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From the Editor

Please be welcomed to Journal of Medical Research and Education (JMRE). This is the first issue of our second year. As usual, in this issue you can explore the various types and areas of research conducted by medical students. Moreover, in the section of perspective, we provide you the information and a case study regarding the approach by the Thai Ministry of Public to alleviate the problem of shortage and retention of doctors in the Thai rural area via the system of medical education. Moreover, I would like, personally, to thank Miss Sila Amatayakul for her contributions of beautiful photo appeared in this issue.

Hope you enjoy reading our journal!

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

Editor-in-Chief of JMRE

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Sila Amatayakul

PERSPECTIVE

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Increase Production of Doctor in Resource Limited Settings: a Case Study of Khon Kaen Medical Education Center, Thailand

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Shortages doctor in rural areas is a global problem regardless of the countries' economics.[1] Moreover, the problem is aggravated by the maldistribution and discrepancy of concentration of doctors in rural and urban areas.[2] Hence, insufficient production as well as inability to maintain doctor in rural areas seems to be the key issues. Regarding World Health Organization (WHO), the ratio doctor to population should of 1:600 is recommended at 2020.[2] However, the current situation is far from the recommendation and might not be possible for many countries. From the projection by the Ministry of Public Health, Thailand, more than 40,000 doctors will be produced by the year 2020, the ratio will be scaled up to the one doctor to approximately 1,500 population.[3]

In Thailand, there were only eight medical schools in the year 1995, at that time, less than a thousand doctors were graduated annually with the ratio of doctor to population of 1:4,180. In 2013, there are 21 medical schools in Thailand with the capacity of doctors production of 2,242. More than 50% of doctors nowadays are from the Collaborative Project to Increase Production of Rural Doctor (CPIRD).[4] The project was initiated in 1995 and Khon Kaen Hospital was the first regional hospital was opted to produce the doctor under the project. [4]

In Thai curriculum, six years in the medical school is compulsory; the first three years are pre-clinical training and the latter three years are clinical clerkship which requires a hospital as a training site rather than a university environment only. Investment a new medical school for increase production of doctor might not be a cost-effective option as its time consuming as well as vast amount of money. One of the pragmatic solution is making use of the existing resources such as regional hospitals through out the country as clinical training site. As a result, Khon Kaen Medical Education Center was established.[4]

Initially, only 10 doctors were graduated in 2001. Over the past decade, more than 45 doctors are produced annually.[5] Moreover, the center was also grown in term of medical teaching staff and infrastructure. The project provides grants for staff to further their studying in medical education in the int well-known international institution regularly and to attend the international medical education conferences every year. Moreover, budgets regarding research presentation both medical education and clinical research are also provided.

In relation to incentives, extra-payment for medical staff for their activities regarding teaching and learning such as lectures, clinical teaching, examinational material construction is offered. Medical services involving with medical education are also paid for the facilitation of teaching and learning. As a result, number of the staff are doubled over the last ten years with lower turn over rate. In term of

infra-structure such as student dormitories, library, clinical skill center, lecture theaters, medical student clubs, they have been built gradually from the support of project.

Researches regarding medical education are produced regularly; four to five researches per year. The quality of medical graduates are comparable to those graduated from universities's hospitals which can be seen by the results of the National Licensing Examination (NLE) with more than 90% pass the overall three steps of NLE in their first and second attempts.[6] For the post-graduate evaluation, it suggested that medical graduates from the Khon Kaen Medical Education were rated as good and excellent in all aspects by their peers, colleagues, patients and the authorities where they worked.

After three-year compulsory to work as the government officer for all medical graduates those trained in public hospitals, graduates from the Khon Kaen Medical Education Center tended to stay longer in the rural areas comparing to those from other CPIRD centers and other medical schools (75%, 69% and 59% three-year retention rates, respectively).[6]

In conclusion, in a situation and setting in which overall resources to establish a new medical school is limited, the production of new doctors could be increased effectively and efficiently by making use the existing resources where appropriate. The medical students can be trained in a regional hospital with comparable standard as the well-established medical school.

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Original Articles

by Medical Students

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Sila Amatayakul

ORIGINAL ARTICLE

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The Association between Vacuum Delivery and Timing of The Third Stage of Labor

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ABSTRACT

BACKGROUND
The evidences of the association between timing of the third of labor and vacuum delivery are relatively scarce. The objective of our study is to ascertain the association.

METHODS
This is a retrospective cohort study comparing the timing of the third stage of labor and vacuum delivery of patients delivered at Khon Kaen Hospital between August and October 2012. The secondary outcomes were timing of the first stage of labor, timing of the second stage of labor, estimated blood loss, APGAR score at 1 and 5 minute and neonatal complications. The factors which the association with timing of placenta delivery were also identify through Cox proportional hazard regression.

RESULTS
A total of 892 patients were included. Seventy cases were undergone vacuum deliveries and 822 cases were normally delivered. The timing of the third stage of labor was significantly longer in normal delivery group (P=0.007). It also found the timing of the first stage of labor was significantly shorter in normal delivery group (P=0.002) as well as the timing of the second stage of labor (P<0.001). APGAR score at 1 minute<7 was significantly lower in normal delivery group (P<0.001), estimate blood loss was significantly lower in normal delivery group (P<0.001), neonatal complication was found less frequent in normal delivery group. From the Cox's proportional hazard regression, meconium amniotic fluid stained was significantly associated with higher the timing of placenta delivery was (HR 1.42; 95% CI, 1.16 to 1.74).

CONCLUSION
The timing of the third stage of labor was significantly longer in normal delivery group compared to those in vacuum delivery group.

INTRODUCTION

The third stage of labor refers to the period from the delivery of the newborn until the complete delivery of the placenta.[1,2] The normal duration of the third stage of labor is not well defined with variations ranging from 10 to 30 minutes, however, retained placenta was generally diagnosed when the third stage of labour has not been completed within 15 minutes of the end of the second stage.[3] Retained placenta affects 0.5–3% of all pregnancies and accounts for 10–19% of all cases of postpartum hemorrhage, leading to major maternal morbidity and mortality worldwide.[4-7] Early identification and prevention of delay the third stage of risk factors can significantly decrease complications and improve obstetrical outcomes.[4] However, The exact etiology behind retained placenta is not known and probably complex.[8]

Vacuum delivery has affected normal mechanism of labor during delivery.[9] Prior study revealed that the mother with traumatic birth experience who used vacuum delivery was associated with delay third stage of labor.[9] Moreover, the indication for vacuum delivery is to shorten second stage of labor. Nonetheless, no previous study can clearly show the association of the timing of the third stage of labor and vacuum delivery. We, thus, conducted this study to ascertain the association between vacuum delivery and the timing of the third stage of labor.

METHODS

Study design

This is a retrospective cohort study comparing the timing of the third stage of labor and vacuum delivery.

Patients

We performed a retrospective chart review of all patients delivered at Khon Kaen Hospital between August and October 2012. The patients were excluded if (i) no medical record from the Hospital's database, (ii) cesarean delivery (Figure 1). A sample of 893 cases were defined as patients who underwent vacuum deliveries compare with those were randomly selected among all uncomplicated normal delivery performed at the same month and year as those in the Khon Kaen Hospital.

Exposure

All records after exclusion were categorized into two groups regarding their types of delivery; (i) normal delivery and (ii) vacuum delivery group.

Outcomes

The primary outcome of the present study was the timing of the third stage of labor. The secondary outcomes were the timing of the first stage of labor, the timing of the second stage of labor, estimated blood loss, APGAR score at 1 and 5 minutes and neonatal complication.

Data collection

The included medical records were reviewed regarding indication for vacuum delivery, success rate of vacuum delivery, maternal age, parity, gestational age, multiple gestation, body-mass index (BMI), history of diabetes, history of hypertension, previous abortion, labor induction, pudendal nerve block, birth weight, placental and cord weight, fetal sex, head circumference, meconium amniotic fluid stain, timing of the first stage of labor, timing of the second stage of labor, timing of the third stage of labor, APGAR score at 1 minute, APGAR score at 5 minute, neonatal complication. After that, all data were recorded onto a designed excel spreadsheet.

Statistical analysis

For descriptive statistics, categorical variables are summarized as number and percent (no. (%)). For scale variables, all numeric data are tested for their normal distribution using Kolmogorov smirnov test, mean and standard deviation (SD) were used if they are normally distributed while median and interquartile range (IQR) were used if there are non-normally distributed. For inferential statistics, compare the difference between two groups, either Chi-square or Fisher's exact test was used for categorical variables where appropriate. Independent t-test and Mann-Whitney U test were used for normally and non-normally distributed variables, respectively. All statistics were significant at $P<0.05$.

RESULTS

Between August and October 2012, there were 1,697 deliveries. Eight hundred and five cases were excluded due to cesarean delivery and no medical record from hospital database (Figure 1). Of the remaining 892 cases were included in these study, 70 cases were undergone vacuum deliveries and 822 cases were normally delivered. The indication for vacuum delivery and success rate is shown in Table 1. Mainly, the vacuum delivery was performed in the case of maternal exhaustion or to shorten second stage of labor (68.6%), Their success rate was as high as 94.3%.

The baseline characteristics and clinical status were similar in the normal delivery group and in the vacuum delivery group in relation to maternal age, gestational age, multiple gestation, history of diabetes, history of previous abortion and fetal sex (Table 2). However, comparing between normal and vacuum delivery, the former tended to have lower proportion of nulliparous parity (46.6% and 51.0% in normal delivery and vacuum delivery, respectively, $P<0.001$),

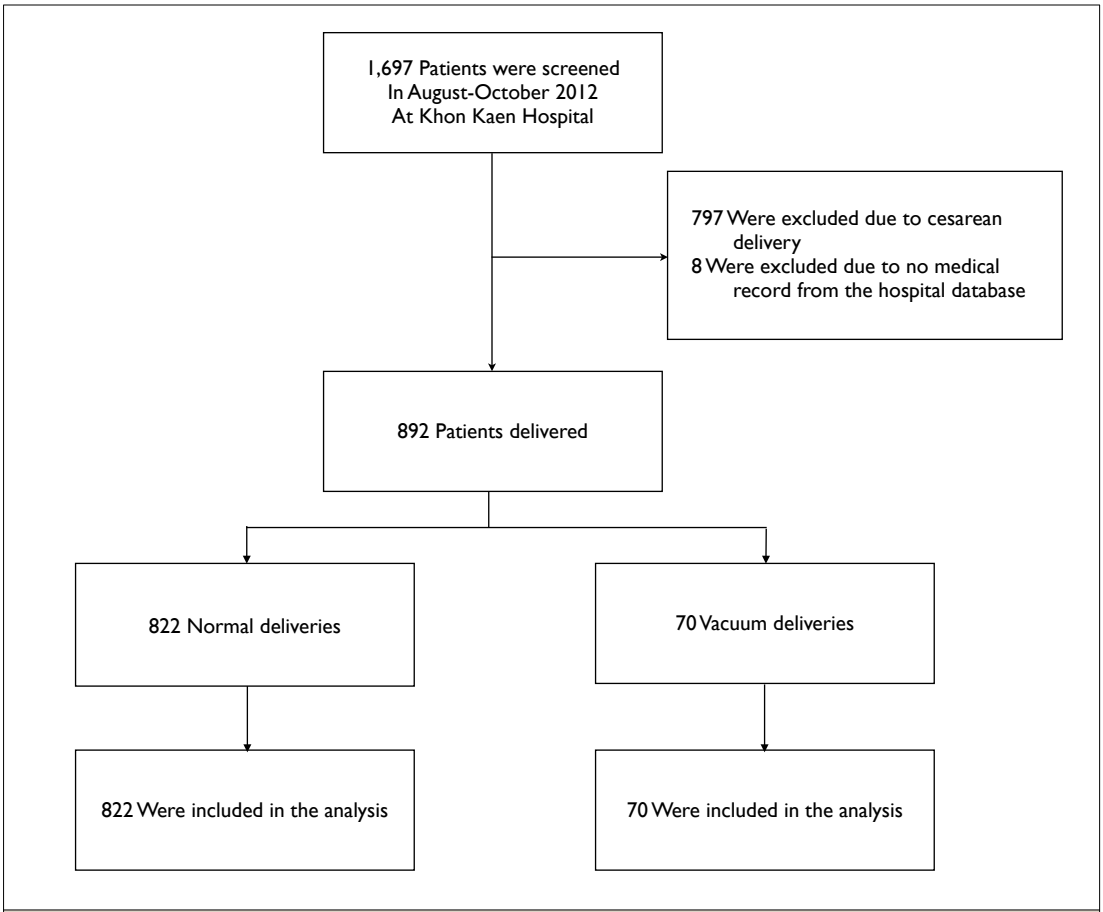

Figure 1. Study Flow Chart.

lower BMI (median 25.8 and 27.5, respectively, P<0.001), lower proportion of mother with history of hypertension (2.1% and 11.4% respectively, P<0.001), lower rate of labor induction (25.7% and 44.3%, P=0.001), lower rate of mother undergone pudendal nerve block (0% and 22.9%, P<0.001), lower birth weight (3010 grams and 3075 grams respectively, P=0.03), lower placenta and cord weight (mean 626.3 grams and 667.6 grams in normal delivery and vacuum delivery, respectively, P=0.001), lower head circumference (mean 32.8 cm and 33.2 cm in normal delivery and vacuum delivery respectively, P=0.03) and lower rate of meconium amniotic fluid stain (11.6% and 30% respectively, P<0.001).

In relation to delivery outcomes, there was no significant difference between the two groups regarding APGAR score at 5 minute<7, fetal anemia, shoulder dystocia, neonatal resuscitation and neonatal death. Nonetheless, the outcomes of the normal delivery and the vacuum delivery group are summarized in Table 3. The former group have significant longer timing of the third stage of labor (median 4 minutes and 3 minutes in normal delivery and vacuum delivery respectively, P=0.007), significant shorter of timing of the first stage of labor (median 508.5 minutes and 577.5 minutes in normal delivery and vacuum delivery, respectively, P=0.002), significant shorter of timing of the second stage of labor (median 12 minutes and 25.5 minutes in normal delivery and vacuum delivery respectively, P<0.001), estimate blood loss (mean 144.3 cc and 172.9 cc in normal delivery and vacuum delivery, respectively, P<0.001), lower proportion of neonate with APGAR score at 1 minutes<7 (2.9% and 17.1% in normal delivery and vacuum delivery, respectively, P<0.001), lower proportion of neonatal complication such as subdural hematoma (0% and 4.3% in normal delivery and vacuum delivery respectively, P<0.001), cephalhematoma (0.6% and 7.1% in normal delivery and vacuum delivery respectively, P<0.001), neonatal jaundice (16.2% and 35.7% in normal delivery and vacuum delivery, respectively, P<0.001) and respiratory distress syndrome (2.2% and 14.3% in normal delivery and vacuum delivery, respectively,

Table 1. Indication and Success Rate of Vacuum Delivery	
Indication for vacuum delivery--no. (%)	**N=70**
Maternal exhaustion or shorten second stage of labor	48 (68.6)
Non-reassuring fetal status	16 (22.9)
Prolong second stage of labor	5 (7.1)
Meconium amniotic fluid stained	1 (1.4)
Vacuum success rate --no. (%)	66 (94.3)

Table 2. Characteristics of the Mother and Neonate in Each Study Group.

Maternal characteristic	**Normal delivery (N=822)**	**Vacuum delivery (N=70)**	**P Value**
Maternal age (yr)			0.45
Median	23.5	24.5	
Interquartile range	19.8-28.0	18.8-29.0	
Nulliparous	383 (46.6)	51 (72.9)	<0.001
Gestational age (wk)			0.11
Median	39	39	
Interquartile range	37.8-39.0	38-40	
Multiple gestation--no. (%)	6 (0.7)	0	1.00
Body-mass index			<0.001
Median	25.8	27.5	
Interquartile range	23.4-28.8	25.6-30.9	
History of diabetes --no. (%)	13 (1.6)	2 (2.9)	0.33
History of hypertension --no. (%)	17 (2.1)	8 (11.4)	<0.001
Previous abortion--no. (%)	150 (18.2)	10 (14.3)	0.41
Labor induction--no. (%)	211 (25.7)	31 (44.3)	0.001
Pudendal nerve block--no. (%)	0	16 (22.9)	<0.001
Neonatal characteristic			
Birth weight (g)			0.03
Median	3010	3075	
Interquartile range	2740-3270	2870.0-3367.5	
Placenta and cord weight (g)			0.001
Median	600	600	
Interquartile range	600-700	600-800	
Male sex--no. (%)	411 (50.0)	32 (45.7)	0.49
Head circumference (cm)			0.03
Median	33	33	
Interquartile range	32-34	32-34	
Meconium amniotic fluid stain--no. (%)	95 (11.6)	21 (30.0)	<0.001

P<0.001). Using the definition of delay of the third stage of labor (longer than 15 minutes)[3], we found sixteen cases were delay, fifteen were normally delivered and one was vacuum delivered.

Kaplan-Meier estimates for the timing of placenta delivery is shown in Figure 2. We found that the timing of placenta delivery was shorter in patient who used pudendal nerve block and not used pudendal nerve block (median survival were 3 minutes and 4 minutes in patient who used pudendal nerve block and not used pudendal nerve block respectively, P=0.01). Moreover, the timing of placenta delivery was shorter in those with meconium amniotic fluid stained and without meconium amniotic fluid stained (median were 3 minutes and 4 minutes with meconium amniotic fluid stained and without meconium amniotic fluid stained respectively, P<0.001). From the Cox's proportional hazard regression (Table 4), factor found to be significantly associated with higher timing of placenta delivery was meconium amniotic fluid stained (HR 1.42; 95% CI, 1.16 to 1.74).

DISCUSSION

Major findings

Our retrospective cohort study in the patient with normal delivery and vacuum delivery showed the timing of the third of labor in normal delivery have significant longer than timing of the third stage of delivery in vacuum delivery. It also found the significant shorter in timing of the first of labor, shorter in timing of the second stage of labor, lower proportion of neonates with APGAR score at 1 minute<7 and lower proportion of neonatal complications among normal delivery as compared with vacuum delivery. From the Kaplan-Meier estimates show the timing of placenta delivery was shorter in patient who use pudendal nerve block and those with meconium amniotic fluid stained. Additionally, from the Cox proportional hazard regression analysis, we found that significant higher timing of placenta delivery associated with meconium amniotic fluid stained.

Table 3. Delivery Outcomes

Outcome	Normal delivery (N=823)	Vacuum delivery (N=70)	P Value
Timing of the third of labor (min)			0.007
Median	4	3	
Interquartile range	3-7	2-6	
Timing of the first stage of labor (min)			0.002
Median	508.5	577.5	
Interquartile range	340-680	475-780	
Timing of the second stage of labor (min)			<0.001
Median	12	25.5	
Interquartile range	7-19	14.8-58.0	
Estimated blood loss (ml)			<0.001
Median	150	150	
Interquartile range	150-150	150-200	
APGAR score at 1 minute<7	24 (2.9)	12 (17.1)	0.00
APGAR score at 5 minute<7	6 (0.7)	1 (1.4)	0.44
Subdural hematoma--no. (%)	0	3 (4.3)	<0.001
Cephalhematoma--no. (%)	5 (0.6)	5 (7.1)	<0.001
Neonatal Jaundice--no. (%)	133 (16.2)	25 (35.7)	<0.001
Anemia--no. (%)	9 (1.1)	1 (1.4)	0.56
Respiratory distress syndrome--no. (%)	18 (2.2)	10 (14.3)	<0.001
Shoulder dystocia--no. (%)	1 (0.1)	0	1.00
Neonatal resuscitation--no. (%)	4 (0.5)	1 (1.4)	0.34
Neonatal death--no. (%)	1 (0.1)	0	1.00

Comparison with existing literature

In this study, the major indication for vacuum delivery was maternal exhaustion or for shortening the second stage of labor which similar to the previous studies.[18,22,26,27,28] Birth weight of neonate who delivery by vacuum extraction in our study were relatively low (median birth weight is 3,075 grams), as compared with those in previous studies such as studies from Italy, Israel where median birth weight were 3,371±403 grams and 3,250 grams, respectively. Median of fetal head circumference of our study was 33 cm compared with previous studies (median fetal head circumference greater than 37 cm).[14,17,29] These differences might be due to the diversity of race and ethnicity. Timing of the first stage of labor in our study was also relatively low (median timing is 508.5 minutes) compared with previous study (median timing was 630 minutes). Timing of the second stage of labor was relatively low (median timing was 25.5 minutes) compare with previous study (median 37 minutes).[31,35] These differences might be due to the lower sample size in our study and clinical practice guideline in induction labor. We also found that neonates delivered in using vacuum extraction had higher risk for APGAR score<7 at 1 minute at birth as well as neonatal complications such as subdural hematoma, cephalhematoma, respiratory distress syndrome and neonatal jaundice that similar to the previous studies. [16,18,,27,29,30,33]

Strengths and limitation

This is the first study to our knowledge that demonstrates the association between timing of the third stage of labor and vacuum delivery. Moreover, missing data from the electronic database was relatively low. However, there were several limitation in our study. Firstly, to the precise accurate of the relationship between vacuum delivery and delay third stage of labor, we should collected more sample. Secondly, some medical records could not be retrieved. However, only eight records were missed. Thirdly, there were still relatively few prior researches related on the our study. Fourthly, as some studies suggested that vacuum extraction should not be used in women with gestational age under 34 weeks, However, in the present study, some patients were applied the use vacuum extraction even their gestational age was under 34 weeks, this might increase proportion of neonatal complication.

Conclusion and implication

Timing of the third stage of labor was significantly longer in normal delivery group compared with vacuum delivery group. However, there was no significant association between delay the third stage of labor and types of delivery. As in the present study, the occurrence of delay the third stage of labor was relatively low, the accurate estimation of the relationship needs larger sample size to distinguish the outcome in term of delay the third stage of labor between the two groups; normal delivery and vacuum delivery. Additionally, we found meconium amniotic fluid stained significant increase timing of placenta delivery. In the future, the study with larger prospective cohort study should be conducted for more accuracy. Furthermore, for those with meconium amniotic fluid stained, longer timing of the third stage of labor should be closely observed.

Table 4. Hazard Ratio of Factors Determining Timing of Placenta Delivery

Factor	Hazard ratio	95% confidence interval
Maternal age	1.01	1.00-1.02
Gestational age	0.97	0.93-1.02
Body-mass index	0.99	0.97-1.00
Regional anesthesia used	1.48	0.89-2.47
Birth weight	1.00	1.00-1.00
Placenta and cord weight	1.00	1.00-1.00
Meconium amniotic fluid stain	1.42	1.16-1.74
Timing of the first stage of labor	1.00	1.00-1.00
Timing of the second stage of labor	1.00	1.00-1.00

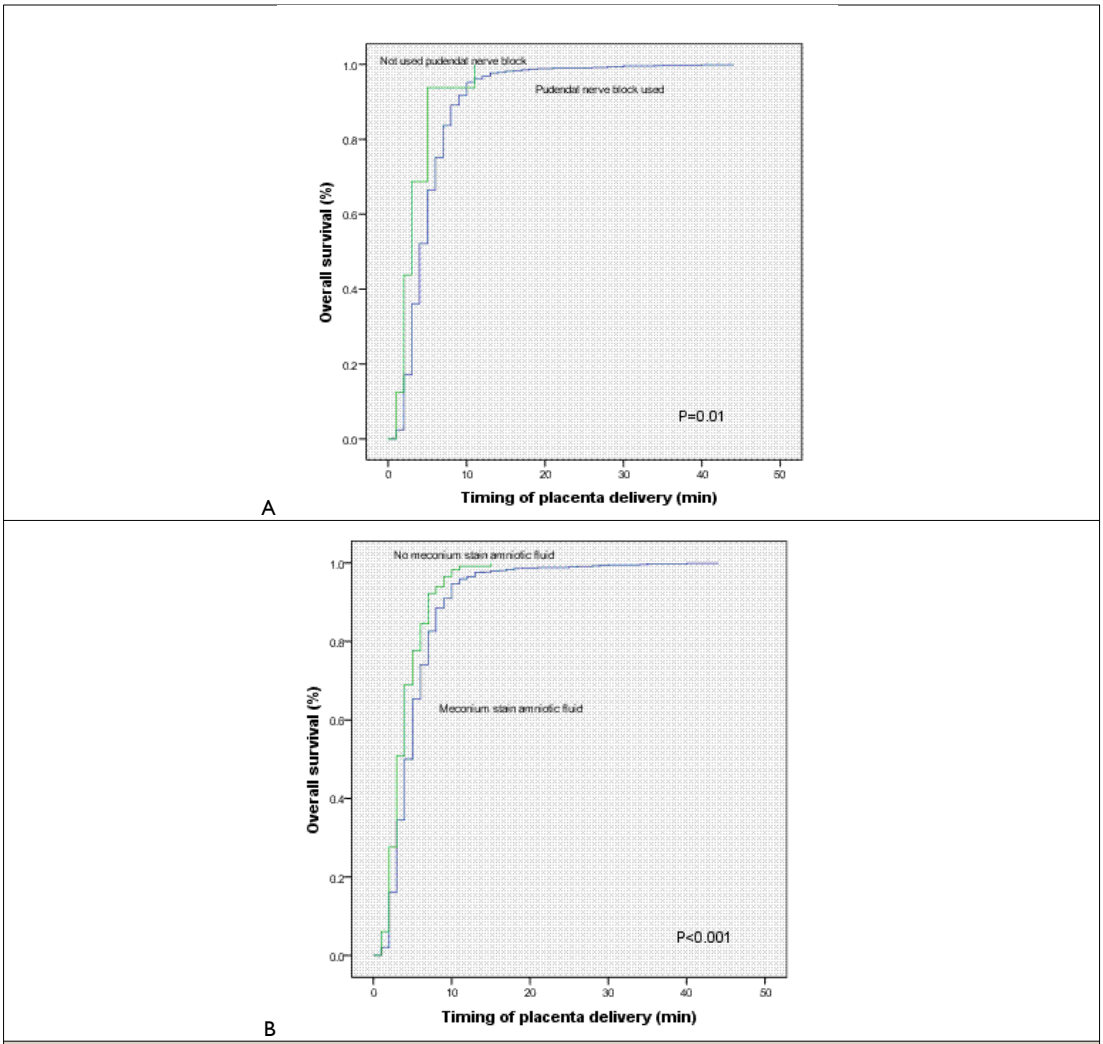

Figure 2. Kaplan-Meier Estimates for the Timing of Placenta Delivery.
Panel A shows survival of patient who had pudendal nerve block used and no pudendal nerve block used. Panel B shows survival of patient who had meconium amniotic fluid stained and no meconium amniotic fluid stained. P values were calculated with the use of the Log-Rank test.

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ORIGINAL ARTICLE

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American Society of Anesthesiologists Classification for Predicting Postoperative Death: a Retrospective Cohort Study

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ABSTRACT

BACKGROUND
Evidences regarding the predictive probability of the American Society of Anesthesiologists (ASA) classification and postoperative death are relatively scarce.

METHODS
In this retrospective cohort study, patients underwent operations under general anesthesia were categorized to 4 groups regarding their ASA classification. Postoperative death as a primary outcome was identified and compared among the 4 groups as well as the secondary outcomes including operation duration time, intraoperative blood loss, postoperative ventilation, cardiac complication, bronchopulmonary infection, wound infection, urinary tract infection and postoperative length of stay.

RESULTS
During the study period, 1,064 patients underwent operations under general anesthesia, 627 medical records were eligible for inclusion criteria. The patients' median age was 49 years (interquartile range [IQR] 22 to 70.8), 53% were women, 58% were emergency operation. Postoperative death occurred in 23 patients. The mortality rate was found to be the lowest in ASA classification I,II and the highest in ASA classification IV-V (0.4% vs. 46.9%, P<0.001), higher survival was found to be associated with ASA classification I and II and no preoperative status, elective operation and no postoperative bronchopulmonary infection (P<0.001, P=0.01, P=0.001, P=0.001, respectively by the log-rank test). ASA classification II and III were found to be associated with death (adjusted odds ration (AOR), 0.03; P=0.004; AOR, 0.15; P=0.006, respectively by the logistic regression analysis). ASA classification II and III were still found associated with death as well as wound infection (hazard ratio (HR), 0.03; P=0.005; HR, 0.21; P=0.006; HR, 0.23; P=0.038, respectively by the Cox proportional hazard regression).

CONCLUSION
The present study found the association between ASA classification and postoperative death in patients underwent operation under general anesthesia; the higher the ASA classification, the higher the mortality rate.

INTRODUCTION

In 2012, it estimated that in developing countries there are more than 21.4 million anesthetic administrations given to patients undergoing general anaesthesia for surgery.[1] Moreover, anesthesia-related mortality decrease over time, from 6.4/10,000 in the 1940s to 0.4/100,000 at 2011 because of the safety standards and improved training.[2] Assessment of the risk of postoperative complication could be done by using American Society of Anesthesiologist (ASA) classification.[3] ASA classification was introduced in 1941 by Saklad for comparison of statistical data for anesthesia to evaluated patients prior to surgery.[4] The classification was last revised in 1963 and was current version, ASA classifies patients according to their physical status as follows; (I) a normal healthy patient; (II) a patient with mild systemic disease; (III) a patient with severe systemic disease; (IV) a patient with severe systemic disease that is not incapacitating; (V) a moribund patient who is not expected to survive without the operation; and (VI) a patient declared brain-dead whose organs are being removed for donor purposes. Furthermore, E is often placed after the classification in case of emergency surgery.[5] Many studies have demonstrated an association between ASA classification and perioperative mortality and have suggested usefulness as predictor patients outcomes.[6] For instance, a prospective study in 1995 with 295 patient with total abdominal hysterectomy found that ASA scores were associated with total blood loss during surgery,[7] a previous study in 1996 suggested that there were the relationship between preoperative disease and postoperative complication; underlying hypertension and history of myocardial infarction tended to increase cardiovascular complication,[8] the study in 2004 reported incidence of postoperative death in elective total hip and total knee arthroplasty (TKA) patients with ASA classification III were more than postoperative death as compared to patients with lower ASA classification.[9]

However, There were specific operation procedure associated among ASA classifications and outcomes but no specific postoperative outcome. To determine the strength of association between ASA classification and specific postoperative outcomes especially incidence of postoperative death in patients with higher ASA classification have been more likely to encounter postoperative death as compared to patients with lower ASA classification in a retrospective cohort study of 627 surgical patients.

METHODS

Study design and patients

We conducted a retrospective cohort study comparing the postoperative outcomes in relation to death of patients with each ASA classification in Khon Kaen Hospital. Medical records of those undergone operations under general anesthesia and 15 years of age or older were screened and reviewed regardless of ASA classification. Patients with ASA classification VI, incomplete medical records and other anesthesia were excluded. A total of patients were categorized to 4 groups according to their ASA classification.[5]

Data collection

Medical record of the included patients were reviewed. Their data in relation to age, gender, weight, height, emergency/elective operation, preoperative status (cardiac disease, electrolyte imbalance, hematologic disease, hypertension and obesity), types and site of surgery were recorded.

Outcomes

The primary outcome was postoperative death. Secondary outcomes included operation duration, intraoperative blood loss, postoperative ventilation time, cardiac complication (new arrhythmias or acute myocardial infarction confirmed by electrocardiographic changes and cardiac biomarkers), bronchopulmonary infection (confirmed by sputum culture or chest radiographic changes), wound infection (wound inflammation or wound discharge), urinary infection (confirmed by urine culture) and postoperative stay (time from operative date to discharge date or death).All of postoperative data were summarized and comparison among the 4 groups.

Statistical analysis

We estimated the sample size on the basis of the primary outcome (postoperative death), with the power of 80%, alpha error 5%, with the difference in mortality rate of 20% between the group with highest and lowest mortality rate, the required sample size would be 404 in total. For the descriptive statistics, median and interquartile range were used for non-normally distributed data. For categorical variable, number and percentage (no. (%)) were used. In relation to inferential statistics, Kruskal Wallis was used to compare the scale variable among the groups of ASA classification. For categorical variable, chi-square and Fisher's exact test were used where appropriate. Risk factors for the primary outcomes were interpreted as adjusted odds ratio (AOR) from logistic regression analysis and hazard ratio (HR) from Cox proportional hazard regression. Kaplan-Meier analysis with log rank test were also performed.

RESULTS

Characteristics of the patients

During the study period, 1,064 patients underwent operations under general anesthesia (Figure 1), 437 were excluded for incomplete medical records (255 patients), age younger than 15 years old (180 patients)

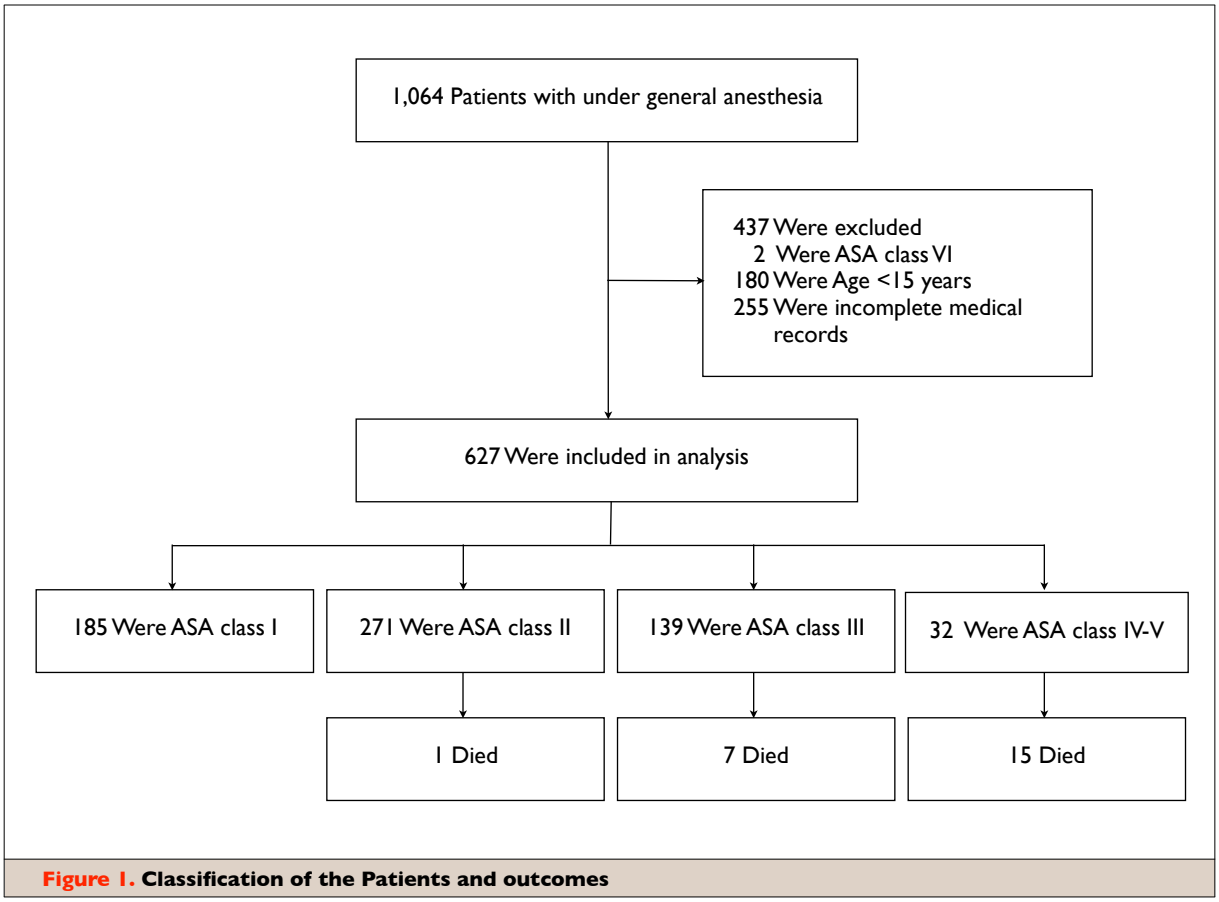

Figure 1. Classification of the Patients and outcomes

and 2 patients were ASA classification VI. In total, 627 medical records were eligible for inclusion criterias, 185 (29.5%) patients were categorized as ASA classification I, 271 (43.2%) patients were categorized as ASA classification II, 139 (22.2%) patients were categorized as ASA classification III and 32 (5.1%) patients were categorized as ASA classification IV-V.

Their median age was 49 years (IQR 22 to 70.8). Majority of them were female (53%) and had emergency operation (58%). Their median body-mass index (BMI) was 22.7 (IQR 19.5 to 27.2). For their preoperative status, 36% had cardiac disease, 25% had electrolyte imbalance and had hematologic diseases, 18% had hypertension and 11% were obese. In relation to types and site of surgery, 23% had head and neck surgery, 3% had cardiovascular thoracic surgery, 2% had breast surgery, 33% had abdominal surgery, 4% had kidney and urinary bladder surgery, 11% had pelvic surgery, 6% had cesarean delivery, 4% had spine surgery, 9% had extremities surgery and 11% had skin and musculoskeletal surgery.

Among the fours groups, ASA classification I tended to be the youngest and ASA classification IV-V tended to be the oldest (P=0.005) (Table 1). ASA classification II seemed to have the highest proportion of female while ASA classification III had the lowest (P=0.005). For BMI, ASA classification II tended to have the highest BMI while ASA classification I had the lowest (P=0.001). ASA classification IV-V had the highest rate of emergency operation while ASA classification III had the lowest rate (P<0.001). In relation preoperative status; the highest proportion of patients with cardiac disease, electrolyte imbalance and hematologic disease were found in ASA class V-IV (P<0.001) while hypertension were the most prevalence in ASA classification III (P<0.001) and obesity were found the highest in ASA classification II (P<0.001). In general, types of operation seemed to be similar across the four groups.

Outcomes

Death (as the primary outcome) occurred in 23 patients (1 in the ASA classification II, 7 in the ASA classification III, and 15 in ASA classification IV-V) (Table 2). The mortality rate was found to be the lowest in ASA classification I,II and the highest in ASA classification IV-V (P<0.001). The longest operation duration were found in ASA classification III and the shortest were found in ASA classification I and IV-V (P<0.001). ASA classification III had the highest

Table 1. Baseline Characteristics of the Patients

Characteristic	ASA I (N=185)	ASA II (N=271)	ASA III (N=139)	ASA IV-V (N=32)	P Value
Age-yr					<0.001
Median	34	43	58	60	
Interquartile range	22-43	29-54	45-68	37.8-70.8	
Female sex-no. (%)	100 (54)	170 (63)	62 (45)	16 (50)	0.005
Body-mass index*					0.001
Median	22.0	23.5	22.9	22.2†	
Interquartile range	19.5-24.5	20.5-27.2	20.1-25.7	20.8-25.4†	
Emergency operation-no. (%)	85 (46)	147 (54)	58 (42)	28 (88)	<0.001
Preoperative status-no. (%)					
Cardiac disease	2 (1)	77 (28)	69 (50)	20 (63)	<0.001
Electrolyte imbalance	2 (1)	36 (13)	50 (36)	16 (50)	<0.001
Hematologic disease	0	35 (13)	45 (32)	18 (56)	<0.001
Hypertension	0	28 (10)	49 (35)	9 (28)	<0.001
Obesity	9 (5)	44 (16)	16 (12)	3 (9)	0.003
Types and Site of surgery-no. (%)					
Head and neck	36 (20)	38 (14)	31 (22)	11 (34)	0.015
Cardiovascular and thorax	1 (1)	5 (2)	9 (7)	1 (3)	0.004
Breast	4 (2)	8 (3)	6 (4)	0	0.676
Abdomen	62 (34)	77 (28)	41 (30)	12 (38)	0.543
Kidney, urinary bladder and urethra	5 (3)	7 (3)	7 (5)	2 (6)	0.158
Pelvis	39 (21)	37 (14)	13 (9)	0	0.002
Cesarean delivery	0	53 (20)	1 (1)	1 (3)	<0.001
Spine	2 (1)	14 (5)	11 (8)	0	0.012
Extremity	26 (14)	22 (8)	15 (11)	1 (3)	0.108
Skin and musculoskeletal	19 (10)	23 (9)	10 (7)	6 (19)	0.207

* The body-mass index is the weight in kilograms divided by the square of the height in meters.
† N=27

amount of intraoperative blood loss while ASA classification I had the lowest. (P<0.001). There was the longest of postoperative ventilation times in ASA classification IV-V (P<0.001). Moreover, the highest proportion of patients with cardiac complication, bronchopulmonary infection, wound infection and urinary tract infection were found in ASA classification IV-V and there were the lowest in ASA classification I (P<0.001). Postoperative length of stay were the longest in ASA classification IV-V and the shortest in ASA classification I (P<0.001).

Factor predicting death

From the log rank test, higher survival was found to be associated with ASA classification I and II, no preoperative status, elective operation and no postoperative bronchopulmonary infection (P<0.001, P=0.01, P=0.001, P=0.001, respectively) (Figure 2). From the logistic regression analysis, ASA classification II and III were found to be associated with death (AOR, 0.03; P=0.004; AOR, 0.15; P=0.006, respectively (Table 3). From the Cox proportional hazard regression, ASA classification II and III were still found associated with death, as well as wound infection (HR, 0.03; P=0.005; HR, 0.21; P=0.006; HR, 0.23; P=0.038, respectively).

DISCUSSION

Major findings

Death occurred in 23 patients. The mortality rate was found to be the highest in ASA classification IV-V . The

Table 2. Postoperative Outcomes in Relation to ASA Classification.

Outcome	ASA I	ASA II	ASA III	ASA IV-V	P Value
Death-no. (%)	0	1 (0.4)	7 (5.0)	15 (46.9)	<0.001
Operation duration-min					<0.001
Median	73	80	100	73	
Interquartile range	50-116	54-154	65-151	51.3-104.5	
Intraoperative blood loss-ml					<0.001
Median	5	50	100	75	
Interquartile range	5-50	5-300	5-250	5-300	
Postoperative ventilation-days					<0.001
Median	0	0	0	5	
Interquartile range	0	0	0-1	1-11.5	
Cardiac complication-no. (%)	0	3 (1)	13 (9)	15 (47)	<0.001
Bronchopulmonary infection-no. (%)	0	1 (0)	29 (21)	20 (63)	<0.001
Wound infection-no. (%)	3 (2)	11 (4)	11 (8)	8 (25)	<0.001
Urinary infection-no. (%)	1 (1)	6 (2)	20 (14)	11 (34)	<0.001
Postoperative length of stay-days					<0.001
Median	2	3	7	10	
Interquartile range	2-3	2-6	3-11	5.0-24.3	

Table 3. Factors determining Death from Logistic and Cox Proportional Hazard Regression.

Factor	Adjusted odds ratio	P Value	Hazard ratio	P Value
Age	1.01	0.498	1.01	0.48
ASA classification				
ASA I	0.00	0.995	0.00	0.930
ASA II	0.03	0.004	0.03	0.005
ASA III	0.15	0.006	0.21	0.006
Female sex	0.45	0.241	0.40	0.111
Emergency	4.28	0.102	4.22	0.072
Cardiac disease	1.60	0.511	1.48	0.488
Electrolyte imbalance	2.74	0.143	1.28	0.658
Hematologic disease	0.46	0.289	0.32	0.084
Hypertension	1.42	0.632	0.74	0.594
Obesity	0.69	0.800	0.41	0.450
Operation duration	0.99	0.135	0.99	0.085
Postoperative ventilation	1.08	0.129	0.95	0.174
Intraoperative blood loss	1.00	0.340	1.00	0.296
Bronchopulmonary infection complication	4.20	0.118	3.03	0.125
Wound infection	0.94	0.948	0.23	0.038
Urinary infection	1.00	1.000	0.48	0.219

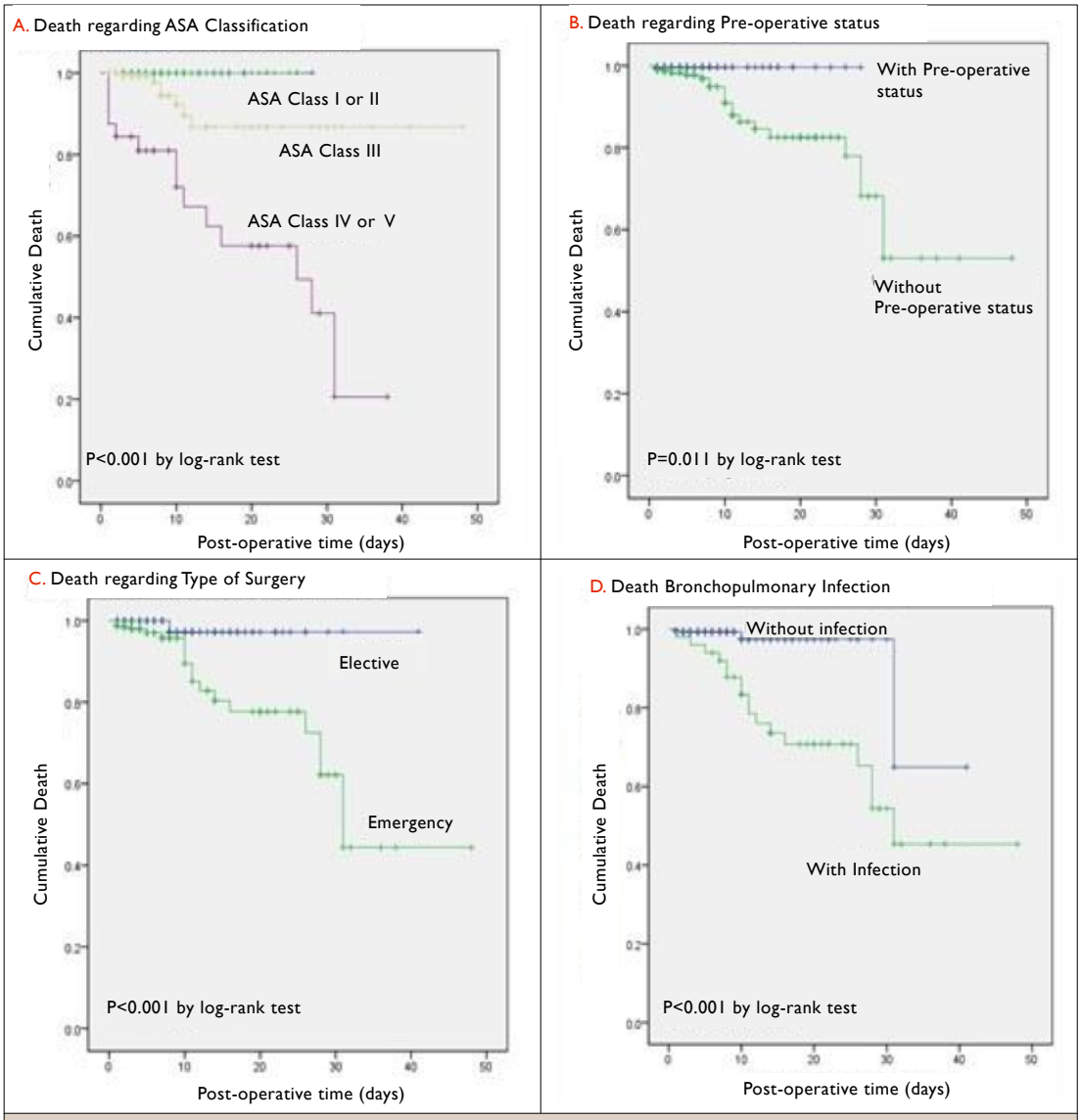

Figure 2. Kaplan - Meier Analysis of the Cumulative Risk of Death.
Shown are Kaplan - Meier estimates for the cumulative risk of death, according to ASA classification (Panel A) preoperative status (Panel B) emergency condition (Panel C) and bronchopulmonary Infection (Panel D).

longest operation duration were found in ASA classification III. ASA classification III had the highest amount of intraoperative blood loss**.** There was the longest of postoperative ventilation times in ASA classification IV-V. Moreover, the highest proportion of patients with cardiac complication, bronchopulmonary infection, wound infection and urinary tract infection were found in ASA classification IV-V. Postoperative length of stay were the longest in ASA classification IV-V. From the log rank test, ASA classification I-II, no preoperative status, elective operation and no postoperative bronchopulmonary infection were found associated with higher survival. From the logistic regression analysis, ASA classification II and III were associated with death while in the Cox proportional hazard regression, ASA classification II-III and wound infection were associated with death.

Comparison with other studies

Other study have demonstrated an association ASA classification, perioperative motality, perioperative variables (intraoperative blood loss, duration of postoperative ventilation) and have suggest postoperative outcomes were found high ASA

classification associated death and operative complication (infection rate, and post operative lengh of stay in hospital, cardiac complication, bronchopulmonary infection).[6,7,9,10-15] Our study was similar to the previous studies.In this study was found the mortality rate to be significant the lowest in ASA classification I,II and the highest in ASA classification IV-V. These study differ from our study with other study have demonstrated an association among ASA classification in specific operation procedure and mortality rate, postoperative complication e.g. ASA classification were important predicting surgical site infection after colorectal resection but in this study which have several operation procedure to determine the strength of association between ASA classification and specific postoperative outcomes(death). Moreover, wound infection associated high ASA classification.We also found wound infection is one of the critical factor for death. Bronchopulmonary infection were not associated ASA classification which differ from previous study.

Strength and limitation

In this study to determine the strength of association between ASA classification and specific postoperative outcomes especially incidence of postoperative death in patients with higher ASA classification compared to patients with lower ASA classification**.** The limitation of this study,firstly, inadequate patients of ASA classification V, we should collected more sample.Secondly, some medical records could not be retrieved.

Conclusion and implication

In the present study, we found the association between ASA classification and postoperative death in patients underwent operation under general anesthesia; the higher the ASA classification, the higher the mortality rate. Thus, preoperative treatment before surgery and avoiding emergency surgery should be encourage for higher survival rate after operation. Moreover, wound infection is one of the critical factors for death found in the present study, hence, prophylaxis of wound infection with proper mandatory and close monitoring of wound infection after operation should be enforced. For further study, large prospective cohort with more patients in ASA classification V should be conducted for more precise estimation of the patient in that specific subgroup.

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Sila Amatayakul

ORIGINAL ARTICLE

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Serum Amylase and Time to Start the Diet in Patients Suspected Acute Pancreatitis

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ABSTRACT

BACKGROUND
Serum amylase was found to be associated with severity and etiology of acute pancreatitis. However, no studies identify the relationship between serum amylase higher than 1000 U/L liter and time to start the diet.

METHODS
A retrospective cohort study was conducted to ascertain the association between serum amylase and time to start the diet in patients suspected acute pancreatitis. We reviewed medical records retrospectively of all patients with suspected of acute pancreatitis (serum amylase 1,000 U/L or lower and 78 had serum amylase more than 1,000 U/L who serum amylase less than 1,000 U/L) in Khon Kaen Hospital between 2009 and 2012. The primary outcome was time to start the diet.

RESULTS
A total of 529 patients who suspected for acute pancreatitis were included, however, only 356 were left in the analysis; 278 had serum amylase 1000 U/L or lower and 78 had serum amylase more than 1000 U/L. The group of patients with serum amylase more than 1000 U/L tended to delay for starting the diet (relative risk (RR), 1.557; 95% CI, 1.050 to 2.310) and from the Cox proportional hazard regression, serum amylase more than 1000 U/L no significant different with serum amylase 1,000 U/L or less than 1,000 U/L in time to start the diet (hazard ratio (HR), 1.306; 95% CI, 0.753 to 2.267).

CONCLUSION
We found serum amylase higher than 1,000 U/L was not significantly associated with time to start the diet.

INTRODUCTION

Acute pancreatitis is an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems.[1] Acute pancreatitis is a common disease with an annual incidence of between 5 and 80 people per 100,000 of the population and suggested that the numbers have been increasing in recent years worldwide.[2-9] The serum amylase is laboratory test for support acute pancreatitis diagnosis.[10-11] The serum amylase activity rises sharply within the first 24 hours of an attack of acute pancreatitis and then declines steadily to normal levels over the following 5-7 days.[12] Serum amylase has been found to be associated with etiology (alcoholic versus non alcoholic causes) and complication of acute pancreatitis e.g., sepsis, shock and necrotizing pancreatitis.[12-14] However there are no studies mentioned the relationship between serum amylase and time to start the diet. Thus, in this study we aimed to establish the association between serum amylase and time to start the diet.

METHODS

Patient and study site

A retrospective cohort study conducted to ascertain the association between serum amylase and time to start the diet in patients suspected acute pancreatitis. We reviewed medical records retrospectively of all patients suspected acute pancreatitis in Khon Kaen Hospital between 2009 and 2012. Those without serum amylase, delayed diagnosis, with history of chronic pancreatitis, pancreatitis from post endoscopic retrograde cholangiopancreatography or treated with surgery were excluded.

Exposure

We defined those suspected acute pancreatitis patients into two groups; serum amylase 1,000 U/L or lower and more than 1,000 U/L. Other variables included gender, age, underlying diseases, body temperature, serum glucose level, white blood cell count, serum lactate dehydrogenase (LDH), serum aspartate aminotransferase (AST), urine amylase and antibiotics on admission were also collected.

Outcome

Primary outcome was time to start the diet after admission (days). Secondary outcomes were death, shock, sepsis, acute respiratory distress syndrome (ARDS), analgesic drug used, afebrile day after admission, complications (e.g., acute renal failure, necrotizing pancreatitis, pancreatic abscess, pancreatic pseudocyst, acute respiratory distress syndrome, shock), change antibiotics, total hospitalization time

Statistical analysis

All variables were recorded onto excel spreadsheet. They were double entered and cleansed. After that they were imported to statistical package for social science (SPSS) version 18.0. Frequency tables for all variables were produced for identify outlier values. After that, all data were cleaned again. Categorical variables included sex, group of serum amylase (1000 U/L or lower and more than 1000 U/L), delay for starting the diet (2 days or earlier and longer than 2 days), with underlying disease (diabetes, hypertension,gallstone, common bile duct stone and liver cirrhosis), analgesic and antibiotics used. Scale variables included age, serum glucose, WBC count, serum LDH, serum AST, urine amylase, body temperature, total hospitalization day.

For descriptive statistics, categorical variables were summarized as number and percent (no. (%)). For scale variables, all numeric data were tested for their normal distribution using Kolmogorov-Smirnov test, 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, compare the difference between two groups,either chi-square or Fisher's exact test was used for categorical variables where appropriate. T-test and Mann-Whitney U test were used for normally and non-normally distributed variables. For risk interpretation relative risk, adjusted odds ratio (AOR) from logistic regression analysis were used. Kaplan-Meier functions was produced for two groups of serum amylase (serum amylase 1,000 U/L or lower and more than 1,000 U/L) and time to start the diet. Finally, hazard ratio from Cox proportional hazard regression was calculated to identify factors predicting time to start the diet, death, shock, sepsis and ARDS.

RESULTS

In the present study, A total of 529 patients who suspected for acute pancreatitis were included (Figure 1), however, only 356 were left in the analysis; 278 had serum amylase 1000 U/L or lower and 78 had serum amylase more than 1000 U/L. Mostly of cases were male (Table 1). In general, there were no significant differences between the two groups in relation to their underlying diseases (e.g., diabetes mellitus, hypertension, common bile duct stone and cirrhosis), body temperature, serum glucose, serum LDH and type of antibiotics on admission. However, the patients with serum amylase more than 1000 U/L tended to be older ($P<0.001$), higher proportion of patients with

Table 1. Characteristics of Patient in Each Study Group

Characteristic	Serum Amylase≤1000 (N=278)	Serum Amylase>1000 (N=78)	P Value
Male sex-no. (%)	243 (87.4)	57 (73.1)	0.002
Age-yr			<0.001
Median	39	54.5	
Interquartile range	31- 51	40.5 - 70.0	
Underlying disease - no. (%)			
Diabetes mellitus	24 (8.6)	9 (11.5)	0.434
Hypertension	31 (11.2)	12 (15.4)	0.311
Gallstone	13 (4.7)	13 (16.7)	<0.001
Common bile duct stone	3 (1.1)	2 (2.6)	0.302
Cirrhosis	7 (2.5)	4 (5.1)	0.266
Others	31 (11.2)	11 (14.1)	0.475
Body Temperature-°C			0.680
Median	37.2	37.4	
Interquartile range	36.7-38.0	36.8-37.9	
Serum glucose-mg/%			0.358
Median	128.0	134.5	
Interquartile range	105.5-160.0	110.8-165.0	
White blood cell count-cell/ml	12069.5±5097.3	13699.0±5116.0	0.014
Serum LDH-IU/L			0.973
Median	220.5	232	
Interquartile range	173.5-314.3	178.5-309.5	
Serum AST-IU/L			0.001
Median	58.5	122	
Interquartile range	28.3-160	46.5-265.5	
Urine amylase-IU/L			<0.001
Median	1570.0	7650.0	
Interquartile range	695.3-2,488.5	1,959.5-12,524.8	
Antibiotics on admission-no. (%)			
Ceftriaxone	92 (33.1)	34 (43.6)	0.087
Metronidazole	55 (19.8)	21 (26.9)	0.174
Others	17 (6.2)	5 (6.4)	0.836
Not use ATB	166 (59.7)	36 (46.2)	0.033

gallstone (P<0.001), higher white blood cell count (P=0.014), higher serum AST (P<0.001), higher urine amylase (P<0.001) and lower proportion of those without antibiotics (P=0.033)In Table 2, it shows the treatment outcomes of those suspected for acute pancreatitis in those with serum amylase 1,000 IU/L or lower and more than 1,000 IU/L. There were no significant differences between the two groups regarding analgesic used, afebrile day after admission day, total hospitalization time, complication, changes of antibiotics. Nonetheless, the group of patients with serum amylase more than 1000 U/L tended to delay for starting the diet (RR, 1.557; 95% CI, 1.050 to 2.310)

From Kaplan-Meier analysis, it found no significant difference between those with serum amylase 1,000 U/L or lower and serum amylase more than 1,000 U/L regarding time to start the diet (P=0.619) (Figure 2).

Table 2. Treatment Outcomes

Outcome	Serum Amylase≤1000 (N=278)	Serum Amylase>1000 (N=78)	P Value	Relative Risk (95% CI)
Delay to start the diet-no. (%)	114 (41.0)	43 (51.1)	0.023	1.557 (1.050-2.310)
Death-no. (%)	10 (3.6)	3 (3.8)	1.000	1.055 (0.384-2.905)
Complication-no. (%)				
Shock	14 (5)	4 (5.1)	1.000	1.015 (0.418-2.465)
Sepsis	10 (3.6)	3 (3.8)	1.000	1.055 (0.384-2.905)
Respiratory distress syndrome	18 (6.5)	4 (5.1)	0.795	0.821 (0.331-2.037)
Acute renal failure	10 (3.6)	3 (3.8)	1.000	1.055 (0.384-2.905)
Pancreatic complication	8 (2.9)	3 (3.8)	0.711	1.255 (0.468-3.361)
Analgesic drug-no. (%)				
Pethidine	71 (25.5)	21 (26.9)	0.805	1.057 (0.681-1.642)
Morphine	10 (3.6)	3 (3.8)	1.000	1.055 (0.385-2.904)
Afebrile day after admission-day			0.430	N/A
Median	2	2		
Interquartile range	1-4	1.0-3.5		
Total hospitalization time-day			0.160	N/A
Median	5	5		
Interquartile range	4-7	4-7		
Changes of antibiotics-no. (%)				
Meropenem	15 (5.4)	4 (5.1)	1.000	0.958 (0.392-2.343)
Others	6 (2.2)	2 (2.6)	0.689	1.114 (0.339-3.864)

N/A denotes not applicable

Table 3. Adjusted Odds and Hazard ratio for Predicting Time to Start the Diet.

Factor	Adjusted odds ratio	95% confidence interval	Hazard ratio	95% Confidence interval
Serum amylase more than 1000 U/L	0.445	0.526-4.322	1.306	0.753-2.267
Male sex	1.597	0.589-4.332	0.910	0.562-1.475
Age	1.029	1.002-1.057	0.990	0.978-1.003
Underlying disease				
Diabetes mellitus	2.804	0.367-21.446	0.507	0.204-1.259
Hypertension	0.277	0.049-1.562	1.653	0.857-3.189
Gallstone	1.102	0.150-8.109	0.847	0.310-2.315
Common bile duct stone	2.998	0.282-31.875	0.967	0.342-2.734
Cirrhosis	1.073	0.060-19.298	1.311	0.280-6.130
Serum glucose	1.005	0.998-1.011	0.999	0.996-1.002
White blood cell count	1.000	1.000-1.000	1.000	1.000-1.000
Serum AST	1.000	0.998-1.002	0.999	0.998-1.000
Serum LDH	1.000	0.999-1.001	1.000	1.000-1.000
Urine amylase	1.000	1.000-1.000	1.000	1.000-1.000

Table 4. Hazard Ratio of Factors Predicting Death, Sepsis, Shock, ARDS from the Cox Regression

Factor	HR and 95% confidence interval			
	Death	Sepsis	Shock	ARDS
Age	1.008 (0.961-1.056)	1.000 (0.043-23.339)	1.090 (0.946-1.256)	0.932 (0.834-1.041)
Serum glucose	1.004 (0.997-1.012)	1.000 (0.094-2.023)	1.005 (0.992-1.019)	0.989 (0.972-1.005)
WBC	1.000 (1.000-1.000)	1.000 (0.998-1.002)	1.000 (1.000-1.000)	1.000 (1.000-1.000)
Serum AST	1.000 (0.998-1.003)	1.000 (0.821-0.218)	1.002 (0.994-1.011)	0.992 (0.980-1.005)
Serum LDH	1.001 (1.000-1.001)	1.000 (0.885-1.130)	1.000 (0.998-1.002)	1.001 (0.998-1.004)
Group of serum amylase	2.372 (0.452-12.436)	N/A	0.734 (0.089-6.033)	0.832 (0.058-11.852)

N/A denotes not applicable

From the logistic regression analysis, patients' age was found to be associated with being delay for starting the diet (longer than 2 days); the older the age, the more likely to be delay for starting the diet (AOR, 1.029,; 95% CI 1.002 to 1.057). However, from Cox proportional hazard regression, there were no factors associated with time to start the diet (Table 3). We also observed that there were no factors predicting death, sepsis, shock and ARDS in the Cox proportional hazard regression (Table 4).

DISCUSSION

Major findings

In this retrospective cohort study of patients suspected acute pancreatitis on patient, it shows that the serum amylase higher than 1000 U/L was not significantly related with being delay for starting the diet and time to start the diet as well as death, sepsis, shock, ARDS, other complications, the use of analgesic drugs, time to be afebrile and length of hospital stay. From logistic regression analysis, only age were found to be associated with being delay for start the diet; the older the age, the more likely to be delay for starting the diet.

Strength and limitation

This is the only study to our knowledge that demonstrates the association between group of serum amylase and time to start the diet using Kaplan Meier and Cox proportional hazard regression. However, there are several limitations to our study. One of these is the potential for unknown confounders that were not recorded in the database. The precise accurate of the relationship between level serum amylase and time to start the diet, the size of the sample should be up to 764 patients.

Comparison with other studies

In our present study, LDH, serum glucose, white blood cell count were found to be not associated with time to start the diet and mortality. However, a study from Glasglow with 347 patients, who have been collected on patients admitted to Glasgow with final diagnosis of acute pancreatitis, serum LDH, serum glucose, white blood cell count and age can predicting mortality.[15] The different findings might be due to a serum amylase greater than 1200 IU/l within 48 hours of admission is inclusion criteria. Moreover, a previous study in 1999 stated that mortality rate was related to the presence of fever at admission.[16] The difference might be due to they included patients with severe acute pancreatitis only, severity was observed by RANSON >3,APACHE II>10. However, in our present study serum amylase found to be not associated with ARDS, acute kidney injury or mortality. Nonetheless, a study by PG Lankish *et al* found that serum amylase increased 3 times or higher predicting complications e.g., ARDS, acute kidney injury death, there were no significant difference.[17] The different findings might be due to the differences in sample as well as the size of the sample which they note stated. There is also a study describing that neutrophil-lymphocyte ratio (NLR) can predict the severity of acute pancreatitis.[18] However, its was done in the intensive care unit patients only. A Chinese study stated that time when infection was confirmed was a better time point for the reassessment of the outcome in patients with severe pancreatitis.[19] The different findings might be due to they studied patients with severe pancreatitis only. In 2003 UK patients with acute pancreatitis was studied, plasma calcitonin precursor concentration of more than 160 fmol/ml on admission was highly accurate (94 per cent) in predicting the development of septic complications and death.[20]

Conclusion and implication

In the present study, we found the level of serum amylase was not significantly associated with time to start the diet, death, shock, sepsis, ARDS. However, with the limitation of underpower of the present study, a larger prospective cohort study should be conducted for more accurate estimation of the relationship between serum amylase and time to start the diet.

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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 cases cefoxitin plus doxycycline (regimen A) and clindamycin plus gentamicin (regimen B). Nevertheless treating pelvic inflammatory disease with ampicillin plus gentamicin plus metronidazole and ceftriaxone plus metronidazole were prescribed more often in Thai practice. However the effectiveness of ampicillin plus gentamicin plus metronidazole and ceftriaxone plus metronidazole were not clear. Thus we conducted a study to compare the treatment outcomes of three combination therapies.

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.

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% relieve 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 significant factor to predicted 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

Patients who were diagnosed pelvic inflammatory disease by clinical in patient summary sheet of Khon Kaen Hospital during from January 2009 to May 2011 were screened reviewed. 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.

Treatment regimens

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. Four secondary treatment outcomes were also recorded. The first, 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. Second, 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% and α error of 0.05. 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 (AOR) and its 95% CI were calculated. A p value<0.05 was considered statistically significant. All analyses were performed using statistical package.

RESULTS

650 patients were enrolled in the present study between January 2009 and May 2011 in Khon Kaen

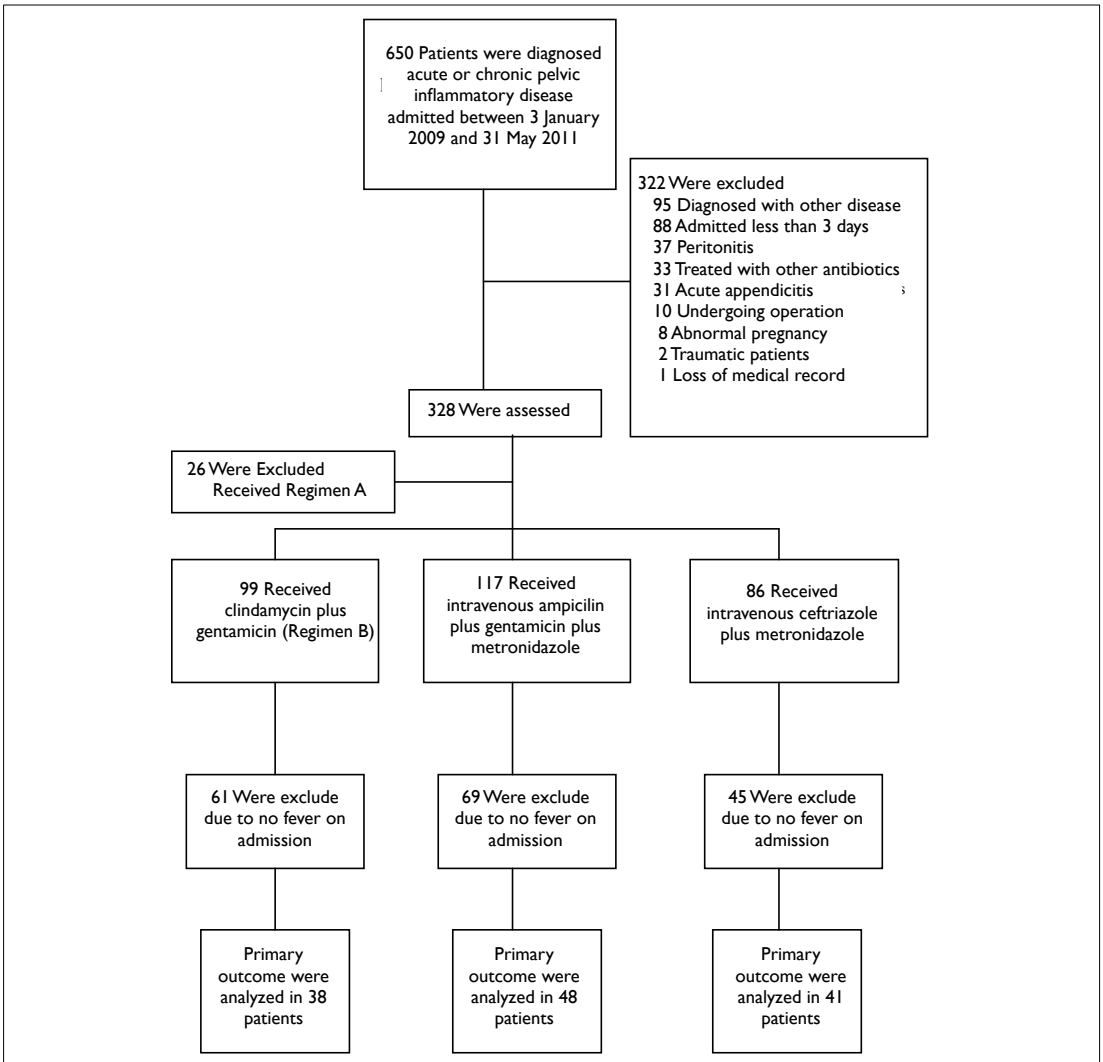

Figure 1. Enrollment of Patients and Assessment of Primary Outcomes.
We enrolled 328 patients to review all of charts after excluded another conditions. However, the number of patients in regimen A was too small to compare with other regimens. Thus, we excluded this regimen from this study so we left 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

Hospital. 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 pelvic inflammatory disease (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 (IR 3000 to 8000) and 50 kilograms (IR 45 to 58) respectively. The mean height was 157.2 centimetres (±6.8).

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 wih 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, patients in clindamycin plus gentamicin group had history of sexual transmitted disease and pelvic inflammatory disease were greater than the others

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)	
Degree	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 –1000 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	

(P<0.00, =0.03 consecutively). Furthermore in ampicillin plus gentamicin plus metronidazole group had higher proportion of nulliparous, smoker and no underlying person (P<0.001, =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 adventage to decrease surgical rate (P=0.00). Additionally duration of intravenous antibiotic were significantly (P=0.00). There were 90.8% relieve from pain in ampicillin plus gentamicin plus metronidazole group, with no significant different (P=0.42).

DISCUSSION

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, duration of intravenous antibiotic received was the only significant factor predicting defervesence. 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.

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. Howover 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.

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 found to had 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]

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. Logistic Regression for Fervesence

Variable	Adjusted odds ratio (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
Nulliparity	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

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, nulliparity 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, 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 differences in the primary outcome. However, potential benefits in relation to secondary outcomes such as switch therapy were also identified suggesting the superiority of alternative treatment, Moreover, closed monitoring in patients with long duration of intravenous antibiotics is required.

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ORIGINAL ARTICLE

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Thirty-day Comparison of the 30-Day-Mortality Rate between of Nosocomial Ventilator-Associated Pneumonia and Community-Acquired Pneumonia Who have the same APACHE II Score in Admitted in the Intensive Care Unit

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ABSTRACT

BACKGROUND
Evidence of direct comparison of 30-day mortality between ventilator-associated pneumonia (VAP) and community-acquired pneumonia (CAP) is still scarce.

METHODS
We conducted a retrospective cohort study to identify the rate of 30-day mortality in those with VAP and CAP admitted to Khon Kaen Hospital, Thailand between Jan 1, 2010 and April 30, 2011.

RESULTS
There were 185 patients in this study, 79 in VAP group and 106 in CAP group. The 30-day mortality rate of patients admitted in the ICU with VAP and CAP were similar. Moreover, APACHE II score less than 23 and ventilator used less than 6 days were highly significant associated with lower 30-day mortality (hazard ratio (HR), 0.47 95% confidence interval (CI) 0.29 to 0.76; HR, 0.89 95% CI 0.85 to 0.93)

CONCLUSION
The 30-day mortality rate of patients admitted in the ICU with VAP and CAP were similar. APACHE II score less than 23 and ventilator used less than 6 days were highly significant associated with lower 30-day mortality

Ventilator associated pneumonia (VAP) or nosocomial pneumonia is the lung infection commonly found in the hospital.[1,2] High mortality and morbidity are observed especially in those admitted in the intensive care unit (ICU).[3] Appropriate antibiotics are required for prompt treatment.[4,5] Moreover, its treatment usually differs from that of community acquired pneumonia (CAP) even they are in the same severity classified using APACHE score which is commonly used as one of the parameters for assessing 30-day - mortality in patients admitted in the ICU.[6,7]

In relation to VAP, one study found that patients with clinical suspected of VAP with mean APACHE II score 19-20 had higher mortality rate than the group that have lesser clinical suspicion VAP or likely to be CAP.[8] ICU-acquired VAP is significant affects hospital mortality after controlling for other clinical factor such as age, sex and APACHE II score.[9] Additionally, APACHE score also has a predictive value for mortality of those patients. In one study, patients with VAP in the ICU with APACHE II score 26±7, their mortality rate could be up to 80%.[10] Similar to another study, it found that VAP patients with APACHE II score more than 27, their median survival period was found to be only 8.3 days.[11] The higher of the APACHE II score, the higher the risk for treatment failure with increasing mortality[12]. High mortality in VAP might be due to the resistance of the organism to the given antibiotics.[13] In one Russian study, the VAP patients infected *Pseudomonas aeruginosa* in ICU had more mortality rate 38% and 50% of them were infected bilateral lung[14] This can be confirmed by one study mentioned that a silver-coated endotracheal tube could reduce the mortality rate of VAP patient.[15]

Even though, many studies identify the higher mortality in of VAP admitted in the ICU, evidence of direct comparison of 30-day mortality between VAP and CAP is still scant.Therefore, in this study, we attempted to compare the 30-day-mortality rate between CAP and VAP of the patients admitted to the ICU nosocomial infection pneumonia and community acquire pneumonia . as well as identify factors affected the mortality in these groups of patients.

METHODS

Study design

This study designed to was a the retrospective cohort study to compared 30-day the mortality rate between VAP and CAP.

Patient and study site

The data was collected from the electrical medical records of four different department including Medical Intensive Care Unit (MICU), Surgery Intensive Care Unit (SICU), Coronary Care Unit (CCU) and Respiratory Intensive Care Unit (RICU) of Khon Kaen Hospital between Jan 1, 2010 and April 30, 2011. Medical records of following patients were reviewed; patients age 15 years or older, admitted to the ICUs and were diagnosed with pneumonia. VAP was diagnosed by history of mechanical ventilator > 48 hr and clinical either sputum culture sensitivity has bacterial growth>10^5, new infiltrate on chest radiographic plus at least two of follow : abnormal body temperature (>38 degrees C or <36degrees C), abnormal white blood cell count (>10 or < 4 x10^3cell/mm^3, or >10% immature bands), or macroscopically purulent sputum.[16,17] For CAP, it was defined as the presence of three symptoms and signs: cough, acute change in the quality of sputum, fever or hypothermia in 24 hour, pulmonary consolidation, new infiltration or consolidation on chest radiographic.[18] All patients had been treated by empirical antibiotics according to standard protocol.[19]

Data collection

Variables regarding age, sex, mean arterial pressure, respiratory rate, heart rate, body temperature, serum sodium, serum potassium, serum bicarbonate, serum creatinine, white blood cell count, history of organ insufficiency or immunocompromised, Glasgow Coma Score, total APACHE II score, duration the ventilator used, comorbidity, types of organism, antiorganism drugs used and time to death were reviewed, verified and recorded into excel spread sheet.

Statistical analysis

We used Statistical Package for Social Science (SPSS) for Window for to analysis the data analysis. All variable were double entered, cleaned and verified for their correctness before preceding the analysis. Data were described in term of percentage, mean or median where appropriate. All numerical data were tested for their distribution using Kolmogorov Smirnov. Student t-test is used for two independent groups comparison with normal distributed data while Mann-Whitney U test was used for non-normal distributed data. Either Chi-square or Fisher's exact test was used for categorical data used where appropriate. Risk for 30-day mortality was calculated regarding relative risk (RR). Kaplan Meier analysis was used to create survival function. Log rank test was used to identify factors that affected the survival function.Cox proportional hazard regression was latter used to adjust the possible confounders that might affect patients' survival. All risk factors were presented in term of hazard ratio (HR) and 95% confidence interval (CI). P-value less than 0.05 were considered to indicate statistical significance.

RESULTS

Between January 1, 2010, and April 30, 2011, 6040 patients were eligible to be included into the present

Table 1. Patient Characteristics.*

Characteristic	VAP (N=79)	CAP (N=106)	P Value
Mean age:Yr	54.8±15.2	55.6±18.2	0.766
Male sex – no. (%)	46 (58.2)	59 (55.7)	0.422
APACHE II score			
Mean arterial blood pressure (mmHg)	88.7±19.9	85.7±20.9	0.324
Serum sodium (mmol/L)			0.112
Median	139	138	
Interquartile range	134-143	133-141	
Hematocrit (%)	30.4±7.6	30.7±7.1	0.880
Serum bicarbonate (mmol/L)	21.7±7.2	21.0±5.3	0.487
History of severe organ insufficiency or immunocompromised.	78 (98.7)	87 (82.1)	0.001
Body temperature (°C)	37.4±1.2	37.4±1.1	0.938
Heart rate (/min)	106.2±23.9	110.6±25.2	0.226
Respiratory rate (/min)			0.980
Median	22	22	
Interquartile range	18-27	20-24	
Serum potassium (mmol/L)	4.1±0.8	4.0±0.8	0.354
Serum creatinine (mg/dL)			0.592
Median	1.6	1.4	
Interquartile range	0.9-3.5	1.0-2.9	
White blood count (cell/mm^3)			0.899
Median	11400	11300	
Interquartile range	7500-16000	7300-19750	
Glasgow Coma Score	8.9±2.6	9.9±3.6	0.046
APACHE II score			0.034
0-5	0	5 (4.7)	
6-10	1 (1.3)	12 (11.3)	
11-15	7 (8.9)	10 (9.4)	
16-20	17 (21.5)	12 (11.3)	
21-25	24 (30.4)	24 (26.6)	
26-30	15 (19.0)	29 (27.4)	
31-35	9 (11.4)	9 (8.5)	
36-40	5 (6.3)	4 (3.8)	
41-45	1 (1.3)	1 (0.9)	
Duration of ventilator used (days)			<0.001
Median	11	3	
Interquartile range	16-19	1-7.3	
Length of stay after ICU admission (days)			<0.001
Median	14	5	
Interquartile range	8-23	2-9	
Comorbidity			
Neurogenic disease	9 (11.4)	6 (5.7)	0.158
Cardiogenic disease	11 (13.9)	22 (20.8)	0.230
Pulmonary disease	37 (46.8)	46 (43.4)	0.642
Cancer	8 (10.1)	3 (2.8)	0.057
Diabetic mellitus	24 (30.4)	23 (21.7)	0.180
Renal disease	25 (31.6)	26 (24.5)	0.284
Gastrointestinal disease	6 (7.6)	15 (14.2)	0.164
Hypertension	20 (25.3)	23 (21.7)	0.564
Acquired immune deficiency syndromes	0	6 (5.7)	0.039
Other	36 (45.6)	41 (38.7)	0.347

*Plus-minus values are means ±SD.VAP denotes Ventilator-associated pneumonia, CAP Community- acquired pneumonia, APACHE II score Acute Physiologic And Chronic Health Evaluation, ICU Intensive Care Units.

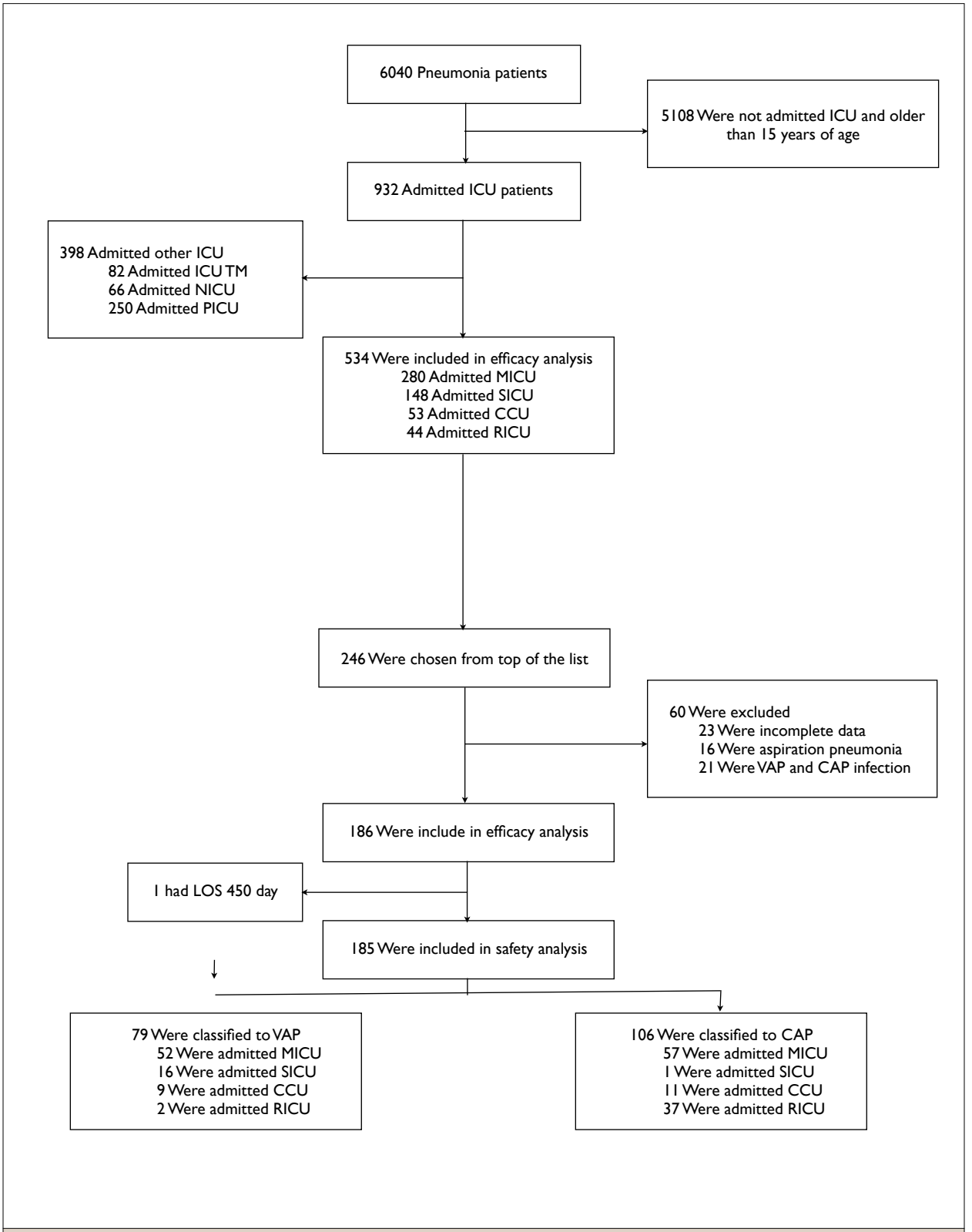

Figure 1. Study Flow Chart

Table 2. Organism Identified from Patients' Sputum and Antibiotics.

Organism/Antiorganism	VAP (N=79)	CAP (N=106)	P Value
Organisms			
Acinetobacter baumannii	22 (27.8)	1 (0.9)	<0.001
Pseudomonas auruginosa	16 (20.3)	1 (0.9)	<0.001
Klebsiella pneumonia	12 (15.2)	9 (8.5)	0.155
Staphylococcus aureus	10 (12.7)	8 (7.5)	0.246
Escherichia coli	6 (7.6)	2 (1.9)	0.075
Gram-negative bacilli	5 (6.3)	5 (4.7)	0.746
Enterobacter spp.	2 (2.5)	1 (0.9)	0.587
Streptococcus pneumonia	1 (1.3)	2 (1.9)	1.000
Pneumucystis jiroveci	0	3 (2.8)	0.262
Unidentified organism	21 (26.6)	49 (46.2)	0.006
Other organism	10 (12.7)	31 (29.2)	0.007
Antiorganism treatment			
Cephalosporin	58 (73.4)	91 (85.8)	0.035
Ceftriaxone	29 (36.7)	41 (38.7)	0.785
Ceftazidime	36 (45.6)	67 (63.2)	0.017
Fluoroquinolones	15 (19.0)	42 (39.6)	0.003
Ciprofloxacin	6 (7.6)	6 (5.7)	0.597
Levofloxacin	10 (12.7)	37 (34.9)	0.001
Tazocin (Piperacillin-tazobactam)	31 (39.2)	15 (14.2)	<0.001
Carbapenems			
Meropenem	26 (32.9)	11 (10.4)	<0.001
Macrolides	8 (10.1)	31 (29.2)	0.002
Clarithromycin	5 (6.3)	21 (19.8)	0.009
Azithromycin	3 (3.8)	10 (9.4)	0.138
Polypeptide			
Colistin	12 (15.5)	4 (3.8)	0.006
Sulfonamide			
Cotrimoxazole	6 (7.6)	12 (11.3)	0.398
Metronidazole	15 (19.0)	1 (0.9)	<0.001
Vancomycin	16 (20.3)	4 (3.8)	<0.001
Sulperazone (sulbactam+cefoperazone)	29 (36.7)	16 (15.1)	0.001
Other antiorganism drugs	24 (30.4)	44 (41.5)	0.120

study (Figure 1). However, there were 185 left for the analysis; 79 cases for VAP and 106 cases of CAP. Their average age was 55.2±16.4 years old with a bit of male more than female (Table 1). The median of their length of hospital stay and duration on ventilator was 7 days and 5 days respectively. Their median APACHE II using assessing their severity regarding was 22. Nearly all of them (89.1%) had history of organ failure or immunocompromised. Their mean Glasgow Coma Score was 9.5±3.2. Furthermore, the vital sign and the lab value that being recorded, were no significant difference between those with diagnosis with VAP and CAP. However, VAP group had higher proportion of patients with history of organ failure or immunocompromised and lower Glasgow Coma Score compared with CAP (P=0.046). In addition, most of VAP patients had APACHE II score 21 and 25 while between 26 and 30 for CAP. We found highly

significant greater the association of longer duration using ventilator in VAP than CAP (P < 0.001). On the other hand, AIDS patients significant associated with CAP more than VAP (P=0.032), but cancer significant associated with VAP more than CAP (P=0.038). Moreover, we found that length of hospital stay (LOS) were likely to longer in group of VAP compare to CAP (P<0.001). The amount of patients with cardiogenic and gastrointestinal disease were about twice greater than VAP patients. Other diseases were no significant difference.

We found that the most common two organisms of VAP were *Acinetobacterter baumannii* and *Pseudomonas aeruginosa* while *Klebsiella pneumonia* were the most common in CAP. However, there was a large proportion of unidentified organism in both groups (Table 2). *Pneumucystis jiroveci* was found only in CAP patients. *Acinetobacter baumannii* and Pseudomonas aeruginosa were highly significant more common in VAP than CAP with P<0.001 and <0.001 respectively. Unidentified organism and other organism were found largely and significantly in CAP with P=0.006 and 0.007 respectively. The most common antibiotics used cephalosporin. Moreover, cephalosporin, fluoroquinolone and macrolides were the antibiotics prescribed more common in CAP significantly than VAP (P= 0.003, 0.035 and 0.002 respectively). In contrary, tazocin, carbapenem,

Table 3. Factors Associated with Death.

Factor	Death (N=92)	Survive (N=93)	Relative Risk (95% CI)*
Age <55 yr	46 (51.1)	40 (42.1)	1.44 (0.81-2.57)
Male sex	56 (62.2)	49 (51.6)	1.55 (0.86-2.78)
APACHE II score <23	32 (35.6)	53 (55.8)	0.44 (0.24-0.79)
Duration of ventilator <6 days	48 (53.3)	45 (47.4)	1.27 (0.71-2.26)
Length of stay after ICU admission <8 days	52 (57.8)	43 (45.3)	1.65 (0.93-2.96)
Type of pneumonia			
Community acquired pneumonia	53 (58.9)	53 (58.9)	0.88 (0.43-1.58)
Organism			
Staphylococcus aureus	9 (10.0)	9 (9.5)	1.06 (0.40-2.80)
Gram-negative bacilli	6 (6.7)	4 (4.2)	1.63 (0.44-5.96)
Acinetobacterbaumannii	12 (13.3)	11 (11.6)	1.18 (0.49-2.81)
Pseudomonas aeruginosa	6 (6.7)	11 (11.6)	0.55 (0.19-1.54)
Klebsiellapneumonia	10 (11.1)	11 (11.6)	0.96 (0.38-2.37)
Antibiotic treatment			
Cephalosporins			
Ceftriaxone	31 (34.4)	39 (41.1)	0.75 (0.42-1.37)
Ceftazidime	57 (63.3)	46 (48.4)	1.84 (1.02-3.31)
Fluoroquinolones			
Ciprofloxacin	2 (2.2)	10 (10.5)	0.19 (0.04-0.91)
Levofloxacin	26 (28.9)	21 (22.1)	1.43 (0.74-2.78)
Tazocin (Piperacillin-tazobactam)	21 (23.3)	25 (26.3)	0.85 (0.44-1.66)
Carbapenems			
Meropenem	24 (26.7)	13 (13.7)	2.29 (1.09-4.85)
Macrolides			
Clarithromycin	11 (12.2)	15 (15.8)	0.74 (0.32-1.72)
Azithromycin	6 (6.7)	7 (7.4)	0.90 (0.29-2.78)
Polypeptide			
Colistin	10 (11.1)	6 (6.3)	1.85 (0.65-5.33)
Sulfonamide			
Cotrimoxazole	10 (11.1)	8 (8.4)	1.36 (0.51-3.62)
Metronidazole	7 (7.8)	9 (9.5)	0.81 (0.29-2.26)
Vancomycin	10 (11.1)	10 (10.5)	1.06 (0.42-2.69)
Sulperazone (sulbactam+cefoperazone)	24 (26.7)	21 (22.1)	1.28 (0.65-2.51)
Other antiorganism drugs	30 (33.3)	38 (40.0)	0.75 (0.41-1.37)

*Relative risks are for the comparison with the survival group.

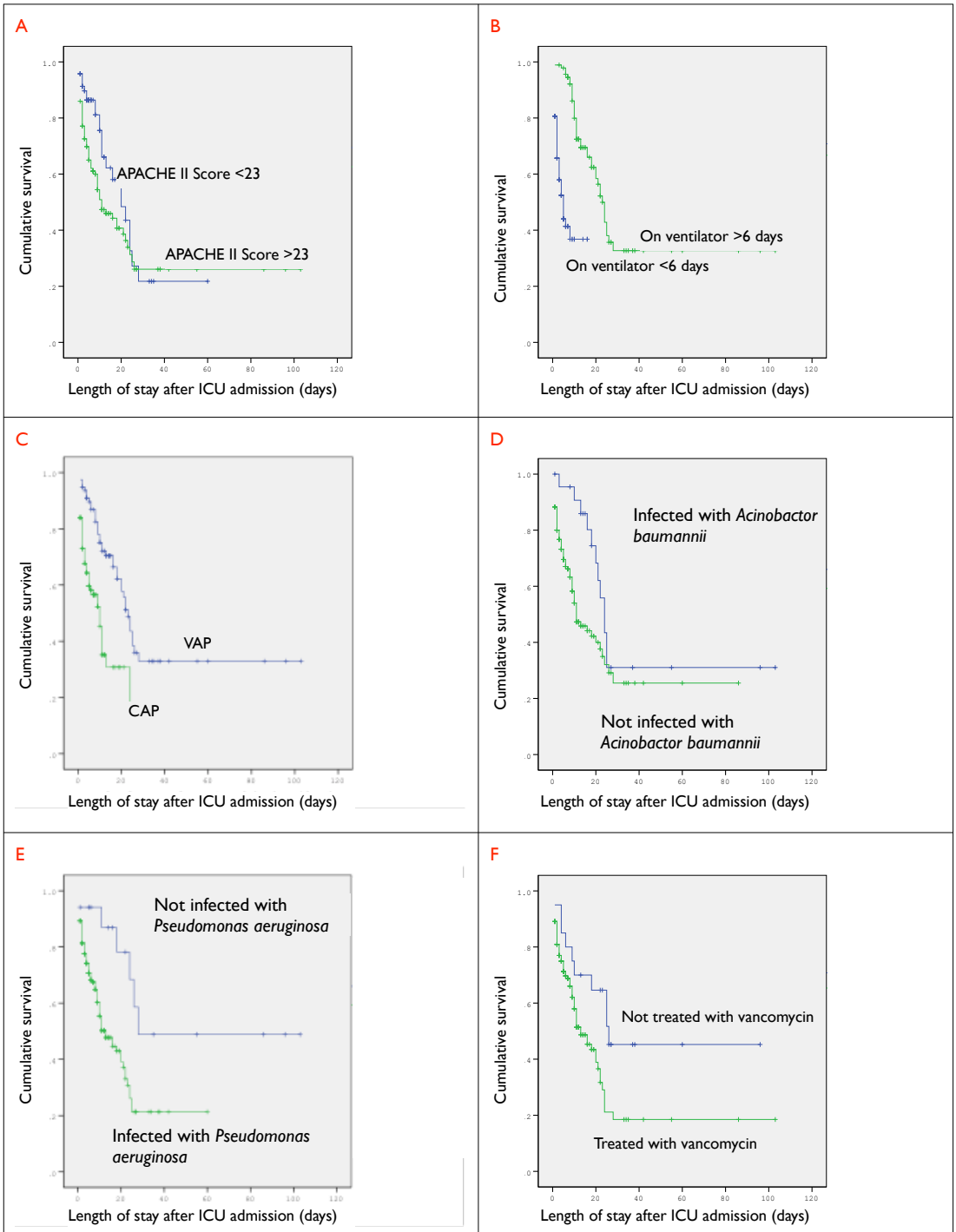

Figure 2. Kaplan-Meier Survival Curves.
The figure shows the probability of survival comparison between group of APACHE II score <23 and ≥23 (Panel A), duration of ventilator used <6 days and ≥6 days (Panel B) type of pneumonia; VAP and CAP (Panel C), infected and not infected with *Acinobactor baumannii* (Panel D), infected and not infected with *Pseudomonas aeruginosa* (Panel E) and treated and not treated with vancomycin (Panel F).

Table 4. Cox Proportional-Hazards Regression Analysis.*

Factor	Hazard ratio	95 % confidence interval
APACHE II score <23	0.47	0.29-0.76
Duration of ventilator <6 days	0.89	0.85-0.93
Community acquired pneumonia	0.71	0.42-1.21
Being infected with *Acinetobacter baumannii*	1.83	0.88-3.78
Being infected with *Pseudomonas aeruginosa*	0.96	0.40-2.33
Being treated with Vancomycin	0.50	0.22-1.10

*APACHE II score denotes APACHE II score Acute Physiologic And Chronic Health Evaluation.

polypeptide, metronidazole, vancomycin and sulperazone were often given in VAP rather in CAP significantly (P <0.001, <0.001, 0.006, <0.001, <0.001 and 0.001 respectively).

In Table 3, relative risks of potential risk factors of 30-day mortality are presented. It found that age, gender, duration of ventilator used, LOS, type of pneumonia, comorbidity, type of infected organism were not associated with 30-day mortality of the patients. However, using ceftazidime and meropenem were associated with higher 30-day mortality (RR, 1.84; 95% CI, 1.02 to 3.31 and RR, 2.29; 95% CI 1.09 to 4.85, respectively). Furthermore, APACHE II score less than 23 and Ciprofloxacin were highly significant decrease 30-day mortality rate (RR, 0.41; 95% CI, 0.22 to -0.76 and RR, 0.19; 95% CI 0.04 to 0.91, respectively).

In Figure 2, Kaplan Meier analysis and log rank test were performed to test the risk contribution of various factors. We found that, APACHE II score less than 23 more than twenty, duration of ventilator longer shorter longer than six days, being VAP, infected with Acinobactor baumannii, infected with Pseudomonas aeruginosa infection , being treated with significantly related with better survival (P= 0.043, <0.001, <0.001 ,0.038, 0.007, 0.023, 0.023 respectively). In addition to this, comorbidity including neurogenic disease, cardiogenic disease, pulmonary disease, cancer, diabetes mellitus, renal disease, gastrointestinal diseases, AIDS was found to be not associated with survival. From Cox proportional-hazards regression analysis presented in Table 4, only two factors found to influence the survival; APACHE II score less than 23 was highly associated with better survival (HR, 0.47; 95% CI 0.29 to 0.76), and patient that were on ventilator shorter than 6 days also tended to have better survival (HR, 0.89; 95% CI 0.85 to 0.93).

DISCUSSION

We conducted the present study to compare the 30-day mortality rate between VAP patients and CAP patients in ICU. We also identified factors that might influence the mortality. We found that the rate of the death was similar between the two groups. Our analyses using the survival function, we found that APACHE II score more than 23, shorter duration on ventilator than six days, being CAP, not infected with Acinetobactor baumannii or Pseudomonas aeruginosa not being treated with vancomycin were associated with higher 30-day mortality from the log rank test. However, only two factors were confirmed to have an effect on 30-day mortality; APACHE II score 23 or higher, duration on ventilator longer than six days were associated with worse survival. The current study is the first to our knowledge that compared 30-day mortality directly in patients with VAP and CAP. However, some limitations were also considered. We first concerned whether in this study might be related to sample size that required large participants, but we presented only 185 persons due to limitation of time and partially incomplete electric medical data. Moreover, most organisms were unidentified.

For the two identified determinants of 30-day mortality, our findings were similar to that described by Ozyilmaz E and Kabbani LS which stated that APACHE II scores on ICU admission were significantly greater in non survivors versus survivors. 21, 22 Moreover, Fagon et al.1 also mentioned that duration of ventilation was increase mortality rate. In our study, there was no significant difference in the mortality rate between VAP and CAP. This might be described by the fact that they had similarly total APACHE II score. Our study also found that Acinetobactor baumannii was more common than Pseudomonas aeruginosa. This also similar to a previous study, however, their findings stated the greater proportion of Pseudomonas aeruginosa than Acinetobactor baumannii and these two were the most common orgasm found in VAP.[11] In the present study, it found that the longer duration of ventilator than six days was associated with increase 30-days mortality. However, duration of ventilator prior to VAP onset was not significantly different between the mortality and non-mortality groups.[11] The mortality rate of VAP and CAP in ICU was found to be relatively high (38% and 55% respectively 22, 23). And

this similar pattern was also observed in the current study (nearly 50% in both VAP and CAP). One Japanese study with patients more than 20,000 patients with VAP in the ICU, the increasing mortality rate was found in those infected with drug resistant pathogen[24] while in our study there was no significant different in pathogen between deaths and survive group. From the log rank test, longer length of stay in the ICU was found to be associated with higher 30-day mortality. This finding was supported by one Canadian study in 300 patients with VAP which found that critical ill patients with longer length of stay in the ICU was associated with higher mortality.[25]

In conclusion, the 30-day mortality rate of patients admitted in the ICU with VAP and CAP were similar. Moreover, higher APACHE II score and longer ventilator used were highly significant associated with higher 30-day mortality. For the further study, we shall include larger sample and prospective study to confirm our findings should be conducted. As we found that higher APACHE II score was related to greater mortality rate, thus, we suggested close monitoring in patients with high APACHE II scores is required. Furthermore, promote patients lung function for shorter ventilator used should be encouraged.

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Combination of Ceftriaxone and Metronidazole for Treating Acute Cholecystitis

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ABSTRACT

BACKGROUND
Many antibiotics are used for treatment acute cholecystitis. However, the comparison between the use of ceftriaxone and ceftriaxone combined with metronidazole is well studied.

METHODS
This is a retrospective study to compare the success conservative rate between ceftriaxone alone and ceftriaxone in combination with metronidazole in acute cholecystitis patients. We conducted a study using the database from Khon Kaen Hospital of patients who admitted to the hospital beween January 2009 and May 2011

RESULTS
There were 366 patients included in the analysis; 328 with successful conservative treatment and 38 in fail to conservative treatment and underwent surgery. The rate of success for conservative treatment was higher in group treated with ceftriaxone alone. Moreover, they tended to have shorter hospital stay than patients who received ceftriaxone combined metroniazole. Being male and elevated white blood count on admission were the independent predictors for undergoing surgery.

CONCLUSION
It was likely that patients treated with ceftriaxone alone were likely to have higher success rate with conservative treatment compare to those treated with ceftriaxone combined with acute cholecystitis.

Treatment options of acute cholecystitis include early cholecystectomy and conservative treatment with antibiotics and interval laparoscopic cholecystectomy for 6–8 weeks.[1] Both early and delayed laparoscopic cholecystectomy (LC) is possible and safe in acute cholecystitis.[2] Several guidelines for the management of acute cholecystitis recommend antimicrobial therapy that include coverage against microorganisms in the Enterobacteriaceae family (e.g., a second-generation cephalosporin or a combination of a quinolone and metronidazole).[3-5] However, evidence on types of antibiotics for optimal management of acute cholecystits is still varied.[6] For instance, one study suggested the benefit of using short course of cefamandole for early cholecystectomy patients in term of shorter hospital stay. The role of early laparoscopic cholecystectomy is recommended from many studies to prevent recurrent attack.[2,7] However, the limitation of doing the operation especially in resource-limited settings is still exists. The use of antibiotics, thus, is still an option. The goal of the present study was to identify the efficacy in term of success conservative treatment with antibiotics between ceftriaxone alone or combination with metronidazole.

METHODS

Study design
This is a retrospective study to compare the success conservative rate between ceftriaxone alone and ceftriaxone in combination with metronidazole in acute cholecystitis patients.

Patient records
Medical records of patients with the diagnosis of acute cholecystitis with age between 18 and 80 years were reviewed. They were excluded if they received antibiotics more than three days, were complicated cholecystitis before admission (e.g., empyematous cholecystitis, gangrenous cholecystitis, with perforation and with septic shock), had other infections such as cholangitis and appendititis, had cholangiocarcinoma, had common bile duct stones or allergic against prescribed antibiotics.

Antibiotics treatment
After an acute cholecystitis patients were admitted in hospital. They were prescribed with either ceftriaxone alone or ceftriaxone in combination with metronidazole according to doctors judgments. Dose ceftriaxone 2 gram intravenous injection once per day, and ceftriaxone 2 gram intravenous injection 2 time per day combine with metronidazole 500 milligram intravenous injection 3 time per day.

Outcome measures
The primary end point was the success conservative treatment with antibiotics. Secondary outcomes included diminish of fever within five days, days of fever diminishing, day of heart rate diminish, day of pain score diminish (pain score <2), complication rate (inflammation gall bladder, gangrenous gall bladder, empysematous gall bladder, perforated gall bladder, septic shock), and day of hospital stay.

Data collection
All databases of patients diagnosed with acute cholecystitis using the International Classification of Diseases (ICD) 10 (K80.0 and K80.1) who admitted in the Khon Kaen Hospital during January 2009 till May 2011 through hospital databases were retrieved. Variable including age, sex, body weight, underlying disease, duration of acute symptoms prior to admission, duration since pain onset to receive antibiotics treatment, body temperature, heart rate, pain score-mark, nausea/Vomiting, right upper quadrant pain, radiated pain to right scapular, Murphy's sign, tenderness at RUQ, guarding at right upper quadrant, palpable mass at right upper quadrant , white blood cell, platelet, blood urea nitrogen, creatinine, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, positive ultrasonography (gall stone sonographic Murphy's sign, pericholecystic fluid, perihalo sign, gall bladder dilatation, thickening wall gall bladder, sludge) hemoculture, bacteria culture from bile were recorded

Statistical analysis
We estimated that with a sample size of approximately 316 patient (158 in each treatment group), the study would have 80% of power to detect 6.8% differences of an success conservative treatment (90.5% and 83.7% in ceftriaxone alone group and ceftriaxone combined with metronidazole group respectively .with 2-sided test for the null hypothesis of a relative risk of 1 at a significance level of 0.05. However, we included up to 366 patients to increase the study power.

The retrospective analyses included all the patients who received different medication to conservative treatment. Time-to-event end point were analyzed with the use of a Cox proportional-hazards regression model Kaplan-Meier plots were constructed, and log-rank tests were also performed. P value were calculated with the use of chi-square statistic, Mann-Whitney U test, T test, and Fisher exact test. .

RESULTS

From Figure 1, 648 patients with acute cholecystitis were included. About 282 were excluded due to receiving antibiotics more than three days, being complicated cholecystitis before admission, having other infections, having cholangiocarcinoma and having common bile duct stones. In total, there were 366 left

Table 1. Characteristics of the Patients.

Characteristic	Successful conservative treatment(N=328)	Surgery (N=38)	P Value
Male sex-no. (%)	164 (50.0)	28 (73.7)	0.06
Age-year			0.85
Median	57.0	54	
Interquartile range	45-64	44-66	
Body weight –kg	58.8±12.6	56.9±8.8	0.58
Underlying disease-no. (%)	165 (50.3)	18 (47.4)	0.73
Diabetes Mellitus	69 (21.0)	5 (13.2)	0.25
HIV infection	6 (1.8)	1 (2.6)	0.54
Hypertension	59 (18.0)	8 (21.1)	0.64
Liver cirrhosis	12 (3.7)	1 (2.6)	1.00
Congestive heart failure	3 (0.9)	0	1.00
Myocardial infarction	2 (0.6)	2 (5.3)	0.06
Chronic kidney disease	15 (4.6)	5 (13.2)	0.045
Abnormal EKG	5 (1.5)	1 (2.6)	0.48
History of stroke	4 (1.2)	0	1.00
Thalassemia	10 (3.0)	2 (5.3)	0.36
Chronic obstructive pulmonary disease/Asthma	11 (3.4)	2 (5.3)	0.63
Duration of acute symptoms prior to admission-day			0.50
Median	1	1.5	
Interquartile range	1-3	1-3	
Duration since pain onset to receive antibiotics treatment-days			0.68
Median	1	1.5	
Interquartile range	1-3	1-3	
Symptoms			
Pain score-mark			0.06
Median	4	5	
Interquartile range	3-7	4.0-8.5	
Nausea/Vomiting-no (%)	135 (41.2)	20 (52.6)	0.18
Right upper quadrant pain-no (%)	323 (98.5)	37 (97.4)	0.48
Radiated pain to right scapular-no (%)	23 (7.0)	2 (5.3)	1.00
Signs			
Body temperature°c	37.6±0.1	37.6±0.9	0.98
Heart rate-beat per minute	87.57±18.6	95.8±19.5	0.02
Murphy's sign-no (%)	23 (7.0)	3 (7.9)	0.74
Tenderness at right upper quadrant-no (%)	202 (61.6)	16 (42.1)	0.02
Guarding right upper quadrant-no (%)	101 (30.8)	19 (50.0)	0.02
Palpable mass at right upper quadrant-no (%)	12 (3.7)	0	0.62

for the analysis; 328 were treated conservatively and 38 were undergone operations. Of these, about half were male with the average age of 57 years old. Their mean (±SD) body weight was 53.6±13.7 kilograms. Their median duration time of both acute symptoms until admission and until receive antibiotics were one day. A bit more than half patients had fever and one third had tachycardia. Right upper quadrant pain and tenderness were commonly found in this study sample. Patient underwent operation were more likely to have chronic kidney disease (P=0.045 respectively), higher heart rates (P=0.02), less tenderness (P=0.02) and more guarding (P=0.02) (Table 1).

Almost all of them were investigated using ultrasonography. Thickening gall bladder was found about 54% of the patients. However, perihalo sign were found in only six patients. From the ultrasonography, the ratio of calculus to acalculus cholecystitis was 4:3. Moreover, all ultrasonographic signs including sonographic Murphy's sign, pericholecystic fluid, perihalo sign, gall bladder dilatation and thickening wall of gall bladder were

Table 2. Laboratory Findings of the Patients.

Laboratory findings	Successful conservative treatment(N=328)	Surgery (N=38)	P Value
White blood cell- cell/dl			0.002
Median	11400	15500	
Interquartile range	8500-16000	11450-19150	
Platelet-10^3 cell/dl	237.7±94.9	238.6±111.6	0.97
Blood urea nitrogen-mg/dl			0.56
Median	12	12	
Interquartile range	9-17	8.8-21.8	
Creatinine –mg/dl			0.03
Median	0.9	1.1	
Interquartile range	0.8-1.2	0.9-1.6	
Total bilirubin- mg/dl			0.34
Median	1.3	0.9	
Interquartile range	0.7-2.9	0.7-1.9	
Direct bilirubin -mg/dl			0.68
Median	0.4	0.3	
Interquartile range	0.2-1.6	0.2-0.7	
Aspartate aminotransferase - µg/dl			0.27
Median	55	41	
Interquartile range	27-127	26.8-82.5	
Alanine transaminase- µg/dl			0.18
Median	46	44	
Interquartile range	33.0-105.8	29.3-64.5	
Alkaline phosphatase-µg/dl			0.77
Median	118	108	
Interquartile range	76-204	71.3-213.5	
Positive ultrasonography-no (%)			
Gall stone	114 (56.2)	7 (50.0)	0.65
Sonographic Murphy's sign positive	112 (55.2)	8 (57.1)	0.89
Pericholecystic fluid	29 (14.3)	5 (35.7)	0.049
Perihalo sign	6 (3.0)	0	1.00
Gall bladder dilatation	129 (63.5)	10 (71.4)	0.55
Thickening wall gall bladder	111 (54.7)	7 (50.0)	0.73
Sludge	63 (31.0)	7 (50.0)	0.15

Table 3. Organisms.

	Success conservative treatment(N=328)	Surgery (N=38)	P Value
Hemoculture-no (%)	13 (4.0)	2 (5.3)	0.66
Escherichia coli	5 (1.5)	1 (2.6)	0.48
Klebsiella spp	6 (1.8)	0	1.00
Enterococcus spp	3 (0.9)	1 (2.6)	0.36
Bacteria culture from bile-no (%)	0	2 (5.3)	0.01
Escherichia coli	0	1 (2.6)	0.10
Enterococcus spp	0	1 (2.6)	0.10

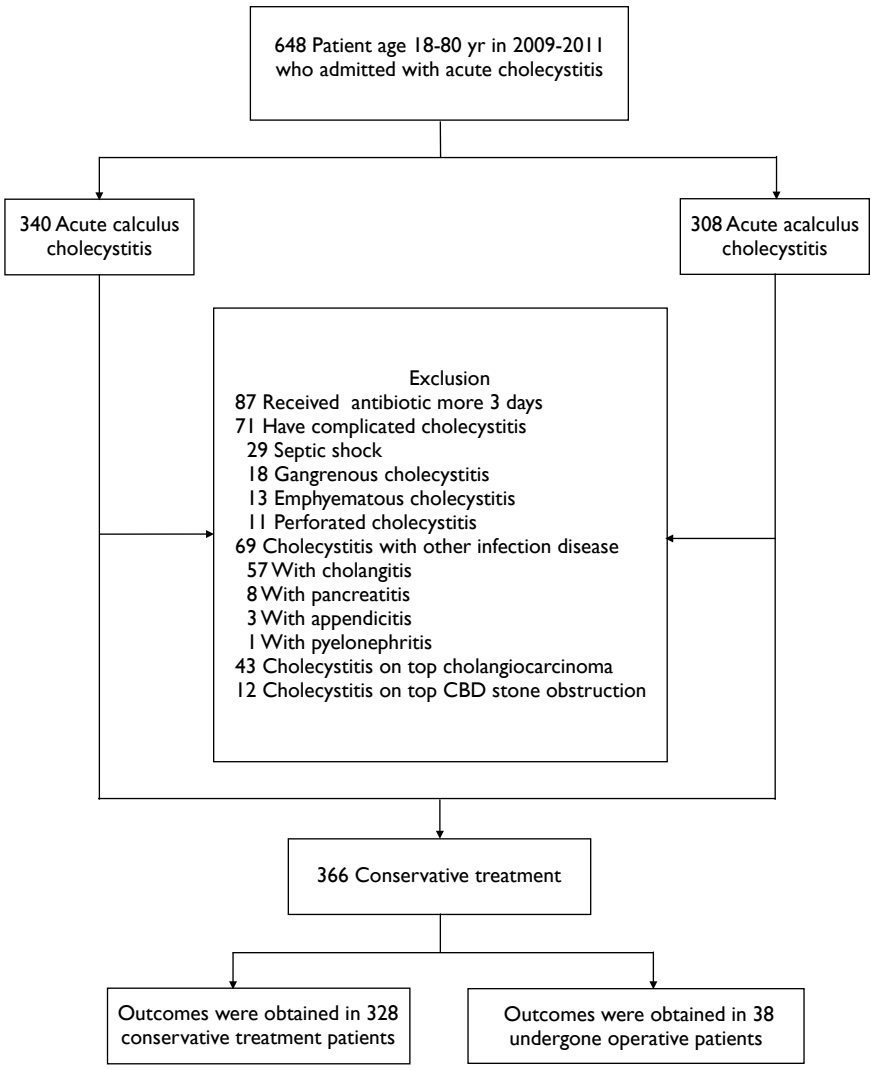

Figure 1. Patients Enrollment,Group Assignment

Figure 1 show an outline of the study, in which 648 patient were initially diagnosis and admitted with acute cholecystitis. After that we group the patients to acute calculus and acalculus cholecystitis. We have 282 patients were exclude form study. Finally 366 were left to conservative treatment analysis. We have 328 outcomes patient who success conservative treatment and 38 patient were fail conservative treatment, all of them undergone operation. Outcomes were obtained in conservative treatment and surgery group. We retrospect analysis to the patient received antibiotics (ceftriaxone alone, ceftriaxone combined with metronidazole) and compared outcomes between antibiotics which the patient received in each group)

found more frequent in acalculus patients. Regarding the laboratory findings, leucocytosis was the only condition that significant found comparing to the normal range. There were no significant differences in the laboratory and ultrasonography of the patients between the two study groups except white blood cell count (P= 0.002), creatinine (P= 0.03) and pericystic fluid (P= 0.049) which were likely to be high in group undergone surgery (Table 2). Few positive results were from hemoculture and bile culture. Escherichia coli, Klebisella spp. and Enterococcus spp. were the only three organisms found in hemoculture from 11 patients. Escherichia coli and Enterococcus spp. were found in each of the two with bile culture (Table 3). Findings regarding treatment outcomes are presented in Table 4. The primary outcomes were obtained in 159 patients in the ceftriaxone group and 178 patients in ceftriaxone combined with

Table 4. Outcomes.

Outcomes	Ceftriaxone alone	Ceftriaxone plus metronidazole					
		At anytime	P Value	Within 24 hours	P Value	More than 24 hours	P Value
Success conservative treatment (n=302)	148 (93.1)	154 (86.5)	0.049	140 (87.5)	0.09	14 (77.8)	0.05
Fever diminishing within five days- no (%)* (n=194)	64 (90.1)	89 (87.3)	0.56	82 (90.1)	1.00	7 (63.6)	0.04
Fever diminishing below 37.8° C-days * (n=194)			0.73		0.75		0.01
Median	2	2		2		4	
Interquartile range	1-4	2-4		2-4		3-8	
Heart rate diminishing below 100 beats per minutes-days (n=127)†			0.52		0.84		0.05
Median	2	3		3		3	
Interquartile range	1-4	2-4		2-4		2-4	
Pain score diminishing below 2 –days (n=269)‡			0.00		0.00		0.00
Median	2	3		2		3.5	
Interquartile range	1-3	2-4		2.0-3.5		2.0-4.5	
Total hospital stay-days			0.00		0.04		0.00
Median	4	5		5		8	
Interquartile range	3-6	4-7		3.0-6.8		5.0-9.3	
Complication -no (%) (n=38)							
Inflammation gall bladder	3 (1.9)	6 (3.4)	0.51	5 (3.1)	0.72	1 (5.6)	0.35
Gangrenous gall bladder	8 (5)	12 (6.7)	0.51	10 (6.3)	0.64	2 (11.1)	0.27
Empysematous gall bladder	0	3 (1.7)	0.25	3 (1.9)	0.25	0	N/A§
Perforated gall bladder	1 (0.6)	2 (1.1)	1.00	1 (0.6)	1.00	1 (5.6)	0.19
Septic shock	2 (1.3)	0	0.22	0	0.25	0	1.00

* The calculation excluded patient s who had body temperature below 37.8 °C on admission
† The calculation excluded patient s who had heart rate below 100 beat per minute on admission
‡ The calculation excluded patient s who had pain score below 3 on admission
§ Not applicable for statistical analysis

metronidazole group. The most of them were success conservative treatment. Both ceftriaxone and ceftriaxone combined with metronidazole can diminish fever in five days. Their median duration time of both fever diminishing below 37.8 C and heart rate diminishing below 100 beats per minute were three days. Their median duration time of pain score diminishing below two and hospital stay were two and three days. Their most common complication was gangrenous gall bladder (Table 4).

In feverish patients who received ceftriaxone combined with metronidazole within 24 hours was not associated with diminishing fever within five days, diminishing fever or diminishing heart rate (P= 1.00, P= 0.75 and P= 0.84). Diminishing of pain score and total length of hospital stay were better in ceftriaxone group (P= 0.00 and P= 0.04 respectively). In general, the efficacy of ceftriaxone combined with metronidazole was not superior to ceftriaxone alone in treatment of acute cholecystitis. Patients received ceftriaxone alone had fewer days of hospitalization and shorter duration of pain than ceftriaxone combined metronidazole group (P=0.02, P=0.009 respectively) with no differences regarding duration of feverish and tachycardia (Figure 2). History of ischemic heart disease, underlying chronic kidney disease, having white blood cell count more than 12,000 cell/dL and male sex were associated were found to be associated with higher rate of undergoing surgery. (Figure 3)

We analyzed potential prognostic factors predictive of operation in the 37 patients who underwent operation using Cox regression. Variables included in this analysis were patient sex and WBC more than 12,000 cell/dl at the time of diagnosis, chronic kidney disease, history of ischemic heart disease. On multivariate analysis, being male and having WBC 12,000 cell/dl or more were associated with significantly increase risk for surgery (p value 0.037 and 0.033 respectively). The prognostic factors analyzed, P values and hazard ratio on Cox regression analysis are summarized in Table 5.

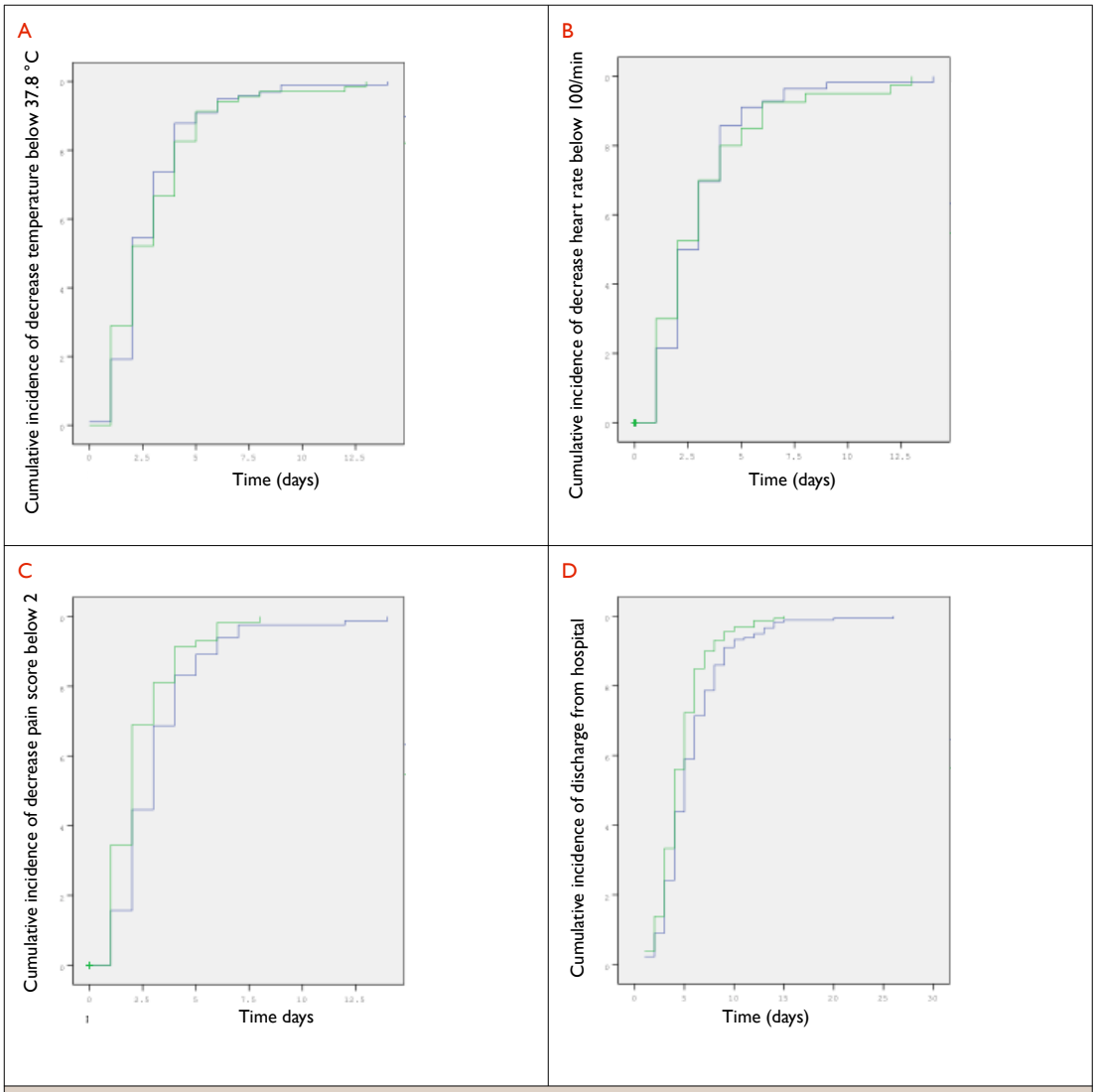

Figure 2. Kaplan Meier Plot of Probability of Treatment Outcomes.
The figure shows among patients with acute cholecystitis who were received ceftriaxone alone (green line) and those who received ceftriaxone combine metronidazole (blue line) by the log-rank test; Panel A shows probability of cumulative incidence of decrease body temperature below 37.8 °C. P=0.830; Panel B shows probability of cumulative incidence of decrease heart rate below 100 beats/min. P=0.963; Panel C shows probability of cumulative incidence of decrease pain scores below 2. P=0.009; Panel D shows probability of cumulative incidence of discharge from hospital. P=0.02

DISCUSSION

This is the first study to our knowledge that affirmed the superiority of using ceftriaxole alone over ceftriaxole combined with metroniazole in relation to higher rate of success conservative treatment of patients with acute cholecystitis. Moreover, patients who received ceftriaxole alone were also found to have shorter hospital stay, time to pain score diminishing. In Cox regression analysis risk factors in patients who undergone operation has higher in male patients and those with WBC 12,000 cell/dl or more. The incidence of emergency cholecystectomy was higher in male patients. Fever and tachycardia present in patients who undergone operation more often than those with success conservative treatment. Same as the white blood cell count and creatinine level were elevated in the surgery group. Pericholecystic fluid, ultrasonography finding, was also likely to be found in those underwent surgery.

This study was the first to investigate the effectiveness of the treatment in Asian population.

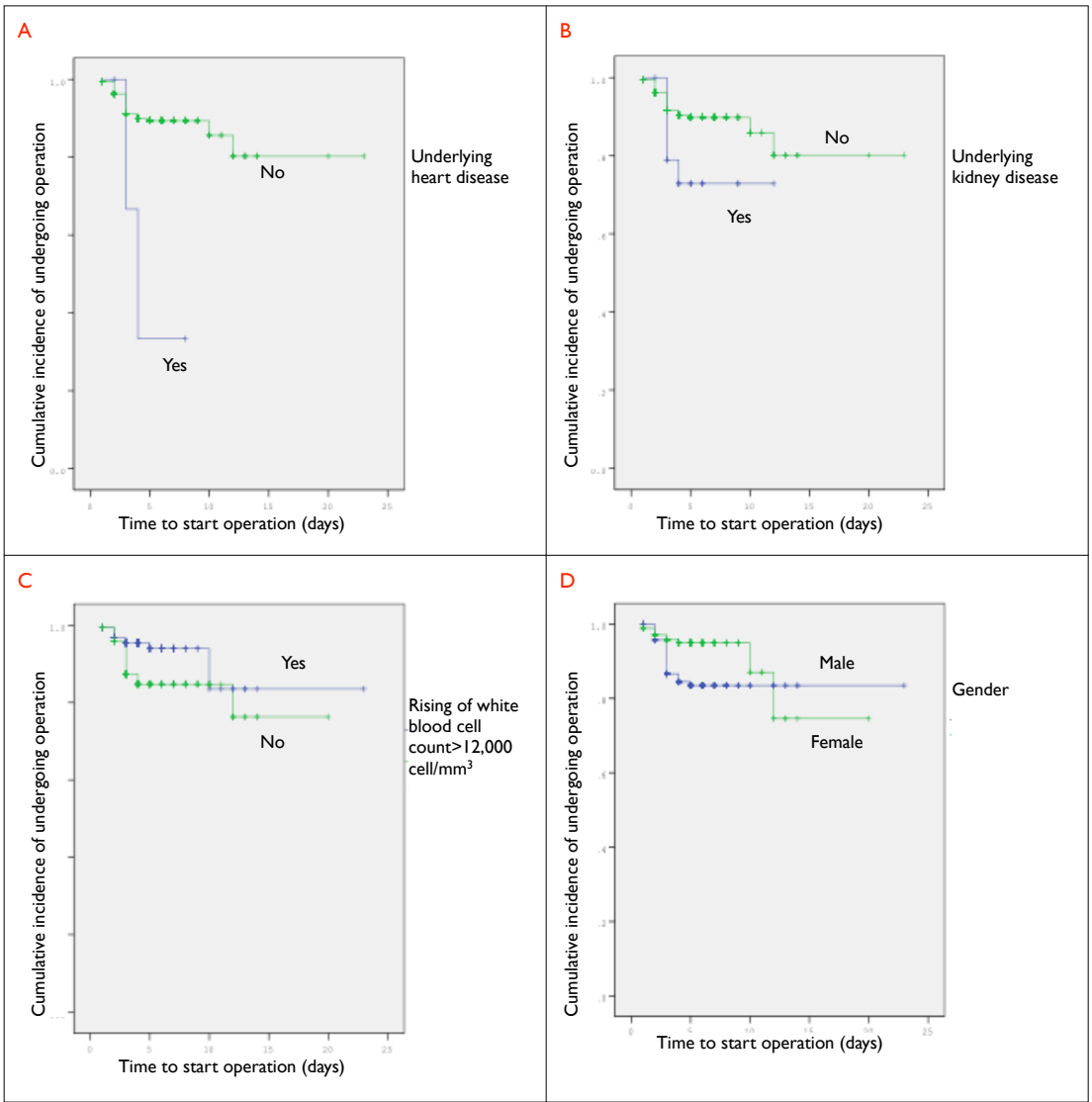

Figure 3. Kaplan Meier Plot of Probability of Treatment Outcomes.
The figure shows associated factor in patients with acute cholecystitis who were success treated conservatively and those who underwent operation by the log-rank test; Panel A shows probability of cumulative incidence of time to start operation in patients who had history of ischemic heart disease. P=0.005; Panel B shows probability of cumulative incidence of time to start operation in patients with chronic kidney disease.P=0.046; Panel C shows probability of cumulative incident of time to start operation in patients with rising white blood cell count more than 12,000 cell/dl. P=0.013; Panel D shows days probability of cumulative incident of time to start operation compare between gender P=0.009

Moreover, we included more than adequate sample size to test our hypothesis, thus, this might be able to generalize to patients with similar characteristics in our studies. However, our study has several limitations due to retrospective nature, and the study had insufficiency statistical power to reach robust conclusion with respect to specific subgroup of patients.

In a previous study, more than 90% of cases of acute cholecystitis were associated with cholelithiasis (acute calculous cholecystitis),8 but our study, only a bit more than half of the patients had cholelithiasis. Acute cholecystitis may begins with an attack of biliary colic in acute calculous cholecystitis,9 but almost all of our patient had persisting pain and localized in the right upper quadrant of the abdomen. They commonly had nausea and vomiting, accompanied by pain that radiates into the back while in radiated pain was the pattern of pain found in a previous study.8 By average pain score was 4 in success conservative treatment and a bit higher in surgery group, still, pain score in not the outcome measured in previous studies.8-10 Tenderness and guarding in the right upper quadrant were a frequent

Table 5. The Prognostic factors for Undergoing Surgery Analyzed, *P* values and Hazard ratio on Cox Regression Analysis

Variable	P-value	Hazard ratio	95% CI	
			Lower	Upper
Male sex	0.037	2.19	1.05	4.58
WBC <12000 cells/dl	0.033	0.42	0.19	0.93
Chronic kidney disease	0.391	1.68	0.51	5.53
Myocardial infarction	0.204	3.65	0.50	26.94

sign that are similar in many previous studies.[8-11] A palpable mass was present in a few success conservative treatment. However, time of mass to be palpable was not recorded in the present study as one study suggested that a palpable mass might be found after 24 hours after onset of symptom.[9] Murphy's sign — the arrest of inspiration while palpating the gallbladder during a deep breath — may be useful, particularly when direct tenderness is absent.[9] However, only 7% were found to have this sign in the current study. In general, the inflammation was initially sterile in most cases, but secondary infection with microorganisms in the Enterobacteriaceae family or with enterococci or anerobes occurs in the majority of patients.[10-11] In our study, microorganisms found in hemoculture and bacterial culture from bile were Escherichia coli,Klebsiella spp and Enterococcus spp.

In conclusion, it was likely that patients treated with ceftriaxone alone were likely to be success with conservative treatment. Moreover, they tended to shorter hospital stay than patients who received ceftriaxone combined metroniazole. Being male and elevated white blood count on admission were the independent predictors for undergoing surgery. With a limitation of early laparoscopic cholecystectomy in some facilities, this study suggested the superiority of using ceftriaxone. A larger cohort with more sample size might be an option for investigating the benefits of various used antibiotics in some specific subgroups.

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Photo by
Sila Amatayakul

Suggestion

Uniform Requirements for Manuscripts Submitted to Biomedical Journal by the International Committee of Medical Journal Editors (ICMJE)

Preparing a Manuscript for Submission to a Biomedical Journal

Editors and reviewers spend many hours reading manuscripts, and therefore appreciate receiving manuscripts that are easy to read and edit. Much of the information in a journal's Instructions to Authors is designed to accomplish that goal in ways that meet each journal's particular editorial needs. The following information provides guidance in preparing manuscripts for any journal.

General Principles

The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is not an arbitrary publication format but rather a direct reflection of the process of scientific discovery. Long articles may need subheadings within some sections (especially Results and Discussion) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, probably need to be formatted differently.

Electronic formats have created opportunities for adding details or whole sections, layering information, cross-linking or extracting portions of articles, and the like only in the electronic version. Authors need to work closely with editors in developing or using such new publication formats and should submit supplementary electronic material for peer review.

Double-spacing all portions of the manuscript— including the title page, abstract, text, acknowledgments, references, individual tables, and legends—and generous margins make it possible for editors and reviewers to edit the text line by line and add comments and queries directly on the paper copy. If manuscripts are submitted electronically, the files should be double-spaced to facilitate printing for reviewing and editing.

Authors should number all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.

Reporting Guidelines for Specific Study Designs

Research reports frequently omit important information. Reporting guidelines have been developed for a number of study designs that some journals may ask authors to follow. Authors should consult the Information for Authors of the journal they have chosen.

The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged also to consult reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (http://www.equator-network.org/home/).

Title Page

The title page should have the following information:

1. Article title. Concise titles are easier to read than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying randomized, controlled trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.

2. Authors' names and institutional affiliations. Some journals publish each author's highest academic degree(s), while others do not.

3. The name of the department(s) and institution(s) to which the work should be attributed.

4. Disclaimers, if any.

5. Contact information for corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript (the "corresponding author;" this author may or may not be the "guarantor" for the integrity of the study). The corresponding author should indicate clearly whether his or her e-mail address can be published.

6. The name and address of the author to whom requests for reprints should be addressed or a statement that reprints are not available from the authors.

7. Source(s) of support in the form of grants, equipment, drugs, or all of these.

8. A running head. Some journals request a short running head or footline, usually no more than 40 characters (including letters and spaces) at the foot of the title page. Running heads are published in most journals, but are also sometimes used within the editorial office for filing and locating manuscripts.

9. Word counts. A word count for the text only (excluding abstract, acknowledgments, figure legends, and references) allows editors and reviewers to assess whether the information contained in the paper warrants the amount of space devoted to it, and whether the submitted manuscript fits within the journal's word limits. A separate word count for the Abstract is useful for the same reason.

10. The number of figures and tables. It is difficult for editorial staff and reviewers to determine whether the figures and tables that should have accompanied a manuscript were actually included unless the numbers of figures and tables are noted on the title page. General Principles

The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is not an arbitrary publication format but rather a direct reflection of the process of scientific discovery. Long articles may need subheadings within some sections (especially Results and Discussion) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, probably need to be formatted differently.

Electronic formats have created opportunities for adding details or whole sections, layering information, cross-linking or extracting portions of articles, and the like only in the electronic version. Authors need to work closely with editors in developing or using such new publication formats and should submit supplementary electronic material for peer review.

Double-spacing all portions of the manuscript— including the title page, abstract, text, acknowledgments, references, individual tables, and legends—and generous margins make it possible for editors and reviewers to edit the text line by line and add comments and queries directly on the paper copy. If manuscripts are submitted electronically, the files should be double-spaced to facilitate printing for reviewing and editing.

Authors should number all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.

Conflict of Interest Notification Page

To prevent potential conflicts of interest from being overlooked or misplaced, this information needs to be part of the manuscript. The ICMJE has developed a uniform disclosure form for use by ICMJE member journals (http://www.icmje.org/coi_disclosure.pdf). Other journals are welcome to adopt this form. Individual journals may differ in where they include this information, and some journals do not send information on conflicts of interest to reviewers. (See Section II. D. Conflicts of Interest.)

Abstract

Structured abstracts are preferred for original research and systematic reviews. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), principal conclusions, and funding sources. It should emphasize new and important aspects of the study or observations. Articles on clinical trials should contain abstracts that include the items that the CONSORT group has identified as essential (http://www.consort-statement.org/?=1190).

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that they

accurately reflect the content of the article. Unfortunately, the information contained in many abstracts differs from that in the text (7). The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list that number the first time they use a trial acronym to refer to either the trial they are reporting or to other trials that they mention in the manuscript.

Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be clear, and any prespecified subgroup analyses should be described. Provide only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods

The Methods section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section.

Selection and Description of Participants

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report—for example, authors should explain why only participants of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way. When authors use such variables as race or ethnicity, they should define how they measured these variables and justify their relevance.

Technical Information

Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

Results

Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Where scientifically appropriate, analyses of the data by such variables as age and sex should be included.

Discussion

Emphasize the new and important aspects of the study and the conclusions that follow from them in the context of the totality of the best available evidence. Do not repeat in detail data or other information given in the Introduction or the Results section. For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

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

References

General Considerations Related to References

Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by using the following search term, where pt in square brackets stands for publication type: Retracted publication [pt] in PubMed.

Reference Style and Format

The Uniform Requirements style for references is based largely on an American National Standards Institute style adapted by the NLM for its databases. Authors should consult NLM's Citing Medicine for information on its recommended formats for a variety of reference types. Authors may also consult sample references, a list of examples extracted from or based on Citing Medicine for easy use by the ICMJE audience; these sample references are maintained by NLM.

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

sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used in the list of Journals Indexed for MEDLINE, posted by the NLM on the Library's Web site. Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

Tables

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

Type or print each table with double-spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Do not use internal horizontal or vertical lines. Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use the following symbols, in sequence:

*, †, ‡, §, ||, ¶, **, ††, ‡‡, §§, ||||, ¶¶, etc.

Identify statistical measures of variations, such as standard deviation and standard error of the mean. Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

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

Illustrations (Figures)

Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. In addition to requiring a version of the figures suitable for printing, some journals now ask authors for electronic files of figures in a format (for example, JPEG or GIF) that will produce high-quality images in the Web version of the journal; authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards.

For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 x 173 mm (5 x 7 inches). Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends--not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background.

Photographs of potentially identifiable people must be accompanied by written permission to use the photograph.

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

For illustrations in color, ascertain whether the journal requires color negatives, positive transparencies, or color prints. Accompanying drawings marked to indicate the region to be reproduced might be useful to the editor. Some journals publish illustrations in color only if the author pays the additional cost.

Authors should consult the journal about requirements for figures submitted in electronic formats.

Legends for Illustrations (Figures)

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

Units of Measurement

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

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

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI). Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

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

aut inveniam viam aut faciam

I shall find either a way or make one

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For

Every support and helps

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In education, we can win all

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