Appendix A

Philosophical context of clinical epidemiology design in this thesis

Philosophical context of clinical epidemiology design in this thesis

Research questions included in this thesis

1. What are clinical indicators for diagnosis of lower abdominal pain in women of reproductive age differentiate appendicitis and common gynecological conditions from non-specific abdominal pain?
2. Is it possible to develop clinical diagnostic scoring scheme for differential diagnosis appendicitis and common gynecological conditions from non-specific abdominal pain in women of reproductive age?
3. Does the developed clinical diagnostic score work with different group of patients?

Research titles for publication

Study I

Clinical indicators for differential diagnosis of acute lower abdominal pain in women of reproductive age

Study II

Clinical scoring for diagnosis of acute lower abdominal pain in female of reproductive age

Study III

Validation of the diagnostic score for acute lower abdominal pain in women of reproductive age

1. Theoretical design

1.1 **Clinical indicators for differential diagnosis of acute lower abdominal pain in women of reproductive age**

This study is a diagnostic descriptive research. The occurrence model of predicted diagnoses is as follow:

Probability (appendicitis or OBGYN condition) =

f (age+anorexia+diarrhea+nausea+vomiting+site+tenderness+pregnancy+ ….)

1.2 Clinical scoring for diagnosis of acute lower abdominal pain in female of reproductive age

This study is a diagnostic prediction research. The occurrence model of predicted diagnoses is as follow:

Probability (appendicitis or OBGYN condition) =

f (age+anorexia+diarrhea+nausea+vomiting+site+tenderness+pregnancy+ ….)

1.3 Validation of the diagnostic score for acute lower abdominal pain in women of reproductive age

This study is a diagnostic prediction research. The occurrence model of predicted diagnoses is as follow:

Probability (appendicitis or OBGYN condition) = f(sum of predictors' scores)

2. Data collection design

2.1 **Study setting and period**

All studies were conducted at Nakornping hospital. It is the tertiary care hospital of Chiang Mai province of Thailand. The electronic medical records of patients who admitted during 2008-2009 were reviewed**.**

2.2 **Study domain**

Study I and II

Patients in these study were female of reproductive age (15 – 50 years) who admitted to surgical or gynecological units during January to December 2008 due to acute lower abdominal pain and their final diagnoses were either appendicitis (ICD 10 code K-35), common obstetrics and gynecological conditions (OB-GYNc) that cause abdominal pain [ectopic pregnancy (ICD 10 code O-00), complicated ovarian cyst (ICD 10 code N-83), pelvic

inflammatory disease (ICD 10 code N-70)], or acute non-specific abdominal pain (ICD 10 code A-09 & R-10).

Study III

Patient domain in this study resembled to study I& II except these patents were admitted during January to July 2009.

2.3 Study design

Study I

Study design was diagnostic descriptive research. Data collection design was delayed type cross-sectional study. The potential diagnostic indicators of the final diagnoses of appendicitis, OB-GYNc , comparing with non-specific abdominal pain (NSAP) were studied.

Study II

This study was derivation phase of diagnostic prediction research. Diagnostic indicators from study I were re-evaluated and statistical modeling for derivation of a diagnostic prediction rule. The diagnostic prediction rule was internally validated for its precision in prediction.

Study III

This study was validation phase of the diagnostic prediction rule from study II. The study was temporal type of external validation study. It was designed as diagnostic test research comparing the predicted diagnosis with the patient's final diagnosis. The diagnostic indices in the validation cohort were compared to those of the derivation cohort.

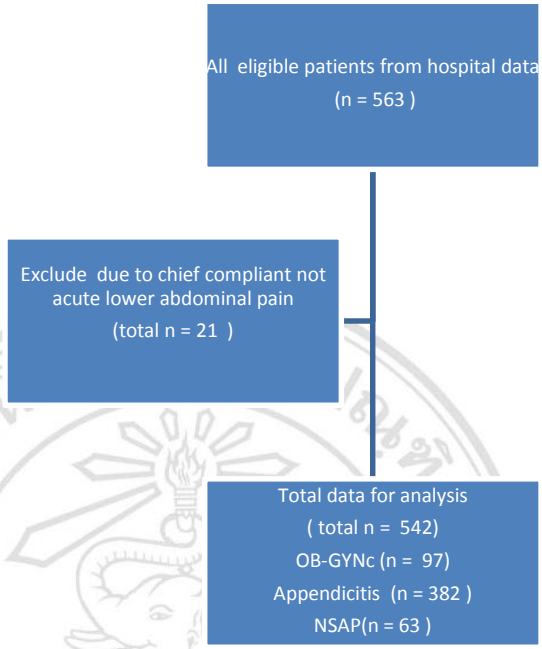
2.4 Data collection process

Medical records were retrieved from the hospital computer system under ICD10 codes. The researcher ascertained the chief complaint and the final diagnosis. Data were extracted from medical record files and were recorded in electrical case record form. Study variables are patients' baseline data, duration of pain, shifting of pain. History presentation of anorexia, nausea, vomiting, diarrhea, pregnancy and abnormal vaginal bleeding at time of admission were recorded. Physical examination of body temperatures, systolic blood pressure, pulse rate, locations of pain on palpation, and signs of peritoneum irritation (guarding and rebound tenderness) were noted. White

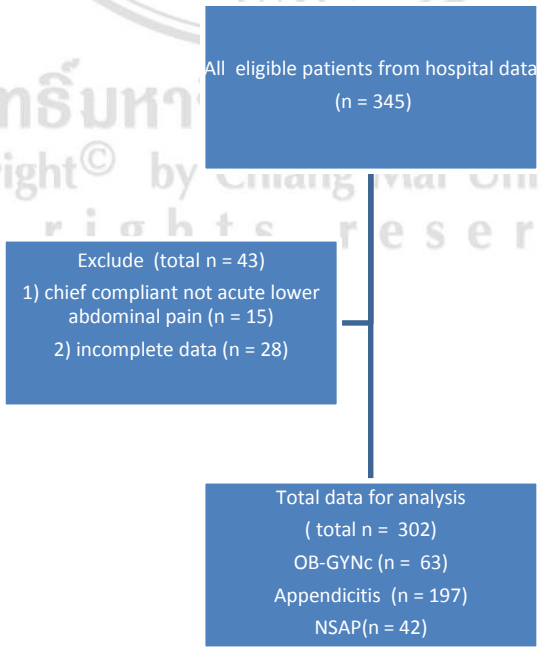
blood cell from completed blood count and urine pregnancy test were recorded. Records with incomplete data were included in study I, II with an aim to perform multiple imputation analysis. Incomplete records were excluded in study III.

2.5 Study flow

Study I, II



Study III



3. Data analysis design

Study I was an exploratory data analysis design. All potential diagnostic indicators were evaluated for diagnostic values in a strategy as follow:

Step 1. Baseline characteristics and diagnostic indicators of each diagnostic group were displayed in frequencies, percentages, means, and standard deviations.

Step 2.Univariable and multivariable polytomous logistic regression will be performed to determine effect of each diagnostic indicator. Exploratory modeling strategy will be applied in multivariable analysis.

Study II is a derivative phase of clinical diagnostic prediction rule. Steps for data analysis were:

Step 1. Baseline characteristics and diagnostic indicators of cases and controls were displayed in frequencies, percentages, means, and standard deviations.

Step 2. Multiple imputation[1] with multivariate normal equation were performed for missing data.

Step 3. Multivariable polytomous logistic regression with estimation method for multiple imputation analysis was performed to determine diagnostic value of each diagnostic indicator.

Step 4. Prediction modeling strategy will be applied in multivariable analysis, using 'Reduction before modeling' strategy and stepwise backward selection to remove diagnostic indicators with low effect (near zero) and non-significant coefficients ($p > 0.05$).

Step 5. The diagnostic prediction rule scores were developed from the final regression model coefficients, item scores were calculated by dividing predictors' coefficients with the lowest absolute number of significant coefficient, the scores were displayed in a scoring chart.

Step 6. The diagnostic prediction rule is based on the principle of relative probabilities of the polytomous logistic regression, that is:

Pr(appendicitis) = 1 – Pr(OB-Gync) – Pr(NSAP)

(The probability of appendicitis is conditional probability relatively to the probability of OB-Gyn; therefore, the vector of each predictor and constants from each model need to be included in the prediction score.)

Step 7. The derived diagnostic prediction rule was tested for its diagnostic accuracy (apparent validation) and diagnostic indices were calculated.

Study III is validation phase of clinical diagnostic prediction study. Data were analyzed in steps as follow:

Step 1. Compare patients' characteristics between validation cohort and derivative cohort.

Step 2.Used the diagnostic prediction rule from study II to predict diagnosis of patients in validation cohort against their final diagnosis as the reference standard. Diagnostic accuracy indices were calculated.

Step 3. Compare diagnostic accuracy indices of validation cohort with diagnostic accuracy indices of derivation cohort.

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Appendix B

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Clinical Indicators for Differential Diagnosis of Acute Lower Abdominal Pain in Women of Reproductive Age

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Abstract

Background: Acute lower abdominal pain in women of reproductive age is a challenging condition for clinical diagnosis. Computerized tomography yields high accuracy, but may not be cost-effective in low-middle income countries. Selective diagnostic approach based on clinical findings may be more appropriate.

Methods: Medical record review was performed on patients aging between 15 - 50 years who admitted to the surgical department or obstetrics and gynecology (OB-GYN) unit because of acute lower abdominal pain during January to December 2008. Patients were eventually categorized into appendicitis, OB-GYN conditions, or non-specific abdominal pain (NSAP). Clinical indicators were studied for diagnostic values using polytomous logistic regression applied to likelihood ratio for positive test (LR+) and confidence interval (CI).

Results: Anorexia, nausea and vomiting, shifting of abdominal pain decreased the likelihood of OB-GYN conditions. Diarrhea increased the likelihood of NSAP. Right lower quadrant tenderness increased the likelihood of appendicitis but decreased the likelihood of OB-GYN conditions. Left lower quadrant tenderness decreased the likelihood of appendicitis but increased the likelihood of OB-GYN. Guarding or rebound tenderness increased the likelihood of appendicitis but reduced the likelihood of NSAP. Leucocytosis (white blood cell count ≥ 10,000) increased the likelihood of appendicitis but reduced the likelihood of OB-GYN and NSAP. Neutrophil ≥ 75% increased the likelihood of OB-GYN but decreased the likelihood of NSAP. Pregnancy reduced the likelihood of appendicitis and increased the likelihood of OB-GYN.

Conclusion: Gastrointestinal symptoms, sites of abdominal tenderness, guarding or rebound tenderness, leucocytosis, neutrophil ≥ 75% and pregnancy are clinical indicators that may help differentiating appendicitis, common OB-GYN conditions, or NSAP in acute lower abdominal pain in women of reproductive age.

Keywords: Lower abdominal pain; Pelvic pain; Appendicitis; Ectopic pregnancy; Ovarian cyst; Non-specific abdominal pain; Likelihood ratio; Polytomous logistic regression

Introduction

Abdominal pain is a common chief complaint of patient at emergency departments. Diagnosis of abdominal pain, especially for lower abdominal pain in women of reproductive age, is challenging. Appendicitis, pelvic inflammatory disease (PID), ectopic pregnancy, and complicated ovarian cyst are common conditions that cause acute lower abdominal pain in childbearing age women [1].

As all common diagnoses of acute lower abdominal pain are emergency conditions, timely diagnosis and management are important. Physical examination alone, for example, pelvic examination has low accuracy in diagnosing lower abdominal pain [2]. Diagnostic investigations such as trans-vaginal ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), and laparoscopy are used with more accuracy [3-8]. These sophisticated investigations, however, require time, resources and medical specialties. The universal uses of these special investigations may not be available in every hospital, and transferring patients for investigation may result in delayed treatment. In appendicitis, for example, a study showed that more accurate diagnosis was associated with higher rate of ruptured appendicitis [9]. In low-middle income countries special investiga-

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Table 1. Demographic Characteristic and Clinical Findings of Patients With Appendicitis, Obstetrics-Gynecological Conditions (OB-GYN), and Non-Specific Abdominal Pain (NSAP)

Characteristics	Appendicitis (n = 382)		OB-GYN (n = 97)		NSAP (n = 63)		P-value
	n	%	n	%	n	%	
Age (yr)							
> 25	169	44.2	41	42.3	27	42.9	
Mean (SD)	30.1	(11.3)	28.9	(8.8)	29.9	(10.4)	0.937*
Single	193	50.8	49	51.0	33	53.2	0.943
Duration of pain (hr)							
> 24	94	24.6	39	40.2	21	33.3	
Mean (SD)	31.2	(32.0)	52.4	(65.9)	34.9	(37.4)	0.413*
Shifting of pain	142	31.2	6	6.2	11	17.5	< 0.001
Anorexia	43	11.3	2	2.1	6	9.5	0.010
Nausea and vomiting	200	52.4	15	15.5	20	31.8	< 0.001
Abnormal vaginal bleeding	1	0.1	28	28.9	2	3.2	< 0.001
Diarrhea	29	7.6	4	4.1	13	20.6	0.002
Temperature ≥ 37.5 °C	124	33.3	14	14.6	12	19.4	< 0.001
Pulse rate (/min)	(n = 374)		(n = 97)		(n = 62)		
Tachycardia (≥ 100)	115	30.6	24	24.7	10	16.3	
Mean (SD)	90.8	(15.5)	88.0	(17.4)	85.2	(17.0)	0.021
Systolic blood pressure (mmHg)	(n = 374)		(n = 97)		(n = 61)		
Hypotension (< 90)	4	1.1	12	12.4	1	1.6	
Mean (SD)	121.8	(15.9)	112.4	(18.5)	117.9	(14.3)	< 0.001
RLQ tender	374	97.9	71	73.2	53	84.1	< 0.001
LLQ tender	15	3.9	48	49.5	6	9.5	< 0.001
Guarding/rebound tenderness	255	66.8	34	35.1	13	20.6	< 0.001
Hematocrit (%)	(n = 336)		(n = 86)		(n = 55)		
Mean (SD)	38.0	(3.9)	33.3	(6.0)	36.5	(5.9)	< 0.001*
WBC (/mm^3)	(n = 292)		(n = 71)		(n = 53)		
≥ 10,000	245	83.9	42	59.2	19	35.9	
Mean (SD)	14,204.5	(4,638.4)	11,875.9	(4,531.9)	9,958.8	(5,200.0)	< 0.001*
Neutrophil (%)	(n = 281)		(n = 69)		(n = 51)		
≥ 75	171	60.9	39	56.5	10	19.6	< 0.001
Pregnancy	7	1.8	47	48.5	3	4.8	< 0.001

* Kruskal-Wallis equality-of-populations rank test.

tions and medical specialties are not widely available. Diagnostic procedures, using combination of clinical findings and routine laboratories as diagnostic indicators, is probably more cost-effective and safe.

Patients and Methods

Patients

Patients were women aged 15 to 50 years who admitted to the surgical department or obstetrics and gynecological department in a tertiary care hospital during January to December 2008 with a chief compliant of acute lower abdominal pain within 14 days. The patients were eventually diagnosed with one of these conditions, appendicitis, common obstetrics and gynecological conditions (complicated ovarian cyst, PID, or ectopic pregnancy), or non-specific abdominal pain conditions (NSAP).

Study variables

Study variables are patients' baseline data (age and marital status), history of abdominal pain including duration of pain, shifting of pain from peri-umbilical area to right lower quadrant. Associated gastro-intestinal symptoms (anorexia, nausea, vomiting, and diarrhea), and gynecological conditions or symptoms (pregnancy and abnormal vaginal bleeding at time of admission) were recorded. Physical examination findings including body temperatures above 37.5 degree Celsius, systolic blood pressure, pulse rate, sites of tenderness, and signs of peritoneum irritation (guarding and rebound tenderness) were noted. Laboratory results from completed blood count and urine pregnancy test were also recorded.

Data source and bias

We used data from medical record reviews. Patients with readmission were excluded to reduce miss-classification bias. To minimize missing data of clinical signs and symptoms, medical records without notes on these variables are recorded as 'negative' for such signs and symptoms. Data were recorded in electronic case record forms.

Statistical analysis

Descriptive statistics (percentages, means, and standard deviations) were used for describing data. To test for differences among the three diagnostic categories, we used exact probability tests for categorical data, one-way ANOVA and Kruskal-Wallis equality-of-populations rank test for continuous data as appropriated. We applied the concept of regression model for likelihood ratios of positive test (LR+) [10] by using polytomous logistic regression to identify significant diagnostic indicators. Results were reported in LR+ and 95% confidence interval (CI).

Results

Medical records of five hundred sixty three (563) patients were reviewed. Twenty one (21) patients were excluded because their chief complaints were not acute lower abdominal pain. Of the 542 patients remaining for analysis, appendicitis was the final diagnosis in 382 patients, obstetrics and gynecological (OB-GYN) conditions in 97 patients, and non-specific abdominal pain (NSAP) in 63 patients. For OB-GYN group, ectopic pregnancies were diagnosed in 48 patients, complicated ovarian cysts in 42 patients, and PID in 7 patients.

Age, marital status, and duration of pain were not different ($P = 0.937$, 0.943, and 0.413). Shifting of abdominal pain was observed more often in appendicitis (31.3%) than in OB-GYN (6.2%) and in NSAP (17.5%, $P < 0.001$). Gastrointestinal symptoms such as anorexia, nausea and vomiting, were less observed in OB-GYN. The proportion of diarrhea in NSAP was higher (31.8%) comparing to OB-GYN (4.1%) and appendicitis (7.6%, $P = 0.002$) (Table 1).

Low-grade fever was found in 33.3% of appendicitis patients, 14.6% of OB-GYN, and 19.4% of NSAP ($P < 0.001$). There were twelve OB-GYN patients (12.4%) presented with hypotension. Left lower quadrant tenderness was predominated in OB-GYN patients (49.5%, 3.9% in appendicitis, and 9.5% in NSAP, $P < 0.001$). Right lower quadrant tenderness was reported in almost every appendicitis patient (97.9%), and in high proportions of OB-GYN (73.2%), and of NSAP (84.1%, $P < 0.001$). Similarly, guarding and rebound tenderness was found more often in appendicitis (Table 1).

Leucocytosis (defined as white blood cell count $\geq$ 10,000/mm^3) was found in 83.9% of appendicitis, 59.2% of OB-GYN, and 35.9% of NSAP ($P < 0.001$). Percentage of neutrophil $\geq$ 75% was less observed in NSAP (19.6%, 60.9% in appendicitis, and 56.5% in OB-GYN, $P < 0.001$). Pregnancy was associated more often with OB-GYN group (Table 1).

Multivariable analysis

We analyzed all diagnostic indicators simultaneously, using the concepts of regression model for likelihood ratio of positive test, with polytomous logistic regression, to determine the effect of each indicator on the likelihood of each of the three diagnostic categories. Diagnostic indicators that increase the likelihood of appendicitis were: right lower quadrant tenderness, guarding and rebound tenderness, and leucocytosis. Left lower quadrant tenderness, pregnancy reduced likelihood of appendicitis. Indicators that increase likelihood of OB-GYN were: left lower quadrant tenderness, neutrophil

Table 2. Likelihood Ratio of Positive Test (LR+) of Diagnostic Indicators From Multivariable Analysis

Indicators	Appendicitis		Obstetric-gynecological conditions		Non-specific abdominal pain	
	LR+ (95%CI)	P	LR+ (95%CI)	P	LR+ (95%CI)	P
Age > 25yr	1.07 (0.91 - 1.26)	0.395	1.09 (0.68 - 1.76)	0.711	0.71 (0.33 - 1.53)	0.379
Single	0.95 (0.80 - 1.12)	0.542	1.34 (0.84 - 2.14)	0.216	1.06 (0.49 - 2.30)	0.884
Duration of pain > 24 hr	1.11 (0.94 - 1.31)	0.237	0.86 (0.51 - 1.44)	0.567	0.89 (0.50 - 1.57)	0.677
Shifting of pain	1.13 (0.99 - 1.28)	0.068	0.36 (0.13 - 0.99)	0.047	0.76 (0.35 - 1.68)	0.501
Anorexia	0.98 (0.81 - 1.17)	0.792	0.34 (0.13 - 0.88)	0.027	1.66 (0.69 - 4.00)	0.258
Nausea and vomiting	1.06 (0.93 - 1.19)	0.375	0.42 (0.23 - 0.76)	0.004	0.90 (0.50 - 1.63)	0.728
Abnormal vaginal bleeding	0.23 (0.03 - 1.51)	0.125	1.15 (0.56 - 2.39)	0.701	0.24 (0.03 - 2.30)	0.217
Diarrhea	0.84 (0.63 - 1.10)	0.207	0.85 (0.32 - 2.25)	0.738	2.93 (1.55 - 5.56)	0.001
Temperature ≥ 37.5 °C	1.00 (0.88 - 1.14)	0.955	0.71 (0.38 - 1.33)	0.282	1.06 (0.54 - 2.06)	0.863
Tachycardia	0.95 (0.83 - 1.09)	0.441	1.05 (0.61 - 1.81)	0.852	1.22 (0.62 - 2.43)	0.565
Systolic BP ≤ 90 mmHg	0.88 (0.33 - 2.31)	0.792	2.08 (0.82 - 5.29)	0.124	0.78 (0.10 - 6.07)	0.816
RLQ tender	2.30 (1.17 - 4.51)	0.016	0.53 (0.31 - 0.93)	0.026	0.75 (0.31 - 1.82)	0.528
LLQ tender	0.22 (0.10 - 0.48)	< 0.001	3.59 (2.27 - 5.66)	< 0.001	0.79 (0.30 - 2.13)	0.647
Guarding/rebound tenderness	1.25 (1.10 - 1.43)	0.001	0.69 (0.42 - 1.12)	0.131	0.37 (0.19 - 0.71)	0.003
Hematocrit < 33%	0.84 (0.65 - 1.09)	0.190	1.61 (0.87 - 2.98)	0.126	0.98 (0.43 - 2.23)	0.960
WBC ≥ 10,000/mm^3	1.74 (1.38 - 2.20)	< 0.001	0.38 (0.20 - 0.74)	0.004	0.36 (0.20 - 0.67)	0.001
Neutrophil ≥ 75%	1.00 (0.88 - 1.15)	0.956	1.96 (1.11 - 3.45)	0.021	0.33 (0.16 - 0.66)	0.002
Pregnancy	0.31 (0.14 - 0.69)	0.004	2.24 (1.18 - 4.25)	0.014	1.18 (0.32 - 4.29)	0.806

Table 3. Summarized Direction of Likelihood of Diagnosis (Appendicitis, Common Obstetric and Gynecological Conditions; OB-GYN, or Non-Specific Abdominal Pain; NSAP) for Each Clinical Indicators

Diagnostic indicators	Likelihood of diagnosis		
	Appendicitis	OB-GYN	NSAP
Anorexia		Decrease	
Nausea/vomit		Decrease	
Shifting of pain		Decrease	
Diarrhea			Increase
RLQ tender	Increase	Decrease	
LLQ tender	Decrease	Increase	
Guarding/rebound tenderness	Increase		Decrease
Pregnancy	Decrease	Increase	
WBC $\geq$ 10,000/mm^2	Increase	Decrease	Decrease
Neutrophil $\geq$ 75%		Increase	Decrease

$\geq$ 75%, and pregnancy. Shifting of abdominal pain, anorexia, nausea and vomiting, right lower quadrant tenderness, and leucocytosis decreased likelihood of OB-GYN. Diarrhea increased likelihood of NSAP, while guarding and rebound tenderness, leucocytosis, and neutrophil $\geq$ 75% reduced likelihood of NSAP (Table 2, 3).

Discussion

Diagnosis of acute lower abdominal pain in a young adult woman is sometimes a challenging clinical situation. Both appendicitis and obstetrics and gynecological conditions need emergency management; therefore, timely and precision of diagnosis is warranted. Studies showed that CT, especially, spiral CT had higher accuracy in diagnosis of appendicitis than ultrasound [11, 12]. In addition, CT scan resulted in changes of diagnosis in 6-36% of acute lower abdominal pain patients [13]. Ultrasound still has its role in pregnant patients because of no radiation exposure [4].

Cost-effectiveness of CT is controversial. In one study, CT showed a reduction of cost in reproductive women with right lower abdominal pain by reducing the cost of unnecessary appendectomy [14]. However, the cost-effectiveness of CT is questionable when health re-imbursement scheme is global budgeting. Selective use of CT, therefore, was advised [15, 16].

Clinical scoring scheme is another approach to diagnosis of appendicitis. Alvarado's scoring scheme was developed for discriminate appendicitis from other causes of abdominal pain [17]. Recently, it was applied for admission criteria rather than as a diagnostic tool [18].

One limitation of clinical scoring schemes for diagnosis of acute lower abdominal pain in reproductive women is that they were designed for diagnosis of single disease. When more than one diagnosis is the outcomes of interest in diagnostic studies, polytomous logistic regression may be applied [19, 20]. In the present study, obstetrics and gynecological conditions were also common causes among these patients and urgent treatments for such conditions were important. The rationale of data analysis in the present study was to study the effect of clinical diagnostic indicators for appendicitis and OB-GYN simultaneously with NSAP. Therefore, polytomous logistic regression was used.

In multivariable polytomous logistic regression for likelihood ratio of positive test, anorexia, nausea and vomiting were associated with decreased likelihood of diagnosis OB-GYN. Anorexia, nausea and vomiting are symptoms associated with gastrointestinal system while OB-GYN is associated with uro-genital system. Signs of peritoneal irritation such as guarding and rebound tenderness, when presented, were associated with decreased likelihood of NSAP.

Effects of clinical indicators that were summarized in Table 3 can be applied in selective approach to women at reproductive age who presented with acute lower abdominal pain. Patients with right lower quadrant tenderness, guarding and rebound tenderness, complete blood counts show leucocytosis and neutrophil more than 75%, but are not pregnant and have no tenderness on left lower quadrant are likely to be appendicitis. General surgeons should be consulted to man-

age these cases. Patients without gastro-intestinal symptoms (anorexia, nausea and vomit), no shifting of abdominal pain, no tenderness on right lower quadrant, no leucocytosis, but present with pregnancy and left lower quadrant tenderness are likely to be OB-GYN conditions. They should be managed by gynecologists. Patients who do not have signs of peritoneal irritation (guarding and rebound tenderness), no leucocytosis and present with diarrhea are possibly NSAP. They can be observed and periodically evaluated for progression of abdominal pain.

Conclusion

Clinical diagnostic indicators that may help differentiate appendicitis, OB-GYN conditions, and NSAP in acute lower abdominal pain in reproductive women are: anorexia, nausea and vomiting, shifting of abdominal pain, diarrhea, site of tenderness, guarding and rebound tenderness, pregnancy, leucocytosis, and neutrophil over 75%.

Conflict of Interest

The authors declared none.

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Appendix C

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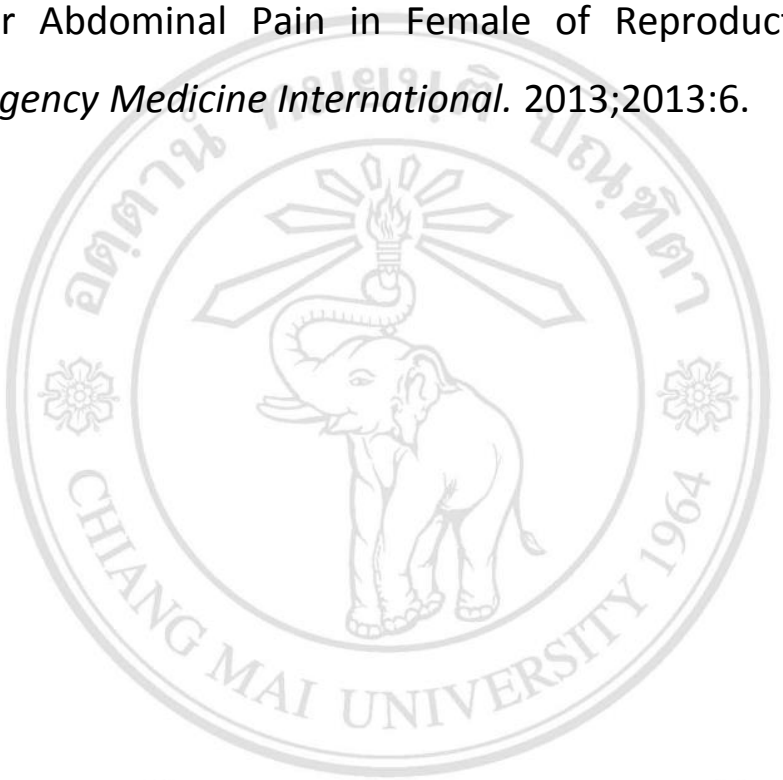

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Research Article

Clinical Scoring for Diagnosis of Acute Lower Abdominal Pain in Female of Reproductive Age

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Background. Obstetrics and gynecological conditions (OB-GYNc) are difficult to be differentiated from appendicitis in young adult females presenting with acute lower abdominal pain. Timely and correct diagnosis is clinically challenging. *Method*. A retrospective data analysis was performed on 542 female patients who were admitted to a tertiary care hospital with a chief complaint of acute lower abdominal pain. Diagnostic indicators of appendicitis and OB-GYNc were identified by stepwise multivariable polytomous logistic regression. Diagnostic performances of the scores were tested. *Result*. The developed clinical score is comprised of (1) guarding or rebound tenderness, (2) pregnancy, (3) sites of abdominal tenderness, (4) leukocytosis, (5) peripheral neutrophils ≥75%, and (6) presence of diarrhea. For diagnosis of appendicitis, the area under the ROC curve was 0.8696, and the sensitivity and specificity were 89.25% and 70.00%. For OB-GYNc, the corresponding values were 0.8450, 66.67%, and 94.85%, respectively. *Conclusion*. The clinical scoring system can differentiate the diagnosis of acute lower abdominal pain in young adult females. Time spent for diagnosis at the emergency room may be shortened, and the patients would be admitted to the appropriate departments in less time.

1. Introduction

Diagnosis of acute lower abdominal pain in young adult female is a clinical challenge. Appendicitis and obstetrics and gynecological conditions (OB-GYNc), such as ectopic pregnancy, pelvic inflammatory diseases, and complicated ovarian cyst, are common causes of acute lower abdominal pain in females during reproductive age [1]. Accurate and timely diagnosis of the condition is critical since incorrect diagnosis can lead to improper surgical intervention, and delayed diagnosis results in delayed management of urgent conditions [2].

Emergency physicians play an important role in early diagnosis and prompt management of the conditions. Experienced emergency physicians can detect important clinical findings and give a provisional diagnosis to a patient before transferring her to general surgery or obstetrics and gynecology departments according to their judgment. Previous studies showed that some clinical indicators were helpful to distinguish appendicitis and common obstetrics and gynecological conditions (OB-GYNc) from nonspecific abdominal pain (NSAP) [3].

To resolve the difficulty in diagnosis of acute lower abdominal pain in female patients, whose appendicitis is confounded by OB-GYNc, imaging studies had been done. Imaging investigations such as ultrasonography, computerized tomography (CT), and magnetic resonance imaging (MRI) have high accuracies in diagnosis of acute lower abdominal pain [4, 5]. However, the universal usage of CT may not be

cost-effective in countries with limited healthcare resources [6]. In addition, time spent for such investigations is also important for the emergency department.

Clinical diagnostic scoring, on the other hand, may be more appropriate for early diagnosis in an emergency department setting. Clinical scoring for diagnosis of appendicitis was studied for its application as a guideline used for admission and investigations [7, 8]. However, such clinical scoring system was not designed for diagnosis of acute lower abdominal pain from obstetrics and gynecology conditions (OB-GYNc), which are also important in young adult females.

The objective of the present study was to develop a clinical scoring for diagnosis of acute lower abdominal pain in females of reproductive age that could either have appendicitis, OB-GYNc, or NSAP.

2. Method

2.1. Patients. We studied medical records of women aging between 15 and 50 years who were admitted to a surgical or obstetrics and gynecology department of a university affiliated tertiary care hospital, with a chief complaint of acute lower abdominal pain within 14 days during January–December 2008. Patients were categorized into 3 groups by their final diagnoses upon discharge. The first group was appendicitis (ICD-10 code K-35), the second group was obstetrics and gynecological conditions (OB-GYNc), such as ectopic pregnancy (ICD-10 code O-00), pelvic inflammatory disease (ICD-10 code N70), and complicated ovarian cyst (ICD-10 code N83). The third group was nonappendicitis and non-OB-GYNc (A-09 and R-10 or other causes of abdominal pain) which was classified as nonspecific abdominal pain (NSAP). The diagnostic criteria for appendicitis were the presentation of any gross inflammation of appendix in operative records or successful conservative treatment with antibiotics in appendiceal abscesses. All medical records were reviewed for operative records, pathological reports, imaging studies, and follow-up records to ascertain their final diagnoses.

2.2. Study Variables. Patients' characteristic (age and marital status), characteristics of pain and associated symptoms (duration of abdominal pain, shifting of pain location, and the presence of anorexia, nausea, vomiting, and diarrhea), and the presence of pregnancy and abnormal vaginal bleeding were reviewed. Body temperature, systolic blood pressure, location of abdominal tenderness, and presence of guarding or rebound tenderness on the first admission day were recorded. Initial laboratory results of complete blood count (hematocrit, white blood cell count, and percentage of neutrophil) and urine pregnancy test were noted. All these clinical indicators were studied for their predictive potential of the final diagnoses.

2.3. Missing Data Management. We had an assumption that the pattern of missing data was missing at random (MAR). Therefore, the multiple imputation method was used in data analysis. We imputed missing data 20 times using the multivariate normal regression method. The imputation model variables included all nonmissing variables and outcome variables (final diagnoses).

2.4. Data Analysis

2.4.1. Derivation of Clinical Scoring. The predictive model for prediction of final diagnosis of appendicitis or OB-GYNc was derived from manual backward stepwise polytomous logistic regression with multiple imputation estimation method, by using NSAP as the base outcome. Nonsignificant clinical diagnostic indicators were manually removed from the model until the remaining coefficients were significant at P values less than 0.05 in one or both diagnoses. Item scores for appendicitis and OB-GYNc were derived from polytomous logistic coefficients of the corresponding diagnosis. We compared the sum of item scores for each diagnosis as the representative of diagnostic possibilities and designed an algorithm for prediction of diagnosis by the scoring system.

2.4.2. Test for Score Performance. Performance of the scoring system was tested with the complete data set. Areas under the receiver operating characteristic (ROC) curves were calculated from disease-specific logistic models to determine discrimination abilities of the score. Accuracy of the scoring system was tested by comparing diagnosis suggested (predicted) from the scoring system with the final (true) diagnosis of patients, and diagnostic indices were calculated.

2.4.3. Ethics. This study was approved from the Ethical Committee of the Faculty of Medicine of Chiang Mai University and the Ethical Committee of Nakornping Hospital.

3. Result

3.1. Patient Characteristic and Score Derivation. A total of 542 female patients were studied, of which final diagnosis were appendicitis in 382 patients, OB-GYNc in 97 patients, and NSAP in 63 patients. Of the OB-GYNc, 48 were diagnosed with ectopic pregnancy, 42 were complicated ovarian cysts, and 7 were pelvic inflammatory disease. The final diagnoses of NSAP were: abdominal pain without specific diagnosis ($n = 31$), enteritis/gastroenteritis ($n = 21$), diverticulitis ($n = 5$), urinary tract infection ($n = 2$), radiation enteritis ($n = 2$), ileitis ($n = 1$), and twisted omentum ($n = 1$). There were 453 patients who underwent surgery, 362 of appendicitis, 69 of OB-GYNc, and 22 of NSAP. Twenty of appendiceal abscesses were treated with antibiotics without surgery. Clinical diagnostic indicators with missing data were: pulse rate (1.6%), systolic blood pressure (1.8%), hematocrit (12.9%), white blood cell count (23.2%), and percentage of neutrophil (26.0%). Significant differences between diagnosis groups were seen in diagnostic indicators of shifting of pain, anorexia, nausea and vomiting, diarrhea, abnormal vaginal bleeding, body temperature, pulse rate, systolic blood pressure, site of abdominal tenderness, guarding or rebound tenderness, hematocrit, white blood cell count, percentage of neutrophil, and pregnancy (Table 1).

Table 1: Demographic characteristics and clinical findings of patients with appendicitis, obstetrics-gynecological conditions (OB-GYNc), and nonspecific abdominal pain (NSAP).

Characteristics	Appendicitis (n = 382)		OB-GYNc (n = 97)		NSAP (n = 63)		P value
	n	%	n	%	n	%	
Age (yr)							
15–20	106	27.8	16	16.5	16	25.4	
21–30	107	28.0	44	45.4	18	28.6	
31–40	74	19.4	25	25.8	14	22.2	
41–50	95	24.9	12	12.4	15	23.8	
Mean (SD)	30.1	(11.3)	28.9	(8.8)	29.9	(10.4)	0.937*
Single	193	50.8	49	51.0	33	53.2	0.943
Duration of pain (hr)							
Mean (SD)	31.2	(32.0)	52.4	(65.9)	34.9	(37.4)	0.413*
Shifting of pain	142	31.2	6	6.2	11	17.5	<0.001
Anorexia	43	11.3	2	2.1	6	9.5	0.010
Nausea and vomiting	200	52.4	15	15.5	20	31.8	<0.001
Abnormal vaginal bleeding	1	0.1	28	28.9	2	3.2	<0.001
Diarrhea	29	7.6	4	4.1	13	20.6	0.002
Temperature ≥ 37.5°C	124	33.3	14	14.6	12	19.4	<0.001
Pulse rate (/min)	(n = 374)		(n = 97)		(n = 62)		
Mean (SD)	90.8	(15.5)	88.0	(17.4)	85.2	(17.0)	0.021
Systolic blood pressure (mmHg)	(n = 374)		(n = 97)		(n = 61)		
Mean (SD)	121.8	(15.9)	112.4	(18.5)	117.9	(14.3)	<0.001
RLQ tender	374	97.9	71	73.2	53	84.1	<0.001
LLQ tender	15	3.9	48	49.5	6	9.5	<0.001
Guarding/rebound tenderness	255	66.8	34	35.1	13	20.6	<0.001
Hematocrit (%)	(n = 336)		(n = 86)		(n = 55)		
Mean (SD)	38.0	(3.9)	33.3	(6.0)	36.5	(5.9)	<0.001*
WBC (/μL)	(n = 292)		(n = 71)		(n = 53)		
Mean (SD)	14204.5	(4638.4)	11875.9	(4531.9)	9958.8	(5200.0)	<0.001*
Neutrophil (%)	(n = 281)		(n = 69)		(n = 51)		
≥75	171	60.9	39	56.5	10	19.6	<0.001
Pregnant/positive pregnancy test	7	1.8	47	48.5	3	4.8	<0.001

*Kruskal-Wallis equality-of-populations rank test, SD: standard deviation, RLQ: right lower quadrant, and LLQ: left lower quadrant.

With multivariable analysis, significant clinical indicators were guarding or rebound tenderness, right lower quadrant (RLQ) tenderness, pregnancy, left lower quadrant (LLQ) tenderness, presence of diarrhea, and leukocytosis (defined as white blood cell ≥10,000/μL). The item score of each clinical indicator for diagnosis of appendicitis or OB-GYNc derived from polytomous logistic coefficients (Table 2). Item scores for diagnosis of appendicitis (appendicitis score) were 1.8 for the presence of guarding or rebound tenderness, −1.7 for pregnancy, 1.5 for leukocytosis, 1.3 for neutrophil ≥75%, 1.5 for RLQ tenderness, 0 for LLQ tenderness, −1.4 for presence of diarrhea, and −1.5 for a constant. Item scores for the diagnosis of OB-GYNc (OB-GYN score) were 0 for the presence of guarding or rebound tenderness, 2.4 for pregnancy, 0 for leukocytosis, 1.6 for neutrophil ≥75%, 0 for RLQ tenderness, 1.9 for LLQ tenderness, and −2.3 for presence of diarrhea.

3.2. Performance of the Scoring System. The median (p25 and p75) of appendicitis score for diagnosis of NSAP was 0 (0, 1.9) for diagnosis of appendicitis was 3.3 (1.9, 4.7), and for diagnosis of (−0.2, 1.8) OB-GYNc was 1.3. The median (p25 and p75) of OB-GYNc score for NSAP was 0 (0, 1.2), 1.6 (0, 1.6) for appendicitis, and 2.4 (1.6, 4.3) for the diagnosis of OB-GYNc (Figure 1). Areas under ROC curves, which reflected discriminative abilities of appendicitis score and OB-GYN score, were 0.8696 for appendicitis versus NSAP and 0.8450 for OB-GYNc versus NSAP, respectively.

By the concept of relative probabilities, an algorithm for diagnosis from the scoring system was created (Table 3). When using this algorithm in 399 patients of the complete data set, the scoring system yielded correct diagnosis (comparing to final diagnosis) of appendicitis in 249 of 285 (positive predictive value, PPV, 87.37%) and correct diagnosis of OB-GYNc in 46 of 63 (PPV 73.02%) (Table 4).

The scoring system had a sensitivity of 89.25%, a specificity of 70.00%, and a likelihood ratio of positive test of 2.97 in diagnosis of appendicitis. For diagnosis of OB-GYNc, the scoring system had a sensitivity of 66.67%, a specificity

Table 2: Coefficients (95% confidence interval: CI) and assigned item scores of selected predictors for diagnosis of appendicitis or common obstetrics and gynecological conditions (OB-GYNc), from polynomial logistic regression analysis*.

Predictors	Appendicitis coefficients (95% CI)	*P* value	OB-GYNc coefficients (95% CI)	*P* value	Assigned score	
					Appendicitis score	OB-GYN score
Guarding/rebound tenderness	1.85 (1.12, 2.59)	<0.001	0.40 (−0.54, 1.34)	0.407	1.9	0
Pregnancy	−1.70 (−3.28, −0.12)	0.035	2.39 (1.05, 3.73)	<0.001	−1.7	2.4
Leukocytosis	1.53 (0.78, 2.29)	<0.001	−0.13 (−1.11, 0.84)	0.787	1.5	0
Neutrophil ≥ 75%	1.25 (0.35, 2.15)	0.007	1.61 (0.49, 2.73)	0.005	1.3	1.6
RLQ tenderness	1.52 (0.40, 2.64)	0.008	−0.42 (−1.46, 0.62)	0.429	1.5	0
LLQ tenderness	−1.11 (−2.26, 0.05)	0.062	1.93 (0.87, 2.98)	<0.001	0	1.9
Diarrhea	−1.44 (−2.41, −0.48)	0.003	−2.26 (−3.79, −0.74)	0.004	−1.4	−2.3
Constant	−1.45 (−2.61, −0.30)	0.014	−0.57 (−1.63, 0.49)	0.290	−1.5	0

*NSAP as baseline group, RLQ: right lower quadrant, and LLQ: left lower quadrant.

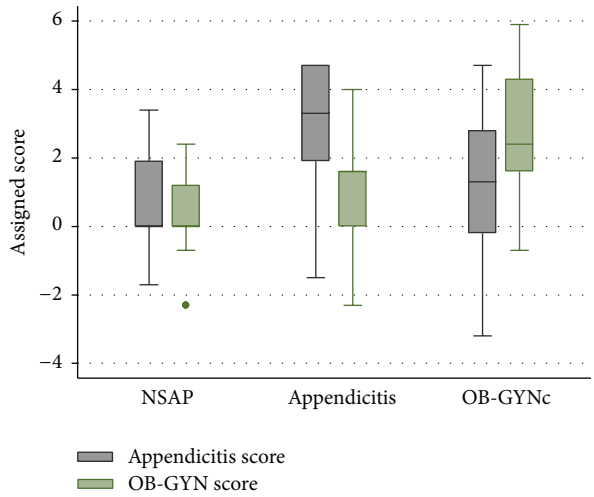

Figure 1: Distribution (box plot) of appendicitis score and OB-GYN score in nonspecific abdominal pain (NSAP), appendicitis, and common obstetrics and gynecological conditions (OB-GYNc).

Table 3: Criteria for diagnostic preferences in acute lower abdominal pain, using the derived scores.

Diagnostic preferences	Criteria
Appendicitis	Appendicitis score > OB-GYN score and appendicitis score > 0
Common OB-GYN conditions (OB-GYNc)	OB-GYN score ≥ appendicitis score and OB-GYN score > 0
Nonspecific abdominal pain (NSAP)	Appendicitis score ≤ 0 and OB-GYN score ≤ 0

of 94.85%, and a likelihood ratio of positive test of 12.94 (Table 5).

Alvarado's score was also calculated for each patient to compare with our scoring system. The means (±sd) of Alvarado's score were 6.19 ± 1.77 for appendicitis, 3.94 ± 2.06 for OB-GYNc, and 3.78 ± 1.63 for NSAP, respectively. At the "cut-off" point at 7, Alvarado's score yielded a sensitivity of 49.8%, a specificity of 90.7%, and a likelihood ratio of positive test of 5.34 for diagnosis of appendicitis. When comparing our appendicitis score and Alvarado's score in their abilities to discriminate appendicitis and "nonappendicitis," the area under ROC of our appendicitis score was 0.8257 (95% CI: 0.78236, 0.86900) and the area under ROC of Alvarado's score was 0.8095 (95% CI: 0.76460, 0.85441). The two areas under ROC were not significantly different at a *P*-value of 0.270 (Figure 2).

4. Discussion

Acute lower abdominal pain in young adult females is a diagnostic challenge for general surgeons, gynecologists, and emergency physicians. Although ultrasonography and CT scan can increase diagnostic accuracy [2, 9, 10], evaluation of patients by clinical specialists is still needed. Diagnosis of acute lower abdominal pain in female patients is more difficult than in male patients; this reflects in negative appendectomies among females were observed more often [11–13]. In case of appendicitis, this can be explained by a wide range of clinical features of the disease [14].

The combination of clinical features and laboratory tests or clinical indicators is useful for the diagnosis of patients' conditions. Mathematically, these clinical indicators can be assigned as scores for diagnosis of difficult conditions. Alvarado's score, for example, was studied for the diagnosis of appendicitis in patients with abdominal pain with good

Table 4: Performance of the diagnostic preferences using the derived scoring scheme for appendicitis, common obstetrics and gynecological conditions (OB-GYNc), and nonspecific abdominal pain (NSAP).

Preference diagnosis using the scoring scheme	Final (true) diagnosis			Total
	Appendicitis	OB-GYNc	NSAP	
Appendicitis (%)	249 (87.37)	14 (4.91)	22 (7.72)	285 (100)
OB-GYNc (%)	9 (14.29)	46 (73.02)	8 (12.70)	63 (100)
NSAP (%)	21 (41.18)	9 (17.65)	21 (41.18)	51 (100)
Total (%)	279 (69.92)	69 (17.29)	51 (12.78)	399 (100)

Table 5: Diagnostic indices (and 95% confidence interval; CI) of the scoring scheme for diagnosis of appendicitis and common obstetrics and gynecological conditions (OB-GYNc).

Diagnostic indices	Appendicitis (95% CI)	OB-GYNc (95% CI)
Sensitivity (%)	89.25 (85.01, 92.63)	66.67 (54.29, 77.56)
Specificity (%)	70.00 (60.96, 78.02)	94.85 (91.88, 96.97)
Positive likelihood ratio	2.97 (2.26, 3.92)	12.94 (7.91, 21.17)
Negative likelihood ratio	0.15 (0.11, 0.22)	0.35 (0.25, 0.49)
Positive predictive value (%)	87.37 (82.94, 90.99)	73.02 (60.35, 83.42)
Negative predictive value (%)	73.68 (64.61, 81.49)	93.15 (89.90, 95.61)

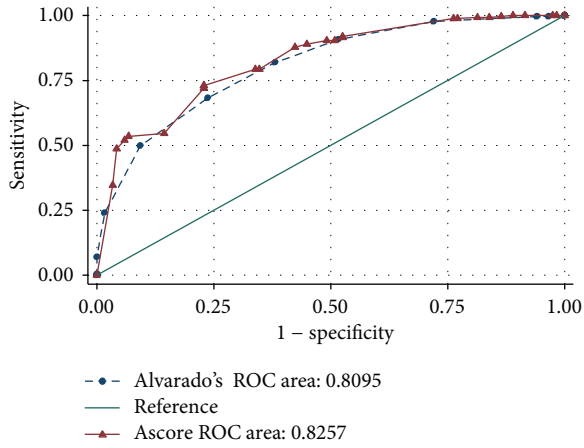

Figure 2: Receiver operating characteristic (ROC) curves of Alvarado's score (dash line) and appendicitis score (ascore, solid line) for diagnosis of appendicitis.

results [15–17]. However, for young adult females, the diagnosis of obstetrics and gynecology conditions is also clinically important.

Polytomous logistic regression had been studied for the diagnosis of conditions that can have more than two possibilities [18, 19]. It can be applied in acute lower abdominal pain in women which could be either appendicitis, OB-GYNc, or NSAP. The present scoring system, which comprised of appendicitis and OB-GYN scores, was derived by applying polytomous logistic regression concept in comparing the relative probabilities of these two conditions. Note that the item scores contained positive and negative values, which reflected increase or decrease probabilities of the corresponding diagnoses in presenting of such clinical indicators.

If we use the present scoring system for diagnosis of acute lower abdominal pain in women of reproductive age, there would be "overdiagnosis" of appendicitis in 36 of 285 patients (4.91% were actually OB-GYNc, and 7.72% were NSAP) while "underdiagnosis" of appendicitis would be observed in 30 of 279 patients. However, a caution should be made to be aware of the scoring system diagnosis of NSAP because of the high risk for appendicitis and OB-GYNc. These patients should be subjected to close observation or further investigations.

Ultrasonography was also performed in uncertain cases in our institute. The results of ultrasonography were helpful in some cases, especially for diagnoses of OB-GYNc. There were 139 patients who underwent ultrasound in this study. Final diagnoses of OB-GYNc correlated well with ultrasound results (27/32 of ectopic pregnancies, 2/2 of PID, and 20/24 of complicated ovarian cysts). However, only 28 of 48 appendicitis patients were correctly diagnosed by ultrasound.

The problem of appendicitis in pregnancy was one caution in using the present scoring system. Of the 37 pregnant women with acute lower abdominal pain in the complete data set, all were categorized into OB-GYNc, which would be correct in 30 of them. However, 4 of them were appendicitis and 3 were NSAP. Therefore, investigation such as ultrasound might be of value for pregnant women with acute lower abdominal pain. Appendicitis should be suspected in pregnant women with right iliac fossa pain unless other causes of pain are evident.

The present scoring system has an advantage of high specificity and high negative predictive value in the diagnosis of OB-GYNc. This could help for ruling out OB-GYNc without further consultation with gynecologists, which may save some extra time in the emergency department. One disadvantage of the scoring system is the need to doubly compute both appendicitis score and OB-GYN score for comparison. However, an electronic calculator can be designed for such purpose.

Some limitations in this study should be taken into consideration. The incompleteness of lower abdominal pain

patients was likely, because patients from the internal medicine department were not included. As our routine practice, the emergency department staff would transfer a young adult female with acute lower abdominal pain to either surgical department or obstetrics and gynecology department rather than to the department of internal medicine or other departments. This preselection may limit the present results to be generalized to other emergency departments. In normal practice, it would be difficult to preselect some patients with overlapping symptoms of abdominal pain. This might possibly explain the low number of patients with diverticulitis or other nonsurgical conditions in our study.

It may also be difficult to generalize the present scoring system to other settings, as it was derived from a tertiary care hospital. The clinical signs and symptoms of early presenting cases at primary settings may be quite different. The retrospective nature of the study may also limit its generalization. A prospective evaluation of the score in different settings should be conducted before it is used in routine clinical practice.

5. Conclusion

The present clinical scoring system can help clinicians distinguish appendicitis and OB-GYNc from NSAP in childbearing age women with acute lower abdominal pain. It may be used as a guideline for admitting patients to the general surgery or the obstetrics and gynecology wards or requesting further investigations. However, validation of the scoring system is needed before being used in clinical practice.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Appendix D

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Research Article

Validation of the Diagnostic Score for Acute Lower Abdominal Pain in Women of Reproductive Age

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Background. The differential diagnoses of acute appendicitis obstetrics, and gynecological conditions (OB-GYNc) or nonspecific abdominal pain in young adult females with lower abdominal pain are clinically challenging. The present study aimed to validate the recently developed clinical score for the diagnosis of acute lower abdominal pain in female of reproductive age. *Method*. Medical records of reproductive age women (15–50 years) who were admitted for acute lower abdominal pain were collected. Validation data were obtained from patients admitted during a different period from the development data. *Result*. There were 302 patients in the validation cohort. For appendicitis, the score had a sensitivity of 91.9%, a specificity of 79.0%, and a positive likelihood ratio of 4.39. The sensitivity, specificity, and positive likelihood ratio in diagnosis of OB-GYNc were 73.0%, 91.6%, and 8.73, respectively. The areas under the receiver operating curves (ROC), the positive likelihood ratios, for appendicitis and OB-GYNc in the validation data were not significantly different from the development data, implying similar performances. *Conclusion*. The clinical score developed for the diagnosis of acute lower abdominal pain in female of reproductive age may be applied to guide differential diagnoses in these patients.

1. Background

Abdominal pain is one of the most common chief complaints of emergency department patients. It was the main symptom of 12.1% to 20.4% of noninjury visits to emergency departments of USA, and 16.8% to 17.8% of them were in severe conditions [1]. It is difficult to diagnose the causes of abdominal pain in some patients. Diagnosis of acute appendicitis, for example, was less accurate in young adult females than in males. The accuracies of diagnosis of acute appendicitis in young adult females were 71.7% to 75.3%, while the accuracies in male were 88.6% to 90.0% [2]. Diagnosis of acute lower abdominal pain in young adult females was particularly difficult due to overlapping symptoms of obstetrics and gynecological conditions with those of acute appendicitis. Negative appendectomies often occurred mostly from missed diagnoses of obstetrics and gynecological conditions [3].

CT scan improved accuracy in diagnosing appendicitis and can detect other causes of abdominal pain in female patients [4]. The use of CT scan can reduce negative appendectomies [5]. However, the universal use of CT scan for diagnosing appendicitis may not be cost-effective in global budget scheme reimbursement for healthcare [6].

Although ultrasound is not as accurate as CT scan, it also showed benefit in diagnosing acute lower abdominal pain [7, 8], especially for pregnant women and children, whom

Table 1: The scoring scheme for appendicitis and obstetrics-gynecological conditions (OB-GYNc) and the criteria used to guide diagnosis of abdominal pain caused by appendicitis, obstetrics, and gynecological conditions (OB-GYNc) or nonspecific abdominal pain (NSAP).

Predictors	Assigned score		Suggested diagnoses	Criteria
	Appendicitis score	OB-GYN score		
Guarding or rebound tenderness	1.9	0	Appendicitis	Appendicitis score > OB-GYN score and appendicitis score >0
Pregnancy	−1.7	2.4		
Leukocytosis (WBC ≥10,000/μL)	1.5	0	OB-GYNc	OB-GYN score ≥ appendicitis score and OB-GYN score >0
Neutrophil ≥75%	1.3	1.6		
RLQ tenderness	1.5	0		
LLQ tenderness	0	1.9	NSAP	Appendicitis score ≤0 and OB-GYN score ≤0
Diarrhea	−1.4	−2.3		
Constant	−1.5	0		

RLQ: right lower quadrant; LLQ: left lower quadrant.

radiation is relatively contraindicated. However, ultrasound alone had low sensitivity in the diagnosis of appendicitis. Its sensitivity was not more than unaided-clinical judgment [9].

Clinical prediction rules, through which clinical findings were systematically applied to predict difficult clinical conditions [10], may be another approach for the diagnosis of acute lower abdominal pain in females of reproductive age. Alvarado's score, although intentionally developed for early diagnosis of acute appendicitis [11], has been studied for admission criteria [12] or criteria for CT scan [13]. However, appendicitis scores were not adequately applicable to abdominal pain in females of reproductive age, because they could not detect obstetrics and gynecological causes. We, therefore, developed a clinical scoring for the diagnosis of acute lower abdominal pain in these particular patients [14]. In this study, we aimed to validate our clinical scoring with patients in a different time period.

2. Method

2.1. The Scoring System. The score is comprised of simple clinical findings, laboratory results, and a constant. Item scores were assigned for guarding or rebound tenderness, pregnancy (either by clinical or urine pregnancy test), tenderness at right lower quadrant of abdomen, tenderness at left lower quadrant of abdomen, leukocytosis (white cell count ≥ 10,000/μL), predominate neutrophil ≥75% in complete blood count, and a constant. The assigned scores and algorithm for diagnostic prediction were shown (Table 1). The item scores had both positive and negative values, which reflected an increase or a decrease in probabilities of the corresponding diagnoses when presenting with those clinical findings.

2.2. Validation Data. The setting hospital is Nakornping Hospital, a tertiary care hospital in Chiang Mai, Thailand. Validation data were extracted from the medical records of female patients aged 15–50 years who were admitted to surgical department or obstetrics and gynecology department during January and July 2009 with a chief complaint of acute lower abdominal pain within 14 days. Patients were classified into three groups upon their final professional diagnoses, which were (1) acute appendicitis (ICD10 code K-35); (2) obstetrics and gynecological conditions (OB-GYNc), including ectopic pregnancy (ICD10 code O-00), pelvic inflammatory disease (ICD10 code N70), and complicated ovarian cyst (ICD10 code N83); and (3) nonspecific abdominal pain (NSAP) (ICD10 code A09, K57, and R10 or other causes of abdominal pain). Study variables were age, marital status, duration of pain, presence of shifting of pain, nausea and vomiting, pregnancy, abnormal vaginal bleeding, presence of fever, systolic blood pressure, site of abdominal pain, presence of guarding or rebound tenderness from abdominal examination, result of complete blood count, and urine pregnancy test. Item scores were calculated and diagnostic prediction was performed for each patient. Final professional diagnoses in the medical records were considered as the reference standard for testing of the score accuracy.

2.3. Statistical Analysis. Patients' characteristics of the development data and the validation data were summarized. Score predicted diagnosis of each patient was compared with final professional diagnosis. Diagnostic indices were calculated in the validation data. The abilities to discriminate appendicitis and OB-GYNc, in terms of areas under the receiver operating curves of the two data sets, were compared with the test for equality of two ROC curves. The positive likelihood ratios for the diagnosis of appendicitis and OB-GYNc of the development data and the validation data were tested with chi-squared for homogeneity test. The probability curves of appendicitis score and OB-GYN score were estimated from logistic regression postestimation function on actual rates of appendicitis and OB-GYNc in the development data and validation data.

2.4. Ethics. The study was approved by the Ethical Committee of Nakornping Hospital and the Ethical Committee of the Faculty of Medicine, Chiang Mai University.

3. Results

The patients' characteristics of the derivation data and the validation data were similar (Table 2). Appendicitis was the most common diagnosis in both data sets (70.5% in

Table 2: Demographic and clinical characteristics of patients in the development data set and validation data set.

Characteristics	Development (n = 542)	Validation (n = 302)
Age (year)		
Mean (SD)	29.9 (10.7)	29.4 (10.3)
Single (%)	51.1	56.0
Duration of pain (hr)		
Mean (SD)	35.4 (41.4)	36.9 (47.2)
Shifting of pain (%)	29.3	16.6
Nausea and vomiting (%)	43.4	42.7
Abnormal vaginal bleeding (%)	5.7	4.6
Diarrhea (%)	8.5	8.9
Temperature ≥37.5°C (%)	28.3	35.3
Pulse rate (/min)		
Mean (SD)	89.6 (16.1)	89.7 (14.7)
Systolic blood pressure (mmHg)		
Mean (SD)	119.6 (16.6)	122.2 (16.6)
RLQ tender (%)	91.9	91.7
LLQ tender (%)	12.7	18.5
Guarding/rebound tenderness (%)	55.7	54.0
Hematocrit (%)		
Mean (SD)	37.0 (4.9)	36.5 (4.6)
WBC (/μL)		
Mean (SD)	13266.1 (4928.0)	12811.3 (4639.4)
Neutrophil (%)		
≥75 (%)	56.9	62.3
Pregnant/positive pregnancy test (%)	10.5	12.6

development data and 65.2% in validation data). The final diagnoses of patients were shown (Table 3).

When comparing the score-predicted diagnoses and the final professional diagnoses in patients from the validation data, the score correctly diagnosed 24 of 33 NSAP patients (72.7%), 181 of 203 appendicitis patients (89.2%), and 46 of 66 OB-GYNc patients (69.7%). The overall accuracy of the score was 83.1% (251/302) (Table 4). The score had a sensitivity of 91.9%, a specificity of 79.0%, and a positive likelihood ratio of 4.39 for diagnosis of appendicitis. For the diagnosis of OB-GYNc, the score had a sensitivity of 73.0%, a specificity of 91.6%, and a positive likelihood ratio of 8.73, respectively. The diagnostic indices and their 95% confidence intervals were displayed (Table 5).

When using the criteria in Table 1 for prediction of diagnoses, the performance of the score in discrimination of appendicitis in terms of ROC analysis and positive likelihood ratio in the validation data were not significantly different from those in the development data. The area under ROC curve for the discrimination of appendicitis and "nonappendicitis" was 0.855 in the validation data and 0.796 in the development data (P = 0.068). The positive likelihood ratios for diagnosis of appendicitis in the validation data and the development data were 4.39 and 2.97, respectively (P = 0.100). The areas under ROC curves for the discrimination of OB-GYNc and "non-OB-GYNc" were not different in the validation data and the development data (0.823 and 0.808; P = 0.706). The ROC areas of the development data reported in this study were different from those reported in our previous study because in previous study we reported the ROC areas of individual scores (appendicitis score for appendicitis and OB-GYN score for OB-GYNc), not as the whole algorithm like in this study. Similarly, the positive likelihood ratios for diagnosis of OB-GYNc were not significantly different in the validation data and the development data (8.73 and 12.94; P = 0.244) (Table 6). The estimate probability curves from actual rates in the development data and the validation data of appendicitis diagnosis from appendicitis score and OB-GYNc from OB-GYN score were shown (Figure 1).

4. Discussion

The present study was the second part of the previous study in clinical prediction rule for the diagnosis of acute lower abdominal pain in females of reproductive age [14]. In general, clinical prediction rule studies are comprised of derivation, validation, and impact studies, with an increase in the level of evidences in each phase [15]. Validation study is important before applying such clinical prediction rule into clinical practice because the results of prediction may not necessarily be reproducible in other settings or in the other time periods [16]. In this validation study, we found no significant differences in the prediction of diagnoses between the validation data and the development data. This could be explained simply by the fact that we conducted the study at the same setting as in the development of the diagnostic score;

Table 3: Final professional diagnosis of patients in the development data and validation data.

Diagnoses	Development (n = 542) n (%)	Validation (n = 302) n (%)
Appendicitis	382 (70.5)	197 (65.2)
OB-GYNc	97 (17.9)	63 (20.9)
Ectopic pregnancy	48	34
Pelvic inflammatory disease	7	5
Complicated ovarian cyst	42	24
NSAP	63 (11.6)	42 (13.9)
Abdominal pain without specific diagnosis	31	20
Enteritis/colitis	21	15
Diverticulitis	5	4
Urinary tract infection	2	3
Radiation enteritis	2	
Twisted omentum	1	

Table 4: Diagnosis suggested by the scoring system and final professional diagnosis in the validation data.

Diagnosis suggested by scoring system	Final professional diagnosis			Total	Correct diagnosis (%)
	NSAP	Appendicitis	OB-GYNc		
NSAP	24	4	5	33	72.7
Appendicitis	10	181	12	203	89.2
OB-GYNc	8	12	46	66	69.7
Total	**42**	**197**	**63**	**302**	**83.1**

Table 5: Diagnostic indices (and 95% confidence interval) of the scoring system for appendicitis (versus nonappendicitis) and OB-GYNc (versus non-OB-GYNc) in the validation data (based on final professional diagnosis).

Diagnostic indices	Appendicitis (versus nonappendicitis)	OB-GYNc (versus non-OB-GYNc)
Sensitivity (%)	91.9 (87.1–95.3)	73.0 (60.3–83.4)
Specificity (%)	79.0 (70.0–86.4)	91.6 (87.4–94.8)
Receiver operating characteristic area	0.855 (0.811–0.898)	0.823 (0.765–0.881)
Positive likelihood ratio	4.39 (3.02–6.37)	8.73 (5.59–13.62)
Negative likelihood ratio	0.10 (0.06–0.17)	0.29 (0.20–0.44)
Positive predictive value (%)	89.2 (84.1–93.1)	69.7 (57.1–80.4)
Negative predictive value (%)	83.8 (75.1–90.5)	92.8 (88.7–95.7)

Table 6: Areas under receiver operating characteristic curves (AuROC) and positive likelihood ratios (and 95% confidence intervals) of the scoring system for appendicitis and OB-GYNc in the development and validation data.

Diagnosis	Development	Validation	P-value
Appendicitis			
AuROC	0.796 (0.751–0.841)	0.855 (0.811–0.898)	0.068
Positive likelihood ratio	2.97 (2.26–3.92)	4.39 (3.02–6.37)	0.100
OB-GYNc			
AuROC	0.808 (0.750–0.865)	0.823 (0.765–0.881)	0.706
Positive likelihood ratio	12.94 (7.91–21.17)	8.73 (5.59–13.62)	0.244

patients' characteristics and patterns of clinical practices were unlikely to be different from time to time.

Clinical scoring for the diagnosis of abdominal pain has been extensively studied for appendicitis [17–22]. There were relatively fewer studies for obstetrics and gynecological conditions [23–25]. However, those studied were applied for the diagnosis of only single disease (appendicitis, ectopic pregnancy, pelvic inflammatory disease, or adnexal torsion). The present diagnostic score has an advantage in inferring differential diagnosis of more than one condition, resembling

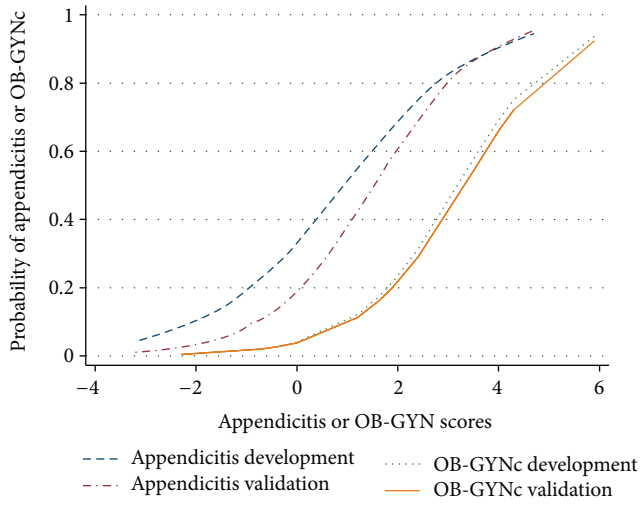

Figure 1: Estimated probabilities of appendicitis (dash and dash-dotted lines) and OB-GYNc (dot and solid lines) from actual rates of final diagnoses in development data set and validation data set.

routine clinical approach to patients. The main advantage of this score is triaging. It can guide emergency room physicians whether to admit the patients, and what specialties to consult. For example, a patient with appendicitis score and OB-GYN score equal to or less than zero, which diagnosis of NSAP is likely; this patient can probably be admitted to the observation room or discharged from emergency room and appointed to followup in the next 24 hours for a case with mild symptoms. The probability of appendicitis in this case would be approximately 20% or less; and the probability of OB-GYNc is very low (Figure 1). In addition, score-predicted probability in Figure 1 can also be applied for selective management. Patients with appendicitis score of 0–2 or OB-GYN score of 2–4, whose probabilities of appendicitis or OB-GYNc are approximately 20% to 60%, would be appropriate candidates for further investigations, such as ultrasound or CT, prior to admission. By triaging and selective management, the time spent in emergency department is expected to be less.

This study has several limitations. The obvious one is retrospective design of the study. Clinical signs and symptoms that were not documented either could be absent of such clinical findings or were not evaluated. The different observers may have different interpretations of physical examination, and clinical signs that change over time may not be well recorded.

Using of final professional diagnoses as the reference standard is another limitation. The problem of different follow-up times and different clinical judgments amongst doctors also leads to misclassification. These limitations can be reduced if a prospective validation study of the diagnostic scoring system is performed, with interobserver agreement of measurements, including standardized criteria for diagnostic indicators, objective criteria for final diagnosis of each condition, and standardized follow-up time.

The result of this study should be used with caution. Patients in our setting were mainly referred from smaller hospitals in Chiang Mai. Most of them needed to be admitted to either general surgery department or obstetrics and gynecology department. Different patients' characteristics and different patient flows in other settings would affect the accuracy of the scoring system. For example, myoma uteri complications such as necrosis or torsion were rare in our settings. In other hospitals where myoma uteri complications are major causes of acute lower abdominal pain, this diagnostic score may not be suitable for such settings. Applying this scoring system to different settings, different patterns of patients flow, could probably lead to misdiagnoses in some conditions. External validation in different settings should be performed prior to adoption into clinical practice in other settings. Further impact studies of the score to assess its impacts on multidimensions of clinical practice, such as time spent in emergency department, additional diagnostic value on top of unaided junior physicians' judgments, and time and cost of diagnosis, should be conducted in the future.

5. Conclusion

The clinical diagnostic score can triage appendicitis, OB-GYNc, and NSAP in female patients with acute lower abdominal pain. The diagnostic score can guide emergency department physicians for proper admissions and selective managements.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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