibody was reported as one of the factors associated with primary SS patients who had renal involvement.²⁴

Moreover, the anti-Ro52 antibody could be found in several other autoimmune and non-autoimmune diseases such as SSc, RA, primary biliary cirrhosis (PBC) and idiopathic inflammatory myopathies (IIM).^{25,26} Therefore, the presence of speckled and homogeneous patterns at high intensities suggest the presence of anti-SSA and anti-Ro52 antibodies, which in turn might indicate SLE, primary SS, and other diseases.

COARSE SPECKLED PATTERN AT HIGH INTENSITIES

The Coarse speckled pattern of intensity 4+ showed an outstanding probability of anti-SSB antibody detection among all ANA patterns (20.8%). This appears to be comparable to the study of Yang et al., where speckled pattern and high fluorescence titer were found to suggest anti-SSA and anti-SSB antibodies detection with a high percentage. Clinically, anti-SSA and anti-SSB antibodies could be found with a higher rate in SLE and SS patients.²⁷ Moreover, Frodlund et al. reported that speckled and homogeneous mixed pattern had the highest anti-SSA and anti-SSB antibodies detection rate in SLE patients.²⁸

Obviously, the coarse speckled pattern at intensity 4+ in this study showed a high probability of anti-RNP antibody detection (66.2%). This is similar to the result of an autoantibody study of Rayes et al. on mixed connective tissue disease (MCTD) patients, where high titer of ANA speckled pattern and a high frequency of anti-RNP antibody were detected in

Table 2. Classification and probabilities

ANA pattern	Fluorescence intensity	Percentage	Anti-ENA antibody
Homogeneous	1+ and 2+	13.5 and 25.5	SSA
	1+ and 2+	5.4 and 21.3	Ro52
	2+ and 3+	14.9 and 21.8	RNP
	3+ to 4+	25.5-35.9	SSA and Ro52
Fine speckle	1+ and 2+	17.5 and 18.9	SSA
	1+ and 2+	7.5 and 20.8	Ro52
	2+ and 3+	15.1 and 23.4	RNP
	3+ to 4+	23.4-27.9	SSA and Ro52
Coarse speckle	1+	5.6	SSA, Ro52, and SSB
	2+	33.3 and 20.0	SSA and Ro52
	3+ to 4+	50.0-63.6	SSA and Ro52
	2+ and 3+	26.7 and 25.0	RNP
	4+	66.2	RNP
	4+	20.8	SSB
	3+ and 4+	18.8 and 33.8	Sm
Nucleolar, Fine speckle, Homogeneous	1+	3.5, 2.5, 5.4	Scl70
	2+	12.0, 5.7, 6.4	Scl70
	3+	26.7, 27.7, 23.6	Scl70
	4+	77.8, 75.2, 60.9	Scl70
Centromere	4+	10.5-26.3 and 15.8	SSA, Ro52, SSB and Scl70

all cases.²⁹ This means the two features tend to be found together, although the present study only found the same tendency in the coarse speckled pattern, but not in fine speckled. In other studies,

the anti-RNP antibody was reported to be detected with a higher rate in MCTD.^{30,31}

Moreover, the anti-Sm antibody could also be detected with relatively high probability in the

coarse speckled pattern of intensity 3+ (18.8%) and it even increased at intensity 4+ (33.8%). In a study by Rodsaward et al., the detection of anti-Sm and anti-RNP antibodies in the coarse speckled pattern was also reported associated with SLE patients.¹⁵ These two anti-ENA antibodies had high significance of classification between SLE and non-SLE.³² Their presence was also associated with a risk of lupus nephritis.³³⁻³⁵ For anti-Sm antibody, in particular, it was the only anti-ENA antibody included in the 2019 European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) classification criteria for SLE as an additive criterion.³⁶

FINE SPECKLED AND HOMOGENEOUS PATTERNS AT LOW INTENSITIES

At fluorescence intensity 1+ (titer 1:100), this study found that fine speckled and homogeneous patterns showed detection of the anti-SSA antibody with the highest probability among all specific antibodies (17.5% and 13.5%, respectively). This is similar to a study of Peen et al., where anti-SSA and anti-SSB antibodies were reported altogether to be predominantly detected at low intensities of speckled pattern, except that anti-SSB did not show up in the present study.¹⁶ Interestingly, in the present study, speckled and homogeneous patterns of intensity 2+ had increasing rate of anti-SSA, anti-Ro52, and anti-RNP antibodies detection compared with intensity 1+. The Low intensity of ANA might still be meaningful in the screening of some ARDs, as previous studies have reported that mothers who had babies with neonatal lupus erythematosus (NLE) or congenital heart block (CHB) could be

detected to have anti-SSA, anti-Ro52, anti-SSB, anti-RNP and anti-Sm antibodies.³⁷⁻⁴¹ Especially, Adelowo, et al. reported that a mother and her child, an NLE patient with complete heart block, who had moderate and low ANA titers (1:320 and 1:160, respectively) were detected to have anti-SSA autoantibody.³⁹ Moreover, Wisuthsarewong, et al. reported anti-SSA or anti-SSB positive in NLE patients who had ANA speckled pattern with moderate to high titer, but some cases with low titer (less than 1:100) could still be detected to have anti-SSA and anti-SSB antibodies as well.³⁷ Hence, as fine speckled and homogeneous patterns at low intensity 1+ are frequently found in routine laboratory, attention should still be paid on the screening results of patients who have clinical symptoms suspicious of autoimmune rheumatic diseases because there is still a low chance of presence of anti-ENA antibodies as shown in this study.

NUCLEOLAR PATTERN

High fluorescence intensity 4+ of the nucleolar pattern showed detection of the anti-Scl70 antibody with the highest probability (77.8%), while low intensity 1+ and 2+ still did with low probability. In previous studies, Bernstein et al. reported finding of nucleolar pattern with fairly high percentage in progressive systemic sclerosis (PSS) patients with at least 1+ intensities, at a dilution of 1:40.⁴² Nevertheless, presence of nucleolar pattern is not specific to SSc, as it has also been reported on other diseases.⁴³ However, anti-Scl70 is the specific antibody that had higher prevalence of detection with immunoblot assay in PSS than in other ARDs like SLE and MCTD.⁴⁴ In

addition, this study found a similar tendency of anti-Scl70 antibody detection from low to a high intensity of nucleolar, nuclear fine speckled and homogeneous patterns, which usually show up in mixed patterns. A similar result had been found in a study of Khan et al., in which patients who were detected to have the anti-Scl70 antibody using immunoblot assay showed a mixture of ANA homogeneous, speckled and nucleolar patterns.⁴³ These IFA staining patterns were part of the Scl70 pattern which was reported in a study of Dellavance et al. to be associated with anti-DNA topoisomerase I (anti-Scl70) antibodies.⁴⁵ And the Scl70 pattern has later been designated as an AC-29 pattern in the international consensus on antinuclear antibody patterns (ICAP) classification algorithm.⁴⁶

CENTROMERE PATTERN AT HIGH INTENSITIES

For intensity 4+ of centromere staining pattern, this study found 10.5%–26.3% of anti-SSA, anti-Ro52, anti-SSB, and anti-Scl70 antibodies detection. High frequency of anti-centromere detection and its association with CREST syndrome has been reported in a study of Bernstein, et al.⁴² Pakunpanya et al. reported that anti-centromere antibodies were detected with higher frequency in autoimmune patients but its titer could not discriminate SSc from other autoimmune diseases.⁴⁷ However, centromere pattern, anti-centromere and anti-Scl70 antibodies were included in ACR-EULAR classification criteria for SSc⁴⁸ and in preliminary criteria for the very early diagnosis of SSc.⁴⁹

LOW INTENSITY OF ANA PATTERNS

In many previous studies of ANA levels, Perilloux et al. reported that autoimmune patients had higher

ANA titers ($\geq 1:160$) than non-autoimmune patients.⁵⁰ Mariz et al and Agustinelli et al. reported that high titer of ANA test using Hep-2 IFA had a higher detection rate in patients with systemic autoimmune rheumatic diseases (SARDs), especially nuclear fine speckled pattern. However, the nuclear fine speckled pattern at low titers as 1:80 and 1:160 could also be found in SARD patients.^{5, 6} In 2019 EULAR/ACR classification criteria for SLE, ANA positive result at titer $\geq 1:80$ on HEp-2 cells was even approved as the entry criterion before applying additive clinical and immunologic criteria.³⁶ In the present study, IFA of ANA detection using HEp-20-10 cells at low fluorescence intensity 1+ (titer 1:100) of homogeneous, fine speckled, coarse speckled and nucleolar patterns still showed low probabilities of anti-ENA antibodies detection as in the data provided. Therefore, in diagnosing SARDs, low fluorescence intensities of ANA detection should not be overlooked, in which case clinical symptoms should also be considered as additional criteria. And as IFA relies on subjective judgment, one should take special caution when judging between negative and low intensity 1+, to avoid ruling out potential patients.

In conclusion, high levels of fluorescence intensity of ANA showed a high detection rate of anti-ENA antibodies, while low intensities could still suggest the detection of some kinds of anti-ENA antibodies. The probabilities reported in this study might be able to supply additional information for diagnosis when combined with the patient's clinical symptoms. In addition, it is important to be cautious in reporting the fluorescence intensity, as low intensities may still provide some hint on the presence of anti-ENA antibodies.

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ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To evaluate the access to palliative care in a hospitalized patients in tertiary care hospital.

METHODS

The retrospective chart review was conducted. All medical records of hospitalized patients were surveyed during January 2019. The survey excluded the medical records of pediatrics, obstetrics and postpartum care, psychiatric, and intensive care unit. When the condition of patients was met criterion of SPICT™(2017), their medical records were verified and reviewed.

RESULTS

There were 1,005 patients admitted to the hospital during the study period. Of these, 215 patients (21.4%) met the Gold Standard Framework of National Health Institute of Scotland, SPICT™ 2017 which should be eligible for palliative care; however, only 13 had consultation with for palliative care while 202 did not. The main primary disease in palliative cases was malignancy while 34.7% of those without consultation for palliative care did not have cancer.

CONCLUSION

Palliative care service in this tertiary care hospital in Thailand was relatively low. A larger study investigating the rate of access to the system to represent Thai palliative care is needed.

INTRODUCTION

The leading causes of death in Thailand are malignancy, AIDS, traffic accident, and cardiovascular disease respectively and the aged population in Thailand also has been increasing.¹ World health organization (WHO) estimates 66% of the world population would be more non-communicable disease and need palliative care.² Palliative care helps to prevent medical futility, decreases the suffering of patients and family and burden of disease. The health care cost in the last year of life in the United States is the highest of overall cost, 26–30%.^{3,4} In Thailand, similar to the US, the health care cost in the last year of life is about 21%. Most of the cost is transportation cost to access analgesic agents at a tertiary hospital; it is about 31-86% of all cost, which causes a financial burden on the patient.⁵ On the other hand, palliative care decreases endotracheal tube intubation and saves the cost of hospitalization 16,669 Baths per person.⁶

By using a criterion of Gold Standard Framework of the United Kingdom to identify palliative patient, the point-prevalence of palliative cases at acute care hospital in each country was 13% in France,⁷ 9.4% in Belgium,⁸ 16.6% in South Africa,⁹ 19.8% in New Zealand,¹⁰ and 36% in the United Kingdom.¹¹ At Songkhanagarind Hospital, a tertiary care hospital in Thailand, the rate of access to the palliative care using the diagnosis code according to the International Statistical Classification of Diseases and Related Health Problems 10th (ICD-10) from medical records between 2012 and 2016 was as low as 0.2%.¹² This is the example of less acknowledgement of palliative care, inadequate palliative care

professionals and poor access to palliative care service in Thailand. The study aimed to evaluate the rate of access to palliative care in a large public tertiary hospital in northeastern Thailand to portray an access to palliative care in Thailand.

METHODS

DESIGN AND PATIENTS

A retrospective medical record review was conducted at Maharat Nakhon Ratchasima Hospital, Thailand. It is the largest tertiary care hospital under the Ministry of Public Health in the country. All medical records of hospitalized patients in the last week of January 2019 were reviewed. Those who met the criterion of Gold Standard Framework of National Health Institute of Scotland, SPICTM 2017, their data would be further collected and analyzed. This study excluded the medical records from the intensive care unit (ICU), pediatric ward, obstetric and post-partum ward, and the psychiatric ward. The collectors were palliative doctors, internists and family medicine residents, who trained and well understood in the SPICTM.

DATA COLLECTION

The collected data included general characteristics such as age, gender, health insurance and admission department. The conditions and given treatments of the patients were documented in detail such as primary disease, comorbidity, unexpected visit or admission, WHO performance status, cognitive function, physical symptoms (e.g., pain, dyspnea), pain medications, consultations, medical procedure, treatment during hospitalization, advance care plan and length of hospital stay.

Table 1. Characteristics of the patients.

Characteristic	Consultation for palliative care (N=13)	No Consultation for palliative care (N=202)	P Value
Female–no. (%)	8 (62)	100 (49.5)	0.400
Age–yr	58.5±14.2	59.2±16.0	0.865
Age group–no. (%)			0.177
<60 years	9 (69)	107 (53.0)	
60–70 years	0	43 (21.3)	
>70 years	4 (31)	52 (25.7)	
Health insurance scheme–no. (%)			0.831
Universal coverage	10 (77)	168 (83.2)	
Civil servant medical benefit scheme	2 (15)	21 (10.4)	
Social security scheme	1 (8)	13 (6.4)	
Department–no. (%)			0.046
Surgery	1 (8)	71 (35.2)	
Medicine	8 (62)	52 (25.7)	
Gynecology	2 (15)	30 (14.9)	
Orthopaedics	2 (15)	28 (13.9)	
Ears, Nose and Throat	0	21 (10.4)	
Cancer as primary diagnosis–no. (%)	13 (100)	132 (65.4)	0.000
Number of unplanned visit within 6 months	1.2±0.3	1.6±0.1	0.535
Performance status–no. (%)			0.228
Normal	4 (31)	82 (40.6)	
Light activity	1 (8)	31 (15.4)	
<50% on bed	1 (8)	13 (6.4)	
>50% on bed	4 (31)	20 (9.9)	
On bed all the time	3 (23)	56 (27.7)	
Cognitive status–no. (%)			0.530
Impairment	3 (23)	26 (12.9)	
No response	0	4 (2.0)	

Plus minus values are mean±SD

STATISTICAL ANALYSIS

The data were summarized using descriptive statistics in terms of number, percentage, mean and standard deviation. For inferential statistics, chi-square, Fisher's exact, t-test and logistic regression were used to analyze comparing between groups of consultation and no consultation for palliative care.

RESULTS

There were 1,005 patients admitted to the hospital during the study period. Of these, 215 patients (21.4%) met the Gold Standard Framework of National Health Institute of Scotland, SPICT™ 2017 which should be eligible for palliative care; however, only 13 had consultation with for palliative care while 202 did not.

Of those 215, their mean age was 59.2 years with the relative equal number of men and women. Most of them were admitted to the Department of Surgery (33%), Internal Medicine (27.9%), and Gynecology (14.9%). Two-third (67.4%) were under the universal coverage health scheme. About 60% could do the daily living activities independently. There was only 13 (6.1%) had consulted for palliative care specialists (Table 1). The main primary disease in palliative cases was malignancy (67.4%); gastrointestinal cancer (17.7%), head and neck cancer (13%), gynecologic cancer (12.1%), hematologic cancer (7%), and lung cancer (6.5%) (Table 2).

Of 13 with consultation for palliative care, they all had cancer (Table 2), while 34.7% of those without consultation for palliative care did not have cancer; dementia and frailty (31.4%), neurological

Table 2. Types of cancer

Type of cancer	Consultation for palliative care (N=13)	No Consultation for palliative care (N=132)
Gastrointestine	0	38
Head&Neck	1	27
Gynecology	2	24
Blood	2	13
Lung	6	8
Breast	1	5
Liver	0	4
Uro-genital system	0	8
Others	1	5

disease and head injury (25.7%), kidney disease (18.6%), stroke (17.1%), cardiovascular disease (4.3%), pulmonary disease (4.3%) and liver disease (1.4%).

The palliative patients reported having unsatisfied symptoms 50.2%, pain 58.6%, dyspnea 35.8%, and gastrointestinal disturbance 32.6% (Table 3). The medical procedure and device, which patients received during hospitalization, were antibiotic administration (48.8%), nasogastric tube insertion (31.2%), chemotherapy (29.3%), endotracheal tube intubation (20.0%) and on ventilator (18.1%) respectively. Unfortunately, 42.8% of palliative patients had not been prescribed any analgesic for their pain. Doctors usually prescribed non-opioids (33.0%), weak opioids (25.1%), strong opioids (19.5%) and other medications (10.7%) for relieving pain. Only 16.3% had an advance care plan. The mean length of stay was 16.1 days.

Table 3. Symptoms and treatments in palliative patients.

Symptom and treatment	Consultation for palliative care (N=13)	No Consultation for palliative care (N=202)	P Value
Symptom			
Pain	12 (92)	114 (56.4)	0.008
Dyspnea	7 (54)	70 (34.7)	0.338
Gastrointestinal symptom	6 (46)	64 (31.7)	0.464
Analgesic treatment			
No analgesics	1 (8)	91 (45.1)	0.008
Non opioids	4 (31)	67 (33.2)	1.000
Weak opioids	7 (54)	47 (23.3)	0.021
Strong opioids	5 (38)	37 (18.3)	0.278
Other medications	2 (15)	21 (10.4)	0.165
Symptom management	11 (85)	97 (48.0)	0.108
Advance care plan	8 (62)	27 (13.4)	0.000
Medical procedure			
Nasogastric tube insertion	3 (23)	64 (31.7)	0.759
Endotracheal tube intubation	1 (8)	42 (20.79)	0.473
Ventilator	1 (8)	38 (18.81)	0.471
Inotropic agent	1 (8)	11 (5.45)	0.537
Total parenteral nutrition/blenderized diet	4 (31)	25 (12.4)	0.080
Antibiotics	7 (54)	98 (48.5)	0.780
Chemotherapy	2 (15)	61 (30.2)	0.354
Palliative surgery	2 (15)	17 (8.4)	0.322
Radiotherapy	2 (15)	32 (15.8)	1.000
Renal replacement therapy	0	12 (5.9)	1.000
Length of stay–days	11.5 \pm (9.3)	16.4 \pm 29.8	0.556

Plus minus values are mean \pm SD

Table 4. Given treatments and procedures

Procedure	Consultation for palliative care (N=12)	No Consultation for palliative care (N=114)	P Value
Pain			
Pain record	8 (67)	67 (58.8)	0.784
No analgesics	1 (8)	17 (14.9)	1.000
Strong Opioids	4 (33)	35 (30.7)	1.000
Dyspnea			
Endotracheal tube intubation	1 (14)	31 (44.3)	0.229
Ventilator	1 (14)	30 (42.9)	0.231
Strong opioids	4 (57)	13 (18.6)	0.039

Nearly three quarters of them stayed in the hospital less than 2 weeks. Comparing between those with and without consultation for palliative care, pain was more common in the former group ($P=0.008$) and analgesic treatment was also more common in the former group; weak opioids prescription ($P=0.021$).

Furthermore, the subgroup analysis was done in aspect of pain and dyspnea comparing between those with and without consultation for palliative care (Table 4), only strong opioids for relieving dyspnea were more common in the former group ($P=0.039$).

DISCUSSION

The rate those eligible for palliative care in Maharat Nakhonratchasima Hospital was found to be 21.4% in our study. However, very few were sent for palliative care consultation. The rate was relatively similar to that of the previous study (19.6%) at Karunrak palliative care center in another tertiary hospital in northeastern Thailand.¹³ The limitation of the present study was that the Thai

prevalence regarding palliative care was still not be able to identify due to the fact that we conducted the study in only one hospital. Thus, the figure cannot be comparable with that found in other countries; ranging from around 10% to 36% in France, Belgium, South Africa, New Zealand, and the United Kingdom.⁷⁻¹² The access rate to palliative care was found to be only 6.1%, comparing to that of the previous studies at Karunrak center (17.3%)¹⁴ and at Songkhanagarind (0.2%).¹²

In the present study, the common symptoms in palliative cases were as same as the other studies including pain, dyspnea and GI disturbance.^{13,15} The proper treatment especially pain and dyspnea control, advance care plan was less than the previous studies.^{12,14} However, the patients who received palliative care showed less to have medical procedures, more pain control, having more opportunity to discuss their advance care plan with health care professionals, even though there was no statistically significant difference, but these were relevant with other studies about less medical futility when using

palliative care approach.¹⁶⁻¹⁷ This study excluded medical records from ICU and pediatric ward and the period of the study was only one week, a larger and more representative study for Thai situation regarding palliative care should be conducted.

In conclusion, access to palliative care services in this tertiary care hospital in northeastern

Thailand showed less accessibility. Inadequate palliative care delivery especially symptom management and discussing advance care plan were also observed. A larger and longer survey should be conducted.

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"I shall either find a way or make one"

-Hannibal Barca

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