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Thammasorn Piriyasupong, M.D., Ph.D.

From the Editor

Please be welcomed to Journal of Medical Research and Education (JMRE). For this second issue, you will have a chance to learn about the reformation of medical education in Japan. Moreover, you can read up to ten studies regarding various fields of clinical medicine conducted by medical students. We do hope you enjoy reading and please do not hesitate to give us feedbacks. In this occasion, I would like to inform your the KKMJ, the Thai journal, please feel free to visit www.kk-mj.com. It is one and only top Thai journal that you can read from the application on iPad. With the second version of the app, you can enjoy more with its rich features.

Thanks and enjoy

Thammasorn Piriyasupong, M.D., Ph.D.

Editor-in-Chief of JMRE

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Perspective

in Medical Education

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PERSPECTIVE

ESTABLISHED IN 2012 December 2012 VOL. 1 NO. 2

Reformation of Medical Education for an Aging Society in Japan

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Recently, in Japan, the so-called "generalist" career has been gaining popularity among medical students and young doctors. For a long time, it has been believed both inside and outside of our country that Japan has no concept of the "family physician" or "general practitioner." However, in April 2010, the Japanese Medical Society of Primary Care, the Japanese Academy of Family Medicine (JAFM), and the Japanese Society of General Medicine merged to form a new organization, the Japan Primary Care Association (JPCA), with a membership of about 6600 in 2012.1) Since the first 14 doctors became "official" family physicians/general practitioners in 2009, their numbers have been increasing every year.2)

There are many factors behind this phenomenon. For more than a decade, the JAFM has been very keen on educating medical students to the caliber of a family physician outside of the formal undergraduate medical education curriculum. In addition, since 2009, the Nippon Hoso Kyokai (Japan Broadcasting Corporation) has been broadcasting the program Doctor G (General), in which the characteristics of a general physician are described through the depiction of his/her outstanding clinical diagnostic skills; this has become very popular among medical students.3) However, a third key factor is the impact of our aging society. Japan has the highest proportion of elderly citizens worldwide (23% over the age of 65 years in 2010) and this is estimated to rise to 39.9% by the year 2060.4) Along with many doctors who opine that we should adopt a more holistic approach towards patients with multiple health problems, the Japanese government has now asked medical educators to train doctors to "see the bigger picture" in regard to elderly patients, thereby managing them in a comprehensive way.5) In recent times, the requirements for medical education in Japan are changing; the hitherto focus on specialized teaching is now being considered less important.

How should we revise our medical education curriculum accordingly? I would like to discuss this issue from a slightly different perspective than that of the family physician. In general, in the discipline of medicine, most students become clinicians and spend a bulk of their working hours treating patients. However, another option for new graduates is to become so-called "physician-scientists," defined as individuals with an MD degree who perform medical research as their primary professional activity. Physician-scientists conduct research along a scientific continuum, from disease-oriented (e.g., seeking mechanisms that cause diseases and the means to diagnose and treat them) to patient-oriented (e.g., using direct patient interfacing to test etiological, pathophysiological, and management hypotheses); however, they usually perform basic research (studying fundamental biological processes).6)

This career pathway has recently lost popularity worldwide; for example, in the United States, the physician-scientist population is smaller and comprises older individuals when compared with the same population 25 years ago6); moreover, we have observed similar trends in Japan as well7). There are a variety of reasons behind this phenomenon; however, considering the issues of aging in Japan, one hypothesis is that medical students have observed that basic science cannot be of much help in a typical modern-day scenario for elderly hospitalized patients in Japan; for instance, a patient who is 92 years old, living alone at home, and with dementia and chronic obstructive pulmonary disease. The role of medicine is now changing and so is the role of medical research.

In facing up to the aging society in Japan, I am convinced that social medicine definitely plays a key

role, including public health, global health, and professional healthcare education. As the proportion of elderly patients increases steadily, we will have to deal with more social problems which could become the subjects in social science research. With regard to the recent trend of increased interest in generalist careers, these professionals may be ideally qualified to conduct research in social medicine, such as population-oriented research (e.g., assessing disease incidence and susceptibility with epidemiological and biostatistical tools) because they are already familiar with the holistic approach. Thus, I hypothesize that the future direction of Japanese medical education should have more generalists and researchers involved in social medicine; I hope to see more collaboration between clinical and social medicine, and the reformation of medical education as outlined above will enable us to deal more effectively with the issues of aging in Japan.

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Original Articles

by Medical Students

Photo by
Rapeepun Sangsomwong, M.D.

ORIGINAL ARTICLE

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Comparison of Efficacy between Cefaclor and Amoxicillin or Amoxicillin/clavulanate in Acute Pharyngitis and/or Tonsillitis: Systematic Review

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ABSTRACT

BACKGROUND
Acute pharyngotonsillitis is one of the most common conditions encountered in general practice, the major treatable pathogen is group A beta hemolytic streptococcus (GABHS). Cefaclor might be superior to standard penicillin therapy as the latter may fail due to poor compliance, or penicillin tolerance in GABHS or microbial co-pathogenicity. However, there is still no consensus in relation to the efficacy and safety whether cefaclor is better than amoxicillin.

METHODS
This is a systematic review. We searched through four online data sources including Medline, Cochrane Library, Scopus and Ovid and collected randomized controlled trials those comparing between the use of cefaclor and amoxicillin or amoxicillin/clavulanate in participants who have GABHS pharyngotonsillitis were screened, reviewed and selected. The risk of bias of each study was assessed using the Cochrane risk of bias tool (Review Manager version 5.1, Cochrane Collaboration). Statistical analysis of dichotomous variables was carried out using relative risk as the summary statistic.

RESULTS
The first study selection yielded 4063 trials. After screening of the corresponding abstracts and full text papers, seven trials were included. In patient use cefaclor versus amoxicillin, clinical response found no superiority of cefaclor over amoxycillin (relative risk (RR) 1.00, 95% confidence interval (CI) 0.96 to 1.04; I2=0%) as well as bacteriological response (RR 0.97, 95% CI 0.92 to 1.02; I2=8%) or the recurrent rate (RR 0.77, 95% CI 0.37 to 1.57; I2=10%) or incidence of side effect (RR 0.89, 95%0.47 to 1.69). In patient use cefaclor versus amoxicillin/clavulanate, clinical response was no significant difference between the two interventions (RR 0.99, 95% CI 0.95 to 1.02; I2=57%) as well as bacteriological response (RR 0.94, 95% CI 0.90 to 1.00; I2=1%) or recurrent rate (RR 0.77, 95% CI 0.37 to 1.57; I2=10%) or side effect (RR 0.35, 95% CI 0.12 to 1.04; I^2 = 73%).

CONCLUSION
This review suggests, cefaclor and amoxicillin or amoxicillin/clavulanate provide a clinically and bacteriologically effective treatment for patients with pharyngotonsillitis caused by GABHS, and the safety of the both is also similar.

Acute pharyngitis is one of the most common conditions encountered in general practice.[1] Multiple pathogens can cause pharyngitis including virus and bacteria.[2] Group A beta hemolytic streptococci (GABHS) can cause rheumatic fever and other complications, such as acute glomerulonephritis or peritonsillar abscess,[3] thus, the prevention and prompt treatment are required.

Antibiotic treatment of GABHS pharyngitis can be varied such as penicillin (including ampicillin and amoxicillin), cephalosporins, macrolides, and clindamycin.[4] Oral penicillin V is the treatment of choice for treatment of GABHS pharyngitis given its proven efficacy, safety, narrow spectrum, and low cost.[5] Amoxicillin is often used in place of oral penicillin in children, since the taste of the amoxicillin suspension is more favorable than that of penicillin. Some data suggest that oral amoxicillin may be marginally superior to penicillin, most likely due to better GI absorption.[6] However, it has been suggested that tolerance of the microorganisms, inactivation by b-lactamase producing commensals and intracellular location of the pathogens may be possible contributory causes of bacteriological failures.[7]

Cefaclor is a well-established second-generation oral cephalosporin, which is available as a generic at substantially reduced cost in many countries, is highly active against GABHS and resists breakdown by a wide variety of b-lactamases.[8,9,10] Hence, the superiority of cefaclor over amoxycillin is suggested. Several studies comparing between penicillin V and oral cephalosporin have shown the latter to be as effective as or more effective than penicillin in eradicating GABHS in patients with acute pharyngotonsillitis.[11-13] Moreover, many studies comparing the efficacy between cefaclor and amoxicillin/clavulanate were conducted.[14-20] Nonetheless, there is still no consensus in relation to the efficacy and safety whether cefaclor is better than amoxicillin. We, then, systematically reviewed all studies evaluating efficacy and safety between cefaclor and amoxicillin or amoxicillin/clavulanate in acute pharyngitis and/or tonsillitis.

METHODS

Study design and search strategy

Our study was a systematic review. We searched for eligible studies through four online databases including Medline, Cochrane Library, Scopus and Ovid. For the search terms, we used the approach of medical subject headings (MESH) or similar with five synonyms of pharyngitis and twenty-seven synonyms of amoxicillin for the highest possibility of studies to be screen into the review. All full texts of the eligible studies were retrieved. We also performed the hand searching using the reference from the retrieved full text to find related articles the potential to be included in our review.

Study selection

We selected each trials from its title and abstract, We selected randomized controlled trials by the authors according to the following criteria; (i) participants who have GABHS pharyngotonsillitis by either clinical symptom or positive on throat swab culture and (ii) the trials have comparison between cefaclor and amoxicillin or amoxicillin/clavulanate.

Data extraction and risk of bias assessment

Two groups of authors independently selected and review of each eligible trial, the consensus between two groups was done over discussion. We extracted data on participants age, publishing time, dosage of amoxicillin, dosage of amoxicillin/clavulanate, dosage of cefaclor, clinical response, recurrent rate, side effect and duration of follow-up.

We used the risk of bias assessment for each study based on the Cochrane risk of bias tool.[21] We estimated a bias risk summary considering six criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting. The studies were described as low risk scoring low risk in all six bias categories, the study were described as moderate risk scoring low risk in two to five of the categories, and the study were described as high risk scoring low risk for bias in one or fewer of the categories.

Statistical analysis

We used RevMan 5.1.4 software for statistical analysis showing the result of individual study and pooled analysis by forest plot. We carried out one analysis, we compared cefaclor and amoxicillin or amoxicillin/clavulanate using random effects model meta-analysis weighted by the Mantel-Haenszel method to estimate pooled relative risk and 95% confidence intervals. A relative risk less than 1 would favor used cefaclor treated population, we considered the point estimate of the relative risk to be significant at the $P<0.05$ level and the confidence interval did not include the value 1. Heterogeneity was analyzed using I^2 test, which measures the percentage of total variation between studies, with values less than 50% representing low variation.

Sensitivity analysis

We evaluated the effect of study quality criteria by we used the twelve years old as the cut off point divided participants to two group and the publishing time was after the year 2000 or else divided into two groups for comparing efficacy of cefaclor and amoxicillin or amoxicillin/clavulanate in each group, if the result have reversed from primary outcome the criteria that we used was sensitive.

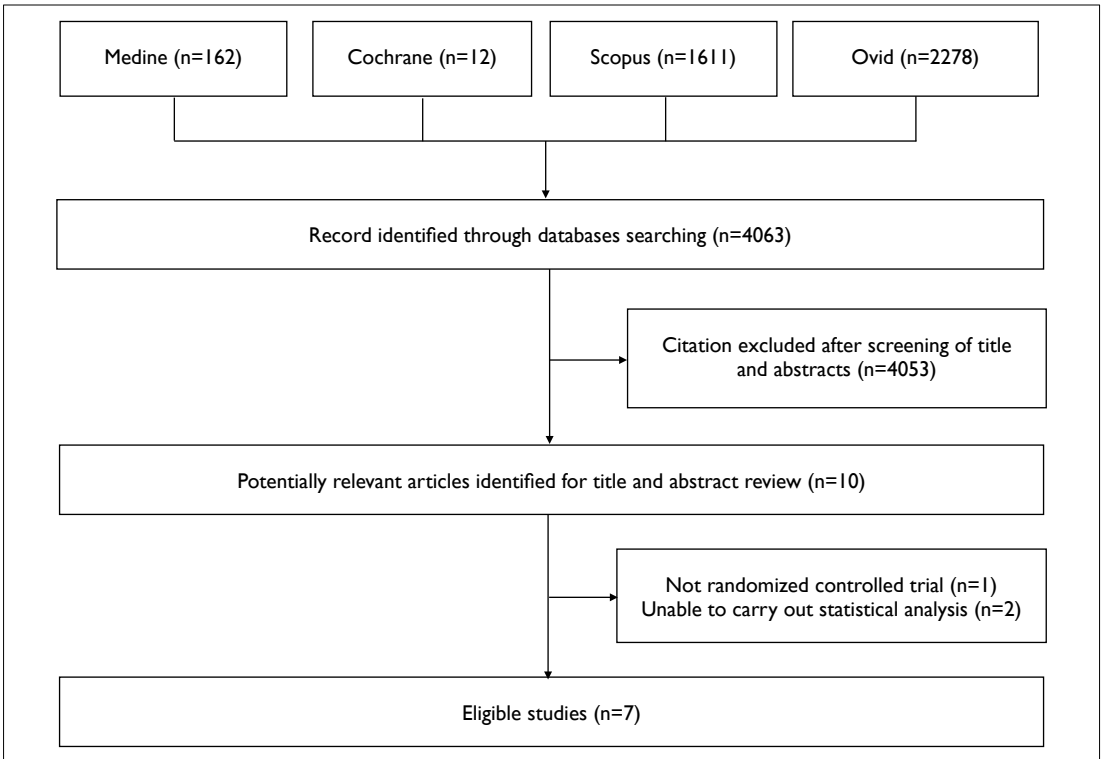


Figure 1. Flow of Participants through Review

RESULTS

Description of studies

Of the 4633 citation retrieved from our searches, 4051 articles were screened on the basis of the titles and abstracts. The remaining 10 articles fulfilled the inclusion criteria. One of these studies was not a randomized control trial, and two studies were unable to carry out statistical analysis .Only Seven eligible randomized controlled study.(Figure 1).[14-20] All eligible article had been published between February 1998 and June 2012. The Among randomized control trials, four studies compared cefaclor with amoxicillin/clavulanate, three studies compared cefaclor with amoxicillin. Table 1 summarise the main characteristics of the include studies.

Quality assessment

Figure 2 shows risk of bias assessment. No studies scored low risk in all six bias categories. Four studies were described as moderate risk scoring low risk in two to five of the categories,[22] and three studies were described as high risk scoring low risk for bias in one or fewer of the categories. All of studies were randomized controlled trials. The most common source of bias was lack of allocation concealment and blinding of outcome assessment .

Descriptive analysis

For the primary outcome, in patient used cefaclor versus amoxicillin, clinical response of cefaclor was not better than those used amoxycillin (RR 1.00, 95% CI 0.96 to 1.04; I^2=0%) as well as bacteriological response (RR 0.97, 95% CI 0.92 to 1.02; I^2=8%). In patient use cefaclor versus amoxicillin/clavulanate, clinical response was no significant difference between the two interventions (RR 0.99, 95% CI 0.95 to 1.02; I^2=57%) as well as bacteriological response (RR 0.94, 95% CI 0.90 to 1.00; I^2=1%)

In relation to the secondary outcomes, the recurrent rate was not lower in those used cefaclor compared with those used amoxycillin (RR 0.99, 95% CI 0.49 to 2.01) as well as adverse effect (generally gastrointestinal complaints) (RR 0.89, 95% CI 0.47 to 1.69). Moreover, the recurrent rate was not significant lower in cefaclor group compared with amoxicillin/clavulanate group (RR 0.77, 95% CI 0.37 to 1.57; I^2=10%), similar to the adverse events (RR 0.35, 95% CI 0.12 to 1.04; I^2=73%).

In patient with age twelve years or younger the use of cefaclor was not better than amoxicillin (RR 0.97, 95% CI 0.89 to 1.06; I^2=38%) or amoxicillin/clavulanate (RR 0.95, 95% CI 0.88 to 1.02; I^2=45%).

Table 1. Main characteristics of randomized controlled trials included in review

Study	Type of study	Blinding	Comparison	Day of treatment (days)	No of participants in group	Age (years)	Outcomes
Esposito S 1998	RCT	-	Cefaclor (25 mg/kg BI) Amoxicillin-clavulanate (15 mg/kg TID)	10/10	85/78	2-12	Clinical response Bacteriological response
Józef 2001	RCT	single blind	Cefaclor (375 mg BID) Amoxicillin/clavulanate (625 mg BID)	10/10	100/100	12-65	Clinical response Bacteriological response Adverse effect
Józef 2003	RCT	single blind	Cefaclor (20 mg/kg/d) Amoxicillin/clavulanate (25 mg/kg/d)	10/10	49/51	Mean 6 yrs	Clinical response Bacteriological response Recurrence rate
Bottaro G 2012	RCT	-	Cefaclor (50 mg/kg/d) Amoxicillin/clavulanate (40 mg/kg/d)	5/10	210/213	children	Clinical response Bacteriological response
Esposito S 2002	RCT	single blind	Cefaclor (40 mg/kg/day) Amoxicillin (40 mg/kg/day)	5/10	175/173	2-14	Clinical response Bacteriological response Recurrent rate Adverse effect
Nakayama 2003	RCT	-	Amoxicillin Cefaclor	7 -10/ 7-10	110/80	children	Bacteriological response
Berezin 2003	RRCT	-	Cefaclor Amoxicillin	10/10	40/42	2-16	Bacteriological response

Similar findings were also observed in patients older than twelve years that used cefaclor versus amoxicillin/clavulanate (RR 0.91, 95% CI 0.78 to 1.05). In relation to the year of publication, the studies that published after 2000, the use of cefaclor was not superior over amoxicillin (RR 0.97, 95% CI 0.89 to 1.06; I^2=38%) or amoxicillin/clavulanate (RR 0.94, 95% CI 0.90 to 1.00;I^2=1%) as well as in the studies that published before 2000 comparing cefaclor with amoxicillin/clavulanate (RR 0.97 95% CI 0.89 to 1.06) (Figure 3 and 4)

DISCUSSION

Main findings

In this systematic review, we found no evidence to support the hypothesis that cefaclor has more efficacy than amoxicillin or amoxicillin/clavulanate in participants with pharyngotonsillitis. In primary outcome, the study has relative risk of 1.00 for clinical response, 0.99 for bacteriological response in comparing cefaclor versus amoxicillin/clavulanate group and relative risk of 0.97 for clinical response, 0.94 for bacteriological response, this results indicate that cefaclor did not have higher efficacy than amoxicillin or amoxicillin/clavulanate. Furthermore in the secondary outcomes (including recurrent rate and bacteriological response) and sensitivity analyses of comparison sorted by age of participants and published time. The findings went in the same direction with primary outcome.

Comparison with other studies

Our study differs from other studies that examined use of different antibiotics such as penicillin V, azithromycin, cephalosporins, and clindamycin in participants with pharyngotonsillitis as we compared only cefaclor with amoxicillin or amoxicillin/clavulanate. This might be due to different patterns of antibiotics used in other countries. Moreover, our findings suggests that the use of cefaclor does not differ from the use of amoxicillin or amoxicillin/clavulanate in relation to clinical response. This findings were similar to a systematic review in 2011 that assessed the comparative efficacy of penicillin V and other antibiotics.[23] The review favoured cephalosporins over penicillin V. However the intention to treat analysis showed no differences between the two treatments. In this review the treatment outcome comparing between macrolides and penicillin V was also found no differences. This might be due to the its limitation of small sample.

Some study have shown that bacteriological response after completion of treatment was lower in those treated with azithromycin (36.5%) than with cefaclor (73.9%), microbiological failure rate was higher in the azithromycin (63.5%) than in the cefaclor group (21.7%).[24] In the cefprozil-cefaclor trial, the pathogen eradication rate for evaluable patients receiving cefprozil was 83%, which was significantly better than that of patients receiving cefaclor (76%) (P=0.035). The rate of satisfactory clinical response was similar with cefprozil (89%) and cefaclor (84%).[25] However, the debates over the best treatment for patients with pharyngotonsillitis are still exist and require further investigation.

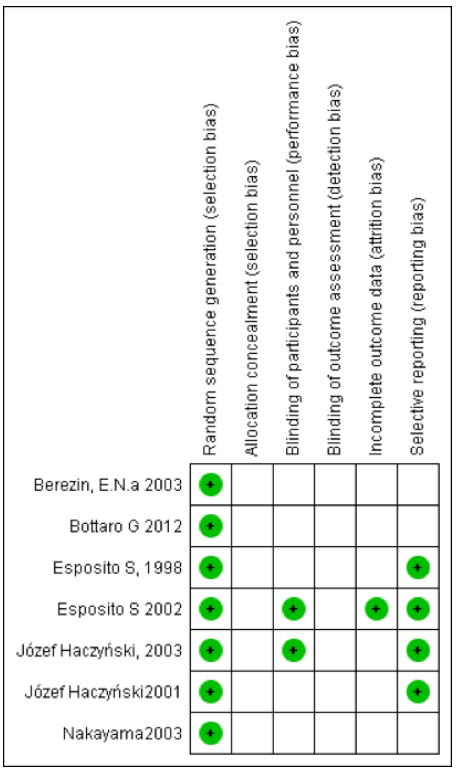


Figure 2. Quality assessment of randomised controlled trials included in meta-analysis

For adverse event, although many studies showed efficacy and adverse effects, Our study reviewed only randomized controlled trials, thus, cohort and case-control were omitted. In the present review, no significant difference of the adverse effects were observed between the use of cefaclor and amoxicillin or amoxicillin/clavulanate. However, a previous systematic review in 2005 that compared five antibiotics (amoxicillin, amoxicillin/clavulanate, cefprozil, penicillin V and azithromycin) have shown that the five antibiotics had higher rate of adverse effect with cefaclor in children with acute bacterial tonsillopharyngitis.[26] However, the prevalence of gastrointestinal adverse effect of cefaclor in that study was similar to our present study.

Strength and limitations of the review

To our knowledge, this is the first study exploring the efficacy between cefaclor and amoxicillin or amoxicillin/clavulanate. Our study has several limitation. Firstly, of the 4063 publications screened, only seven were eligible for included. We can retrieve full text in only four studies. Therefore, we were unable to carry out subgroup analysis for patients' characteristics. Secondly, we have few detail to assess risk of bias due to three studies can approach to only abstract. Thus, there was three studies were described as high risk scoring. Thirdly, variation in dosing and duration of antibiotics were observed across included studies. Fourthly, we saw heterogeneity more than 50% between studies in some risk parameters (comparison clinical response of cefaclor versus amoxicillin/clavulanate, comparison side effect of cefaclor versus amoxicillin/clavulanate). Although we defined inclusion criteria carefully to ensure that the participants of included studies were similar. Fifthly, the insignificant results in the present study might be due to the population size was not large enough to distinguish the difference of the two treatment. Finally, some studies have unclear reports of clinical response and bacteriological response for comparison of efficacy, time of treatment or follow up and age of patients.

Recommendations and conclusions

This review suggests that cefaclor and amoxicillin or amoxicillin/clavulanate provide a clinically and bacteriologically effective treatment for patients with pharyngotonsillitis caused by GABHS, and the safety of the both is also similar. This would have better

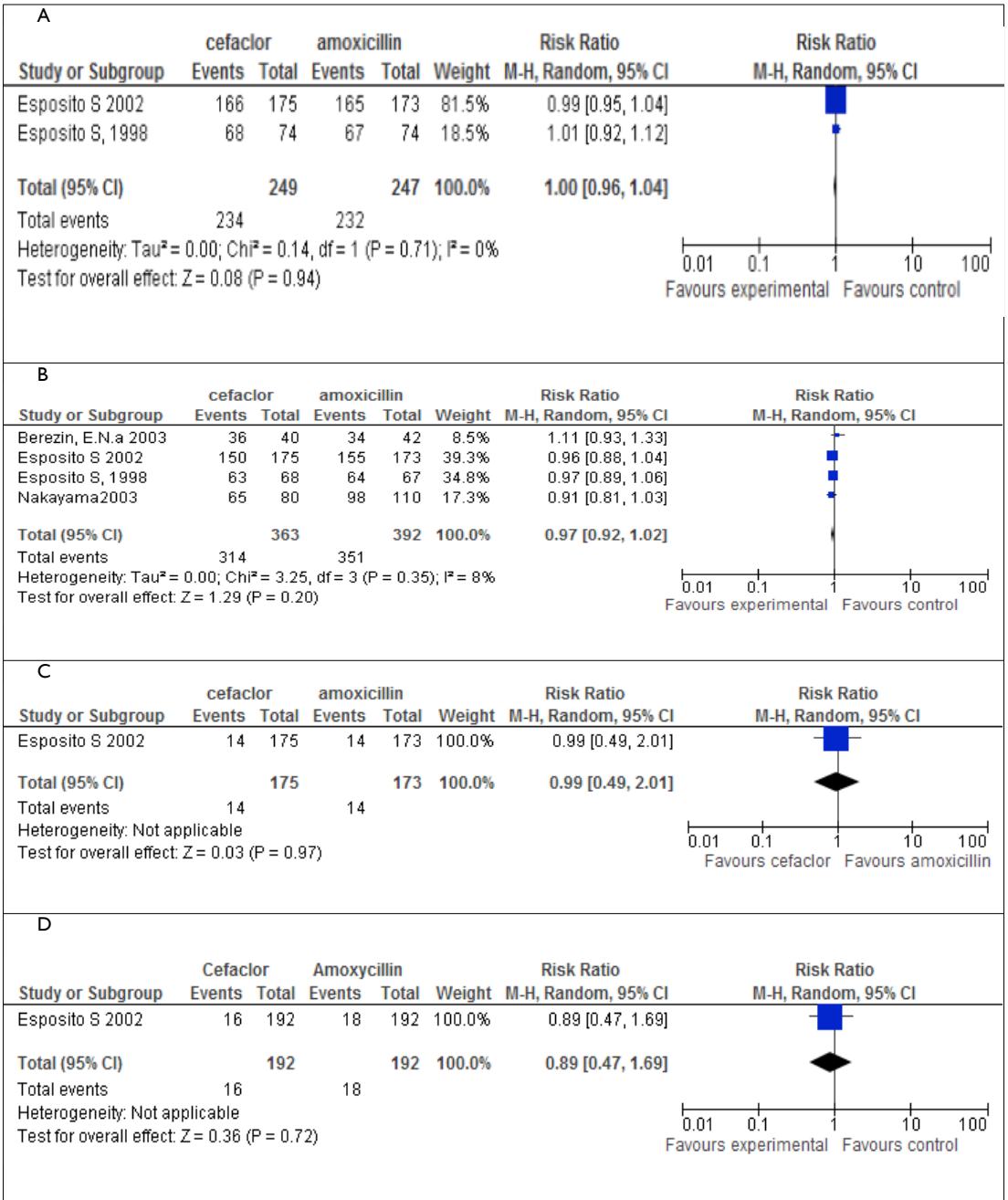
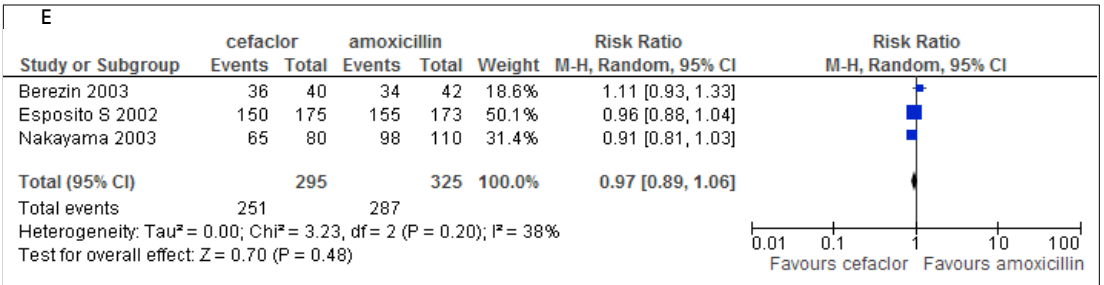
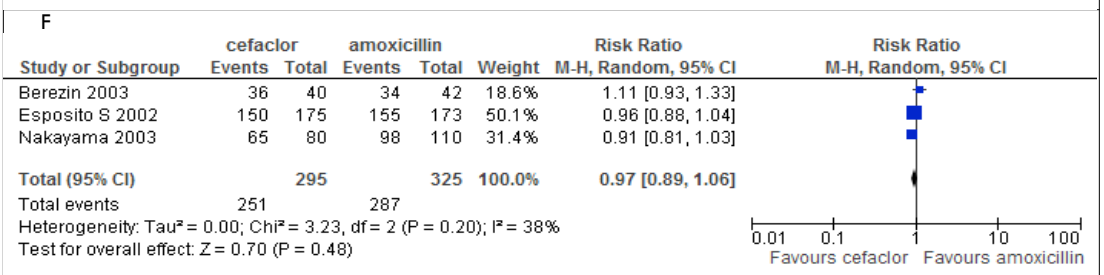


Figure 3. Outcomes of Using Cefaclor versus Amoxicillin in Patients with Acute Pharyngitis and/or Tonsillitis

In patient use cefaclor versus amoxicillin. clinical response (Panel A), bacteriological response (Panel B), recurrent rate (Panel C), side effect (Panel D), efficacy in patient with age twelve years or younger (Panel E), efficacy in published after 2000 (Panel F) .

prospects for the reviews, cefaclor may be effects and safety better than amoxicillin or amoxicillin/ clavulanate of additional testing in the large randomized controlled trial that should have reported allocation concealment, blinding of participant and personnel, detection bias, incomplete outcome data and selective reporting for the best approximate of the results.





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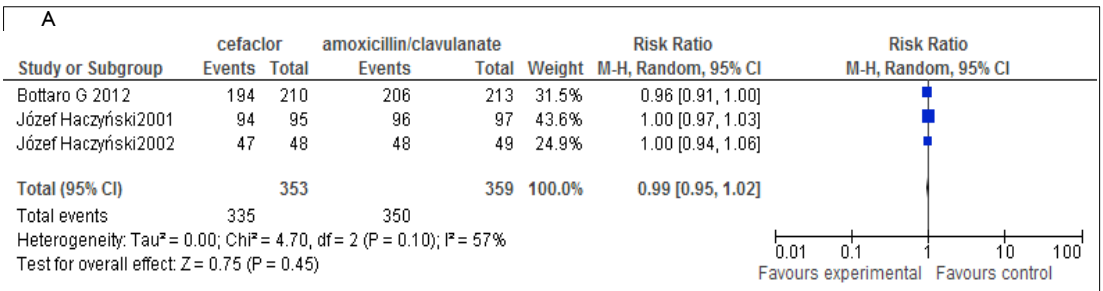
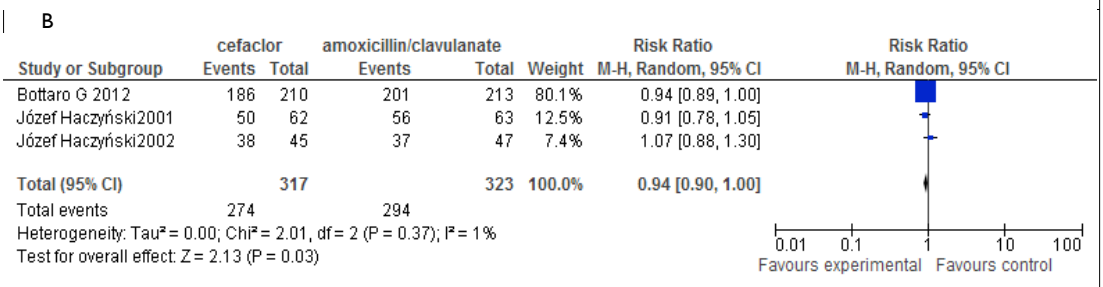




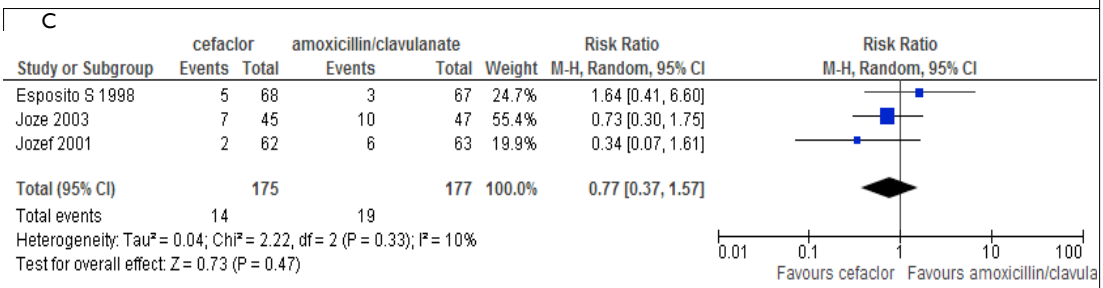
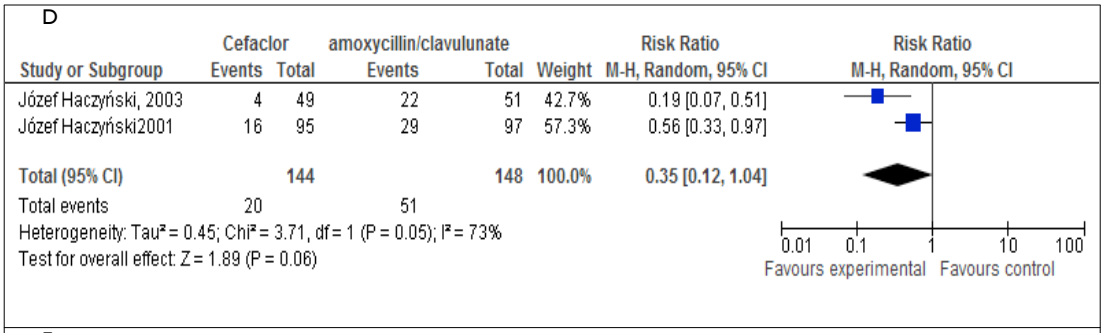


Figure 4. Outcomes of Using Cefaclor versus Amoxicillin/clavulanate in Patient with Acute Pharyngitis and/or Tonsillitis

In patient use cefaclor versus amoxicillin/clavulanate. clinical response (Panel A), bacteriological response (Panel B), recurrent rate (Panel C), side effect (Panel D), efficacy in patient with age twelve years or younger (Panel E), efficacy in patient older than twelve years (Panel F), efficacy in published before 2000 (Panel G), efficacy in published after 2000 (Panel H).

D



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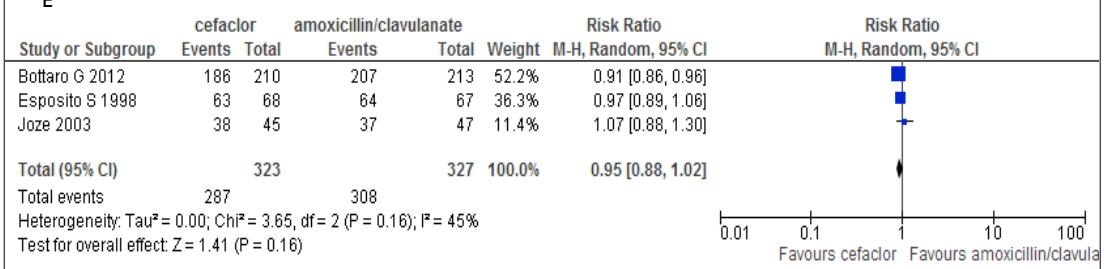

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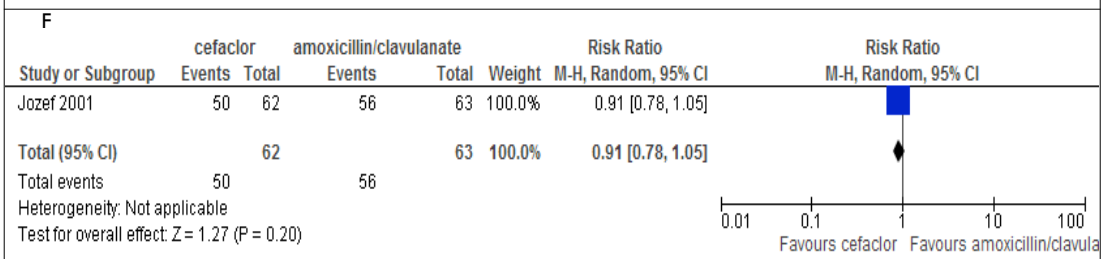

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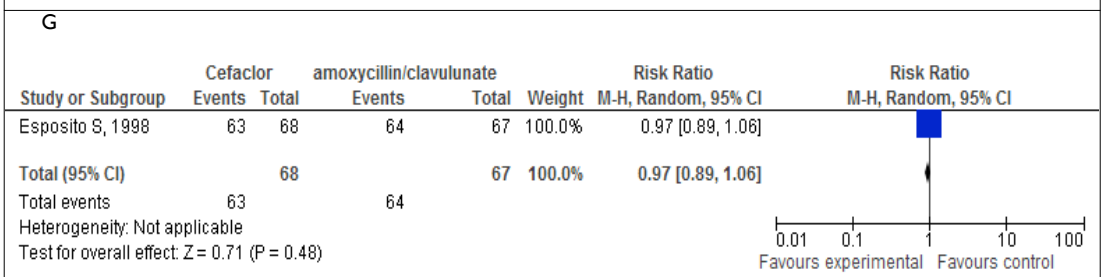

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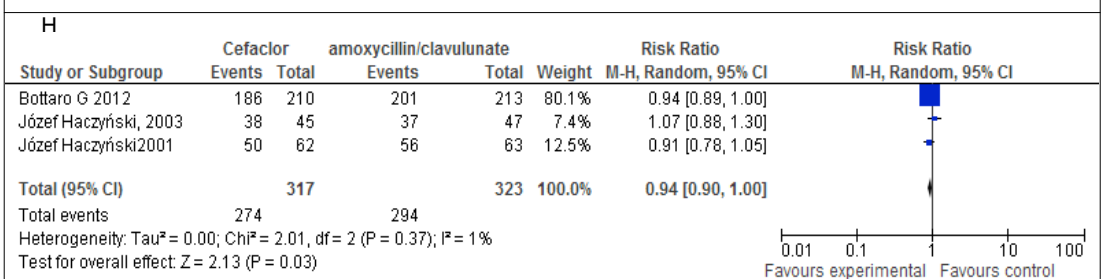

Figure 4. (Continued.)

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ORIGINAL ARTICLE

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Antibiotics in Clinically Diagnosed Pelvic Inflammatory Disease

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ABSTRACT

BACKGROUND
According to Centers for Disease Control and Prevention (CDC) guidelines, current treatments of inpatient pelvic inflammatory disease (PID) include cefoxitin plus doxycycline and clindamycin plus gentamicin . Nevertheless treating PID with ampicillin plus gentamicin plus metronidazole and ceftriaxone plus metronidazole were prescribed quite often in Thai practice. However the effectiveness of ampicillin plus gentamicin plus metronidazole and ceftriaxone plus metronidazole were not well established.

METHODS
We conducted a retrospective cohort study in admitted patients who diagnosed PID in Khon Kean Hospital between January 2009 to May 2011. We excluded those that had another conditions such as other gynecologic conditions, abnormal pregnancy, peritonitis, acute appendicitis, traumatic conditions, were admitted for fractional and curettage, were treated with other antibiotics, were admitted less than three days and loss of medical record. Our primary outcome was defervescense after treatment within two days.

RESULTS
The clinical outcomes occurred in 127 patients, there was no significantly difference in defervesence rates amongst three groups (P=0.77). On the other hand clindamycin plus gentamicin group was shown superiority in term of fewer number of patients switched to other intravenous antibiotics but ampicillin plus gentamicin plus metronidazole group had an advantage to decrease surgical rate (P=0.01). Additionally duration of intravenous antibiotic were significantly (P=0.04). There were 94.9% relieved from pain in ampicillin plus gentamicin plus metronidazole group, with no significant different (P=0.31). In logistic regression analysis, only duration of intravenous antibiotics received was shown as a significant factor to predict defervesence (adjusted odds ratio 1.54; 95% CI, 1.16 to 2.05; P=0.00).

CONCLUSIONS
In summary, treating PID with the three combinations of board spectrum antibiotics had no significant difference in relation to the defervesence rates but only treating with ampicillin plus gentamicin plus metronidazole had fewer proportions of patients switched to surgery and treating with clindamycin plus gentamicin had fewer proportion of patients switch to other treatment regimens.

Pelvic inflammatory disease (PID) is an infectious and inflammatory disorder of the upper female reproductive tract such as the uterus, fallopian tubes, and adjacent pelvic structures, that may cause long term reproductive sequelae including re-infection, tubal factor infertility, ectopic pregnancy and chronic pelvic pain.[1-3] The infected microorganisms are varied including *Chlamydia trachomatis, Neisseria gonorrhea* and a variety of Gram positive and negative microorganisms, therefore the treatment of PID requires broad spectrum antibiotics which cover polymicrobial pathogens.[2-4,8] According to Centers for Disease Control and Prevention (CDC) guidelines, current treatments of inpatient cases cefoxitin plus doxycycline (regimen A) and clindamycin plus gentamicin (regimen B).[5] However, the efficacy of ampicillin plus gentamycin plus metronidazole (triple therapy) that prescribed often in Thailand was found to be comparable to the guidelines.[3] Only one previous study with small sample sizes had compared the efficacy of regimen B and triple therapy and the findings suggested no differences in term of short term outcomes.[3] In addition to this, ceftriaxone plus metronidazole, another combination of broad spectrum antibiotics, are also prescribed more often in the Thai practice. Little is known regarding the efficacy of these new combination antibiotics. Thus, we conducted a retrospective cohort to compare the treatment outcomes of regimen B regarding the CDC guidelines, triple therapy and ceftriaxone plus metronidazole.

METHODS

Study design

We conducted a retrospective cohort study to compare the treatment outcomes of regimen B regarding the CDC guidelines, triple therapy and ceftriaxone plus metronidazole of patients with PID and were admitted in Khon Kaen Hospital during from January 2009 to May 2011.

Patients and prescribed regimen

Patients who were clinically diagnosed as pelvic inflammatory disease in patient summary sheet of Khon Kaen Hospital during from January 2009 to May 2011 were screened and reviewed using the ICD code as ICD10 –N70.0, N70.1, N70.9, N71.0, N71.1, N71.9, N73.0, N73.1, and N73.9. We excluded those that had another conditions such as other gynecological conditions, abnormal pregnancy, peritonitis, acute appendicitis, traumatic conditions, were admitted for fractional and curettage, were treated with other antibiotics, were admitted less than three days and loss of medical record. From the medical record review, patient were treated with one of the four regimens; (i) cefoxitin 1 g intravenous every 6 hours plus doxycycline 100 mg oral or intravenous every 12 hours (regimen A), (ii) clindamycin 900 mg intravenous every 8 hours plus gentamicin 240 mg intravenous once a day (regimen B), (iii) ampicillin 1 g intravenous every 6 hours plus gentamicin 240 mg intravenous once a day plus metronidazole 500 mg intravenous every 8 hours (triple therapies), and (iv) ceftriaxone 2 g intravenous once a day plus metronidazole 500 mg intravenous every 8 hours.

Outcome assessment

The primary outcome was defervesense within two days. The defervesense defined by body temperature more than 37.8 degree Celsius on admission date and diminished to less than 37.8 degree Celsius after two days after received antibiotics. Three secondary treatment outcomes were also recorded. Firstly, relief from pain defined as pain score (visual analog scale: 0-10) on admission date diminished at least 1 score after 2 days of intravenous antibiotics. Secondly, the switch therapy defined as no defervesence of body temperature after the first antibiotics treatment in two days and required switch therapy to the others such as other antibiotics regimens or surgical treatment. Finally, the secondary outcome was the amount of days of intravenous antibiotics.

Statistical analysis

The number of patients required for the study was calculated based on our working hypothesis that patients in each treatment regimens had no difference in term of defervesence. We estimated that our sample size could detect with a power of 80% with α error of 5%, therefore, a minimum of 32 per group was required.

Statistical analysis included descriptive statistics. All data were cleaned and put in the excel spreadsheet using the double entry method. For scale variables, mean and standard deviation (SD) were used if they are normally distributed while median and interquartile range (IQR) were used if there are not normally distributed after testing with Komolgorov-Smirnov test. For categorical variables, frequency distribution and percentages were used. Regarding inferential statistics, either Pearson Chi-square test or Fisher's exact test was used for categorical variables where appropriate. Comparisons between numerical variables were tested using one-way analysis of variance (ANOVA) if data was normal distribution and Kruskal–Wallis test if data was not normal distribution we were conducted. Logistic regression analysis was performed to determine whether factors affecting the treatment outcomes. The estimated of adjusted odds ratio and its relative 95% CI were calculated. A p-value<0.05 was considered statistically significant. All analyses were performed using statistic software package.

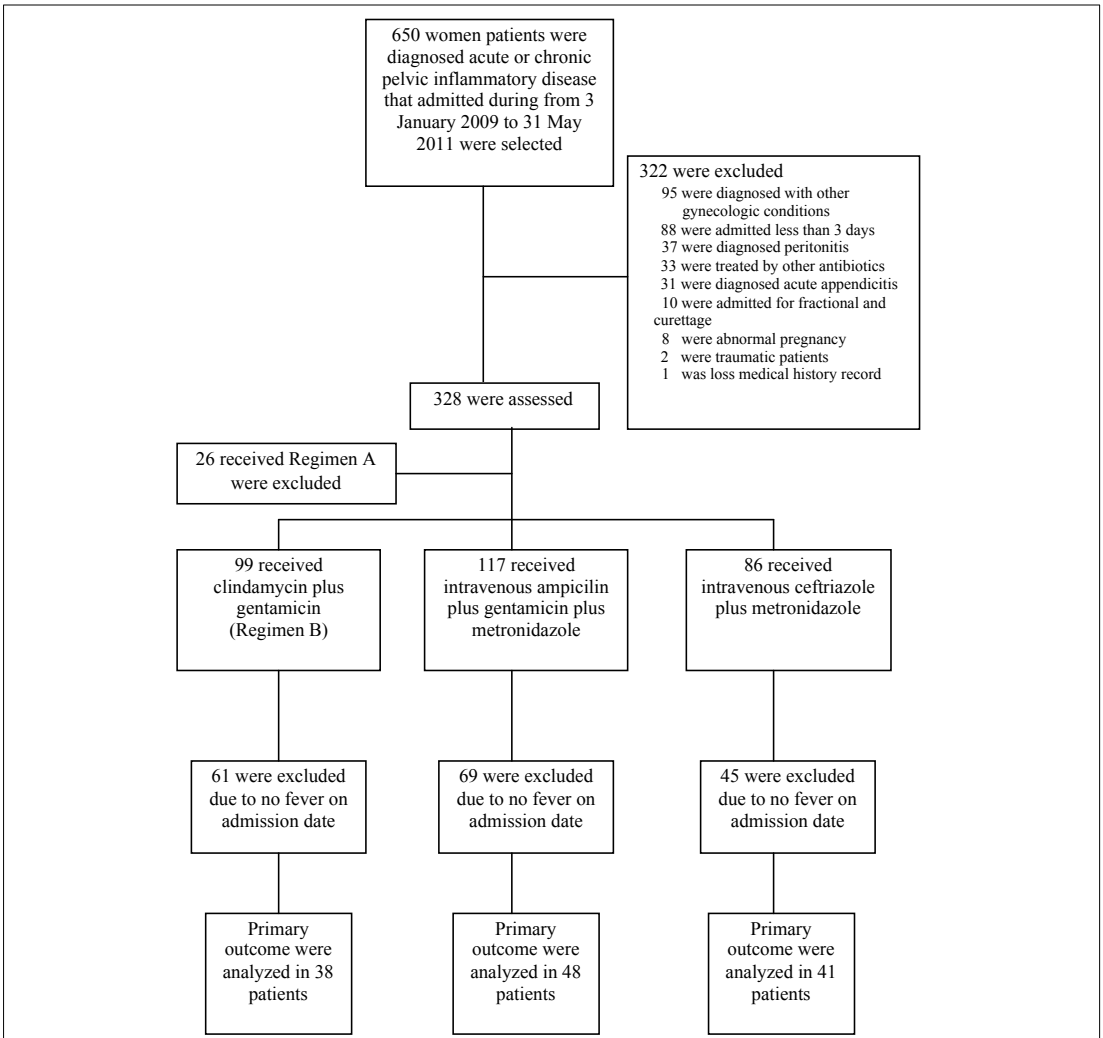

Figure 1. Enrollment of Patients and Assessment of Primary Outcomes.
We enrolled 328 patients to review all of charts after excluded another conditions. However, the number of patients in regimen A was too small to compare with other regimens. Thus, we excluded this regimen from this study so we left 302 patients for the analysis. In addition,175 patients had no fever on admission date so we left 127 patients to analyze the primary outcomes

RESULTS

Up to 650 patients between January 2009 and May 2011 in Khon Kaen Hospital were included in the present study. However, the number of patients in regimen A was too small to compare with other regimens. Thus, we excluded this regimen from this study so we left 302 patients for the analysis (Figure 1). They had stayed in hospital with a median of four days (interquartile range (IQR) 3 to 5). In addition, 175 patients had no fever at admission date so we have 127 patients for outcomes analysis. In general, their average age and menarche were 29 years (IQR 20 to 42) and 14 years (IQR 13 to 15) respectively (Table 1). Most of them had secondary education (36.4%), worked as employee (48.3%), had no underlying disease (79.8%), had no drugs allergy (93.0%) and were diagnosed unspecific PID (37.7%). Most of them had been pregnant (68.9%), had contraception (60.1%), were non- smoker (93.4%) and did not drink alcohol (79.8%). One fourth of patients had history of sexual transmitted disease and pelvic inflammatory disease. The median incomes and body weight were 5000 baht per month (IQR 3000 to 8000) and 50 kilograms (IQR 45 to 58) respectively. The mean height was 157.2 centimetres (±6.8).

Table 1. Baseline Characteristics

Characteristic	Clindamycin plus gentamicin	Ampicillin, gentamicin plus metronidazole	Ceftriaxone plus metronidazole	P Value
Age –years				0.00
Median	32	24	34.5	
Interquartile range	22-42	19.0-35.5	25-46	
Educations –no. (%)				0.20
No	4 (4.2)	1 (0.9)	1 (1.2)	
Primary school	35 (36.5)	29 (26.9)	35 (43.2)	
Secondary school	36 (37.5)	48 (44.4)	26 (32.1)	
Diploma	11 (11.5)	10 (9.3)	9 (11.1)	
Bachelor degree or higher	10 (10.4)	20 (18.5)	10 (12.3)	
Occupations –no. (%)				0.05
Student	20 (20.2)	40 (34.2)	14 (16.3)	
Farmer	15 (15.2)	13 (11.1)	12 (14.0)	
Employee	52 (52.5)	53 (45.3)	41 (47.7)	
Others	12 (12.1)	11 (9.4)	19 (22.1)	
Incomes –1,000 Baht per month				0.98
Median	5	5	5	
Interquartile range	3.0-8.1	3-8	1.1-8.0	
Smoking –no. (%)	6 (6.1)	13 (11.1)	1 (1.2)	0.02
Alcohol drinking –no. (%)	23 (23.2)	23 (19.7)	15 (17.4)	0.61
Body weight – kilograms				0.87
Median	51	50	50	
Interquartile range	45-60	45-56	45-59	
Height –centimeters	156.2±6.2	158.4±7.3	157.2±7.1	0.25
Underlying disease – no. (%)				
No	74 (74.7)	104 (88.9)	63 (73.3)	0.01
Diabetes mellitus	5 (5.1)	2 (1.7)	5 (5.8)	0.26
Hypertension	4 (4.0)	2 (1.7)	4 (4.7)	0.47
HIV infection	3 (3.0)	0	1 (1.2)	0.14
Others	16 (16.2)	12 (10.3)	16 (18.6)	0.20
Drug allergy – no. (%)	11 (11.1)	6 (5.1)	4 (4.7)	0.16
Menarche –years				0.07
Median	14	13	14.5	
Interquartile range	12.8-15.0	12-15	14-17	
Nulliparous –no. (%)	31 (32.3)	47 (40.2)	14 (16.9)	0.00
History of sexual transmitted disease –no. (%)	26 (38.8)	15 (15.6)	8 (13.8)	0.00
History of pelvic inflammatory disease –no. (%)	24 (37.5)	21 (21.9)	10 (17.9)	0.03
Contraception –no. (%)				0.08
No	35 (46.1)	35 (35.4)	23 (39.7)	
Contraceptive drugs	11 (14.5)	26 (26.3)	8 (13.8)	
Condom	5 (6.6)	10 (10.1)	4 (6.9)	
Intrauterine device	11 (14.5)	7 (7.1)	9 (15.5)	
Tubal resection	9 (11.8)	20 (20.2)	13 (22.4)	
More than one methods	5 (6.6)	1 (1.0)	1 (1.7)	
Body temperature at admission date –degree Celsius				0.72
Median	37.5	37.5	37.7	
Interquartile range	37.0-38.4	37.0-38.3	37.1-38.2	
Pain score at admission date				0.01
Median	4	3	2	
Interquartile range	0-6	0-5	0-4	
White blood cells count –cubic centimeters				0.51
Median	12450	12000	11900	
Interquartile range	9600-17150	8500-17000	7900-16400	

Amongst the three regimens, patients in ceftrixone plus metronidazole were likely to be older than the others. Their median age was 34 years compared 24 and 32 years in those treated with ampicillin plus gentamicin plus metronidazole and clindamycin plus gentamicin, respectively (P=0.01). The majority of each group worked as employee but a large number of students in ampicillin plus gentamicin plus metronidazole group was present (P=0.05). In addition, clindamycin plus gentamicin group had more patients with history of sexual transmitted disease and pelvic inflammatory disease than the others (P=0.00, 0.03, consecutively). Furthermore, ampicillin plus gentamicin plus metronidazole group had higher proportion of nulliparous, smoker and no underlying person (P=0.00, 0.02 and 0.01, respectively). The rate of primary outcomes did not differ significantly amongst the three regimens (Table 2).

The defervesence in 2 days after admission occuring 82.1% in clindamycin plus gentamicin group, 87.2% in ampicillin plus gentamicin plumetronidazole group and 87.8% in ceftriaxone plus metronidazole group (P=0.77). On the other hand clindamycin plus gentamicin group was shown superiority in term of fewer number of patients switched to other intravenous antibiotics but ampicillin plus gentamicin plus metronidazole group had an advantage to decrease surgical rate (P<0.001). Additionally duration of intravenous antibiotic were significantly (P<0.001). There were 90.8% relieve from pain in ampicillin plus gentamicin plus metronidazole group, with no significant different from the others (P=0.42).

In the logistic regression analysis with the eight variable included, R square was found to be 37.6%. After adjusting with age, regimen of antibiotics, education, occupation, underlying disease, parity, length of intravenous antibiotics received and alcoholic consumption (Table 3.), duration of intravenous antibiotic received was the only significant factor predicting defervesence (adjusted odds ratio 1.54; 95% CI, 1.16 to 2.05; P=0.00). Prolong duration of intravenous antibiotics associated with non-resolve from fever.

In the subsequent analysis exclusively for ampicillin plus gentamicin plus metronidazole vs. ceftriaxone plus metronidazole which are the regimen not recommended by the CDC, it found that outcomes in relation to defervesence, relief of pain and duration of intravenous antibiotics did not differ between the two regimens. However, ampicillin plus gentamicin plus metronidazole seemed to be better in term of switching to other regimen or surgery with P<0.001.

DISCUSSION

Key findings

We compared clinical outcomes (defervesence) of patient who diagnosed pelvic inflammatory disease in clindamycin plus gentamicin group, ampicillin plus gentamicin plus metronidazole and ceftriaxone plus metronidazole with current used in Khon Kaen Hospital. No evidence of a difference of effectiveness was found. However clindamycin plus gentamicin group was associated with decrease rate of switch to other regimens and ampicillin plus gentamicin plus metronidazole group had no rate of surgical procedure. Duration on the intravenous antibiotics was the only predictor for defervescence or vice versa, the longer use of antibiotics might be the results from prolong fever even the treatment given. Moreover, our findings were consistent after the analysis of the only two latter regimens which still suggested the superiority of triple therapies over the ceftriaxone plus metronidazole.

Table 2. Primary and Secondary Outcomes

Outcome	Clindamycin plus gentamicin	Ampicillin plus gentamicin plus metronidazole	Ceftriaxone plus metronidazole	P value
Primary outcomes				
Defervesence –no. (%)	32 (82.1)	41 (87.2)	36 (87.8)	0.77
Secondary outcomes				
Relieve from pain –no. (%)	71 (89.9)	79 (90.8)	47 (83.9)	0.42
Switch therapy –no. (%)				0.00
Switch intravenous antibiotics	1 (1.0)	7 (6.0)	8 (9.3)	
Switch to surgery	6 (6.1)	0	9 (10.5)	
Duration of intravenous antibiotics				0.00
Median	3	3	3	
Interquartile range	3-4	2-3	2.8-4.0	

Table 3. Multivariable Analyses of Fervesence

Variable	Adjusted odds ratio for fervesence (95% CI)		P Value
Age	0.96	(0.88-1.05)	0.41
Regimen			
Clindamycin plus gentamicin		Reference	
Ampicillin plus gentamicin plus metronidazole	2.56	(0.39-17.15)	0.33
Ceftriaxone plus metronidazole	2.59	(0.32-20.91)	0.37
Education			
No education		Reference	
Primary school	21.21	(0.39-1164.55)	0.14
Secondary school	6.72	(0.27-165.36)	0.24
Diploma	4.96	(0.27-90.63)	0.28
Degree	10.16	(0.33-315.17)	0.19
Occupations			
No job		Reference	
Student	1.95	(0.08-50.53)	0.69
Farmer	0.20	(0.02-2.68)	0.23
Employee	0.56	(0.03-10.18)	0.70
Others	0.46	(0.06-3.67)	0.46
Underlying disease	2.42	(0.38-15.35)	0.35
Nulliparous	1.21	(0.23-6.51)	0.82
Alcohol drinking	2.88	(0.36-23.13)	0.32
Duration of intravenous antibiotics received	1.54	(1.16-2.05)	0.00

Comparison with other studies

The previous study shown that the defervesence did not has statistical significant after treated with regimen B and triple therapies.[3] Likewise, the defervesence was no statistical significance amongst the three groups of antibiotics even ceftriaxone plus metronidazole were used in the comparison in our study. On the other hand, the previous studies had investigated the vaginal swab culture or hemoculture to identify the causative organisms However, the practice is not common in Thailand. Hence, choices of antibiotics were based solely on the judgment of the clinicians as causative organisms cannot be identified.[1-2, 7-8]

Strengths and limitation of the study

This is the first study to our knowledge that compared the efficacy of three board spectrum antibiotics in treating PID. The strengths of our study including comparison of effectiveness of three regimens that common used in the Thai practice, adequate sample size and adjusted confounding factor such as age, education, incomes, underlying disease, nulliparous and alcoholic consumption were also performed. However, the major problem of our study was missing data could not be recorded due to a retrospective design. For instance, the severity of patients was not retrievable. As treatment regimens were usually considered based on clinical severity. Thus, fail to take this confounder into consideration might introduce the bias into our conclusion. Subjective recorded data for example history of pelvic inflammatory disease, history of sexual transmitted disease, smoking, alcohol drinking and pain scores might not be accurate. In addition to this, the diagnosis of PID in our study site was done clinically. Thus, the irrelevant inclusion of cases might not be avoidable.

Conclusion and implications

In summary, treating PID with the three combinations of board spectrum antibiotics had no significant difference in relation to the defervesence rate of these groups but only treating with ampicillin plus gentamicin plus metronidazole had fewer proportions of patients switched to surgery and treating with clindamycin plus gentamicin had fewer proportion of patients switch to other treatment regimens.

However, to establish proper antibiotics administration to treated groups, it requires further

studies randomized controlled trial with large sample size is the best alternation. The inclusion criteria should include the method of definite diagnosis of PID. The causative organism should have made an attempt to collect. Nonetheless, our findings suggested no difference in the primary outcome, potential benefit in relation to secondary outcomes were also identified. Suggest alternative treatment, closed monitoring in patients with long duration of intravenous antibiotics.

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ORIGINAL ARTICLE

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Validity of Modified Child-Turcotte-Pugh Scoring System for Predicting the Occurrence of Spontaneous Bacterial Peritonitis in Patients with Cirrhosis.

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ABSTRACT

BACKGROUND
Spontaneous bacterial peritonitis (SBP) is the common and severe complication of ascites. However, the accuracy existing model to predict the occurrence of SBP is still restricted.

METHODS
We conducted a nested case-control diagnostic study in patients with cirrhosis diagnosed SBP who admitted in Department of Medicine and Surgery, Khon Kaen Hospital between November 2009 through October 2011. We used multivariable logistic regression analyses to determine their independent contribution to predict SPB. This "clinical model" was analysis to assess the association with many variables based on the likelihood ratio test. We calculated sensitivity, specificity, and likelihood ratio with 95% confidence intervals for the variables included in the final model. We used the area under the receiver operating characteristic curve (ROC area) to estimate the ability of models to discriminate between Child-Turcotte-Pugh score and combination of Child-Turcotte-Pugh score, MELD score, predisposing factors such as upper gastrointestinal bleeding and previous spontaneous bacterial peritonitis and regression coefficients (log odds ratios) for over-fitting.

RESULTS
There were 301 patients with the diagnosis of SBP eligible for the inclusion in the present study; 143 were excluded due to incomplete medical records, nephrotic syndrome, cardiac cirrhosis and the patient who has continuous ambulatory peritoneal dialysis (CAPD). At the end there were 158 cases of patients with cirrhosis and SBP left for the analysis. For control, there were 158 patients that matched with cases regarding sex and age. In the logistic regression analysis, only previous history of upper gastrointestinal bleeding (adjusted odds ratio (AOR), 0.38; 95% CI, 0.19 to 0.76), ascites (AOR, 261.86; 95% CI, 50.35 to 1361.85), serum bilirubin (AOR, 3.26; 95% CI, 1.31 to 8.13) and serum creatinine (AOR, 4.45; 95% CI, 1.44 to 13.70) were found to be associated with SBP (Table 2). We calculated the occurrence of SBP in patients with cirrhosis based on the sum of the score points. The total score of the patients ranged from 6 to 18 points. We selected cut point by used appropriate sensitivity and specificity to found the highest AUC to created range of score, the range of score was 6-9 (sensitivity; 99.4%, specificity; 24.1%), 10-12 (sensitivity; 70.3%, specificity;70.3%), 13- 18 (sensitivity; 0%, specificity 100%). Addition of CTP Scoring System to the clinical history previous SBP items and serum creatinine significantly increased the ROC area from 0.737 to 0.759 (table 4).

CONCLUSIONS
The newly designed Modified Child Pugh Score had the superior validity over the original Child Pugh Score.

Spontaneous bacterial peritonitis (SBP) is the common and severe complication of ascites characterized by spontaneous infection of the ascites fluid without an intraabdominal source. Its prevalence among patients with ascites ranges between 10 and 30 percent.[1] The diagnosis of SBP is made when the fluid sample has an absolute neutrophil count more than 250/μL.2 Bedside culture should be obtained when ascites fluid is tapped.[2,3] Patient with SBP may present with fever, alteration of mental status, elevated white blood cell count, an abdominal pain or discomfort, or they may present without any of these features.[2] Therefore, it is necessary to have a high degree of clinical suspicion. [2]

However, at the present, there are limitation of the accuracy of the existing models to predict the occurrence of SBP. For instance, Child-Turcotte-Pugh (CTP) scoring system has been used to predict the severity of cirrhosis and the risk of its complications. [2,4] It comprises two clinical signs and symptoms and three laboratory tests including presence of ascites, presence of hepatic encephalopathy, serum bilirubin, serum albumin and International normalized ratio (INR). In this scoring system, patients are defined into class A, B and C by assigning a value from 1 to 3 to the clinical variables by increasing level of severity, about 70% of the patients which develop SBP are in Child C classification.[5,6, 7] For another model, severe liver cirrhosis with Model for End-Stage Liver Disease (MELD score) higher than 18 was associated with an increase risk of SBP, with a prevalence of SBP of 30.6%.[8] It comprises three laboratory tests including serum bilirubin, INR and serum creatinine. This scoring system is calculated according to the formula: MELD score = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43. This scoring system is defined to group that have score ≥ 40, 30-39, 20-29, 10-19, ≤ 9.[9,10,11,12]

However, there are some predisposing factors that are not included in the CTP and MELD scoring system, such as acute gastrointestinal bleeding and previous history of SBP episodes as well as liver function tests that were found to be associated with SBP in patients with cirrhosis.[5,13] The accuracy of existing model to predict the occurrence of SBP is still restricted. In the present study, we aimed to create a new model to for better validity for predicting the SBP in patients with cirrhosis. We evaluate each component of CTP, MELD scoring system and other potential risk factors for the association of SBP. Later we constructed a model that included all relevant factors. The validity was tested at the end of our study.

METHODS

Study design

This is a nested case-control study to evaluate the association of components in CTP, MELD scoring system and other factors with SBP. The diagnosis design was added in the later process to assess the validity of our newly constructed model to predict the occurrence of spontaneous bacterial peritonitis.

Study site

This study was conducted in Department of Medicine and Surgery, Khon Kaen Hospital, Thailand.

Participants

The study was conducted in the patients with cirrhosis, who diagnosed by ultrasonography and clinical diagnosis from November 2009 through October 2011 and followed up by the Department of Medicine and Surgery. Of these participant, cases were patients with cirrhosis with SBP defined by their abdominal fluid sample with an absolute neutrophil count more than 250/μL. We excluded those with incomplete medical record, nephrotic syndrome, cardiac cirrhosis or those with continuous ambulatory peritoneal dialysis (CAPD).[14,15,16]Controls were patients with cirrhosis without SBP that matched with cases regarding sex and age.

Data sources

We indentified medical record use using the Khon Khaen Hospital electronic database that provided details of patients characteristics, diagnosis, procedural information, physical examination laboratory regarding hospital admission. Variables including presence of ascites, hepatic encephalopathy, cause of liver cirrhosis, history of gastrointestinal bleeding, previous SBP episodes and ongoing alcohol drinking, INR, serum bilirubin, serum albumin, prothrombin time (PT), serum creatinine, serum aspartate aminotranferase (AST), serum alanine transaminase (ALT), serum alkaline phosphatase (ALP) were reviewed and verify before proceeding to the analysis.

Statistical Analysis

We imputed data by double entry and cleaned all data before the analysis using statistic software package. The imputation was based on the correlations between each variable and SBP. We quantified the relation of each diagnostic variable or test to SBP in patients with cirrhosis. We followed recording in which investigations are administered in standard practice. Firstly, we included all findings from the history, physical examination and laboratory tests such as serum albumin, serum bilirubin, Serum creatinine, INR, PT, AST ALT and ALP to quantify their added diagnostic value.

All category data were test by either Pearson's chi-squared test or Fisher's exact test where appropriate and all scale data was test for their normal distribution using student t-test. Non-normal distributed data were using the Mann-Whitney U test. Risk was express using odds ratio. We used logistic regression analysis to estimate the adjusted odds ratios (ORs) and its 95 percent confidence intervals (CIs) for association between the variables in CPT, MELD score and predisposing factors for

Table 1. Baseline Characteristics of the Participants.

Characteristic	Non spontaneous bacterial peritonitis (N=158)	Spontaneous bacterial peritonitis (N=158)	P Value
Mean age —Yr	53.1±1.0	53.3±1.0	0.871
Male sex — no. (%)	128 (81.0)	126 (79.7)	0.777
Cause of cirrhosis — no. (%)			
Alcoholic cirrhosis	109 (69.0)	90 (57.0)	0.027
Hepatitis B virus related cirrhosis	14 (8.9)	29 (18.4)	0.014
Hepatitis C virus related cirrhosis	31 (19.6)	34 (21.5)	0.676
Autoimmune cirrhosis	3 (1.9)	5 (3.2)	0.723
Cholestatic cirrhosis	11 (7.0)	9 (5.7)	0.644
Unspecified cirrhosis	8 (5.1)	17 (10.8)	0.061
Previous upper gastrointestinal bleeding —no. (%)	78 (49.4)	51 (32.3)	0.002
Previous spontaneous bacterial peritonitis—no. (%)	1 (0.6)	11 (7.0)	0.003
Ongoing alcohol use — no. (%)	71 (44.9)	65 (41.1)	0.495
Hepatic encephalopathy — no. (%)			0.115
None	126 (79.7)	115 (72.8)	
Controlled	13 (8.2)	25 (15.8)	
Uncontrolled	19 (12.0)	18 (11.4)	
Ascites— no. (%)			0.000
None	80 (50.6)	2 (1.3)	
controlled	43 (27.2)	46 (29.1)	
uncontrolled	35 (22.2)	110 (69.6)	
Serum albumin — g/dL			0.003
Median	1.9	1.8	
Interquartile range	1.5-2.5	1.4-2.2	
Serum bilirubin — mg/dL			0.002
Median	2.3	4.0	
Interquartile range	1.2-6.9	2.2-8.4	
Serum creatinine — mg/dL			0.012
Median	1.4	1.6	
Interquartile range	0.9-2.2	1.1-2.5	
International normalized ratio			0.003
Median	1.5	1.7	
Interquartile range	1.3-2.0	1.4-2.3	
Prothrombin time — sec			0.002
Median	17.9	20.2	
Interquartile range	15.0-23.4	16.4-26.6	
Serum aspartate aminotranferase — IU/L			0.814
Median	106	98	
Interquartile range	60-186	62-184	
Serum alanine transaminase — IU/L			0.570
Median	49	52	
Interquartile range	33-81	34-84	
Serum alkaline phosphatase — IU/L			0.477
Median	125	129	
Interquartile range	82-202	90-217	
Child-Pugh classification score — no. (%)			0.000
A	9 (5.7)	0	
B	81 (51.3)	30 (19.0)	
C	68 (43.0)	128 (81.0)	
MELD score— no. (%)			0.000
Median	17.4	23.3	
Interquartile range	11.9-25.4	16.3-30.1	

*Plus–minus values are means±SD.

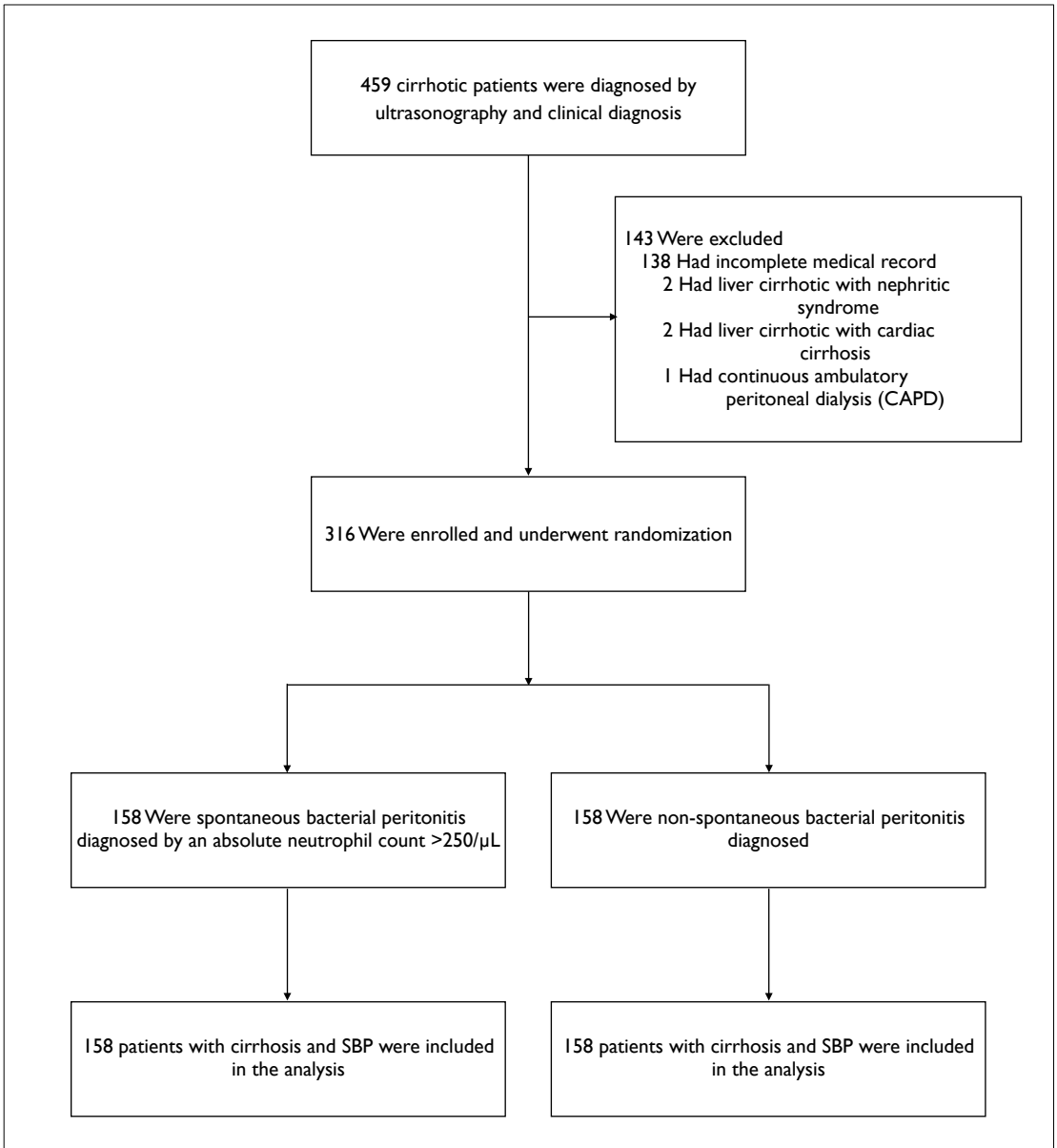

Figure 1. Screening and Enrollment of Study patients.

predicted the occurrence of SBP. The new model was created by gathering the potential risk factors identify from the logistic regression analysis. The model was tested for its validity in relation to sensitivity, specificity, likelihood ratio (LR) and its accuracy using the receiver operating characteristic curve (ROC area) to estimate the ability of models to discriminate among CTP, MELD scoring system and the new model that combined CTP, MELD scoring system and predisposing factors such as upper gastrointestinal bleeding and history of previous SBP.

RESULTS

There were 301 patients with the diagnosis of SBP eligible for the inclusion in the present study; 143 were excluded due to incomplete medical records, nephrotic syndrome, cardiac cirrhosis and the patient who has continuous ambulatory peritoneal dialysis (CAPD). At the end there were 158 cases of patients with cirrhosis and SBP left for the analysis (Figure 1).

For control, there were 158 patients that matched with cases regarding sex and age, however, we were unable to match sex for two cases.

About 80% of them were male with the average age of 53 years old. Alcohol associated was the leading cause of cirrhosis (Table 1). More than half was on going alcohol drinking. The causes of cirrhosis in this study were alcohol (63.0%), hepatitis B virus (13.6%), hepatitis C virus (20.6%), cholestasis (6.3%), autoimmune (2.5%) and unspecified (7.9%). Two in three patients aged less than 20 years had cirrhosis caused by autoimmune disease diagnosed by the positive of anti-nuclear antibody (ANA). Less than half had of history of GI bleeding and very few had history of previous diagnosis with SBP. One in five patients had clinical hepatic encephalopathy (23.7%) and more than half had of clinical ascites (74.1%). In our study, most of the patients were in child C classification (62.0%) and child B classification (35.1%). Their median MELD was 20.0 (Interquartile range (IQR), 13.7 to 28.5) with the median serum bilirubin, INR, PT, serum albumin, serum AST, ALT and ALP were 3.1 (IQR, 1.5 to 8.2), 1.6 (IQR, 1.3 to 2.2), 19.0 (IQR, 15.8 to 25.2), 1.8 (IQR, 1.4 to 2.4), 100.5 (IQR, 61.0 to 114.8), 50.0 (IQR, 33.0 to 84.0) and 127.0 (IQR, 85.3 to 209.3) respectively. The group of cirrhosis and SBP tended to have more ascites (p value 0.000), higher serum bilirubin (p value 0.002), higher serum creatinine (p value 0.012), higher INR (p value 0.003), longer PT (p value 0.002), greater CTP and MELD Score (p value 0.000 and 0.000 respectively). However, they also less likely to have serum albumin (p value 0.003) (Table 1).

On bivariable analysis, the significant risk factors for SBP were hepatitis B virus related cirrhosis (OR, 2.31; 95% confidence interval [CI], 1.12 to 4.83), previous gastrointestinal bleeding (OR, 0.49; 95% CI, 0.30 to 0.79), previous SBP (OR, 11.75; 95% CI, 1.55 to 246.43), ascites (OR, 125.71; 95% CI, 28.22 to 780.19), serum bilirubin (OR , 2.55; 95% CI, 1.48 to 4.42), creatinine (OR, 2.20; 95% CI, 1.11 to 4.38), INR (OR, 1.89 95% CI, 1.04 to 3.41), PT (OR, 2.23; 95% CI, 1.12 to 4.45) were likely to associate with the occurrence of SBP (Table 2). However in the logistic regression analysis, only previous history of upper gastrointestinal bleeding (adjusted odds ratio (AOR), 0.38; 95% CI, 0.19 to 0.76), ascites (AOR, 261.86; 95% CI, 50.35 to 1361.85), serum bilirubin (AOR, 3.26; 95% CI, 1.31 to 8.13) and serum creatinine (AOR, 4.45; 95% CI, 1.44 to 13.70) were found to be associated with SBP (Table 2).

To create a practical scoring system, we calculated regression coefficient and standard error by using binary logistic regression and equaled the coefficient of the variables to score points (Table 3). The table shows the results of multiple score points of CTP and the new model and each sensitivity and specificity by using ROC curve. We calculated the occurrence of SBP in patients with cirrhosis based on the sum of the score points. The total score of the patients ranged from 6 to 18 points. We selected cut point by used appropriate sensitivity and specificity of each score point and used many two of cut points to found the highest AUC for set the cut point to created range of score, the range of score was 6-9 (sensitivity; 99.4%, specificity; 24.1%), 10-12 (sensitivity; 70.3%, specificity; 70.3%), 13- 18 (sensitivity; 0%, specificity 100%)

CTP Scoring System for diagnostic test to predicted the occurrence of SBP in patients with cirrhosis s from the clinical assessment with an ROC area of 0.737. Addition of CTP Scoring System to the clinical history previous SBP items and serum creatinine significantly increased the ROC area from 0.737 to 0.759 (Table 4). Using the scoring system of the final model, we can estimate a patient's probability of SBP in patients with cirrhosis based on their clinical profiled and laboratory test (Figure 2).

DISCUSSION

In this study, we found previous history of upper gastrointestinal bleeding, presence of ascites, serum bilirubin and serum creatinine had significantly associated with occurrence of SBP after input data into logistic regression analysis. We constructed the new model by using original CPT scoring system included previous history of upper gastrointestinal bleeding and serum creatinine. However, after input data into ROC curve, we found AUC of the new model was modestly higher than AUC of CTP scoring system, and then we looked for the other variables that could increase AUC of our new model more than this. Finally we added previous history of SBP to our new model that more significantly increased the AUC. Thus the new model was more accurate than original CPT scoring system.

The study had several strengths. Firstly, This is the first study were constructed the modified Child-Pugh scoring system by combines with CPT, MELD scoring system, previous history gastrointestinal bleeding and previous history of SBP. Secondly, the modified Child-Pugh scoring system had accuracy more than original CTP scoring system. Moreover, the model we used was exclusively based on the patients with cirrhosis age 16-82 years and several cause of cirrhosis. Thus, generalization of the findings to other group of population might be wide.

The limitation of this study is that the medical record was recorded by various physicians. Therefore, it may cause measurement bias such as severity of ascites and hepatic encephalopathy effecting validity of the study. Moreover, the sample size was relatively

Table 2. Potential Predictors the occurrence of Spontaneous Bacterial Peritonitis.

Variable	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Age-Yr		
<45	1.00 (Reference)	
45 – 52	0.97 (0.50 – 1.90)	0.67 (0.25 – 1.75)
52 – 62	0.98 (0.50 – 1.90)	0.65 (0.24 – 1.72)
>62	1.05 (0.54 – 2.05)	0.87 (0.26 – 2.92)
Male sex	0.92 (0.51 – 1.67)	0.37 (0.12 – 1.16)
Cause of cirrhosis		
Alcoholic cirrhosis	0.59 (0.37 - 0.97)	1.01 (0.30 – 3.34)
Hepatitis B virus related cirrhosis	2.31 (1.12 - 4.83)	2.69 (0.76 – 9.60)
Hepatitis C virus related cirrhosis	1.12 (0.63 - 2.01)	0.63 (0.20 – 1.99)
Autoimmune cirrhosis	1.69 (0.34 - 9.08)	2.32 (0.22 -24.93)
Cholestatic cirrhosis	0.81 (0.30 - 2.17)	0.63 (0.12 – 3.39)
Unspecified cirrhosis	2.26 (0.89 - 5.92)	6.75 (0.92 - 9.25)
Ongoing alcohol use	0.86 (0.53 - 1.37)	1.48 (0.68 - 3.21)
Previous upper gastrointestinal bleeding	0.49 (0.30 - 0.79)	0.38 (0.19 – 0.76)
Previous spontaneous bacterial peritonitis	11.75 (1.55 - 6.43)	6.25 (0.66 – 59.35)
Hepatic encephalopathy		
None	1.00 (Reference)	
Controlled	2.11 (0.98 – 4.59)	1.67 (0.53 – 5.26)
Uncontrolled	1.04 (0.49 – 2.19)	0.67 (0.24 – 1.90)
Ascites		
None	1.00 (Reference)	
Controlled	42.79 (9.48 –268.18)	77.17 (14.79 – 402.71)
Uncontrolled	125.71 (28.22 – 780.19)	261.86 (50.35 – 1361.85)
Serum albumin — g/dL		
> 3.5	1.00 (Reference)	
1.8– 3.5	1.39 (0.20 – 11.87)	0.76 (0.06 – 8.92)
<2.8	4.66 (0.90 – 2.39)	1.95 (0.21 – 17.68)
Serum bilirubin — mg/dL		
<2	1.00 (Reference)	
2 – 3	2.70 (1.29 – 5.66)	3.73 (1.17 – 11.93)
>3	2.55 (1.48 – 4.42)	3.26 (1.31 – 8.13)
Serum creatinine — mg/dL		
<1	1.00 (Reference)	
1 – 1.5	1.89 (0.98 – 3.63)	2.78 (1.11 – 6.94)
1.6 – 2.4	2.29 (1.15 – 4.60)	4.45 (1.44 – 13.70)
>2.4	2.20 (1.11 – 4.38)	2.43 (0.87 – 6.78)

Table 2. (Continued.)

Variable	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
International normalized ratio		
< 1.7	1.00 (Reference)	
1.7– 2.3	1.89 (1.04 – 3.41)	0.73 (0.17 -3.11)
>2.3	1.75 (0.95 – 3.22)	2.66 (0.36 – 19.77)
Prothrombin time — sec		
< 15.8	1.00 (Reference)	
15.8 – 19.0	1.48 (0.75 – 2.92)	0.65 (0.25 – 1.69)
19.1 – 25.2	2.16 (1.09 – 4.30)	1.11 (0.27 – 4.65)
>25.2	2.23 (1.12 – 4.45)	0.31 (0.04 – 2.41)
Serum aspartate aminotranferase — IU/L		
<61	1.00 (Reference)	
61 – 100	1.23 (0.63 – 2.41)	0.81 (0.27 – 2.38)
100 – 185	0.97 (0.50 – 1.90)	0.40 (0.13 – 1.22)
>185	1.02 (0.52 – 2.00)	0.73 (0.17 – 3.14)
Serum alanine transaminase — IU/L		
< 33	1.00 (Reference)	
33 – 50	1.02 (0.52 – 2.00)	1.11 (0.40 – 3.04)
50 – 84	1.22 (0.63 – 2.37)	1.17 (0.38 – 3.60)
>84	1.08 (0.55 – 2.11)	0.49 (0.12 – 1.94)
Serum alkaline phosphatase — IU/L		
< 85	1.00 (Reference)	
85 – 127	1.46 (0.75 – 2.84)	2.87 (0.95 - 8.66)
127– 209	1.33 (0.67 – 2.62)	1.91 (0.65 – 5.59)
>209	1.29 (0.66 – 2.53)	1.42 (0.53 - 3.85)

* Odds ratios were adjusted for age, sex, cause of cirrhosis, ongoing alcohol use, previous gastrointestinal bleeding, previous spontaneous bacterial peritonitis, hepatic encephalopathy, serum albumin, serum bilirubin, serum creatinine, INR, PT, AST, ALT, ALPv

small and the study failed to match sex for two cases which inevitably limited the prediction of the occurrence of SBP.

The characteristics of the patients with cirrhosis in the present study were comparable to those in previous studies. It found that most patients with cirrhosis with SBP were in Child C classification.[5] For another study, patients with cirrhosis and SBP had MELD score higher than 18 was associated with an increase risk of SBP,[8] these findings were similar to our study as we found that the patients with cirrhosis and SBP had average MELD score 23.3. Another prospective study evaluated the SBP patients and found that three significant independent predictive factors of in-hospital mortality; a high MELD score, renal failure and SBP caused by extended-spectrum a-lactamase-producing organisms. and in patients with a high MELD score was the risk of SBP,[17] while in our study, we found that two variables in the MELD scoring system, serum bilirubin and serum creatinine associated with the occurrence of SBP. In one study exploring asymptomatic ascites fluid infection in patients with cirrhosis attending an outpatient clinic and undergoing therapeutic paracentesis, there was no association between cirrhotic outpatients with and without infection and age, gender, alcohol consumption, etiology of cirrhosis, Child-Pugh score, serum albumin and ascites fluid total protein,[18]unlike to our study, we found that serum albumin had significantly difference in cirrhotic patients with and without SBP .

In conclusion, high validity was found using the Child-Pugh scoring system predicting the occurrence of SBP together with serum creatinine, previous history of gastrointestinal bleeding and previous history of SBP in the patients with cirrhosis from the various model purposed and give the highest accuracy rate than original Child-Pugh scoring system. For more precise prediction model, study with larger sample should be conducted and for more insight in those with other underlying disease such as congestive heart failure, cancers of the organs in abdominal cavity, chronic pancreatitis and nephritic syndrome, a further study of the application of the model in these groups should be examined for proper management.

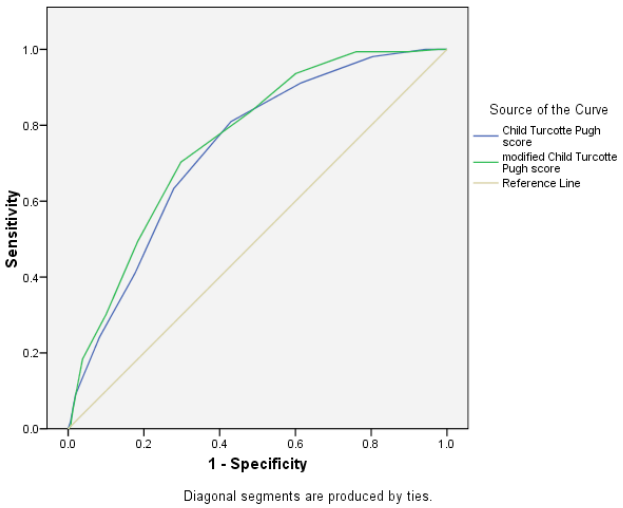

Figure 2. ROC curve compare with Modifed Child-Turcotte-Pugh score and Child-Turcotte-Pugh score.

Table 4. Clinical and Laboratory Variables Score.

Variable	New model	Child-Pugh scoring system
Hepatic encephalopathy		
None	1	1
Mild – moderate	2	2
severe	3	3
Ascites		
None	1	1
Controlled	2	2
Uncontrolled	3	3
Serum albumin — g/dL		
> 3.5	1	1
2.10 – 3.5	2	2
< 2.8	3	3
Serum bilirubin — mg/dL		
<2	1	1
2 – 3	2	2
>3	3	3
International normalized ratio		
< 1.7	1	1
1.8 – 2.3	2	2
> 2.3	3	3
Previous upper gastrointestinal bleeding	1	-
Previous spontaneous bacterial peritonitis	1	-
Serum creatinine — mg/dL		-
<1.2	0	-
≥1.2	1	-
Total	18	15

Table 5. Sensitivity, specificity, accuracy and Likelihood ratio of Child -Pugh score and the new model to predict the occurrence of spontaneous bacterial peritonitis.

	Score	Sensitivity	Specificity	Likelihood ratio	Accuracy
					0.737
	4.00	1.000	0.000	1.000	
	5.50	1.000	0.019	1.019	
	6.50	1.000	0.057	1.060	
	7.50	0.098	0.196	1.220	
	8.50	0.911	0.386	1.485	
Child-Pugh scoring system	9.50	0.810	0.570	1.882	
	10.50	0.633	0.722	2.273	
	11.50	0.411	0.823	2.321	
	12.50	0.241	0.918	2.923	
	13.50	0.089	0.981	4.667	
	14.50	0.019	0.994	3.000	
	16.00	0.000	1.000		
					0.759
	6.00	1.000	0.000	1.000	
	7.50	1.000	0.025	1.026	
	8.50	0.994	0.101	1.106	
	9.50	0.994	0.241	1.308	
	10.50	0.937	0.399	1.558	
	11.50	0.835	0.519	1.737	
Modified Child-Turcotte-Pugh score	12.50	0.703	0.703	2.362	
	13.50	0.494	0.816	2.690	
	14.50	0.304	0.899	3.000	
	15.50	0.184	0.962	4.833	
	16.50	0.051	0.987	4.000	
	17.50	0.006	0.994	1.000	
	19.00	0.000	1.000		

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ORIGINAL ARTICLE

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Nasogastric Tube Intubation and the Risk Factors for Ventilator Associated Pneumonia in Patients with Mechanical Ventilator, a Retrospective Cohort Study.

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ABSTRACT

BACKGROUND
Nosocomial pneumonia is the most common complications that occur in patients receiving mechanical ventilation for longer than 48 hours. Ventilator-associated pneumonia (VAP) is the most common type of nosocomial pneumonia. VAP is associated with increases in morbidity and mortality, length of hospital stay and costs. The aim of this study was to compare mortality rate of VAP and non-VAP patients and identify the risk factors of VAP in patients with mechanical ventilator, including the most common organisms that cause VAP.

METHODS
This retrospective cohort study included 384 patients, by systematic randomizations, which were placed by mechanical ventilator. The data were collected by reviewed of an electronic data of patients admitted in the hospital during January to December 2011. The diagnostic criteria of VAP were described by clinical examination and chest film x-ray. At baseline, treatment with antibiotics, sedative agents and immunosuppressive agents, included steroid, were recorded since the admission of patients until they turned to be VAP or were discharged from hospital. Laboratory investigations were done at the time of admission also, anemia and leukocytosis was described.

RESULTS
Our study, 69 from 384 patients on mechanical ventilator turned to VAP (18%). No different death rate between groups of VAP vs. Non-VAP. After adjusting, risk factors associated with VAP are age more than 50 years (AOR, 2.47; 95% CI 1.09 to 5.61), cardiovascular disease (AOR, 3.21; 95% CI 1.14 to 9.06), NG or OG intubation (AOR, 4.31; 95% CI 2.01 to 9.24), alteration of consciousness (AOR, 2.21; 95% CI 1.02 to 4.79), treated with sedative drugs (AOR, 3.13; 95% CI 1.33 to 7.33) and immunosuppressants used (AOR, 3.06; 95% CI 1.18 to 8.39), when analyzed risk factors associated with death, only age more than 50 years (AOR, 2.01; 1.12 to 3.62) and alteration of consciousness (AOR, 5.12; 2.93 to 8.97) are significantly increased risk of death. The common organisms of VAP are *S.aureus, A.baummanii, K.pneumoniae*.

CONCLUSIONS
This study suggest multiple risk factors associated with VAP in the patients on mechanical ventilator (e.g. nasogastric or orogastric intubation, treated with sedative drugs on admission) and death.

World health organization (WHO) stated that the amount of patients and the number of those that have to stay in hospitals has been increasing with high rate[1] and this can cause more nosocomial complication including ventilator associated pneumonia (VAP).[2] VAP is a form of nosocomial pneumonia that occurs in patients receiving mechanical ventilation for longer than 48 hours.[3] VAP is associated with increases in morbidity and mortality as well as length of hospital stay and cost.[4,5] For instance, one study from the US stated that VAP doubled the mortality and incurred and addition cost more than USD $10,000 per case.[4] The most common cause of VAP is bacterial infection, for example *P. aeruginosa*, *A. baummanii* and *S. aureus*.[6] For the risk factors of VAP, one study from the US with 277 patients in the intensive care unit (ICU), organ system failure, age more than 60 years, prior administration of antibiotics and supine head position during on ventilator were highly associated with VAP.[3] One review form the BMJ in 2005 also added that APACHE II score more than 16, underlying lung disease, sedative and muscle relaxant used, enteral nutrition, state of consciousness and smoking were the risk for VAP.[7] Furthermore, from the Guideline for Management of Adult with Hospital Acquired Ventilator Associated and Health Care Associated Pneumonia of the American Thoracic Society, it mentioned that re-intubation, previous lung pathology, colonization of the ventilator circuit also increased the incidence of VAP in the ICU patients.[8] Other risk factors have been reported including the duration of mechanical ventilation, sepsis, acute respiratory distress syndrome (ARDS), neurological disease, trauma, prior use of antibiotics, red cell transfusions and nasogastric intubation.[2,5] However, these risk factors are still debatable.[5]

From the previous studies, most of them were conducted in the ICU environment from the Western countries. This study, thus, aims to explore the risk factors of VAP in both inside and outside ICU. Moreover, we also made an attempt to ascertain the potential risk factors for VAP including the placement of NG tube, age, patients underlying diseases, state of the patient consciousness and drug used.

METHODS

Study design and patients

This is a retrospective cohort study conducted in Khon Kaen Hospital, the data were collected by reviewed of an electronic data of patients admitted in the hospital during January to December 2011. The inclusion criteria were patients that used mechanical ventilator via endotracheal tube or tracheostomy intubation, an age of 15 to 80 years without history of previous intubation. Our null hypothesis was that the rate of VAP in those with NG and without NG placement was similar. With type I error 0.05, type II error 0.2, expected different of rate of VAP in those with NG and without NG placement was 20%, the required sample was 206 in total.

Firstly, there were 5934 patients, and 1134 patients were excluded by previous pulmonary disease diagnosed by ICD-10 such as chronic obstructive pulmonary disease (COPD), asthma, pulmonary emphysema, pulmonary tuberculosis, community acquired pneumonia (CAP), aspirated pneumonia and neoplasm of lung or lung metastasis. The left 4,800 were selected using systematic randomization with the interval of 12, 384 were included in the analysis.

The diagnosis criteria of VAP were patients mechanically ventilated for greater than 48 hours with at least three of the following: fever, physical examination that show lower respiratory tract infection, leukocytosis or leukopenia, tracheal suction culture and chest X-ray have new infiltration.[7] At baseline, all patients were intubated either endotracheal tube or tracheostomy. Laboratory investigations were done at the time of admission to be base line for each patient, anemia was described by hemoglobin (Hb) level less than 12 g/dl and leukocytosis was described by white blood cell count more than 10,000/ml. The treatment with antibiotics, sedative agents and immunosuppressive agents, including steroid, were recorded since the admission of patients until they turned to be VAP or were discharged from hospital.

Study outcomes

The primary outcome of this study was to identify the risks of patients that on mechanical ventilator turned to be VAP. The risks were observed since the patients were used mechanical ventilator until developed VAP. This included sex, age, diagnosis, underlying disease, NG or OG intubation, alteration of consciousness, anemia, leukocytosis, sedative used, antibiotics used and immunosuppressant used.

The comparison of the mortality rate (either death in the hospital or desire to die at home) of patients after treated in the hospital between VAP group and non-VAP group was observed as the secondary outcome of this study. Clinical improved before discharge from hospital was also considered as another secondary outcome as well as the length of hospital stay. The length of stay was measured since the patients were admitted in hospital until they were discharged, by the physicians, or until patients dead. The microbiological organisms, from tracheal suction cultured at the day of diagnosed VAP, among the patients were recorded in this study to describe the most common organism that tended to be the cause of VAP.

Statistical analysis

Descriptive data are reported as median with interquartile range (IQR) or percentages, as

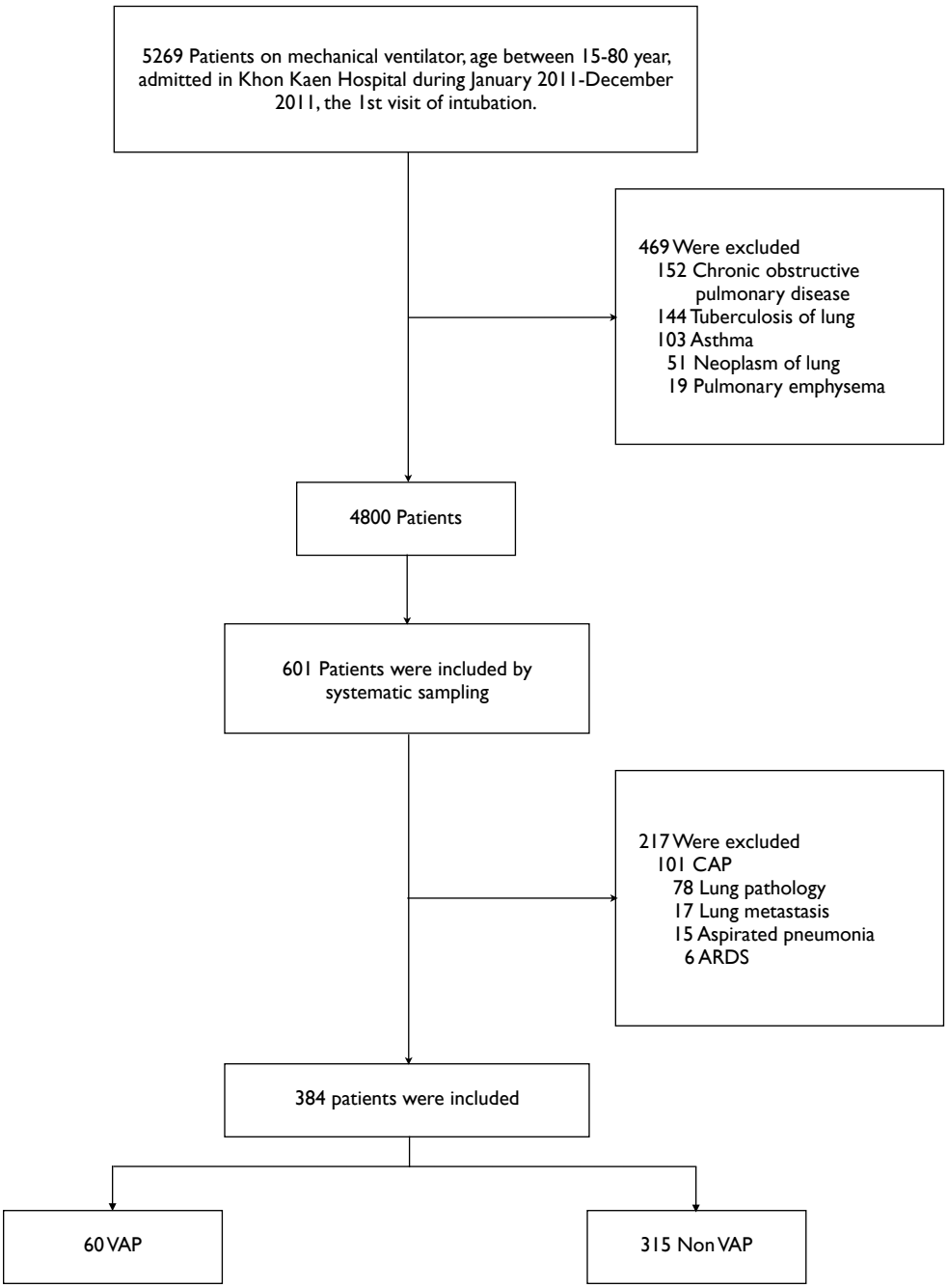

Figure 1. Patient Flow Chart.
COPD = Chronic Obstructive Pulmonary Disease; CAP = Community Acquired Pneumonia; ARDS = Acute respiratory distress syndrome; VAP = Ventilator Associated Pneumonia.

appropriate. Chi-square was used to compare between the two categorical data. Mann Whitney U test was used for compare two scale non-normally distributed variables. Crude odds ratio (COR) and adjusted odds ratio (AOR) from the logistic regression analysis were use to describe the risks and any dichotomous outcomes. P<0.05 were defined as statistical significant. Statistic software package was used to calculate data and WinPepi version 11.18 was used to calculate sample size of patients.

RESULTS

Characteristic of Patients

A total of 384 patients on ventilator (256 men) were included in the study (Figure 1). The characteristics of the entire study population are shown in Table 1. Majority of them were male with the median age is 53.5 years. Most of them were admit due to the trauma causes. Hypertension and diabetes were found in nearly half of the patients. Approximately half of them were placed with either NG or OG. More than 60% of them had alteration of consciousness. On the admission, more than half of them had hemoglobin level less than 12 g/dl and had leukocytosis. About 66% were prescribed with sedative agents. Nearly 70% were treated with antibiotics on admission. About 13% were used or treated with immunosuppressive agents before. Nearly all were on endotracheal tube, only six had tracheostomy. In general, there were no significant differences between the two groups (VAP and non-VAP) regarding their baseline characteristics. However, the median ages of patients have significant different between the two groups (62 year in VAP and 53 year in non-VAP; P=0.02), and patients with VAP tended to be intubated with either NG or OG (73.9% in VAP group and 47.3% in non-VAP group; P<0.001). Moreover, they were more likely to have higher proportion of patients with alteration of consciousness and prior sedative agents used (72.5% in VAP and 58.7% in non-VAP; P=0.03 and 79.5% in VAP and 63.5% in non-VAP; P=0.01, respectively) (Table 1).

VAP and Risk Factors Associated with VAP

From 384, 69 developed VAP. Table 2 shows the potential risk factors associated with VAP and presents in term of COR and AOR. It found that age more than 50 years (COR, 1.87; 95% CI 1.08 to 3.25), NG or OG intubation (COR, 3.16; 95% CI 1.77 to 5.64), alteration of consciousness (COR, 1.85; 95% CI 1.04 to 3.28), treated with sedative drugs on admission (COR, 2.26; 95% CI 1.20 to 4.24) were associated with VAP. However, after adjusting with other confounders in the logistic regression analysis, factors that found to be associated with an increased risk of VAP were an age older than 50 year (AOR, 2.47; 95% CI 1.09 to 5.61), cardiovascular disease (AOR, 3.21; 95% CI 1.14 to 9.06), nasogastric or orogastric intubation (AOR, 4.31; 95% CI 2.01 to 9.24), alteration of consciousness (AOR, 2.21; 95% CI 1.02 to 4.79), treated with sedative drugs on admission (AOR, 3.13; 95% CI 1.33 to 7.33), immunosuppressants used (AOR, 3.06; 95% CI 1.18 to 8.39). However, diabetes mellitus or treated with antibiotics on admission not associate with VAP.

Mortality Rate and Length of Hospital Stay

Table 3 shows that there was no significant different in the result of mortality rate after treatment in patients with VAP group compare with non-VAP group (55.1% in VAP and 54.6% in non-VAP, P=0.80). Median total length of hospital stay (IQR) were higher in group of the patients with VAP than group of the patients with Non-VAP (17 (8-28) Days and 4 (1-7) Days, P<0.001).

Microbiological Results

Total 64 patients of 69 patients with VAP (92.7%) were bacterial infections recorded, record of the other five were irretrievable. Most of patients with VAP were polymicrobial infected. The most common type of Gram positive bacteria was S.aureus (15%) and the first three most common types of Gram negative bacteria were *A. Baummanii* (33.3%), *K. pneumoniae* (27.0%) and *P. aeruginosa* (22.2%). (Table 4)

Risk Factors Associated with Death

From Table 5, we analyzed risk factors associated with death in the overall of patients. The outcomes was alteration of consciousness had significant association with death of patient (COR, 3.69; 95%CI 2.39 to 5.71). Furthermore, after adjusting with potential related factors, we found age more than 50 years and alteration of consciousness had significantly increased risk of death (AOR, 2.01; 95% CI 1.12 to 3.62 and AOR, 5.12; 95% CI 2.93 to 8.97, respectively).

DISCUSSION

The risk of VAP is higher among patients who had been intubated by either endotracheal tube or tracheostomy together with nasogastric or orogastric tube. The other factor that increased the risk of VAP were ages over 50 years, underlying of cardiovascular disease, alteration of consciousness, treated with sedative drugs on admission and immunosuppressive agents used. Furthermore, risk of death has been found in patients who age more than 50 years and patients who had alteration of consciousness. Most of VAP were caused by polymicrobial infection and the most common organisms is Gram negative bacteria, *A. baummanii, K.pneumoniae, P. aeruginosa*. This study showed there was no difference in outcome between

Table 1. Baseline Characteristics of the Patients.

Characteristics	All patients (N = 384)	Patients with VAP (N = 69)	Patients with Non-VAP (N = 315)	P Value
Age --- years				0.02
Median	53.5	62	53	
Interquartile range	40-66	42.5-71.0	40-65	
Male sex --- no. (%)	256 (66.7)	48 (69.6)	208 (66.0)	0.57
Principle diagnosis --- no. (%)				0.23
Trauma	112 (29.2)	21 (30.4)	91 (28.9)	
Cerebrovascular disease	69 (18.0)	18 (26.1)	51 (16.2)	
Gastrointestinal disease	48 (12.5)	9 (13.0)	39 (12.4)	
Sepsis	34 (8.9)	5 (7.2)	29 (9.2)	
Neoplasms	26 (6.8)	2 (2.9)	24 (7.6)	
Others	95 (24.6)	14 (20.4)	81 (25.7)	
Comorbidity --- no. (%)				
Hypertension	108 (28.1)	25 (36.2)	83 (26.3)	0.10
Diabetes mellitus	78 (20.3)	12 (17.4)	66 (21.0)	0.51
Renal insufficiency	48 (12.5)	8 (11.6)	40 (12.7)	0.80
Gastrointestinal disease	40 (10.4)	4 (5.8)	36 (11.4)	0.17
Cardiovascular disease	39 (10.2)	11 (15.9)	28 (8.9)	0.08
Neurological disease	35 (9.1)	9 (13.0)	26 (8.3)	0.21
Nasogastric or orogastric intubation --- no. (%)	200 (52.1)	51 (73.9)	149 (47.3)	<0.001
Alteration of consciousness --- no. (%)	235 (61.2)	50 (72.5)	185 (58.7)	0.03
Anemia --- no. (%)	203 (52.9)	42 (70.0)	161 (59.4)	0.13
White blood cell ---no. (%)				0.85
Less than 4,000 cell/mm3	7 (1.8)	1 (1.9)	6 (2.3)	
4,000-10,000 cell/mm3	93 (24.2)	14 (6.9)	79 (30.6)	
More than 10,000 cell/mm3	210 (54.7)	37 (71.2)	173 (67.1)	
Treated with sedative agents on admission --- no. (%)	255 (66.4)	55 (79.7)	200 (63.5)	0.01
Treated with antibiotics on admission --- no. (%)	265 (69.0)	51 (73.9)	214 (67.9)	0.33
Immunosuppressant --- no. (%)	53 (13.8)	12 (17.4)	41 (13.0)	0.34

those with VAP and without VAP due to the similar death rate between the two groups. Nonetheless the median total length of hospital stayed had significantly longer in those with VAP.

Comparison with other studies

In the present study the number of patients developed VAP is about 18% (69 from 384 patients), this was comparable with previous studies which stated that VAP in patients whom was on mechanical ventilator was about 8-28% of normal patients and 15.5% in ICU patients.[9,10] In our study, the significantly risk associated VAP included Age and sedative drug used. This two factors had been confirmed to associated with VAP from a review in 2005 in BMJ.

In relation to organism, the most common responsible for early onset of VAP were largely due to *S. aureus*, *S. pneumoniae*, and *H. influenzae*, while late onset VAP is often caused by resistant nosocomial pathogens such as *P. aeruginosa* MRSA, *S. aureus*, *Klebsiella species*, and *A. baumannii*.[7] Overall, the most common organisms that cause VAP were *P. aeruginosa* and *S. aureus*.[7] Unlike this study, the three most common organisms were *A. baummanii, H. influenzae, P. aeruginosa.* This difference might be due to the difference prevalence of pathogen in various settings.

Table 2. Odds ratio and 95% Confidence Interval of Potential Variable Associate with Ventilator Associated Pneumonia.

Variable	Crude odds ratio	95% CI	Adjusted odds ratio	95% CI
Sex (female)	0.85	0.48-1.49	0.52	0.25-1.12
Age > 50 years	1.87	1.08-3.25	2.47	1.09-5.61
Hypertension	1.59	0.92-2.76	1.62	0.72-3.65
Diabetes mellitus	0.79	0.40-1.57	0.84	0.33-2.14
Renal insufficiency	0.90	0.40-2.02	0.52	0.17-1.58
Gastrointestinal disease	0.48	0.16-1.39	0.14	0.02-1.14
Cardiovascular disease	1.94	0.92-4.13	3.21	1.14-9.06
NG or OG intubation	3.16	1.77-5.64	4.31	2.01-9.24
Alteration of consciousness	1.85	1.04-3.28	2.21	1.02-4.79
Anemia	1.59	0.87-2.91	2.02	0.95-4.31
White blood cell (Leukocytosis)	1.21	0.63-2.33	1.15	0.55-2.41
Treated with sedative drugs on admission	2.26	1.20-4.24	3.13	1.33-7.33
Treated with antibiotics on admission	1.34	0.74-2.41	1.30	0.58-2.92
Immunosuppressants	1.41	0.70-2.84	3.06	1.11-8.39

Table 3. Secondary Outcomes.

Outcomes	Patients with VAP	Patients with Non-VAP	P Value
Discharge status ---no. (%)			0.80
Improved	30 (43.5)	134 (42.5)	
Refer to higher admission hospital	1 (1.4)	9 (2.9)	
Death	38 (55.1)	172 (54.6)	
Total length of hospital stay ---days			<0.001
Median	17	4	
Interquartile range	8-28	1-7	

Mortality from the present study was 55%. This was a bit higher than those reported from other studies with the range of 24-50% in normal patients, this might be higher in patients with high risk pathogen of lung infection and 37.2% in ICU patients.[9,10] The higher mortality in the present study might be largely due to the difference of environment between ICU and non-ICU in our study.

Strengths and limitations

This study has several advantages. To our knowledge, this was the first study that described the risks of patients ventilated mechanically developed VAP in normal setting of patients rather than in the ICU without previous lung disease. Moreover, we could establish the relationship between the higher risks of VAP in patient with NG or OG intubation after a long debate. Aside from that, the population included in this study was 384 patients that sufficient to test our hypothesis. This allowed us to do multivariable analysis to adjust for other covariates with precise confidence interval.

However, the present study has some limitation. This study was a retrospective cohort study. Due to its nature, there were some missing data in an electronic database and they required clarification before preceding the analysis. For instance, criteria for diagnose VAP were still controversy because there were none definite criteria for diagnosis by ICD-10 or others. However, we attempted to retrieve all missing data and verify their validity through the consensus of our research team as well as the hospital staff who responded for the records. Overall, there were less than 3% of data were missing.

Conclusion and implication

In summary, 18% of the patients in our study with mechanical ventilator turned to VAP, no different death rate between those with or without VAP were observe. However, VAP patients tended to stay in

Table 4. Organisms Found in Patient with Ventilator Associated Pneumonia.

Organisms	Patients with VAP (N=64)
Gram positive bacteria ---no. (%)	
S. aureus	10 (15.9)
S. pneumoniae	1 (1.6)
Others	4 (6.3)
Gram negative bacteria ---no. (%)	
A. baummanii	21 (33.3)
K. pneumoniae	17 (27.0)
P. aeruginosa	14 (22.2)
H. influenzae	2 (3.2)
Others	10 (15.9)

Table 5. Odds ratio and 95% Confidence Interval of Potential Variable Associate with Death.

Variables	Crude odds ratio	95% CI	Adjusted odds ratio	95% CI
Sex (female)	0.85	0.55-1.31	0.80	0.45-1.40
Age > 50 years	1.50	0.99-2.27	2.01	1.12-3.62
Hypertension	1.03	0.65-1.62	0.87	0.46-1.66
Diabetes mellitus	0.78	0.47-1.30	0.89	0.43-1.82
Renal insufficiency	1.08	0.57-2.03	1.01	0.44-2.29
Gastrointestinal disease	1.95	0.96-3.96	2.24	0.88-5.72
Cardiovascular disease	1.03	0.52-2.04	1.20	0.48-2.96
NG or OG intubation	0.72	0.48-1.09	0.66	0.39-1.11
Alteration of consciousness	3.69	2.39-5.71	5.12	2.93-8.97
Anemia	1.14	0.73-1.79	1.33	0.76-2.32
White blood cell (Leukocytosis)	0.81	0.50-1.34	0.86	0.49-1.51
Treated with sedative drugs on admission	0.69	0.44-1.07	0.81	0.45-1.46
Treated with antibiotics on admission	0.70	0.44-1.09	1.01	0.56-1.82
Immunosuppressants	1.42	0.78-2.61	1.69	0.77-3.69

hospital longer. The multivariable analysis suggests that multiple risk factors associated with VAP including age more than 50 years, NG or OG intubation, cardiovascular disease, alteration of consciousness, treated with sedative drugs and immunosupressants used and risks for death could be found in patients whose age more than 50 years and those with alteration of consciousness. We suggest that close monitoring for patients with sedative drugs and immunosuppressants used to reduce the rate of VAP in mechanical ventilator patients. Moreover, patients with alteration of consciousness might need more attention due to the higher mortality rate. In the future study, the prospective cohort study is recommended with time factor should be taken into consideration to be able to calculate hazard ratio for describing the outcomes more appropriate and to minimize the possible bias.

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ORIGINAL ARTICLE

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The Association between Placental Weight and Neonatal and Maternal Outcomes.

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ABSTRACT

BACKGROUND
Relationship of placental and neonatal and maternal outcome has received more attention. However, association between placental weight and APGAR score at first minute has not been well described.

METHODS
The retrospective cohort study was conducted. The medical records of pregnant women who delivered the babies during September 2011-January 2012 in Khon Kaen Hospital were retrieved and reviewed. Data regarding characteristics of the mother, placental weight, infant and maternal outcomes were collected. The association of the placental weight and the outcomes were interpreted using adjusted odd ratio from the logistic regression analysis.

RESULTS
There were 1,285 records of the pregnant women were included. It found that there was no association between placenta weight and APGAR score at first minute (adjusted odds ratio (AOR) 0.99; confidence interval (CI) 0.997-1.002), fifth minute (AOR 0.998; CI 0.992-1.005) and tenth minute (AOR 0.984; CI 0.956-1.012). Moreover, no association between placental weight and maternal outcomes in relation to post-partum hemorrhage (P=0.060), episiotomy wound infection (P=0.520) and time to start breast feeding (P=0.502) were observed. However, birth weight was associated with APGAR score at first minute (AOR 0.999; CI 0.998-0.999), maternal who had preeclampsia was also associated with APGAR score at fifth minute (AOR 0.049; CI 0.007-0.330).

CONCLUSION
There was no association between placental weight and APGAR score at first minute, only birth weight was significantly associated with APGAR score at first minute. Moreover, preeclampsia was also significantly related with APGAR score at fifth minute.

Placenta is an organ that connects the developing fetus to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's blood supply.[1-5] Many changes happen in placental shape and function that reflects changes in needs of fetus in different growth.[6,7] Placental weight reflects placental development and functions and is correlated with maternal age, gestational age, history of maternal diabetes, preeclampsia, birth weight, parity, route of delivery, and APGAR score and fetal distress.[8-14] It shows that placental weight has a significant role in fetal growth.[15]

Currently, many studies shows that weight of placenta, histology and pathology of placenta as well as placental weight/birth weight ratio have relationship with maternal and neonatal outcomes.[8,16-21] Lower APGAR score in neonates is observed in those with low-weight placenta. Moreover, fetal distresses and cesarean delivery are also found to be more common in women with abnormal weight of the placenta.[22] Fetal and placental weight were linearly related, low weight placentas were found in under 2500 grams neonates but not in over 3500 grams neonates weight group. Low-weight placentas were found in those aged under 19 years and pre-eclampsia mother while more high-weight placentas were found in those age 30-45 years or older and diabetic mothers.[23,24] Moreover, the high of fetal/placental weights ratio greater than 10-11 is associated with increased rates of admission to the neonatal intensive care unit (NICU), of APGAR score<7.[25]

However although many studies revealed the association between placental weights and five and ten minutes APGAR score but none have shown the relationship between placental weight and APGAR score at one minute, thus, we conducted the current study to determine the association between placental weight and first minute APGAR score.

METHODS

Study overview

This was a retrospective cohort study conducted during September 2011 to January 2012, in Khon Kaen Hospital. Preliminarily, the database of the pregnant women and their babies who delivered were reviewed. Later, women who delivered twins, dead fetal in utero, women that delivered babies at gestational age less than 37 weeks, women that delivered by cesarean section or those with incomplete records were excluded. The sample size was calculated based on the hypothesis that there was an association between placental weight and APGAR score at first minute. with 0.05 alpha error, 0.2 beta error, mean difference of APGAR score at first minute between groups regarding placenta weight of 0.36, standard deviation of the two groups were 0.96 and 1.57, the required sample size was 207 for each group.

In our study, we categorized the placenta weight into three group; ≤500 grams (low placenta weight group), 501-700 grams (moderate placenta weight) and >700 grams (high placenta weight group) regarding the percentile of the placenta weight of women included in the present study . The hypothesis for the calculation above was based on the different of the two groups, thus the total required sample in the present study was 207 for each group or 621 in total. However, we included up to 1285 for the best approximation.

Outcomes

Outcomes included both maternal and neonatal outcomes. For maternal outcomes, postpartum hemorrhage, maternal infection (e.g., wound infection and chorioamnionitis) and duration of time to start breast feeding were recorded. Neonatal outcomes comprised birth weight, APGAR score at one minute, APGAR score at five minutes, APGAR score at ten minutes, occurrence of respiratory distress syndrome, admission to the neonatal intensive care unit (NICU), present of neonatal jaundice and intrapartum fetal distress.

Data collection

Data of maternal and neonates that included in the study were reviewed and recorded regarding maternal and neonatal characteristics. These included maternal age, gestational age, pre-pregnant weight, gestational weight gain, parity, underlying (e.g., gestational diabetes mellitus and preeclampsia) and placental weight.

Statistical analysis

Before we proceeded the analysis, all data were cleaned and verified using double-entry approach. After that frequency tables were generated for all variables to identify the wild values. After verification, the analysis was then carried on. All statistical analysis was done using statistical package software. Initially, we described variables in using number and % for categorical variables. For scale variables, we described using mean and standard deviation (SD) if they were normally distributed. If they were non normally distributed, we described using median and interquartile range (IQR). For inferential statistics, we used chi-square test for test association between two categorical variables. We also used Kruskal Wallis for testing the hypothesis involving with non normally distributed variables. The association between placenta weight and the outcomes was presented in term of odd ratio (OR) and adjusted odd ratio (AOR) using the logic regression analysis.

Table 1. Characteristics of Cohort Members.

Characteristic	Placental weight (g) ≤ 500 (N=302)	501-700 (N=756)	>700 (N=227)	P Value
Maternal age — yr				0.06
Median	23	25	25	
Interquartile range	19.8-28.0	20-29	20-31	
Gestational age — wk				<0.001
Median	38	39	39	
Interquartile range	37-39	38-40	38-40	
Maternal weight — kg				
Pre-pregnancy weight				<0.001
Median	48	51	52	
Interquartile range	44-55	46-56	48-60	
Gestational weight gain				0.001
Median	12	13.6	14	
Interquartile range	9-16	10-17	11-18	
Maternal disease				
Gestational DM — no. (%)	12 (4.0)	23 (3.0)	8 (3.5)	0.74
Preeclampsia — no. (%)	14 (4.6)	28 (3.7)	14 (6.2)	0.27
Parity — no. (%)				0.05
1	165 (54.6)	360 (47.6)	94 (41.4)	
2	91 (30.1)	260 (34.4)	89 (39.2)	
>2	46 (15.2)	136 (18.0)	44 (19.4)	
Median	1	2	2	

RESULTS

Patients

In Figure 1, a total of 2,682 pregnant women were screened for eligibility, 1397 pregnant women were excluded, three-fourths had cesarean delivery delivered. Of 1,285 pregnant woman and their baby were included. They were then organized into three placental weight groups, 302 women were placental weight 500 grams or less, 756 women were placental weight more than 500 to 700 grams and 227 women were placental weight more than 700 grams. Their baseline characteristics of those who eligible are listed in Table 1. Their median age was 24 (IQR of 20-29) years old. Their median gestational age was 39 (IQR 38-40) weeks. The median of their weight gain was 13.1 (IQR 10-17) kilograms. Only 3.3% of the women had gestation diabetes and 4.4% had preeclampsia. The median of the birth weight was 3080 (IQR 2830-3300) grams.

Outcomes

From the univariable analysis, we found significant association between three placental weight groups and APGAR score at one minute (P=0.008) as well as at five minutes (P=0.001); APGAR score at one and five minutes of high placental weight group and low placental weight group were lower than that of moderate placental weight groups (Table 2). Moreover the placenta weight was significantly associated with birth weight (P<0.001) and rate of NICU admission (P=0.044). However, after adjusted with maternal age, gestational age, pre-pregnancy weight, gestational weight gain, gestational diabetes, preeclampsia,parity and birth weight, we found no significant association between placental weight and APGAR score at one minute (AOR 0.999; CI 0.997-1.002), five minutes (AOR 0.998; CI 0.992-1.005) and ten minutes (AOR 0.987; CI 0.967-1.007) (Table 3). Nevertheless, we found statistically significant association between birth weight with APGAR score at one minute (AOR 0.999; CI 0.998-0.999). Preeclampsia was also found to be significant associated with APGAR score at five minutes (AOR 0.049; CI 0.007-0.316).

Table 2. Relationship Between Placental Weight and Outcome of Neonatal and Maternal.

Variable	Placental weight (g) ≤ 500 (N=302)	501-700 (N=756)	>700 (N=227)	P Value
APGAR score at 1st minute				0.008
0-6	12 (4.0)	22 (2.9)	17 (7.5)	
7-10	290 (96.0)	734 (97.1)	210 (92.5)	
Median	10	10	10	
Interquartile range	9-10	10-10	10-10	
APGAR score at 5th minute				0.001
0-6	2 (0.7)	1 (0.1)	6 (2.6)	
7-10	300 (99.3)	755 (99.9)	221 (97.4)	
Median	10	10	10	
Interquartile range	9-10	10-10	10-10	
APGAR score at 10th minute				0.005
0-6	0	0	3 (1.3)	
7-10	302 (100.0)	756 (100.0)	224 (98.7)	
Median	9	9	10	
Interquartile range	9-10	9-10	10-10	
Birth weight — g				<0.001
Median	2805	3090	3350	
Interquartile range	2590.0-3042.5	2892.5-3330.0	3140.0-3610.0	
Respiratory distress syndrome— No. of patients (%)	8 (2.6)	14 (1.9)	11(4.8)	0.044
Rate of NICU admission— No. of patients (%)	1 (0.3)	3 (0.4)	6 (2.6)	0.007
Interquartile range	1-2	1-2	1-2	
Birth weight — g				<0.001
Median	2805	3090	3350	
Interquartile range	2590.0-3042.5	2892.5-3330.0	3140-3610	
Rate of infection in maternal— No. of patients (%)	4 (1.3)	9 (1.2)	5 (2.2)	0.520
Time to start breast feeding (hours) — No. of patients (%)				0.502
≤ 24	249 (84.7)	643 (86.8)	184 (83.3)	
25-48	36 (12.2)	85 (11.5)	30 (13.6)	
49-72	9 (3.1)	13 (1.8)	7 (3.2)	

DISCUSSION

In this retrospective cohort study, we have shown and confirmed that there is no association between placental weight and APGAR score at one, five and ten minutes. In addition to this, we found birth weight was significantly associated with APGAR score at one minute and preeclampsia was also significantly related with APGAR score at five minutes. Maternal age, gestational age, weight gain during pregnancy, underlying of gestational diabetes, parity were found no association with the APGAR score.

Comparison with previous studies

Previous studies have examined the relationship between placental weight and birth weight and some adverse pregnancy outcomes but there have been no

Table 3. Independent Predictors of APGAR Score after Adjustment with the Use of Logistic Regression Model.

Variable	Adjusted Odd Ratio and 95% confidence interval of APGAR score between 7-10		
	At 1 minute	At 5 minutes	At 10 minutes
Placental weight	0.999 (0.997 -1.002)	0.998 (0.992-1.005)	0.987 (0.967-1.007)
Maternal age	0.998 (0.941-1.057)	0.960 (0.836-1.103)	N/A
Gestational age	1.239(0.931-1.649)	1.287 (0.597-2.775)	5.671 (0.252-127.654)
Pre-pregnancy weight	0.982 (0.929-1.039)	1.106 (0.943-1.297)	N/A
Gestational weight gain	0.884 (0.656-1.192)	1.115 (0.594-2.090)	0.401(0.129-1.244)
Gestational DM	2.823 (0.780-10.217)	N/A	N/A
Preeclampsia	0.513 (0.165-1.596)	0.047 (0.007-0.316)	0.00 (0.000-10.185)
Parity	1.578 (0.967-2.574)	1.538 (0.435-5.440)	N/A
Birth weight	0.999 (0.998-0.999)	0.998 (0.995-1.000)	0.989 (0.976-1.002)

studies regarding APGAR score at one minute. Perhaps the placental weight is associated with APGAR score at five and ten minutes, birth weight, maternal age, gestational age, history of maternal diabetes, preeclampsia, parity, route of delivery, and fetal distress in previous studies.[8-14] Moreover, some other studies have shown histology and pathology of placenta as well as placental weight/birth weight ratio had relationship with maternal and neonatal outcomes.[8,16-21], we found no association between placental weight and APGAR score at one, five and ten minutes. Furthermore, we also found significant association between and birth weight with APGAR score at one minute. Preeclampsia was also found to be significantly associated with APGAR score at five minutes.

Strength and limitation

To our knowledge, this was the first study investigated the association between placenta weight and APGAR score of the neonates. The large sample (1,285) of mothers and neonates more than the required calculated sample allowed this study to precisely estimate the association of placenta weight and both maternal and neonatal outcomes. However, due to the retrospective nature of the present study, some missing data were observed. However, we tried to retrieve, verify and complete all data as much as possible and keep the missing data at the best minimum. In the present study, we excluded those with cesarean delivery, preterm and post-term pregnancy as well as twins, thus, the limitation for generalization of our findings to this group should be careful.

Conclusion and implication

There was no association between placental weight and APGAR score at first minute, only birth weight was significantly associated with APGAR score at first minute. Moreover, preeclampsia was also significantly related with APGAR score at fifth minute. From our findings, history of preeclampsia of the mothers was a strong factor that affect the APGAR score at five minutes. We recommend to be alert for the neonatal resuscitation in this group of neonates. For the future study, we suggest that large concurrent cohort study should be conducted to confirm our findings. Moreover, our findings were exclusive from those with vaginal delivery only, more comprehensive sample should be included in the future study.

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ORIGINAL ARTICLE

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Association of the Use of Oxytocin Induction of Labor and Neonatal Hyperbilirubinemia

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ABSTRACT

BACKGROUND
It had no consensual conclusion of the association between oxytocin induction of labor and neonatal hyperbilirubinemia.

METHODS
This is a retrospective cohort study to ascertain the association between using oxytocin induction of labor and hyperbilirubinemia in neonates. We reviewed the medical records of pregnant women delivered at Khon Kaen Hospital during the period from May 1, 2011 to July 31, 2011. Those with incomplete medical records were excluded. Data of each pregnant woman and her infant were recorded in relation to (i) maternal characteristics e.g., age, gestational age, history of oxytocin induction of labor, mode of delivery, perinatal complication composed of gestational diabetes mellitus, pregnancy induced hypertension, thyroid diseases and thalassemia; (ii) neonatal characteristics e.g., sex, birth weight, neonatal hyperbilirubinemia and onset of hyperbilirubinemia after birth.

RESULTS
A total of 1,394 pregnant women were included. Our findings suggests no statistical significant association between oxytocin induction of labor and neonatal hyperbilirubinemia (COR 0.99; 95% CI 0.69-1.42; AOR 0.473; 95% CI 0.57-1.30). Time-dependent Cox regression analysis showed positive relationships between low birth weight, high birth weight, and delivered by vacuum extraction and neonatal hyperbilirubinemia (HR 2.99; 95% CI 1.96-4.57; HR 2.78; 95% CI 1.44-5.34; HR 2.21; 95% CI 1.27-3.85, respectively) and the other factors including maternal age, preterm delivery, cesarean delivery, infant sex, perinatal complications (gestational mellitus and pregnancy induced hypertension) and thyroid diseases were not significantly associated with neonatal hyperbilirubinemia.

CONCLUSIONS
This study provides the evidence that the use of oxytocin induction of labor was not associated with neonatal hyperbilirubinemia.

Each year in the US, approximately 10.5% in newborns suffers from hyperbilirubinemia, the condition in which unconjugated serum bilirubin level of more than 30 μmol/L (1.8 mg/dL) during the first week of life.[1] Moreover, in some infants, serum bilirubin levels may excessively rise, which can cause neurotoxic and death in the newborns and lifelong neurologic sequelae in the infants who survive.[2]

Neonatal hyperbilirubinemia is found to have positive relationship with vacuum extraction, preterm delivery, low birth weight, antepartum complication, intrapartum complication, forceps delivery.[3,4,5,6,7] Regarding the use of oxytocin, various studies have been conducted to identify its association with hyperbilirubinemia, however, inconsistent finding are found and the conclusion cannot be drawn. For instance, many studies revealed that oxytocin induction increased risk of developing significant hyperbilirubinemia.[3,4,6,8,9,10] However, another study stated that there was not a significant difference in the rate of hyperbilirubinemia in those with and without oxytocin induction of labor, and it cannot conclude that oxytocin use for labour induction was responsible for increased frequency of neonatal hyperbilirubinemia.[5,11,12,13,14,15,16,17,18]

The associations are less clear between oxytocin induction and neonatal hyperbilirubinemia. To our knowledge, no study to date since the last decade has concluded the association between oxytocin and neonatal hyperbilirubinemia.[8,11,13,19,20] In addition to this, neonatal hyperbilirubinemia has been found more frequently and oxytocin was commonly use in induction labor in pregnancy. The present study, thus, aims to ascertain the relationship between neonatal hyperbilirubinemia and oxytocin induction for the awareness of harm of oxytocin usage.

METHODS

Study design and site

The study is a retrospective cohort study. Our primary objective was to explore the association between oxytocin induction and neonatal hyperbilirubinemia.

Patients

The medical records of pregnant women delivered at Khon Kaen Hospital during the period from May 1, 2011 to July 31, 2011 were reviewed. Those with incomplete medical records were excluded.

Data collection

Data of each pregnant woman and her infant were recorded in relation to (i) maternal characteristics e.g., age, gestational age, history of oxytocin induction of labor, mode of delivery, perinatal complication composed of gestational diabetes mellitus, pregnancy induced hypertension, thyroid diseases and thalassemia; (ii) neonatal characteristics e.g., sex, birth weight, neonatal hyperbilirubinemia and onset of hyperbilirubinemia after birth.

Outcome

Hyperbilirubinemia that required medical attention after birth was defined according to Bhutani nomogram.[21,22,23,24]

Statistical analysis

All recorded data were double entered. Frequency tables for all variable were generated to identify wild value. All data were cleaned before the analysis. The statistical analysis was performed by the use of statistical package. For continuous variables with an approximately normal distribution, means (±SD) are reported. For variables not distributed normally, medians and interquartile ranges are reported. Characteristics of the mothers of oxytocin exposed group and unexposed group were compared with the use of either chi-square test or Fisher's exact test for categorical variables and student's t-test or Mann-Whitney U test for continuous variables where appropriate. The risk of hyperbilirubinemia for each factor was interpreted in term of crude odds ratio (COR) with its 95% confidence interval (CI). We used binary logistic regression to identify the independent risk factors predicting hyperbilirubinemia and interpreted in term of adjusted odds ratio (AOR) with its 95% CI. Time to event analysis was also conducted using Kaplan-Meier method. To compare the Kaplan-Meier curve amongst groups, we used log rank test. Cox proportional hazard regression was used to identify the independent risk factors with the consideration of time, hazard ratios (HR) were reported in the final model.

RESULTS

During the study period, a total of 1,421 pregnant women were included in the retrospective cohort study. Twenty-seven were excluded as 26 had incomplete medical records and one was gender ambiguous baby. Of these 1,394 pregnant women, 378 were exposed to oxytocin during labor (oxytocin group), and 1,016 were in the non-oxytocin group. Characteristics of mothers and infants of the two groups are presented in Table 1. In summary, those in oxytocin group tended to had longer gestational age ($P<0.001$), less preterm delivery ($P<0.001$), more normal birth weight babies ($P=0.003$), more vaginal delivery but less cesarean delivery ($P<0.001$), for other characteristics, they tended to be similar between the two groups.

Table 1. Demographic and Clinical Characteristics of the Patients.

Maternal characteristic	Oxytocin (N = 378)	Non-oxytocin (N = 1016)	P Value
Maternal age			0.096
Median	25	25.5	
Interquartile range	20.0-29.3	21.0-30.0	
Gestational age – wk.			<0.001
Median	39	38.1	
Interquartile range	38-40	37.6-39.3	
Preterm delivery– no.(%)*	44 (11.6)	217 (21.4)	<0.001
Perinatal complication– no.(%)			
Gestational diabetes mellitus	15 (4.0)	57 (5.6)	0.218
Pregnancy induced hypertension	12 (3.2)	45 (4.4)	0.293
Thyroid diseases	1 (0.3)	12 (1.2)	0.095
Thalassemia	7 (1.9)	11 (1.1)	0.191
Neonatal characteristic			
Male infant sex– no.(%)	203 (53.7)	520 (51.2)	0.402
Birth weight -1000 gm			0.108
Median	3.1	3.1	
Interquartile range	2.8-3.4	2.8-3.4	
Birth weight– no.(%)			0.003
Normal birth weight	346 (91.5)	859 (84.5)	
Low birth weight†	24 (6.3)	123 (12.1)	
High birth weight‡	8 (2.1)	34 (3.3)	
Mode of delivery – no.(%)			<0.001
Vaginal delivery			
Spontaneous	293 (77.5)	486 (47.8)	
Vacuum extraction	38 (10.1)	32 (3.1)	
Cesarean delivery	46 (12.2)	498 (49.0)	
Disease in newborn – no.(%)			
G6PD deficiency	4 (1.1)	5 (0.5)	0.207
Hemolytic jaundice	9 (2.4)	22 (2.2)	0.808
Cholestatic jaundice	2 (0.5)	4 (0.4)	0.516

*Preterm delivery is gestational age below 37 weeks
†Low birth weight is birth weight lower than 2500 gm.
‡High birth weight is birth weight more than 4000 gm.

Table 2. Odds Ratios of Factor Potentially Associated with Hyperbilirubinemia.

	Hyperbilirubinemia (N = 167)	Non-hyperbilirubinemia (N = 1227)	Crude Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
	no. (%)					
Oxytocin induction	45 (26.9)	333 (27.1)	0.99	0.69-1.43	1.10	0.73-1.66
Preterm delivery	55 (32.9)	206 (16.8)	2.43	1.71-3.47	1.47	0.96-2.27
Mode of delivery						
Vaginal delivery						
Spontaneous	89 (53.3)	690 (56.2)	1.00	-	-	-
Vacuum	16 (9.6)	54 (4.4)	2.30*	1.26-4.19	3.02	1.61-5.65
Cesarean delivery	62 (37.1)	482 (39.3)	1.00*	0.71-1.41	1.06	0.72-1.55
Infant male sex	89 (53.3)	635 (52.0)	1.07	0.77-1.48	1.14	0.82-1.60
Birth weight						
Normal birth weight	108 (64.7)	1097 (89.4)	1.00	-	-	-
Low birth weight	49 (29.3)	98 (8.0)	5.08†	3.42-7.54	4.56	2.85-7.32
High birth weight	10 (6.0)	32 (2.6)	3.17†	1.52-6.63	3.15	1.48-6.71
Maternal age						
Normal age pregnancy	107 (64.1)	809 (65.9)	1.00‡			
Teenage pregnancy	45 (26.9)	280 (22.8)	1.22‡	0.83-1.76	1.22	0.83-1.81
Elderly pregnancy	15 (9.0)	138 (11.2)	0.82‡	0.46-1.45	0.84	0.46-1.51
Gestational diabetes mellitus	12 (7.2)	60 (4.9)	1.506	0.79-2.86	1.40	0.70-2.77
Pregnancy induced hypertension	11 (6.6)	46 (3.7)	1.810	0.92-3.57	1.08	0.52-2.25
Thyroid diseases	1 (0.6)	12 (1)	0.610	0.08-4.72	0.77	0.10-6.14
Thalassemia	0	18 (1.5)	0.879	0.86-0.90		

*Comparing with spontaneous vaginal delivery
†Comparing with normal birth weight
‡Comparing with normal age pregnancy

In the univariable analysis, the rate of neonatal hyperbilirubinemia in the oxytocin group was 26.9% (45 of 167 infants) as compared with the rate of 73.9% (122 of 167 infants) in the non-oxytocin group (COR 0.99; 95% CI 0.69-1.42; AOR 0.473; 95% CI 0.57-1.30). It shows no statistical significant association between oxytocin induction of labor and neonatal hyperbilirubinemia. Factors that were associated with a risk of significant hyperbilirubinemia included preterm delivery, vacuum extraction, low birth weight, high birth weight and thalassemia (COR 2.43; 95% CI 1.71-3.47; COR 2.30; 95% CI 1.26-4.19; COR 5.08; 95%CI 3.42-7.54; COR 3.17; 95%CI 1.52-6.63; COR 0.879; 95%CI 0.86-0.90, respectively) (Table 2).

From the logistic regression analysis, we found that the low birth weight, high birth weight and delivered by vacuum extraction was still associated with hyperbilirubinemia (AOR 4.56; 95% CI 2.85-7.32; AOR 3.15; 95% CI 1.48-6.71; AOR 3.02; 95% CI 1.61-5.65, respectively). However, we found that preterm delivery was not significantly associated with neonatal hyperbilirubinemia (AOR 1.47; 95% CI 0.96-2.27).

Figure 2 presents the Kaplan Meier of onset of hyperbilirubinemia. Time-dependent Cox regression analysis showed positive relationships between low birth weight, high birth weight, and delivered by vacuum extraction and neonatal hyperbilirubinemia (HR 2.99; 95% CI 1.96-4.57; HR 2.78; 95% CI 1.44-5.34; HR 2.21; 95% CI 1.27-3.85, respectively) (Table 3), However, the other factors were found not to have significant association with neonatal hyperbilirubinemia.

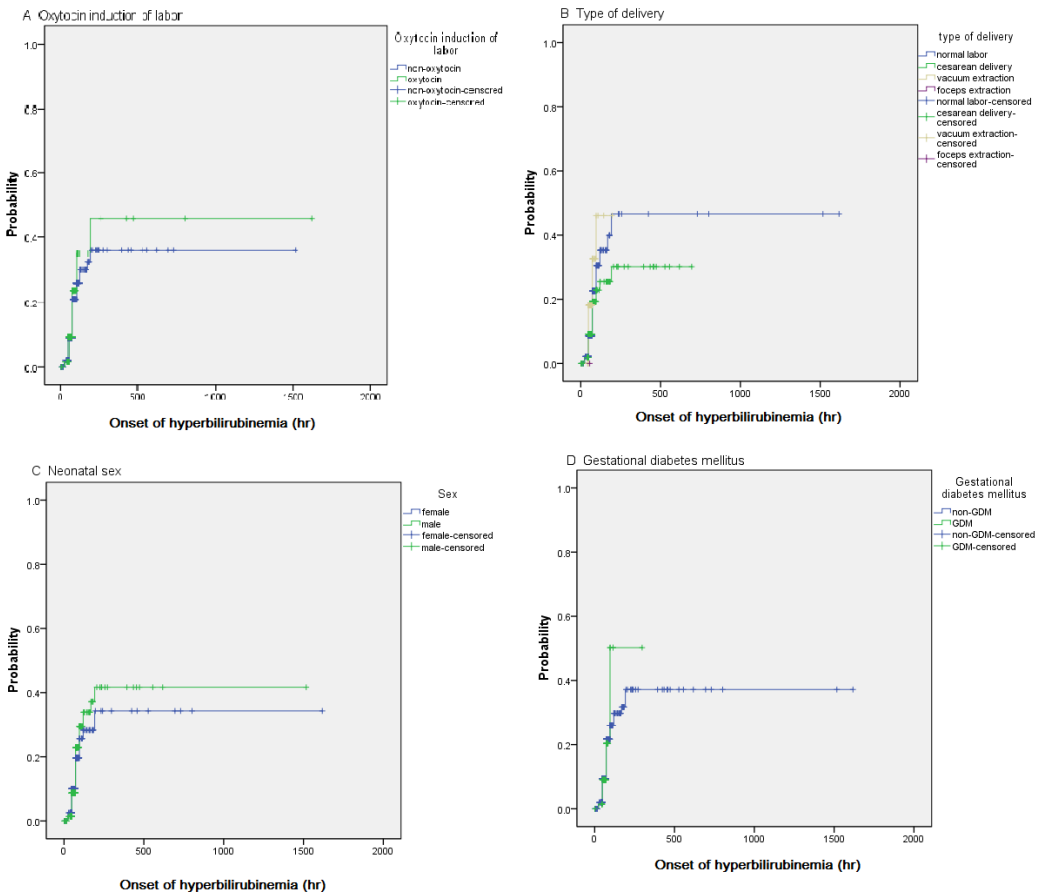

Figure 2. Kaplan-Meier Estimates for the Onset of Hyperbilirubinemia
Panel A shows the Kaplan-Meier one minus survival curves for patients with neonatal hyperbilirubinemia and use or non-use oxytocin induction of labor. Panel B shows the Kaplan-Meier one minus survival curves for patients with neonatal hyperbilirubinemia and type of delivery. Panel C shows the Kaplan-Meier one minus survival curves for patients with neonatal hyperbilirubinemia and neonatal sex. Panel D shows the Kaplan-Meier one minus survival curves for patients with neonatal hyperbilirubinemia and gestational diabetes mellitus.

DISCUSSION

This study provides evidence against a causal relation between oxytocin induction of labor and neonatal hyperbilirubinemia. Low birth weight, high birth weight and delivered by vacuum extraction were significant independent risk factors for neonatal hyperbilirubinemia. The others including maternal age, preterm delivery, cesarean delivery, infant sex, perinatal complications (gestational mellitus and pregnancy induced hypertension) thyroid diseases, and thalassemia were not independently associated with neonatal hyperbilirubinemia. The results of binary logistic regression and Cox regression analysis in our study were similar which suggested that the onset of neonatal hyperbilirubinemia occurred at the same rate over time.

Comparison with other studies

As the number of studies in this field were relatively small, so fare, we found only one previous study that

Table 3. Hazard ratio of Factor Potentially Associated with Hyperbilirubinemia.

	Hazard ratio	95% confidence interval
Oxytocin induction	1.15	0.78-1.67
Preterm delivery	1.41	0.94-2.10
Mode of delivery		
Vaginal delivery		
Spontaneous	Reference	-
Vacuum extraction	2.21*	1.27-3.85
Cesarean delivery	0.98*	0.69-1.38
Infant male sex	1.05	0.77-1.42
Birth weight		
Normal birth weight	Reference	-
Low birth weight	2.99†	1.96-4.57
High birth weight	2.78†	1.44-5.34
Maternal age		
Normal age pregnancy	Reference	-
Teenage pregnancy	1.19‡	0.84-1.70
Elderly pregnancy	0.79‡	0.46-1.37
Gestational diabetes mellitus	1.17	0.64-2.14
Pregnancy induced hypertension	1.03	0.54-1.94
Thyroid diseases	0.93	0.13-6.68

*Comparing with spontaneous vaginal delivery
†Comparing with normal birth weight
‡Comparing with normal age pregnancy

might match with our findings. In one previous prospective cohort study with as many as 14,458 pregnant women that were approached for interview following delivery during 3 years period (Aug 8, 1977 to March 3, 1980) to identify the association between maternal characteristics and neonatal hyperbilirubinemia, the findings were similar to our present study with the negative relationship between the use of oxytocin and hyperbilirubinemia.[25] In that study, the number of sample and study design made it seemed to be reliable, however, there were some limitation in term of analysis. From our binary logistic regression and Cox regression analysis, our findings went into the same direction with that previous study and we added that onset of neonatal hyperbilirubinemia occurred relatively constantly over time.

Strengths and weaknesses of the study

This retrospective analysis is accompanied by some limitations; this study was retrospective and thus subject to unanticipated biases in case selection due to the use or nonuse of oxytocin in the mothers was not randomly assigned but depended solely on the decision of the attending physician. In term of sample size, we included up to 1,300 mothers and infants, however, the sample size was relatively small due to the little effect of oxytocin on hyperbilirubinemia.

Conclusion and clinical implication

In conclusion, oxytocin induction during labor or delivery was not associated with neonatal hyperbilirubinemia. The factors that increased risk of neonatal hyperbilirubinemia were low birth weight, high birth weight and vacuum extraction. With the high risk of hyperbilirubinemia in those with low birth weight, high birth weight and vacuum extraction, we suggests the close monitoring and periodically follow-up of bilirubin levels in this group of the infants. In the future study, cohort study with larger sample to establish the relationship with oxytocin and hyperbilirubinemia should be conducted.

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ORIGINAL ARTICLE

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Peritonitis in End Stage Renal Disease Patients with Diabetes and Non-Diabetes Post Continuous Ambulatory Peritoneal Dialysis: A Retrospective Cohort Study

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ABSTRACT

BACKGROUND
It has no conclusion about the rate of peritonitis in diabetic and non-diabetic end-stage renal disease (ESRD) status post continuous ambulatory peritoneal dialysis (CAPD).

METHODS
This is a retrospective cohort study that we have studied patient with ESRD on CAPD, compared diabetes and non-diabetes group for peritonitis. We have reviewed medical records from medical wards at Khon Kaen Hospital during the period from January 1, 2009 to March 30, 2012 to collect all ESRD on CAPD's medical records. Without exclusion, the patients were separated into underlying diabetic group and non-diabetic group

RESULTS
A total of 274 episodes of ESRD patients with CAPD, 154 episodes (56.2%) were in non-diabetic group and 120 episodes (43.8%) were in diabetic group. There was not associated with significantly increased in peritonitis (43.8% and 56.2%, respectively; adjusted odds ratio [AOR], 0.51; 95 % CI 0.23-1.15). From the logistic regression analysis, higher serum albumin was associated with less rate of peritonitis (AOR 0.37; 95 % CI 0.22-0.63). On the other hand, higher capillary blood sugar was associated with higher rate of peritonitis (AOR 1.01; 95 % CI 1.01-1.02). From the log rank test, it found that higher age, coexisted heart diseases, lower systolic blood pressure, lower albumin, higher serum creatinine and lower hemoglobin had significant association with higher mortality rate (P=0.03, 0.04, 0.04, 0.02, 0.001, 0.02, respectively). Moreover, higher blood urea nitrogen had significant association with higher mortality rate (P<0.001). From the Cox proportional hazard regression, it found that lower serum albumin was significant association with peritonitis (hazard ratio [HR] 0.47; 95 % CI 0.29-0.74). Furthermore, it showed that higher blood urea nitrogen and lower serum albumin related to increasing in the rate of death from peritonitis (HR 1.01; 95 % CI 1.01-1.02, HR 0.57; 95 % CI 0.39-0.84, respectively)

CONCLUSION
There was no association between diabetes and the rate of peritonitis. Additionally, we found that the risk of peritonitis was increased in those with lower serum albumin. In addition, higher blood urea nitrogen and lower serum albumin were significantly associated with higher mortality rate.

End-stage renal disease (ESRD) is the end-stage of severe irreversible chronic renal insufficiency, the patients have the poor function of glomerular infiltration and require hemodialysis or kidney transplantation.[1] The causes of ESRD are various but the most common cause is diabetes mellitus (DM).[2] In some countries, DM is the single most important cause, for ESRD.[3] In USA, there were 116,000 new case of ESRD in 2009 with the prevalence about 571,414 in USA in 2009.[4] In Europe, the incidence of ESRD was 116 per 1 million population in 2007, 110 and 109 per 1 million in Australia and New Zealand in 2007.[5] Both incidence and prevalence of ESRD are rising in the developing countries.[6]

The treatment of choice of ESRD is renal replacement therapy comprising hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), hemofiltration and renal transplantation.[1] Usually, the first step of treatment is peritoneal dialysis and switch to hemodialysis then end up by renal transplantation.[7] Nonetheless, complications of CAPD such as peritonitis and death are unavoidable.[8,9,10] Moreover, many factors attribute to those complication including their underlying disease (e.g., cardiovascular diseases and diabetes)[11] and some laboratory values (e.g., blood urea nitrogen, serum creatinine, serum albumin, capillary blood sugar, hemoglobin).[8] peritoneal dialysis-related peritonitis did not differ substantially between those with diabetes and non-diabetes.[1,8] However, another study, it revealed that diabetes appeared to more mortality and morbidity.[12,13]

In relation to diabetes, previous two studies found that the rate of CAPD peritonitis associated with higher incidence of tunnel infection of CAPD and leaded to peritonitis.[14] Furthermore, peritonitis were more frequently found in those with type 2 diabetes comparing with those without diabetes and type 1 diabetes significantly.[15] We found that findings from these studies are still controversial whether the rate of peritonitis among those with diabetes and ESRD on CAPD is higher than those with non-diabetes. Thus, we conducted a retrospective cohort study to answer this question. Moreover, outcome regarding mortality rate (death), length of stay at hospital, uremic encephalopathy, acute respiratory failure, pneumonia, urinary tract infection and organisms cultured during peritonitis that may relate to diabetes were also collected.

METHODS

Study design

This is a retrospective cohort study that aims to compare peritonitis in ESRD with DM and non-DM post CAPD as well as the other outcomes and complications followed CAPD.

Patients and record reviewing

The hospital records of patients with ESRD at Khon Kaen Hospital between January 2009 and March 2012 were all included into the study, and were all reviewed. ESRD was defined as severe irreversible kidney damage (as measured by the level of proteinuria) that affects deterioration in kidney function, glomerular filtration rate, to less than 15 ml per minute/1.73 m^2.[1] We excluded out-patients and ESRD patients without CAPD from all episodes of visit of ESRD patients.

Outcomes

The study objectives primarily focus on peritonitis. Peritonitis was defined as the inflammation of the peritoneal lining the abdominal cavity as the result of infectious processes.[16] The diagnosis of peritonitis was initiated in those with the criteria of white blood count of 100 cells/mm^3 or more with with 50% of polymorphonuclear cells as well as the clinical of abdominal pain and tenderness together with cloudy appearance of peritoneal drainage. Additionally, mortality, length of hospital stay, uremic encephalopathy, acute respiratory failure, pneumonia, urinary tract infection and organisms cultured during peritonitis were congregated as the secondary objectives.

Data collection

Variables included sex, age, comorbidities (hypertension, coexisted heart disease), systolic blood pressure, diastolic blood pressure, blood urea nitrogen (BUN), serum creatinine (Cr), serum albumin, capillary blood sugar and hemoglobin and organisms cultured during peritonitis were verified, abstracted from the hospital records and collected.

Statistical analysis

All variables were recorded onto spreadsheet. They were double entered. They were cleaned for duplicated entry and were verified for their correctness. After that they were imported statistical package for social science (SPSS) version 18.0. Frequency tables were generated for all variables. Wildcard variables were detected and corrected. For descriptive statistics, categorical variables were summarized as number and percent (no. (%)). For scale variables, mean and standard deviation (SD) were used if they were normally distributed while median and interquartile range (IQR) were used if there were non-normally distributed. For inferential statistics, either chi-square or Fisher's exact test was used for categorical variables. T-test and Mann-Whitney U test were used for normally and non-normally distributed variables, respectively. For risk interpretation, crude odds ratio (COR) was used. Adjusted odds ratio (AOR) was identified from the logistic regression analysis. Kaplan-Meier functions

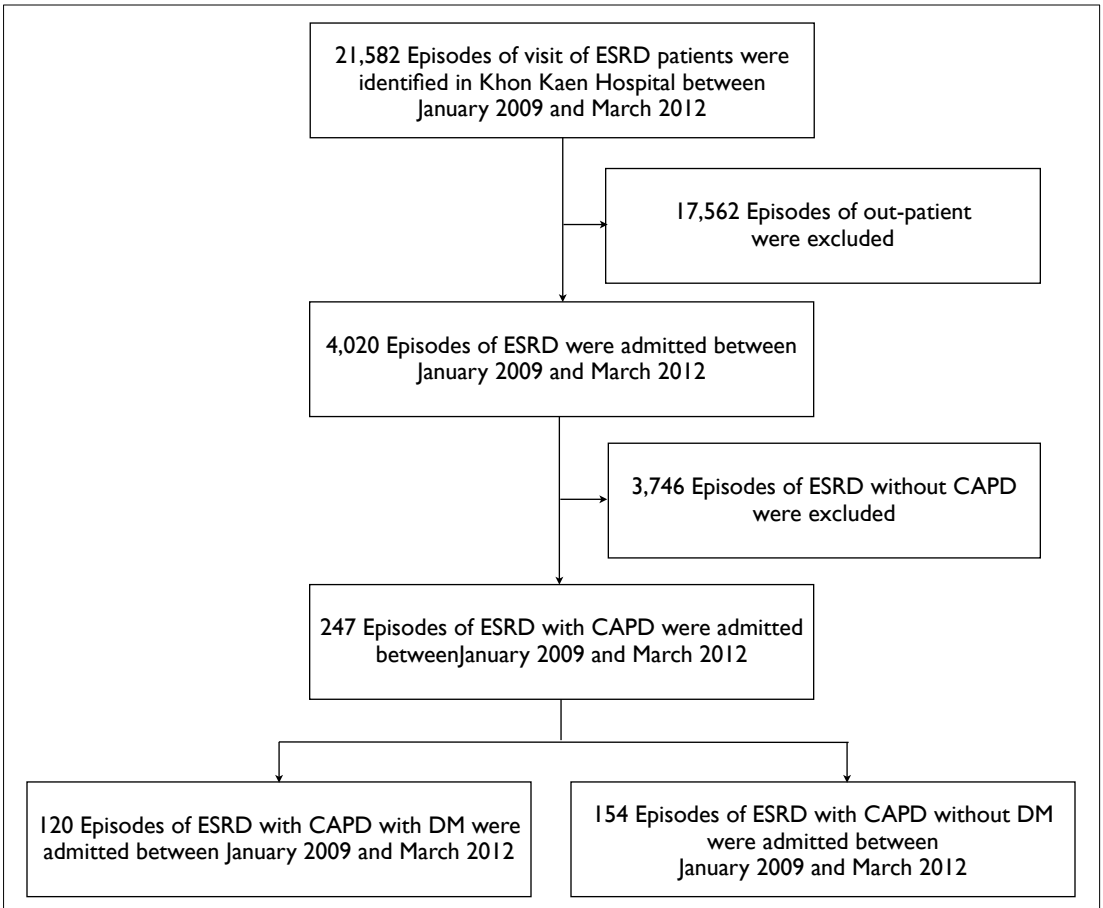

Figure 1. Flow Chart of Admission and Study Completion.

were created. Log rank test was used to test for two or more different survival or time-to-event curves. Finally, Cox proportional hazard regression was used and hazard ratio (HR) were identified.

RESULTS

A total of 21,582 episodes of ESRD between January 2009 and March 2012 were screened for the study, 17,562 episodes of ESRD out-patient were excluded. 4,020 episodes of ESRD in-patient were included and 3,746 episodes of non-CAPD patients among this group were selectively excluded. Of the remaining 274 episodes of in-patient with ESRD on CAPD were included in this study, 154 episodes were from patients with diabetes and 120 episodes were from non-diabetic patients (Figure 1).

Mostly they were male with the average age of 53 years old. Hypertension was commonly found as the underlying disease in more than 85% of the patients. Patients who were included in this study had a baseline median blood pressure of 143/78 mmHg. From the routine laboratory baseline results, they showed that median blood urea nitrogen (BUN), serum creatinine (Cr) and capillary blood sugar were 104.0, 12.0 and 155.0 mg/dl, respectively. The medians of serum albumin (Alb) and hemoglobin (Hb) were 2.6 and 7.0 g/dl, respectively.

Between the two groups, those with diabetes were likely to be female and older (P=0.003 and <0.001, respectively) (Table 1). They tended to have higher proportion of episode of patient with hypertension (P<0.001), higher capillary blood sugar (P<0.001) and higher hemoglobin (P=0.035). They were inclined to have higher proportion of episode of patient with heart diseases (P=0.668), higher systolic blood pressure (SBP) (P=0.195), higher diastolic blood pressure (DBP) (P<0.001), higher BUN (P=0.007), higher Cr (P<0.001) and higher Alb (P=0.073).

As Table 2, it shows the outcome, comparison in the amount of episode between diabetic and non-diabetic group in ESRD on CAPD patients that it

Table 1. Characteristics of the Patients.

Characteristic	End stage renal disease without diabetes	End stage renal disease with diabetes	P Value
Number of episodes (%)	154 (56.2)	120 (43.8)	NA
Number of patients (%)	130 (55.1)	106 (44.9)	NA
Male sex-no. (%)	95 (61.7)	52 (43.3)	0.003
Age-Yr	49.2±16.6	57.6±10.8	<0.001
Comorbidities-no. (%)			
Hypertension	101 (65.6)	104 (86.7)	<0.001
Coexisted heart diseases	22 (14.3)	15 (12.5)	0.668
Systolic blood pressure (mmHg)			0.195
Median	146	140.5	
Interquartile range	128.0-160.0	121.0-160.8	
Diastolic blood pressure (mmHg)	82.9±17.6	74.6±17.4	<0.001
Blood urea nitrogen (mg/dl)			0.007
Median	116.5	92.5	
Interquartile range	61.8-185.2	56.3-139.3	
Serum creatinine (mg/dl)			<0.001
Median	14.1	10.7	
Interquartile range	9.4-24.6	7.2-16.0	
Serum albumin (g/dl)	2.7±0.7	2.5±0.7	0.073
Capillary blood sugar (mg/dl)			<0.001
Median	131.5	179.0	
Interquartile range	109.5-179.5	134.3-237.0	
Hemoglobin (g/dl)	6.9±1.9	7.4±1.9	0.035

Table 2. Outcomes of the Present Cohort.

Outcome	End stage renal disease without diabetes	End stage renal disease with diabetes	P Value
Peritonitis-no. (%)	27 (17.5)		0.343
Death-no. (%)	35 (22.7)	33 (27.5)	0.364
Length of hospital stay-days			0.272
Median	6	5	
Interquartile range	4-12	3-10	
Uremic encephalopathy-no. (%)	16 (10.4)	12 (10.0)	0.916
Acute respiratory failure-no. (%)	44 (28.6)	29 (24.2)	0.413
Pneumonia-no. (%)	28 (18.2)	19 (15.8)	0.609
Urinary tract infection-no. (%)	18 (11.7)	18 (15.0)	0.421

Table 3. Organisms Cultured during Peritonitis.

Organisms	Peritonitis without diabetes *n=27*	Peritonitis with diabetes *n=16*
Staphylococcus spp.	4	2
Streptococcus spp.	1	0
Enterococcus spp.	1	0
Enterobacter spp.	1	0
Escherichia coli	0	1
Acinetobacter baumannii	1	3
Klebsiella pneumoniae	1	0
Candida albicans	1	1
Unknown*	17	9

*Unknown: no growth

Table 4. Odds Ratios of Factor Predicting Peritonitis.

Factor	Crude odds ratio	95 % confidence interval	Adjusted odds ratio	95 % confidence interval
Age >53 Yr.	1.57	0.77-3.21	2.06	0.93-4.55
Male sex	1.39	0.68-2.85	1.46	0.69-3.07
Diabetes	0.72	0.35-1.48	0.51	0.23-1.15
Hypertension	0.74	0.34-1.61	0.82	0.37-1.84
Coexisted heart diseases	1.30	0.48-3.41	1.66	0.61-4.53
Systolic blood pressure <143 mmHg	1.68	0.83-3.44	0.60	0.24-1.49
Diastolic blood pressure	NA	NA	1.00	0.97-1.03
Blood urea nitrogen	NA	NA	1.00	0.99-1.00
Serum creatinine >12 mg/dl	0.84	0.42-1.69	1.45	0.55-3.78
Serum Albumin	NA	NA	0.37	0.22-0.63
Capillary blood sugar	NA	NA	1.01	1.01-1.02
Hemoglobin	NA	NA	0.82	0.66-1.01

tended to have no significant difference in peritonitis, mortality rate, length of hospital stay and uremic encephalopathy, acute respiratory failure, pneumonia and urinary tract infection (P=0.343, 0.364, 0.272, 0.916, 0.413, 0.609, respectively). There were 43 episodes of peritonitis, from the culture, the most common two organisms found positive from the peritoneal fluid culture respectively were *Staphylococcus spp. and Acinetobacter baumannii* (Table 3). *Staphylococcus* spp. was most often organism found in diabetic group (14.8%). On the contrary, *Acinetobacter baumannii* was mostly found in non-diabetic group (18.8%).

Interpreting the risk using COR, age, sex, diabetes, hypertension, coexisted heart diseases, creatinine, SBP were not associated with peritonitis (P>0.05) (Table 4). However, from the logistic regression analysis, higher Alb was associated with less rate of peritonitis (AOR 0.37; 95% CI 0.22-0.63). On the other hand, higher capillary blood sugar was associated with higher rate of peritonitis (AOR 1.01; 95% CI 1.01-1.02).

From the log rank test (Figure 2.), it found that higher albumin at the cut point of 2.6 mg/dl had no significant association with lower rate of peritonitis (P=0.06)

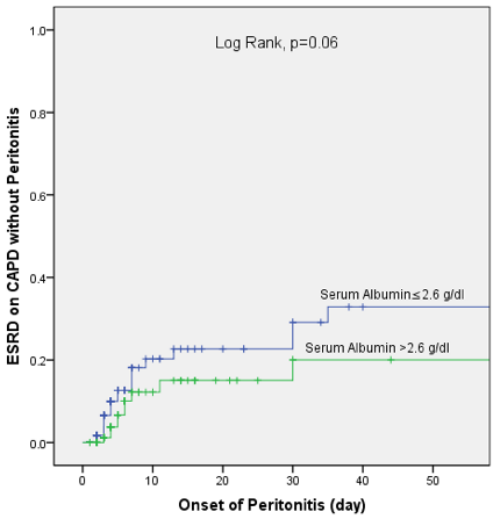

Figure 2. Kaplan-Meier Estimates for the Onset of Peritonitis
Figure 2 shows the Kaplan-Meier of time-to-event curves for end-stage renal disease (ESRD) on continuous ambulatory peritoneal dialysis (CAPD) patients with peritonitis and serum albumin≤2.6 mg/dl or serum albumin>2.6 mg/dl.

From the log rank test (Figure 3.), it found that higher age, coexisted heart diseases, lower systolic blood pressure, lower albumin,higher Cr and lower hemoglobin had significant association with higher mortality rate (P=0.03, 0.04, 0.04, 0.02, 0.001, 0.02, respectively). Moreover, higher BUN had significant association with higher mortality rate (P<0.001).

From the Cox proportional hazard regression, it found that lower serum albumin was significant association with peritonitis (HR 0.47; 95% CI 0.29-0.74). Furthermore, it showed that higher blood urea nitrogen and lower serum albumin related to increasing in the rate of death (HR 1.01; 95% CI 1.01-1.02, HR 0.57; 95% CI 0.39-0.84, respectively) (Table 5).

RESULTS

Important findings

In this retrospective cohort study of ESRD on CAPD patients, it shows that the rate of peritonitis does not increase among diabetic group. We found that it has no significant differences in the mortality rate, length of hospital stay and rate of uremic encephalopathy, acute respiratory failure, pneumonia and urinary tract infection among diabetic group as compared with non-diabetic group. From the Kaplan-Meier estimates of the onset of peritonitis shows that higher serum albumin does not decrease the rate of peritonitis. In relation to death, the Kaplan-Meier shows that patients with younger age, no coexisted heart diseases, systolic blood pressure<143 mmHg, serum albumin>2.6 g/dl, BUN<104 mg/dl, serum Cr<12 mg/dl and hemoglobin>7 g/dl statistically significantly obtain higher survival rate. Additionally, from the Cox proportional hazard regression analysis, we found that higher serum albumin is the protective factors of peritonitis. We noticed that higher BUN and lower serum albumin are associated with higher mortality rate in ESRD on CAPD patients.

Strengths and limitation

This is the only study to our knowledge that demonstrates the association between various factors and peritonitis as well as mortality using Kaplan Meier and Cox proportional hazard regression with significant number of included patients even the amount of patients with ESRD on CAPD was relatively scarce. However, there are several limitations to our study. One of these is the potential for unknown confounders that were not recorded in the database. This missing data then could not be put into the analysis for risk factor identification. To the precise accurate of the relationship between diabetes and peritonitis in patients with ESRD on CAPD, the size of the sample should be up to 2,600 patients.

Comparison with other studies

This study supports the evidence from the previous study in Turkey with 109 patients that found the rates of peritonitis in those with ESRD were 0.23 and 0.22 episode/person-year in the diabetic and non-diabetic group respectively with no significant differences.[17] Regarding other factors, hypoalbuminemia is associated to the higher rate of peritonitis and death. This findings was similar to the previous two studies; a Mexican study in 2001, a Nepalese study in 2010 and that all found lower blood albumin level was

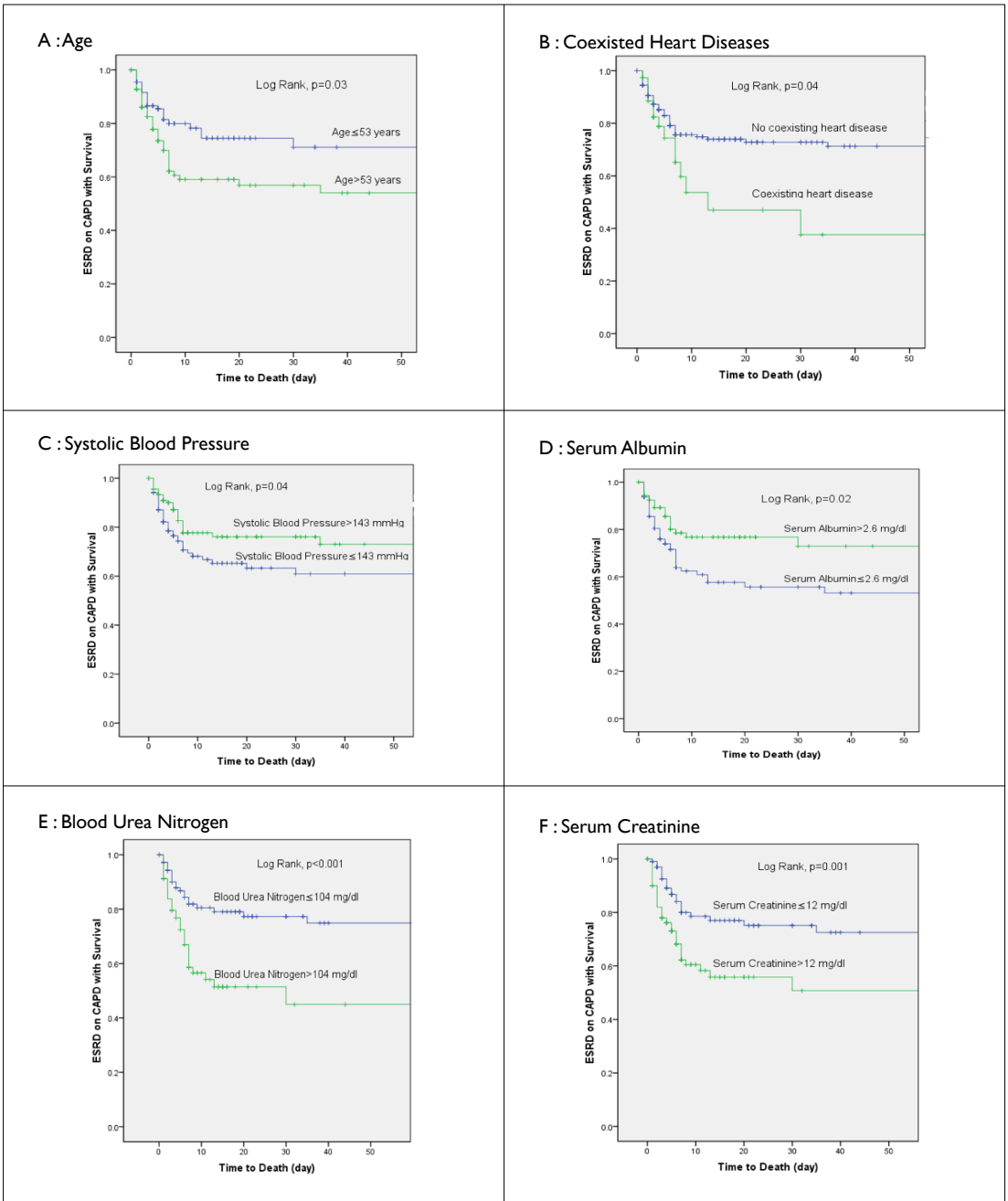

Figure 3. Kaplan-Meier Estimates for the Time to Death.
Panel A shows the Kaplan-Meier survival curves for end-stage renal disease (ESRD) patients on continuous ambulatory peritoneal dialysis (CAPD) with age<53 years or >53 years. Panel B shows the Kaplan-Meier survival curves for ESRD patients on CAPD with coexisted heart diseases or non-coexisted heart diseases. Panel C shows the Kaplan-Meier survival curves for ESRD patients on CAPD with systolic blood pressure<143 mmHg or systolic blood pressure>143 mmHg. Panel D shows the Kaplan-Meier survival curves for ESRD patients on CAPD with serum albumin<2.6 g/dl or albumin>2.6 g/dl. Panel E shows the Kaplan-Meier survival curves for ESRD patients on CAPD with blood urea nitrogen<104 mg/dl or blood urea nitrogen>104 mg/dl. Panel F shows the Kaplan-Meier survival curves for ESRD patients on CAPD with serum creatinine<12 mg/dl or serum creatinine>12 mg/dl. Panel G shows the Kaplan-Meier survival curves for ESRD patients on CAPD with hemoglobin<7 g/dl or hemoglobin>7 g/dl.

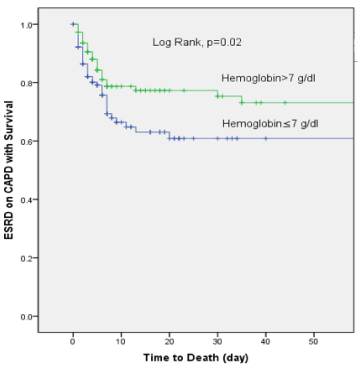

Figure 3. (Continued.)

associated with higher peritonitis and mortality respectively.[18,19,20] In relation to the infectious organism. the most common organism found in the current study was *Staphylococcus* spp. relevant to outcome of most studies such as a study from the USA in 283 patients in 1996 and a study from the UK with 168 patients in 2009.[21,22] About sex and age of the patient, our study revealed that sex and onset age of peritonitis was not associated to mortality rate according to several study as the patients in those studies were relatively older comparing to the patients in our study.[19,23,24,25], But there are still some study conflict our result that sex is associated to mortality rate.[25]

Conclusion and implication

In conclusion, there was no association between diabetes and peritonitis in patients with ESRD on CAPD. However, the accurate estimation of the relationship needs larger sample size to distinguish the outcome between two groups. In the future, the study with larger sample size of prospective cohort study should be conducted for more precise estimation of the results.

Table 5. Cox Proportional Hazard Regression.

	Peritonitis		Death	
	Hazard ratio	95 % Confidence interval	Hazard ratio	95 % Confidence interval
Age >53 Yr.	1.52	0.73-3.13	1.67	0.97-2.85
Male sex	1.20	0.62-2.35	1.16	0.69-1.96
Diabetes	0.53	0.24-1.14	1.18	0.68-2.06
Hypertension	0.82	0.39-1.74	0.87	0.49-1.55
Coexisted heart diseases	1.38	0.54-3.57	1.52	0.82-2.84
Systolic blood pressure ≤143 mmHg	0.97	0.40-2.35	1.08	0.55-2.13
Diastolic blood pressure	1.00	0.97-1.02	0.99	0.97-1.01
Blood urea nitrogen	1.00	0.99-1.01	1.01	1.01-1.02
Serum creatinine >12 mg/dl	1.85	0.68-4.99	1.10	0.53-2.30
Serum albumin	0.47	0.29-0.74	0.57	0.39-0.84
Capillary blood sugar	1.00	1.00-1.01	1.00	1.00-1.01
Hemoglobin	0.88	0.72-1.07	1.07	0.93-1.23

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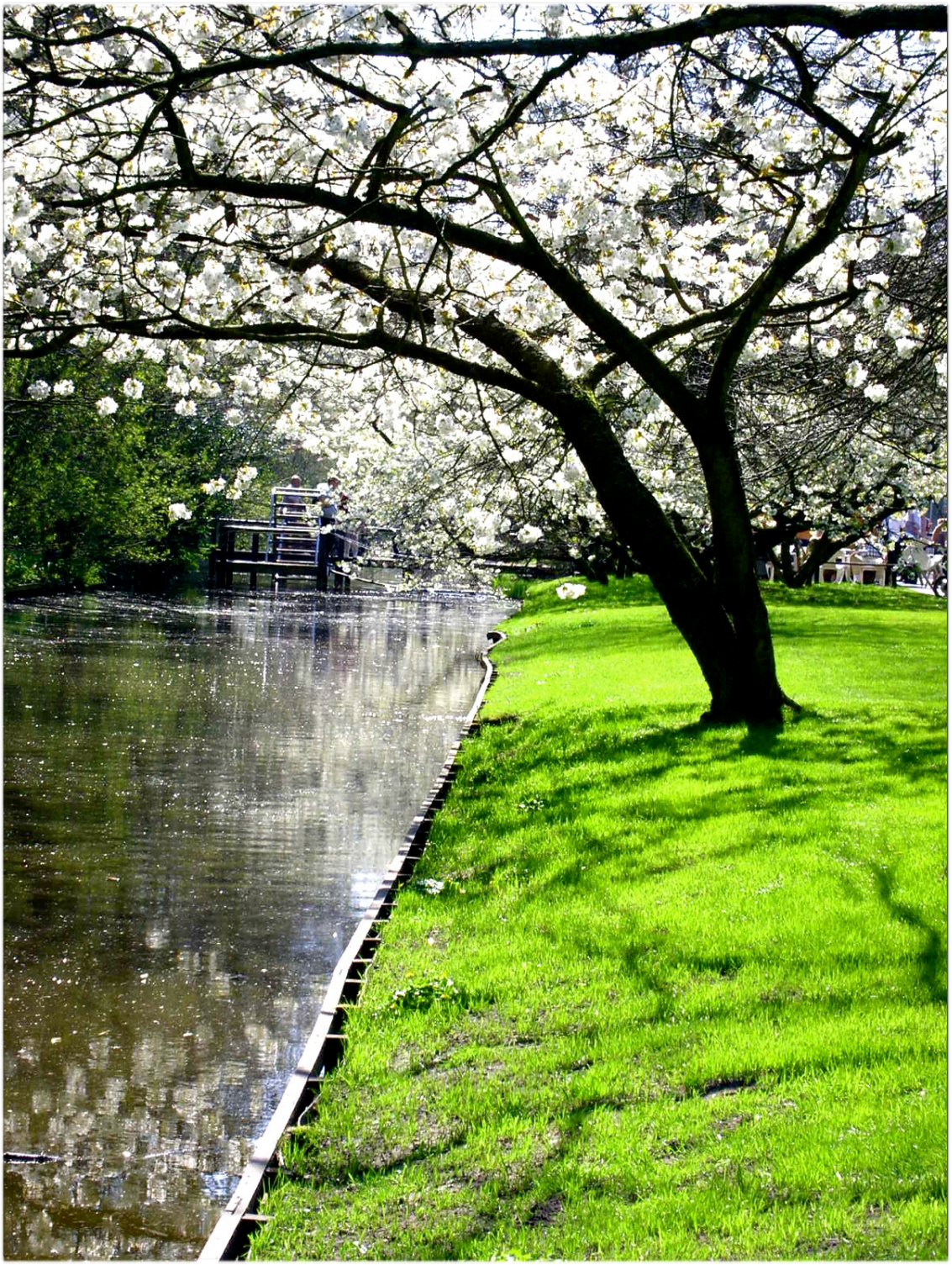

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ORIGINAL ARTICLE

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Validity of Predictors of Mortality and Rebleeding in Patients Suspected of Acute Upper Gastrointestinal Bleeding

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ABSTRACT

BACKGROUND
Effective management of upper gastrointestinal bleeding (UGIB) in relation to hospital admission and timing of the endoscopic procedures relies on the application of clinical risk scores. Rockall risk and Glasgow-Blatchford scores are still the most acceptable in common practice for predicting outcomes such as re-bleeding and mortality, nonetheless, they are still controversial.

METHODS
This is a retrospective cohort with diagnostic study to identify the validity of predictors for predicting mortality and rebleeding in patients suspected of acute UGIB in Department of Surgery, Khon Kaen Hospital during the period from May 2010 to May 2012 and we excluded patients with other principal diagnosis rather than acute UGIB and lower gastrointestinal bleeding. We collected variables regarding patients characteristics and laboratory results. Risks were interpreted using crude and adjusted odds ratio as well as hazard ratio. The modified Rockall scores were created based on the original clinical Rockall score added up with factors with the association with outcomes from Cox proportional hazard regression. The modified scores were tested for their performance in relation to sensitivity, specificity, likelihood ratio and area under the receiver operating characteristic (ROC) curve.

RESULTS
A total of 397 patients were included. Death and re-bleeding occurred in 148 and 165 cases, respectively. From the Cox's proportional hazard regression, red bright hematemesis (hazard ratio (HR) 2.02; 95% confidence interval (CI), 1.10 to 3.70), diabetes mellitus (HR 2.20; 95% CI, 1.22 to 3.97), Blood urea nitrogen (HR 1.02; 95% CI, 1.01 to 1.02) were found to be associated with mortality while previous UGIB (HR 2.03; 95% CI, 1.22 to 3.39), Hematocrit between 25.0% and below 30.0% (HR 2.01; 95% CI, 1.20 to 3.39), Packed red blood cell (HR 2.09; 95% CI, 1.14 to 3.84) and Fresh frozen plasma (HR 1.04; 95% CI, 1.01 to 1.07) were found to be associated with re-bleeding. The modified Rockall score was superior to the Rockall score for predicting of mortality (AUC 0.736 vs. 0.723) and re-bleeding (AUC 0.617 vs. 0.535).

CONCLUSION
Modified rockall scores had higher accuracy than the original clinical rockall score for predicting mortality and re-bleeding in patients suspected acute UGIB.

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a common presentation to emergency departments with an incidence of approximately 45–172/100 000 people per year in many European countries.[1-5] UGIB, which is defined as a bleeding above the ligament of Treitz, is found more frequent in older male patients and peptic ulcers is one of the leading cause of UGIB.[2,5,6] Effective management of UGIB in relation to hospital admission and timing of the endoscopic procedures relies on the application of clinical risk scores.[6]

Existing risk scores including Rockall score and Glasgow-Blatchford scores aim to stratify patients regarding their risks. Rockall score has been mentioned in previous literatures;[7-12] its scoring system uses both clinical criteria (e.g., age, comorbidity and presence of shock) and endoscopic findings (e.g, diagnosis and stigmata of recent hemorrhage) to identify patients at risk of adverse outcomes such as re-bleeding and mortality.[13] For Glasgow-Blatchford scores, in contrary, are based on presentation of melena, syncope, underlying diseases such as hepatic disease and cardiac failure, systolic blood pressure (SBP), pulse rate (PR), hemoglobin (Hb) and blood urea nitrogen (BUN).[14] However, the performance of these scoring systems is still unsatisfactory and controversial.[18] For instance, in one study stated that Rockall scoring system provided an acceptable tool to predict the risk of death, but performs poorly for endpoints of re-bleeding and surgical procedures[18] while another found that clinical Rockall Score without endoscopy may be a useful prognostic indicator for both re-bleeding and mortality.[19]

Many studies later tried to add more predictor such as condition of hemorrhagic shock, heart failure, infection, diastolic blood pressure on admission, Hb and red blood cell count on admission and during treatment in hospital in patients with acute UGIB admitted to the medical intensive care unit.[15] The new scoring systems were also created; PNED and ANNs scores are claimed to have a better predictive property over Rockall score regarding death especially in those with non-variceal bleeding.[16,17] Nonetheless, to date, the Rockall risk scoring system and Glasgow-Blatchford scores are still the most acceptable in common practice, and because of many controversies, we, thus, aimed to identify factors and create new scoring system that might associated and help predict outcomes of treatment in term of death and re-bleeding in the patients suspected of UGIB.

METHODS

Study design

This is a retrospective cohort with diagnostic study that aimed to create the new scoring systems and assess validity of the new scoring system for prediction of mortality and rebleeding after admission for those suspected with acute UGIB.

Patients and medical record review

We retrospectively studied all patients who were admitted to Department of Surgery of Khon Kaen Hospital with symptoms of red bright hematemesis, coffee hematemesis, melena or hematochezia and were suspected of having acute UGIB during from May 2010 until May 2012. We excluded patients with other principal diagnosis rather than acute UGIB and lower gastrointestinal bleeding.

Outcomes

The primary outcome was the hospital mortality which was defined as death occurred during hospital stay. Secondary outcome was re-bleeding as defined by presence of hemodynamic instability and decrease in serum hematocrit≥3% and required for packed red blood cell.

Collected variable

All medical records of the patients were reviewed. We recorded factors including age, sex, clinical presentation (red bright hematemesis, coffee ground hematemesis, melena and hematochezia), comorbidity (ischemic heart disease (IHD), stroke, valvular heart disease (VHD), hypertension (HT), chronic kidney diseases (CKD), liver cirrhosis, malignancy, diabetes mellitus (DM)), previous smoking, previous alcohol drinking, previous UGIB, previous esophagogastroduodenoscopy (EGD), current medication (antiplatelets, anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids and herb), SBP, diastolic blood pressure (DBP), PR, body temperature (BT), clinical Rockall score, laboratory (BUN, creatinine, Hb, Hematocrit (Hct), white blood cell (WBC), platelet count, prothrombin time (PT), partial thromboplastin time (PTT) and International Normalized Ratio (INR)), treatment (vitamin K, omeprazole, somatostatin, Sengstaken-Blakemore tube, packed red blood cell (PRC) and fresh-frozen plasma (FFP)), length of hospital stay, gastroscopic findings and diagnosis (time to endoscopy, endoscopic findings, diagnosis and endoscopy treatment)

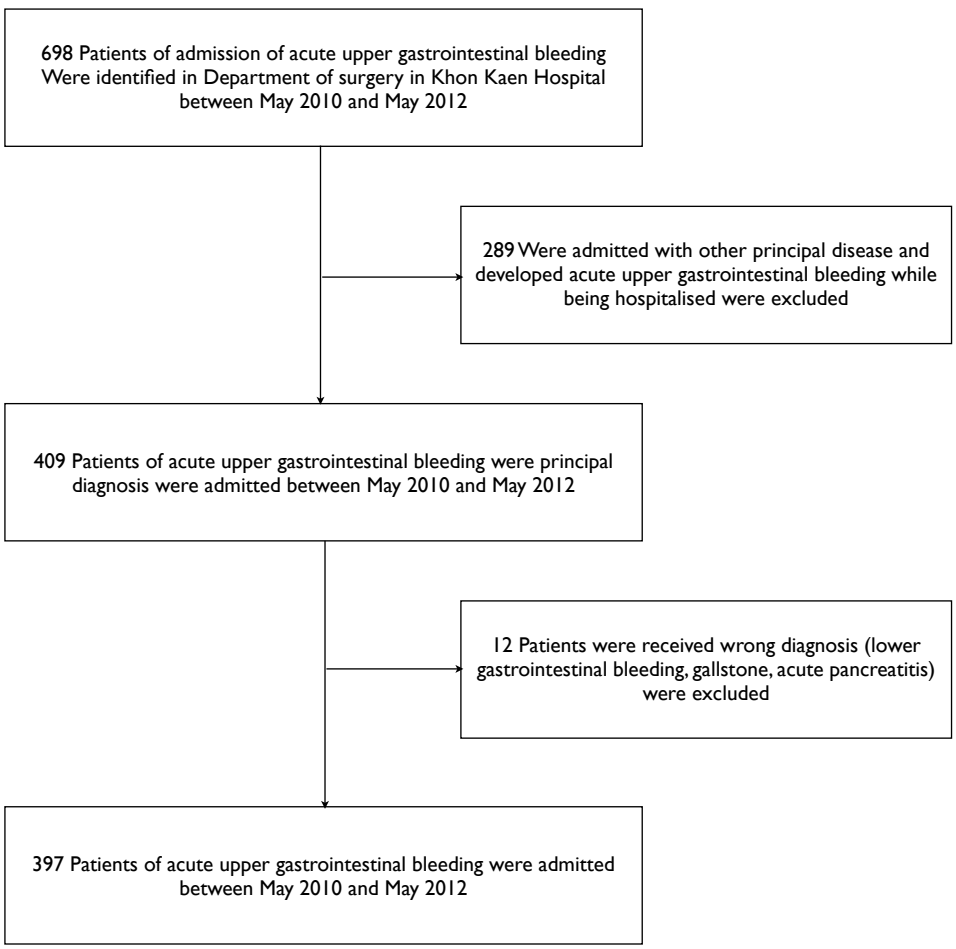

Figure 1. Flow Chart of Admission and Study Completion.

Statistical analysis

All variables were recorded onto spreadsheet. They were double entered. They were cleaned for duplicated entries and were verified for their validity. Later they were analyzed using the statistics package. Characteristics table were generated for all variables. Wildcard variables were detected and corrected. For descriptive statistics, categories variables were summarized as number and percent (no. (%)). For scale variables, median and interquartile range (IQR) were used for non-normal distributed variables while mean and standard deviation (SD) were used for normally distributed variables. For inferential statistics, either chi-square or Fisher's exact test was used for categorical variables where appropirate. T-test and Mann-Whitney U test were used for normally and non-normally distributed variables, respectively. For risk interpretation, crude odds ratio (COR) was used. Adjusted odds ratio (AOR) was identified through the logistic regression analysis. Log rank test was used to test for two or more different survival or time-to-event curves of categorical data. Cox proportional hazard regression was used and hazard ratio (HR) were identified. Scores were assigned for each variable that associated with the outcomes from regression. Finally, after assigned score, the new models were tested for their sensitivity, specificity, likelihood ratio and area under receiver operating characteristics (ROC) curve was identified.

Table 1. Baseline Characteristics

Characteristic	All (N=397)	Mortality			Rebleeding		
		Survival (N=249)	Death (N=148)	P Value	Non-rebleeding (N=232)	Rebleeding (N=165)	P Value
Age□yr□no. (%)							
<60	241 (60.7)	145 (58.2)	96 (64.9)		133 (57.3)	108 (65.5)	
60-79	129 (32.5)	83 (33.3)	46 (31.1)		84 (36.2)	45 (27.3)	
≥80	27 (6.8)	21 (8.4)	6 (4.1)		15 (6.5)	12 (7.3)	
Male sex□no. (%)	300 (75.6)	185 (74.3)	115 (77.7)	0.445	168 (72.4)	132 (80.0)	0.083
Clinical presentation□no. (%)							
Red bright hematemesis	244 (61.5)	131 (52.6)	113 (76.4)	<0.001	142 (61.2)	102 (61.8)	0.902
Coffee ground hematemesis	103 (25.9)	69 (27.7)	34 (23.0)	0.298	62 (26.7)	41 (24.8)	0.674
Melena	260 (65.5)	172 (69.1)	88 (59.5)	0.051	151 (65.1)	109 (66.1)	0.840
Hematochezia	72 (18.1)	39 (15.7)	33 (22.3)	0.097	40 (17.2)	32 (19.4)	0.583
Comorbidity□no. (%)							
Ischemic heart disease	13 (3.3)	12 (4.8)	1 (0.7)	0.037	5 (2.2)	8 (4.8)	0.137
Stroke	7 (1.8)	4 (1.6)	3 (2.0)	0.715	5 (2.2)	2 (1.2)	0.704
Valvular heart disease	11 (2.8)	10 (4.0)	1 (0.7)	0.060	7 (3.0)	4 (2.4)	1.000
Hypertension	76 (19.1)	60 (24.1)	16 (10.8)	0.001	46 (19.8)	30 (18.2)	0.681
Chronic kidney disease	51 (12.8)	30 (12.0)	21 (14.2)	0.538	28 (12.1)	23 (13.9)	0.583
Liver cirrhosis	167 (42.1)	64 (25.7)	103 (69.6)	<0.001	87 (37.5)	80 (48.5)	0.029
Malignancy	29 (7.3)	14 (5.6)	15 (10.1)	0.095	21 (9.1)	8 (4.8)	0.113
Diabetes mellitus	61 (15.4)	30 (12.0)	31 (20.9)	0.017	34 (14.7)	27 (16.4)	0.642
Previous smoking (N=363)	183 (50.4)	117 (50.2)	66 (50.8)	0.919	101 (48.6)	82 (52.9)	0.413
Previous alcohol drinking (N=371)	254 (68.5)	153 (65.1)	101 (74.3)	0.067	145 (68.1)	109 (69.0)	0.852
Previous upper gastrointestinal bleeding□no. (%)	138 (34.8)	96 (38.6)	42 (28.4)	0.040	77 (33.2)	61 (37.0)	0.436
Previous esophagogastroduodenoscopy□no. (%)	88 (22.2)	60 (24.1)	28 (18.9)	0.230	57 (24.6)	31 (18.8)	0.172
Anti-platelets□no. (%)	30 (10.6)	26 (10.4)	4(2.7)	0.005	21 (9.1)	9 (5.5)	0.181
Anticoagulants□no. (%)	7 (1.8)	6 (2.4)	1 (0.7)	0.265	7 (3.0)	0 (0.0)	0.045
Non-steroidal anti-inflammatory drugs□no. (%)	56 (14.1)	44 (17.7)	12 (8.1)	0.008	34 (14.7)	22 (13.3)	0.709
Steroids□no. (%)	35 (8.8)	26 (10.4)	9 (6.1)	0.138	21 (9.1)	14 (8.5)	0.844
Herb□no. (%)	16 (4.0)	9 (3.6)	7 (4.7)	0.585	8 (3.4)	8 (4.8)	0.484
Systolic blood pressure□mmHg□no. (%)				<0.001			0.732
<100	112 (28.2)	44 (17.7)	68 (45.9)		67 (28.9)	45 (27.3)	
≥100	285 (71.8)	205 (82.3)	80 (54.1)		165 (71.1)	120 (72.7)	
Diastolic blood pressure□mmHg				<0.001			0.564
Median	65	66	60		64	65	
Interquartile range	54-77	57-79	50-72		53.3-77	54.5-78.5	
Pulse rate□bpm□no. (%)				0.551			0.665
<100	217 (54.7)	140 (56.2)	77 (52.0)		133 (57.3)	84 (50.9)	
≥100	180 (45.3)	109 (43.8)	71 (48.0)		99 (42.7)	81 (49.1)	
Body temperature□degree celsius				0.001			0.523
Median	36.8	36.9	36.7		36.8	36.8	
Interquartile range	36.4-37.1	36.5-37.2	36.3-37.0		36.4-37.1	36.4-37.1	
Clinical Rockall score□no. (%)							
≤2	135 (34.0)	116 (46.6)	19 (12.8)		90 (38.8)	45 (27.3)	
3-7	262 (66.0)	133 (53.4)	129 (87.2)		142 (61.2)	120 (72.7)	

Table 2. Laboratory and Treatment

Laboratory test and given treatment	All	Mortality			Re-bleeding		
		Survival	Death	P Value	Non-re-bleeding	Re-bleeding	P Value
Blood urea nitrogen□mg/dl□ no. (%)				<0.001			0.962
Median	27	23.5	36.5		27.5	26.5	
Interquartile range	15-51	13.0-46.3	17.0-64.3		14.3-53.5	15.0-49.8	
<6.5	12 (3.8)	11 (5.8)	1 (0.8)		7 (4.0)	5 (3.6)	
6.5-<7.9	10 (3.2)	8 (4.2)	2 (1.6)		6 (3.4)	4 (2.9)	
8.0-<9.9	15 (4.7)	14 (7.4)	1 (0.8)		11 (6.3)	4 (2.9)	
10.0-24.9	114 (36.1)	68 (35.8)	46 (36.5)		60 (34.1)	54 (38.6)	
≥25.0	165 (52.2)	89 (46.8)	76 (60.3)		92 (52.3)	73 (52.1)	
Creatinine□ mg/dl				<0.001			0.585
Median	1.3	1.1	1.8		1.3	1.4	
Interquartile range	0.9-2.2	0.8-1.6	1.2-3.8		0.9-2.1	0.9-2.4	
Hemoglobin□g/dl□ no. (%)				0.028			0.364
Median	7.4	7.7	6.8		7.2	7.7	
Interquartile range	5.2-9.4	5.3-10.1	5.0-8.8		5.2-9.1	5.4-9.5	
<10.0	313 (79.6)	183 (74.4)	130 (88.4)		186 (80.9)	127 (77.9)	
10.0-12.0	48 (12.2)	39 (15.9)	9 (6.1)		21 (9.1)	27 (16.6)	
12.1 -13.0	9 (2.3)	6 (2.4)	3 (2.0)		7 (3.0)	2 (1.2)	
>13.0	23 (5.9)	18 (7.3)	5 (3.4)		16 (7.00)	7 (4.3)	
Hematocrit □%□ no. (%)				0.018			0.201
Median	23	23	21		22	23	
Interquartile range	16-29	17-30	15-27		16-27	17-29	
<25.0	252 (63.5)	153 (61.4)	99 (66.9)		160 (69.0)	92 (55.8)	
25.0-29.9	70 (17.6)	37 (14.9)	33 (22.3)		28 (12.1)	42 (25.5)	
≥30.0	75 (18.9)	59 (23.7)	16 (10.8)		44 (19.0)	31 (18.8)	
White blood cell□1,000/mm3				<0.001			0.074
Median	10.7	6.5	12.5		10.3	11.4	
Interquartile range	72.0-15.1	6.8-13.5	9.0-18.7		7.0-14.4	7.8-16.5	
Platelet count□1,000/mm3□ no. (%)				<0.001			0.037
Median	160	182	119		165	153	
Interquartile range	90.5-259.0	107.8-288.0	74.0-193.0		103.8-268.5	64.0-242.0	
<100	110 (28.0)	57 (23.2)	53 (36.1)		55 (23.9)	55 (33.7)	
≥100	283 (72.0)	189 (76.8)	94 (63.9)		175 (76.1)	108 (66.3)	
Prothrombin Time□sec				<0.001			0.034
Median	16.3	14.2	25.9		15.5	17.7	
Interquartile range	13.3-24.6	12.7-17.1	18.4-36.6		13.2-22.7	13.5-27.5	
Partial thromboplastin time□sec				<0.001			0.175
Median	30.5	26.8	44.5		29.5	32.3	
Interquartile range	25.3-43.6	24.2-32.0	33.2-65.0		25.4-38.7	25.2-48.6	

Table 2. (Continued)

Laboratory test and given treatment	All	Mortality			Re-bleeding		
		Survival	Death	P Value	Non-re-bleeding	Re-bleeding	P Value
Interquartile range	1.1-2.1	1.0-1.4	1.5-3.1		1.1-1.9	1.1-2.4	
<1.0	48 (12.2)	47 (19.0)	1 (0.7)		30 (13.2)	18 (11.00	
1.0-1.5	185 (47.2)	150 (60.7)	35 (24.1)		119 (52.2)	66 (40.2)	
>1.5	159 (40.6)	50 (20.2)	109 (75.2)		79 (34.6)	80 (48.8)	
Vitamin K□no.(%)	283 (71.3)	146 (58.6)	137 (92.6)	<0.001	152 (65.5)	131 (79.4)	0.003
Omeprazole□no.(%)	387 (97.5)	240 (96.4)	147 (99.3)	0.098	224 (96.6)	163 (98.8)	0.205
Somatostatin□no.(%)	127 (32.0)	39 (15.7)	88 (59.5)	<0.001	60 (25.9)	67 (40.6)	0.002
Sengstaken-Blakemore tube□no(%)	46 (11.6)	6 (2.4)	40 (27.0)	<0.001	23 (9.9)	23 (13.9)	0.217
Packed red blood cell□unit□no. (%)				<0.001			<0.001
Median	3	2	4		2	3	
Interquartile range	1-4	1-4	2-6		1-4	2.0-5.5	
<2	275 (69.3)	156 (62.7)	119 (80.4)		149 (64.2)	126 (76.4)	
≥ 2	122 (30.7)	93 (37.3)	29 (19.6)		83 (35.8)	39 (23.6)	
Fresh-frozen plasma□unit□ no. (%)				<0.001			<0.001
Median	0	0	4		0	2	
Interquartile range	0-4	0.0-1.5	0-10		0-2	0-10	
<3	266 (67.0)	207 (83.1)	59 (39.9)		175 (75.4)	91 (55.2)	
≥3	131 (33.0)	42 (16.9)	89 (60.1)		57 (24.6)	74 (44.8)	
Length of hospital stay□day□ no. (%)				<0.001			<0.001
Median	2	3	1		2	3	
Interquartile range	1-4	2-5	1-3		1-4	2-6	
<2	132 (33.2)	46 (18.5)	86 (58.1)		99 (42.7)	33 (20.0)	
2-5	191 (48.1)	143 (57.4)	48 (32.4)		106 (45.7)	85 (51.5)	
>5	74 (18.6)	60 (24.1)	14 (9.5)		27(11.6)	47 (28.5)	

RESULTS

There were 698 patients preliminary included in the study, 301 were excluded as their diagnoses were not acute UGIB, in total 397 were left for the analysis (Figure 1). Of these 397, mostly they were male with the median age of 53 years old (Table 1). Most of them were presented with melena (65.5%). Liver cirrhosis were found in nearly half of the patients. Half of them were smokers, nearly 70% drank alcohol. About 35% had the history of acute UGIB and about 22% used to undergo EGD. On admission, 28.2% were shock, and 66% had the clinical Rockall score more than 3 which indicated as high risk group. More than half had risen BUN with the median Hct 23% (Table 2). Mild coagulopathy were found this group. They were treated with vitamin K, omeprazole and PRC in almost all of the cases. Other treatment given included Sengstaken-Blakemore tube, somatostatin and FFP. The median length of stay was 2 days.

One hundred and six were undergone EGD (Table 3). The scope was done in 24 hours in about half of the cases and for diagnosis purpose only. Gastric ulcer was found in 27.4%, gastritis 18.9% and duodenal ulcer 11.3%. Complete Rockall score, after adding up the scope findings, 58.5% had the score between 3 and 7 with no difference from the clinical Rockall score. In Table 4, odds ratios are presented. From the univariable analysis, factors found to be significantly associated with lower mortality included SBP≥100 mmHg (COR 0.25; 95% CI, 0.16 to 0.41), HT (COR 0.38; 95% CI, 0.20 to 0.72), Hb between 10.0 g/dl and 12.0 g/dl (COR 0.32; 95% CI, 0.14 to 0.73), Hct≥30.0 % (COR 0.42; 95% CI, 0.22 to 0.80), and platelet count≥100000 /mm3 (COR 0.53; 95% CI, 0.33 to

Table 3. Gastroscopic Findings and Diagnosis.

Findings	All (N=106)	Mortality			Re-bleeding		
		Survival	Death	P Value	Non-re bleeding	Re-bleeding	P Value
Time to esophagogastroduodenoscopy□hr□no. (%)							
<24	59 (55.7)	54 (53.5)	5 (100.0)		39 (62.9)	20 (45.5)	
24-48	33 (31.1)	33 (32.7)	0		18 (29.0)	15 (34.1)	
>48	14 (13.2)	14 (13.9)	0		5 (8.1)	9 (20.5)	
Esophagogastroduodenoscopy findings□no. (%)							
No lesion	80 (75.5)	77 (76.2)	3 (60.0)	0.594	50 (80.6)	30 (68.20)	0.142
Dark spot	1 (0.9)	1 (1.0)	0	1.000	0	1 (2.3)	0.415
Blood in upper GI tract	17 (16.0)	15 (14.9)	2 (40.0)	0.181	9 (14.5)	8 (18.2)	0.612
Adherent clot	6 (5.7)	5 (5.0)	1 (20.0)	0.257	1 (1.6)	5 (11.4)	0.080
Visible or spurting	4 (3.8)	4 (4.0)	0	1.000	2 (3.2)	2 (4.5)	1.000
Diagnosis□no. (%)							
Mallory-Weiss tear	7 (6.6)	7 (6.9)	0	1.000	3 (4.8)	4 (9.1)	0.446
Gastric ulcer	29 (27.4)	29 (28.7)	0	0.320	21 (33.9)	8 (18.2)	0.074
Duodenal ulcer	12 (11.3)	12 (11.9)	0	1.000	11 (17.7)	1 (2.3)	0.014
Gastritis	20 (18.9)	19 (18.8)	1 (20.0)	1.000	11 (17.7)	9 (20.5)	0.725
Duodenitis	3 (2.8)	3 (3.0)	0	1.000	2 (3.2)	1 (2.3)	1.000
Dieulafoy lesion	2 (1.9)	2 (2.0)	0	1.000	1 (1.6)	1 (2.3)	1.000
Neoplasia	5 (4.7)	4 (4.0)	1 (20.0)	0.218	2 (3.2)	3 (6.8)	0.647
Esophageal varice	9 (8.5)	7 (6.9)	2 (40.0)	0.056	6 (9.7)	3 (6.8)	0.732
Gastric varice	2 (1.9)	1 (1.0)	1 (20.0)	0.093	1 (1.6)	2 (2.3)	1.000
Other	26 (24.5)	23 (22.8)	3 (60.0)	0.094	13 (21.0)	13 (29.5)	0.312
Esophagogastroduodenoscopy only□no. (%)	75 (70.8)	70 (69.3)	5 (100.0)	0.318	43 (69.4)	32 (72.7)	0.707
Esophagogastroduodenoscopic with adrenaline injection□no. (%)	22 (20.8)	22 (21.8)	0	0.581	13 (21.0)	9 (20.5)	0.949
Esophagogastroduodenoscopic with ligation□no. (%)	10 (9.4)	10 (9.9)	0	1.000	6 (9.7)	4 (9.1)	1.000
Esophagogastroduodenoscopic with sclerosing injection□no. (%)	1 (0.9)	1 (1.0)	0	1.000	1 (1.6)	0	1.000
Complete Rockall score□no. (%)							
≤2	40 (37.7)	40 (39.6)	0		29 (46.8)	11 (25.0)	
3-7	62 (58.5)	57 (56.4)	5 (100.0)		29 (46.8)	33 (75.0)	
≥8	4 (3.8)	4 (4.0)	0		4 (6.5)	0	

0.86). Factors found to be significantly associated with higher mortality included red bright hematemesis (COR 2.91; 95% CI, 1.81 to 4.70), liver cirrhosis (COR 6.62; 95% CI, 4.11 to 10.67), DM (COR 1.93; 95% CI, 1.08 to 3.47), clinical Rockall score between 3 and 7 (COR 5.92; 95% CI, 3.34 to 10.58), BUN≥25.0 mg/dl (COR 9.39; 95% CI, 1.21 to 199.04), INR between 1.0 and 1.5 (COR 10.97; 95% CI, 1.54 to 220.94), INR≥1.5 (COR 102.46; 95% CI, 14.54 to 2053.82), vitamin K (COR 8.79; 95% CI, 4.36 to 18.11), somatostatin (COR 7.90; 95% CI, 4.79 to 113.06), Sengstaken-Blakemore tube (COR 15; 95% CI, 5.87 to 40.65), PRC≥2 units (COR 2.45; 95% CI, 1.48 to 4.07) and FFP≥3 units (COR 7.43; 95% CI, 4.54 to 12.21).

Table 4. **Odds Ratio of Factors Determining Mortality and Re-Bleeding.**

Factors	Mortality		Re-bleeding	
	Crude odds ratio and 95% confidence interval	Adjusted odds ratio and 95% confidence interval	Crude odds ratio and 95% confidence interval	Adjusted odds ratio and 95% confidence interval
Age□yr				
<60	Reference	Reference	Reference	Reference
60-79	0.84 (0.52-1.33)	1.89 (0.72-4.95)	0.66 (0.41-1.05)	0.75 (0.35-1.60)
≥80	0.43 (0.15-1.18)	0.90 (0.09-9.05)	0.99 (0.41-2.34)	0.76 (0.19-3.12)
Male sex	1.21 (0.73-2.01)	0.39 (0.11-1.38)	1.52 (0.92-2.53)	0.53 (0.22-1.28)
Systolic blood pressure ≥100 mmHg	0.25 (0.16-0.41)	0.75 (0.31-1.80)	1.08 (0.68-1.73)	1.11 (0.53-2.32)
Pulse rate ≥100 bpm	1.18 (0.77-1.82)	0.95 (0.43-2.11)	1.30 (0.85-1.97)	1.24 (0.66-2.33)
Red bright hematemesis	2.91 (1.81-4.70)	4.37 (1.55-12.32)	1.03 (0.67-1.58)	1.16 (0.56-2.42)
Coffee ground hematemesis	0.78 (0.47-1.28)	1.13 (0.44-2.94)	0.91 (0.56-1.47)	0.82 (0.39-1.72)
Melena	0.61 (0.42-1.03)	2.10 (0.84-5.29)	1.04 (0.67-1.63)	1.79 (0.88-3.65)
Hematochezia	1.55 (0.89-2.67)	3.57 (1.13-11.29)	1.15 (0.67-1.99)	1.82 (0.79-4.22)
Hypertension	0.38 (0.20-0.72)	0.25 (0.06-1.02)	0.90 (0.52-1.54)	0.35 (0.13-0.91)
Chronic kidney disease	1.21 (0.64-2.29)	2.08 (0.36-12.07)	1.18 (0.63-2.22)	1.45 (0.48-4.36)
Liver cirrhosis	6.62 (4.11-10.67)	10.07 (2.09-48.50)	1.57 (1.03-2.40)	0.29 (0.09-1.00)
Malignancy	1.89 (0.83-4.30)	6.20 (1.09-35.14)	0.51 (0.20-1.26)	0.14 (0.03-0.64)
Diabetes mellitus	1.93 (1.08-3.47)	4.65 (1.38-15.61)	1.14 (0.63-2.04)	1.13 (0.48-2.70)
Previous upper gastrointestinal bleeding	0.63 (0.40-1.00)	0.53 (0.17-1.60)	1.18 (0.76-1.83)	3.62 (1.42-9.22)
Previous esophagogastroduodenoscopy	0.73 (0.43-1.25)	0.49 (0.13-1.77)	0.71 (0.42-1.19)	0.32 (0.11-0.92)
Previous smoking	1.02 (0.65-1.65)	2.00 (0.73-5.48)	1.19 (0.77-1.84)	1.72 (0.80-3.70)
Previous alcohol drinking	1.55 (0.94-2.54)	0.40 (0.13-1.25)	1.06 (0.66-1.69)	0.79 (0.32-1.95)
Clinical Rockall score 3-7	5.92 (3.34-10.58)	0.28 (0.06-1.43)	1.69 (1.07-2.67)	3.73 (1.20-11.60)
Blood urea nitrogen□mg/dl		1.03 (1.01-1.05)		
<6.5	Reference		Reference	Reference
6.5-<8.0	2.75 (0.15-93.30)		0.93 (0.12-7.15)	1.53 (0.14-16.45)
8.0-<10.0	0.79 (0.02-33.14)		0.51 (0.07-3.36)	1.35 (0.15-12.03)
10.0-<25.0	7.44 (0.94-159.39)		1.26 (0.33-4.91)	4.28 (0.77-23.85)
≥25.0	9.39 (1.21-199.04)		1.11 (0.30-4.23)	6.27 (1.01-38.80)

Regarding bleeding, from the univariable analysis, factors found to be significantly associated with lower re-bleeding included platelet count≥100000 /mm3 (COR 0.62; 95% CI, 0.39 to 0.99). Factors significantly found to be associated with higher re-bleeding included liver cirrhosis (COR 1.57; 95% CI, 1.03 to 2.40), clinical Rockall score between 3 and 7 (COR 1.69; 95% CI, 1.07 to 2.67), Hct between 25.0% and <30.0% (COR 2.61; 95% CI, 1.47 to 4.65), vitamin K (COR 2.03; 95% CI, 1.24 to 3.32), somatostatin (COR 1.96; 95% CI, 1.25 to 3.08) and FFP≥3 units (COR 2.50; 95% CI, 1.59 to 3.92).

From the logistic regression analysis,factor found to be significantly associated with higher mortality

Table 4. (Continued)

Factors	Mortality		Re-bleeding	
	Crude odds ratio and 95% confidence interval	Adjusted odds ratio and 95% confidence interval	Crude odds ratio and 95% confidence interval	Adjusted odds ratio and 95% confidence interval
<10.0	Reference		Reference	Reference
10.0-12.0	0.32 (0.14-0.73)		1.88 (0.98-3.63)	3.36 (0.85-13.33)
>12.0-13.0	0.70 (0.14-3.23)		0.42 (0.06-2.24)	1.00 (0.09-11.10)
>13.0	0.39 (0.12-1.16)		0.64 (0.23-1.72)	0.62 (0.09-4.48)
Hematocrit□%				
<25.0	Reference	Reference	Reference	Reference
25.0-<30.0	1.38 (0.78-2.43)	3.38 (1.06-10.75)	2.61 (1.47-4.65)	6.23 (2.37-16.37)
≥30.0	0.42 (0.22-0.80)	0.93 (0.20-4.25)	1.23 (0.70-2.14)	2.58 (0.66-10.09)
Platelets count□/mm3		1.00 (0.99-1.01)		
<100,000	Reference		Reference	Reference
≥100,000	0.53 (0.33-0.86)		0.62 (0.39-0.99)	0.56 (0.26-1.17)
International Normalized Ratio		1.40 (0.91-2.16)		0.5 (0.34-0.81)
<1.0	Reference		Reference	
1.0-1.5	10.97 (1.54-220.94)		0.92 (0.46-1.88)	
>1.5	102.46 (14.54-2053.82)		1.69 (0.83-3.45)	
Vitamin k	8.79 (4.36-18.11)	3.02 (0.76-11.63)	2.03 (1.24-3.32)	0.8 (0.37-1.87)
Omeprazole	5.51 (0.71-117.35)	NA	2.91 (0.56-20.11)	0.53 (0.04-6.93)
Somatostatin	7.90 (4.79-113.06)	1.43 (0.55-3.74)	1.96 (1.25-3.08)	1.06 (0.43-2.58)
Sengstaken-Blakemore tube	15 (5.87-40.65)	6.21 (1.40-27.56)	1.47 (0.76-2.84)	0.86 (0.28-2.65)
Packed red blood cell ≥2 units	2.45 (1.48-4.07)	2.56 (0.80-8.16)		3.16 (1.22-8.18)
Fresh-frozen plasma□unit				1.27 (1.14-1.41)
<3	Reference	Reference	Reference	
≥3	7.43 (4.54-12.21)	2.53 (0.95-6.74)	2.50 (1.59-3.92)	

included red bright hematemesis (AOR 4.73; 95% CI, 1.55 to 12.32), hematochezia (AOR 3.57; 95% CI, 1.13 to 11.29), liver cirrhosis (AOR 10.07; 95% CI, 2.09 to 48.50), malignancy (AOR 6.20; 95% CI, 1.09 to 35.14), DM (AOR 4.65; 95% CI, 1.38 to 15.61), BUN (AOR 1.03; 95% CI, 1.01 to 1.05), Hct between 25.0% and <30.0% (AOR 3.38; 95% CI, 1.06 to 10.75) and Sengstaken-Blakemore tube (AOR 6.21; 95% CI, 1.40 to 27.56).

Regarding bleeding, from the logistic regression analysis, factors found to be significantly associated with lower re-bleeding included HT (AOR 0.35; 95% CI, 0.13 to 0.91), malignancy (AOR 0.14; 95% CI, 0.03 to 0.64), previous EGD (AOR 0.32; 95% CI, 0.11 to 0.92) and INR (AOR 0.50; 95% CI, 0.34 to 0.81). Factors found to be significantly associated with higher re-bleeding included previous UGIB (AOR 3.62; 95% CI, 1.42 to 9.22), clinical Rockall score between 3 and 7 (AOR 3.73; 95% CI, 1.20 to 11.60), BUN ≥25 mg/dl (AOR 6.27; 95% CI, 1.01 to 38.80), Hct 25.0% or more but less than 30.0% (AOR 6.23; 95% CI, 2.37 to 16.37), PRC≥2 units (AOR 3.16; 95% CI, 1.22 to 8.18) and FFP (AOR 1.27; 95% CI, 1.14 to 1.41)

From the Cox's proportional hazard regression (Table 5), factors found to be significantly associated with lower mortality included HT (HR 0.33; 95% CI, 0.14 to 0.81). Factor found to be significantly associated with higher mortality included red bright hematemesis (HR 2.02; 95% CI, 1.10 to 3.70), DM (HR 2.20; 95% CI, 1.22 to 3.97), BUN (HR 1.02; 95% CI, 1.01 to 1.02), vitamin K (HR 3.14; 95% CI, 1.05 to 9.36) and Sengstaken-Blakemore tube (HR 2.05; 95% CI, 1.18 to 3.54). In addition, factors found to be significantly associated with lower incidence of re-bleeding included liver cirrhosis (HR 0.46; 95% CI, 0.23 to 0.93), malignancy (HR 0.34; 95% CI, 0.14 to 0.83) and previous EGD (HR 0.53; 95% CI, 0.29 to

Table 5. Hazard Ratio of Factors Determining Mortality and Re-Bleeding.

Factors	Mortality		Re-bleeding	
	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
Age□yr				
<60	Reference		Reference	
60-79	1.17	0.69-1.97	0.98	0.60-1.62
≥80	0.93	0.23-3.83	0.95	0.37-2.47
Male sex	0.67	0.34-1.32	0.99	0.57-1.72
Systolic blood pressure ≥100 mmHg	0.81	0.52-1.24	0.82	0.53-1.27
Pulse rate ≥100 bpm	1.01	0.64-1.57	1.18	0.80-1.75
Red bright hematemesis	2.02	1.10-3.70	1.10	0.67-1.79
Coffee ground hematemesis	1.14	0.67-1.93	0.85	0.53-1.37
Melena	1.36	0.84-2.20	1.41	0.88-2.26
Hematochezia	1.18	0.69-2.00	1.29	0.76-2.19
Hypertension	0.33	0.14-0.81	0.62	0.34-1.12
Chronic kidney disease	1.20	0.58-2.51	1.07	0.53-2.16
Liver cirrhosis	2.27	0.98-5.26	0.46	0.23-0.93
Malignancy	1.31	0.64-2.67	0.34	0.14-0.83
Diabetes mellitus	2.20	1.22-3.97	1.12	0.66-1.90
Previous upper gastrointestinal bleeding	0.92	0.48-1.74	2.03	1.22-3.39
Previous esophagogastroduodenoscopy	0.86	0.41-1.82	0.53	0.29-0.98
Previous smoking	1.45	0.87-2.45	1.12	0.71-1.77
Previous alcohol drinking	0.58	0.31-1.08	0.81	0.48-1.37
Rockall score				
Clinical Rockall score 3-7	0.63	0.25-1.57	1.80	0.93-3.51
Blood urea nitrogen□mg/dl	1.02	1.01-1.02		
<6.5			Reference	
6.5-<8.0			1.13	0.26-4.91
8.0-<10.0			0.86	0.19-3.81
10.0-<25.0			1.39	0.47-4.16
≥25.0			1.41	0.45-4.37
Creatinine	0.94	0.87-1.01	0.97	0.92-1.02
Hemoglobin□g/dl	1.01	0.90-1.14		
<10.0			Reference	
10.0-12.0			1.91	0.91-4.01
>12.0-13.0			2.00	0.39-10.25
>13.0			0.79	0.18-3.39
Hematocrit□%				
<25.0	Reference		Reference	
25.0-<30.0	1.01	0.60-1.98	2.01	1.20-3.39
≥30.0	0.92	0.38-2.20	1.33	0.58-3.03
Platelet count □/mm3	1.00	0.99-1.01		
<100000			Reference	
≥100000			0.67	0.42-1.06
International Normalized Ratio	1.15	0.99-1.33	0.83	0.67-1.04
Vitamin k	3.14	1.05-9.36	1.05	0.60-1.84
Omeprazole			0.69	0.09-5.68
Somatostatin	1.12	0.64-1.95	1.38	0.79-2.41
Sengstaken-Blakemore tube	2.05	1.18-3.54	0.76	0.40-1.47
Packed red blood cells ≥2 units	1.35	0.68-2.66	2.09	1.14-3.84
Fresh-frozen plasma□unit			1.04	1.01-1.07
<3	Reference			
≥3	1.22	0.72-2.08		

Table 6. Component of Clinical Rockall Score and the Modified Clinical Rockall Score

Clinical Rockall score	Mortality Assigned score	Re-bleeding Assigned score
Age□yr		
<60	0	0
60-79	1	1
≥80	2	2
Shock		
Systolic blood pressure ≥100 mmHg and pulse rate <100 bpm	0	0
Systolic blood pressure ≥100 mmHg and pulse rate ≥100 bpm	1	1
Systolic blood pressure <100 mmHg	2	2
Comorbidity		
No major comorbidity	0	0
Ischemic heart disease,cardiac failure,any major comorbidity	2	2
Renal or liver failure or disseminated malignancy	3	3
Additional factors		
Comorbidity		
Hypertension or Diabetes mellitus	2	
Hypertension and Diabetes mellitus	3	
Clinical presentation		
Hematochezia	2	
Red bright hematemesis	3	
Blood urea nitrogen ≥25 mg/dl	1	
Previous upper gastrointestinal bleeding		3
Previous esophagogastroduodenoscopy		2
Hematocrit (25.0%-<30.0%)		3
International Normalized Ratio ≥1.5		2
Packed red blood cell ≥2 units		3
Fresh frozen plasma ≥2 units		3
Total	16	23

0.98). Factors found to be significantly associated with higher incidence of re-bleeding included previous UGIB (HR 2.03; 95% CI, 1.22 to 3.39), Hct between 25.0% and <30.0% (HR 2.01; 95% CI, 1.20 to 3.39), PRC≥2 units (HR 2.09; 95% CI, 1.14 to 3.84) and FFP (HR 1.04; 95% CI, 1.01 to 1.07).

From the regression, factor associated with mortality and re-bleeding were assigned for the score added up to the original clinical Rockall score (Table 6). The modified clinical Rockall score contained more variable including HT or DM, HT and DM, hematochezia, red bright hematemesis and BUN ≥25 mg/dl for prediction of mortality and previous UGIB, previous EGD, Hct (25.0%-<30.0%), INR≥1.5, PRC≥2 units, FFP≥3 units for prediction of re-bleeding.

Table 7 and 8 shows the validity in relation to sensitivity, specificity, positive likelihood ratio and area under the ROC curve for prediction of mortality and re-bleeding during the admission of the two scoring systems, respectively. It found that the modified clinical Rockall score gain higher accuracy (area under the ROC curve) more than the original clinical Rockall score as shown in Figure 2 for both outcomes.

Table 7. Validity of the Modified Rockall Score I for Mortality

Score	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Area under the receiver operating characteristic curve
Clinical Rockall score				0.723
0				
1	95.9	17.3	1.16	
2	91.2	39.0	1.50	
3	85.1	51.8	1.77	
4	70.9	63.5	1.94	
5	42.6	81.1	2.25	
6	14.2	96.8	4.44	
7	2.0	99.6	5	
Modified clinical Rockall score I				0.736
1	97.6	4.2	1.02	
2	97.6	11.6	1.10	
3	96.8	22.1	1.24	
4	92.1	33.2	1.38	
5	84.9	46.8	1.60	
6	75.4	58.4	1.81	
7	60.3	75.8	2.49	
8	41.3	86.3	3.01	
9	23.0	93.7	3.65	
10	12.7	95.8	3.02	
11	4.80	97.9	2.29	
12	1.60	98.9	1.45	
14	0.00	100	0	

DISCUSSION

Important findings

In this study, we have identified various factors found other predictors that significantly associated with higher risk for mortality and re-bleeding. In relation to predictor of mortality, associated factors from univariable analysis included red bright hematemesis, clinical Rockall score between 3 and 7, INR between 1.0 and 1.5, INR≥1.5, vitamin K, somatostatin, using Sengstaken-Blakemore tube, PRC≥2 units and FFP≥3 units. From the logistic regression analysis, the associated factors included red bright hematemesis, hematochezia, BUN, and Sengstaken-Blakemore tube. From the Cox's proportional hazard regression, associated factors included red bright hematemesis, BUN, vitamin K and Sengstaken-Blakemore tube. It show that red bright hematemesis always significantly found to be associated with higher mortality. Regarding predictors for re-bleeding, From the univariable analysis included clinical Rockall score between 3 and 7, vitamin K, somatostatin and FFP≥3 units. From the logistic regression analysis, included previous UGIB, clinical Rockall score between 3 and 7, Hct between 25.0% and below 30.0%, PRC≥2 units and FFP. From the Cox's proportional hazard regression, included previous UGIB, Hct between 25.0% and below 30.0%, PRC and FFP. It show that FFP always significantly found to be associated with higher re-bleeding.

However We found that findings from this studies compared with Rockall score and Glasgow-Blatchford scores are still controversial. Because it show that factors significantly found to be associated lower risk mortality included hypertension (COR 0.38; 95% CI, 0.20 to 0.72) From the Cox's proportional hazard regression and from the univariable analysis and with lower risk rebleeding included malignancy. Moreover, From the logistic regression analysis, previous esophagogastroduodenoscopy and INR include in that factors significantly found to be associated with lower risk rebleeding.

After adding associated factors from Cox proportional hazard regression, to the original clinical

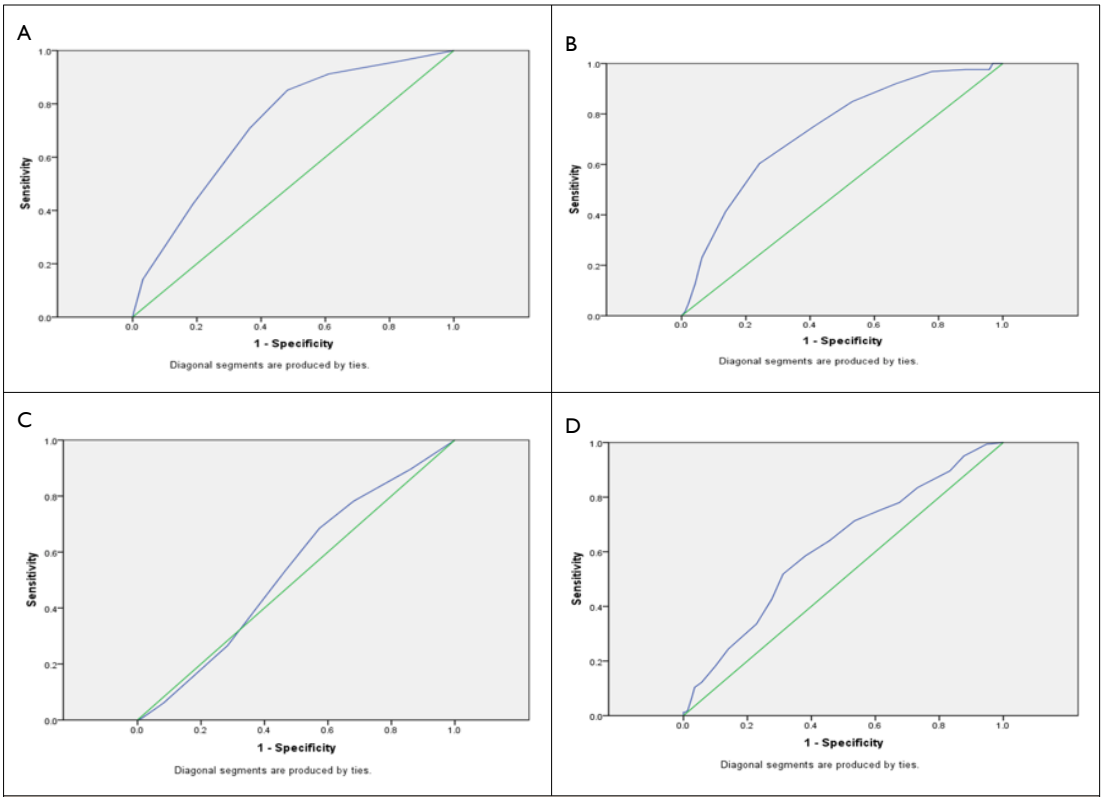

Figure 2. Receiver Operating Characteristics Curve of Modified and Original Rockall Score. Panel A original clinical rockall score for mortality. Panel B modified clinical rockall score for mortality. Panel C original clinical rockall score for rebleeding. Panel D modified clinical rockall score for rebleeding

Rockall score to create modified Rockall scores for predicting mortality and re-bleeding, the modified Rockall score was more accurate than the clinical Rockall score (AUC 0.736 vs. 0.723) as the modified clinical Rockall score contained more variable including hypertension or diabetes mellitus, hypertension and diabetes mellitus, hematochezia, red bright hematemesis and BUN≥25 mg/dl for prediction of mortality.For predicting re-bleeding, The modified Rockall score also had higher more accurate than the clinical Rockall score (AUC 0.617 vs. 0.535) as the modified clinical Rockall score contained more variable including previous upper gastrointestinal bleeding, previous esophagogastroduodenoscopy, Hct (25.0%-<30.0%), INR≥1.5, PRC≥2 units, FFP≥2 units for prediction of rebleeding.

Strength and limitation of the study

Our study found significant factors to predict mortality and rebleeding in acute UGIB from logistic regression and Cox's proportional hazard regression. It found the modified clinical Rockall score gain more accuracy (area under the ROC curve) more than the original clinical Rockall score. However, there are limitations to our study. The data were recorded incompletely thus the missing data could not be put into the analysis. There are many patients without esophagogastroduodenoscopy that could not be analysed.

Comparison with other studies

Several risk scores have been developed to predict for mortality or re-bleeding in patients with UGIB.[20-24] Rockall score and Glasgow-Blatchford Score are widely used in common practice. In many studies, Rockall score and Glasgow-Blatchford Score were validated about prediction of mortality or rebleeding in UGIB. In 1999, Netherlands, Rockall score was useful for stratifying patients with acute UGIB into high and low risk factor for prediction of mortality but cannot predict for re-bleeding in 951 patients with UGIB.[25] In 2006, Canada, Rockall score can predict mortality but poorly predict re-bleeding in 1869 patients with nonvariceal UGIB.[26] In 2011, United Kingdom, Glasgow-Blatchford Score was as effective as the clinical (area under ROC curve 0.084 vs. 0.081; P=0.91) and complete Rockall score (AUROC 0.741 vs. 0.790; P=0.20) in predicting mortality in 1555 patients with UGIB.[27] In 2012

Table 8. Validity of the Modified Rockall Score for Re-Bleeding

Factor	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Area under the receiver operating characteristic curve
Clinical Rockall score				0.535
0				
1	89.7	13.8	1.04	
2	78.2	31.9	1.15	
3	68.5	42.7	1.20	
4	53.3	53.4	1.14	
5	26.7	71.6	0.94	
6	6.1	91.8	0.74	
7	0.6	98.7	0.46	
8	0.0	100	0.00	
Modified clinical Rockall score II				0.617
1	99.4	5.3	1.05	
2	97.0	9.2	1.07	
3	95.1	12.3	1.08	
4	89.6	16.7	1.08	
5	83.5	26.8	1.14	
6	78.0	32.5	1.16	
7	75.0	39.9	1.23	
8	71.3	46.5	1.33	
9	64.0	54.4	1.40	
10	58.5	61.8	1.53	
11	51.8	68.9	1.67	
12	42.7	72.4	1.55	
13	33.5	77.2	1.47	
14	22.4	86.0	1.74	
15	18.3	89.9	1.81	
16	12.2	94.3	2.14	
17	10.4	96.5	2.97	
18	6.7	97.4	2.57	
19	1.8	98.7	1.38	
20	1.2	99.6	3.00	
21	1.2	100	1.2	
22	0.0	100	0	

Ireland, Complete Rockall score was predictive of rebleeding (P=0.004, AUC 0.80) but Blatchford score did not predict rebleeding or mortality.[28] We found that findings from these studies are still controversial. Later, New scores were modified from Rockall score; PNED score showed high accurate to the Rockall score in predicting mortality (AUC 0.81; 95% CI, 0.72 to 0.90) versus (AUC 0.66; 95% CI, 0.60 to 0.72) in 1,360 patients with UGIB in 2010 Italy,[16] and ANNs significantly superior to the Rockall score for predicted 30-day mortality and rebleeding in 2,380 patients with nonvariceal UGIB in 2011 Italy.[17] In addition to, New score called AIMS65 not relate to Rockall score, high predictive accuracy (AUROC 0.80; 95% CI, 0.78 to 0.81) to predict in-hospital mortality in 29,222 patients with acute UGIB in USA

2011.[29] In this study, our score is more accurate than clinical Rockall score to predict mortality and rebleeding in UGIB.

Conclusion and implication

At present, score for predict risk of mortality and re-bleeding in upper gastrointestinal bleeding mainly use rockall score but some patient who cannot used esophagogastroduodenoscopy due to them has prohibition such as gastrointestinal perforation, acute uncontrolled unstable angina, severe untreated coagulopathy, uncontrolled respiratory decompensation, unexperienced endoscopist, patient agitation and uncooperation. That cannot fulfills complete rockall score. This study looks for other predictor that can improve the original clinical rockall score become modified rockall score has more accuracy than the original rockall score for predict risk factor of mortality and re-bleeding.

In the study find that red bright hematemesis, hematochezia, HT, DM and BUN≥25 mg/dl has significant for increased risk of mortality. And patient has history of previous UGIB, previous EGD, Hct between 25 to 30 % at admission, INR≥1.5, received blood transfusion PRC≥2 units and FFP≥2 units during admission has increase risk of rebleeding.

More studies are needed to find other predictor associated with risk factor of mortality and rebleeding that more accuracy than old predictor. Future study should test for other predictor that nobody never used before or gather every studies to analyzed for systemic review.

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Data sharing: Proposals and manuscript for data sharing should be sent to all authors mentioned in this study.

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ORIGINAL ARTICLE

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Intra-operative Blood Loss and Intra-hospital Death in Patients with Postoperative Cardiac Arrest: A Retrospective Cohort Study

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ABSTRACT

BACKGROUND
Cardiac arrest is the emergency medical condition and the mortality rate is increasing each year. In the recent study, the most common electrical mechanism of cardiac arrest is ventricular fibrillation, and the most common cause is coronary heart disease. However, among the patients underwent surgery with cardiac arrest, the data on the severity of blood loss during operation relate to the postoperative cardiac arrest and death are incomplete.

METHODS
We conducted a retrospective study of patients underwent surgery with postoperative cardiac arrest to determine factors influencing rate of death in those patients. The main investigation of the present study was to establish the association between estimated intra-operative blood loss (EBL)—low EBL and high EBL.

RESULTS
Among 173 surgical patients with postoperative cardiac arrest, high EBL was associated with death (hazard ratio (HR), 1.99; 95% confidence interval (CI), 1.17 to 3.37). Other factors that increased the death rate significantly were the underlying stroke (HR, 2.92; 95% CI, 1.03 to 8.26), the principal diagnosis of blunt abdominal injury (HR, 2.40; 95%CI, 1.12 to 5.16), necrotizing fasciitis (NF) or cellulitis or pyomyositis or myonecrosis (HR, 5.10; 95% CI, 1.55 to 16.83), non NF infections (HR, 2.90; 95% CI 1.12 to 7.54) and hyperkalemia (HR, 2.16; 95% CI, 1.14 to 4.11). However, patient age, male sex, time of operation, type of incision, other underlying disease, history of drug use, history of prior cardiac arrest, other principal diagnosis and other serum potassium status before or during cardiac arrest were found not to be associated with death.

CONCLUSION
Estimated intra-operative blood loss 660 ml or more resulted in significant risk to death in patient with postoperative cardiac arrest.

Cardiac arrest is a medical emergency that, in certain situations, is potentially reversible if treated early.[1] Unexpected cardiac arrest sometimes leads to sudden cardiac death.[1,2] The majority of such sudden deaths are caused by acute ventricular tachyarrhythmias or ventricular fibrillation.[1,3–5] In a previous study explored the cause of myocardial infarction (MI) or cardiac arrest after surgery, it found that dependent functional status, abnormal creatinine level, increasing age and types of surgery (included aortic surgery, brain surgery, cardiac surgery, foregut-hepatopancreaticobiliary surgery, gall bladder, appendix, adrenals or spleen surgery, intestinal surgery, orthopedics surgery, other abdominal surgery, peripheral vascular surgery and skin surgery) were increasing risk of MI or cardiac arrest after surgery.[6] Other previous study survey the cause and outcome of peri-operative cardiac arrest, found that the major risk factors of peri-operative cardiac arrest were neonates, infants, the elderly, male patient with American Society of Anesthesiologists' (ASA) class 3 or poorer physical status, in emergency surgery under general anesthesia. And the causes of cardiac arrest and death included sepsis and multiple organ failure (MOF), trauma and intra-operative exsanguinating hemorrhage associated with primary disease.[7] Another previous study retrospectively reviewed the cause of peri-operative cardiac arrest and death on operating table in operating room, found that the major cause of cardiac arrest was hypoxia from airway problem that not detected early.[8] A case report in Japan suspected cardiac arrest might have been due to preexisting cardiac dysfunction enhance by septic shock.[19] Another study found that the one of the main cause of cardiac arrest and death in the operating room was bleeding that requires massive blood transfusion, and its mortality varies widely between 15 and 54%.[9] However, there is no adequate evidence suggest the relationship between intra-operative blood loss and death in those with cardiac arrest after surgery, thus, we conducted a retrospective cohort to verify this relationship as well as to identify other factors that might associate with higher death rate in patients with postoperative cardiac arrest after.

METHODS

Study design

A retrospective cohort study was used to determine factors associated with death in patients underwent surgery with cardiac arrest. The study was conducted in Khon Kaen Hospital, Thailand during December 2008 to June 2012.

Patients and medical records

Patients underwent surgery with cardiac arrest were included. Medical records of those patients were retrieved and reviewed. Patients had to be aged more than 15 years old. Patients with preoperative arrest, cancellation of the operation, minor surgery, patients with otorhinolaryngologic condition, esophagogastroduodenoscopy, colonoscopy, placement with the central line were excluded. Later, patients were divided into two groups according to the EBL—low EBL and high EBL—on the basis of compensated and uncompensated hemorrhagic shock level,10 and the volume of EBL was calculated from the mean weight of Thai people. With the alpha error of 0.05, power 80%, different of death rate between high and low EBL of 20%, the required sample size should be 90 in total. However, we expected to collect more than twice of the required number.

Outcomes

The primary outcome of the present study was death after the event of cardiac arrest of patients underwent surgery in the same hospital admission. The other outcomes included time to death and discharge (in survived patients) and infections as comorbidity occurred on the admission.

Collected variables

All medical records of patients with cardiac arrest after surgery were reviewed for data extraction. Collected variables were patient age, sex, EBL, time of operation, type of incision, underlying disease, principal diagnosis, history of drug use, history of prior cardiac arrest, serum potassium before or during cardiac arrest and electrocardiogram (ECG) pattern during cardiac arrest.

Statistical analysis

All data were double entered and cleaned. After that frequency tables were generated for all variable for wide card values. After cleaning, they were all analyzed using statistics software. For descriptive statistics, number and percentage were used for categorical variables. For normally distributed variables, mean and standard deviation (SD) were used. For non-normally distributed variable, median and interquartile range (IQR) were used. Regarding inferential statistics, either chi-square and Fisher's exact test was used where appropriate for categorical variables, for scale variable Mann Whitney were used to compare the variable of independent two groups of non-normally distributed variables. In relation to risk interpretation, crude odds ratio (COR), adjusted odds ratio (AOR) and HR were used together with their 95% CI. AORs interpreted here were from logistic regression analysis and HRs were from Cox proportional hazard regression.

RESULTS

Characteristics of the patients

From 372 patients, 199 were excluded as shown in Figure 1. The study cohort included 173 surgical patients with postoperative cardiac arrest, between

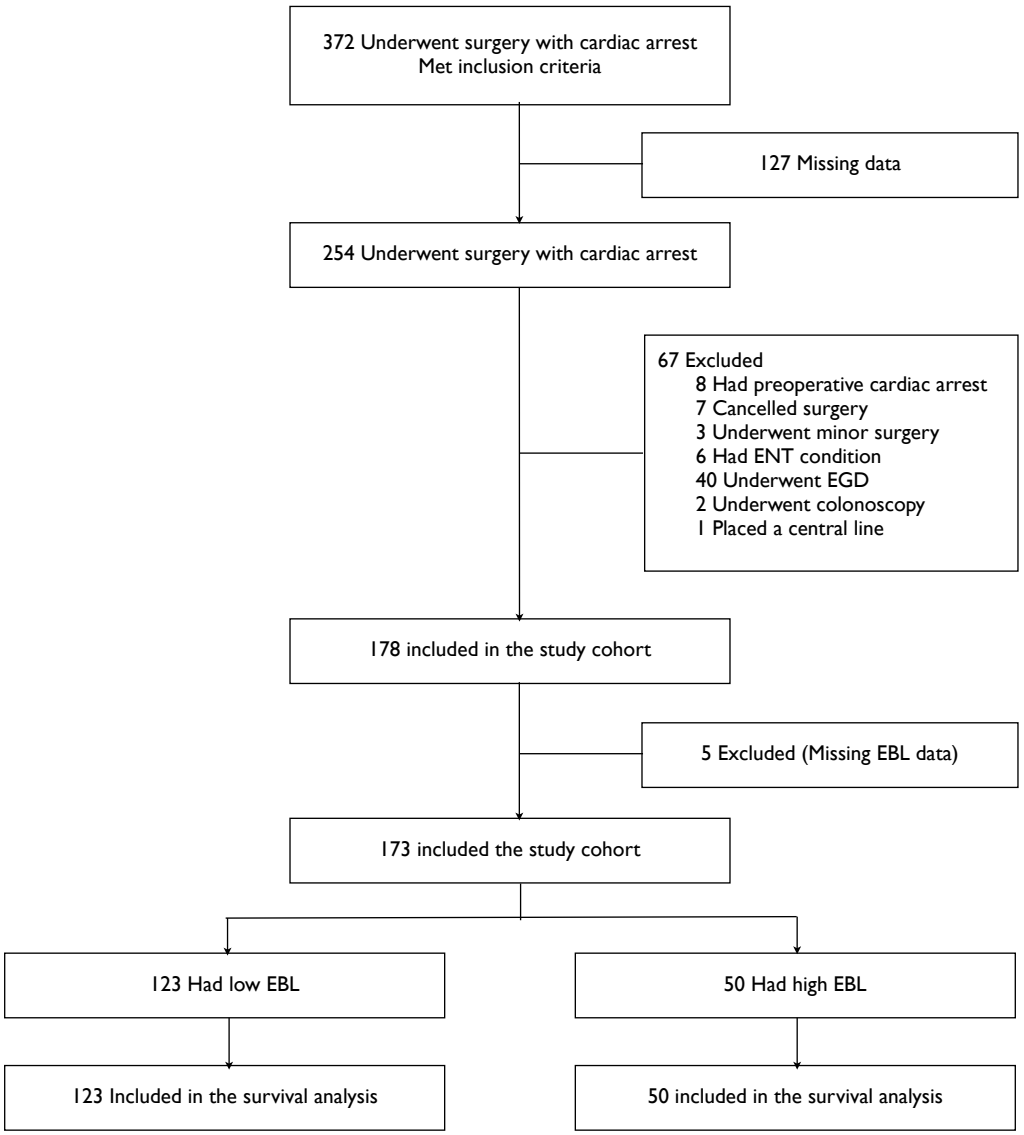

Figure 1. Patient Flow Chart.
According to the figure, ENT indicates ear, nose and throat or otorhinolaryngology; EGD, esophagogastroduodeno- scopy; EBL, estimated intra-operative blood loss.

December 2008 and June 2012. The characteristics of the low EBL group and high EBL group are shown in Table 1. The high EBL group were primarily men (76.0%), had a median age of 38.5 years, most had no underlying disease, prior cardiac arrest, and history of drug use. In this group, most had blunt abdominal injury, were taken more than 60 minutes of time of operation, and underwent exploratory laparotomy (EL). In this group, the ECG pattern during cardiac arrest was mostly pulseless electrical activity (PEA), serum potassium status was mostly normokalemia.

For the outcomes, patients with high EBL tended to died more ($P<0.01$). Most died in 8 hr after surgery ($P<0.01$) but had no infection after surgery ($P<0.01$). Patients with low EBL tended to died more ($P<0.01$). Most died in 51 hr after surgery ($P<0.01$) and tended to have sepsis after surgery ($P<0.01$) (Table 2).

Table 1. Characteristics of 173 Postoperative Patients with Cardiac Arrest, According to the Severity of Intra-Operative Blood Loss.

Characteristic	Low EBL (<660 ml) (n=123)	High EBL (≥660 ml) (n=50)	P Value
Age—yr			<0.01
Median	63.0	38.5	
Interquartile range	50.0-74.0	24.8-62.3	
Male sex—no. (%)	74 (60.2)	38 (76.0)	0.05
Time of operation—min			<0.01
Median	60.0	87.5	
Interquartile range	40.0-95.0	59.8-126.3	
Type of incision—no. (%)			<0.01
Exploratory laparotomy(REF)	61 (49.6)	38 (77.6)	
Debridement	25 (20.3)	1 (2.0)	
Craniectomy or craniotomy or ventriculostomy	12 (9.8)	7 (14.3)	
Amputation	7 (5.7)	2 (4.1)	
Others	18 (14.6)	1 (2.0)	
Underlying disease—no. (%)			
Diabetes mellitus	37 (30.1)	5 (10.0)	<0.01
Hypertension	44 (35.8)	6 (12.0)	<0.01
Dyslipidemia	10 (8.1)	2 (4.0)	0.51
Heart diseases	13 (10.6)	1 (2.0)	0.07
Stroke	7 (5.7)	1 (2.0)	0.44
History of drug use—no. (%)			
Diuretics	10 (8.1)	1 (2.0)	0.18
Aspirin	12 (9.8)	1 (2.0)	0.11
Antiarrhythmics	2 (1.6)	0	1.00
Digitalis	2 (1.6)	0	1.00
Steroid	15 (12.2)	0	<0.01
History of prior cardiac arrest—no. (%)	6 (4.9)	15 (30.0)	<0.01
Principal diagnosis—no. (%)			<0.01
Blunt abdominal injury	5 (4.1)	22 (44.0)	
Intracranial hemorrhage	14 (11.4)	9 (18.0)	
Necrotizing fasciitis or cellulitis or pyomyositis or myonecrosis	25 (20.3)	1 (2.0)	
Hollow viscus organ perforation	31 (25.2)	2 (4.0)	
Gastrointestinal obstruction	12 (9.8)	1 (2.0)	
Non necrotizing fasciitis infection	22 (17.9)	2 (4.0)	
Other diseases	14 (11.4)	13 (26.0)	
Serum potassium before or during cardiac arrest[15-17]—mmol/L			0.56
Median	3.6	3.7	
Interquartile range	3.2-4.4	3.3-4.6	
Electrocardiogram during cardiac arrest—no. (%)			0.51
Pulseless electrical activity	32 (33.3)	10 (35.7)	
Asystole	31 (32.3)	12 (42.9)	
Ventricular tachycardia	16 (16.7)	1 (3.6)	
Ventricular fibrillation	6 (6.3)	1 (3.6)	
Atrial fibrillation	7 (7.3)	3 (10.7)	
Supraventricular tachycardia	4 (4.2)	1 (3.6)	

Table 2. Outcome

Outcome	Low estimated blood loss (<660 ml) (N=123)	High estimated blood loss (≥660 ml) (N=50)	P Value
Death—no. (%)	74 (60.2)	44 (88.0)	<0.01
Time to death—hr			<0.01
Median	51.0	8.0	
Interquartile range	24.0-144.8	1.0-72.0	
Time to discharge if survived—hr			0.61
Median	72.0	172.0	
Interquartile range	27.0-213.5	18.5-460.3	
Infection—no. (%)			<0.01
Local infection	29 (23.6)	7 (14.0)	
Sepsis	68 (55.3)	3 (6.0)	

From the univariable analysis, factors associated higher rate of death were high EBL (COR, 4.86; 95% CI. 1.81 to 13.76) and blunt abdominal injury (COR, 15.29; 95% CI, 1.70 to 349.11). Factors associated with lower death rate were history of aspirin use (COR, 0.18; 95% CI, 0.04 to 0.68). However, patient age, male sex, time of operation, type of incision, underlying disease, history of other drug use, history of prior cardiac arrest, other principal diagnosis were found not associated with death (Table 3).

From the logistic regression analysis, factors associated with higher rate of death were high EBL (AOR, 7.52; 95% CI 1.70 to 33.23), underlying stroke (AOR, 130.30; 95% CI, 3.70 to 4583.5), blunt abdominal injury (AOR, 21.30; 95% CI, 1.73 to 262.42) and hyperkalemia (AOR, 6.79; 95% CI, 1.02 to 45.17). Factors associated with lower death rate were history of aspirin use (AOR, 0.02; 95% CI, 0.00 to 0.41). However, patient age, male sex, time of operation, type of incision, other underlying disease, history of other drug use, history of prior cardiac arrest, other principal diagnosis, serum potassium status before or during cardiac arrest and infection (complication) were found not associated with death (Table 3).

From the Cox's proportional hazard regression, the overall median survival was 72 hours. Factors associated with higher rate of death were high EBL (HR, 1.99; 95% CI 1.17 to 3.31), stroke (HR, 2.92; 95% CI 1.03 to 8.26), the principal diagnosis of blunt abdominal injury (HR, 2.40; 95%CI 1.12 to 5.16), necrotizing fasciitis or cellulitis or pyomyositis or myonecrosis (HR, 5.10; 95% CI, 1.55 to 16.83),non necrotizing fasciitis infections (HR, 2.90; 95% CI 1.12 to 7.54) and hyperkalemia (HR, 2.16; 95% CI, 1.14 to 4.11). Factors not associated with death rate was patient age, male sex, time of operation, type of incision, underlying disease (DM, HT, dyslipidemia, heart disease), history of other drug use, history of prior cardiac arrest, other principal diagnosis and hypokalemia (Table 4).

DISCUSSION

Principal findings

In the 173 patients that underwent surgery with cardiac arrest, the overall median survival was 72 hours. EBL of 660 ml or more, underlying stroke, blunt abdominal injury, NF, non NF infection and hyperkalemia were found to be significantly associated with higher death rate. However, age, sex, time of operation, type of incision, other underlying diseases (DM, HT, dyslipidemia, heart disease), history of drug use, history of prior cardiac arrest, other principal diagnosis and hypokalemia were not significantly associated with death.

Strength and limitation

This is the first study to our knowledge that explore the relationship between EBL and death in those with postoperative cardiac arrest. Moreover, the sample size was more than adequate to ascertain the relationship. However, a larger sample is required for more precise estimation. Our study is a retrospective cohort. Missing data were inevitable. Still we verified and retrieved data as much as possible and kept the proportion of those data less than 5% for each variable. In the present study, the term intra-operative blood loss is from estimation. Thus, the accuracy might be indefinite. However, the estimation was based on the standard practice universally.

Table 3. Crude and Adjusted Odds Ratio of Factors Potentially Associated with Death from Logistic Regression.

Variable	Death (n=118) no. (%)	Survival (n=55) no. (%)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age—yr				
16-40	37 (31.4)	11 (20.0)	1.00	1.00
41-60	25 (21.2)	11 (20.0)	0.68 (0.23-2.00)	2.29 (0.52-10.00)
More than 60	56 (47.5)	33 (60.0)	0.50 (0.21-1.20)	3.81(0.90-14.29)
Male sex	81 (68.6)	31 (56.4)	1.69 (0.83-3.46)	0.99 (0.35-2.85)
Intra-Operative estimated blood loss 660 ml or more	44 (37.3)	6 (10.9)	4.86 (1.81-13.76)	7.52 (1.70-33.23)
Time of operation 60 min or longer	60 (50.8)	28 (50.9)	0.90 (0.44-1.83)	0.54 (0.18-1.64)
Type of incision				
Exploratory laparotomy	68 (58.1)	31 (56.4)	1.60 (0.52-4.84)	1.02 (0.21-4.94)
Debridement	18 (15.4)	8 (14.5)	1.64 (0.40-6.75)	0.78 (0.10-6.30)
Craniectomy or craniotomy or ventriculostomy	15 (12.8)	4 (7.3)	2.73 (0.54-14.64)	3.48 (0.13-91.73)
Amputation	5 (4.3)	4 (7.3)	0.91 (0.14-5.95)	0.71 (0.05-10.86)
Others	11 (9.4)	8 (14.5)	1.00	1.00
Underlying disease				
Diabetes mellitus	26 (22.0)	16 (29.1)	0.69 (0.31-1.52)	1.38 (0.42-4.57)
Hypertension	29 (24.6)	21 (38.2)	0.53 (0.25-1.11)	0.59(0.18-1.88)
Dyslipidemia	6 (5.1)	6 (10.9)	0.44 (0.12-1.63)	0.38 (0.06-2.29)
Heart diseases	8 (6.8)	6 (10.9)	0.59 (0.17-2.06)	1.84 (0.32-10.54)
Stroke	7 (5.9)	1 (1.8)	3.41 (0.40-75.50)	130.30 (3.70-4583.50)
History of drug use				
Diuretics	5 (4.2)	7 (12.5)	0.36 (0.09-1.42)	0.87 (0.16-4.78)
Aspirin	4 (3.3)	9 (16.1)	0.18 (0.04-0.68)	0.02 (0.00-0.41)
Digitalis	1 (0.8)	1 (1.8)	0.46 (0.01-17.25)	7.40 (0.13-429.68)
Steroid	9 (7.5)	6 (10.7)	0.67 (0.20-2.28)	0.86 (0.22-3.37)
History of prior cardiac arrest	15 (12.7)	6 (10.9)	1.19 (0.40-3.68)	0.42 (0.08-2.28)
Principal diagnosis				
Blunt abdominal injury	26(21.3)	1 (1.8)	15.29 (1.70-349.11)	21.30 (1.73-262.42)
Intracranial hemorrhage	20 (16.4)	5 (8.9)	2.12 (0.51-9.06)	0.98 (0.05-21.18)
Necrotizing fasciitis or cellulitis or pyomyositis or myonecrosis	18 (14.8)	8 (14.3)	1.32 (0.37-4.84)	4.34 (0.46-41.44)
Hollow viscus organ perforation	19 (15.6)	14 (15.0)	0.80 (0.25-2.57)	2.37 (0.47-11.97)
Gastrointestinal obstruction	6 (4.9)	7 (12.5)	0.50 (0.11-2.33)	1.36 (0.20-7.84)
Non necrotizing fasciitis infections	14 (11.5)	10 (17.9)	0.82 (0.23-2.94)	2.01 (0.37-10.98)
Other diseases	19 (15.6)	11 (19.6)	1.00	1.00
Serum potassium status before or during cardiac arrest				
Normokalemia	50 (42.4)	26 (47.3)	1.00 (0.52-1.91)	1.00
Hypokalemia	53 (44.9)	25 (45.5)	0.91 (0.44-1.88)	0.75 (0.32-1.76)
Hyperkalemia	15 (12.7)	4 (7.3)	1.78 (0.49-7.05)	6.79 (1.02-45.17)

Table 4. Hazard ratios of Factors Potentially Associated with Death from Cox Proportional Hazard Regression.

Variable	Hazard ratios	95% confidence interval
Age—yr		
16-40	Reference	
41-60	0.62	0.34-1.14
More than 60	0.57	0.31-1.07
Male sex	0.74	0.46-1.20
Intra-Operative estimated blood loss 660 ml or more	1.99	1.17-3.37
Time of operation 60 min or longer	0.75	0.45-1.23
Type of incision		
Exploratory laparotomy	1.69	0.71-4.03
Debridement	0.40	0.13-1.24
Craniectomy or craniotomy or ventriculostomy	1.48	0.44-5.04
Amputation	0.27	0.06-1.34
Others	Reference	
Underlying disease		
Diabetes mellitus	0.97	0.52-1.84
Hypertension	0.78	0.43-1.42
Dyslipidemia	1.48	0.52-4.21
Heart diseases	0.60	0.25-1.47
Stroke	2.92	1.03-8.26
History of drug used		
Diuretics	0.52	0.19-1.42
Aspirin	0.43	0.12-1.57
Digitalis	0.54	0.06-5.05
Steroid	0.50	0.22-1.13
History of prior cardiac arrest	0.58	0.31-1.09
Principal diagnosis		
Blunt abdominal injury	2.40	1.12-5.16
Intracranial hemorrhage	0.83	0.26-2.63
Necrotizing fasciitis or cellulitis or pyomyositis or myonecrosis	5.10	1.55-16.83
Hollow viscus organ perforation	1.18	0.49-2.84
Gastrointestinal obstruction	0.88	0.30-2.55
Non necrotizing fasciitis infections	2.90	1.12-7.54
Other diseases	Reference	
Serum potassium status before or during cardiac arrest		
Normokalemia	Reference	
Hypokalemia	0.85	0.54-1.34
Hyperkalemia	2.16	1.14-4.11

Comparison with other studies

In the present study found that high EBL was increasing the death rate, supports the result of the study in Brazil that the third largest cause of cardiac arrest and death was intra-operative exsanguinating hemorrhage associated with primary disease.[7] And it also supports the result of the study in Uruguay that the one of the main cause of cardiac arrest and death in the operating room was bleeding that requires massive blood transfusion.[9] For the result that the underlying stroke was associated with higher death rate, it supports the result of the study in Canada that acute stroke could impair central autonomic control, triggering myocardial injury, ECG abnormalities, cardiac arrhythmias and sudden cardiac death.[14] According to hyperkalemia, it supports the results of a review in UK that concluded that serum potassium 8.0 mmol/L or more increased the risk of cardiac arrest.[16] Although the previous studies found that age, DM, DLP, history of diuretic drug use, history of digitalis use and craniectomy were associated with higher death rate,[11–13] but in the present study found that those factors were not associated with death.

Conclusion and implication

This study shows high EBL of 660 ml or more is a significant risk factor for death in patient with postoperative cardiac arrest. Thus, patients in the first high EBL should be monitoring closely especially in the first 72 hours after the operation. Moreover, those with stroke, blunt abdominal trauma, NF and non NF infection and hyperkalemia should be under close supervision as well. For the further study, larger prospective cohort should be conducted to confirm our findings, and for the investigation of efficacy of blood transfusion in those with high EBL.

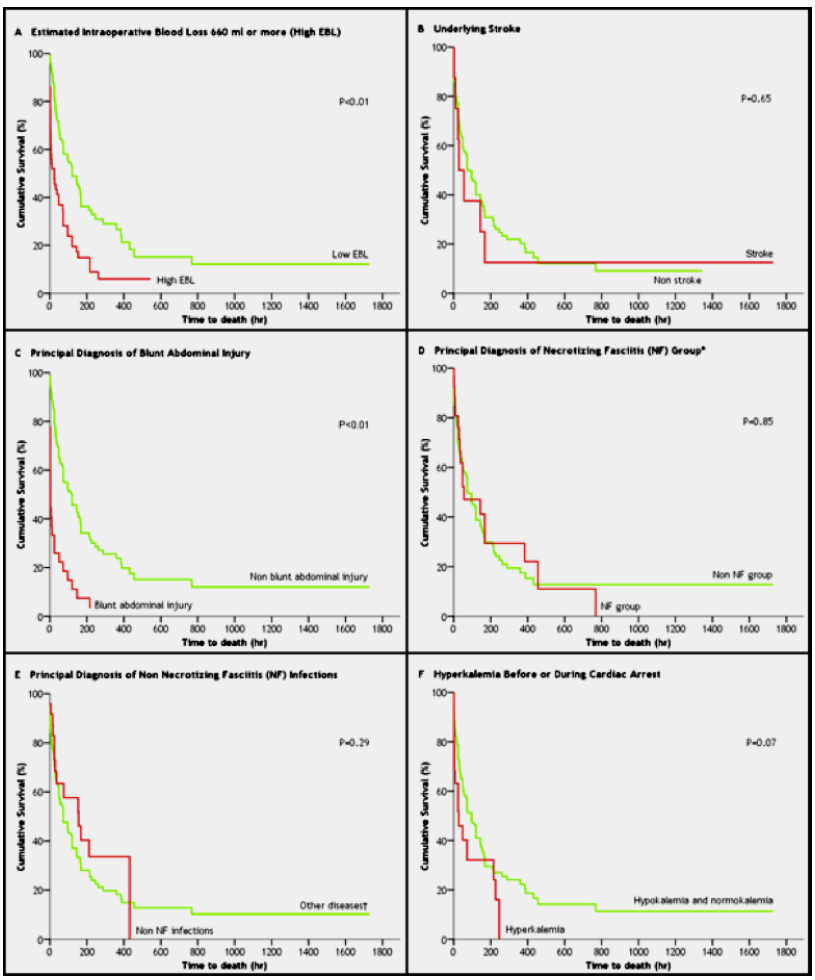

Figure 2. Survival Analysis and Kaplan-Meier Curves Showing Cumulative Survival of Patients with Postoperative Cardiac Arrest. Factors Associated with Higher Death Rate were High EBL (Panel A), Stroke (Panel B), Blunt Abdominal Injury (Panel C), NF Group (Panel D), Non NF Infections (Panel E) and Hyperkalemia (Panel F)

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ORIGINAL ARTICLE

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Comparison of Treatment Outcome between Multiple Antibiotics and Ceftazidime Alone for Melioidosis

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ABSTRACT

BACKGROUND
Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, the organism is a major cause of human morbidity and mortality especially in northeastern Thailand. Current treatment of choice is ceftazidime alone or ceftazidime plus cotrimoxazole. In some case, multiple antibiotics were used, but there were little published clinical data regarding the use of multiple antibiotics in the treatment of melioidosis.

METHODS
This was retrospective cohort study analyzing the medical records of all patients who diagnosed as melioidosis that admitted to Khon Kaen Hospital between January 2009-September 2012. Patients who had no evidence for melioidosis diagnosis, did not take interested antibiotics, readmission and no medical record from the Hospital's database were all excluded. Outcomes were death rate and complications in two groups between treated with ceftazidime alone and treated with multiple antibiotics group.

RESULTS
321 patients with melioidosis were screened by culture for B.pseudomallei was positive, 202 patients treated with ceftazidime alone and 119 patients treated with multiple antibiotics. Lung infection, sputum culture and others specimens culture (cerebrospinal fluid (CSF), pleural fluid and liver tissue) were three baseline characteristics which were significant difference between two groups of the study. Lung infection (35.6% and 58.0%; P<0.001), sputum culture (16.8% and 29.4%; P=0.008) and others specimens culture (17.9% and 1.7% P= 0.019). The significant difference outcomes were death (12.4% and 46.2%; P<0.001), time to death since hospital admission (54.2+13.8 days and 29.9+23.5 days; P<0.001), acute kidney injury (AKI) (18.8% and 47.9%; P<0.001), acute respiratory failure (17.8% and 55.5%; P<0.001), electrolyte and/or acid base imbalance (63.4% and 82.4%; P<0.001), cardiac arrest (5.0% and 17.6%; P<0.001) and septic shock (16.8% and 41.2%; P<0.001). In thebinary logistic regression analysis to evaluate factors determining death, we found treating with ceftazidime alone was a dependent factor (adjusted odds ratio 6.38; 95% confidence interval 3.58-11.37).

CONCLUSION
Multi-antibiotic drug such as meropenem, sulperazone and tazocin are a safe and effective treatment for melioidosis septicemia and may be considered an alternative to ceftazidime.

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, the organism is widely distributed in the soil and water in the tropics, highly endemic northeastern Thailand, and is a major cause of human morbidity and mortality in northeastern Thailand.[1,2,3] Death occurred in 956 of 2,243 patients, mortality rate is 40.5% in 2006.[4]

Current treatment of choice of melioidosis is considered to use ceftazidime alone or ceftazidime plus cotrimoxazole.[5,6,7] Ceftazidime alone can decrease mortality rate from 74% to 37% P=0.009 compared to conventional therapy; chloramphenicol plus doxycycline plus cotrimoxazole.[5] Ceftazidime plus cotrimoxazole can decrease mortality rate from 47% to 18.5% P=0.039 compared to conventional therapy.[6] Moreover, ceftazidime plus cotrimoxazole is not significant difference to ceftazidime alone for the treatment outcomes (odds ratio, 0.88; 95% CI, 0.48-1.6; stratified P=0.70).[7]

To our knowledge, there have been little published clinical data regarding the use of multiple antibiotics (ceftazidime with meropenem and/or sulperazone and/or tazocin) in the treatment of melioidosis.[8] We, thus, conducted retrospective cohort study to evaluate efficacy of multiple antibiotics compare with ceftazidime in patients who had positive *Burkholderia pseudomallei* cultured.

METHODS

Study design
We conducted a retrospective, cohort study from January 2009 through September 2012 aimed to compare the two treatments for melioidosis; ceftazidime alone and multiple antibiotics.

Patient selection
All patients admitted to Khon Kaen Hospital (a tertiary-care hospital in Northeastern Thailand) between January 2009-September 2012 who diagnosed as melioidosis by medical record was included.The patients were excluded by the following criteria; (i) no evidence for melioidosis diagnosis (blood, sputum, pus, urine, or other bacteriology specimens culture covered a *B. pseudomallei*)[8,9], (ii) re-admission, (ii) did not take interested antibiotics and (iv) no medical record from the Hospital's database (Figure 1). On the assumption, a sample of 66 patients per group would be required to detect the difference between the treatments of melioidosis.

Interested intervention
Indications for the use of multiple antibiotics included patients with critical illness (including septicemic) admitted to intensive care for management, clinical failure, or intolerance to ceftazidime and relapse following therapy with ceftazidime. Other patients received ceftazidime as initial therapy. We specifically sought details of possible adverse events, treatment failure requiring a change in therapy.

Comparison
For this study, clinical details were reviewed for patients who were treated for melioidosis from January 2009 through September 2012. For this study, we defined two groups; the multiple antibiotics group comprised patients that received multiple antibiotics as part of their therapy for melioidosis (including patients switched from ceftazidime), and the ceftazidime alone group received ceftazidime as treatment.

Outcome
The primary outcome of the present study was death rate in two groups between treated with ceftazidime alone and treated with multiple antibiotics group. Secondary outcomes were complications; acute kidney injury, congestive heart failure, acute respiratory failure, electrolyte and/or acid base imbalance, disseminated intravascular coagulopathy, cardiac arrest, septic shock and adrenal insufficiency.

Data collection
Data collection was also performed using a computerized database of a Khon Kaen Hospital. Demographic data, underlying disease, methods of melioidosis diagnosis, patient's diagnosis, history of re-admission, treatment on admission, complication on admission, and discharge status were recorded retrospectively. Underlying disease was classified into five groups, diabetes mellitus, hypertension, chronic kidney disease (CKD), cirrhosis, and others (SLE, thalassemia, benign prostatic hypertrophy (BPH), epilepsy, hyperthyroid, hypothyroid, dyslipidemia, asthma and chronic obstructive pulmonary disease). Specimens culture positive *B. pseudomallei* was classified into five group, blood, pus, sputum, urine, and others specimens culture (cerebrospinal fluid (CSF), pleural fluid and liver tissue). Complication from melioidosis was classified into eight group, acute kidney injury (AKI), congestive heart failure, acute respiratory failure, electrolyte and/or acid base imbalance, disseminated intravascular coagulopathy (DIC), cardiac arrest, septic shock and adrenal insufficiency. A result of treatment was classified into two groups, death, and survival. Time to death was using time since admission to death. All reviewed and collected from medical records onto a designed excel spreadsheet.

Statistical analysis
All statistical analysis was performed with statistic software package[18]. For descriptive statistics, categorical data were presented in relation to number and percentage. All numeric data were tested for their normal distribution using Kolmogorov test and presented in relation to median and interquartile range (IQR) if they were not normally distributed. For

Table 1. Baseline Characteristics of the Patients

Characteristic	Ceftazidime alone (N=202)	Multiple antibiotics (N=119)	P Value
Age-yr			0.551
Median	52	55	
Interquartile range	46-59	44-61	
Male sex-no. (%)	156 (77.2)	83 (69.7)	0.138
Underlying disease-no. (%)			
Hypertension	26 (12.9)	23 (19.3)	0.120
Diabetes mellitus	132 (65.3)	69 (58.0)	0.188
Chronic kidney disease	26 (12.9)	17 (14.3)	0.719
Cirrhosis	6 (3.0)	4 (3.4)	1.000
Other	64 (31.7)	47 (39.5)	0.155
Type or site of infection-no. (%)			
Melioidosis septicemia	130 (64.4)	87 (73.1)	0.106
Lung	72 (35.6)	69 (58.0)	<0.001
Skin and soft tissue	36 (17.8)	13 (10.9)	0.097
Bone and joint	30 (14.9)	16 (13.4)	0.728
Liver abscess	20 (9.9)	14 (11.8)	0.600
Splenic abscess	17 (8.4)	12 (10.1)	0.615
Urogenital organ	17 (8.4)	11 (9.2)	0.800
Specimen culture positive for *B.pseudomallei* -no. (%)			
Blood	127 (62.9)	84 (70.6)	0.159
Pus	41 (20.3)	18 (15.1)	0.248
Sputum	34 (16.8)	35 (29.4)	0.008
Urine	5 (2.5)	4 (3.4)	0.731
Others	16 (17.9)	2 (1.7)	0.019

Table 2. Treatment Outcomes

Outcome	Ceftazidime alone (N=202)	Multiple antibiotics (N=119)	P Value
Death-no. (%)	25 (12.4)	55 (46.2)	<0.001
Time to death since hospital admission-days	54.2±13.8	29.9±23.5	<0.001
Complication-no. (%)			
Acute kidney injury	38 (18.8)	57 (47.9)	<0.001
Congestive heart failure	7 (3.5)	3 (2.5)	0.750
Acute respiratory failure	36 (17.8)	66 (55.5)	<0.001
Electrolyte and/or acid base imbalance	128 (63.4)	98 (82.4)	<0.001
Disseminated intravascular coagulopathy	9 (4.5)	11 (9.2)	0.086
Cardiac arrest	10 (5.0)	21 (17.6)	<0.001
Septic shock	34 (16.8)	49 (41.2)	<0.001
Adrenal insufficiency	9 (4.5)	6 (5.0)	0.810

Table 3. Factors Determining Death

Variable	Crude odds ratio	95% Confidence interval	Adjusted odds ratio	95% Confidence interval
Age	NA	NA	0.99	0.96-1.01
Male sex	1.24	0.70-2.19	0.99	0.52-1.91
Diabetes mellitus	1.23	0.73-2.10	0.70	0.38-1.29
Hypertension	1.58	0.81-3.05	1.12	0.49-2.59
Chronic kidney disease	1.98	1.01-3.90	0.47	0.20-1.08
Cirrhosis	0.33	0.04-2.62	4.33	0.47-39.79
Melioidosis septicemia	2.30	1.25-4.22	0.49	0.21-1.17
Treating with ceftazidime only	0.16	0.09-0.29	6.88	3.58-11.37
NA not applicable				

inferential statistics, chi-square was used for the analysis of categorical data or exact test where appropriate. Mann-Whitney U test was used for not normally distributed numeric data to compare the difference between two groups. Epi Info™ 7 were used for crude odds ratio. Multivariable analysis, using the binary logistic regression to determine factors associated with death, presented by adjusted odds ratio, 95% confidence interval (CI). All statistics were significant at the level of 0.05. Kaplan-Meier analysis was used for analysis of survival according to melioidosis septicemia and survival according to CKD presented by median survival, P values and survival graph (Figure 2).

RESULTS

The retrospective cohort study from January 2009 through September 2012, a total of 1,179 patients were preliminarily included (Figure 1). Eight hundred and fifty-eight cases were excluded due to no evidence of melioidosis diagnosis, readmission, no interested drugs and no medical record from the hospital's database. Thus, 321 were eligible: 202 (62.9%) in group treated with ceftazidime alone and 119 (37.1%) in group treated with multiple antibiotics. Their baseline characteristics shown in Table 1. They had a median age of 52 years old (IQR, 46.0 to 59.0). Most of them were male. Nearly 50 patients had hypertension, 201 patients had diabetes mellitus, 43 patients had CKD. Only ten patients had cirrhosis and 111 were diagnosed with other underlying disease.In relation to site of infection, the secound most commonly prescribed were septicemia and lung infection (Table 1). However, few cases were infected skin and soft tissue, bone and joint, Liver abscess, Splenic abscess and urogenital organ. The most of specimens culture positive for *B.pseudomallei* were hemoculture. Pus culture was positive in 59 cases and sputum culture 69 cases. Only nine case had positive urine culture and 18 cases were positive culture in others site. In general, the baseline characteristics of the patients between those treated with ceftazidime alone and ceftazidime combined with other in this study were not significantly difference among the group. However, lung infection (P<0.001), sputum culture (P=0.008) and others specimens culture (P=0.019) were significant in Table 1.

Treatment Outcomes

Of the 321 patients, they were divided into two groups regarding the treatment; ceftazidime alone and multiple antibiotics. The patients died was 12.4 percent in the treatment by ceftazidime alone and 46.2 percent in the treatment by multiple antibiotics. Time to death since hospital admission of patients was shown significantly (P<0.001) (Table 2). In relation to the outcome of the treatment between two group.

Patients with complication had significant higher rate of acute kidney failure (P<0.001), acute respiratory failure (P<0.001), electrolyte and/or acid base imbalance (P<0.001), cardiac arrest (P<0.001) and septic shock (P<0.001) (Table 2). However, there were no significantly difference between the two groups in relation to congestive heart failure, disseminated intravascular coagulopathy and adrenal insufficiency.

Melioidosis septicemia and CKD were found to be factors that significantly associated with death (Crude odds ratio (COR) 2.30; 95% confidence interval (CI) 1.25-4.22 for septicemia and COR 1.38; 95% CI 1.01-3.90 for Chronic kidney disease) (Table 3). Treating with ceftazidime only was found as the factor that significantly decreasing death (COR 0.16; 95% CI 0.09-029) (Table 3) but others factors; sex and underlying disease such as diabetes mellitus, hypertension, and cirrhosis were also found to be independent factors associated with death.

The binary logistic regression analysis was used in factors determining death, treating with ceftazidime

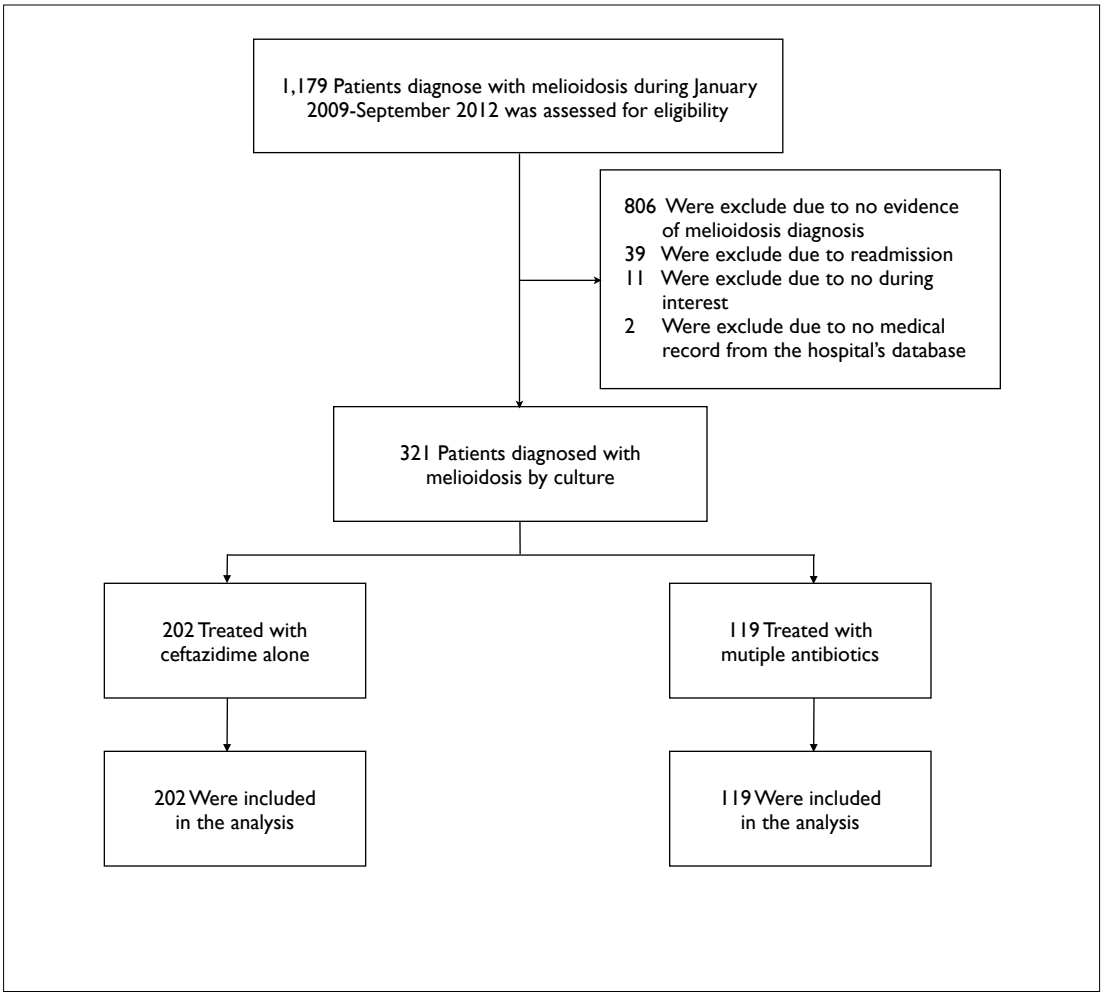

Figure 1. Study Flow Chart.

only were found to be a dependent factor for death (adjusted odds ratio 6.38; 95% confidence interval 3.58-11.37) (Table 3). Nevertheless, age, sex, diabetes mellitus, hypertension, chronic kidney disease, cirrhosis and septicemia were found not significantly associated with death.

In the patients with melioidosis septicemia and without melioidosis septicemia were significant difference in the time to death. The median survival for the group of melioidosis septicemia patients was 32 days, and the median survival for the group of patients who did not have melioidosis septicemia is 52 days, P=0.020 (Fig 2A). In CKD patients, COR shown significantly associated with death, were not significant difference in the time to death compared to non CKD patients. The median survival for CKD patients group was 29 days, and 45 days for the non CKD patients group P=0.121 (Fig. 2B).

DISCUSSION

Our retrospective cohort study in the patients with melioidosis were screened by culture positive for *B.pseudomallei* showed that the treatment with ceftazidime only was an dependent factor for death. It also found associated with melioidosis septicemia. Comparison between ceftazidime only and multiple antibiotic, It found that complications such as acute kidney injury, acute respiratory failure, electrolyte and/or acid base imbalance, cardiac arrest and septic shock were significantly.

Comparison with others studies

From our knowledge, this is the first study which has sample size more than 300 patients to determine

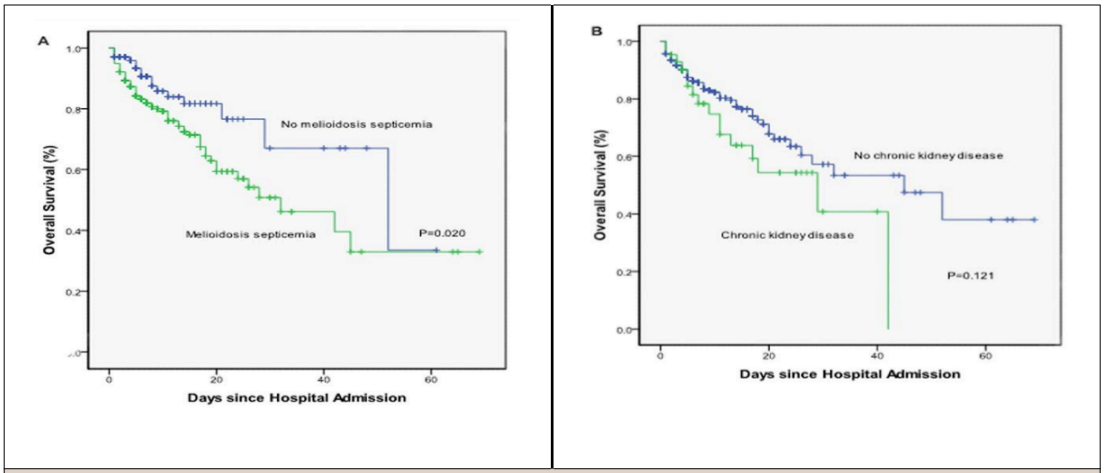

Figure 2. Kaplan-Meier Analysis of Survival according to Melioidosis septicemia and Survival according to Chronic kidney disease (CKD).
Panal A shows survival of patients who had melioidosis septicemia and no melioidosis septicemia. Panel B shows survival of patients who had CKD and no CKD. P values were calculated with the use of the log-rank test.

efficacy of treatment of melioidosis.[6,7,10-13] Other data such as epidemiology and patients characteristics supported previous studies reported elsewhere. This study shows that male have a higher risk of melioidosis than female, which supports seven other studies in Australia, Malaysia and Thailand.[6,7,10-14] The median age found in this study appeared to be similar with studies in Australia, Malaysia, Thailand and Singapore with a median age of 50, 51, 51 and 55 years respectively. [7,10,14] Of the 10 articles, they present that 42-65% of the melioidosis patients are diabetes mellitus, our study found that 62.6% of all included patients are diabetes mellitus.[4,7,10-13,15-18] Our study is consistent with those studies. The present practice and knowledge suggest ceftazidime alone is the treatment of choice, but our study found that ceftazidime alone is a dependent factor to time to death, this is a conflict which should be studied further.[5-7]

Strength and Limitations

The main strength of this study is that the sample size, this study was conducted in an endemic area with the highest incidence of melioidosis (21.31 per 100,000 people per year).[4] Secondly, to our knowledge this is the first study which try to determine efficacy of treatment of melioidosis between ceftazidime alone and multiple antibiotics treatment.

There were several limitation in our study. Firstly, some patients admitted are those who have been partially treated and referred to community hospital. Thus, some patients included in the study tended to have incomplete recovery, leading to a biased result. Secondly, the loss of some medical record, bad handwriting and the ambiguous record were difficult to sampling and grouping because we could not know exactly how many antibiotics were used per patient, so we could lose patients who received the interested antibiotics or we could miss in grouping the sample. Thirdly, many of multiple antibiotics treatments in this study were not absolute combination, but those were a switch therapy.

Conclusions and implication

In summary, our retrospective cohort study suggested that the treatment with ceftazidime only was a dependent factor for death. Melioidosis septicemia was a significant risk factor for time to death. We suggested that patients with melioidosis septicemia should be closely monitored. Future study, we suggest RCT for control confounders and decrease limitation in study, and report absolute risks of either individual outcomes are recommendation.

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ฉันจักเจอหนทาง หรือมิฉะนั้นฉันจักสร้างมัน
I shall find either a way or make one

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IN EDUCATION, WE CAN WIN ALL

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