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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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Our journal is an opened access international journal devoted to peer-reviewed contributions dealing with clinical medicine and medical education from experimental to clinical aspects. Our journal publishes only high quality research, review and other types of original articles, technical and clinical reports every two months. Reviews of various global and Asian aspects will be solicited. Innovation or epidemiological aspects as well as health system research will be addressed. Rigorous systematic review and neglected tropical diseases are our priority

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message from the editor

This issue is going to be the last for our 43rd volume. Of course, the last but not least, in this issue, you will find two original articles regarding laboratory investigation, one is very innovative for diagnosis of the cervical squamous cell carcinoma and another is about using the expired CLO test for diagnosis of H. pylori infection which the knowledge can be transfer to the resource-limited setting. We also have two systematic reviews in this issue as well. These are from doctors once there were medical students at Khon Kaen Medical Education Center, Thailand. Aside from new information they generate, this is also the evidence proving the ability of medical students to synthesize knowledge and make a contribution to medical society.

Thammasorn Jeeraaumponwat, M.D., Ph.D.
Editor-in-Chief of The Clinical Academia

submission

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Our issues of each volume will be published online
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All accepted articles are classified into two main categories;
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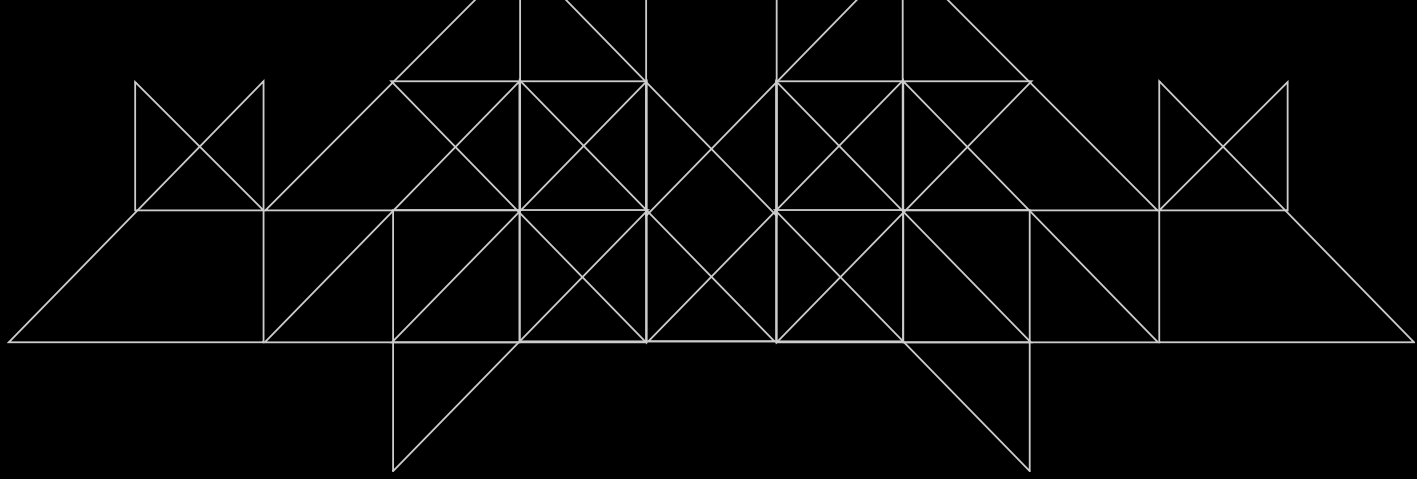
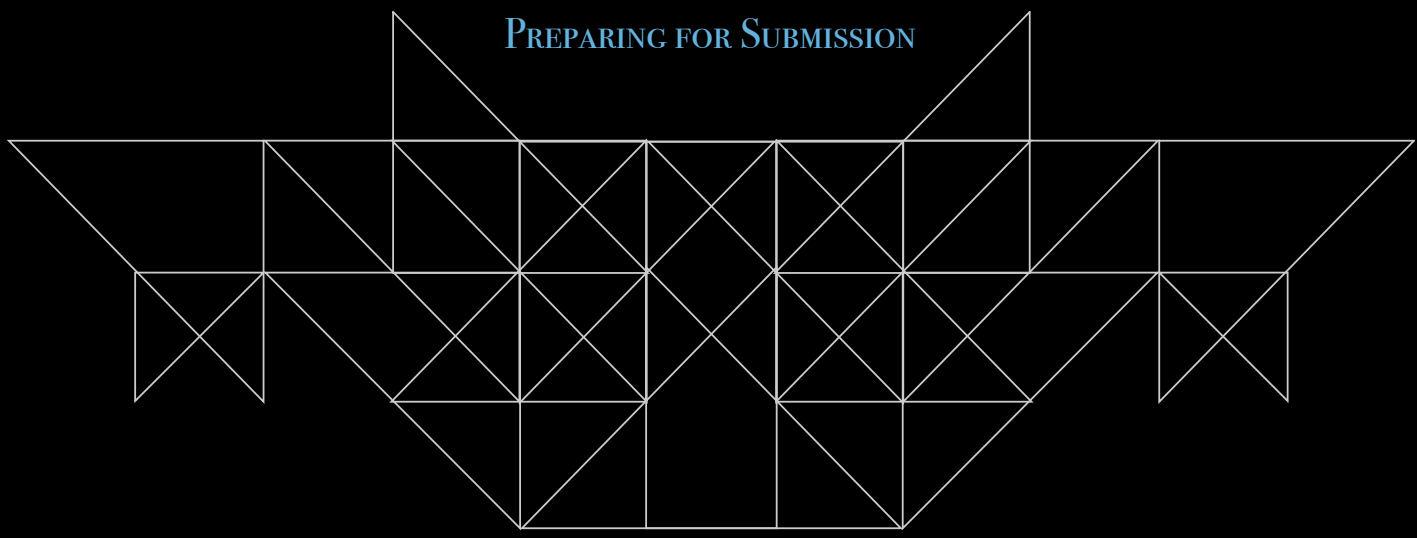
Contents



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, select¬ing, 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

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

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.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

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registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository, authors should state at the end of the abstract the data set name, repository name and number.

c. Introduction

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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The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

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Specify the study's main and secondary objectives–usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

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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.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, 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."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

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It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your finings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

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.

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Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

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Serum YKL-40 as a diagnostic biomarker for cervical squamous cell carcinoma

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To assess the diagnostic properties of serum YKL-40 cervical squamous cell carcinomas (SCC) diagnosis.

METHODS

Blood samples were collected from 56 patients who attended the Obstetrics and Gynecology Clinic at Khon Kaen Hospital, Thailand. Serum YKL-40 levels were detected using enzyme-linked immunosorbent (ELISA) assay in 56 patients with SCC and in 40 healthy women donors as a control.

RESULTS

Serum YKL-40 was significant higher in those with SCC (median, 63.5 ng/ml; interquartile range (IQR), 23 to 309) compared to the controls (median, 20.8 ng/ml; IQR, 3 to 97). At the cut-off value of 30.5 ng/ml of serum YKL-40, area under the curve of the receiver operator characteristic curve was 0.958 (95% confidence interval (CI), 0.916 to 0.999) for SCC diagnosis with 90.6% accuracy, 94.6% sensitivity, 87.5% specificity. No association of high serum YKL-40 level and overall survival time was found.

CONCLUSION

The study suggest the diagnostic potential of serum YKL-40 for SCC diagnosis.

INTRODUCTION

Cervical cancer was accounted for one-third of women cancer worldwide between 2014 and 2018.[1-2] Although most cervical cancer patients undergo standard treatment related to their tumor stages, some are resistant and develop recurrence and metastasis afterward.[3] Some glycoproteins are found to be associated with treatment response.[3-6] For instance, YKL-40, a type of glycoprotein, acts as an angiogenic factor is found to be associated with cancer metastasis and it is linked to clinical applications as a prognostic marker and targeted therapy for cervical cancer.[7] It is a mammalian chitinase-like protein with no chitinase activity, and is generally known as chitinase 3 like 1 (CHI3L1) or human cartilage glycoprotein-39.[8] It is found in various cell types such as synoviocytes, chondrocytes, macrophages,
neutrophils, and vascular smooth muscle cells.[8-10] The increase of serum YKL-40 is reported in many solid tumors such as breast cancer, colorectal cancer, lung cancer, ovarian cancer and is associated with short disease-free survival time.[11-17] However, the evidence for its linkage to cervical squamous cell carcinoma (SCC) is still scarce. Hence, the aim of this study is to identify the diagnostic properties of serum YKL-40 for cervical SCC diagnosis.

METHODS

STUDY DESIGN AND ETHICAL APPROVAL

This was a cross-sectional diagnostic study with follow up of a component of the cohort of patients with cervical SCC to identify their free survival time. Khon Kaen Hospital Institutional Review Board in Human Research approved the present study protocol with KE 58029. Written informed consent was attained from all patients. Blood samples were derived from 56 cervical cancer patients who attended the Obstetrics and Gynecology Clinic at Khon Kaen Hospital, Thailand. All were new firstly diagnosed of cervical SCC at the hospital. They were all histopathologically confirmed as SCC and were staged according to The International Federation of Gynecology and Obstetrics (FIGO) staging. Sera were separated from collected blood by centrifugation for 10 min with speed of 3,000 rounds per minute (rpm) at room temperature, and then stored in aliquots at -20°C until the enzyme-linked immunosorbent (ELISA) assay. Sera of 40 healthy female donors with negative human immunodeficiency virus (HIV) and hepatitis B virus (HBV) were provided by Blood Bank, Khon Kaen Hospital as the control. Characteristics of SCC patients are shown in Table 1.

SERUM YKL-40 ASSAY

Serum YKL-40 was determined in duplicate by a commercial two-site, sandwich ELISA method (Boster's biological technology, Pleasanton, California, the United States of America) according to the manufacturer's recommendations. The limit of detection of this assay was 10 pg/ml.

DIAGNOSIS AND SURVIVAL DATA

The diagnosis of cervical SCC was confirmed histopathologically by the pathologist at Khon Kaen Hospital. Their survi

STATISTICAL ANALYSIS

To test the normality of data, Shapiro-Wilk was applied. The difference of each parameter between two groups was analyzed using Mann-Whitney U test. Scatter plot was produced for visualizing the differences between groups. The performance of a

Table 1. Characteristics of the patients with cervical squamous cell carcinoma

Characteristic	Values (n=56)
Age-years	
Median	54
Interquartile range	41-66
FIGO stage-no. (%)	
IIA	6 (11)
IIB	33 (59)
IIIA	2 (3)
IIIB	14 (25)
IVB	1 (2)
Histological differentiation-no. (%)	
Well	6 (11)
Moderately	28 (50)
Poorly	22 (39)
No differentiation report	1 (2)

FIGO, International Federation of Gynecology and Obstetrics.

diagnostic test was evaluated using receiver operator characteristic (ROC) curve and area under its curve together with sensitivities and specificities from various cut-off points. The selected cut-off value was determined using Youden's Index. To estimate the probability of survival time, Kaplan-Meier was performed. $P<0.05$ was considered statistically significant. The SPSS Ver. 23 statistical programs and graph with Graph Pad Prism5 software were applied for all statistical analysis.

RESULTS

PATIENTS

In the present study, we collected sera from 56 histopathological confirm of cervical squamous cell carcinoma. Most of them were age more than 50 years old. More than half were in Stage IIB with moderately or poorly differentiation (Table 1).

SERUM YKL-40 AS A DIAGNOSTIC MARKER

The medians of YKL-40 in healthy controls and SCC patients were 20.8 ng/ml (IQR, 3 to 97) and 63.5 ng/ml (IQR, 23 to 309), respectively, and the latter was higher significantly ($P<0.0001$; Mann-Whitney test) (Figure 1, Panel A).

From various cut-off values, the area under the ROC curve (AUC) was 0.958 (95% confidence interval (CI), 0.916 to 0.999) (Figure 1, Panel B). From Youden's Index, the selected cut-off value was 30.5 ng/ml. At this point, the sensitivity and specificity of YKL-40 for cervical SCC diagnosis were 94.6 and 87.5%, respectively. Moreover, the accuracy, negative predictive value (NPV) and positive predictive value (PPV) were 90.6%, 91.9% and 89.9%, respectively, and they are all shown in Table 2.

SERUM YKL-40 AND SURVIVAL TIME

From Figure 2, more than half of cases died at the end of the follow-up period. Fifty-four out of 56 cases of cervical SCC, one was lost to follow-up and another died within the first four weeks, were divided into low and high YKL-40 level regarding the median of its median, 63.5 ng/ml. No association of serum YKL-40 levels with overall survival time were observed ($P=0.986$).

DISCUSSION

YKL-40 at the cut-off value of 30.5 ng/ml could be used as a diagnostic marker with high sensitivity and specificity, 94.6% and 87.5%, respectively, with the AUC of 0.958. While the previous study used the cut-off value of 92.2 ng/ml and the result showed that the AUC, specificity, and sensitivity were 0.898, 89% and 75%, respectively.[11] However, these were merely the findings to assess the YKL-40 for diagnosis of the cervical adenocarcinoma.

The increase of serum YKL-40 level was reported in many solid tumors such as breast cancer, colorectal cancer, lung cancer, ovarian cancer, glioblastoma and cervical cancer which was associated with short disease free survival time.[11-17] Furthermore, the up-regulated of YKL-40 was reported in advanced cervical cancers.[6] Single nucleotide polymorphisms of YKL-40 are associated with overall survival and recurrence of cervical cancer patients.[18] The study demonstrated that serum YKL-40 between healthy controls and SCC patients was significantly different, which agreed with the previous study.[11] It also showed that serum YKL-40 was correlated with disease free survival indicating the usefulness as an unfavorable prognostic marker[11] while Kaplan-Meier analysis in the present study didn't show any correlation between serum YKL-40 level and OS. Hence, this may be due to the small number of cases included in our study.

In conclusion, the present study found that serum YKL-40 was relatively higher in those with cervical SCC than that of healthy controls. It also found to have high sensitivity and specificity at the cut-off value of 30.5 ng/m. However, its association with overall survival was not observed. Further studies with a larger sample size is also required before the wild application of serum YKL-40 in terms of a screening and diagnostic marker for cervical SCC.

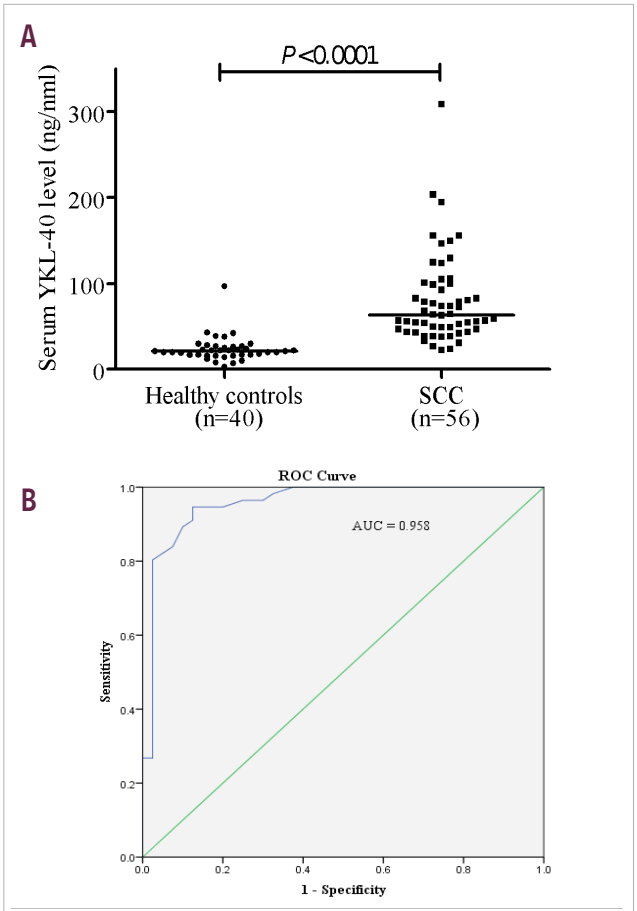

Figure 1. Scatter plot and receiver operator characteristic curve.

Panel A, median line graphics of serum YKL-40 levels in healthy controls and those with cervical squamous cell carcinoma. Horizontal bars indicate the medians of YKL-40 level; Panel B, receiver operator characteristic curve of YKL-40 levels for cervical squamous cell carcinoma diagnosis.

Table 2. Sensitivities and specificities at different cut-off values of the serum YKL-40 for cervical SCC diagnosis

Cut-off value	Sensitivity	Specificity
23.50	98.2	67.5
24.50	96.4	70
25.50	96.4	72.5
26.50	96.4	75
27.50	94.6	80
29.00	94.6	82.5
30.50	94.6	87.5
32.00	92.9	87.5
35.50	91.1	87.5
38.50	89.3	90
40.50	83.9	92.5
42.50	82.1	95
43.50	80.4	97.5
45.50	76.8	97.5
48.00	73.2	97.5

ACKNOWLEDGMENTS & DECLARATION

First and foremost, we would like to thank all clinicians, nurses and technical staff at the departments of Obstetrics and Gynecology, and Clinical Pathology of Khon Kaen Hospital for their tremendous work on specimen collection, specimen preparation and laboratory test as well as clinical data.

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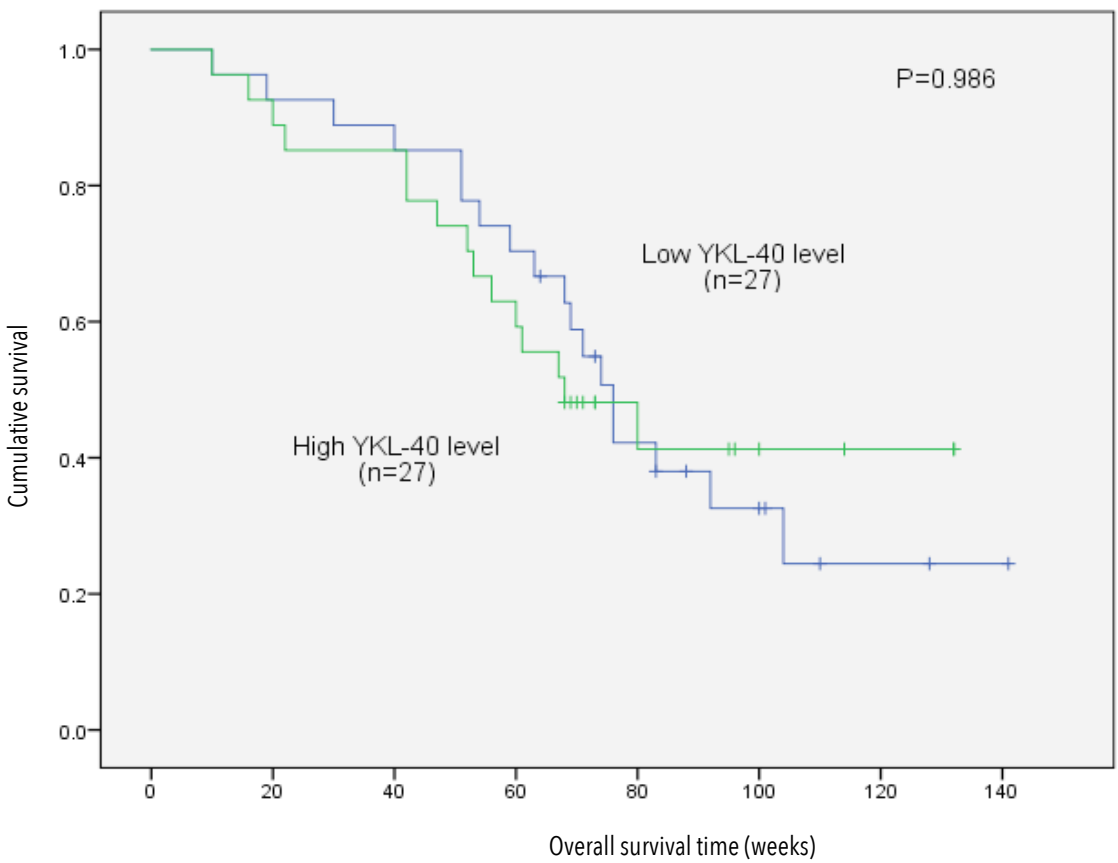

Figure 2. Kaplan-Meier survival curve
Survival curve of low vs. high serum YKL-40 levels at 63.5 ng/ml as a cut-off value.

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Diagnostic properties of expired and reused negative expired ASAN® Helicobacter Test

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To evaluate the efficacy of expired ASAN® Helicobacter Test (CLO test) and a color-changing property of negative expired CLO test.

METHODS

This cross-sectional diagnostic study was conducted at Kalasin Hospital, Thailand. The negative expired CLO test pellets were obtained from the patients undergoing endoscopy from December 2017 to March 2018. Gastric mucosa from positive expired CLO test pellets was reinserted into the negative expired CLO test pellets. Color changing, the interval after expiration and the interval from the first use were recorded. Pathological examination was used as a gold standard.

RESULTS

We test the diagnostic property of 20 negative reused expired CLO test pellets. It yielded 92.9% sensitivity, 76.5%s specificity, 62.0% positive predictive value, 96% negative predictive value, and 81.3% accuracy. All test pellets had a color changing from yellow to magenta within 1 to 4 hours after reinsertion with the positive CLO test gastric mucosa. The median interval from the first use was 15 days (interquartile range (IQR), 5 to 28), the median expired interval was 139 days (IQR, 9 to 191).

CONCLUSION

This was the first study that tried to confirm the diagnostic property of the expired CLO test. Its color-changing property of negative expired CLO test remained with high sensitivity and high negative predictive value.

INTRODUCTION

Since 1985 by Barry Marshall and Robyn Warren, *Helicobacter pylori* (HP) has been recognized as the causation of dyspepsia.[1] It is the most common gastrointestinal problem in general practice and contributes for 23.7% indication for the esophagogastroduodenoscopy (EGD).[2-4] Campylobacter-like organism (CLO) test is one of the common tests for diagnosis of HP with 80-100% of sensitivity and 97-99% specificity.[5-7] Theoretically, unchanged substrate in a negative expired CLO test can change its color from yellow to magenta after insertion of the new HP infected gastric mucosa which the sensitivity ranging from 80 to 95%, and the accuracy is found to be as high as 98.3%.[8-13] However, the previous studies never mention the accuracy of expired CLO test which occasionally occurs in the settings of a limited resource. Thus, the aim of this study is to test the accuracy of expired CLO test for the diagnosis of HP infection and assess the capability of color change of negative expired CLO test.

METHODS

STUDY DESIGN AND OVERSIGHT

This is a cross-sectional diagnostic test. This study was conducted at Endoscopic Unit, Kalasin Hospital, Northeastern Thailand. The area had the highest prevalence of HP in the country, 60.6%, whereas 46.9% in Northern, 39.0% in Central, 14.4% in Southern Thailand.[14]

PATIENTS

The inclusion criteria were patients 18 years of age or older undergoing endoscopy regardless

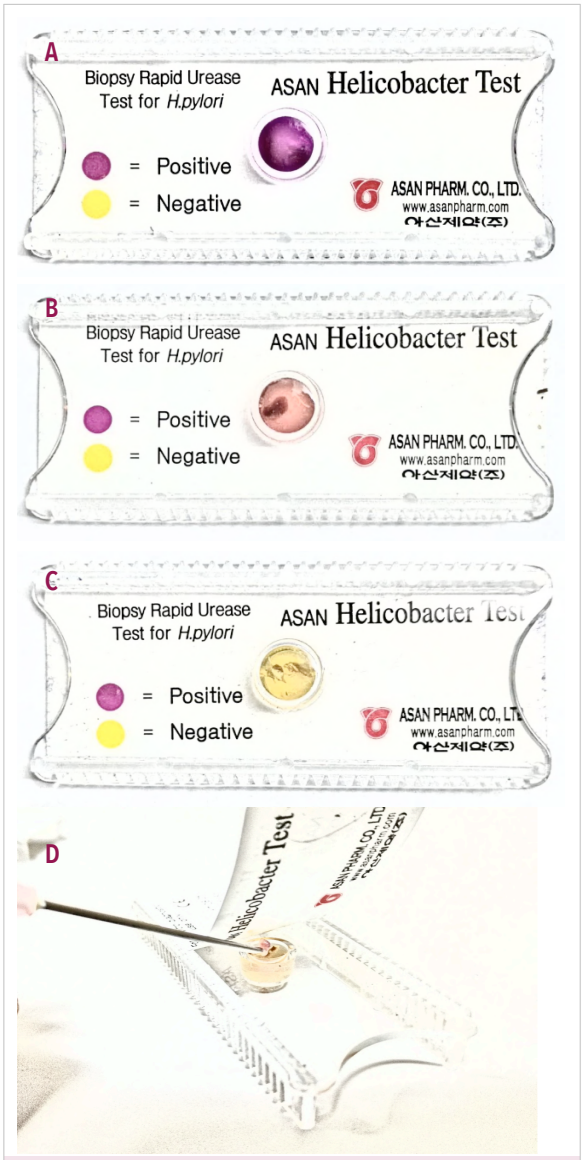

Figure 1. ASAN® Helicobacter Test
Panel A, magenta or positive CLO test; Panel B, equivocal color; and Panel C, yellow or negative CLO test; and Panel D, insertion technique

indications from December 2017 to March 2018, although the common indications were upper gastrointestinal bleeding (34%), chronic dyspepsia (32%) and the screening for esophageal varices (15%). The author biopsied 4 pieces of gastric

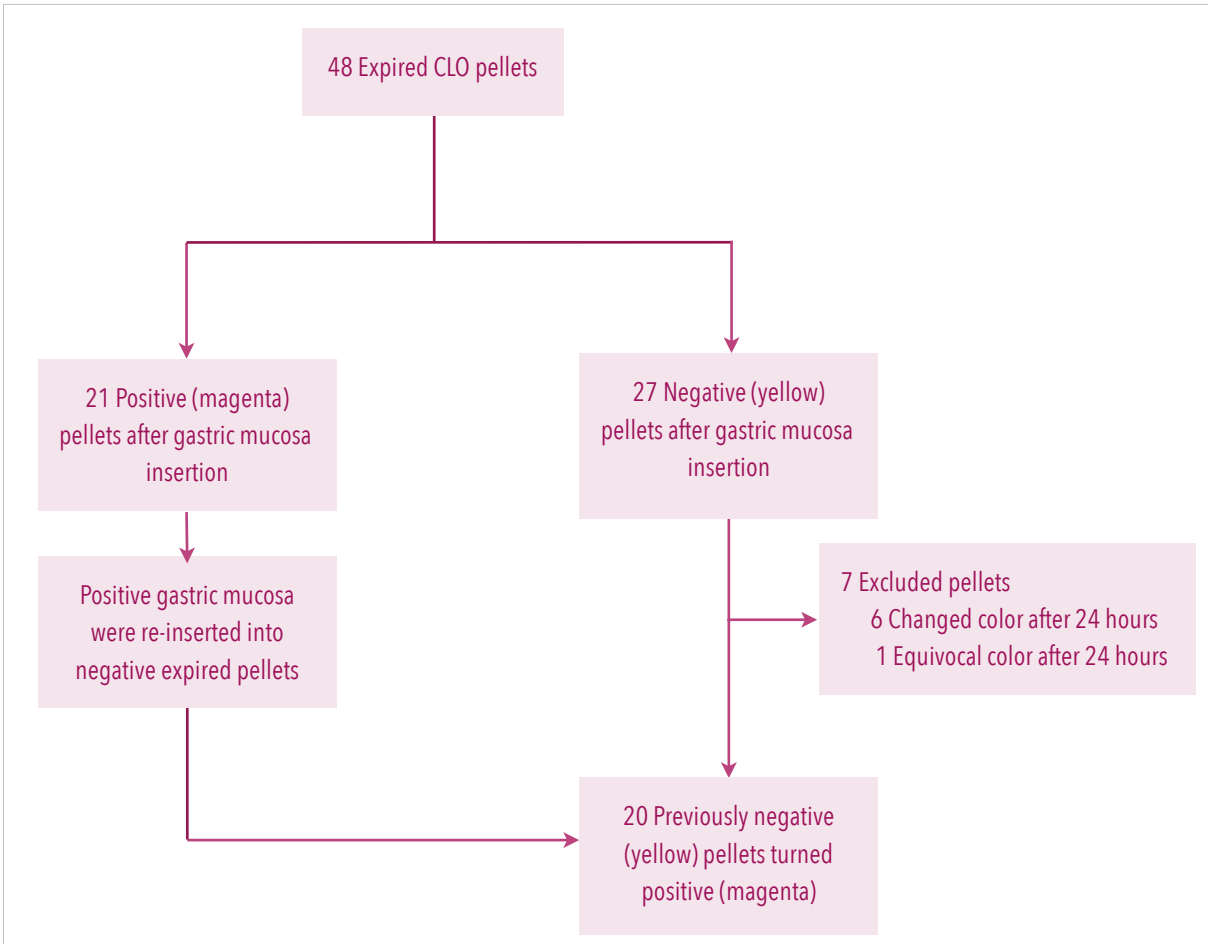

Figure 2. Flow of the study

mucosa without blood contamination, 2 pieces from antrum and 2 pieces from the gastric body, each pair of the antrum and gastric body mucosa was used for pathological examination and CLO test. Whenever expired CLO test pellets turned positive (Figure 1), the author picked up one piece of positive gastric mucosa and inserted into the negative expired CLO test pellets immediately without removing the old gastric mucosa. Color changing, an interval between insertion time and color changing time were recorded. All CLO test pellets were left at room temperature for observation of up to 24 hours.

REUSED CLO TEST® PALLETS

The author collected reused negative expired CLO test pellets (ASAN® pharm. Co., Seoul, Korea) which stored at room temperature at the hospital after the first use (average temperature from December 2017 to March 2018 was 15 to 35 degrees Celsius). The interval from the first use and reuse were recorded. All test pellets were expired, pale or deep yellow (negative test) and they were not damaged or shrinkage. The magenta color pellets (positive test), equivocal color pellets and the pellets that returned magenta after 24 hours were not included in this study (Figure 2).

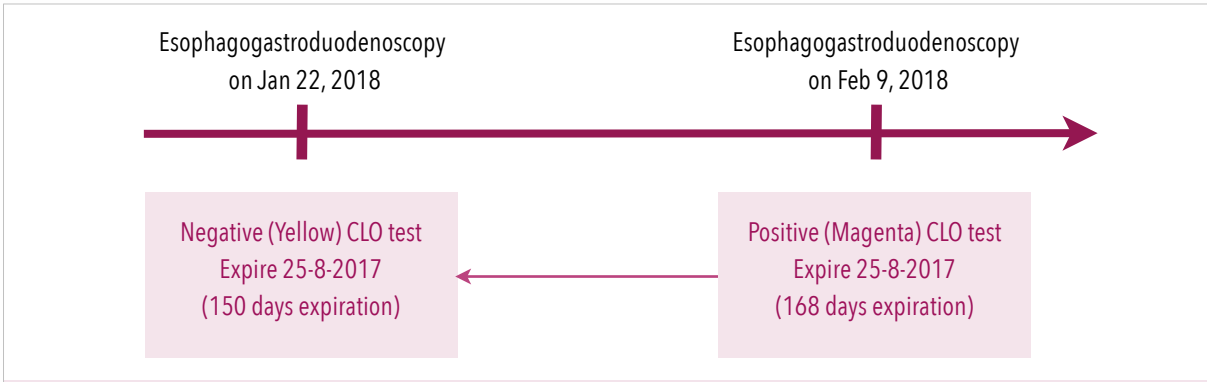

Figure 3. Example of reused CLO test® pallets
In this case, the Esophagogastroduodenoscopy was performed on Jan 22, 2018, after the insertion of gastric mucosa, the test expired reused test was negative. The author still kept this negative pallet. Later on Feb 9, 2018, with the new patient, another reused expired pallet turned positive after gastric mucosa insertion. The positive tissue was, then, re-inserted into the previous negative pallet immediately.

STATISTICAL ANALYSIS

The validity of the reused expired CLO test was interpreted regarding sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) together with accuracy using the pathological examination as a gold standard

RESULTS

Table 1 shows characteristics of the patients contributing their gastric mucosa in the present study. A total of 48 expired pellets were included in this study for the evaluating diagnostic validity of the reused expired CLO test. Primarily, 21 expired CLO test pellets turned positive (magenta) and 27 expired CLO test pellets were still negative (yellow), however, 7 negative expired pellets were excluded due to 6 pellets returned magenta after 24 hours, 1 pellet had equivocal color. Later, the rest 20 negative expired pellets changed color from yellow to magenta within 1 to 4 hours after re-insertion of the positive CLO test gastric mucosa (Figure 3). The median interval from the first use to reuse was 15 days (interquartile range (IQR), 5 to 28 days), the median interval from expiration to reuse was 139 days (IQR, 9 to 91 days). HP infection was confirmed by pathological examination, only 1 from 27 negative expired CLO test was reported HP infection by the pathologist (false negative). All 48 expired CLO test pellets had 92.9% sensitivity (95% confidence interval (CI), 66 to 99), 76.5% specificity (95% CI, 59 to 89), 62% PPV (95% CI, 47 to 75), 96% NPV (95% CI, 79 to 0.99), and 81.3% accuracy (95% CI, 67 to 91) (Table 2).

DISCUSSION

An unchanged substrate in negative expired CLO test pellets can change its color from yellow to magenta as confirmed by previous studies.[8-13] However, expired pellets may be a loss the ability

Table 1. Characteristics of the patients

Characteristic	
Age-yr	55±13
Male sex (%)	46
Indication (%)	
Dyspepsia	32
Gastrointestinal bleeding	28
Anemia with occult blood	6
Screening for esophageal varices	15
Others	19

Plus minus values are means plus minus SD

to change color due to the expiration of substrate i.e., urea, phenol red, buffers, and bacteriostatic agent. To the best of our knowledge, this is the first study to confirm the efficacy of expired CLO test. As a result, expired CLO test has very high sensitivity and NPV. Moreover, the ability to change the color of negative expired CLO test pellets were confirmed. The possibility of color changing in negative expired CLO test pellets could be caused by either urease in HP infected gastric mucosa or ammonia that already presented in the substrate. The maximum reused interval in this study was 28 days.

Table 2. Sensitivity and specificity of expired CLO test

Test result	Pathological confirmation of *Helicobacter pylori*	No pathological confirmation of *Helicobacter pylori*
Positive	13	8
Negative	1	26

In the region that has a higher prevalence of HP infection, the CLO test usage can cause substantial expense to the hospital with limited resources. For instance, at Kalasin Hospital, CLO test usage estimates to be around 40 to 50 pellets monthly, thus reused CLO test can save up to nearly 70,000 THB annually (116 THB per pellet). Both expired and negative expired CLO test pellets have greater benefit for environment and economy. The negative expired CLO test can be safely reused with good infectious control such as package sealing for prevention of contamination, however, some negative expired CLO test kept in room temperature had an unpleasant odor when reopening. The limitations of this study were a small sample size which causes a wide 95% confidence interval. Comparison between expired and unexpired CLO test pellets should be confirmed with the future larger diagnostic study.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: Non-financial associations that may be relevant or seen as relevant to the submitted manuscript.
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Efficacy of single dose compared with extended dose itraconazole in pityriasis versicolor: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the efficacies of a single dose and the extended dose of itraconazole to identify the optimal dose of the drug for treating extensive Pityriasis versicolor (PV).

METHODS

Three authors independently searched electronic databases including the Cochrane Library, Pubmed, Scopus, and Trip Database. The other resources that we searched included google scholar and hand searching was also performed. We individually screened titles and abstracts for randomized controlled trials (RCTs) carried out between 1950 and 2015 comparing a single dose of itraconazole (400 mg oral) and extended dose (200 mg/day oral 5 to 7 days) of itraconazole for extensive PV. Our primary outcome was the clinical cure; disappearance of skin lesions by Wood's lamp examination. The secondary outcome was negative hyphi from mycological results.

RESULTS

We included 4 RCTs carried out between 2002 and 2012 with 287 patients with extensive PV; 94 participants in a single dose of itraconazole (400 mg oral), 95 participants in extended dose and 98 participants received other regimens. Comparing between efficacy of single dose of itraconazole and that of extended dose of itraconazole for extensive PV, the meta-analysis showed that the former had similar rate of patients with clinical cure as that of the latter (61.7% vs. 85.3%; relative risk (RR), 0.67; 95% confidence interval (CI), [0.42 to 1.09]; I^2=86%). For the secondary outcome, the former had a similar rate of patients with negative hyphi evaluated at 4th to 6th week as that of the latter (60.8% vs. 78.9%; RR 0.77, 95% CI [0.50 to 1.20]; I^2 = 75%).

CONCLUSION

A single dose of itraconazole had a similar rate of clinical cure as the extended dose of itraconazole. However, due to high heterogeneity, a larger double-blind RCTs comparing single dose and the extended dose of itraconazole in patients with extensive PV should be conducted.

INTRODUCTION

Pityriasis versicolor (PV) is a *Malassezia furfur* infection of an outer layer of the epidermis that leads to scaly macules pigment changes oily areas of the skin of upper extremities and trunk.[1] It is common in summer, considering 3% of patients in the dermatological clinic.[1,2] PV is a benign skin condition, however, its recurrent rate is reported up to 60% in 1 year and 80% in 2 years.[1,2] Patient who has a lesion that is extensive and resistant to topical therapy is indicated for systemic agents.[3] Extensive PV can be treated with systemic medications.[3] The first line systemic agents including oral fluconazole and itraconazole have been recommended.[3] In term of dosage regimen, a randomized controlled trial (RCT) in 1996 suggested that 200 mg/day for 7 days of itraconazole was more effective than placebo for treatment of extensive PV.[4] However, an RCT in 2002 with 50 patient with extensive PV comparing the two regimens (400 mg/day single-dose and 200 mg/day for more than 5 days) showing the same efficacies.[5] Still, the later RCTs suggested controversial results.[6-8] We, thus, aimed to systematically identify all relevant studies and pooled their results to assess the benefit of a single dose compared to the extended dose of itraconazole for extensive PV treatment.

METHODS

We conducted a systematic review according to Cochrane Overviews of Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 Checklist.

SEARCH STRATEGIES

We searched for all relevant studies electronically through the Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, Scopus, and Trip Database without any language restriction. The other sources we searched including google scholar and hand searching was also performed. We used Medical Subject Headings (MeSH) for Pubmed; (("Tinea Versicolor"[Mesh]) AND "Itraconazole"[Mesh]) and keywords "pityriasis versicolor" or "tinea* versicolor" and "itraconazole" for other databases.

INCLUSION CRITERIA

TYPES OF PARTICIPANTS

We considered all randomized controlled trials in which participants were diagnosed with extensive PV.

TYPES OF INTERVENTIONS

We included RCTs of oral itraconazole for extensive PV, the dose, and the duration of administration of the therapies.

OUTCOME MEASURES

The primary outcome was clinical cure defined as disappearance of skin lesions by Wood's lamp examination. The secondary outcome was mycological results which included no hyphi in a direct microscopic potassium hydroxide preparation.

EXCLUSION CRITERIA

We did not have specific exclusion criteria in the present review.

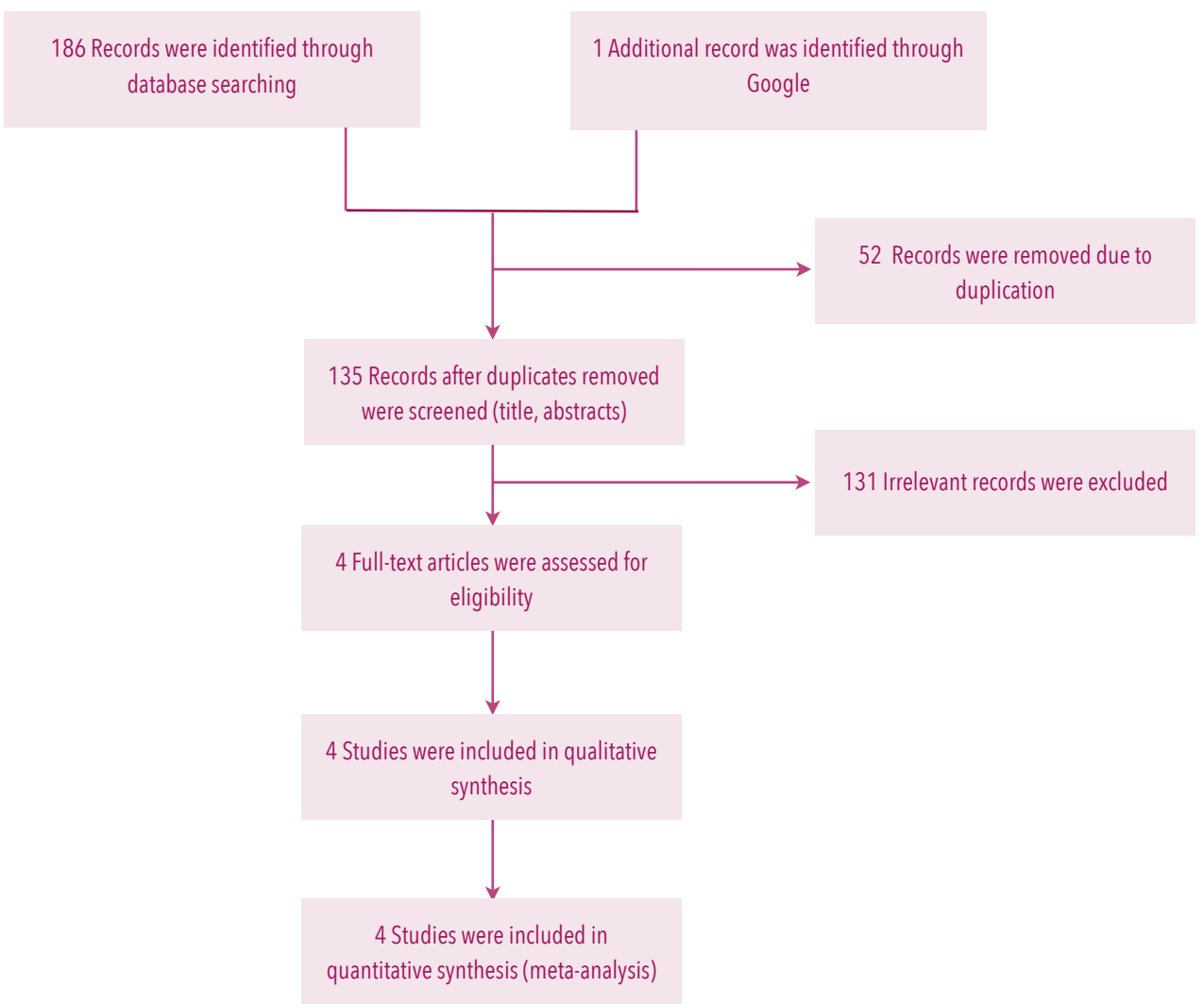

Figure 1. Study flow diagram

DATA SELECTION

Three authors individually searched for all relevant RCTs that assessed the association between the treatment outcomes of those with extensive PV and dose of itraconazole; a single dose vs. the extended dose. We independently screened the titles and abstracts to exclude irrelevant articles then the full-text relevant ones were read and were selected into the present review. Any disagreements among the authors were resolved by discussion.

DATA EXTRACTION

All review authors extracted and recorded data individually from the included studies in relation to

criteria of diagnosis, inclusion and exclusion criteria, interventions (dose of itraconazole, follow up period), number of participant and outcome measures (skin lesion). We extracted data into simple standard spreadsheet.

QUALITY OF REPORTING AND RISK OF BIAS

Our three review authors independently assessed the methodological quality using the Cochrane risk of bias tool. Each included study was regarded to sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias. Disagreements were resolved by discussion with our senior advisor. The authors of original articles were contacted, if necessary.

DATA ANALYSES

For outcome measures, the clinical cure and mycological results were expressed as risk ratios with 95% confidence intervals calculated by Review Manager V5.3 (RevMan, the programme provided by the Cochrane Collaboration). Heterogeneity in the results was evaluated by means of X^2 test and I^2 test. High heterogeneity was considered when $P<0.05$ in statistically X^2 test and I^2 statistic more than 50%. A random effect model was used for the meta-analysis when heterogeneity was statistical significance and funnel plots were created to showing the standard error and the random effect size to identify potential of publication bias. X^2 test and I^2 test were calculated from Review Manager version 5.3 (Revman); The Cochrane Collaboration's software.

RISK OF BIAS ACROSS STUDIES

A funnel plot was created to identify publication bias.

RESULTS

STUDY SELECTION

Our search strategies recognized 187 publications, 52 were removed due to duplication, 131 were excluded in the assessment because titles and abstracts were not relevant (Figure 1). The remaining four studies were included in the qualitative analysis and included to the meta-analysis.

We identified and included 4 RCTs with 287 patients who had extensive PV. Details of all trials were showed in (Table 1). All trials compared the clinical cure (disappearance of skin lesions by Wood's lamp examination) between a single dose and the extended dose of itraconazole. They were all published between 2002 and 2012.

BIAS RISK ASSESSMENT

The quality of all studies was assessed by Cochrane Collaboration's tool (Figure 2, Panel A). The risk of bias graph and summary is shown in Figure 2, Panel A and B.

RANDOM SEQUENCE GENERATION

All included studies did not report the methods of generating random sequence and they were classified as "unclear risk".

ALLOCATION CONCEALMENT

All did not report details on allocation concealment and were classified as "unclear risk".

Table 1. Characteristics of studies included in systematic review

Study	Country	Study design	Participants	Intervention	Outcome
A Kokturk et al. 2002	Turkey	RCT	60 Patients with extensive PV	20 patients (Group I) received itraconazole 400 mg/day in two doses for 1 day; 20 patients (Group II) received itraconazole 200 mg/day in two doses for 5 days; 20 patients was another group.	Group I had lower rate of clinical cure than that of Group II at 6th week. Group I had lower rate of negative hyphi than that of Group II at 6th week.
Maytham M et al. 2012	Iraq	RCT	117 Patients with extensive PV	20 patients (Group I received itraconazole 400 mg single dose; 19 patients (Group II) received itraconazole 200 mg/day for one week; 78 patients were others group that received other regimens.	Group I had lower rate of clinical cure than that of Group II at 6th week. Group I had similar rate of relapse as that of Group II at 6th week.
O Kose et al. 2002	Turkey	RCT	50 Patients with extensive PV	24 patients (Group I) received itraconazole 400 mg single dose; 26 patients (Group II) received 200 mg itraconazole daily dose for one week.	Group I had same rate of clinical cure as that of Group II at 6th week. Group I had similar rate of negative hyphi as that of Group II at 6th week.
Wahab MA et al. 2010	Bangladesh	RCT	60 Patients with extensive PV	30 patients (Group I) received itraconazole 400 mg single dose; 30 patients (Group II) received itraconazole 200 mg 7 days.	Group I had similar rate of clinical cure as that of Group II at 4th week. Group I had similar rate of negative hyphi as that of Group II at 4th week.

PV= pityriasis versicolor; RCT= randomized controlled trial

BLINDING OF PARTICIPANT AND PERSONNEL

All did not report details on blinding of participant and personnel and were classified as "unclear risk".

BLINDING OF OUTCOME ASSESSMENT

All did not report details on outcome blinding assessment and were classified as "unclear risk".

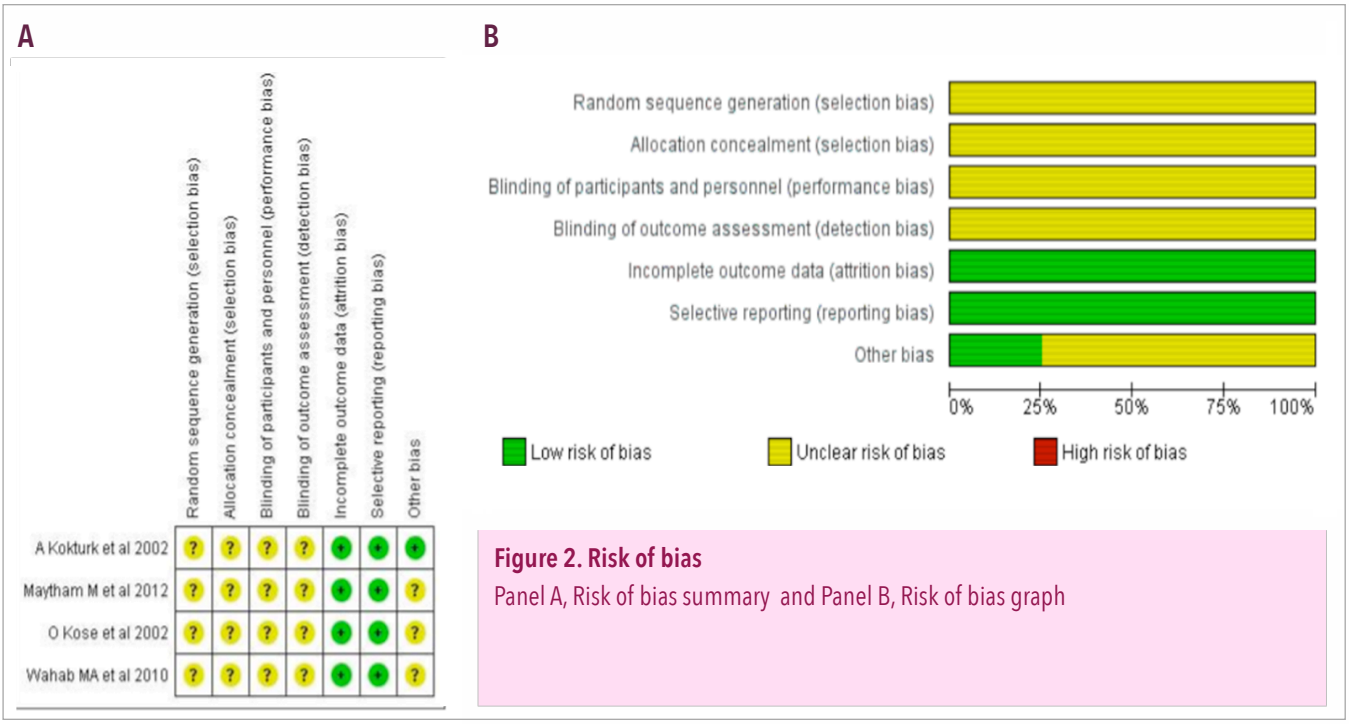

Figure 2. Risk of bias
Panel A, Risk of bias summary and Panel B, Risk of bias graph

INCOMPLETE OUTCOME DATA

All included studies reported the incomplete outcome data or dropped-out patients and they were classified as "low risk".

SELECTIVE REPORTING

All included studies properly described the clinical cure and mycological results. They were classified as "low risk".

OTHER POTENTIAL SOURCES OF BIAS

One studies reported that non-industry-sponsored and it was classified as "low risk". The others did not report about potential sources of bias so they were classified as "unclear risk".

PRIMARY SECONDARY OUTCOME

The single dose of itraconazole had a similar rate of the patient with clinical cure evaluated at 4th to 6th week as that of the extended dose of itraconazole (61.7% vs. 85.3%; RR, 0.67; 95% CI, [0.42 to 1.09]; I^2=86%) (Figure 3). However, the high heterogeneity was observed

SECONDARY OUTCOME

The single dose of itraconazole had a similar rate of negative hyphi mycological results evaluated at 4^{th} to 6^{th} week as that of the extended dose of itraconazole (60.8% vs. 78.9%; RR, 0.77; 95% CI, [0.50 to 1.20]; I^2=75%) (Figure 4). The high heterogeneity was also observed

DISCUSSION

MAJOR FINDINGS

In our systematic review showed the non-statistical difference between the proportion of patient with clinical cure in the single dose of itraconazole

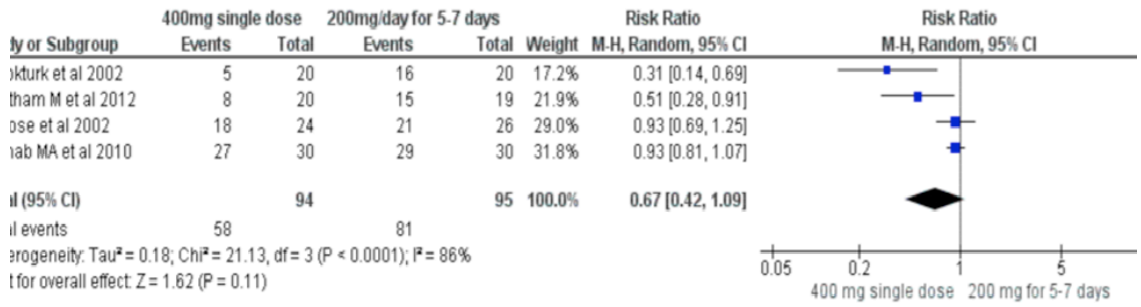

Figure 3. The Forest Plot of Comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Clinical Cure

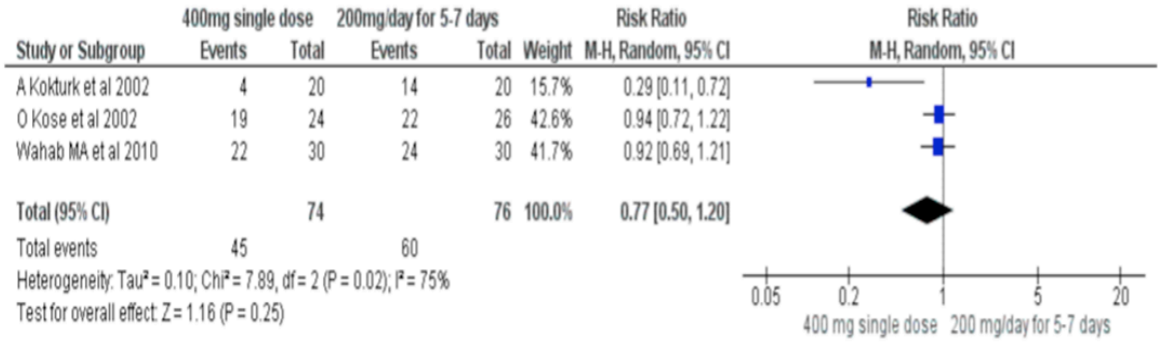

Figure 4. The Forest Plot of Comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Negative Hyph

group and that of the extended dose of itraconazole group. Moreover, there was high heterogeneity. We found a non-statistically significant difference of proportion of patients with negative hyphi in those using 400 mg single dose of itraconazole compared with that of 200 mg/day of itraconazole for more 5 days. Furthermore, its high heterogeneity was observed. Implication of the results should be careful.

STRENGTH AND LIMITATION OF THE REVIEW

This systematic review has intermediate strength. Three reviewers searched for eligible randomized controlled trial by screening all titles and abstracts and read full-text articles to assess relevant studies, then we got proper studies and can be assured not to missed important data. The data extraction has been performed by individual reviewers and independently.

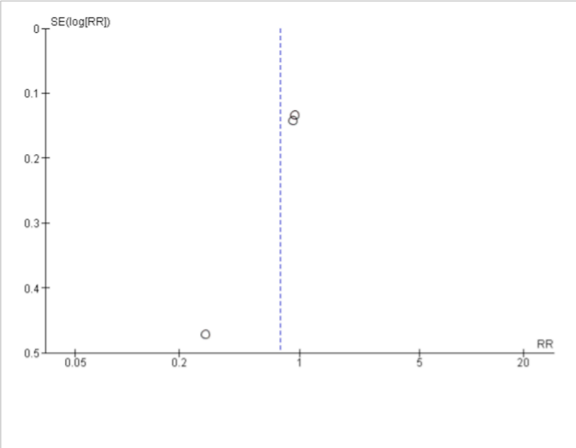

Figure 5. The Forest Plot of Comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Clinical Cure.

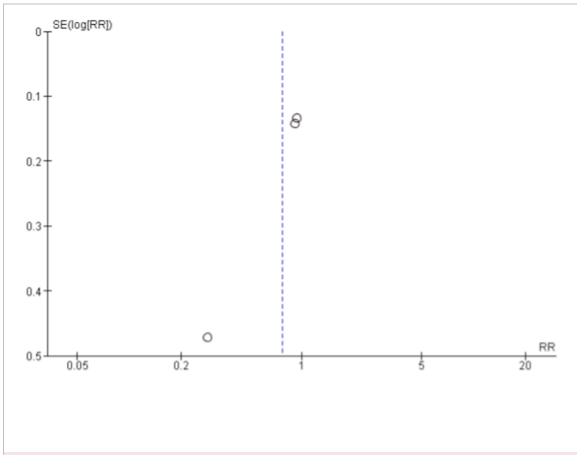

Figure 6. Funnel plot of comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Negative Hyphi.

The limitation of this review is that our conclusion was based on low-quality RCTs. All studies had many unclear risks of bias. Moreover, included studies had a small number of participants and outdated; the oldest study was published in 2002. Each study had different methods of outcome measurement as the time to follow up patients with clinical cure and negative hyphi. In the primary outcome, there were three studies evaluated the outcome at 6th week while only one at 4th week. Interpretation of the combination of the results should be careful. This pattern was also found in the evaluated time of the secondary outcome as 2 RCTs followed up patients at 4th week and only one followed up at 6th week. The funnel plots of both outcomes (Figure 5 and Figure 6) suggested the potential of unpublished bias.

COMPARISON WITH OTHER STUDIES

Our systematic review showed that there was no statistically significant difference between a single dose and the extended dose of itraconazole for treatment PV based on the included four RCTs. However, in 2015 there was also a systematic review reported the same findings as ours, however, it included only two RCTs without meta-analysis.[9]

CONCLUSION

Our systematic review and meta-analysis showed that the single dose of itraconazole for treating extensive PV had a similar rate of clinical cure and negative hyphi as that of the extended dose of itraconazole. However, there was no clinical implication for practice, due to low-quality, small number of participants and high heterogeneity of the included studies. We, thus, suggest a further multi-center double-blind controlled trial comparing the single dose and the extended dose of itraconazole in patients with extensive PV should be conducted for the better precision of their effects estimation.

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COMPETING INTERESTS: This study has no competing on interest.
FUNDING: None

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Optimal dose of intrathecal morphine used for cesarean delivery anesthesia: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE
To identify the optimal dose of intrathecal morphine (ITM) for cesarean delivery anesthesia.

METHODS
We searched for the studies regarding anesthetic ITM with elective cesarean delivery patients which reported efficacy and adverse effects of ITM through online databases and hand-searching. Inclusion criteria included is a randomized controlled trial which compared doses of ITM in postoperative analgesia and adverse effects (pruritus, postoperative nausea, and vomiting). Three authors independently assessed reference for inclusion and study quality and extracted data. We used the Cochrane risk of bias for assessing the risk of bias of the studies and the Review Manager version 5.3 for risk of bias summary.

RESULTS
There were four randomized controlled trial studies met the inclusion criteria with 300 participants. However, the results of these trial were unable to combine. No meta-analysis was performed due to the different interventions used in each study. Nonetheless, we observed the trend that the higher the dose of ITM, the more effective and the more common adverse effects.

CONCLUSION
This study were unable to conclude the optimal dosage of ITM for elective cesarean operation.

INTRODUCTION

Intrathecal morphine (ITM) is widely used in the cesarean section because of its effectiveness and long-lasting analgesic effect.[1–4] However, morphine has various adverse reactions including pruritus, postoperative nausea and vomiting (PONV), and respiratory depression.[1–6] The effectiveness of analgesia and adverse effects of ITM are dose-related.[7] Low dose of ITM commonly co-administered with a spinal anesthetic.[8–15] ITM is a common analgesic technique because of prolonged postoperative analgesia following cesarean delivery.[6,16–18] However, a high incidence of bothersome side effects, observed even with reduced doses, has limited the use of ITM for labor analgesia.[6,8,19-20]

Although a systematic review in 1999 had shown that 0.1 mg ITM was a drug and dose of choice to reduce the postoperative pain of cesarean section patients but it still had evidence of side effects in many patients.[5,9,21-22] Newer studies showed a lower dose of ITM that has the same efficacy of reducing pain with fewer side effects.[5,20,22] The main objective of this study was to determine the optimal dose for postoperative Cesarean section analgesia with the lowest side effect.

METHODS

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials, Pubmed, Scopus, Google scholar without any languages restriction. We used a combination of Medical Subject Headings (MeSH) for Pubmed and Cochrane Library searching ("Morphine"[Mesh]) AND "Cesarean Section"[Mesh], ("Injections, Spinal"[Mesh]) AND "Cesarean Section"[Mesh], (("Injections, Spinal"[Mesh]) AND "Analgesics, ("Analgesics, Opioid" [Pharmacological Action]) AND "Cesarean Section"[Mesh], (("Injections, Spinal"[Mesh]) AND "Morphine"[Mesh]) AND "Cesarean Section"[Mesh]

In Scopus we used keywords "intrathecal morphine" AND "Cesarean section", "intrathecal morphine" AND "Cesarean delivery", "intrathecal opioid" AND "Cesarean section", "spinal inject*" AND "morphine" AND "Cesarean delivery", "spinal inject*" AND "opioid" AND "Cesarean delivery", "intrathecal morphine" AND "anesthesia" AND "Cesarean delivery", "intrathecal morphine" AND "anesthesia" AND "Cesarean section", "intrathecal opioid" AND "anesthesia" AND "Cesarean section" and in Google Scholar we used the keywords "intrathecal morphine" "anesthesia" "Cesarean section", "intrathecal opioid" "anesthesia" "Cesarean section". The studies screening and selection process will be performed independently by three reviewers and will be verified by ourselves.

INCLUSION AND EXCLUSION CRITERIA

Studies were eligible for inclusion if there were randomized controlled trials of a pregnant woman who have scheduled for elective Cesarean section were received ITM compared between 0.1 mg ITM and the other doses of morphine. We excluded studies that did not have a control group as 0.1 mg ITM and outcome that was not measured by a visual analog pain scale.

DATA EXTRACTION AND MANAGEMENT

Data were extracted and recorded by the three review authors individually. Extracted data included criteria for diagnosis, inclusion and exclusion

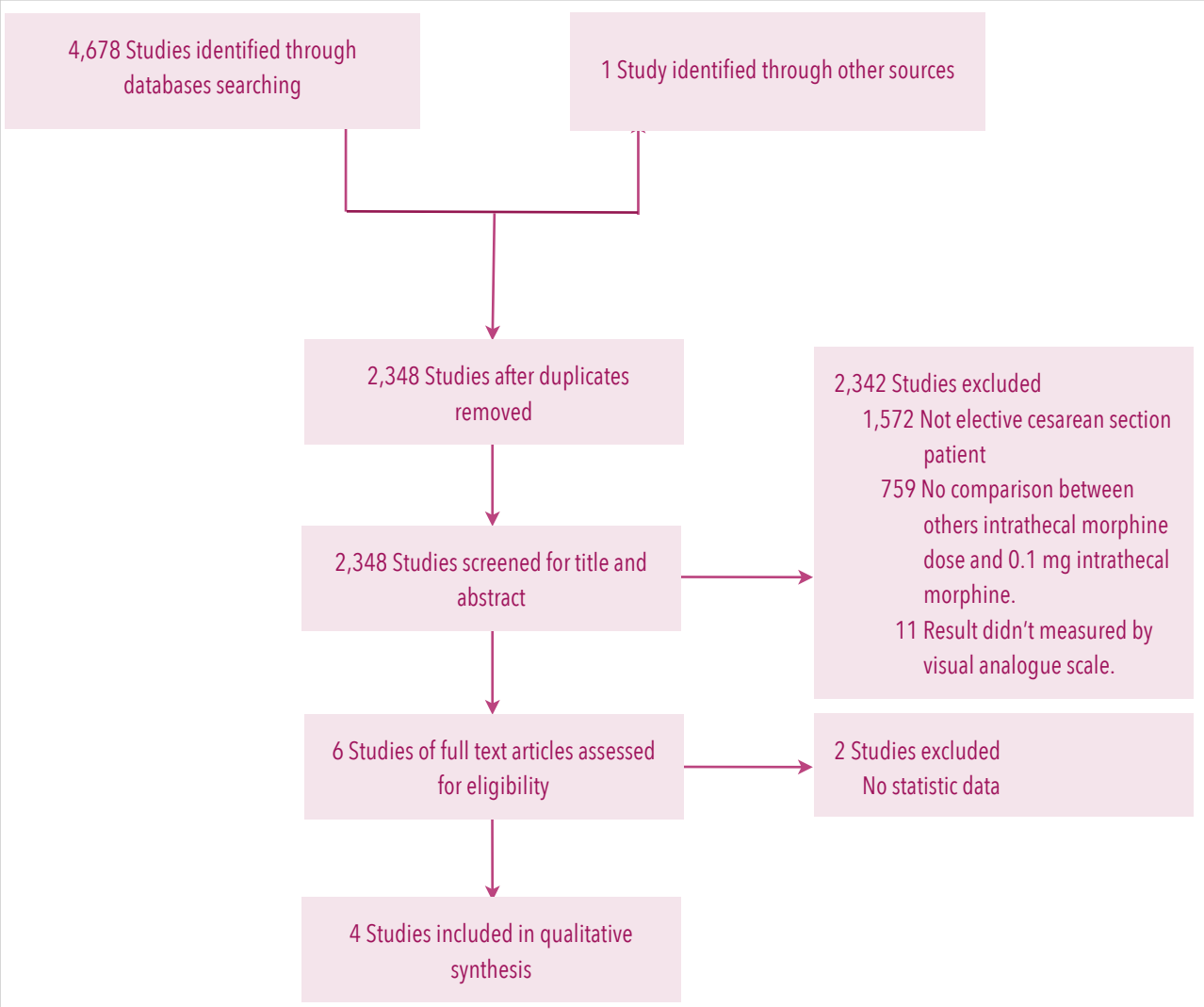

Figure 1. Study flow diagram

criteria, languages of publication, interventions, number of participant, date, and duration of the study and outcomes. We simplified all data into standard spreadsheet.

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

The three reviewers assessed the methodological quality using Cochrane risk of bias for randomized controlled trials regarding random sequence generation, allocation concealment, blinding of participants and personnel, allocation concealment, incomplete outcome data, selective reporting, and other sources of bias.

RESULTS

From searching strategies, there were 4,678 studies identified through databases searching. The remaining 2,348 studies after duplicates were removed. After screening for title and abstract,

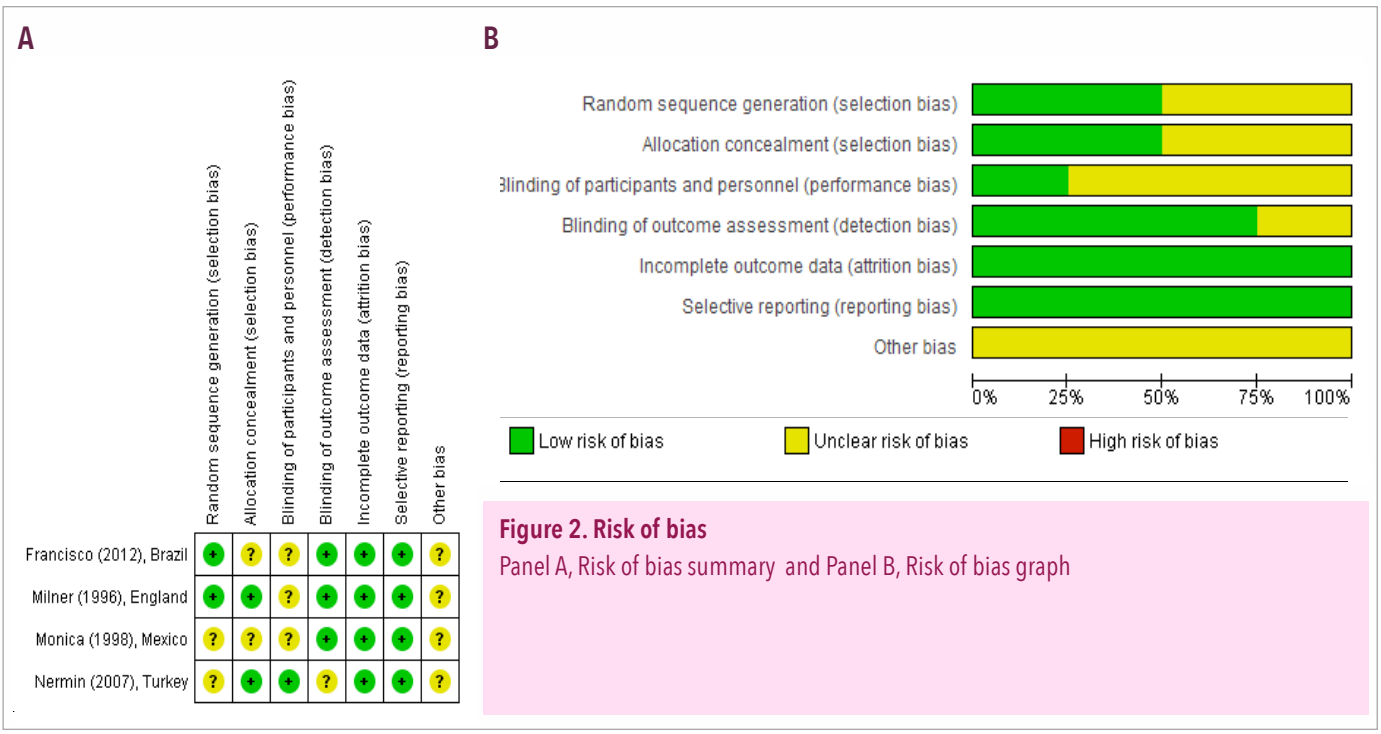

Figure 2. Risk of bias
Panel A, Risk of bias summary and Panel B, Risk of bias graph

2,342 studies were excluded, the full-text of the left 6 studies were assessed for eligibility. Two studies were excluded as having no statistical data. These four studies were included in qualitative synthesis (Figure 1) and the other one was identified by hand searching methods.

STUDIES CHARACTERISTIC

The included studies were published between 1996 and 2012. All were randomized controlled trials with 300 participants that had 0.1 mg ITM participant intervention. One study was placebo-controlled compared with 0.1 to 0.4 mg ITM and the other three studies compared 0.1 mg ITM with varying doses of ITM. Characteristics of the included studies are shown in Table 1.

BIAS RISK ASSESSMENT

Four trials were assessed by the Cochrane Risk of Bias Tool. Risk of bias was assessed according to seven components; random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Four studies were assessed as having a low risk of bias[7,19,23,24] (Figure 2, Panel A). The risk of bias graph was summarized in Figure 3 (Figure 2, Panel B).

RANDOM SEQUENCE GENERATION

Two studies[19,24] reported a specific method of generating a random sequence, they were classified as low risk of bias. The others[7,23] were not and classified as unclear risk of bias.

ALLOCATION CONCEALMENT

There was allocation concealment in two studies[7,19] and we classified as "low risk". The others[23-24] were classified as unclear risk of bias.

Table 1. Characteristics of the included studies

Study	Participants	Intervention	Results	
			Primary outcome (VAPS)	Secondary outcomes
Milner (1996), England[19]	50 patients with 2.5 ml bupivacaine of 0.5% in 8% dextrose	0.1 mg ITM (n=25) vs. 0.2 mg ITM (n=25) 50	At 4 h (P=0.180) 0.1 mg ITM median 13 mm 0.2 mg ITM median 3 mm At 8 h (P=0.380) 0.1 mg ITM median 13 mm 0.2 mg ITM median 5 mm At 12 h (P=0.110) 0.1 mg ITM median 12.5 mm 0.2 mg ITM median 8 mm At 24 h (P=0.310) 0.1 mg ITM median 15 mm 0.2 mg ITM median 13 mm.	Incidence rate of no pruritus 0.1 mg ITM 24% 0.2 mg ITM 12% Incidence rate of mild/moderate pruritus 0.1 mg ITM 68% 0.2 mg ITM 80% Incidence rate of severe/very severe pruritus 0.1 mg ITM 8% 0.2 mg ITM 8% Incidence rate of no nausea or vomiting 0.1 mg ITM 72% 0.2 mg ITM 44% Incidence rate of nausea or vomiting (P=0.044) 0.1 mg ITM 28% 0.2 mg ITM 56%
Nermin (2007), Turkey[7]	100 patients with 7.5 mg of 0.5% bupivacaine combined in saline (2 mL total volume)	placebo (n=19) 0.1 mg ITM (n=18) vs. 0.2 mg ITM (n=19) vs. 0.3 mg ITM (n=20) vs. 0.4 mg ITM (n=19)	Time to the first PCA demand placebo mean 5.6±3.4 h 0.1 mg ITM mean 16.3±7.0 h† 0.2 mg ITM mean 17.5±8.3 h† 0.3 mg ITM mean 17.4±9.0 h† 0.4 mg ITM mean 18.2±8.1 h‡ PCA-morphine use at 24 h placebo mean 60.0±20.0 h 0.1 mg ITM mean 28.0±18.0 h§ 0.2 mg ITM mean 25.0±16.0 h§ 0.3 mg ITM mean 2.01±13.0 h§ 0.4 mg ITM mean 20.0±14.0 h§ VAPS at 4 h placebo mean 1.7±1.4 cm 0.1 mg ITM mean 1.5±1.4 cm 0.2 mg ITM mean 1.4±1.1 cm 0.3 mg ITM mean 1.1±0.8 cm 0.4 mg ITM mean 1.0±0.8 cm VAPS at 24 h placebo mean 0.1±0.7 cm 0.1 mg ITM mean 0.2±0.7 cm 0.2 mg ITM mean 0.1±0.3 cm 0.3 mg ITM mean 0.2±0.3 cm 0.4 mg ITM mean 0.1±0.4 cm	Mean pruritus scores (ANOVA P<0.001) placebo mean 1.6±1.5 cm 0.1 mg ITM mean 2.8±2.7 cm 0.2 mg ITM mean 5.5±2.7 cm 0.3 mg ITM mean 5.3±3.1 cm 0.4 mg ITM mean 7.5±3.1 cm Mean nausea scores (ANOVA P=0.731) placebo mean 1.2±1.3 cm 0.1 mg ITM mean 2.1±1.5 cm 0.2 mg ITM mean 2.4±2.4 cm 0.3 mg ITM mean 2.0±2.4 cm 0.4 mg ITM mean 2.2±2.2 cm Mean vomiting scores (ANOVA P=0.388) placebo mean 0.7±0.9 cm 0.1 mg ITM mean 0.8±0.9 cm 0.2 mg ITM mean 1.0±0.8 cm 0.3 mg ITM mean 1.5±0.9 cm 0.4 mg ITM mean 1.2±1.2 cm

Table 1. Characteristics of the included studies

Study	Participants	Intervention	Results	
			Primary outcome (VAPS)	**Secondary outcomes**
Monica (1998), Brazil[23]	120 patients with 15 mg of 0.5% hyperbaric bupivacaine	0.025 mg ITM+D every 8 h (n=20) 0.025 mg ITM+D on demand request (n=20) vs. 0.05 mg ITM+D every 8 h (n=20) 0.05 mg ITM+D on demand request (n=20) vs. 0.1 mg ITM+D every 8 h (n=20) 0.1 mg ITM+D on demand request (n=20)	0.025 mg ITM+D every 8 h mean 0.2±0.3 cm 0.025 mg ITM+D on demand request mean 0.7±0.6 cm 0.05 mg ITM+D every 8 h mean 0.4±0.3 cm 0.05 mg ITM+D on demand request mean 0.5±0.4 cm 0.1 mg ITM+D every 8 h mean 0.2±0.4 cm* 0.1 mg ITM+D on demand request mean 0.3±0.3 cm*	Incidence rate of pruritus 0.025 mg ITM 32.5% 0.05 mg ITM 32.5% 0.1 mg ITM 57.5% (P<0.05) Incidence rate of vomiting 0.025 mg ITM 10% 0.05 mg ITM 15% 0.1 mg ITM 25%
Francisco (2012), Brazil[24]	130 patients with 12 mg of 0.5% hyperbaric bupivacaine	0.05 mg ITM (n=60) VS. 0.1 mg ITM (n=63)	Pain at rest 1st evaluation (P=0.974)¶ 0.05 mg ITM median 0.7 cm 0.1 mg ITM median 0.6 cm Pain when coughing 1st evaluation (P=0.757)¶ 0.05 mg ITM median 3.8 cm 0.1 mg ITM median 3.4 cm Worst pain period 1st evaluation (P=0.540)¶ 0.05 mg ITM median 5.1 cm 0.1 mg ITM median 4.7 cm Pain at rest 2nd evaluation (P=0.862)¶ 0.05 mg ITM median 0.6 cm 0.1 mg ITM median 0.4 cm Pain when coughing 2nd evaluation (P=0.387)¶ 0.05 mg ITM median 0.6 cm 0.1 mg ITM median 0.4 cm Worst pain period 2nd evaluation (P=0.192)¶ 0.05 mg ITM median 4.6 cm 0.1 mg ITM median 3.2 cm	Incidence rate of pruritus (P=0.026) 0.05 mg ITM 18.3% 0.1 mg ITM 23.8% Incidence rate of nausea/Vomiting (P=0.512) 0.05 mg ITM 70% 0.1 mg ITM 87.3% Incidence rate of voiding difficulty (P=0.194) 0.05 mg ITM 58.3% 0.1 mg ITM 69.8% Incidence rate of dizziness (P=0.635) 0.05 mg ITM 15% 0.1 mg ITM 19.1%

n=total participant; VAPS=visual analog pain scale; mg=milligram; cm=centimetre; ITM=intrathecal morphine; D=75 mg intramuscular diclofenac; PCA=patient-controlled analgesia; ANOVA=analysis of variance

* P<0.05, 0.1mg morphine<0.05 mg morphine=0.025 mg morphine.

† P<0.05 versus placebo group.

‡ P<0.01 versus placebo group.

§ P<0.001 versus placebo group.

¶ Nonparametric Mann-Whitney test, P<0.05.

BLINDING OF PARTICIPANTS AND PERSONNEL

The only one study[7] had a double-blind technique to minimize the effect of bias while three studies[19,23-24] did not report so they were classified in low risk and unclear risk of bias, respectively.

BLINDING OF OUTCOME ASSESSMENT

Three studies[19,23-24] mentioned about blinding of assessment were sorted in a low risk of bias. Another[7] one did not mention, and classified as "unclear risk".

INCOMPLETE OUTCOME DATA

Two studies[7,24] reported a number of patients who failed to complete follow-up. Two studies[17,25] had no lost follow-up patients for the main outcome measures.

SELECTIVE OUTCOME REPORTING

All studies[7,19,23-24] were sorted in a low risk of bias as they reported all of their intended primary outcomes and secondary outcomes.

OTHER POTENTIAL SOURCE

All of the included studies did not mention financial support, so they were classified as unclear risk.[7,19,23-24]

PRIMARY OUTCOME

From these four included studies, aside from the varied dosages of ITM, dosages of bupivacaine were also diverse. Thus, the primary outcome, the visual analog pain scale (VAPS) from each study was not pooled in the meta-analysis. Moreover, the baseline pain scale was not taken into account the efficacy of the interventions. Thus, the combined VAPS was not possible and not interpretable.

The trial by Milner has shown that there was no was no difference in the quality of analgesia between 0.1 and 0.2 mg ITM at any time of assessment (P=0.18, 0.38, 0.11, and 0.31 at 4, 8, 12, and 24 hr, respectively) (Table 1). However, the trial by Monica comparing the three doses of ITM; 0.1, 0.05 and 0.025 mg ITM revealed that 0.1 mg ITM had significantly greater decreased pain than the other groups (P<0.05). The study by Nermin with four various groups of 0.1 mg, 0.2 mg, 0.3 mg, and 0.4 mg of ITM comparing with placebo. There was no significant difference among the groups regarding VAPS at 24 h postoperative. The last study by Francisco which measured VAPS (at rest, when coughing and worst pain period) at 9th to 11th and 22nd to 24th hours after anesthesia showed that it was no statistically significant difference in pain evaluation between both 0.05 mg and 0.1 mg ITM groups.

SECONDARY OUTCOME

PRURITUS

For the secondary outcome, the pooled incidence rate of pruritis was not appropriate as mentioned earlier in the primary outcome. However, the trend was found across the four included trials, the study by Milner showed that the rate of pruritus was higher in those with 0.2 mg ITM. The study by Nermin also showed mean pruritus scores for 0.1 mg ITM and placebo group were both lower than the other three groups with 0.2, 0.3 and 0.4 ITM. There was a significant difference of incidence rates

of pruritus among the three doses of ITM; 0.025 mg, 0.05 mg and 0.1 mg in the trial by Monica and tended to be more common in the higher dose. In the trial by Francisco, the pruritus incidence was higher significantly in those with 0.1 mg ITM comparing with that of 0.05 mg.

NEUSAE AND VOMITING

There was also a trend that higher dose ITM was associated with a higher rate of nausea and vomiting. However, only one trial by Milner found the significant difference in this outcome; 28% in 0.1 mg ITM and 56% in 0.2 mg ITM, P=0.044)

DISCUSSION

MAJOR FINDINGS

From the four included studies, varied dosages of ITM and dosages of bupivacaine were also varied. Both primary and secondary outcomes were not be able to pool using the meta-analysis. Even we pooled, the findings would not be interpretable. However, we found some trends. the higher the dose of ITM, the more efficacy in term of pain and the more adverse effects of both pruritus and nausea and vomiting.

COMPARISON WITH OTHER STUDY

The previous published systematic review showed that ITM decreased pain scores and consumption of postoperative supplemental analgesia in 24 hours after operation and increased the time to first administration of analgesia with increasing doses of ITM.[5] However, their conclusion was based on the pooled effects of various dosage of ITM and various types and dosage of local anesthesia. Nonetheless, logistic regression analysis in that systematic review reported that the relative risk of postoperative pruritus, nausea and vomiting increased in dose-relationship with ITM which was similar to our findings.

LIMITATIONS OF THE REVIEW

This was a study aimed to identify all relevant trials to identify the optimal dose of ITM considering both benefit and harm of the treatment for those undergoing the elective cesarean delivery. However, our limitation was that we were unable to combine the findings from those included studies due to the difference in term of intervention and other treatments given in each trial. We then can observe only the trend without identifying the right dose for ITM for those undergoing the elective cesarean operation.

CONCLUSION

In the present systematic review without meta-analysis, the trend association of dose of ITM and treatment outcome in term of pain reduction and adverse effects including pruritus and nausea and vomiting for an elective cesarean operation was observed; the higher the dose of ITM, the more effectiveness and more common of adverse effects. However, the optimal dose of ITM was unable to identify due to the uncombinable of the effect size from the various dose of ITM and local anesthesia. Moreover, the included studies also suffered from the small samples. A larger randomized controlled trial comparing various dosages of ITM is needed.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.
FUNDING: None

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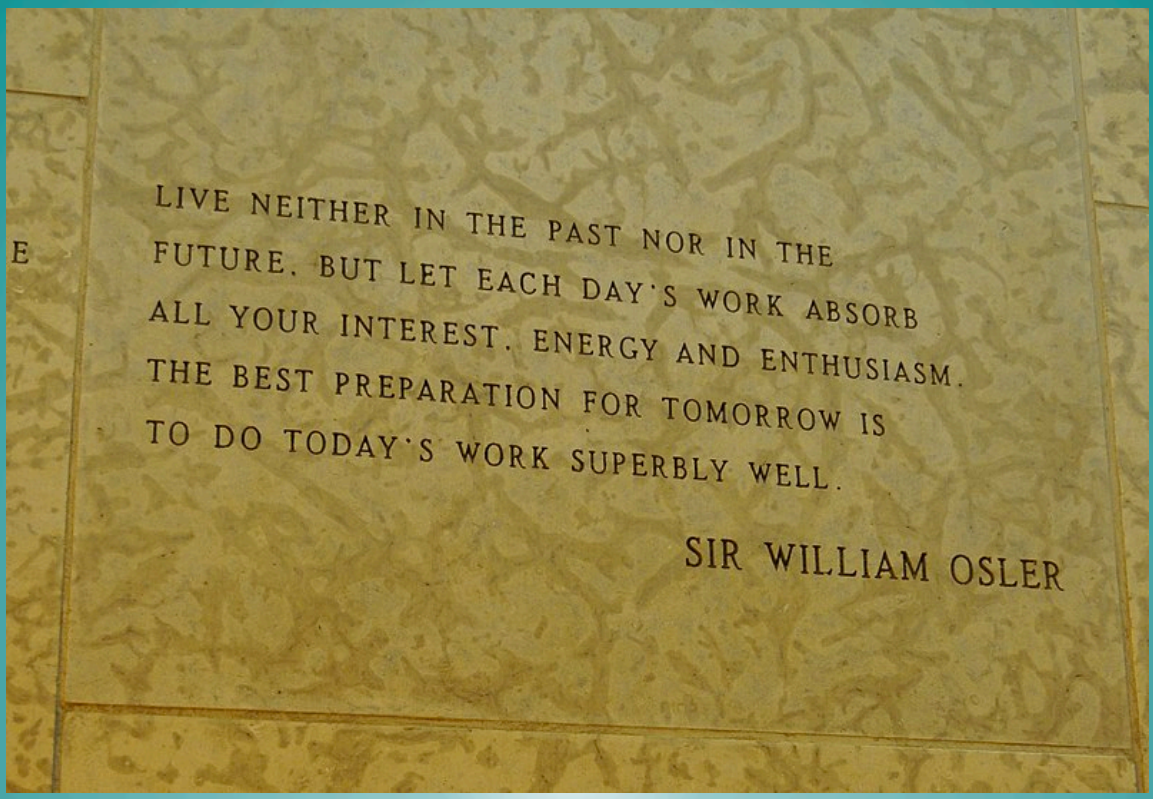
LIVE NEITHER IN THE PAST NOR IN THE
FUTURE. BUT LET EACH DAY'S WORK ABSORB
ALL YOUR INTEREST. ENERGY AND ENTHUSIASM.
THE BEST PREPARATION FOR TOMORROW IS
TO DO TODAY'S WORK SUPERBLY WELL.
SIR WILLIAM OSLER

"I shall either find a way or make one"

-Hannibal Barca

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