THE CLINICAL ACADEMIA

VOLUME **41** ISSUE **5**
SEPTEMBER-OCTOBER 2017

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WWW.THECLINICALACADEMIA.ORG

PRINTED IN THE USA
ISSN: 2465-4027


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

the clinical academia

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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

I was just back from Eighth International Congress on Peer Review and Scientific Publication which held in Chicago, USA. This my second time at the Congress and it is four years apart. New concepts and new platform emerge as well as new problems for scientific publication. It is time for us to move beyond our beliefs. Research is not for publication, it serves something higher. Research is for research itself, for a better science and better world we all live in at the end.

The world of medicine is ever changing. Here now and then are its places. Keep going is the best suggestion for all of us. Hope you enjoy reading The Clinical Academia.

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

submission

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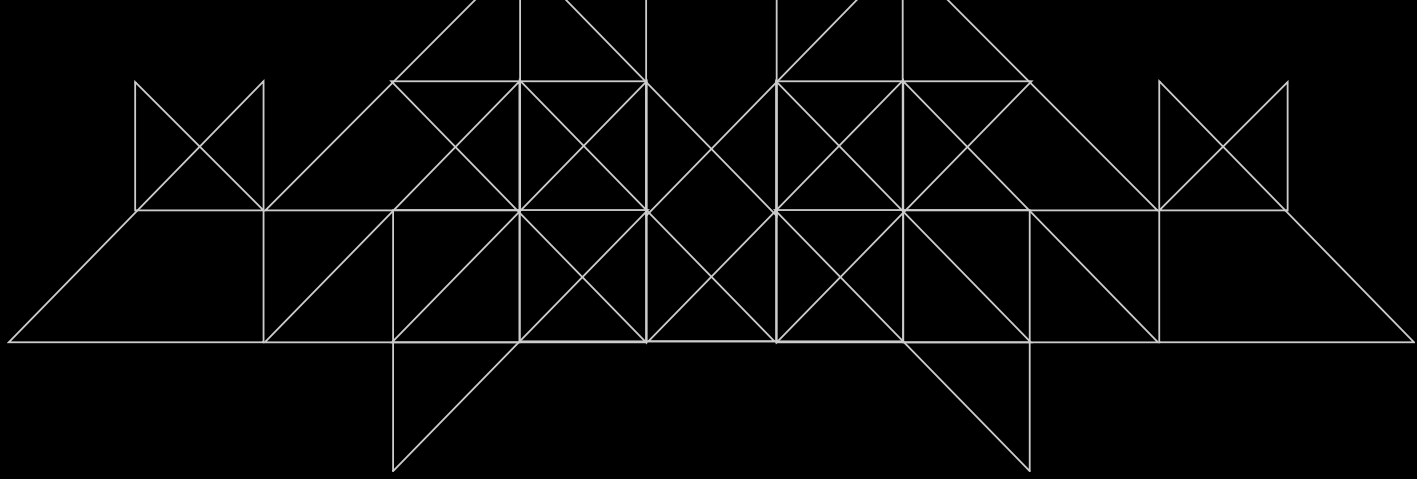
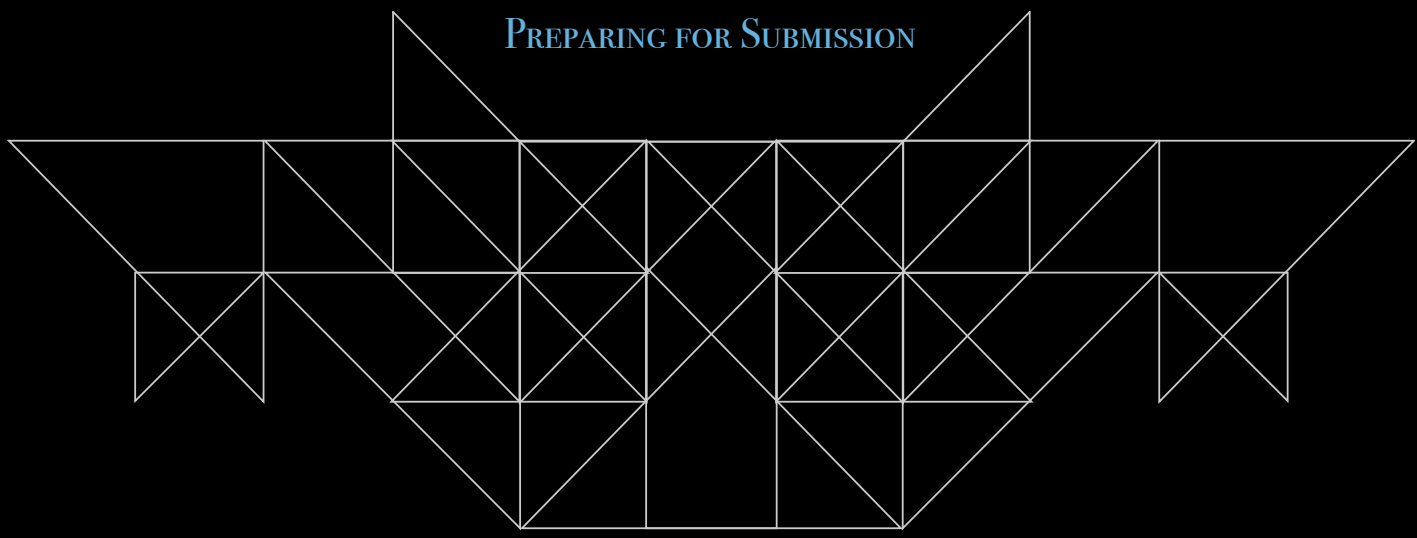


International Committee of Medical Journal Editors (ICMJE) Recommendation for Preparing for Submission



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, 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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Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the Abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of Figures and Tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because Tables and Figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

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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.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a

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.

d. Methods

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.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer)." Authors should define how they measured race or ethnicity and justify their relevance.

ii. Technical Information

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.

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.

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.

f. Discussion

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.

g. References

i. General Considerations Related to References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests.Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

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References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Reference Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References webpage and detailed in the

NLM's Citing Medicine, 2nd edition. These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

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For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

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.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

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j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

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k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Clinical features and predisposing factors for mediastinal extension in deep neck infections

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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Accepted: August 2017
Latest revision: September 2017
Printed: October 2017

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ABSTRACT

OBJECTIVE

To identify the clinical features and predisposing factors of descending necrotizing mediastinitis (DNM) in deep neck infection (DNI) patients.

METHODS

A retrospective case-control study using the database of Khon Kaen Hospital from October 2011 to May 2017 was conducted. Inpatients who were diagnosed DNI and needed to undergo incision and drainage were eligible. A case-patient was one who had DNI with the complication of DNM while a control patient was one who had only DNI. The clinical features and predisposing factors for mediastinal extension were compared between both groups.

RESULTS

There were 362 eligible patients; 354 patients were control group while 8 patients were case group. Dyspnea, dysphagia and septic shock were the clinical features associated with DNM with the crude odds ratio (OR), 81.50; 95% confidence interval (CI) 9.68 to 686.18, OR, 9.09; 95% CI, 1.11 to 74.67 and OR, 23.00; 95% CI, 4.75 to 111.32, respectively. Moreover, comorbidities including diabetes mellitus (OR, 25.18; 95% CI, 3.05 to 207.80), hypertension (OR, 4.80; 95% CI, 1.17 to 19.73), chronic liver disease (OR, 16.71; 95% CI, 1.54 to 181.25) and anemia (OR, 8.74; 95% CI, 1.61 to 47.55), more than one space infection (OR, 20.23; 95% CI, 2.46 to 166.67), present of necrotizing fasciitis (OR, 145; 95% CI, 25.65 to 829.08), time to surgery after admission more than 24hr (OR, 10.44; 95% CI 1.78 to 61.27), widening mediastinum (OR, 33.00; 95% CI,5.45 to 199.64) and pleural effusion (OR, 101; 95% CI, 9.09 to 1122.69) were also associated with mediastinal extension.

CONCLUSION

The clinical features of DNM in this study were dyspnea, dysphagia, and septic shock and the predisposing factors were comorbidity especially diabetes mellitus, hypertension, chronic liver disease and anemia, present of necrotizing fasciitis, time to surgery after admission more than 24hr, more than one space infection, widening mediastinum and pleural effusion.

INTRODUCTION

Deep neck infection (DNI) is an infection in fascial planes and spaces of the neck that can be either abscess or cellulitis.[1,2] Common sources of the infection are odontogenic infection (12-51%)[2–5] and oropharyngeal infection (46%-85%).[6–8] Moreover, it can cause life-threatening complications including descending necrotizing mediastinitis (DNM), septic shock, and disseminated intravascular coagulopathy.[9–11] Among these complications, DNM is a life-threatening form of mediastinitis which is caused by downward spread of DNI to the mediastinum.[12–16] The clinical presentations of DNM are still not well specified and the predisposing factors vary from study to study. Mortality rates of DNM still high up to 40%,[14,16,17] moreover standard treatment (surgical approaches) remain controversial.[14,18–20] Therefore, identifying of the predicting factors is crucial to decrease the mortality rates.

METHODS

STUDY DESIGN AND PATIENTS

A Retrospective case-control study was conducted at a tertiary referral hospital using the medical records of patients who were diagnosed with DNI and treated at Khon Kaen Hospital, Thailand from October 2011 to May 2017.

Inclusion criteria were DNI patients that needed to be undergone incision and drainage. Exclusion criteria were superficial and other unspecified space of infection, isolated buccal space/canine space, infections related to external neck wounds (traumatic or surgical) nor head and neck tumors and medical records that could not be found. Those with DNI and complication of DNM was considered as case-patients while those with only DNI was considered as control patients. Demographic data, comorbidities, the cause of infection, treatment before admission, symptoms, spaces of infection, causative organism, imaging, treatment, time to surgery, complications, treatment outcome and length of stay were the study variables.

ETHICS CONSIDERATION

The protocol of this study was reviewed and it was approved by the Institutional Review Board of Khon Kaen Hospital (approval number: KE60091) followed the principles of Declaration of Helsinki, October 2013.

STATISTICAL ANALYSIS

All data were cleaned before the analysis. The demographic data and characteristics were summarized using number and percentage for categorical data. We used mean and standard deviation for normally distributed continuous data and median and interquartile range (IQR) for non-normally distributed continuous data. Characteristics of cases and controls were compared using the t-test or Mann-Whitney U-test for continuous data where appropriate. Chi-squared and Fisher's exact test was used for categorical data. The influence of predisposing factors on a mediastinal extension in DNI was identified using odds ratio (OR) and 95% confidence interval (CI) from the logistic regression model.

Table 1. Characteristics affecting descending necrotizing mediastinitis

Characteristics	DNM (n=8)	DNI (n=354)	Odds Ratio	95% confidence interval	P Value
Male sex-no. (%)	6 (75.0)	188 (53.1)	1	0.08-1.9	0.237
Age-median (IQR)	56 (51-66)	48 (34-60)	1.04	0.99-1.08	0.108
Day before admission-median (IQR)	7 (3-10)	4 (3-7)	1.01	0.94-1.09	0.818
Chronic substance abuse-no. (%)			2.19	0.54-8.91	0.274
Nicotine	4 (50)	90 (25.4)	NA	NA	NA
Alcohol	4 (50)	95 (26.8)	NA	NA	NA
Comorbidities-no. (%)					
DM	7 (87.5)	77 (21.8)	25.18	3.05-207.80	0.003
Hypertension	4 (50)	61 (17.2)	4.80	1.17-19.73	0.030
Dyslipidemia	1 (12.5)	7 (1.9)	7.08	0.77	0.085
Chronic kidney disease	1 (12.5)	14 (3.9)	3.47	0.40-30.16	0.260
Chronic liver disease	1 (12.5)	3 (0.9)	16.71	1.54-181.25	0.021
Pulmonary disease	0	2 (0.6)	NA	NA	NA
Anemia	2 (25)	13 (3.7)	8.74	1.61-47.55	0.012
Symptoms-no. (%)					
Sore throat	5 (62.5)	162 (45.8)	1.98	0.46-8.39	0.356
Neck swelling	8 (100)	221 (62.4)	NA	NA	NA
Dyspnea	7 (87.5)	28 (7.9)	81.50	9.68-686.18	<0.001
Dysphagia	7 (87.5)	154 (43.5)	9.09	1.11-74.67	0.040
Odynophagia	3 (37.5)	54 (15.3)	3.33	0.77-14.36	0.106
Retrosternal pain	3 (37.5)	0	NA	NA	NA
Septic shock	3 (37.5)	9 (2.5)	23	4.75-111.32	<0.001
More than one space-no. (%)	7 (87.5)	91 (25.7)	20.23	2.46-166.67	0.005
Present of necrotizing fasciitis-no. (%)	5 (62.5)	4 (1.2)	145.83	25.65-829.08	<0.001
Chest radiographic findings	*n=8*	*n=102*			
Widening mediastinum	4 (50)	3 (2.94)	33	5.45-199.64	<0.001
Pleural effusion	4 (50)	1 (0.98)	101	9.09-1122.69	<0.001
Time to surgery >24hr-no. (%)	2 (25)	16 (4.6)	10.44	1.78-61.27	0.009
Complications-no. (%)					
Septic shock	4 (50)	10 (2.8)	34.40	7.51-157.78	<0.001
Upper airway obstruction	4 (50)	8 (2.3)	43.25	9.15-204.40	<0.001
Pneumonia	3 (37.5)	5 (1.4)	41.88	7.79-225.09	<0.001
Dead-no. (%)	3 (37.5)	6 (1.7)	NA	NA	NA
Length of hospital stay-median (IQR)	21.5 (9-26.5)	3 (2-6)	NA	NA	NA

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

There were 602 medical records of DNI, 362 patients were eligible. Eight case were identified as case group while the control group was 354 cases. Prevalence of DNM was 2.2% while mortality rate was 37.5%. Most of the patients were male sex and their median age was 48 years (IQR 34 to 60) in control and 56 years (IQR 51 to 66) in case. Comorbidities diabetes mellitus, hypertension and anemia were found in case higher proportion than control significantly (DM; 87.5%, hypertension; 50.0% and anemia: 25% in case and DM; 21.8%, hypertension; 17.2% and anemia: 3.7% in control with P<0.001, 0.038 and 0.039, respectively).

For the presenting symptoms, the case group tended to have a higher proportion of symptom neck swelling (P=0.029), dyspnea (P<0.001), retrosternal pain (P<0.001) and septic shock (P=0.001). Comparing between case and control groups, it found that the former tended to have higher proportion of patients with more than one space infection (P=0.001), higher proportion of patients presented with necrotizing fasciitis (P<0.001), higher proportion of complications (P<0.001), higher proportion of dead (37.5%, P=0.001) and longer length of the hospital stay, 21.5 days (IQR 9 to 26.5) in case and 3 days (IQR 2 to 6) in control with P=0.002.

CAUSES OF INFECTION

Odontogenic cause (50%) was found to be the most common cause of infection follow by unknown cause (37.5%) and foreign body (12.5%) respectively in case while control was found pharyngotonsillar infection (40.1%) was the most common cause followed by odontogenic cause (24.6%), unknown cause (17.2%) and salivary gland in origin (16.9%) with P=0.004.

SPACES OF INFECTION

This study separated spaces of infection into two categories; single space, and more than one space infection. We found that in the case group, it tended to have more than one space infection (retropharyngeal space 85.7%, parapharyngeal space 71.4%, anterior visceral space 71.4%, Ludwig's angina 57.1%, masticator space 42.9% and prevertebral space 28.6%). On the other hand, control group tended to have more of single space infection and peritonsillar space (53.6%) was the most common single space infection followed by parotid space (35.4%) and parapharyngeal space (5.3%).

CAUSATIVE ORGANISM

In the case group, the causative organism varied in each case, one *Proteus mirabilis*, one *Enterococcus faecalis*, one *Staphylococcus epidermidis*, one candida, one *Corynebacterium,* two no growth and one had not been sent for culture. *Streptococcus spp.* (47.3%) was found to be the most common organism in control group especially *Streptococcus viridans* (55.8%), followed by *Klebsiella pneumoniae* (18.7%), *Staphylococcus coagulase negative* (7.7%), *Enterobacter spp.*(6.6%), *Staphylococcus coagulase positive* (5.5%), *Burkholderia psudomallei* (4.4%) and *Acinetobacter spp.* (3.3%).

Table 2. Space infection

Spaces infection	DNM	DNI
Single space-no. (%)	***(n=1)***	***(n=263)***
Peritonsillar space	0	141 (53.6)
Parotid space	0	93 (35.4)
Parapharyngeal space	0	14 (5.3)
Retropharyngeal space	1	5 (1.9)
Submandibular space	0	3 (1.1)
Masticator space	0	3 (1.1)
Sublingual space	0	2 (0.8)
Submental space	0	2 (0.8)
Ludwig angina	0	1 (0.4)
More than one space-no. (%)	***(n=7)***	***(n=91)***
Retropharyngeal space	6	19 (20.9)
Parapharyngeal space	5	59 (64.8)
Anterior visceral space	5	7 (7.7)
Ludwig angina	4	10 (10.9)
Masticator space	3	35 (38.5)
Prevertebral space	2	1 (1.1)
Carotid space	1	1 (1.1)
Danger space	1	0
Buccal space	1	15 (16.5)
Submandibular space	1	39 (42.9)
Parotid space	0	29 (31.9)
Peritonsillar space	0	11 (12.1)
Sublingual space	0	2 (2.1)
Submental space	0	10 (10.9)
Acute epiglottitis	1	2 (2.1)

CHEST RADIOGRAPHIC FINDINGS

All of 8 case-patients had chest radiography while only 102 (28.8%) control patients had. There was only 1 case-patient who had a normal chest radiography, most common abnormal finding in case patients were widening mediastinum and pleural effusion. The proportion of widening mediastinum and pleural effusion on chest radiography in the case was 50% which was higher than control (2.9% and 0.9% respectively with $P<0.001$).

FACTORS ASSOCIATED WITH DNM

The associated clinical presentations of mediastinal extension in DNI were dyspnea (OR, 81.5; 95% CI, 9.68 to 686.18), dysphagia (OR, 9.09;95% CI, 1.11 to 74.67) and septic shock (OR, 23.00; 95% CI, 4.75 to 111.32) while comorbidities which associated with mediastinal extension were diabetic mellitus (OR, 25.18; 95% CI, 3.05 to 207.80), hypertension (OR, 4.80; 95% CI, 1.17 to 19.73), chronic liver disease (OR, 16.71; 95% CI, 1.54 to 181.25) and anemia (OR, 8.74; 95% CI, 1.61 to 47.55). Moreover, variables more than one space infection (OR, 20.23; 95% CI, 2.46 to 166.67), present of necrotizing fasciitis (OR, 145; 95% CI, 25.65 to 829.08), time to surgery after admission more than 24hr (OR, 10.44; 95% CI 1.78 to 61.27), widening mediastinum (OR, 33.00; 95% CI,5.45 to 199.64) and pleural effusion (OR, 101; 95% CI, 9.09 to 1122.69) on radiographic finding were also associated with mediastinal extension.

DISCUSSION

MAJOR FINDINGS

This study found dyspnea, dysphagia and septic shock were the clinical features that associated with DNM. For the associated predisposing factors of DNM were comorbidity (diabetes mellitus,

hypertension, chronic liver disease and anemia), present of necrotizing fasciitis, time to surgery after admission more than 24 hours, more than one space infection, widening mediastinum and pleural effusion on chest radiography. Among the 3 patients who died in the case group, all of them were men with diabetes mellitus and presented with necrotizing fasciitis, 2 patients got delayed mediastinal drainage more than 24 hours and died from sepsis, while one patient had no surgery because he had cardiac arrest 2 hours after admission, therefore underlying disease of diabetes mellitus combined with present of necrotizing fasciitis and delayed mediastinal drainage more than 24 hours seemed to be a poor prognostic factors.

COMPARISON WITH OTHER STUDIES

The presenting symptoms of DNM (dyspnea, dysphagia, and septic shock) in this study were comparable with previous studies,[11,15,18] but for comorbidity factors still varied. Ridder et al found that impaired tissue oxygenation was a risk factor for the development of DNM.[15] In this present study, only diabetes and anemia could be explained with this theory. This present study also found chronic liver disease (cirrhosis) was one of the associated comorbidity, which was different from previous studies,[11,21] this might be explained from 50% of the case group had alcohol abuse, however, there was no correlation between chronic substance abuse with DNM by using logistic regression analysis. The study from Italy,[21] concluded that diabetes and chronic substance abuse (e.g. alcohol and nicotine abuse) represented predisposing factors for developing DNM, but there was no association between chronic alcohol abuse with DNM in this present study. The present of necrotizing fasciitis was one of the predisposing factors of DNM in the present study, this finding consistent with the study from Slovenia,[19] which found a high risk of DNM particularly necrotizing fasciitis that spread along the pretracheal lamina.

One interesting finding from this present study was the prevalence of DNM (2.2%) and the other studies' prevalence in Thailand (0.3% and 1.6% respectively)[3,4] were surprisingly lower than developed countries (8-21.4%),[2,8,14] this might reflect the more common use of computer tomography (CT) scan in DNI in developed countries, which help to early detect DNM. Many studies,[5,8,11,18,19] suggest that contrast-enhanced CT is the method of choice for evaluation of DNM and simple chest radiography shows limit role in diagnosis DNM. The author of this present study agree with the high accuracy of CT, however, in developing countries, simple chest radiography still useful as the result of widening mediastinum and pleural effusion on chest radiography in the current study was correlated with DNM significantly.

In the present study, odontogenic infection is the most common cause of DNM infection, this finding was comparable with the two previous studies,[8,11] but the causative organism could not be concluded because there were only 5 different positive culture in the present study, moreover, the setting of this present study could not perform anaerobic culture, therefore, there was no report of

anaerobic bacteria. However, in control group, the most common organism was *Streptococcus spp*. (47.3%) especially *Streptococcus viridans* (55.8%) which were comparable with most of the previous studies regarding DNI and DNM.[3,4,8,14,1 5,19]

Involvement of two or more spaces is a significant predicting factor for descending mediastinitis,[2,8] there are several routes for spreading to the mediastinum, retropharyngeal space route is the most common (70%), follows by carotid space (21%) and prevertebral space (8%).[22] This present study also found more than one space infection was one of the associated predisposing factor and retropharyngeal space was also the most common space (85.7%) in DNM group, however, the following spaces were parapharyngeal space (71.4%) and anterior visceral space (71.4%) which were different from the previous study. [22]

STRENGTH AND LIMIATION

To the present knowledge, this is the first case-control study about complication of descending necrotizing fasciitis in DNI in Thailand, however, according to the low prevalence of the case, so there were too small sample sizes to use the multivariate analysis, moreover, there were also some missing data in case patients, so adjusted odds ratio could not be evaluated. Secondly, anaerobic culture is not available in the setting of this study, therefore, there was no report of anaerobic bacteria in this study.

CONCLUSION AND IMPLICATION

In conclusion the clinical features that associated with DNM in this study were dyspnea, dysphagia and septic shock and the predisposing factors of DNM were comorbidity especially diabetes mellitus, hypertension, chronic liver disease and anemia, present of necrotizing fasciitis, time to surgery after admission more than 24hr, more than one space infection, widening mediastinum and pleural effusion on chest radiography. Present of widening mediastinum and pleural effusion on chest radiography in DNI patient should be a warning sign for DNM and CT imaging should be considered as soon as possible. For better understanding of the predisposing factors of DNM, the result of anaerobic culture should be reported and a larger multi-center study should be conducted in the future.

ACKNOWLEDGMENTS & DECLARATION

The author would like to thank Dr. Thammasorn Jeeraaumponwat for his nice suggestions and Dr. Theeranuch Khongsawadi from Saraburi Hospital who always give me support, even from a distance.

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

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Infection rate of using sterile versus non sterile strips in postoperative cesarean delivery

ORIGINAL ARTICLE

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Accepted: August 2017
Latest revision: September 2017
Printed: October 2017

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ABSTRACT

OBJECTIVE

To compare the rate of surgical wound infection post cesarean delivery between using using sterile strip and no sterile strip.

METHODS

We conducted a retrospective cohort study by verifying and reviewing all medical records of patients undergoing cesarean delivery with or without using the sterile strip in Khon Kaen Hospital from January 2013 through July 2013 using hospital database. The primary outcome was surgical wound infection after surgery. Secondary outcomes included other cesarean delivery complications.

RESULTS

The study comprised a total of 921 patients (182 in using sterile strip group and 739 in non using sterile strip group). Surgical wound infection rate was not significantly lower in using sterile strip group than in non using sterile strip group (0.5% vs. 0.9%; adjusted odds ratio (AOR), 0.676; 95% confidence interval (CI), 0.078 to 5.837). In using sterile strip was decreasing postoperative fever (AOR, 0.329; 95% CI, 0.173 to 0.625).

CONCLUSION

Using sterile strip was not decrease the risk of surgical wound infection rate in postoperative cesarean delivery.

INTRODUCTION

Cesarean delivery is method to deliver an infant through laparotomy and hysterotomy.[1] Approximately, 27% of the women undergoing cesarean delivery in Indonesia, Malaysia, the Philippines, and Thailand in 2005.[2] Cephalopelvic disproportions (CPD) is the most common indication in Thailand.[2] Sutures and staples are the standard methods for skin closure.[3-7] The sterile strip is frequently used in small cuts and wounds or to support the wound after suture or staple removal.[8] Several studies showed that sterile strip had significantly less edema and erythema than patient with a suture closure.[9-11] However, another two studies stated that surgical wound infection rate was not significantly different between using sterile strip and suture.[12-13] Still, the controversial evidence of efficacy using the sterile strip in surgical incision still were relied on relatively small sample size, less than seventy patients for each study and were subjected to conflict of interest from the support of the pharmaceutical company. Thus we conducted a large retrospective cohort study to evaluate the rate of infection in cesarean delivery case that using the sterile strip.

METHODS

STUDY DESIGN

This is a retrospective cohort study comparing infection rate of surgical wound between using sterile strip and non using the sterile strip in women undergoing cesarean delivery.

PATIENTS

The medical records of pregnant women delivered by cesarean section at Khon Kaen Hospital between January and July 2013 were all verified and reviewed. Patients with hypertension, diabetes mellitus, AIDS, congestive heart failure, urinary tract infection, endometritis, chorioamnionitis, other infection, severe intraoperative and postoperative complications, and mother with footling breech presentation were excluded. Those with incomplete medical records were also excluded.

DATA COLLECTION

Data of each pregnant woman that included in the study was reviewed and recorded regarding baseline characteristics. These included age, type of skin closure, gestational age, indication for cesarean delivery, number of parity, intraoperative bleeding, operative time and postoperative antibiotics using.

OUTCOMES MEASURES

The primary outcome was surgical wound infection defined by surgical site infection criteria of the Centers for Disease Control and Prevention[11] that mentioned purulent drainage from the incision site, found organisms from superficial incision fluid or tissue, one of sign of infection: pain or tenderness; localized swelling; redness; fever and diagnosed by attending physician. The secondary outcome was postoperative fever within three days, duration of postoperative admission and wound separation.

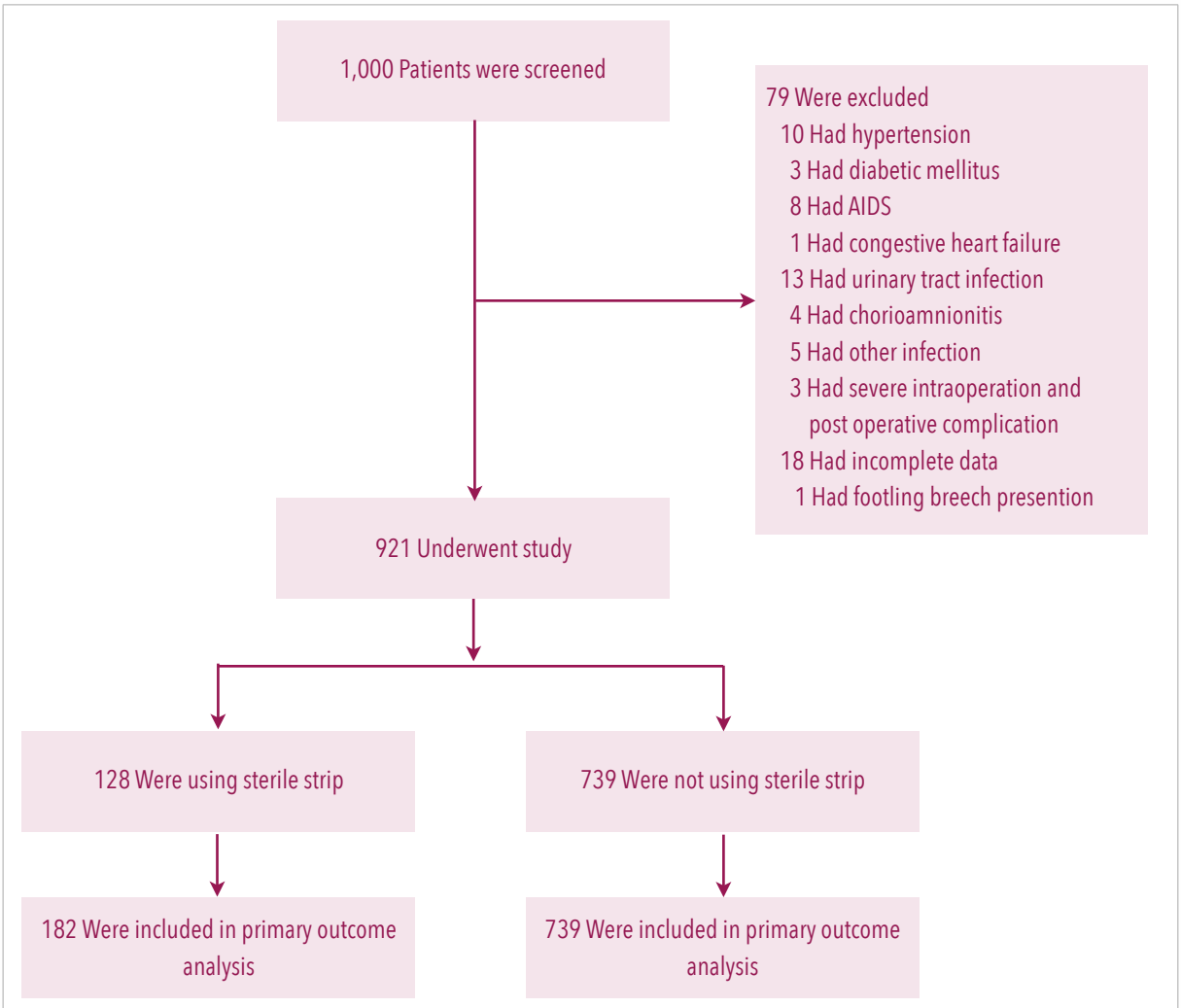

Figure 1. Enrollment and Analyses of Primary Outcomes. The numbers of patients who excluded from the study.

STATISTICAL ANALYSIS

We imputed data by double entry and cleaned all data before analysis. Frequency tables for all variable were generated to identify wild value. All statistical analyses were performed using the statistical software. We described variables in using number and % for categorical variables. For non-normally distributed scale data, we described using median and interquartile range (IQR). For inferential statistics, we used either chi-square or Fisher's exact test to identify the relationship between two categorical variables where appropriate. The association between using the sterile strip and the outcomes were presented in term of relative risk (RR) and its 95% confidence Interval (95% CI). The others factor that related to the outcomes we used logistic regression analysis to identify adjusted odds ratio (AOR).

Table 1: Patients' characteristics

Characteristic	Using sterile strip (N=182)	Non using sterile strip (N=739)	P Value
Age–yr			<0.001
Median	29.1	27.2	
Interquartile range	25.5-32.1	23.2-31.1	
Skin closure by using staple–no. (%)	115 (63.2)	630 (85.3)	<0.001
Estimated gestational age–wk			0.018
Median	38.0	38.0	
Interquartile range	38.0-39.0	38.0-39.0	
Indication for cesarean delivery–no. (%)			
Previous cesarean delivery	49 (26.9)	269 (36.4)	0.016
Cephalopelvic disproportion	91 (50.0)	241 (32.6)	<0.001
Placenta previa	11 (6.0)	21 (2.8)	0.035
Fetal distress	20 (11.0)	117 (15.8)	0.100
Severe preeclampsia	2 (1.1)	22 (3.0)	0.198
Fetal malposition	8 (4.4)	91 (12.3)	0.002
Multiple pregnancy	1 (0.5)	17 (2.3)	0.226
Abruptio placenta	0	2 (0.3)	1.000
Failed induction	2 (1.1)	11 (1.5)	1.000
Prolapsed cord	0	6 (0.8)	0.605
Parity–no. (%)			<0.001
0	94 (51.6)	257 (34.8)	
1	59 (32.4)	335 (45.3)	
2	21 (11.5)	114 (15.4)	
3 or more	8 (4.4)	33 (4.5)	
Intraoperative bleeding–(ml)			0.359
Median	300.0	300.0	
Interquartile range	300.0-400.0	300.0-400.0	
Operative time–(min)			0.383
Median	36.0	37.0	
Interquartile range	30.0-42.0	30.0-45.0	

Table 2: Outcomes and prescribed antibiotics

Clinical information and medications	Using sterile strip (N=182)	Non using sterile strip (N=739)	Relative risk (95% confidence interval)
Wound infection–no. (%)	1 (0.5)	7 (0.9)	0.580 (0.072-4.685)
Postoperative fever within 3 day–no. (%)	20 (11.0)	310 (41.9)	0.262 (0.172-0.400)
Wound Separation–no. (%)	0	2 (0.3)	0
Duration of postoperative administration > 3 days–no. (%)	19 (10.4)	52 (7.0)	1.484 (0.900-2.446)
Using antibiotics postoperative–no. (%)			
Cefazolin	175 (96.2)	702 (95.0)	1.012(0.979-1.047)
Ceftriaxone	0	16 (2.2)	0
Amoxicillin	156 (85.7)	55 (7.4)	11.517 (8.871-14.953)
Dicloxacillin	11 (6.0)	7 (0.9)	6.381 (2.508-16.231)
Cloxacillin	2 (1.1)	3 (0.4)	2.707 (0.456-16.082)
Ampicillin	0	11 (1.5)	0
Metronidazole	1 (0.5)	6 (0.8)	0.677 (0.082-5.587)
Clindamycin	1 (0.5)	8 (1.1)	0.508 (0.064-4.033)
Penicillin group	156 (85.7)	72 (9.7)	8.798 (7.009-11.043)
Cephalosporins group	175 (96.2)	706 (95.5)	1.007 (0.974-1.040)

RESULTS

PATIENTS

A total of 1,000 pregnant women underwent cesarean delivery from January to July 2013. Seventy-nine patients were excluded from this study; 10 had hypertension, 3 had diabetes mellitus, 8 had HIV infection, 13 had urinary tract infection, 13 had endometritis, 4 had chorioamnionitis, 1 had congestive heart failure, 5 had others infection, 3 had severe intraoperative and postoperative complications, 1 had preterm cesarean delivery at 24 weeks, 18 had incomplete data (Figure 1). Of the 921 patients, who were included in the study, 182 using the sterile strip and 739 not using the sterile strip. The median age of the patients was 27.1 years old with the median gestational age of 38.0 weeks. Most of them used staple for their skin closure. The most common indication for cesarean delivery was cephalopelvic disproportion. Nearly all patients were given cefazolin preoperatively.

The group with sterile strip tended to be older (P<0.001) (Table 1), less proportion of patients using staple for skin closure (P<0.001), less proportion of those with history of previous cesarean delivery (P=0.016), more proportion of those with cephalopelvic disproportion (P<0.001),

Table 3: Factors Related Post Cesarean Section Delivery Complications

Factor	Wound infection Adjusted odds Ratio (95% CI)	P Value	Postoperative fever Adjusted Odds Ratio (95% CI)	P Value
Sterile strip	0.676 (0.078-5.837)	0.722	0.329 (0.173-0.625)	0.001
Age	0.939 (0.802-1.098)	0.429	0.957 (0.928-0.988)	0.006
Skin closure by using staple	1.488 (0.176-12.608)	0.716	1.180 (0.794-1.753)	0.410
Previous cesarean delivery	0.258 (0.031-2.152)	0.210	0.773 (0.569-1.049)	0.098
Operative time	1.032 (0.985-1.082)	0.180	1.024 (1.011-1.036)	<0.001
Amoxicillin	N/A		0.470 (0.269-0.822)	0.008

more proportion of those with placenta previa (P=0.035), less proportion of those with fetal malformation (P=0.002), higher proportion of those without history of pregnancy (P<0.001). However, gestational age, indication for cesarean delivery regarding fetal distress, severe preeclampsia, multiple pregnancy, abruptio placenta, failed induction, prolapse cord, intraoperative bleeding and operative time were similar across the two groups.

OUTCOMES

For the primary outcome, there were only eight cases of surgical wound infection, of these, seven patients were in the non using sterile strip group and one patient was in the using sterile strip group (RR, 0.580; 95% CI, 0.072 to 4.685) (Table 2). In relation to the secondary outcomes, In using sterile strip group there was 20 patients had the postoperative fever but 310 patients in non using sterile strip group (RR, 0.262; 95% CI, 0.172 to 0.400) (Table 2). There were two patients who had wound separation in the non using sterile strip group but none in using sterile strip group. Using sterile strip group had longer duration of postoperative administration than another group (RR, 1.484; 95% CI, 0.900 to 2.446)

FACTORS ASSOCIATED WITH INFECTION

From the logistic regression analysis, no factors related to wound infection and we found risk factors of postoperative fever; age (AOR, 0.957; 95% CI, 0.928 to 0.988), operative time (AOR, 1.024; 95% CI, 1.011 to 1.036), and using amoxicillin (AOR, 0.470; 95% CI, 0.269 to 0.822) (Table 3).

CONCLUSION

PRINCIPAL FINDINGS

Our retrospective cohort study compares surgical wound infection rate between using sterile strip group and non using in cesarean delivery. We found that surgical wound infection rate in using sterile strip group in cesarean delivery was not less than in those not using the sterile strip. Although, age, skin closure by using staple, previous cesarean delivery and operative time were not associated

significantly with wound infection. In addition, we found using the sterile strip, age and using amoxicillin after operation tended to decrease the rate of postoperative fever while longer operative time increased the rate of postoperative fever.

STRENGTH AND LIMITATION

This study found that using sterile strip was not decreasing surgical wound infection rate. Due to our study is retrospective cohort design, lost of medical record causing missing data. However, we excluded those with incomplete data. Moreover, others recorded data such as gestational age, operative note and progression note during administration might not be exactly accurate. Nevertheless, we attempted to verify all data before recording onto the spreadsheet. To precisely estimate the relationship between using the sterile strip and wound infection in the cesarean delivery patient based on the rate of infection found in our study, the sample size should be up to 26,000 patients. Moreover, our results were merely based on the environment that preoperative antibiotics were given routinely.

COMPARISON WITH OTHER STUDIES

There were five studies that comparing sterile strip and conventional skin closure including two studies conducted in the USA, one in Ireland, one in Canada and one in Greece.[12-16] Of these five studies, their primary outcome was not surgical sites infection. Only three studies mentioned wound infection as secondary outcome including two in the USA and one in Greece, and their results supported our findings; no association between using the sterile strip and wound infection.[12,14,16] Moreover, those studies also supported our results that using sterile strip did not decrease wound separation rate[12,14,16] while one study in Canada suggested that using sterile strip increase wound separation.[15] However, the Canadian study included all wound types not only surgical wound. Other outcomes postoperative fever and duration of postoperative administration were not found in other studies.

CONCLUSION AND IMPLICATION

In conclusion, this retrospective-cohort study suggested that using the sterile strip and other factors were not associated with surgical wound infection in the post-cesarean delivery patient. Older age, using sterile strip and amoxicillin were likely to decrease the rate of postoperative fever. Longer operative time tended to increase the rate of postoperative fever.

Compare with the others, our study lacks variable regarding wound healing processes such as wound closure time, pain and cosmetic result. Nonetheless, there are still little studies on the association between using the sterile strip and the rate of wound infection, the prospective cohort with larger sample is required.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his advice and suggestion.

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

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Alteration of serum liver enzyme in patients receiving levetiracetam

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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Accepted: August 2017
Latest revision: September 2017
Printed: October 2017

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ABSTRACT

OBJECTIVE

Levetiracetam is the second line antiepileptic drug that absent of hepatic metabolism. However, very few studies can demonstrate its safety regarding serum liver enzymes.

METHODS

We conducted retrospective cohort study by reviewing of medical records and serum liver enzyme using the hospital online database of those who received levetiracetam as a monotherapy as both outpatient and inpatient in Khon Kaen Hospital from March 2010 to May 2014. We compared baseline of serum liver enzymes e.g., aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and after received levetiracetam in period of one year after drug started.

RESULTS

There were 29 patient who received levetiracetam in all indications. No significant elevation of serum AST and ALT level at 3, 6, 9 and 12 month were observed. Serum ALT levels tended to decrease in the first 3 months after receiving the drug significantly (mean difference, -79.2 U/L, (95% confidence interval [CI], -151.0 to -7.5), and it start rising gradually since then. The same pattern was also observed for the serum AST level without significantly changes.

CONCLUSION

We were unable to demonstrate the risk of hepatotoxicity from using levetiracetam over the period of one year.

INTRODUCTION

Epileptic or seizure treatments usually depends on types of the disease and background of the patients with balancing the risks and benefits.[1] Treatment and refractory are still common.[1-3] There are more than 15 antiepileptic drugs (AEDs) available in the market but new drugs are few.[2] Levetiracetam is a new AED with more several advantages over the old AEDs.[4-6]

Its effectiveness is found in the adjunctive therapy for treatment seizure, epilepsy, head trauma, brain tumor, brain infection and other medications such as a stroke or Alzheimer's disease.[7-15] However, there are some evidence of an increased serum liver enzymes in patients after receiving levetiracetam in Italy and Australia; one case report stated the fulminant liver failure after received levetiracetam for 6 days in the patient with neurocysticercosis with seizure and 14 case-series of the patient with epilepsy and chronic liver disease who received levetiracetam. This case-series showed no worsening of liver function after receiving levetiracetam.[2,15-18] However, its sample is not enough power to conclude levetiracetam is the therapeutic option in the patient with epilepsy with no side effect of hepatitis. Our objective is to examine the association between levetiracetam and patients' serum liver enzyme in various patient conditions including those with epilepsy, concomitant chronic hepatopathy with epilepsy, prevention seizure from intracranial causes.

METHODS

STUDY DESIGN

This is a retrospective cohort study with before and after study comparing the alteration of serum liver enzyme level before and after received levetiracetam.

PATIENTS

We reviewed medical records and serum liver enzyme of the patient who received levetiracetam as a monotherapy as both outpatient and inpatient from March 2010 to May 2014. Patients who loss to follow up, no serum liver enzyme at baseline before receiving the drug, no serum liver enzymes after receiving the drug, age below than 15 years, using combined antiepileptic drug therapy, using with other drug-induced hepatitis, dead case in IPD, unknown cause of seizure, patient denying continuing the prescribed medical treatment were excluded.

DATA COLLECTION

Patients who were included in this study were reviewed and recorded baseline characteristics comprising age, sex, indication for levetiracetam use, epilepsy type, seizure type, baseline of serum liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) before received levetiracetam and serum AST, ALT after received levetiracetam in period of 1 year after drug started.

Table 1. Baseline characteristics of the patients

Characteristic	Value
Age-yr.	44.5±16.2
Male sex-no. (%)	13 (45)
Indication for levetiracetam use-no. (%)	
Concomitant chronic hepatopathy	
Chronic hepatitis C	1 (3)
Alcoholic hepatitis	4 (14)
Prevention seizure from intracranial causes	
Brain tumor	2 (7)
Meningoencephalitis	3 (10)
Cerebral infarction	5 (17)
Intracerebral hemorrhage	2 (7)
Subarachnoid hemorrhage	1 (3)
Epilepsy with no specific cause	12 (41)
Epilepsy type-no. (%)	
Symptomatic localised epilepsy	1 (3)
Generalised epilepsy	
Idiopathic	7 (24)
Symptomatic	16 (55)
Symptomatic undetermined epilepsy	1 (3)
Presentation of seizure-no. (%)	
Generalised	
Tonic clonic	21 (72)
Tonic	1 (3)
Myoclonic	1 (3)
Status epilepticus	3 (10)
Baseline AST-U/L	
Median	37
Interquartile range	24-112
Baseline ALT-U/L	
Median	36
Interquartile range	17-96

OUTCOMES MEASURES

We measured the alteration of serum AST and ALT levels at 3, 6, 9 and 12 month after receiving levetiracetam comparing with baseline serum AST and ALT levels before receiving drug and incidence of patients that serum AST and ALT elevated significantly (either serum AST or ALT elevate>500 U/L).[20]

STATISTICAL ANALYSIS

The data were exported from the study database that using double data entry in spreadsheet software and analyzed with the use of Statistical Package for the Social Science (SPSS) software version 18. All analyses were performed and detected missing data and impossible data then we report the number of available and make no assumptions about the missing data and impossible data. We described the demographic characteristics, clinical at baseline variables in number and percentages (no. %), other variables, e.g., age scale was using mean and standard deviation (mean±SD), baseline serum AST, ALT level were using median and interquartile range. The incidence of elevated serum AST, ALT after receiving levetiracetam in three conditions are presented as the number of patients who had the event at all time point.Differences between measures of mean serum AST, ALT level before and after receiving levetiracetam were analyzed with the use of means difference (±SD), and we use forest plot for the subgroup to compare different serum AST and ALT level between groups in different time of follow up.

Table 2. Number of patients with levated serum liver enzymes after receiving levetiracetam.

Patients	No.	Number of patients having elevated serum liver enzyme after 3 Months		No.	Number of patients having elevated serum liver enzyme after 6 Months		No.	Number of patients having elevated serum liver enzyme after 9 Months		No.	Number of patients having elevated serum liver enzyme after 12 Months	
		Significant	Not significant		Significant	Not significant		Significant	Not significant		Significant	Not significant
All patients												
AST	17	0	4	9	0	4	7	0	2	4	0	2
ALT	17	0	7	9	0	5	7	0	5	4	0	2
Concomitant chronic hepatopathy												
AST	5	0	0	0	0	0	0	0	0	1	0	0
ALT	5	0	1	0	0	0	0	0	0	1	0	0
Prevention seizure from intracranial causes												
AST	6	0	3	4	0	1	4	0	2	2	0	1
ALT	6	0	3	4	0	2	4	0	3	2	0	1
Epilepsy												
AST	6	0	1	5	0	3	3	0	0	1	0	1
ALT	6	0	3	5	0	3	3	0	2	1	0	1

RESULTS

From February 2010 through May 2014, we screen 443 adult patients who had received levetiracetam regardless conditions. Of these, 414 patients were excluded; by exclusion criteria, the most patients had been excluded due to the combination of drug therapy and no baseline serum liver enzymes before received levetiracetam. Twenty-nine patients were included to study in three groups according to the indication of levetiracetam use; 5 in those with concomitant chronic hepatopathy, 12 for prevention of seizure from intracranial cause and 12 in those with epilepsy. Most subjects were female with an average age of 45 years old with generalized tonic-clonic seizure in the majority. The demographic characteristics, clinical and liver enzyme level at baseline are presented in Table 1.

There were no significant elevation at all points of time (Table 2). In 5 concomitant chronic hepatopathy, we follow up the patient in 3 months for 5 patients and in 9 months for 1 patient, the result showed that only 1 (20%) patient had elevated of serum ALT level non-significantly, with no elevation of AST level. In 12 patients who received levetiracetam for prevention of seizure from intracranial causes, we follow up patient in 3, 6, 9 and 12 months, the results suggested the possibility of elevation of serum AST and ALT level after receive levetiracetam non-significantly and most elevation occurred in the first 3 months. This was similar to the findings in 12 patients with

Table 3. Differences in Mean of Serum Liver Enzyme Before and After Receiving Levetiracetam.

Variable	Serum liver enzyme level at 3 months		Serum liver enzyme level at 6 months		Serum liver enzyme level at 9 months		Serum liver enzyme level at 12 months	
	AST	ALT	AST	ALT	AST	ALT	AST	ALT
All patients	142.7±289.8	-79.2±139.6	-1.8±27.0	-3.6±37.7	-6.4±15.5	7.6±17.9	18.8±57.3	18.0±73.8
Age-yr.								
≤44.5	-51.6±99.2	-32.9±56.4	-37.0±21.2	-53.5±29.0	0.0	5.0	-34.0	-41.0
>44.5	-361.4±473.4	-190.4±217.5	8.3±19.0	10.7±26.2	-7.5±16.7	8.0±19.6	36.3±55.4	37.7±76.4
Sex								
Male	-282.3±417.0	-142.3±190.0	6.8±26.1	-1.4±50.9	1.0±13.2	6.8±24.9	4.5±7.8	-6.0±15.6
Female	-45.0±87.0	-12.5±27.4	-16.3±14.2	33.0±94.8	-35.1±72.9	-6.3±17.9	8.7±5.5	42.0±117.4
Concomitant hepatopathy	-405.8±441.8	-192.0±209.3					-34.0	-41.0
Chronicn hepatitis C	-63.0	- 91.0					-34.0	-41.0
Alcoholic hepatitis	-74.0±44.8	-75.3±55.8						
Prevention seizure	-62.2±110.7	-48.5±85.5	5.8±25.3	15.5±35.9	-1.5±17.7	10.5±22.8	4.5±7.8	-6±15.6
Brain tumor	-26.0±5.7	-28.0±17.0						
Meningoen cephalitis	-5.0±22.6	-12.0±18.4	-10.0	3.0				
Cerebral infarction			-41.0±32.7	-60.7±54.1	-33.0±9.2	-46.3±22.9	-29.5±21.9	-27.0±14.1
Intracerebral bleeding	-80.0	-47.0	-29.0	-33.0	-29.0	-27.0		
Subarachnoid bleeding	-260.0	-203.0						
Presentation of seizure								
Generalised								
Tonic clonic	-157.9±312.8	-77.9±148.3	-5.4±28.6	-3.4±16.7	-11.5±16.3	10.0±7.1	21.7±69.8	29.7±85.7
Tonic					-16.0	-9.0		
Myoclonic			0.0	-8.0		-14.0	0.0	
Status epilepticus	11.0	1.0	23.0	8.0	-16.0	-9.0		
Epilepsy	-186.6±349.6	-96.0±163.2	-7.8±29.5	-18.8±34.9	-13.0±11.8	3.7±12.0	33.0±94.72	42.0±117.4
Localised								
symptomatic			-29.0	-33.0	-29.0	-27.0		
Generalised								
Idiopathic	-130.3±135.2	-65.5±68.95	14.0±12.7	6.0±2.8			-17.5±23.3	-18.0±32.5
Symptomatic	-164.5±369.4	-87.9±172.4	-15.4±23.2	-22.2±32.3	-9.8±11.6	-0.8±13.2	100.00	125.0
Undetermined								
Symptomatic	-19.0	-28.0						

Plus-minus values are mean differences±SD. Figures without plus-minus indicate no SD as N=1

epilepsy that their serum ALT were all elevated non-significantly at 9 and 12 months.

Serum ALT levels tended to decrease (minus mean difference) in the first 3 months after receiving the drug significantly (mean difference, -79.2 U/L, (95% confidence interval [CI], -151.0 to -7.5), and it start rising gradually since then. The same pattern was also observed for the serum AST level without significantly changes as well as in the subgroup of those with concomitant chronic hepatopathy, prevention seizure from intracranial causes group and epilepsy group, especially in early follow up at 3 and 6 months serum liver enzyme levels obviously decreased as presented in Table 3.

DISCUSSION

MAIN FINDINGS

In our retrospective cohort study with 29 patients who received levetiracetam as monotherapy in three subgroups according to their indications, we found the possibility of non-clinically significant elevation of serum AST and ALT level over the study period. It mostly occurred in patient who received the drug for preventing seizure from intracranial cause. Those who had high serum liver enzymes at baseline before drug taking tended to have sharply decline of serum liver enzymes at the first 3 months of follow up especially for the serum ALT which decreased statistically significantly.

COMPARISON WITH OTHER STUDIES

There are two studies that compare levetiracetam and elevation of serum liver enzymes, one of these is case series that conducted in Italy and another one is a case report from Australia.[2,19] In our study we found some of these patients had elevated non-significant of AST and ALT level over the period of one year. This was similar to the findings from the case series that showed no worsening of serum liver enzymes after using levetiracetam in concomitant hepatopathy.[2] However, in the case reported stated the occurrence of fulminant liver failure after received levetiracetam for 6 days.[19] Still, a larger study should be conducted.

STRENGTH AND LIMITATION OF THE STUDY

To our knowledge, this is the largest cohort study described the alteration of serum liver enzyme in patients receiving levetiracetam in order to see the relationship between using levetiracetam and elevation of serum liver enzymes in difference indication of the drug used. Nonetheless, in our study, we followed up patients' serum liver enzymes over 4 years time span; 2010 to 2014. However, this study had limitations, including a small number of patients. We could identify only 29 cases over the period of 4 years due to levetiracetam was recently used in our setting. The study design was retrospective cohort study using secondary data that might risk for missing data. However, we tried to verify all the data before we collected on the data collection sheets as well as we excluded those with incomplete data. Moreover, most patients had an irregular interval of serum liver enzymes measurement causing less precise estimation of serum liver enzymes at specific points of times and their trends. Furthermore, one of the important confounders is that we failed to

acknowledge patients compliance to the medication as we did not have data regarding this. The non-significant decrease of serum liver enzyme might be due to poor compliance, thus, we might not conclude the relationship between using levetiracetam and elevation of serum liver enzymes properly.

CONCLUSION AND IMPLICATION

We were unable to demonstrate the risk of hepatotoxicity from using levetiracetam over the period of one year because this study was not powered for equivalence. Ideally, the study should be repeated with a larger sample size with prospective in nature using primary data collection approach from multi-center to confirm the risk of hepatotoxicity for more accurate data and examine in other small adverse effects of levetiracetam e.g., the eosinophilia, thrombocytopenia, teratogenic effect and suicidal thought/attempt. A post-market surveillance should also be planned in countries where the drug is marketing.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his advice and suggestion.

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

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Validity of the symptom 7-item questionnaire for verbal screening for diagnosis of pulmonary TB in the inmates

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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Accepted: August 2017
Latest revision: September 2017
Printed: October 2017

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ABSTRACT

OBJECTIVE

To assess the validity of the symptom 7-item questionnaire for verbal screening for diagnosis of pulmonary tuberculosis (TB) in the inmates.

METHODS

This is a cross-sectional diagnostic study to assess the validity of the modified 7-item questionnaire for verbal screening for diagnosis of pulmonary TB in inmates. The study was conducted in the inmates with Khon Kaen Central Prison, Thailand from February to May 2017. The participants were all inmates regardless to gender aged 20 years old or older. The questionnaire used in the present study comprised 7 questions for verbal screening for diagnosis of pulmonary TB.

RESULTS

There were 4,490 inmates underwent verbal screening, 531 were positive for at least 1 out of the 7 questions, 3 were found positive from sputum AFB stain and 6 were positive from Xpert® MTB/RIF assay. In total, there were 9 cases pulmonary tuberculosis. The single question regarding currently on tuberculosis treatment had the highest sensitivity (67.6%) and positive likelihood ratio (2.1), while the question regarding palpable mass around the neck has the highest specificity (93.9%). The combined set of questions using "OR" affected higher sensitivity which it was able to achieve 100% while nothing change for specificity and positive likelihood ratio.

CONCLUSION

The questionnaire for verbal screening for diagnosis of pulmonary TB in the inmates had high sensitivity with no difference regarding specificity and positive likelihood ratio comparing to using the single question.

INTRODUCTION

Tuberculosis is the worldwide epidemic with the estimated of nearly 10 million new infected cases and more than 1 million deaths from the disease yearly.[1] The incidence is even higher in the inmate population due to the high density in nature.[2-4] Active screen is still crucial especially in resource-limited setting.[5-9] Verbal screening using symptom questionnaire is used to identify an individual at risk for tuberculosis in large scale as it is inexpensive, quick and convenient for the health care provider.[10-12] Its variety depends largely on the number of questions and the implemented population.[13-15] However, the validity of the verbal screening is still poor. [13-15] The add-on questions[16] or modification of the question, for instance, expansion from 2-week cough to 3-week cough aim to increase the validity of the test.[15] A previous study, in Thai population, the 7-item questionnaire was used, however, that study tended to analyze for each question rather than the combined set of its questions.[17] The main objective of this study aims to identify the validity of the 7-item questionnaire for verbal screening for diagnosis of pulmonary TB in the inmate.

METHODS

STUDY DESIGN AND PARTICIPANTS

This is a cross-sectional diagnostic study to assess the validity of the modified 7-item questionnaire for verbal screening for diagnosis of pulmonary TB in inmates. The study was conducted in the inmates with Khon Kaen Central Prison, Thailand from February to May 2017. The participants were all inmates regardless to gender aged 20 years old or older. We excluded those were unable to communicate and those were released before final diagnosis.

Box 1. The 7-item questionnaire for verbal screening for diagnosis of pulmonary tuberculosis (REF)

Within the last month, have you....?

1.Had cough lasting more than 2 weeks

2. Had fever lasting more than 1 week

3. Had weight loss more than 5% of your weight last month

4. Had night sweating

5.Had hemoptysis

6. Were on any tuberculosis treatment

7. Had any palpable mass around your neck

QUESTIONNAIRE

The questionnaire used in the present study was the 7-item questionnaire for verbal screening for diagnosis of pulmonary TB recommended by WHO. (REF) This was a one-page questionnaire. The questions comprise characteristics of the participants (e.g., age, gender, duration in the prison, underlying diseases (e.g., diabetes, hypertension, chronic obstructive pulmonary disease/asthma, HIV infection, chronic kidney disease and other diseases) followed by 7 questions of verbal screening. (Box 1)

DATA COLLECTION AND PARTICIPANT PROCESS

There were five research assistants for data collection. All of them were experienced registered nurses and had to pass the 6-hour training to be

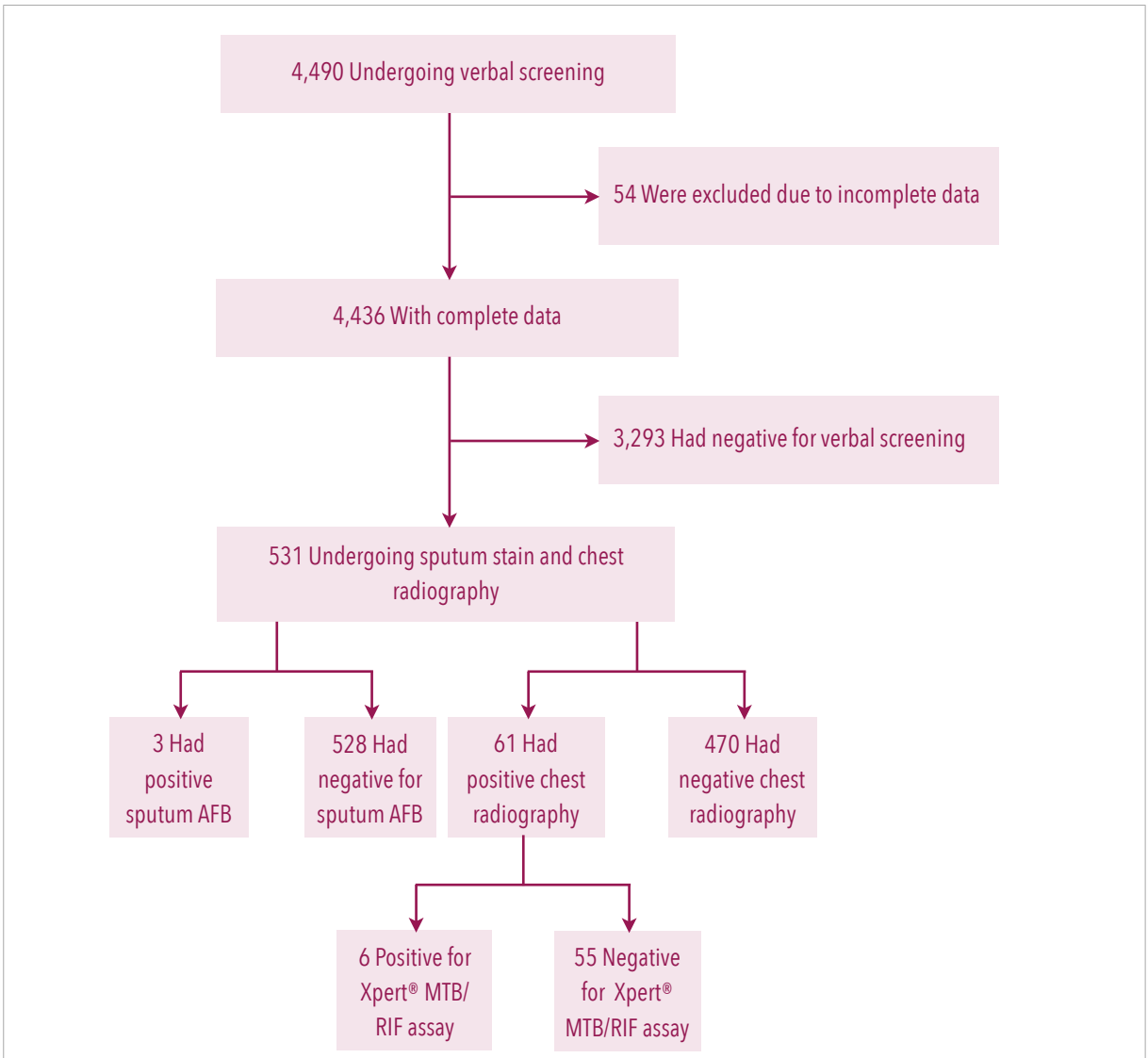

Figure 1. Study flow

able to use the questionnaire and interview the inmate. The inmates were interviewed by the research assistants approximately 10 minutes per person using the one-page questionnaire. With only 1 positive from the 7 questions, they were then undergoing sputum acid fast bacilli (AFB) stain for mycobacteria and plain anteroposterior chest radiography. For those with positive for sputum AFB, confirmed diagnosis of tuberculosis was given. For those with positive from chest radiography by the principal researcher and one radiologist, they would later be sent for Xpert® MTB/RIF assay for the confirmation of tuberculosis infection.

Table 1. Characteristics of the patients

Characteristic	Value (n=531)
Age-years	
Median	34
Interquartile range	27.0-42.3
Male sex-no. (%)	486 (91.0)
Co-morbidity disease-no. (%)	
HIV infection	11 (2.1)
Diabetes	10 (1.9)
Substance-induced psychiatric conditions	9 (1.7)
Asthma	8 (1.5)
Hypertension	7 (1.3)
Gout	7 (1.3)
Time in prison-months	
Median	29
Interquartile range	17-57
Positive for verbal screening-no. (%)	
Cough for 2 weeks or more	305 (57.1)
Fever	308 (57.5)
Weight lost	175 (32.8)
Night sweating	85 (15.9)
Hemoptysis	78 (14.6)
History with previous tuberculosis treatment	85 (15.9)
Self report of palpable mass around the neck	33 (6.2)
Positive for sputum AFB-no. (%)	3 (0.6)
Positive for chest radiography -no. (%)	61 (11.4)
Positive for Xpert® MTB/RIF assay-no. (%)	6 (1.1)
Confirmation of tuberculosis diagnosis -no. (%)	9 (1.7)

STATISTICAL ANALYSIS

All data were clean before analysis. For descriptive statistics, categorical variables were summarized using number and percentage while normally distributed continuous variables were summarized using mean and standard deviation (SD) and non-normally distributed continuous variables were present using median and interquartile range (IQR). For validity of questionnaire, it was interpreted regarding sensitivity, specificity,

Table 2. Validty of the 7-item questionnaire

Characteristic	Sensitivity	Specificity	Likelihood ratio (+)
#1	55.6	42.5	1.0
#2	42.5	42.1	0.8
#3	44.4	67.6	1.7
#4	42.1	84.0	0.7
#5	55.6	85.5	1.5
#6	67.6	84.4	2.1
#7	11.1	93.9	1.8
#1 or #2	15.4	13.3	0.2
#1 or #3	66.7	32.4	1.0
#1 or #4	55.6	34.3	0.8
#1 or #5	55.6	37.7	0.9
#1 or #6	88.9	30.5	1.3
#1 or #7	66.7	39.8	1.1
#2or#3	55.6	35.8	0.9
#2or#4	100.0	0.0	1.0
#2or#5	44.4	36.0	0.7
#2or#6	77.8	29.5	1.1
#2or#7	44.4	38.5	0.7
#3or#4	55.6	60.6	1.4
#3or#5	55.6	60.2	1.4
#3or#6	88.9	54.1	1.9
#3or#7	55.6	64.0	1.5
#4or#5	22.2	73.1	0.8
#4or#6	44.4	70.3	1.5
#4or#7	22.2	80.4	1.1
#5or#6	55.6	70.5	1.9
#5or#7	33.3	80.2	1.7
#6or#7	44.4	79.6	2.2

Table 2. (Continued)

Characteristic	Sensitivity	Specificity	Likelihood ratio (+)
#1or#2or#3	66.7	14.9	0.8
#1or#2or#4	66.7	15.8	0.8
#1or#2or#5	66.7	13.3	0.8
#1or#2or#6	66.7	15.8	0.8
#1or#2or#7	66.7	14.0	0.8
#1or#3or#4	100.0	0.0	1.0
#1or#3or#5	100.0	0.0	1.0
#1or#3or#6	100.0	5.5	1.1
#1or#3or#7	66.7	14.3	0.8
#1or#4or#5	55.6	34.3	0.8
#1or#4or#6	88.9	27.6	1.2
#1or#4or#7	100.0	0.0	1.0
#1or#5or#6	88.9	25.3	1.2
#1or#5or#7	66.7	34.7	1.0
#1or#6or#7	100.0	28.8	1.4
#2or#3or#4	55.6	32.4	0.8
#2or#3or#5	55.6	31.2	0.8
#2or#3or#6	88.9	24.2	1.2
#2or#3or#7	55.6	33.0	0.8
#2or#4or#5	44.4	32.2	0.7
#2or#4or#6	77.8	26.1	1.1
#2or#4or#7	44.4	35.0	0.7
#2or#5or#6	77.8	23.6	1.0
#2or#5or#7	44.4	32.4	0.7
#2or#6or#7	77.8	26.6	1.1
#3or#4or#5	55.6	54.1	1.2
#3or#4or#6	88.9	48.0	1.7
#3or#4or#7	55.6	58.1	1.3

Table 2. (Continued)

Characteristic	Sensitivity	Specificity	Likelihood ratio (+)
#3or#5or#6	88.9	46.9	1.7
#3or#5or#7	55.6	56.8	1.3
#4or#5or#6	55.6	59.6	1.4
#4or#5or#7	33.3	69.9	1.1
#5or#6or#7	66.7	66.5	2.0
#3or#6or#7	88.9	51.6	1.8
#4or#6or#7	55.6	67.8	1.7
#1or#2or#3or#4	66.7	13.9	0.8
#1or#2or#3or#5	66.7	12.2	0.8
#1or#2or#3or#6	100.0	4.6	1.0
#1or#2or#3or#7	66.7	12.6	0.8
#1or#2or#4or#5	66.7	12.6	0.8
#1or#2or#4or#6	100.0	5.1	1.1
#1or#2or#4or#7	66.7	13.5	0.8
#1or#2or#5or#6	100.0	2.1	1.0
#1or#2or#5or#7	66.7	10.9	0.7
#1or#2or#6or#7	100.0	4.2	1.0
#1or#3or#4or#5	66.7	27.2	0.9
#1or#3or#4or#6	100.0	20.2	1.3
#1or#3or#4or#7	66.7	28.4	0.9
#1or#3or#5or#6	100.0	17.9	1.2
#1or#3or#5or#7	66.7	26.3	0.9
#1or#3or#6or#7	100.0	19.8	1.2
#1or#4or#5or#6	88.9	23.0	1.2
#1or#4or#5or#7	66.7	32.0	1.0
#1or#4or#6or#7	100.0	26.5	1.4
#1or#5or#6or#7	100.0	23.6	1.3
#2or#3or#4or#5	55.6	28.2	0.8

Table 2. (Continued)

Characteristic	Sensitivity	Specificity	Likelihood ratio (+)
#2or#3or#4or#6	88.9	21.5	1.1
#2or#3or#4or#7	55.6	30.1	0.8
#2or#3or#5or#6	88.9	19.8	1.1
#2or#3or#5or#7	55.6	28.4	0.8
#2or#4or#5or#6	77.8	20.6	1.0
#2or#4or#5or#7	44.4	29.3	0.6
#2or#5or#6or#7	77.8	21.1	1.0
#3or#4or#5or#6	88.9	41.7	1.5
#3or#4or#5or#7	55.6	51.8	1.2
#4or#5or#6or#7	66.7	57.5	1.6
#1or#2or#3or#4or#5	66.7	11.4	0.8
#1or#2or#3or#4or#6	100.0	4.2	1.0
#1or#2or#3or#4or#7	66.7	11.8	0.8
#2or#3or#4or#5or#6	88.9	17.5	1.1
#2or#3or#4or#5or#7	55.6	25.9	0.7
#3or#4or#5or#6or#7	88.9	40.4	1.5
#1or#2or#3or#4or#5or#6	100.0	1.7	1.0
#1or#2or#3or#4or#5or#7	66.7	9.3	0.7
#2or#3or#4or#5or#6or#7	88.9	16.2	1.1
#1or#2or#3or#4or#5or#6or#7	100.0	0.6	1.0

Questions in the 7-item questionaire; Within the last month, have you....?
#1, Had cough lasting more than 2 weeks;
#2, Had fever lasting more than 1 week;
#3, Had weight lost more than 5% of your weight last month;
#4, Had night sweating;
#5, Had hemoptysis;
#6, Were on any tuberculosis treatment ; and
#7, Had palpable mass around your neck.

positive likelihood ratio (LR) and receiver operating characteristic (ROC) curve together with their 95% confidence interval (CI). The number needed to screen (NNS) in order to detect one active TB were also calculated.

RESULTS

Initially, 4,490 inmates underwent verbal screening using the 7-item questionnaire (Figure 1). Of these after excluding those with incomplete data, 531 were positive for at least 1 out of the 7 questions and they underwent sputum AFB stain for chest radiography. Later 3 were found positive from sputum AFB stain. There were 61 inmates with positive chest radiography and were sent for Xpert® MTB/RIF assay, 6 were positive. In total, there were nine cases with the diagnoses of tuberculosis. They were all treated with the anti-tuberculosis agent.

For those 531 with positive at least 1 out of 7 questions from the verbal screening, more than 90% of them were male with the median age of 34 years old. Very few of them had underlying diseases. Their median time in the prison was 29 months. For more of their detail can be found in Table 1.

Table 2 shows the validity of the 7-item questionnaire in term of sensitivity, specificity, and positive predictive value for each question and in combination. It found that question #6 regarding tuberculosis treatment had the highest sensitivity (67.6%) and positive likelihood ratio (2.1) while question #7 had the highest specificity (93.9%). From the various combination, sensitivity was improved with adding questions, however, positive for either question #2 or #4 yielded the 100% sensitivity and this was the 100% sensitivity with the least numbers of combined questions. Of course, specificity would be highest from the single question rather than combined question using "or". Thus the adding questions would not help for higher specificity. Positive for either #6 and #7 had the highest positive likelihood ratio (2.2), and the positive likelihood ratio would not be improved by adding the questions as well. The best NNS for our questionnaire was 59 (9 confirmed diagnoses out of 531 screening cases; given 100% sensitivity)

DISCUSSION

MAIN FINDINGS

The single question regarding currently on tuberculosis treatment had the highest sensitivity (67.6%) and positive likelihood ratio (2.1), while the question regarding palpable mass around the neck has the highest specificity (93.9%). The combined set of questions using "OR" affected higher sensitivity which it was able to achieve 100% while nothing change for specificity and positive likelihood ratio.

COMPARISON WITH OTHER STUDIES

In this study, there were 9 cases of pulmonary tuberculosis out of 4,490 inmates. The prevalence was around 200 per 100,000 population. This is relatively lower than we expected as the incidence of the disease is about 242 per 100,000 in Thai population[1] and the prevalence of TB in the inmates has been reported to be significantly

higher in many previous studies.[2-4] The low prevalence might be due to relatively shorter median time in the prisons of the inmates in the current study, around 2.5 years.

This 7-item questionnaire was used in a previous study in Northern Thailand in the IPD patients, sensitivity and specificity were relatively similar to that of our study even with some differences in the question detail, however, that study fails to combine the question to explore the validity of the overall questionnaire.[17]

In term of verbal screening symptom questionnaire itself, the latest standard question is provided by World Health Organization (WHO).[19] However, many prior studies used various types of question and modified to suit their own settings before the launch of the standard version.[10-16] A recent systematic review summarized the findings from the primary study in term of the NSS of the studies identified through the electronic database searching.[18] The review acknowledged the TB incidence as a major confounder.[18] In our study settings, it was considered as medium incidence, 100-300 per 100,000 population.[18] The NNS of the studies from the inmate population was found to be 75-175 depends on types of confirmation test.[18] However, the NNS from our study was found to be 59. This discrepancy might reflect a better process of gathering information during the question interview in our study.

STRENGTH AND LIMITATION

To our knowledge, this was the largest study regarding the verbal screening in the inmate population with 7-item questionnaires. Due to the resource constrain, not all of the inmates were sent for chest radiography and Xpert® MTB/RIF assay. Thus the real prevalence, as well as, the validity of the questionnaire were not well estimated. Moreover, the interpretation of the results depends largely on the number of confirmed diagnosis, nine cases in the current study, thus, the generalization beyond the stated prevalence has to be done very carefully.

CONCLUSION AND IMPLICATION

In conclusion, the questionnaire for verbal screening for diagnosis of pulmonary TB in the inmates had high sensitivity with no difference regarding specificity and positive likelihood ratio comparing to using the single question. Without the resource limitation, all inmates should undergo confirmation test for more precise estimation of the prevalence and the validity of the test.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank staff at Department of Social Medicine, Khon Kaen Hospital, Thailand for their helps with the data collection as well as the officers at Khon Kaen Central Prison, Thailand for their co-operation.

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

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- H.G. Wells

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-Hannibal Barca

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