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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

the clinical academia

Aim and Scope

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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the clinical academia

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message from the editor

Dear readers,

Welcome to The Clinical Academia. This is our third issue of this year. In this issue, you can learn about encephalitis which is still one of the deadly diseases in many parts of the world, and learn about the association between cerebrospinal fluid pressure and mortality among these patients. Also, we also have an article regarding tuberculosis and HIV in this issue. The article is about the times of initiation of antiretroviral therapy in patients with tuberculosis and human immunodeficiency virus co-infection in patients with low CD4 cell count. We hope that the articles will help you gain more knowledge about these infectious diseases.

Enjoy!

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

submission

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For online submission

Our issues of each volume will be published online
IN
March, June, September, and December

reviewing process

All accepted articles are classified into two main categories;
"***standard submission***" with the approximated processing time of 3-4 months and "***expression submission***" with the approximated processing time of 1-2 months. For the latter category, the author must submit as standard submission with notifying our journal for express submission.

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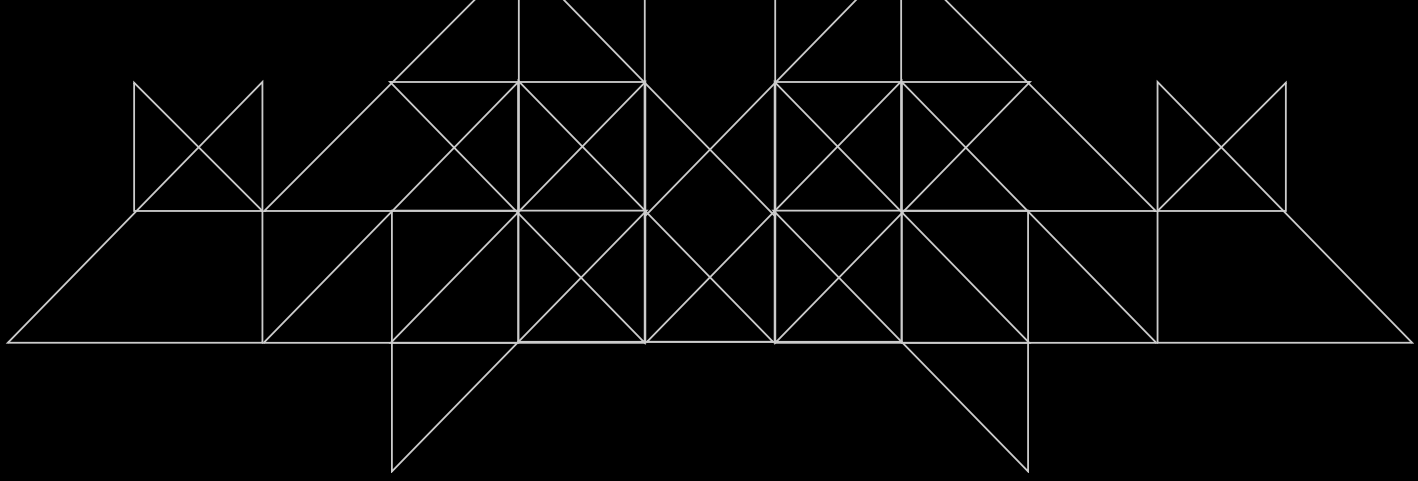
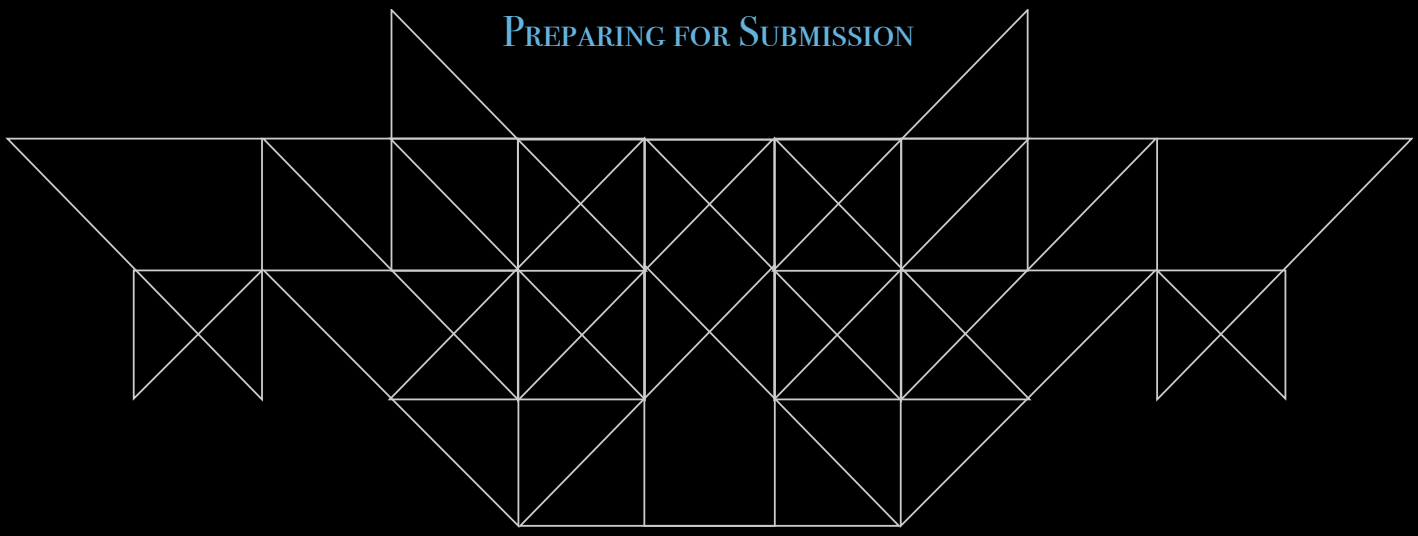
Contents



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. Author information: Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

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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.

Conflict of Interest declaration. Conflict of interest information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform conflict of interest disclosure form for use by ICMJE member journals and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require conflict of interest declarations on the manuscript title page to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

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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Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

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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.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

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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.

High cerebrospinal fluid pressure measured at first lumbar puncture and mortality in acute infectious encephalitis

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the association between increased intracranial pressure and mortality in patients with acute encephalitis.

METHODS

We conducted a retrospective cohort study using the database from Khon Kaen Hospital, Thailand from January 2011 to May 2017 with preliminary diagnosis as acute infectious encephalitis undergoing lumbar puncture with measured open pressure. Mortality was our primary outcome.

RESULTS

From 291 patients with acute infectious encephalitis. From Cox regression model analysis, we found no significant association between high open pressure (more than or equal 27 cmH_2O) and mortality (hazard ratio (HR), 1.34; 95% confidence interval (CI), 0.79 to 2.28). Also, by using Kaplan-Meier survival analysis, there was no significant association between high open pressure and mortality (P=0.263). However, the incidence density of mortality significantly increased 1.02 times in each year of patient age (HR, 1.02; 95% CI, 1.01 to 1.04), and a subgroup analysis of various cut-point showed incidence density of mortality significantly increased 2.18 times in patients with open pressure more than or equal to 20 cmH2O (HR, 2.18; 95% CI, 1.29 to 3.70).

CONCLUSION

High cerebrospinal fluid open pressure was not associated with mortality of patients with acute infectious encephalitis.

INTRODUCTION

Encephalitis has its worldwide annual incidence of 0.07 to 12.6 cases per 100,000 population.[1] There were 3,777 cases of acute encephalitis per year in Thailand between 1993 to 1998.[2] The condition can increase intracranial pressure (ICP).[3,4] Consequently, this might affect the treatment outcomes. In patients with head injuries, we found that ICP more than 20 millimeters of mercury (mmHg) increased the mortality rate of the patient from 17% to 47%.[5] Moreover, the mortality rate increases 3.12 times per every 10 mmHg higher from the average ICP of 20 mmHg.[6] For patients with acute encephalitis, very few studies have defined the effects of ICP on mortality; a prospective cohort study in the US; 1988 in ten patients with acute viral encephalitis showed that six patients with ICP higher than 20 mmHg, five of whom died and four patients with ICP lower than 20 mm. Hg, all survived.[7] A later cohort study in Vietnam; in 2002 with 91 patients with acute viral encephalitis showed the same result that patients with increased ICP more than 25 cmH_2O had 8.69 times higher mortality rate.[8] However; the results of the two previous studies did not show a precise relationship between ICP and mortality in acute viral encephalitis patients because of their small sample sizes. We aimed to conduct a study with a larger sample size to ascertain the relationship between high ICP and the mortality of the patient with acute viral encephalitis as well as acute infectious encephalitis.

METHODS

STUDY DESIGN

We conducted a retrospective cohort study by reviewing medical records using the database of Khon Kaen Hospital, Thailand between January 2011 and May 2017. We used the recorded data to identify open pressure measured at first lumbar puncture (LP) and mortality as our primary outcome of the present study to ascertain the relationship between ICP and mortality. Khon Kaen Hospital is one of the largest tertiary health care facilities in Thailand that has more than 65,000 in-patients admitted annually between 2009 and 2016 and more than 650,000 outpatients visits between 2009 to 2016.[9]

PATIENTS

The medical records of the patients with the first visit of preliminary diagnosis of acute infectious encephalitis with ICD10 code including G04 and A80 to A89 and undergoing lumbar puncture (LP) were verified and reviewed. We excluded the medical records of the patients without data regarding open pressure after the first LP.

EXPOSURE

High open pressure defined as cerebrospinal fluid (CSF) open pressure more than or equal to 27 cmH_2O from the first LP was identified as the exposure of the current study collected by reviewing the medical record of the patients.

OUTCOMES

The primary outcome was the mortality of patients identified by reviewing the medical records and searching the database of Civil registration where appropriate. The secondary outcomes were neurological complications of the patients in the admission; classified into four groups (i) severe impairment defined as patients with quadriparesis i.e., gross flaccid paralysis of all limbs and trunk in one patient, (ii) moderate impairment defined as patients develop seizure and status epilepticus

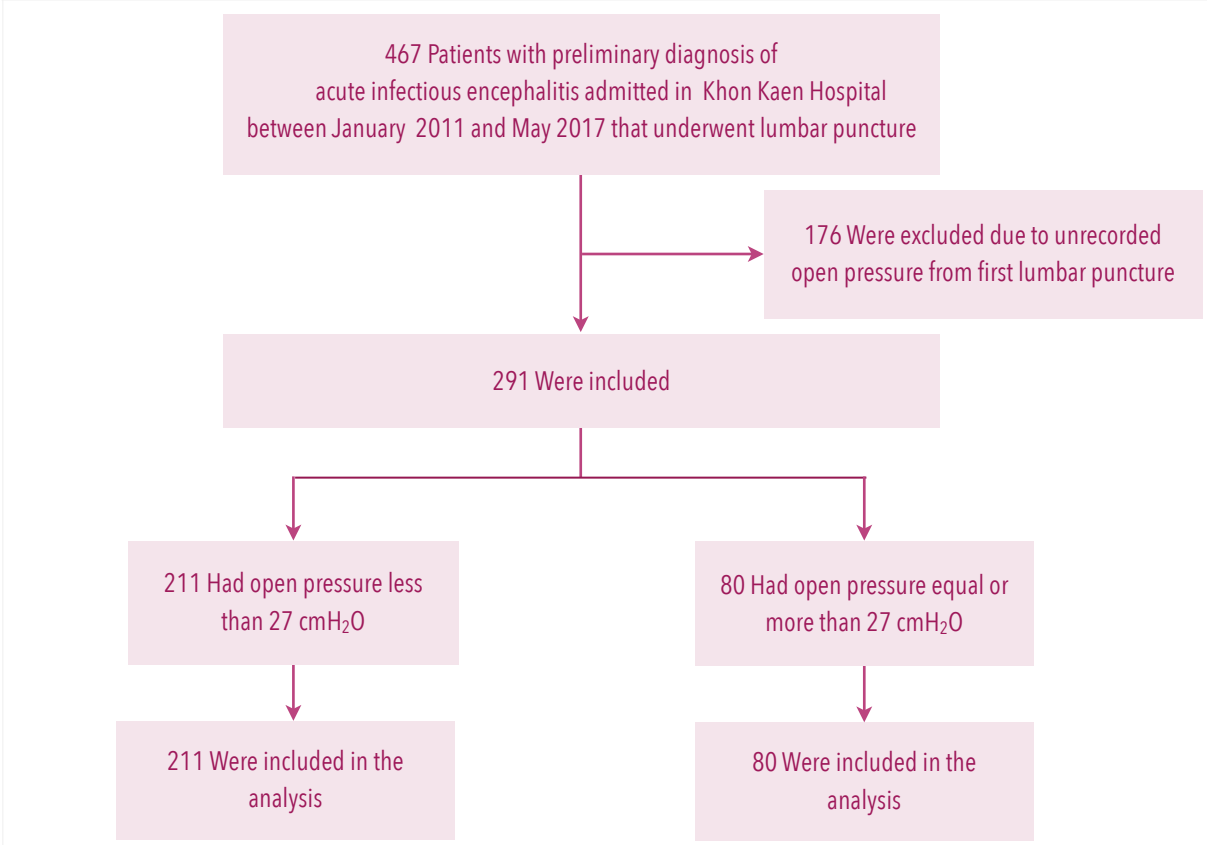

Figure 1. The patients flow in the analysis

after admission or paraparesis i.e., weakness of lower limb of the body defined as motor power between grade two and three according to medical research council scale or hemiparesis i.e., weakness on one side of the body defined as motor power between grade two and three according to medical research council scale or diplegia i.e., gross flaccid paralysis of two limbs defined as motor power grade zero or grade one according to medical research council scale or monoplegia i.e., gross flaccid paralysis of one limb defined as motor power grade zero or grade one according to medical research council scale that reduce functional score lower than three, (iii) mild impairment defined as patients with diparesis i.e., weakness on two limb of the body defined as motor power between grade two and three according to medical research council scale or monoparesis i.e., weakness on one limb of the body defined as motor power between grade two and three according to medical research council scale or other neurological deficit that functional score greater than or equal to three, and (iv) patients who fully recovery. The other secondary outcomes were cardiac arrest i.e., having the evidence of cardiopulmonary resuscitation (CPR) in medical records, admission to the intensive care unit (ICU), developing of nosocomial infection i.e., an infection that occurred after 48 hours after admission ,and use of a mechanical ventilator, length of ICU stay in days, length of hospital stay in days.

DATA COLLECTION

The other variables collected in the present study included age, sex, the present of altered mental

Table 1. Characteristics of patients

Characteristics	Systemic Corticosteroid (N = 211)	Non Systemic Corticosteroid (N = 80)	P Value
Age -yr			0.02
Median	54.9	44.8	
Interquartile range	27.1–67.9	25.9–57.5	
Male sex–no. (%)	114 (54.0)	51 (63.7)	0.14
Altered mental status–no. (%)	184 (87.2)	68 (85.0)	0.62
New onset of seizure–no. (%)	64 (30.3)	20 (25.0)	0.37
New onset of Status epilepticus–no. (%)	21 (10.0)	8 (10.0)	0.99
History of seizure–no. (%)	14 (6.6)	3 (3.8)	0.42
Comorbidities–no. (%)			
Diabetes mellitus	51 (24.4)	8 (10.0)	0.01
Hypertension	53 (25.4)	13 (16.3)	0.10
HIV infection	11 (5.3)	4 (5.0)	1.00
Tuberculosis infection	8 (3.8)	2 (2.5)	0.73
Gouty arthritis	8 (3.8)	2 (2.5)	0.73
Cirrhosis	2 (1.0)	4 (5.0)	0.05
Vital sign			
Body temperature-degree celsius			0.13
Median	37.5	37.9	
Interquartile range	36.8–38.4	37.0--38.5	
Pulse rate-beat per minute			0.34
Median	99	100	
Interquartile range	84–112	90-116	
Systolic blood pressure-mmHg			0.90
Median	128	126	
Interquartile range	115–149	115–154	
Diastolic blood pressure-mmHg			0.04
Median	74	79	
Interquartile range	66–85	68.5–90.8	

Table 1. (continued)

Characteristics	Systemic Corticosteroid (N=211)	Non Systemic Corticosteroid (N=80)	P Value
Cranial nerve defects–no. (%)	18 (8.7)	5 (6.5)	0.55
Positive upper motor neuron sign–no. (%)	32 (15.7)	10 (13.3)	0.63
Focal neurological deficit–no. (%)			
Quadriparesis–no. (%)	27 (13.8)	10 (13.0)	0.86
Hemiparesis–no. (%)	12 (6.1)	2 (2.6)	0.36
Paraparesis–no. (%)	5 (2.6)	0	0.33
Glasgow coma scale			0.07
Median	11	10	
Interquartile range	8–14	7.5–13	
On mechanical ventilation on admission–no (%)	62 (29.4)	30 (37.5)	0.18
Thrombocytopenia–no. (%)	18 (9.2)	9 (12.7)	0.41
Serum sodium level–mmol/dl			0.57
Median	136	135.5	
Interquartile range	132–140	131–139	

status, new onset of a seizure, new onset of status epilepticus, history of seizure, comorbidities i.e. history of diabetes mellitus, hypertension, human immunodeficiency virus (HIV) infection, Mycobacterium tuberculosis (TB) infection, gouty arthritis, cirrhosis. Also, a body temperature, pulse rate, systolic blood pressure, diastolic blood pressure, the presence of cranial nerve defects, quadriparesis, hemiparesis, paraparesis, positive upper motor neuron sign, Glasgow coma scale, on mechanical ventilation on admission, thrombocytopenia, and serum sodium were collected. Furthermore, the CSF profile of the patient and the treatment that patients receive after admission included CSF close pressure, CSF leukocyte count, CSF protein level, glucose CSF: blood ratio, CSF polymorphonuclear leukocyte (PMN) proportion, CSF lymphocyte proportion, administration of systemic corticosteroid, mannitol, antibiotic in the various group i.e. penicillin group, cephalosporin group, macrolide group, fluoroquinolone group, aminoglycoside group,

Table 2. Cerebrospinal fluid profile of acute infectious encephalitis patients in first lumbar puncture

Cerebrospinal fluid profile	Low open pressure (N=211)	High open pressure (N=80)	P Value
Closed pressure–cmH_2O*			<0.001
Median	14	26	
Interquartile range	10-18	22.5-30	
Leukocyte count-cells/μL			<0.001
Median	39.3	195	
Interquartile range	0-405	30-2,110	
Protein level-mg/dL			0.06
Median	91	139	
Interquartile range	43.3–279.9	52.7–378.6	
Glucose CSF:blood ratio <0.5–no. (%)	95 (53.1)	48 (68.6)	0.03
PMN proportion–no. (%)			<0.001
Median	20	90	
Interquartile range	0–90	17–96	
Lymphocyte cell proportion–no. (%)			0.27
Median	6.5	7	
Interquartile range	0–35.3	3–40	

* Closed pressure measured from first LP.

metronidazole, polymyxin group, glycopeptide group, lincosamide group, tetracycline group, carbapenem group were also collected. In addition to this, the data on the length of antibiotic use and acyclovir treatment were also collected in the present study.

STATISTICAL ANALYSIS

We compared the characteristics of the medical records of the included patients at the time of admission that could be potentially confounded to our primary and secondary outcomes. We divided the patients into two groups, a high open pressure

Table 3. Treatment that patients received after admission

Treatment	Low open pressure (N=211)	High open pressure (N=80)	P Value
Therapy of cerebral edema–no. (%)			
None	139 (65.9)	48 (60.0)	0.35
Systemic corticosteroid	62 (29.4)	28 (35.0)	0.36
Mannitol	23 (10.9)	9 (11.3)	0.93
Antibiotic use–no. (%)	203 (96.2)	79 (98.8)	0.45
Penicillin group	99 (46.9)	42 (52.5)	0.40
Cephalosporin group	186 (88.2)	74 (92.5)	0.28
Macrolide group	19 (9.0)	4 (5.0)	0.26
Fluoroquinolone group	9 (4.3)	2 (2.5)	0.73
Aminoglycoside group	3 (1.4)	0	0.56
Metronidazole	11 (5.2)	7 (8.8)	0.28
Polymyxin group	17 (8.1)	8 (10.0)	0.60
Glycopeptide group	39 (18.5)	15 (18.8)	0.96
Lincosamide group	18 (8.5)	10 (12.5)	0.31
Tetracycline group	15 (7.1)	8 (10.0)	0.41
Carbapenem group	60 (28.4)	26 (32.5)	0.50
Length of antibiotic use–day			0.50
Median	9	7	
Interquartile range	4-14	3-14	
Acyclovir treatment–no. (%)	83 (39.3)	25 (31.3)	0.20

group i.e., open pressure exceeds 27 cmH_2O, and a lower open pressure group i.e., open pressure does not exceed 27 cmH_2O. We used descriptive statistics to summarize the characteristics of the patients in each group; using numbers with percentages for the categorical variables, using

Table 4. Outcomes of the treatment

Outcome	Low open pressure (N=211)	High open pressure (N=80)	Relative risk (95% CI)	Mean difference (95% CI)
Primary outcome				
Death–no. (%)	71 (33.6)	33 (41.3)	1.23 (0.89–1.69)	
Secondary outcome				
Cardiac arrest–no. (%)	24 (11.4)	15 (18.8)	1.65 (0.91–2.98)	
Neurological complication–no. (%)				
Severe impairment	2 (0.9)	0		
Moderate impairment	48 (22.7)	16 (20.0)	0.88 (0.53–1.46)	
Mild impairment	1 (0.5)	1 (1.3)	2.64 (0.17–41.67)	
Fully recovery	160 (75.8)	63 (78.8)	1.04 (0.91–1.19)	
ICU admission–no. (%)	27 (12.8)	19 (23.8)	1.86 (1.10–3.15)	
Developing of nosocomial infection–no. (%)	61 (28.9)	31 (38.8)	1.34 (0.95–1.90)	
Using of mechanical ventilation–no. (%)	118 (55.9)	55 (68.8)	1.23 (1.02–1.49)	
Length of the ICU stay–day				–4.22 (–17.53–9.09)
Median	5.9	5.4		
Interquartile range	3.9–12.8	2.5–10.6		
Length of Hospital stay–day				–1.07 (–4.30–2.17)
Median	6	6		
Interquartile range	3.0–12.9	3.4–10.7		

mean together with standard deviation (SD) for the normally distributed continuous variables, median with interquartile range (IQR) for non-normally distributed continuous variables. For inferential statistics, we use either Pearson's chi-squared test, Fisher's exact test, or Mann-Whitney U test which appropriate to compare the characteristic of the patients in the two groups. Also, we used relative risk (RR), crude odds ratio (COR) to compare the outcomes between the two groups. To identify the factors that might influence our primary outcome, we used binary logistic regression analysis and Cox proportional hazard regression together with an adjusted odds ratio (AOR) and hazard ratio (HR) with their 95% confidence intervals (95% CI), respectively. We also used a Kaplan-Meier plot to

demonstrate time against cumulative survival within 30 days of admission between the two groups.

RESULTS

CHARACTERISTIC OF PATIENTS

Between January 2011 and May 2017, 467 patients who were preliminarily diagnosed with acute infectious encephalitis admitted in Khon Kaen Hospital and underwent lumbar puncture. One hundred and seventy-six patients with no open pressure records were excluded. Finally, a total of 291 patients were included in the analyses, 211 patients who had the open pressure less than 27-centimeter water (cmH_2O) as the low open pressure group and 80 patients who had the open pressure equal or more than 27 cmH_2O as high open pressure group (Figure 1).

The characteristics between the low open pressure group and high open pressure group were different in terms of (i) age of patients (median 54.9 years in the lower group vs. 44.8 years in the higher group, P=0.02), (ii) patients with diabetes mellitus (24.4% vs. 10%; P=0.01), (iii) Diastolic blood pressure (median 74-millimeter mercury [mmHg] vs. 79 mmHg; P=0.04). There was no significant difference between the two groups in other characteristics (Table 1).

CSF profile between the two groups were significantly different in most of parameters except lymphocyte cell proportion was relatively similar; (i) closed pressure from first LP (median 14.0 cmH_2O. vs. 26.0 cmH_2O; P<0.001), (ii) leukocyte count from CSF (median 39.3 cell per microliter [cell/µL] vs. 195.0 cell/µL, P=<0.001), (iii) glucose CSF:blood ratio<0.5% (53.1% vs. 68.6%; P=0.03), (iv) PMN proportion from CSF (median 20 vs. 90; P<0.001) (Table 2). Treatments that patients received after admission between the two groups were all relatively similar (Table 3).

STUDY OUTCOMES

There was no significant difference in mortality rates between the high open pressure group and the low open pressure group (41.3% in high open pressure group vs. 33.6% in low open pressure group; RR, 1.23; 95% CI, 0.89 to 1.69). Also, other outcomes were relatively similar between the two groups. However, there was a significant difference in an increased risk of ICU admission 1.86 times (23.8% vs. 12.8%; RR, 1.86; 95% CI, 1.10 to 3.15) and increased risk of using mechanical ventilation 1.23 times in the high open pressure group (68.8% vs. 55.9%; RR, 1.23; 95% CI, 1.02 to 1.49) (Table 4).

FACTORS DETERMINE OUTCOME

From the crude analysis of the odds ratio; there was a small but significant increase in mortality rate every year older (COR, 1.03; 95% CI, 1.02 to 1.04) and every milligrams higher level of CSF protein (COR, 1.002; 95% CI, 1.001 to 1.003). Moreover, mortality rate significantly increase in patient with diabetes mellitus (COR, 2.43; 95% CI, 1.36 to 4.35), hypertension (COR, 3.30; 95% CI, 1.87 to 5.82), on mechanical ventilation on admission (COR, 2.12; 95% CI, 1.28 to 3.53), systemic corticosteroid use times (COR, 1.71; 95% CI, 1.03 to 2.85) and thrombocytopenia (COR, 2.58; 95% CI, 1.15 to 5.78). However, mortality rate decrease with higher Glasgow coma scale (GCS) (COR, 0.88; 95% CI, 0.82 to 0.95) and antiviral treatment (COR, 0.46; 95% CI, 0.27 to 0.78). On the contrary, high open pressure and other factors were not significantly associated with the mortality rate (Table 5).

From binary logistic regression model analysis; there was a significant increase in mortality rate in patients with high open pressure (AOR, 3.58; 95% CI, 1.10 to 11.68), systemic corticosteroid use (AOR, 3.15; 95% CI, 1.16 to 8.52), higher age (AOR, 1.04; 95% CI, 1.01 to 1.08), higher body temperature (AOR, 1.63; 95% CI, 1.02 to 2.60) and a higher level of CSF protein

Table 5. Multivariable analysis of factors associated with mortality in acute infectious encephalitis patient

Factor	Odds ratio (95% confidence interval)		Hazard ratio (95% confidence interval)
	Crude analysis	Adjusted analysis	
High open pressure	1.38 (0.82–2.35)	3.58 (1.10–11.68)	1.53 (0.91–2.57)
Age–yr	1.03 (1.02–1.04)	1.04 (1.01–1.08)	1.02 (1.01–1.04)
Male sex	0.55 (0.34–0.89)	0.40 (0.15–1.06)	0.52 (0.33–0.84)
Altered mental status	1.13 (0.55–2.31)	0.43 (0.09–2.00)	0.59 (0.29–1.22)
New onset of seizure	0.50 (0.28–0.88)	0.83 (0.23–2.94)	0.60 (0.32–1.11)
History of seizure	0.37 (0.10–1.31)	0.06 (0.001–5.58)	0.57 (0.13–2.52)
Diabetes mellitus	2.43 (1.36–4.35)	0.79 (0.21–2.90)	
Hypertension	3.30 (1.87–5.82)	2.05 (0.58–7.19)	
Body temperature–degree celsius	1.05 (0.85–1.30)	1.63 (1.02–2.60)	1.06 (0.85–1.31)
Pulse rate–beat per minute	1.003 (0.99–1.01)	1.02 (0.99–1.05)	1.00 (0.99–1.02)
Systolic blood pressure–mmHg	1.01 (1.00–1.02)	0.99 (0.97–1.02)	1.00 (0.99–1.01)
Diastolic blood pressure–mmHg	1.01 (1.00–1.03)	1.02 (0.98–1.07)	1.01 (0.99–1.03)
Glasgow coma scale	0.88 (0.82–0.95)	0.94 (0.76–1.16)	0.93 (0.84–1.03)
On mechanical ventilation on admission	2.12 (1.28–3.53)	0.47 (0.10–2.16)	1.50 (0.76–2.95)
Administration of corticosteroid	1.71 (1.03–2.85)	3.15 (1.16–8.52)	1.09 (0.67–1.78)
Acyclovir treatment use	0.46 (0.27–0.78)	0.71 (0.20–2.54)	1.07 (0.61–1.85)
CSF Leukocyte count–cells/μL	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
CSF Protein level–mg/dL	1.002 (1.001–1.003)	1.004 (1.001–1.006)	1.001 (1.001–1.002)
CSF PMN proportion–%	1.01 (1.00–1.01)	0.99 (0.97–1.002)	
CSF Lymphocyte cell proportion–%	0.99 (0.98–1.00)	0.998 (0.98–1.01)	
CSF Thrombocytopenia	2.58 (1.15–5.78)	1.55 (0.36–6.72)	
Serum sodium level–mmol/dl	0.98 (0.95–1.01)	0.97 (0.92–1.02)	0.97 (0.95–1.00)

Table 6. Subgroup analysis of various cut-off point of open pressure

Cutpoint of open pressure (cmH_2O)	High open pressure patients	Death	Hazard ratio (95% confidence interval)
>20	150	65 (43.3)	2.18 (1.29–3.70)
>25	97	40 (41.2)	1.46 (0.88–2.43)
>30	63	27 (42.9)	1.64 (0.92–2.92)
>35	37	14 (37.8)	1.26 (0.59–2.70)
>40	21	9 (42.9)	1.40 (0.56–3.50)

(AOR, 1.004; 95% CI, 1.001 to 1.006). However, no other factors were significantly associated with the mortality rate (Table 5).

From Cox proportional hazard regression model analysis using the length of hospital stay within 30 days, the incidence density of mortality significantly increased 1.02 times in each year of patient age (HR, 1.02; 95% CI, 1.01 to 1.04) and slightly increased 1.001 times per milligram of CSF protein higher (HR, 1.001; 95% CI, 1.001 to 1.002). On the other hand, the incidence density of mortality decreased 0.52 times in male patients (HR, 1.02; 95% CI, 0.33 to 0.84). Nevertheless, high open pressure was not significantly associated with mortality congruently with the Kaplan-Meier plot (Figure 2). Also, other investigated factors were found not be significantly associated with mortality (Table 5).

SUBGROUP ANALYSIS

From Cox proportional hazard regression model analysis using various cutpoint of open pressure, the incidence density of mortality significantly increased 2.18 times in patients with open pressure more than or equal to 20 cmH_2O (HR, 2.18; 95% CI, 1.29 to 3.70). The results of other cutpoints of open pressure were similar between the two groups (Table 6).

DISCUSSION

MAIN FINDINGS

In this retrospective cohort study based on 291 patients with acute infectious encephalitis, we found no significant difference in mortality rate between those with or without high open pressure. Also, after additional adjustment still no significant association between high open pressure and incidence density of mortality. However, the incidence density of mortality rate significantly increases when the definition of high open pressure group change to CSF open pressure more than or equal to 20 cmH_2O.

COMPARISON WITH OTHER STUDIES

To our knowledge, there were two studies have defined the effects of ICP on mortality in patients with acute encephalitis.[7, 8] However, our findings contrast with the previous two studies.[7, 8] The first study in ten patients showed that four patients with an ICP less than 20 mmHg survived, whereas five of six patients with ICP higher than 20 mmHg died ($P<0.05$). But because of the small sample size, there were no inferential statistics to generalize the outcome to the population.[7] The second study found that patients with CSF open pressure greater than or equal to 25 cmH_2O had significant 8.69

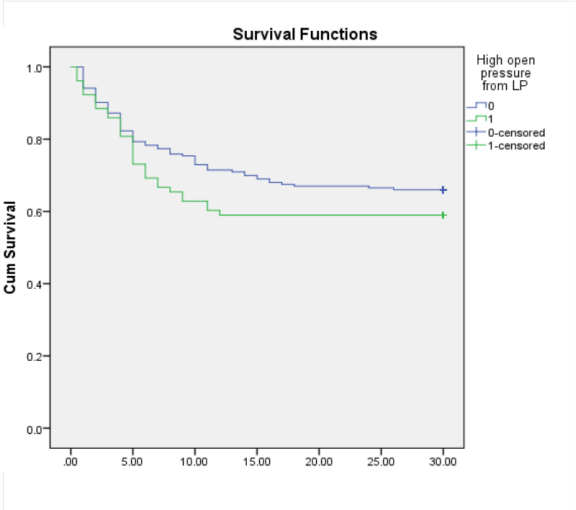

Figure 2. Kaplan-Meier comparing mortality in 30 days versus high open pressure record at first LP.

times higher mortality rate than those who were not. From our perspective, the difference in findings was because of the difference in the median age of patients in our study and the previous study. The median age of the patient in the previous study was 8 to 9 years old. However, in our study, the median age of patients was 54 years old in patients with CSF open pressure greater than or equal to 27 cmH_2O, and the median age of 44 years old in the other group. The difference in the median age of the patients in the two groups has the potential to affect the mortality rate in the two groups. Owing to the increase in age of patients also increases the mortality rate of patients with infectious disease.[26-28]

STRENGTHS AND LIMITATIONS OF STUDY

The strength of our study was the size of the database that we used. This is one of the world's largest databases of patients with encephalitis at the current period.

The limitations of the current study; first, the database that we used was from the medical records of the tertiary care unit that is a referral center. However, some of the patients may undergo LP from the primary or secondary care unit before. Thus; the open pressure we collected may not be the precise one to show the relationship between increased ICP and mortality. Second, there were many missing data in our medical records. As a result, it increased missing bias. Third, the methods of measurement ICP are varied because we were not able to standardize the method of measurement. Fourth, the difference of age in the two groups between the low open pressure group and high open pressure group.

CONCLUSION AND IMPLICATIONS

Our study showed that there was no relationship between high open pressure and mortality rate. However, our study still has the limitation in aspects of missing data and unstandardized measurement of open pressure resulting in missing bias and uncertain open pressure. Thus, further studies with adequate data and more accurate open pressure are required.

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Times of initiation of antiretroviral therapy in patients with tuberculosis and human immunodeficiency virus co-infection with CD4 count less than 350 cells/mm^3

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To examine the mortality rates of various initiation times of antiretroviral therapy (ART) after starting tuberculosis treatment.

METHODS

We conducted a retrospective cohort study using medical records of outpatients with the diagnosis of TB/HIV co-infection in Khon Kaen Hospital, Thailand between January 2007 and August 2017. We included the patients who started tuberculosis treatment and various times of starting ART with CD4 count less than 350 cells/mm^3. We separated patients into 3 groups by the time of initiated ART starting within the first 4 weeks, 5 to 8 weeks, and 9 to12 weeks after starting tuberculosis treatment. We compared the risk of all-cause mortality within 1 year after start tuberculosis treatment among three groups as our primary outcome. Our secondary outcomes were sputum conversion at 2 months after starting tuberculosis treatment and rate of CD4 count increasing in 1 year after tuberculosis treatment.

RESULTS

A total of 132 patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3 were included in the study; 62 patients started ART within the first 4 weeks after TB treatment, 45 patients started in 5 to 8 weeks and 25 patients started in 9 to 12 weeks. The primary outcome was reached by 1 (2%) patient in the first group, 2 (8%) patients in the second group, and 1 (4%) patient in the third group. (relative risk [RR], 2.76, 95% CI, 0.26 to 29.47 and RR, 2.48, 95% CI, 0.16 to 38.13). Only 28 of 132 patients (21%) had been recorded data on sputum conversion at 2 months after tuberculosis treatment, the result showed no significant difference in improving sputum conversion between starting ART at 5 to 8 weeks and starting ART within the first 4 weeks (RR, 1.30, 95% CI, 0.77 to 2.21). CD4 level increasing rates among the three groups were not significantly different (mean difference (MD), 2556.79, 95% CI, -1011.56 to 6125.14 and MD, 86.67, 95% CI, -1333.69 to 1507.04).

CONCLUSION

The study showed no significant difference between mortality rate and various initiation time of ART after start tuberculosis treatment.

INTRODUCTION

Tuberculosis (TB) is a leading cause of morbidity and mortality among people living with human immunodeficiency virus (HIV) infection worldwide, it was estimated that about one-third of new HIV patients infected with TB were death in 2014.[1] Using of antiretroviral therapy (ART) decreased a large number of the morbidity and mortality of patients with TB/HIV co-infection.[2,3] A systematic review study in 2015 including 8 trials with 4,368 patients with TB/HIV co-infection showed starting ART within 4 weeks after starting TB treatment improved survival in those with CD4 count less than 50 cells/mm^3, and it associated with a 2-fold higher frequency of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS), and it also stated that there is not enough evidence to support or refute a survival benefit for starting ART within 4 weeks compared with starting within 8 to 12 weeks after starting TB treatment or starting after finished TB treatment in patients with CD4 count more than 50 cells/mm^3.[4] There is a randomized controlled trial study in four countries of Africa in 2014 including 1,538 patients with TB/HIV co-infection with CD4 count more than 220 cells/mm^3, it showed no difference of mortality rate between starting ART after 2 weeks of starting TB treatment and starting at the end of TB treatment.[5] There is another randomized controlled trial study in 2011 in Cambodia include 661 patients with CD4 count less than 200 cells/mm^3 showed starting ART at 2 weeks after the starting TB treatment significantly improved survival rate compared with starting ART at 8 weeks after starting TB treatment.[6] Furthermore, there is a randomized controlled trial study in Thailand in 2012 including 156 patients with TB/HIV co-infection, and CD4 count less than 350 cells/mm^3 showed no difference in mortality rate in starting ART at 4 weeks compared with 12 weeks after tuberculosis treatment.[7] However, no study showed the risks or benefits of starting ART in a different period during 1 to 12 weeks after tuberculosis treatment in patients with CD4 count less than 350 cells/mm^3. Thus, we aim to identify the risks and benefits of ART in various starting times; within the first 4 weeks, 5 to 8 weeks, and 9 to 12 weeks in patients with TB/HIV co-infection.

METHODS

STUDY DESIGN

This was a retrospective cohort study to determine the optimal initiation time of ART during tuberculosis treatment and to identify the association between the initiation time of ART and mortality rate in patients with TB/HIV co-infection. The present study was approved by the Khon Kaen Hospital Institutional Review Board (IRB). All patient's data will be kept confidentially without disclosed. All patient's data were collected in a closed system that people cannot access to patients' data except the researcher team.

PATIENTS

We included patients who have diagnosed with both TB and HIV infection by using ICD A15 to A19 and B20 to B24. Inclusion criteria as follows (i) tuberculosis was confirmed by a positive smear for acid-fast bacilli (AFB) stain or positive mycobacterial culture or positive polymerase chain reaction (PCR) for tuberculosis in any body fluid or confirmed by clinical symptoms and radiological findings, (ii) HIV infection was confirmed by any tests. Exclusion criteria as follows (i) age<18 years, (ii) previous treatment by ART, (iii) patients with CD4 count more than 350 cells/mm^3, (iv) patients who died before start ART, (v) previous TB treatment more than 12 weeks before starting ART.

INTERVENTION

We separated time to initiate ART during tuberculosis treatment into three groups (within

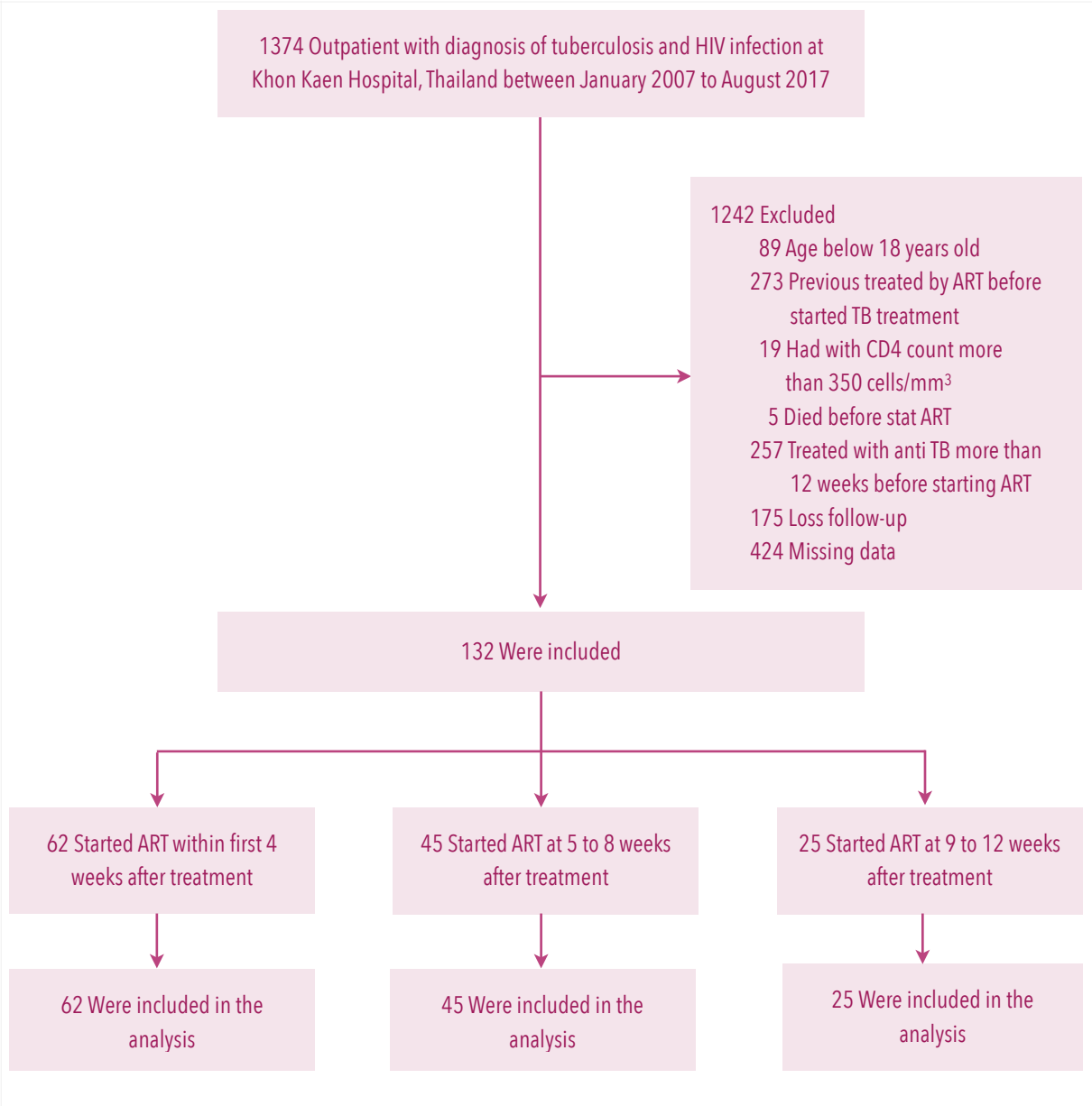

Figure 1. Study flow

the first 4 weeks, 5 to 8 weeks, and 9 to 12 weeks after start tuberculosis treatment) collected by reviewing the medical record of the patients.

OUTCOMES

The primary outcome was all-cause mortality within 1 year after start tuberculosis treatment. The secondary outcomes were sputum conversion rate at 2 months after starting tuberculosis treatment in patients with pulmonary tuberculosis confirmed by positive sputum AFB and percent change of CD4 level in 1 year after tuberculosis treatment.

DATA COLLECTION

We confirmed the medical record of outpatients with the diagnosis of tuberculosis and HIV infection

Table 1. Characteristics of the patients

Characteristic	Initiation time of ART after tuberculosis treatment			P Value
	The first 4 weeks (N=62)	5-8 weeks (N=25)	9-12 weeks (N=25)	
Age–yr				0.08
Median	35.1	32.5	37.8	
Interquartile range	29.3–39.1	27.7–38.6	33.3–39.6	
Male sex–no. (%)	45 (72.6)	37 (82.2)	14 (56.0)	0.06
BMI–kg/m^2	18.7 3.2	18.5 2.5	19.0 2.5	0.76
Range of CD4 count level at time of diagnosis–cells/mm^3				0.91
50	32 (51.6)	20 (44.4)	14 (56.0)	
51– 200	22 (35.5)	18 (40.0)	8 (32.0)	
201–350	8 (12.9)	7 (15.1)	3 (12.0)	
CD4 count level at time of diagnosis–cells/mm^3				0.89
Median	45.5	59.0	30.0	
Interquartile range	20.8–119.3	14.0–136.0	15.0–147.0	
Opportunistic infections–no. (%)				
Pneumocystis jiroveci pneumonia	7 (11.3)	4 (8.9)	2 (8.0)	0.93
Candidiasis	1 (1.6)	5 (11.1)	0	0.05
Cryptococcosis	2 (3.2)	5 (11.1)	1 (4.0)	0.21
Herpes virus infection	4 (6.5)	4 (8.9)	0	0.36
Toxoplasmosis	1 (1.6)	2 (4.4)	1 (4.0)	0.53
Cytomegalovirus infection	1 (1.6)	5 (11.1)	3 (12.0)	0.06
Histoplasmosis	0	0	1 (4.0)	0.19
Hemoglobin level–g/dl	10.12.5	10.2 2.2	9.52.2	0.48
Positive AFB smear–no. (%)	26 (47.3)	22 (48.9)	10 (43.5)	0.91
Positive culture for TB–no. (%)	7 (46.7)	4 (44.4)	2 (33.3)	0.90

Table 1. (Continued)

Characteristic	Initiation time of ART after tuberculosis treatment			P Value
	The first 4 weeks (N=62)	5-8 weeks (N=25)	9-12 weeks (N=25)	
Type of tuberculosis–no. (%)				
Pulmonary	45 (72.6)	32 (71.1)	19 (76.0)	0.91
Spine	0	1 (2.2)	0	0.53
Lymphadenitis	21 (33.9)	14 (31.1)	7 (28.0)	0.86
Pleura	0	4 (8.9)	1 (4.0)	0.03
Meningitis	1 (1.6)	5 (11.1)	1 (4.0)	0.08
Pericarditis	1 (1.6)	0	0	1.00
Colitis	2 (3.2)	2 (4.4)	0	0.82
Peritonitis	3 (4.8)	1 (2.2)	1 (4.0)	0.85
Miliary	1 (1.6)	0	0	1.00

and follow-up at Khon Kaen Hospital, Thailand between January 2007 and August 2017. The primary outcome was the mortality of patients identified by reviewing the medical records and searching the database of Civil registration.

STATISTICAL ANALYSIS

We compared the characteristics of the included patients that could be potentially confounded to our primary and secondary outcomes. We used descriptive statistics to summarize the characteristics of the patients. Number and percentage were used for categorical variables. Mean with standard deviation (SD) were used for summarizing normally distributed scale variables while median and interquartile range (IQR) for non-normally distributed scale variables. For inferential statistics, we used either Pearson's chi-squared test, Fisher's exact test, ANOVA, or Kruskal-Wallis test which appropriate to compare the characteristic of the patients among the three groups. We used relative risk (RR) to compare outcomes among the three groups. Also, to identify the factors that might affect our primary outcome, we used binary logistic regression analysis and Cox proportional hazard regression together with crude odds ratio, adjusted odds ratio, the crude hazard ratio (CHR), and adjusted hazard ratio (AHR). All tests were interpreted together with either P-Value or a 95% confidence interval (CI). $P<0.05$ and 95% CI do not include 1.00 were considered as statistically significant. We also used the Kaplan-Meier plot to demonstrate time against cumulative survival within 1 year after tuberculosis treatment among the three groups. All analyses were performed with SPSS.

Table 2. Treatment outcomes

Outcome	Initiation time of ART after tuberculosis treatment			Relative risk (95% CI) *	Relative risk (95% CI)†	Mean difference (95% CI)‡	Mean difference (95% CI)§
	The first 4 weeks (N=62)	5-8 weeks (N=25)	9-12 weeks (N=25)				
1-Year mortality-no. (%)	1 (2)	2 (8)	1 (4)	2.76 (0.26– 29.47)	2.48 (0.16–38.13)		
Sputum conversion at 2 months-no. (%)	8 (13)	8 (32)	5 (20)	1.30 (0.77–2.21)	N/A *		
Percent change of CD4 level in 1 year							
Median	336.4	230.1	480.1			2556.79	86.67
Interquartile range	147.2–796.9	106.5–1066.3	27.3–1418.6			-1011.56 to 6125.14	-1333.69 to 1507.04

* Relative risk from the comparison between the group of 5-8 week compared to the first 4 weeks
† Relative risk from the comparison between the group of 9-12 week compared to the first 4 weeks
‡ Mean difference from the comparison between the group of 5-8 week compared to the first 4 weeks
§ Mean difference from the comparison between the group of 9-12 week compared to the first 4 weeks

RESULTS

CHARACTERISTICS OF THE PATIENTS

Among 1,374 patients who diagnosed with tuberculosis and HIV infection at Khon Kaen Hospital, Thailand between January 2007 to August 2017, a total of 132 patients were included in the study; 62 patients who started ART within the first 4 weeks after TB treatment, 45 patients who started in 5 to 8 weeks and 25 patients who started in 9 to12 weeks (Figure 1). Most of them were male with an average age of 35 years old and average body mass index (BMI) of 18.7 kg/m^2. The median of CD4 count level at the time of diagnosis was 45.5 cells/mm^3 in the first 4 weeks group, 59.0 cells/mm^3 in the 5 to 8 weeks group and 30.0 cells/mm^3 in the 9 to 12 weeks. There were no statistically significant differences among the three groups regarding to baseline characteristics (Table 1). In addition, clinical characteristics including opportunistic infections, hemoglobin level, positive AFB, positive culture for TB, positive PCR for TB in any fluid and types of tuberculosis were relatively similar among three groups except pleural tuberculosis; no pleural tuberculosis in the first 4 weeks group, 4 patients (8.9%) with pleural tuberculosis in the 5 to 8 weeks group while only one patient (4%) with pleural tuberculosis in the 9 to 12 weeks group.

ALL-CAUSE MORTALITY

Overall, there are 4 patients died in 10 years among 3 groups, 1 (2%) patient who started ART within the first 4 weeks, 2 (8%) patients who started at 5 to 8 weeks, and 1 (4%) patient who started at 9 to 12 weeks. Our study showed no significant difference in one-year all-cause mortality (RR, 2.76; 95% CI, 0.26 to 29.47 and RR, 2.48; 95% CI, 0.16 to 38.13) as shown in Table 2.

SPUTUM CONVERSION AT 2 MONTHS.

Only 28 of 132 patients (21.2%) had been recorded data on sputum conversion at 2 months after tuberculosis treatment, the result showed no significant difference in improving sputum conversion between starting ART at 5 to 8 weeks and starting ART within the first 4 weeks (RR, 1.30; 95% CI, 0.77 to 2.21) as shown in Table 2.

RATE OF CD4 LEVEL INCREASING IN 1 YEAR.

The result shows CD4 level increasing rate medians 336.4% (IQR, 147.2 to 796.9%) inpatient who started ART within the first 4 weeks, 230.1% (IQR, 106.5 to 1066.3%) inpatient who started at 5 to 8 weeks, and 480.1% (IQR, 27.3 to 1418.6%) inpatient who started at 9 to 12 weeks. However, there is no significant difference among 3 groups (Mean difference, 2556.79; 95% CI, -1011.56 to 6125.14 and Mean difference, 86.67; 95% CI, -1333.69 to 1507.04)

FACTORS DETERMINE OUTCOME

The result of the binary logistic regression analysis and the Cox regression analysis of the outcome were summarized in Table 3. We found no factors significantly associated with a 1-year mortality rate in patient with TB/HIV co-infection and CD4 count less than 350 cells/mm^3 including various initiation time of ART during tuberculosis treatment, age group (age<40 yr. vs. age≥ 40yr.), sex, BMI (BMI<18 kg/m^2 vs. BMI≥18 kg/m^2) and hemoglobin level (Hb<8 g/dL vs. ≥ 8 g/dL). Figure 2 Kaplan-Meier showed that the three groups of various initiation times of ART during tuberculosis treatment had no statistical difference in the survivors within 1 year.

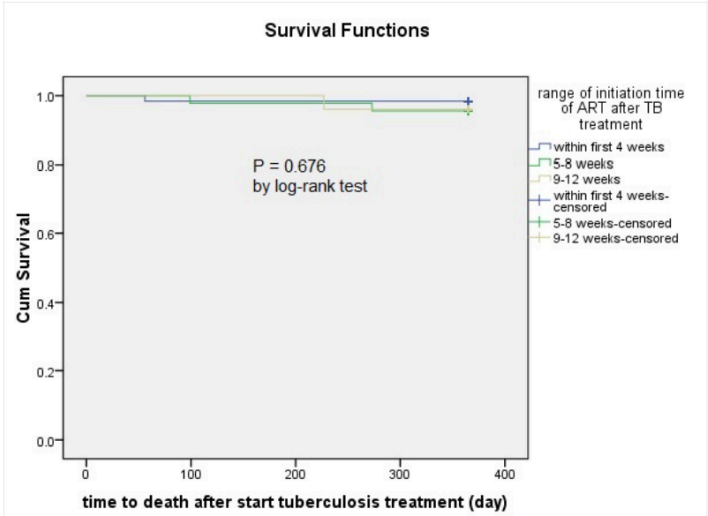

Figure 2. Kaplan-Meier comparing mortality in various initiation time of ART during tuberculosis treatment .

DISCUSSION

MAIN FINDINGS

In this retrospective cohort study based on 132 patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3, we found that one year all-cause mortality rate were not significantly difference among three groups of various initiation time of ART after starting tuberculosis treatment. The other outcomes including sputum conversion in two months and rate of CD4 count increasing in one year after tuberculosis treatment were no significantly difference as well.

COMPARISON WITH OTHER STUDIES

Our findings showed no difference in mortality in patients who initiated ART within the first 4 weeks group compared with 5 to 8 weeks group and 9 to12 weeks group. The first previous study showed no difference in mortality rate in starting ART at 4 weeks compared with 12 weeks after TB treatment in patients with CD4 count less than 350 cells/mm^3.[7] So, our result goes along with this study. However, this study did not mention.

LIMITATIONS OF STUDY

We collected data by the reviewed medical record of outpatients within ten years retrospectively. Thus, there are some limitations to our study. First,

Table 3. Factor determining death

Factor	Odds ratio (95% CI)		Hazard ratio (95% CI)	
	Crude analysis	Adjusted analysis	Crude analysis	Adjusted analysis
Initiation time of starting ART after tuberculosis treatment				
Within first 4 weeks	Reference	Reference	Reference	Reference
5-8 weeks	2.84 (0.25–32.29)	5.01 (0.32–78.10)	2.75 (0.25–30.36)	5.10 (0.35–75.17)
9-12 weeks	2.54 (0.15–42.29)	2.19 (0.12–39.88)	2.48 (0.16–39.57)	2.12 (0.13–34.65)
Age 40 year	4.12 (0.55–30.69)	4.71 (0.58–38.39)	3.93 (0.55–27.87)	4.61 (0.62–34.46)
Male sex	0.36 (0.05–2.67)	0.21 (0.02–2.46)	2.65 (0.37–18.82)	0.23 (0.02–2.40)
BMI 18 kg/m^2	2.12 (0.22–20.94)	5.11 (0.33–77.92)	2.12 (0.22–20.36)	5.18 (0.36–73.91)
Hemoglobin level 8 g/dL	0.66 (0.07–6.61)	0.43 (0.04–5.03)	0.66 (0.07–6.33)	0.39 (0.04–4.13)

there are a lot of incomplete and missing medical records and it probably missed some variables. Second, we studied only in one hospital. So, we had a small sample size, only four patients died through ten years. Third, we did not study the specific cause of death, so non TB/HIV associated cause of death might be included in this study. Due to the limitations, using our results in clinical practice should be considered.

CONCLUSION AND IMPLICATION

Our study showed no association between the various initiation time of ARV during tuberculosis treatment and mortality rate in patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3. So, ART can be delayed until 12 weeks after start tuberculosis treatment in patients with TB/HIV co-infection and CD4 count less than 350 cells/mm^3. However, our study has several limitations including small sample size, missing data due to a retrospective study in nature, and study design as a retrospective study. Thus, further studies with larger sample size and prospective study design to determine precise results are required.

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"I shall either find a way or make one"

-Hannibal Barca

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