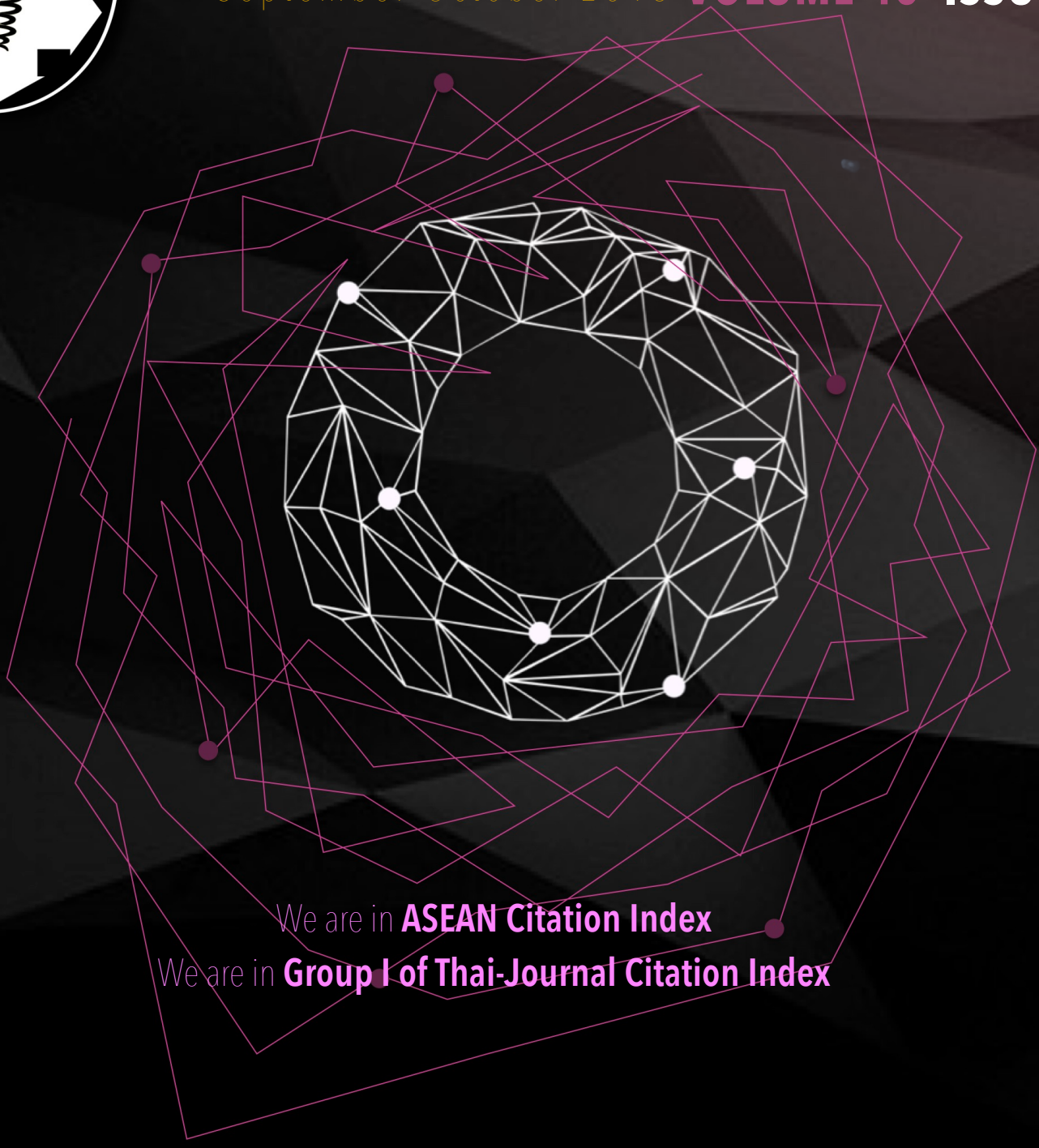


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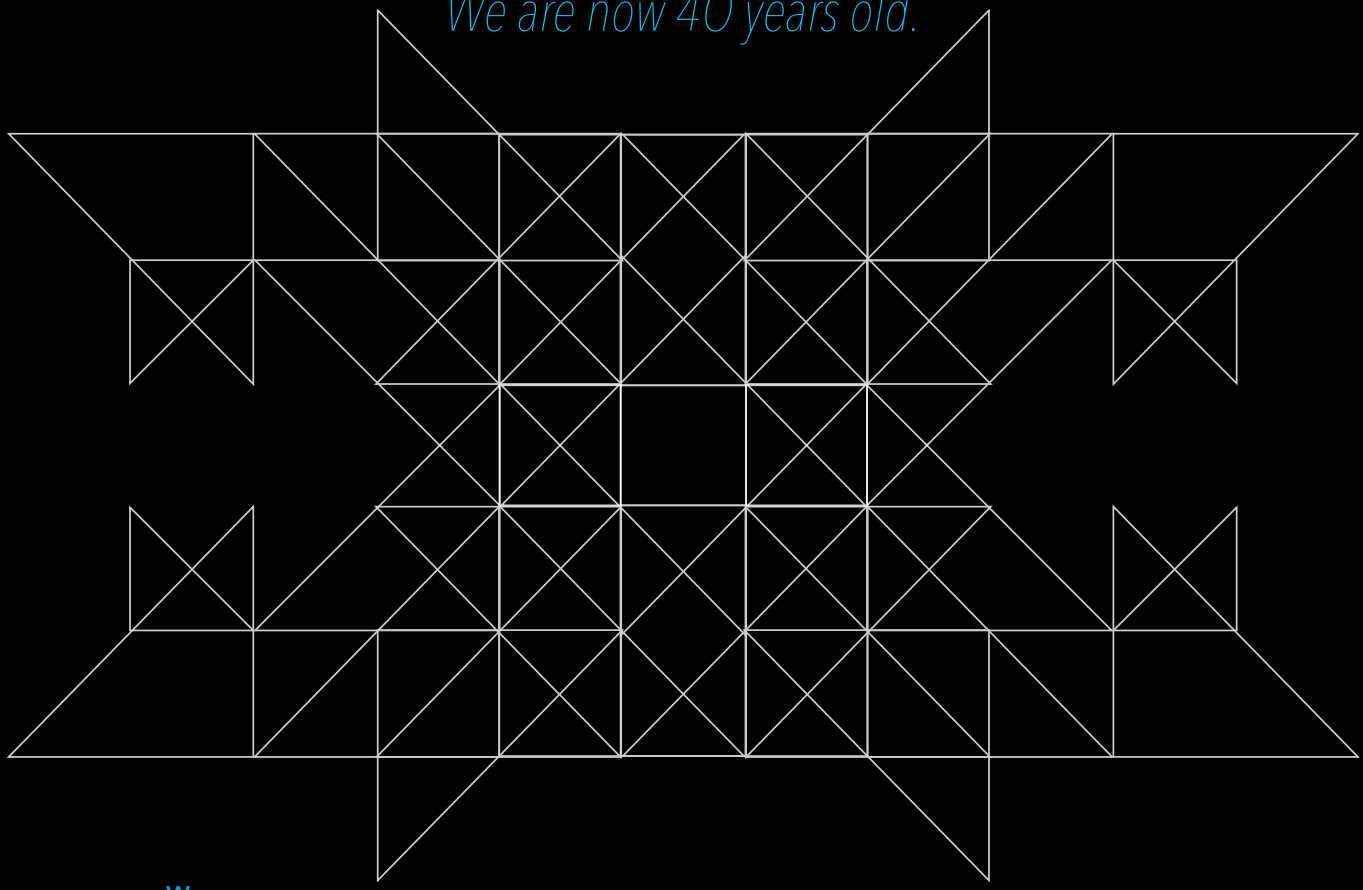
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message from the editor

We are 40, but we are still excited!

Since the dawn of 2016, there have been many changes in our journal. There are things we want to do to improve our quality. Our passion is to bring out the best in every research presented in our journal and deliver properly to our audiences. 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

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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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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 overinterpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential. Funding sources should be listed separately after the Abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

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

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c. Introduction

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

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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.

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

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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 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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Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

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.

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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).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

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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.

Original Article



Development of clinical nursing practice guidelines for hospitalized moderate to high risk mild traumatic brain injury

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To develop clinical nursing practice guidelines (CNPGs) for hospitalized moderate to high risk mild traumatic brain injury.

METHODS

This was a development research for developing CNPGs starting from the emergency department, inpatient department till discharge in those with. The development of the CNPGs were done following the conceptual framework of Soukup model; (i) evidence triggered phase; identified problem, (ii) evidence supported phase; searching and identifying for best evidence based practice, (iii) evidence observed phase; implementing and evaluating of the results and (iv) evidence based phase; conclusion and disseminating of the results. Compliance, opinions and satisfactions of users were recorded. Treatment outcomes were regarding death, re-visit and re-admission were also collected.

RESULTS

Five CNPGs were newly developed followed the Soukup model;. After three cycles of drafting, the final version was produced comprising guidelines regarding (i) patient assessment, (ii) monitoring for increased intracranial pressure, (iii) symptom management, (iv) giving information to patient and (v) discharge planning. Two hundred and sixty patients with moderate to high risk, mild traumatic brain injury were included. The guidelines were highly complied with high satisfaction of users. No death and no readmission after implementation of the CNPGs, 5% were re-visited. The nurses also 100% assessed the patients. Twenty six patients with signs of increased intracranial pressure with dropped Glasgow Coma Scales were all recognized after using the guidelines. All of them survived and were discharged home.

CONCLUSION

Five CNPGs were newly developed. The guidelines were highly complied with high satisfaction of users. No death and no readmission after implementation of the CNPGs. Those with increased intracranial pressure survived and were discharged home.

INTRODUCTION

Traumatic brain injury can be classified 3 groups regarding neurological sign followed Glasgow Coma Scale (GCS); severe traumatic brain injury with GCS 3-8, moderate traumatic brain injury with GCS 9-12 and mild traumatic brain injury with GCS 13-15.[1] Mild traumatic brain injury is considered to be about 90% of all traumatic brain injury globally.[2] Most of them have only minor symptoms with no sign, thus, would be ignore for close monitoring.[3] Mild traumatic brain injury can also be classified three categories regarding risk for intracranial hemorrhage; low risk, moderate and high risk. Those with moderate to high risk should be admitted for observation even though they had only mild traumatic brain injury as they have risk for increased intracranial pressure in the first hour or even weeks after the injury.[4] About 6-10% [5] of them in previous studies from Western countries and only 3% of them from a Thai study will develop secondary brain injury which may result in death and disability.[6] Approximately 0.24-0.9 % of them will die.[7]

Guidelines for those with mild traumatic brain injury suggest for assessing patients regarding to their risks.[8] Those with moderate to high risk should be monitored for changes in vital signs, levels of consciousness and neurological signs together with intravenous fluid and oxygen.[9] However, most of the Thai studies regarding management of patients with mild traumatic brain injury conducted at the emergency department and often in moderate to severe brain injury. Thus, this study aims to develop clinical nursing practice guidelines (CNPGs) starting from the emergency department, inpatient department till discharge in those with moderate to high risk, mild traumatic brain injury.

METHODS

Study design and oversight

This was a development research for developing CNPGs starting from the emergency department, inpatient department till discharge in those with .The study period was between March and July 2016.

The protocol of the study was submitted to the Institutional Review Board of Khon Kaen Hospital with the approval number of KE 59028. The study was conducted follow the principle of World Medical Association Declaration of Helsinki; respect for person, beneficence and justice.

Participants

Participants in the present study were patients identified using purposive sampling for those fulfilled the following criteria (i) moderate to high risk, mild traumatic brain injury aged 18 years or older, (ii) injury within 24 hours, (iii) admitted for observation at least 6 hours, (iv) no or minor injuries of other organs. We excluded those with life threatening conditions. For nurses, we included all 78 nurses involving with care of the included patients from the emergency department, inpatient department till discharge.

Conceptual framework and process of data gathering

The development of the CNPGs was done following Soukup model (Figure 1) comprising four steps; (i) evidence triggered phase; identified problem, (ii) evidence supported phase; searching and

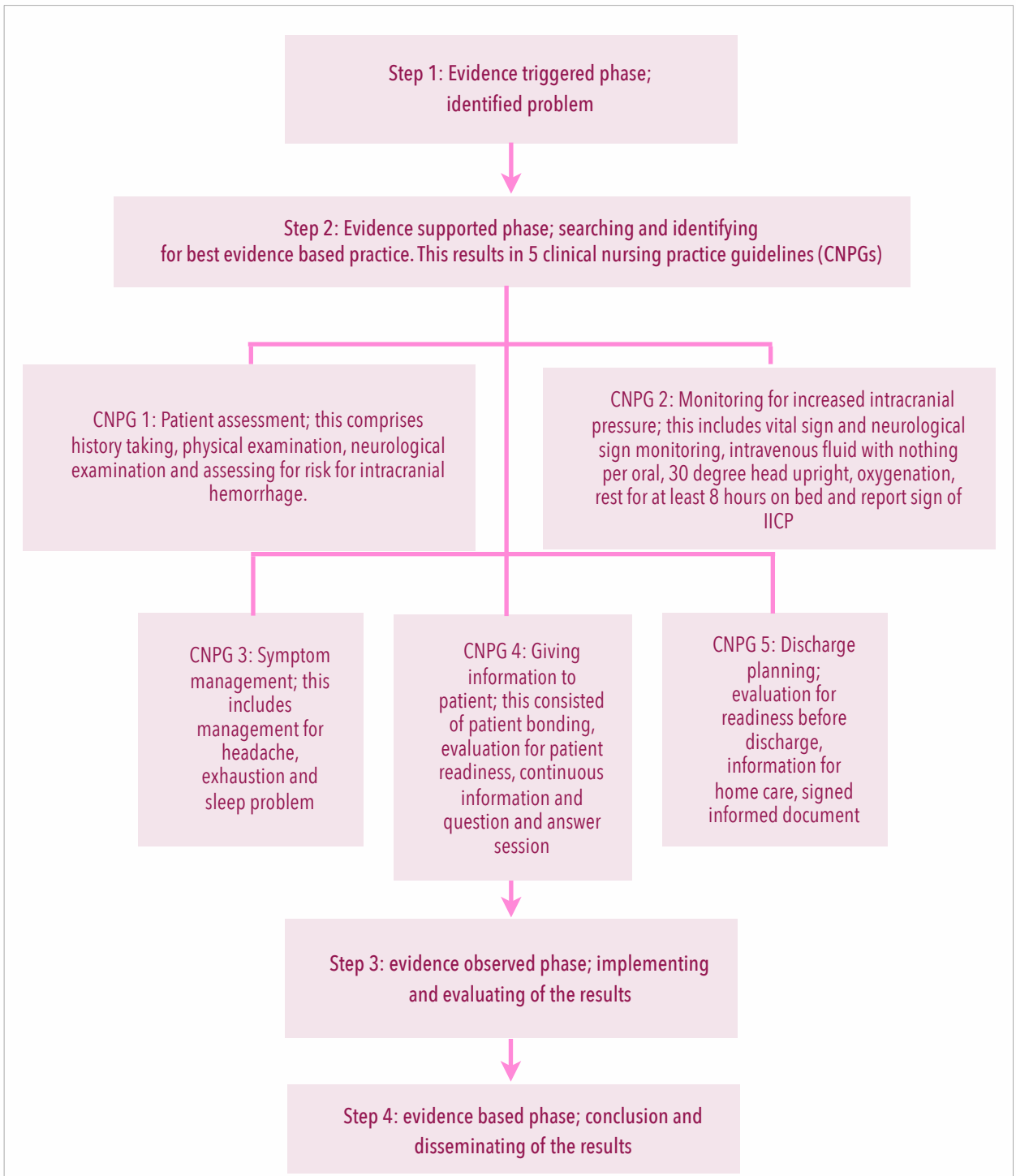


Figure 1. Process of developing clinical nursing practice guidelines

Table 1. Characteristics of the participants

Characteristic	Number	%
Patients	260	
Male	225	86.7
Marital status as couple	146	56.5
Age between 45 and 50 year	100	39.0
Elementary education	121	46.7
Cause of injury		
Traffic accident	182	70.0
Fall	61	23.3
Assault	17	6.7
Initial Glasgow coma scale		
Score 13	26	10.0
Score 14	69	26.7
Score 15	165	63.3
Risk		
Moderate	155	59.6
High	105	40.4
Length of hospital stay hours		
<24	101	39.2
24-72	140	53.8
>72	19	7.0
Type of discharge		
Home discharge	259	99.6
Refer to other hospitals	1	0.4
Nurses	78	
Female	72	91.7
25-40 year	35	45.0
Bachelor degree of education	74	94.9
Experience-years		
3-5	29	37.2
>5	22	28.1

identifying for best evidence based practice, (iii) evidence observed phase; implementing and evaluating of the results and (iv) evidence based phase; conclusion and disseminating of the results. In the first steps, 10% of all cases of patients with mild traumatic brain injury in 2015 with approximately 100 cases were reviewed. Out of these, five were death. By reviewing medical records, the processes of cares with risk were identified, for instance, no document regarding continuous vital signs or neurological signs monitoring or assessing for mild, moderate or high risk. Moreover, the researchers went seeing the real process of care and interviewing nurses for tracking down the potentially erroneous process of care. All data in this step were concluded regarding process of care and care delivers were later feedbacked.

For the second step, seven guidelines, two systematic reviews, one quasi-experimental study, one randomized controlled trial, two descriptive studies and one related articles were identified from searching through seven databases using the combination of keywords of "mild traumatic brain injury" or "cerebral concussion" or "mild head injury" and "management" or "assessment" or "discharge plan "or "CNPG". At the end, 14 related articles were identified. Six nurses and doctors were then drafted for the first CNPG. Five content experts were later reviewed the draft, the second draft were then produced with five CNPGs; CNPG 1: Patient assessment, CNPG 2: Monitoring for increased intracranial pressure, CNPG 3: Symptom management, CNPG 4: Giving information to patient and CNPG 5: Discharge planning. A pilot of the second draft was conducted in 10 patients with moderate to high risk, mild traumatic brain injury. However, the guidelines for patient assessment and monitoring for increased intracranial pressure were difficult to comply by nurses. Context feasibility was then taken into consideration. The final draft was produced with consensus of both doctors and nurses.

For the third step, the final draft of the CNPGs was used in 260 consecutive patients with moderate to high risk, mild traumatic brain injury. Self report of compliance of nurses to the guidelines together with opinion and satisfactory of the final draft was done for those delivered cares. Conclusions was made regarding these patients as the fourth, final, step. Outcomes followed the new CNPG were summarized in relation to death, readmission, re-visit with 48 hours, GCS stable or equal to 15, management for those with increased intracranial pressure, pain scale reduced 4 or less in those with headache and understanding of given information. Correction of patient assessment was also record as the successful implementation of the guidelines.

Statistical analysis

Frequency table was generated for each variable to identify the wide values. All data were cleaned before analysis. For descriptive statistics, number and percentage were used to summarized categorical variables while median were used to summarized normally distributed continuous data and median together with interquartile range (IQR) were used to summarized non-normally distributed continuous data.

RESULTS

There were 260 patients with moderate to high risk, mild traumatic brain injury included in the present study. Most of them were male with the median age

Table 2. Self report of compliance of nurses following the clinical nursing practice guidelines

List	Quantity/Total (%)
CNPG 1: Patient assessment	
History taking	201/260 (77.3)
Physical examination	156/260 (60.0)
Evaluation of Glasgow coma scale	195/260 (75.0)
Radiological investigation	256/256 (100)
Assessing of injury	260/260 (100)
Documentation of the assessment	180/260 (69.2)
CNPG 2: Monitoring for increased intracranial pressure	
Monitoring of vital and neurological signs	241/260 (92.6)
Laboratory investigation	235/235 (100)
30 degree head up position	230/260 (88.4)
Proper oxygenation	200/200 (100)
Rest on bed for the first 8 hours	250/260 (96.1)
Intravenous isotonic solution	260/260 (100)
Evaluation and record of headache	220/220 (100)
Report of abnormal signs and symptoms within 5 minutes	26/26 (100)
CNPG 3: Symptom management	
Monitoring of post concussion symptom	260/260 (100)
Head positioning	193/193 (100)
Management of weakness	11/11 (100)
Management of sleep	11/11 (100)
Management of body balance	11/11 (100)
CNPG 4: Giving information to patient	
Establishment of relationship	260/260 (100)
Evaluation of readiness for information	260/260 (100)
Openness for questions from patient's relatives	260/260 (100)
Continuous information given	260/260 (100)
CNPG 5: Discharge planning	
Evaluation of readiness before discharge	260/260 (100)
Information given regarding head injury	260/260 (100)
Management symptoms after injury	250/260 (96.1)
Information as leaflet	260/260 (100)
Signing after information receiving	250/260 (96.1)
Evaluation of knowledge before discharge	260/260 (100)

Table 3. Opinion and satisfaction of the clinical nursing practice guidelines by nurses

Opinion and satisfaction	Highly agree	Agree	Neither agree or disagree	Disagree	Highly disagree
			No. (%)		
Easy to use	14 (18.0)	38 (48.7)	13 (16.7)	10 (12.8)	3 (3.9)
Clear to use	5 (6.4)	37 (47.4)	29 (37.2)	5 (6.4)	2(2.6)
Comprehensive	22 (28.2)	44 (56.4)	10 (12.8)	2 (2.6)	0
Practical	6 (7.7)	54 (69.2)	15 (19.2)	3 (3.9)	0
Aid decision making	5 (6.4)	36 (46.2)	32 (41.0)	5 (6.4)	0
Multidisciplinary collaboration	4 (5.1)	43 (55.1)	29 (37.2)	2 (2.6)	0
Benefit for patients	28 (35.9)	42 (53.9)	7 (9.0)	1 (1.3)	0
Overall satisfaction	10 (12.8)	43 (55.1)	18 (23.1)	6 (7.7)	1 (1.3)

of 31 years (IQR, 24 to 46) (Table 1). Approximately 70% had injuries from traffic accidents. Most of them had initial GCS of 15. Nearly 60% were moderate risk. Characteristics of nurses included in the study are also presented in Table 1. More than 90% of them were female. Their median age was 27 (IQR, 24 to 30.5). More than half of them had experience 3 years or more.

Compliances to the five new nursing guidelines of nurses are summarized in Table 2. Overall compliance was 95.2%; 80.3% for patient assessment, 97.1% for monitoring for increased intracranial pressure, 100% for symptom management, 100% for giving information to patient and 98.7% for discharge planning. Nurse opinions and satisfactions are shown in Table 3. More than 50% had high or very high satisfied with the new CNPGs. The areas with lowest satisfaction were clarity of the guidelines and aid-ability for decision making. For outcomes of treatment, no death and no readmission after implementation of the CNPGs, 5% were re-visited. Details of other outcomes are presented in Table 4. The nurses also 100% assessed the patients. Twenty six patients with signs of increased intracranial pressure with GCS dropped were all recognized after using the guidelines. Eight out of these, literally had increased intracranial pressure and required for treatment, all of them underwent computed tomography of the brain, one underwent craniotomy, one on ventilator and six received medical treatment. All of them survived and were discharged home.

DISCUSSION

Principal findings

Five CNPGs were newly developed followed the Soukup model;. After three cycles of drafting, the final version was produced comprising guidelines regarding (i) patient assessment, (ii) monitoring for increased intracranial pressure, (iii) symptom management, (iv) giving information to patient and (v) discharge planning. The guidelines were highly complied with high satisfaction of users. No death or readmission were found after implementation of the guidelines.

Table 4. Clinical outcomes after using the clinical nursing practice guidelines

Outcome	Number/Total (%)
Patient	
GCS 15 or stable before discharge	258/260 (99.2)
Further management for those with increased intracranial pressure	8*/26 (30.8)
Pain scale for headache decreased <4	176/193 (91.1)
High level of knowledge before discharge	180/250 (90.0)
Re-visit within 48 hours	13/260 (5.0)
Re-admission	0
Death	0
Nurse	
Correct risk assessment	260/260 (100)

*Of eight, one underwent craniotomy, one underwent intubation and six received supportive medical treatment.

Strengths and limitations

To our knowledge, this is the largest study with highest number of patients with moderate to high risk, mild traumatic brain injury in the world demonstrated outcomes after implementation of the newly developed evidence-based CNPGs. Non-preferred outcomes were averted with prompt treatments. The guidelines involving with doctor-nurse-patients collaboration. However, there were several limitations; these guidelines pose question regarding long-term sustainability, satisfactories were not high in some areas especially clarity of the guidelines and aid-ability for decision making as the guidelines were relatively complex with adding no new knowledge for decision making.

Comparison with other studies

Our guidelines were implemented in those with moderate to high risk mild traumatic brain injuries. Guidelines like this were used to be developed before.[10-15] However, that study in 2015 conducted in inpatient department only with fewer sample size compared to ours[10] while our study developed the guidelines starting since the entry of the patients with larger sample. Their findings also demonstrated positive outcomes of both patients and nurses after implementation of their guidelines.[10] Another study in 2015 in only 53 patients with hospitalized mild traumatic brain injuries at the inpatient department, positive outcomes were also observed. [11] Prior to these in 2013, a study with 626 patients with all risks of mild traumatic brain injury at the emergency department, it found that 31 secondary brain injury were all detected with no death found.[12] Another quasi-experimental study in 2012 conducted for developing discharge plan at the emergency department only, it found that good information regarding symptoms care at home resulted in low re-visited rate. All four Thai studies mentioned earlier, they were all conducted in all risk groups of patients

and focus either only at emergency department or inpatient department.[10-13] Close monitoring for every 1 to 2 hours for detection of alarming signs and symptoms was all found in these four studies.[10-13] Thus, it might be the key for all positive outcomes after implementation of their own guidelines in all four studies.[10-13]

There was an Italian study implementing newly developed clinical practice guideline in 2000 patients with 4,536 minor head injuries, it found that 458 patients were admitted, only one died from extradural haematoma after one year of study.[14] Close monitoring every 30 minutes for vital and neurological signed in the first 2 hours after injury was the key to high survival rate.[14] However, this might be not practical in resource-limited settings like in Thailand. Another Swedish study in 2013 with 71 nationwide emergency departments, after implementation of the new own developed clinical practice guideline for patients with mild traumatic brain injury, the mean hospital stay was 1.2 days in 2013, compared with 1.6 days in 1996. From the two latter study, benefits were found higher and larger when the guidelines were developed thoroughly processes of care deliver beyond merely only nursing guidelines.

Conclusion and implication

Five CNPGs were newly developed with high compliance and satisfaction from users. No death and readmission after the implementation of the guidelines. However, long term monitoring is still required. A large, cluster randomized controlled trial comparing the new guidelines with standard treatment in larger sample should be conducted for clearer estimation of the effect of the newly developed evidence-based CNPGs. For better outcomes, the study for developing larger scope of guideline rather than only nursing guideline would benefit patients and care deliverers in all disciplines.

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REFERENCES

1. The Royal College of Neurological Surgeons of Thailand, et al. Clinical Practice Guidelines for Traumatic Brain Injury. 2013; Bankok: Tanapress Ltd.

2. Vos PE, Alekseenko Y , Battistin L, Mild traumatic brain injury. European Journal of Neurology 2012;19:191–98.

3. Pornpean P. Development of the clinical nursing practice guideline for initial assessment of patients with mild traumatic brain injury emergency phase[Thesis].Khonkaen.Khonkaen University; 2015

4.Cifu D, Steinmetz BD, Drake DF. Repetitive head injury syndrome. [Accessed August 29, 2008];eMedicine. 2016 March 1; Available at:http://www.emedicine.com/sports/TOPIC113.HTM.

5. Fabbri A, et al. Prospective validation of a proposal for diagnosis and management of patients attending the emergency department for mild head injury. J Neurol Neurosurg Psychiatry 2004;75:410-416.

6. National Institute for Emergency Medicine. Injury and Advance Emergency Caring. 2010; Khon Kaen: Penprinting.

7. Carroll LJ,et al. PROGNOSIS FOR MILD TRAUMATIC BRAIN INJURY: RESULTS OF THE WHO COLLABORATING CENTRE TASK FORCE ON MILD TRAUMATIC BRAIN INJURY. J Rehabil Med 2004; Suppl. 43: 84–105.

8. Kraisri B, Development of care practice guidelines for mild head injury patients in emergency room at NongKhai Hospital. [Thesis].Khonkaen.Khonkaen University; 2012.

9.Mock, C., Lemand, J.D., Goodsen, J., Joshipura, M. & Peden, M. Guideline for essential trauma care. ;2004: Geneva:World Health Organization.

10.Wanpen C., Varin B.,Nam-oy P.Feasibility and Clinical Outcomes of Nursing Care Protocol for Persons with Mild Head Injury in Emergency Medical Ward.RSU National Research Conference 2015:1535-45.

11. Varunee K. The Development of clinical nursing practice guidelines for the patients with mild head injury who admitted into emergency surgery unit of Kalasin Hospital: A pilot study. [Thesis].Khonkaen.Khonkaen University; 2015

12.Withirong S. Nursing practice system development in caring for persons with mild head injury in emergency department.[Thesis]. Bangkok, Rangsit University; 2013.

13. WIMON M. EFFECTS OF A DISCHARGE PREPAREDNESS PROGRAM FOR MILD TRAUMATIC BRAIN INJURY PATIENTS AND CAREGIVERS ON POST CONCUSSION SYMPTOMS AND RE – HOSPITALIZATION)[Thesis]. Chonburi, Burapha University; 2012.

14. Viola L, Zotta D, Martino V, Barbato R, Schisano G. Minor head injuries: one year experience according to the new Italian guideline. Acta Neurochir (Wien). 2000;142(11):1281-5.

15 Carlsson S., af Geijerstam J-L. Management of Mild Traumatic Brain Injuries in Emergency Departments in Sweden: Evidence of a Change in Clinical Practice.J Rehabil Med 2013; 45: 718–720.

Diabetes mellitus and amputation in necrotizing fasciitis: retrospective cohort study

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the relationship between diabetes and outcomes of treatment in relation to amputation, re-debridement, septic shock, death and lengths of stay in the hospital in patients with necrotizing fasciitis (NF).

METHODS

This was a retrospective cohort study verifying and reviewing medical records of patients with NF who admitted to Khon Kaen Hospital, a major tertiary care center and teaching hospital in Khon Kaen, Thailand, between January 2010 and August 2011. Diabetes was interested risk factors and primary outcome was amputation. Secondary outcomes included redebridment, septic shock, death and organ failure as well as the length of hospital stay.

RESULTS

There were 317 patients included in the study. Of these, 128 (40.4%) were diabetes. Twenty five patients were amputated (7.9%), 30 had re-debridement (9.5%), 47 had septic shock (14.8%), 21 died (6.6%) and 18 had organ failures (5.7%) with the median overall length of hospital stay of five days. Comparing between those with and without diabetes, rate of amputation were higher in the former group (15.6% vs 2.6%; crude odds ratio, 6.81; 95% CI confidence interval, 2.49 to 18.68). However, from logistic regression analysis, diabetes was found not to be the risk factor for amputation (adjusted odds ratio (AOR), 1.03, 95% CI, 0.97 to 1.09). History of chronic wound and high capillary blood sugar were found to be associated with higher rate of amputation (AOR 10.74, 95% CI 1.48 to 78.25; AOR 1.01, 95% CI 1.00 to 1.02, respectively).

CONCLUSION

In the present study, having diabetes was found not to be the risk factor for amputation. History of chronic wound and high capillary blood sugar were the two factors found to be the associated with higher rate of amputation.

BACKGROUND

A Confederate army surgeon named Joseph Jones firstly described "necrotizing fasciitis"(NF) during the Civil War.[1] Wilson coined the named NF in 1952, from necrosis, which means death of a portion of tissue, and fascia occured in all areas of the body.[2] NF is an infection of fascia and subcutaneous tissues with rapid extensive and progressive necrosis of the tissues.[3] Its presentations are specific to skin ecchymosis or necrosis with hemorrhagic bleb or gas in subcutaneous tissue and sometimes there are symptoms of systemic toxicity including high fever, tachycardia, tachypnea and hypotension which usually late course of disease.[4] The gold standard diagnosis is debridement with tissue biopsy, however, the diagnosis was commonly from clinical findings.[5] It can occur in any age group and without any an underlying major medical illness.[6] Treatment should be initiated as soon as a NF is suspected. The treatment should include broad-spectrum antibiotics and early debridement with surgical exploration.[7] NF was associated with high mortality and morbidity.[8] Nearly half of patients with NF have multiple organ dysfunctions.[8] Its mortality can be varied from 6-76%.[8] It can be as high as 73% if left untreated.[9] Early diagnosis and prompt surgical intervention are considered critical to obtain an improved survival and a delay in surgery of more than 24 hours adversely affects the outcome.[10]

Risk factors for NF include diabetes mellitus (DM), old age, high body mass index, liver disease, cancer, alcohol dependent and other immunosuppressive disorders.[11] DM is the predisposing factor present in 32–66% of all cases especially in type I NF that caused by polymicrobial infection[12,13] like *Staphylococcus aureus*, Streptococci, enterococci and *Escherichia coli*.[12,13]

High glucose level in those with DM is thought to have impacts on the clinical outcomes of NF in term of higher morbidity and mortality.[14] Although many studies have cited DM to be an important risk factor that can predispose patients develop to NF but most of the studies have not comprehensively reflected the of complication in DM and non DM patients with NF. [12,13,14,15] Thus, the present study aims to identify the relationship between diabetes and outcomes of treatment concerning amputation, re-debridement, septic shock, death and lengths of stay in the hospital in patients with NF.

METHODS

Study design

This was a retrospective cohort study verifying and reviewing medical records of patients with NF who admitted to Khon Kaen Hospital, a major tertiary care center and teaching hospital in Khon Kaen, Thailand, between January 2010 and August 2011.

Participants

Medical records of all patients with NF aged 18-75 were included in the process of review. Those who left against advise or admitted for skin graft were excluded. Sample size calculation was based on significant level 5%, power 80%, expected difference of the primary outcome, amputation rate, of 10.6%, estimated sufficient sample would be 123 in each group and 246 in total. However, the current study included up to 317 participants to conclude the relationship between DM and amputation.

Table 1. Characteristics of the patients

Characteristic	NF with DM N=128	NF without DM N=189	P Value
Male sex – no. (%)	66 (51.6)	142 (75.1)	<0.001
Mean age – years	58.7±9.1	54.7±14.0	0.002
Underlying disease – no. (%)			
Hypertension	47 (36.7)	21 (11.1)	<0.001
Cardiovascular disease	8 (6.3)	7 (3.7)	0.295
Chronic renal disease	15 (11.7)	9 (4.8)	0.022
Chronic liver disease	3 (2.3)	10 (5.3)	0.194
Alcoholic abuse	0	6 (3.2)	0.085
Location of NF – no. (%)			
Multiple site	1 (0.8)	9 (4.8)	0.054
Shoulder region	1 (0.8)	0	0.404
Upper arm	0	2 (1.1)	0.517
Forearm	3 (2.3)	12 (6.3)	0.099
Hand	10 (7.8)	22 (11.6)	0.267
Pelvic region and thigh	4 (3.1)	5 (2.6)	>0.999
Lower leg	36 (28.1)	81 (42.9)	0.008
Ankle and foot	71 (55.5)	59 (31.2)	<0.001
Severities on admission – no. (%)			0.158
Stage 1	18 (14.1)	38 (20.1)	
Stage 2	49 (38.3)	55 (29.1)	
Stage 3	61 (47.7)	96 (50.8)	
Predisposing factor – no. (%)			
Acute puncture wound	23 (18.0)	45 (23.8)	0.214
History of NSAIDs use	1 (0.8)	2 (1.1)	>0.999
History of operation	2 (1.6)	1 (0.5)	0.568
History of trauma	36 (28.3)	75 (39.7)	0.038
History of animal bite	4 (3.1)	5 (2.6)	1.000
Burn	1 (0.8)	0	0.404
Chronic wound	14 (10.9)	5 (2.6)	0.002
Unknown	46 (36.2)	56 (29.9)	0.244

Plus-minus values are means±standard deviations

Outcomes

The main outcome was amputation. The secondary outcomes included redebridment, septic shock, death and organ failure as well as the length of hospital stay.

Data collection

For each medical record variable regarding patients' characteristics, vital signs, investigation, outcomes of treatment and medication given were verified and reviewed. Patients characteristics were sex, underlying disease e.g., hypertension, cardiovascular disease, chronic renal disease, chronic liver disease, alcohol abuse, location of the NF e.g., multiple site, shoulder region, upper arms, forearm, hand, pelvic region and thigh, lower leg, ankle and foot, stage of severity was admitted including stage 1, stage 2, stage 3, predisposing factor e.g., acute puncture wound, history of non-steroidal anti-inflammatory drug (NSIAD) used, history of operation, history of trauma, history of animal bite, burn, chronic wound, unknown cause. Vital signs on admission including blood pressure, pulse rate, respiratory rate, body temperature. Values of laboratory measurement (capillary blood sugar on admission, complete blood count, blood sugar, blood urea nitrogen (BUN), serum creatinine, serum electrolyte, antibiotics treatment e.g., cloxacillin, ceftriaxone, ceftazidime, metronidazole, ciprofloxacin, clindamycin), length of hospital stay.

Statistical analysis

All data were double entered into spread sheet. All data were cleaned before preceding the analysis. Frequency tables for each variable were generated for checking of potential outliers and wide values. For categorical variables, they were described in term of number and percentage. Either chi-square or Fisher's exact test was used for the inferential statistics where appropriate. For scale variable, they were tested for their distribution using Kolmogorov Smirnov test. For those normally distributed, they were summarized using mean$\pm$standard deviation (SD) and t-test for inferential statistics. For non normally distributed data, they were described using median and interquartile range and Mann-Whitney U test for inferential statistics. Crude odds ratio (COR) was used to calculated risk together with its 95% confidence interval (CI). Adjusted odds ratio (AOR) from logistic regression was also used.

RESULTS

Characteristics of participants

In the present study, 602 medical records were preliminary reviewed. At the end, a total 285 were excluded, only 317 were left for the analysis. Of these, 128 (40.4%) were diabetes. Most of them were male (63.4%) and their average age was 56.3 years old (Table 1). Hypertension was the most common underlying disease among these patients (21.5%). However, dyslipidemia, anemia, rheumatoid arthritis, gout, steroid abuse, renal insufficiency, coagulopathy, thalassemia, asthma, chronic obstructive pulmonary disease, benign prostatic hyperplasia and thrombocytopenia were also found in these patients. Lower limbs were the most common site for NF (77.9%). In addition to this, ten had multiple site infection. Majority of the participants were in stage III (49.5%). Trauma was the most common known cause (35.0%).

Table 2. Vital sign and laboratory measurements

Vital sign on admission	NF with DM N=128	NF without DM N=189	P Value
Temperature– Celsius	37.4±0.9	37.4±0.8	0.511
Blood pressure – mmHg			
Systolic	127.2±26.3	121.9±23.8	0.066
Diastolic	71.5±11.7	70.3±13.5	0.419
Pulse rate – beat/min			0.213
Median	90	93	
Interquartile range	80–100	79-103	
Respiratory rate – breaths/min			0.915
Median	20	20	
Interquartile range	20-20	20-20	
Laboratory measurements			
Capillary blood sugar on admission – no. (%)			<0.001
Median	202	111	
Interquartile range	128-292	95.5-138.8	
Hemoglobin– mg%	10.2±1.9	10.9±2.1	0.003
Hematocrit– %	30.0±6.0	32.2±5.9	0.001
White blood cell count-1,000 cell/ul	17.9±9.4	15.4±9.5	0.022
Platelet-1,000 cell/ul			0.002
Median	269	232	
Interquartile range	218.3–358.0	159-335	
Blood sugar – mg%			<0.001
Median	191.5	102	
Interquartile range	123.3-237.8	91-131	
Blood urea nitrogen – mg%			0.109
Median	20	15	
Interquartile range	11.5–30.0	10.0-29.5	
Creatinine – mg%			0.543
Median	1.2	1.1	
Interquartile range	0.9–1.9	0.9-1.7	

Table 2. Vital sign and Laboratory measurements (continued)

Vital sign on admission	NF with DM N=128	NF without DM N=189	P Value
Serum sodium – mEq/l	133.7±5.9	136.0±5.1	<0.001
Serum potassium– mEq/l	3.8±0.7	3.7±0.7	0.631
Serum chloride– mEq/l	100.6±6.8	103.0±5.2	0.001
Serum HCO3– mEq/l			0.525
Median	23.4	23.4	
Interquartile range	20.0–25.2	19.9-25.6	

Comparing between those with diabetes and without diabetes, the latter had higher proportion of male to female (P<0.001), were less likely to have those with hypertension (P<0.001) and chronic renal disease (P=0.022) where lower leg was the common site of infection in this group (P=0.008). Chronic wound were less found in this group as well (P=0.002).

Vital sign and laboratory measurements

On admission, there were 101 patients (31.9%) who had fever, 72 patients (22.7%) were shock (Table 2). There were no significant differences between the two groups in relation to body temperature (P=0.511), systolic blood pressure (P=0.066), diastolic blood pressure (P=0.419), pulse rate (P=0.213), respiratory rate (P=0.915) BUN (P=0.109) and creatinine (P=0.543), potassium (P=0.702) and bicarbonate (P=0.525). More than three quarter of the patients had leukocytosis (79.2%), 126 (39.7%) were anemia, 50 (15.8%) were thrombocytopenia, 143 (45.1%) had hyponatremia and 122 (38.5%) had hypokalemia.

Comparing between those with diabetes and without diabetes, the former group tended to have higher white blood cell count (P=0.022), higher platelet count (P=0.002), higher blood sugar (P<0.001), higher capillary blood sugar on admission (P<0.001), less hemoglobin (P=0.003) and less hematocrit (P=0.001). In the blood chemistry, the diabetes group tended to have lower serum sodium and chloride (P<0.000 and P=0.001, respectively).

Prescribed antibiotics and treatment outcomes

Ceftriaxone was the most prescribed antibiotics (86.8%) (Table 3). Penicillin G sodium, gentamycin, tazocin, vancomycin, meropenem, co-trimoxazole, tazocin and cefazolin were also given. Generally, there were no significant differences in relation to prescribed antibiotics between the two groups.

Treatment outcomes

Twenty five patients were amputated (7.9%), 30 had re-debridement (9.5%), 47 had septic shock (14.8%), 21 died (6.6%) and 18 had organ failures (5.7%) with the median overall length of hospital stay of five days. Comparing between those with and without diabetes, there were no significant differences regarding rate of septic shock

Table 3. Prescribed antibiotics

Antibiotics	NF with DM N=128	NF without DM N=189	P Value
Cloxacilin	56 (43.8)	81 (42.9)	0.875
Ceftriaxone	111 (86.7)	164 (86.8)	0.989
Ceftazidime	18 (14.1)	16 (8.5)	0.114
Metronidazole	45 (35.2)	72 (38.1)	0.595
Ciprofloxacin	4 (3.1)	4 (2.1)	0.719
Clindamycin	88 (68.8)	118 (62.4)	0.247

(P=0.109), death (P=0.246), organ failure (P=0.177) and length of hospital stay (P=0.071). However, rate of amputation were higher in former group (15.6% vs 2.6%; COR, 6.81; 95% CI, 2.49 to 18.68) as well as the rate of re-debridement in diabetes (14.1% vs 6.3%; COR, 2.41; 95% CI, 1.12 to 5.20) (Table 4).

Concerning with primary outcomes, the logistic regression analysis was used to identify risk factors for amputation (Table 5). History of chronic wound and high capillary blood sugar were found to be associated with higher rate of amputation (AOR 10.74, 95% CI 1.48 to 78.25; AOR 1.01, 95% CI 1.00 to 1.02, respectively). However, diabetes was found not to be the risk factor for amputation.

DISCUSSION

Principal findings

This is the first comprehensive study to show the relationship of outcomes those with and without diabetes in NF. Rate of amputation were higher in those with diabetes. However, from logistic regression analysis, diabetes was found not to be the risk factor for amputation. History of chronic wound and high capillary blood sugar were found to be the associated with higher rate of amputation

Comparison with other studies

In one previous study from Qatar in 94 NF patients has stated that DM was a comorbid disease in 56.4% of the NF patients[16] but the present study show that less than half (40.4%) in patient NF that had DM. The high proportion of patients with NF and DM might be due to the study sites that were both were conducted in tertiary hospitals. In relation to our primary outcomes, 15.6% of diabetic patients suffered from amputation vs 2.6% in non diabetic patients. However, this was relatively low comparing to a previous study from Iran in 24 NF patients that the rate of limb loss was also significantly higher in diabetic cases (71.4% of those with diabetes suffered from amputation vs 15.4% in non diabetes).[17] The present study has demonstrated that the length of hospital stay was similar between those with and without DM. These findings were similar to the that

Table 4. Outcomes of the treatment

Outcomes	NF with DM N=128	NF without DM N=189	Crude odds ratio (95% confidence interval)
Primary outcome – no. (%)			
Amputation	20 (15.6)	5 (2.6)	6.81 (2.49-18.68)
Secondary outcome – no. (%)			
Re-debridement	18 (14.1)	12 (6.3)	2.41 (1.12-5.20)
Septic shock	14 (10.9)	33 (17.5)	0.58 (0.30-1.13)
Death	11 (8.6)	10 (5.3)	1.68 (0.69-4.09)
Organ failure	10 (7.8)	8 (4.2)	1.92 (0.74-5.00)
Length of hospital stay - days			
Median	6	4	
Interquartile range	3–9	3-8	

of the Turkish study in 23 NF patients.[18] Moreover, in this Turkish study, death rate was higher in those with DM (53% in DM group and 12% in non DM group).[18] The controversial findings as the death rates between the two groups might be due to a very limited sample size (N=23) of the previous study.[18] The number of surgical re-debridements in this Turkish was not different between those with DM.[18] However, in our study, the rate of re-debridement was higher in those with DM significantly. The other complications like septic shock, organ failure were not reported in previous studies. In the current study showed that two group of patient NF had no significantly different turned to septic shock and organ failure.

Strength and limitations of the study

Our study has several strengths, the sample size was adequate and we had sufficient statistical power to examine the relationship between DM and amputation. Limitations of our study included that our study was set up in an Asian hospital which differs from most studies. We examined only people in the Northeast of Thailand which endemic area of NF, and difference regarding ethnicities might have influence over the results. Another limitation is that the diagnosis of NF was delayed in first stage. Its clinical was likely to be cellulitis, thus at first, some were diagnosed as having cellulitis that caused delayed treatment and lead to increase rate of mortality and morbidities. In this study was a retrospective study causing missing data like blood sugar on admission, some basic laboratory, length of clinical time before admission, cause of NF.

Conclusion and implication

This present study shown that diabetic was not likely to be a cause of amputation. Capillary blood sugar on admission and history of chronic wound were the only two predictors for amputation. The findings

Table 5. Adjusted odds ratios from the logistic regression for amputation as the primary outcome

Variables	Adjusted odds ratio	P value	95% confidence interval
Age-Years	1.03	0.341	0.97–1.09
Underlying diabetes mellitus	1.2	0.803	0.27-5.23
Predisposing factor			
Acute puncture wound	4.5	0.068	0.90-23.12
History of trauma	2.2	0.296	0.51-9.17
Chronic wound	10.74	0.019	1.48-78.25
Location of NF			
Lower leg	0.4	0.294	0.07-2.28
Ankle and foot	1.5	0.597	0.33-6.80
Staging			
Stage 2	1.7	0.645	0.19-15.3
Stage 3	6.7	0.065	0.89-49.9
Body temperature	1.3	0.415	0.67-2.66
Systolic blood pressure	1.0	0.508	0.88-1.07
Diastolic blood pressure	1.0	0.689	0.82-1.14
Hematocrit	0.9	0.093	0.84-1.01
White blood cell count	1.0	0.706	1.00-1.00
Capillary blood sugar	1.0	0.003	1.00-1.02
Debridement			
Single debriderment	0.3	0.210	0.06–1.85
Redebriderment	0.7	0.734	0.08–5.83
Septic shock	0.2	0.125	0.02–1.58

suggested the closed monitoring of those with NF and high capillary sugar on admission and those with chronic wound. Control blood sugar would benefit for this outcome. Further study should focus on other outcomes such as rate of death, septic shock, organ failure which required larger-sample cohort study to conclude the association of DM and those outcomes.

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REFERENCES

1. Patino JF, Castro D. Necrotizing lesions of soft tissues. World J Surg 1991;15:235-239.

2. Gonzalez MH, Garst J, Nourbash P, Pulvirenti J, Hall Jr RF. Abscesses of the upper extremity from drug abuse injection. J Hand Surg 1993; 18A:868-870.

3. McHenry CR, Piotrowski JJ, Petrinic D et al (1995) Determinants of mortality for necrotizing soft-tissue infections. Ann Surg 221(5):558-563

4. Gonzalez MH, Bochar S, Novotny J et al (1999) Upper extremity infections in patients with diabetes mellitus. J Hand Surg Am 24(4): 682-686

5. Sarani B, Strong M, Pascual J, Schwab W. Necrotizing fasciitis: current concepts and review of the literature (published online ahead of print December 12, 2008]. J Am Coll Sur. 2009; 208(2):279-288.

6. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. N Engl J Med 2005;352:1445-53.

7. Hung CC, Chang SC, Lin SF, Fang CT, Chen YC, Hsieh WC. Clinical manifestations, microbiology and prognosis of 42 patients with necrotizing fasciitis. J Formos Med Assoc 1996;95:917–22.

8. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO.Necrotizing fasciitis: clinical presentation, microbiology and determinants of mortality. J Bone Joint Surg Am 2003;85-A: 1454-60.

9. Kotrappa KS, Bansal RS, Amin NM. Necrotizing fasciitis. Am Fam Phys 1996;53(5): 1691-6.

10. McArdle P, Gallen I. Necrotising fasciitis in diabetics. Lancet 1996;348:552.

11. Baskin LS, Carroll PR, Cattolica EV, McAninch JW. Necrotizing soft tissue infection of perineum and geitalia. Bacteriology, treatment and risk assessment. Br J Urol 1990;65:524-9.

12. Clinical and microbiological features of necrotizing fasciitis.AU Brook I, Frazier EH SO J Clin Microbiol. 1995;33(9):2382.

13. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality.AU Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low COSO J Bone Joint Surg Am. 2003;85-A(8):1454.

14. Gardam \L-\, Low DE, Saginur R, It al: Group B streptococ- cal necrotizing fasciitis and streptococcal toxic shock-like syndrome in adults. .1cc/ 6rlervr Alert 1998; 158:1704-1708

15. Oncula, , C. Erenoglub, C. Topc, Y. Küçükarda lıc, O. Karabudakd, Y. Kurtb, M.L. Akinb, S. Cavus luaand T. Celenkb Necrotizing fasciitis: A life-threatening clinical disorder in uncontrolled type 2 diabetic patients doi:10.1016/j.diabres. 2007.12.001

16. Necrotizing fasciitis and diabetes mellitus: Nissar Shaikh. Department of Anesthesia and Intensive Care, Hamad Medical Corporation, Doha-Qatar

17. Necrotizing fasciitis of the extremities: a prospective study, Ramin Espandar, Siamak Yousef Sibdari, Elham Rafiee, Shideh Yazdanian.Dermatology Department, Tehran University of Medical Sciences, Imam Khomeini Hospital Complex, Tehran, Iran

18. Necrotizing fasciitis: A life-threatening clinical disorder in uncontrolled type 2 diabetic patients, O. Oncul, S. Cavuslu, Department of Infectious Diseases and Clinical Microbiology, C. Erenoglu, M.L. Akin,T. Celenk, Y. Kurt, Department of General Surgery, C. Top, Y. Küçükardalı, Department of Internal Medicine, O. Karabudak, Department of Dermatology, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, Istanbul, Turkey

Risk factors for developing Weil's disease in patients with leptospirosis

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To determine risk factors for developing Weil' disease in patients with leptospirosis infection.

METHODS

We conducted a nested case-control in retrospective cohort study without matching. This study included patients with the clinical diagnosis of either leptospirosis or Weil's disease at all age whom admitted between January 2009 and October 2011. We reviewed and collected data from an electronic database of Khon Kaen Hospital, Thailand. The primary study outcome was Weil's disease and the secondary outcomes were death, acute renal failure, severe hepatitis and pulmonary hemorrhage.

RESULTS

At the beginning, 835 patients were included in this study. Later, 390 patients were excluded due to no record of serum Leptospira titer for the diagnosis confirmation. At the end, 445 remained in the study and were divided into two groups; 236 patients developing Weil's disease and 209 not developing Weil's disease. From the multivariable analysis using a logistic regression, independent risk factors for developing Weil's disease were platelet count≤50,000/cu.mm (AOR, 2.02; 95% CI; 1.12 to 3.65), albumin<2.5 mg% (AOR, 2.76; 95% CI, 1.41 to 5.41), blood urea nitrogen (BUN)>60 mg% (AOR, 5.67; 95% CI, 1.53 to 20.98) and creatinine>4.5 mg% (AOR, 2.92; 95% CI, 1.17 to 7.31).

CONCLUSION

The risk factors for developing Weil's disease were low platelet count, low serum albumin, high total bilirubin, high serum BUN and high serum creatinine.

INTRODUCTION

Leptospirosis is a zoonotic disease presenting in human, and usually found in tropical countries.[1-3] Human leptospirosis most occurs by contact with water contaminated by urine of infected animal.[2] The clinical presentation is wide range from subclinical to fulminant disease known as Weil's disease. Its clinical manifestations are fever, headache, nausea myalgia, acute renal failure, hemorrhagic diathesis, jaundice and multiple organ failure.[1-4] Its mortality rate varies from 15-20% and has a higher rate in Weil's disease up to 30%.[1,5]

Many studies reveal factors associated lethality of leptospirosis and Weil's disease including pulmonary involvement and oliguria,[5,6] For instance, four out of eight leptospirosis patients with pneumonia, pulmonary effusion and pulmonary hemorrhage died in one Japanese study in 2009.[5] Moreover, one Brazilian study found that patients with oliguria had approximately 9 times higher mortality comparing to those without oliguria in 110 patient with Weil's disease in 1999.[6] However, there is no consensus whether what risk factors for becoming Weil's disease in patients with leptospirosis. In the present study, we, thus, attempted to examine the possible risk factors for developing Weil' disease in patients with leptospirosis infection.

METHODS

Study design and patients

We conducted a nested case-control in retrospective cohort study without matching. The present study involved with inpatient department of Khon Kaen Hospital, Khon Kaen, Thailand. This study included patients with the clinical diagnosis of either leptospirosis or Weil's disease at all age whom admitted between January 2009 and October 2011. For those without Leptospira titer were excluded. The study sample was calculated based on the null hypothesis that there was no difference in relation to proportion of patients with oliguria in those developing and not developing Weil's disease group. With the 5% of alpha error, 80% power, the expected difference of proportion of patients with oliguria were 0.1, the required sample size would be 400 in total. However, in the present study, we aimed to included the sample up to 450 patients.

Data collection

We reviewed and collected data from the hospital electronic database regarding age, sex, body temperature (BT), length of hospital stay, blood pressure (BP), oliguria,[8] hemoglobin (Hb), leukocyte count (WBC), platelet count, absolute neutrophil count (ANC), albumin, total bilirubin (TB), direct bilirubin (DB), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), Leptospira titer, blood urea nitrogen (BUN), serum creatinine and death or survival for each included patient. All values were on admission.

Study outcomes

The primary study outcome was Weil's disease and the secondary outcomes were death, acute renal failure, severe hepatitis and pulmonary hemorrhage.

Statistical analysis

All data were verified and cleaned before preceding the statistical analysis using double entry methods.

Table 1. Characteristics of the patients

Characteristic	Developing Weil's disease	Not developing Weil's disease	P Value
Male sex-no. (%)	178 (85.2)	179 (75.8)	0.014
Age-Yr			0.231
Median	45.6	44.2	
Interquartile range	33.6-55.5	28.4-54.5	
Body temperature-^{o}C			0.775
Median	37.6	37.5	
Interquartile range	36.9-38.4	36.8-38.5	
Blood pressure-mmHg			
Systolic			0.001
Median	105	115	
Interquartile range	91-128	100-132	
Diastolic			0.028
Median	60	61	
Interquartile range	50-70	54-73	
Oliguria –no. (%)	35 (16.7)	17 (7.2)	0.002
Urine output –cc/hr			0.008
Median	56.2	69.2	
Interquartile range	28.6-94.3	45.8-100.0	
Hemoglobin-g/dL			0.000
Median	11.0	11.9	
Interquartile range	9.6-12.4	10.4-13.0	
Leukocyte count -10^3/mm^3			0.005
Median	12.6	10.8	
Interquartile range	9.0-16.7	7.9-14.1	
Absolute neutrophil count-10^3/ mm^3			0.000
Median	10.5	8.7	
Interquartile range	7.9-14.1	6.2-11.9	

Table 1. Characteristics of the patients (continued)

Characteristic	Developing Weil's disease	Not developing Weil's disease	P Value
Platelet count -10^3/ mm^3			0.000
Median	38.0	106	
Interquartile range	16.0-102.8	42-207	
Albumin-g/dL			0.000
Median	2.1	2.5	
Interquartile range	1.9-2.4	2.1-3.0	
Total bilirubin-mg%			0.000
Median	5.1	1.5	
Interquartile range	2.1-9.9	0.8-3.4	
Direct bilirubin-mg%			0.000
Median	3.1	0.8	
Interquartile range	1.8-8.2	0.3-2.5	
Aspartate transaminase - U/L			0.000
Median	92.5	67.5	
Interquartile range	59.3-178.5	40.0-121.8	
Alanine transaminase - U/L			0.063
Median	85.0	56	
Interquatile range	45.0-100.8	39-90	
Alkaline phosphatase - U/L			0.002
Median	150	122	
Interquartile range	106-219	87-193	
Blood urea nitrogen-mg%			0.000
Median	56	21	
Interquartile range	40-85	12-43	
Creatinine-mg%			0.000
Median	4.8	1.5	
Interquartile range	2.6-6.7	1.0-3.5	
Leptosira titer positive –no. (%)	63 (30.1)	58 (24.6)	0.188

Moreover, frequency tables for all entered variables were generated to examine for wide values and outliers. Characteristics of the patients of those developing and not developing Weil's disease were compared using chi-square test for categorical variables. Median and interquartile ranges were used to summarize continuous variables and Mann-Whitney U test was used for comparing the variables between two groups. The risk factors associated with developing Weil's disease, mortality, acute renal failure, severe hepatitis and pulmonary hemorrhage were computed and reported in term of crude odds ratio (COR) with 95% confidence interval (CI). To determine the independent risk factors, binary logistic regression models were used to control the effects of confounding variables and were reported as adjusted odds ratio (AOR) and 95% CI. Cox proportional hazard models were used to estimate hazard ratio (HR) and 95% CI for the mortality outcome with the cut-off point at 60 days after admission date of non death patients.

RESULTS

At the beginning, 835 patients were included in our study. Later, 390 patients were excluded due to no information regarding serum Leptospira titer for the diagnosis confirmation. At the end, 445 remained in the present study and were divided into two groups; 236 patient developing Weil's disease and 209 not developing Weil's disease. More than three quarters were male with the median age of 45 years old. Less than half had fever. About 14% had urine output less than 500 ml per day. Nearly half of the patients had platelet count less than 50,000/mm^3. In relation to the treatment, nearly all of them were treated using doxycycline and ceftriaxone.

It found that those developing Weil's disease group were likely to be male (P=0.014) (Table 1). Moreover, their systolic and diastolic BP tended to be lower than another group (P=0.001 and 0.028, respectively) as well as the platelet count (P<0.001), their urine output (P=0.008), hemoglobin (P<0.001) and albumin (P<0.001). They were likely to have more proportion of patients with oliguria (P=0.002). Their levels of BUN were also greater than the another group (P<0.001) as well as their creatinine (P<0.001), ANC (P<0.001), TB (P<0.001), DB (P<0.001), AST (P<0.001) and ALP (P=0.002).

Risk factors for developing Weil's disease

The results of univariable analysis revealed that being male, oliguria, age>35 years, BP<90/45 mmHg, Hb<10.5 g/dl, WBC<5,000 or >10,000/mm^3, platelet count<50,000/mm^3, ANC>12,000/mm^3, albumin<2.5 mg%, TB 3 mg% or more, DB 2 mg% or more, ALT>100 U/L, ALP>100 U/L, BUN >60 mg% and creatinine>4.5 mg% were statistically significant associated with developing Weil's disease with COR more than 1 (Table 2). However, from the multivariable analysis using a logistic regression, independent risk factors for developing Weil's disease were platelet count≤50,000/cu.mm (AOR, 2.02; 95% CI; 1.12 to 3.65), albumin<2.5 mg% (AOR, 2.76; 95% CI, 1.41 to 5.41), BUN>60 mg% (AOR, 5.67; 95% CI, 1.53 to 20.98) and creatinine>4.5 mg% (AOR, 2.92; 95% CI, 1.17 to 7.31).

Risk factors for secondary outcomes

Mortality

The results of univariable analysis revealed that being female, oliguria, age>35 years, BP<90/45

Table 2. Odds ratios of factors for developing Weil's disease, mortality, acute renal failure, severe hepatitis and pulmonary hemorrhage

Factor	Weil's disease		Mortality		Acute renal failure		Severe hepatitis		Pulmonary hemorrhage	
	Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)	Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)	Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)	Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)	Crude Odds ratio (95% CI)	Adjusted Odds ratio (95%CI)
Male	1.83 (110-3.05)	1.45 (0.65-3.22)	0.45 (0.14-0.86)	0.36 (0.12-1.13)	1.15 (0.7-1.9)	0.54 (0.25-1.20)	0.60 (0.28-1.31)	0.34 (0.11-1.06)	1.03 (0.5-2.13)	0.73 (0.27-2.02)
Age >35 yr.	1.92 (1.17-3.14)	0.52 (0.27-0.98)	3.66 (1.36-10.69)	6.02 (1.23-29.54)	1.87 (1.16-3.01)	0.71 (0.37-1.34)	1.50 (0.62-3.84)	0.73 (0.26-2.01)	0.49 (0.26-0.92)	0.40 (0.19-0.88)
Body temperature >37.8°c	1.13 (0.76-1.69)	1.66 (0.90-3.04)	1.04 (0.58-1.58)	0.99 (0.35-2.84)	0.63 (0.42-0.94)	0.83 (0.46-1.48)	1.1 (0.56-2.20)	1.48 (0.60-3.66)	2.06 (1.16-3.67)	2.84 (1.32-6.09)
Systolic ≤90 mmHg	2.24 (1.32-3.83)	1.19 (0.46-3.06)	3.15 (1.67-5.91)	0.66 (0.11-3.79)	1.76 (1.00-3.11)	1.86 (0.63-5.47)	2.83 (1.35-5.87)	1.38 (0.41-4.71)	2.38 (1.24-2.54)	2.62 (0.87-7.94)
Diastolic ≤45 mmHg	2.67 (1.37-5.24)	0.90 (0.11-7.56)	3.57 (1.73-7.31)	2.81 (0.10-76.54)	1.51 (0.77-3.00)	0.66 (0.09-4.72)	2.74 (1.17-6.33)	1.25 (0.27-5.74)	2.18 (1.00-4.67)	1.63 (0.14-18.90)
Oliguria <500 ml/day	2.49 (1.29-4.86)	1.06 (0.46-2.46)	13.75 (6.14-31.15)	15.47 (4.91-48.72)	2.98 (1.29-7.12)	1.35 (0.49-3.75)	4.07 (1.72-9.29)	5.75 (1.93-17.17)	2.80 (1.33-5.86)	1.82 (0.71-4.71)
Hemoglobin <10.5 g/dL	2.16 (1.39-3.36)	1.11 (0.60-2.95)	2.15 (1.20-3.85)	2.10 (0.73-6.10)	3.09 (1.91-4.99)	0.90 (0.48-1.70)	0.89 (0.42-1.87)	0.52 (0.18-1.45)	1.57 (0.87-2.83)	1.37 (0.12-3.01)
Leukocyte count ≤5000/mm^3	1.91 (0.93-3.96)	1.80 (0.52-6.29)	3.16 (1.41-7.02)	0.83 (0.14-2.89)	0.78 (0.38-1.6)	1.02 (0.32-3.25)	1.42 (0.46-4.11)	1.25 (0.19-8.47)	1.4 (0.53-3.52)	0.38 (0.08-1.75)
Leukocyte count >10000/mm^3	1.70 (1.73-2.56)	0.95 (0.42-1.99)	0.79 0.44-1.41)	0.42 (0.12-1.52)	2.07 (1.37-3.13)	1.34 (0.65-2.72)	1.11 (0.55-2.26)	2.71 (0.77-9.58)	0.79 (0.44-1.41)	0.73 (0.28-1.91)
Platelet count ≤ 50000/mm^3	4.24 (2.79-6.45)	2.02 (1.12-3.65)	2.44 (1.36-4.41)	1.25 (0.37-4.28)	5.45 (3.42-8.7)	2.93 (1.54-5.57)	1.88 (0.95-3.72)	1.96 (0.89-5.55)	3.74 (2.01-7.01)	6.09 (2.50-14.86)
Absolute nuetrophil count ≥12000/mm^3	1.89 (1.24-2.89)	0.92 (0.46-1.84)	2.18 (1.06-4.49)	2.21 (0.59-8.22)	1.74 (1.11-2.73)	1.43 (0.69-2.96)	1.30 (0.64-2.61)	0.84 (0.30-2.36)	1.02 (0.55-1.87)	1.30 (0.52-3.24)
Albumin <2.5 g/dL	4.18 (2.61-6.70)	2.76 (1.41-5.41)	1.96 (0.81-4.89)	0.53 (0.15-1.89)	2.86 (1.81-4.55)	2.07 (1.11-3.86)	1.17 (0.56-2.50)	1.12 (0.35-3.53)	1.33 (0.69-2.56)	1.13 (0.45-2.85)
Total bilirubin ≥3 mg%	6.22 (3.9-9.94)	3.99 (1.12-13.11)	1.86 (1.00-3.47)	0.18 (0.02-1.74)	2.96 (186-4.72)	1.64 (0.45-5.97)	2.21 (1.05-4.71)	0.29 (0.05-1.60)	1.62 (0.88-2.99)	1.72 (0.31-9.57)
Direct bilirubin ≥2 mg%	6.09 (3.83-9.71)	0.96 (0.29-3.23)	2.08 (1.11-3.94)	3.20 (0.32-32.07)	2.92 (1.84-4.65)	0.61 (0.17-2.24)	2.70 (1.24-5.97)	10.02 (1.56-64.50)	1.65 (0.90-3.05)	0.87 (0.15-5.13)
Aspartate transaminase >200 U/L	1.65 (0.93-2.92)	1.27 (0.31-5.16)	3.08 (1.56-6.06)	8.79 (1.39-55.81)	0.85 (0.47-1.53)	0.60 (0.16-2.22)	2.66 (1.21-5.77)	0.93 (0.09-9.23)	1.32 (0.62-2.78)	1.78 (0.41-7.80)
Alanine transaminase >100 U/L	2.52 (1.56-4.09)	1.9 7(0.76-5.13)	3.19 (1.33-8.00)	2.14 (0.36-12.91)	2.17 (1.34-3.51)	1.26 (0.51-3.09)	1.68 (0.71-4.11)	3.18 (0.80-12.62)	0.96 (0.50-1.86)	2.28 (0.69-7.55)
Alkaline phosphatase ≥100 U/L	2.49 (1.53-4.06)	1.33 (0.70-2.54)	3.70 (1.46-9.91)	1.35 (0.40-4.56)	2.08 (1.28-3.38)	1.74 (0.93-3.24)	1.61 (0.68-3.94)	0.55 (0.19-1.59)	0.92 (0.48-1.78)	0.73 (0.32-1.66)
Lepto titer positive	1.32 (0.85-2.06)	1.46 (0.77-2.78)	0.83 (0.43-1.61)	3.18 (0.98-10.32	1.67 (1.04-2.67)	1.56 (0.80-3.05)	0.58 (0.24-1.36)	1.28 (0.44-3.74)	0.68 (0.33-1.35)	0.94 (0.38-2.34)
Blood urea nitrogen >60 mg%	3.59 (2.32-5.58)	5.67 (1.53-20.98)	5.74 (2.68-12.54)	0.35 (0.02-7.72)	2.43 (4.51-3.86)	1.63 (0.45-5.93)	0.97 (0.47-1.97)	1.03 (0.32-3.26)	0.49 (0.24-0.97)	0.31 (0.10-0.97)
Creatinine >4.5 mg%	5.02 (3.24-7.77)	2.92 (1.17-7.31)	3.84 (2.11-7.05)	2.78 (0.67-11.61)	4.12 (2.58-6.62)	19.04 (2.38-152.15)	1.32 (0.67-2.59)	0.45 (0.15-1.40)	0.87 (0.40-1.58)	0.69 (0.26-1.81)
Weil 's disease			3.23 (1.80-5.79)	1.60 (0.51-5.02)	5.44 (3.53-8.38)	1.98 (1.03-3.81)	2.56 (1.13-4.98)	1.34 (0.48-3.70)	4.73 (2.52-8.87)	4.88 (1.99-11.96)

Table 3. Hazard ratios of potential risk factors for mortality in all patients and in those developing Weil's disease

Factor	All Patients		Patients developing Weil's disease	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Male	0.41	0.16-1.08	0.41	0.09-1.87
Age >35 yr.	4.05	1.09-15.03	9.96	0.78-126.79
Body temperature >37.8°C	1.01	0.39-2.59	0.92	0.28-2.30
Systolic ≤90 mmHg	0.66	0.11-4.07	1.61	0.24-10.69
Diastolic ≤45 mmHg	2.80	0.25-31.41	1.80	0.23-14.05
Oliguria <500 ml/day	8.89	3.61-21.95	7.85	2.26-27.27
Hemoglobin <10.5 g/dL	2.02	0.82-4.99	5.61	1.35-23.37
Leukocyte ≤5000/mm^3	1.12	0.27-4.64	0.67	0.17-2.64
Leukocyte >10000/mm^3	0.51	0.17-1.56	1.71	0.38-7.79
Platelet≤ 50000/mm^3	1.48	0.49-4.35	0.43	0.10-1.86
Absolute neutrophil count ≥12000/mm^3	1.32	0.43-3.99	0.36	0.06-2.23
Albumin<2.5 g/dL	0.50	0.17-1.50	1.17	0.27-5.11
Direct bilirubin≥2 g/dL	0.54	0.20-1.45	4.72	0.55-40.45
Aspartate transaminase >200 U/L	3.22	1.04-9.97	3.64	0.55-24.12
Alanine trasferase>100 U/L	1.12	0.30-4.18	2.84	0.33-24.51
Alkaline phosphatase≥100 U/L	1.47	0.51-4.20	4.24	1.94-17.27
Leptospira titer positive	2.01	0.77-5.30	2.78	0.20-38.55
Blood urea nitrogen>60 mg%	0.67	0.07-6.28	2.24	0.41-12.13
Creatinine >4.5 mg%	2.41	0.74-7.90	0.41	0.09-1.87

mmHg, Hb<10.5 g/dl, WBC<5,000 /mm^3, platelet count<50,000/mm^3, ANC>12,000/mm^3, TB 3 mg% or more, DB 2 mg% or more, AST>200 U/L , ALT>100 U/L, ALP>100 U/L, BUN>60 mg%, creatinine>4.5 mg% and being Weil's disease were statistically significant associated with higher mortality rate (Table 2). After adjusting with covariates, independent risk factors for higher mortality were age≥35 years (AOR, 6.02; 95% CI, 1.23 to 29.54), oliguria (AOR, 15.47; 95% CI, 4.91 to 48.72) and AST>200 U/L (AOR, 8.79; 95% CI to 1.39-55.81).

Acute renal failure

The results of univariable analysis revealed that being oliguria, positive Leptospira titer, age>35 years, Hb<10.5 g/dl, WBC>10,000/mm^3, platelet count<50,000/mm^3, ANC>12,000/mm^3, albumin <2.5 mg%, TB 3 mg% or more, DB 2 mg% or more, ALT>200 U/L, ALP>100 U/L, BUN>60 mg%, creatinine>4.5 mg% and being Weil's disease were statistically significant associated with developing acute renal failure. However, from the multivariable analysis using a logistic regression, independent risk

factors for developing acute renal failure were platelet count≤50,000/mm^3 (AOR, 2.39; 95% CI, 1.54 to 5.57), albumin<2.5 g/dl (AOR, 2.07; 95% CI, 1.11 to 3.86), creatinine>4.5 mg% (AOR, 19.04; 95% CI, 2.38 to 152.15) and being Weil's disease (AOR, 1.98; 95% CI, 1.03 to 3.81).

Severe hepatitis

The results of univariable analysis revealed that being, oliguria, BP less than 90/45 mmHg, TB 3 mg% or more, DB 2 mg% or more, AST>200 U/L and being Weil's disease were statistically significant associated with having severe hepatitis (Table 2). However, from the multivariable analysis using a logistic regression, independent risk factors for severe hepatitis were determined to be oliguria (AOR, 5.75; 95% CI, 1.93 to 17.7) and DB≥2g/dl (AOR, 10.02; 95% CI, 1.56 to 64.50).

Pulmonary hemorrhage

The results of univariable analysis revealed that BT>37.8^{o}C, being oliguria, positive Leptospira titer, BP<90/45 mmHg, platelet count<50,000/mm3 and being Weil's disease were statistically significant associated with developing pulmonary hemorrhage. Nonetheless, from the multivariable analysis using a logistic regression, independent risk factors for pulmonary hemorrhage were determined to be BT>37.8^{o}C (AOR, 2.84; 95% CI, 1.32 to 6.09), platelet count≤50,000/mm^3 (AOR, 6.09; 95% CI, 2.50 to 14.86) and being Weil's disease (AOR, 4.88; 95% CI, 1.99 to 11.96).

Mortality from Log rank test and Cox proportion hazard regression

According to Kaplan-Meier estimation, mortality at day 60 was significantly higher in those with age>35 years old, oliguria and AST>200 U/L (all with P<0.001). After adjusting with other covariates in the Cox model, the mortality was higher in those with age>35 years, oliguria and AST>200 U/L were significant at day 60 (HR, 4.05; 95% CI, 1.09 to 15.03; HR, 8.89; 95% CI, 3.61 to 21.95 and HR, 3.22; 95% CI, 1.04 to 9.97 respectively) (Table 3).

For the subgroup analysis of this outcome exclusively for those with Weil's disease, in Cox model, factors that were associated with higher mortality rate were oliguria, hemoglobin<10.5 mg%l and ALP≥100 U/L (HR, 7.85; 95% CI, 2.26 to 27.27; HR, 5.61; 95% CI, 1.35 to 23.37 and HR, 4.24; 95% CI, 1.94 to 17.27, respectively).

DISCUSSION

Our study found that the risk factors for turning from leptospirosis to Weil's disease were low platelet count<50,000/mm^3, low serum albumin<2.5 mg%, high total bilirubin of 3 mg% or more, BUN >60 mg%, creatinine>4.5 mg% and risk factors of mortality in the leptospirosis patients were age>35 years, having oliguria and AST >200 U/L.

Strength and limitation

To our knowledge, this is the first study demonstrating various risk factors for turning from leptopsirosis to Weil's disease and risk factors for death, acute renal failure, severe hepatitis and pulmonary hemorrhage. We examined as many as 20 factors including clinical signs and laboratory investigations for early prediction of various complications and co-morbidities. All of these data were analyzed and adjusted for the potential confounders. Various cut-off points for each risk factor such as age, body temperature and platelet were generated for better understanding of its relationship with the interested outcomes.

Moreover, our study can collected up to 445 patients that satisfied with the power to investigate our hypothesis. However, the limitation of this study included that there is no definite diagnosis for Weil's disease, as most of the diagnosis was from clinical criteria e.g., presentation of icterus and renal failure. Due to the retrospective nature of the study, missing data were unavoidable. However, the attempts to gather of those data were made. Averagely, less than ten percents of data were irretrievable and all the outcomes were totally complete.

Compared with other studies

Oliguria was found to be a significant risk factor for death as it is the result of immune complex process in renal damage and instability of hemodynamic which reflect the severity of leptospirosis. This is similar to a previous study in 1999 in 110 Brazilian patients with leptospirosis.[6] The odds ratio for this factor was 13.75 in the present study and 8.98 in the Brazilian study. However, with four times larger sample size in our study, the precision might be greater. Moreover, in our study, doxycycline and ceftriaxone were the most prescribed regimen for the patients, in that Brazilian study, penicillin G was primarily given in the patients as well as another study from the same country.[1,6] In relation to age, we found that age older than 35 was highly associated with higher mortality which is different to the previous study which stated that age more than 40 years old was not a significant factor for mortality in leptospirosis patients.[6] This might also be due to the scale of sample size.

Conclusion and implication

In summary, the risk factors for developing Weil's disease were low platelet count, low serum albumin, high total bilirubin, high serum BUN and high serum creatinine. We suggested that leptospirosis patients with these factors should be monitored closely for early management. Further diagnosis study should be conducted for creation of the clinical scoring system for better validity and accuracy of the Weil's disease diagnosis.

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REFERENCES

1. Elizabeth F Daher, Rafael SA Lima, Geraldo B Silva Júnior. Clinical presentation of leptospirosis: a retrospective study of 201 patients in a metropolitan city of Brazil. UFC 2009.

2. Eliete Calo ROMERO, Carla Cristiane da Motta BERNARDO, Paulo H. YASUDA. Human leptospirosis. Rev. Inst. Med. Trop. 2003; 45(5): 245-248.

3. Adrian Covic, David J. A. Goldsmith, Paul Gusbeth-Tatomir, et al. Nephrol Dial Transplant 2003; 18: 1128–1134.

4. Anne S. Spichler, Pedro J. Vilaça, Daniel A. Athanazio, et al. Predictors of Lethality in Severe

Leptospirosis in Urban Brazil. Am J Trop Med Hyg. 2008; 79(6): 911–914.
5. Eko Budiono, Sumardi, Bambang Sigit Riyanto, Barmawi Hisyam, Anggoro Budi Hartopo. Pulmonary involvement predicts mortality in severeleptospirosis patients.
6. Elizabeth Daher, Dirce M. Trevisan Zanetta, Marcelo Borges Cavalcante. Risk factors of death and changing patterns in leptospirosis acute renal failure. Am. J. Trop. Med. Hyg. 1999; 61(4); 630–634.
7. Ana Flávia C Azevedo, Demócrito de B Miranda-Filho, Gustavo T Henriques-Filho. Treatment of pulmonary involvement in severe leptospirosis. BMC Infectious Diseases 2011; 11:186.
8. Dan Longo, Anthony Fauci, Dennis Kasper, et al : Harrison's Pinciples of internal medicine, 18th editions. 2008.




I don't want you to be only
a doctor but I also want you
to be a man
A quotation by His Royal Highness Prince Mahidol of Songkla

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our motto

"I shall either find a way or make one"

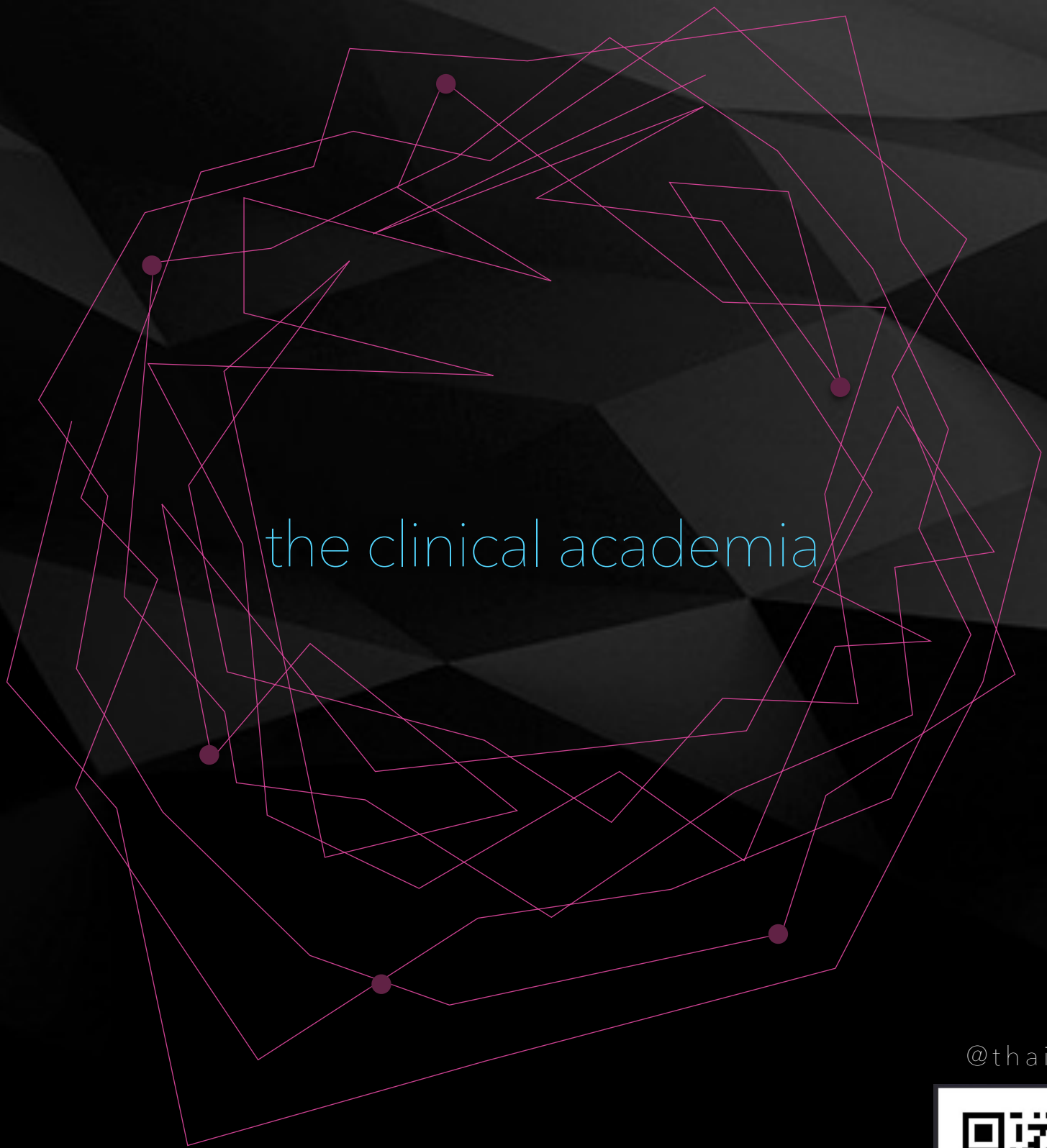
-Hannibal Barca



"You are the king of kings...

To you the God in heaven has given

dominion and strength, power and glory..." (Daniel 2;37)



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