ORIGINAL RESEARCH

Development of a simplified diagnostic indicators scoring system and validation for peptic ulcer perforation in a developing country

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Objective: To perform and confirm a simplified diagnostic indicators scoring system for predicting peptic ulcer perforation (PUP).

Methods: A case–control study was conducted including 812 consecutive patients with PUP from retrospective medical records. Each diagnostic indicator measurable at the time of admittance was analyzed by a multiple regression. Stepwise logistic regression was applied with backward elimination of statistically significant predictors from the full model, with $P \geq 0.05$ for exclusion. The item scores were transformed from regression coefficients and computed to a total score. The risk of PUP was interpreted using total scores as a simple predictor. This system was internally validated in 218 consecutive patients and compared to existing systems.

Results: A PUP risk score was determined from the diagnostic indicators associated with PUP: gender, age, nonsteroidal antiinflammatory drugs used, history of peptic ulcer, intense abdominal pain, guarding, X-ray free air positive, and referral from other hospitals. Item scores ranged from 0–6.0 and the total score ranged from 0–34.0. The area under the receiver operating characteristic curve shows that there was 91.73% accuracy in the total scores predicting the likelihood of PUP. The likelihood of PUP among low risk (scores <10.5), moderate risk (scores 11–21), and high risk (scores ≥ 21.5) patients was 0.13, 11.44, and 1.95, respectively.

Conclusion: This scoring system is an effective diagnostic indicator for identifying the complex cases of PUP. It is a simple system and can help guide clinicians, providing them with a more efficient way to accurately subgroup patients while also reducing potential biases.

Keywords: peptic ulcer perforation, risk scoring, prediction

Introduction

Patient safety is attracting worldwide attention in all disciplines of medicine. Peptic ulcer perforation (PUP) is a major crucial complication of peptic ulcer.[1,2,4] PUP accounts for about 10%–15% of peptic ulcer patients and accounts for more than 70% of deaths.[1] The mortality rate after PUP is approximately 10%–15% upon delayed diagnosis.[2,3,5]

Severe upper abdominal pain is the most prominent symptom of PUP. About half of patients with PUP usually present with nausea, vomiting reflex, and vomiting – mostly food debris and gastric juice mixed with blood or coffee-like liquid, and can lead to intestinal paralysis. Approximately 1–5 hours after perforation, a patient's stomach content can spill into the abdominal cavity due to an increase in peritoneal exudates. This may provide varying degrees of relief from abdominal pain and abdominal tension, but the tenderness is still significant. At this point, it would be easy to misdiagnose. In the first 10–12 hours after perforation, with peritoneal exudates absorption and

secondary bacterial infection, late diagnosis and treatment of patients infected with severe peritonitis can lead to chills, fever, or even toxic intestinal sepsis, and physicians must be highly vigilant to avoid death due to toxic shock.[6]

The literature suggests that the diagnosis of PUP should rarely be made on the basis of physical examination,[5,7] whereas in clinical practice, the diagnosis of PUP is mainly established by patient history, signs and symptoms, physical examination, radiology investigation, and laboratory findings.[1]

A major limitation of scoring systems is their dependence on sophisticated methods, which may not be available in developing countries. A simplified diagnostic indicators scoring system for predicting PUP – which can be easily used in developing countries – is needed.

Materials and methods
Definition
The definition of PUP according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision includes gastric ulcer (coded K25, subcategories 25.1, 25.2, 25.5, 25.6) and duodenal ulcer (coded K26, subcategories 26.1, 26.2, 26.5, 26.6).[8] The subcategories are defined as acute with perforation, acute with both hemorrhage and perforation, chronic or unspecified with perforation, and chronic or unspecified with both hemorrhage and perforation, respectively.

Development of the scoring system
A case–control study was conducted using medical records of PUP patients (cases and controls) – enrolled between January 1, 2005 and December 31, 2008 – that were reviewed retrospectively. PUP patients aged ≥15 years who were hospitalized in Nakornping Hospital (Chiang Mai, Thailand) were included in the cases group of the study, while nonperforation patients were included in the control group. Invariably, the diagnosis for PUP was obtained during the postoperation diagnosis by surgeons. The PUP patients with malignant ulcers or trauma were excluded.

It was important to estimate a sufficient sample size to achieve adequate statistical power. To yield a significant finding at $\alpha = 0.05$, $\beta = 0.20$, and minimum detectable odds ratio $= 4.9$, the best sample size required 812 cases. There were 406 cases in the medical records; therefore 406 controls were analytically selected from nonperforated peptic ulcer patients immediately before and after the cases. Patient characteristics of cases and controls were compared using Student t-tests

and exact probability tests to determine their suitability for possible risk indicators. The diagnostic indicators computable at the time of admittance were designated and analyzed by a stepwise logistic regression to determine a set of statistically significant predictors. Mathematical predictors were divided into three levels; the cutoff points of which were clarified from the values that produced all statistically significant regression coefficients and the utmost area under the receiver operating characteristic (ROC) curve of the logistic regression model. Regression coefficients of all diagnostic indicator predictors were changed into item assigned scores, which were then built into a total score (diagnostic indicators score) for each item. The total scores signified the summary measure of risk for PUP. Total scores were then evaluated as the sole predictor in the logistic regression model.

Validation of the scoring system
The medical records of 218 patients aged ≥15 years who underwent PUP surgery at the same setting (Nakornping Hospital) between January 1, 2009 and December 31, 2009 were reviewed retrospectively. All patient profiles for the PUP operation were assessed. The patients in whom histological diagnosis confirmed a malignant lesion in the peptic ulcer area were excluded.

The research protocol was accepted by the Chiang Mai University's Faculty of Medicine Research in Human Subjects Ethical Review Committee and the Director of Nakornping Hospital. Information was analyzed by using Stata® statistical software package version 11.0 for Windows (StataCorp LP, College Station, TX).

Results
Patient characteristics
There were statistically significant differences between cases and controls in female gender, median age, underlying illness (diabetes mellitus $P < 0.001$, hypertension $P < 0.001$, liver disease $P < 0.001$, renal disease $P < 0.01$, arthritis $P = 0.013$, and history of peptic ulcer $P < 0.001$), patient lifestyles (tobacco smoking $P < 0.001$, alcohol used $P < 0.001$, and nonsteroidal antiinflammatory drugs used $P = 0.006$), signs and symptoms (hematemesis $P = 0.002$, intense abdominal pain $P < 0.001$, tenderness $P < 0.001$, guarding $P < 0.001$, melena $P < 0.001$, and systolic blood pressure $P < 0.001$), laboratory investigations (blood urea nitrogen/creatinine ratio $P < 0.001$), radiological finding (X-ray with free air $P < 0.001$), and treatment role (referral from other hospitals $P < 0.001$) (Table 1). The backward stepwise logistic regression analysis was used to develop a

Table 1 Characteristics of patients with peptic ulcer perforation (cases) and nonperforation (controls)

Characteristics	Cases (n = 406)	Controls (n = 406)	P value
Gender			
Female	335 (82.51%)	152 (37.44%)	<0.001
Male	71 (17.49%)	254 (62.56%)	
Age (years)			
Median (IQR)	71 (15–92)	52 (32–85)	0.0003
Underlying illness			
Diabetes mellitus			
No	381 (93.84%)	336 (82.76%)	<0.001
Yes	25 (6.16%)	70 (17.24%)	
Hypertension			
No	338 (83.25%)	270 (66.50%)	<0.001
Yes	68 (16.75%)	136 (33.50%)	
Liver disease			
No	400 (98.52%)	365 (89.90%)	<0.001
Yes	98.52 (1.48%)	41 (10.10%)	
Renal disease			
No	377 (92.86%)	355 (87.44%)	0.010
Yes	29 (7.14%)	51 (12.56%)	
Arthritis			
No	14 (3.45%)	30 (7.39%)	0.013
Yes	392 (96.55%)	376 (92.61%)	
History of peptic ulcer			
No	200 (49.26%)	329 (81.03%)	<0.001
Yes	206 (50.74%)	77 (18.97%)	
Patient lifestyles			
Tobacco smoking			
No	113 (27.83%)	211 (51.97%)	<0.001
Yes	293 (72.17%)	195 (48.03%)	
Alcohol used			
No	238 (58.62%)	232 (57.14%)	<0.001
Yes	168 (41.38%)	174 (42.86%)	
NSAIDs used			
No	295 (72.66%)	328 (80.79%)	0.006
Yes	111 (27.34%)	78 (19.21%)	
Signs and symptoms			
Hematemesis			
No	288 (70.94%)	246 (60.59%)	0.002
Yes	118 (29.06%)	160 (39.41%)	
Intense abdominal pain			
No	28 (6.90%)	205 (50.49%)	<0.001
Yes	378 (93.10%)	201 (49.51%)	
Tenderness			
No	43 (7.14%)	274 (61.58%)	<0.001
Yes	363 (92.86%)	132 (38.42%)	
Guarding			
No	43 (10.59%)	274 (67.49%)	<0.001
Yes	363 (89.41%)	132 (32.51%)	
Melena			
No	366 (90.15%)	308 (75.86%)	<0.001
Yes	40 (9.85%)	98 (24.14%)	
Systolic blood pressure (mmHg)			
Mean ± SD	115.02 ± 20.51	119.84 ± 18.04	0.002
Laboratory investigation			
Hemoglobin (mg/dL)			
Mean ± SD	10.51 ± 2.32	10.30 ± 2.45	0.222

(Continued)

Table 1 (*Continued*)

Characteristics	Cases (n = 406)	Controls (n = 406)	*P* value
Hematocrit (5)			
Mean ± SD	30.71 ± 6.91	30.56 ± 7.56	0.777
BUN/Cr ratio			
Mean ± SD	19.00 ± 18	10.00 ± 7.50	<0.001
Radiological finding			
X-ray free air positive			
No	167 (41.13%)	356 (87.68%)	<0.001
Yes	239 (58.87%)	50 (12.32%)	
Treatment role			
Referral from other hospitals			
No	34 (8.37%)	160 (39.41%)	<0.001
Yes	372 (91.63%)	246 (60.59%)	

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; IQR, interquartile range; NSAIDs, nonsteroidal antiinflammatory drugs; SD, standard deviation.

logistic regression model. The eight risk predictors were gender, age, nonsteroidal antiinflammatory drugs used, history of peptic ulcer, intense abdominal pain, guarding, X-ray free air positive, and referral from other hospitals (Table 2).

Table 2 Regression coefficient, risk ratio, and 95% confidence interval of diagnostic indicators for peptic ulcer perforation from logistic regression

Diagnostic indicators	Coefficient	OR	95% CI of OR	*P* value
Gender				
Female	–	1.00	Reference	0.004
Male	0.74	2.09	1.07–3.51	
Age (years)				
<60	–	1.00	Reference	
61–70	0.33	1.39	0.78–2.50	0.267
≥71	1.61	5.02	3.00–8.40	<0.001
NSAIDs used				
No	–	1.00	Reference	<0.001
Yes	1.02	2.77	1.66–4.60	
History of peptic ulcer				
No	–	–	Reference	<0.001
Yes	0.91	2.50	1.61–3.87	
Intense abdominal pain				
No	–	1.00	Reference	0.017
Yes	1.56	3.21	1.24–8.36	
Tenderness				
No	–	1.00	Reference	0.002
Yes	1.25	3.29	1.57–6.88	
Guarding				
No	–	1.00	Reference	0.002
Yes	1.25	3.29	1.57–6.88	
X-ray free air positive				
No	–	1.00	Reference	<0.001
Yes	2.04	7.60	4.77–12.11	
Referral from other hospitals				
No	–	1.00	Reference	<0.001
Yes	1.43	4.27	2.51–7.27	

Note: Area under the receiver operating characteristic curve = 94.46%.
Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio.

Development of the risk score

A risk score was determined from these eight predictors to predict the risk for PUP. Numerical predictors were categorized into three levels. Substantially better outcomes were confirmed when a greater area under the ROC curve was obtained (94.46%). The regression coefficients were transformed by dividing with the smallest coefficient in the model (0.33) and rounded up to the nearest 0.5 to obtain item scores. Every item score ranged from zero up to 2.0 or 6.0. After item scores were added to get the total scores, they ranged from zero to 34 (Table 3). The area under the ROC curve shows that there was 91.73% accuracy in the total scores predicting the likelihood of PUP (Figure 1).

Validation of the scoring system

A graph mapping the proportion of PUP against total scores shows that the actual risk for higher total scores correlates well with the predicted risk from logistic estimation (Figure 2). Classification of the validation cohort risk score resulted in three levels: low risk (scores < 10.5), moderate risk (scores 11–21), and high risk (scores ≥ 21.5). Of the cases that were classified as low risk, 10.16% had PUP, compared with 51.56% in the moderate-risk group and 38.28% in the high-risk group. Of the controls, 76.79% were categorized as low risk, 3.57% as moderate risk, and 19.64% as high risk. The intended likelihood ratio shows that low-risk cases were only 0.13 times more likely to result in PUP, while moderate-risk cases were 14.44 times, and high-risk cases were 1.95 times more likely to result in PUP. Even supposing that PUP occurs, the relationship between scores and treatment show that the higher scores have a higher likelihood of surgery (Table 4).

Discussion

The development of a simplified diagnostic indicators score was based on the philosophy of clinical prediction rules

Table 3 Item scoring scheme for predictors of peptic ulcer perforation derived from coefficients of select diagnostic indicators

Diagnostic indicators	Coefficient	Transformed coefficient	Assigned score
Gender			
Female	–	–	0
Male	0.74	2.24	2.0
Age (years)			
<60	–	–	0
61–70	0.33	1.0	1.0
≥71	1.61	4.88	5.0
NSAIDs used			
No	–	–	0
Yes	1.02	3.09	3.0
History of peptic ulcer			
No	–	–	0
Yes	0.91	2.76	3.0
Intense abdominal pain			
No	–	–	0
Yes	1.56	4.73	4.5
Guarding			
No	–	–	0
Yes	1.25	6.18	6.0
X-ray free air positive			
No	–	–	0
Yes	2.04	6.18	6.0
Referral from other hospitals			
No	–	–	0
Yes	1.43	4.33	4.5

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; NSAIDs, nonsteroidal antiinflammatory drugs.

Figure 2 Score predicted risk (dots) and logistic estimated risk (solid line) of peptic ulcer perforation (%) for each total score.

of a variety of clinical outcomes.[10–16] However, not one of these methods was relevant for estimating the risk of PUP in routine clinical practice. The process currently used to appraise the risk of PUP is very complicated. In the field, clinicians have been undergoing a paradigm shift recently as the importance of evidence is realized in practice.[1] Effective use of current evidence requires the clinician to draw on clinical experience and assess patient values as well as to collect, analyze, and implement the research into practice. The easy-to-use and proficient risk score for PUP might enable prompt identification of patients at high risk for PUP.

This report demonstrated a method for multivariable logistic regression analysis dividing the continuous variables into a dichotomous score yielding arithmetically identical estimates of risk. The benefit of the methodology over the typical appearance of logistic regression is that essentially anyone is able to estimate the risk of an event associated with given predictors. The risk score for predicting PUP was explained by an area under the ROC curve of 91.73%. The proportion of PUP increased sharply when the score increased from low risk to high risk.

An easy and realistic risk score was determined to predict the risk of PUP, which gained high prediction precision. To encourage the risk score to be successful in its forecasting, only the variables identifiable at the time of hospitalization were chosen.

This study demonstrated a simple and realistic method of computing the risk score to enable categorization of peptic ulcer patients into levels of PUP risk. The area under the ROC curve for PUP risk score was 91.73%. High prediction accuracy observed in this study was a result of the rigorous diagnostic indicators definition for PUP from a previous study to avoid misclassification.[1] It was previously known that when diagnostic indicators are transformed to a risk score, the prediction accuracy is reasonably reduced. The current

applied to some areas in PUP,[9] such as a score to predict postoperative morbidity and mortality,[10–13,15] poor outcome,[14] and to compare with a validated risk score for PUP.[15]

Clinicians and their team prefer to be able to precisely predict the presence or nonappearance of PUP. Statistical methods using logistic regression have estimated the risk
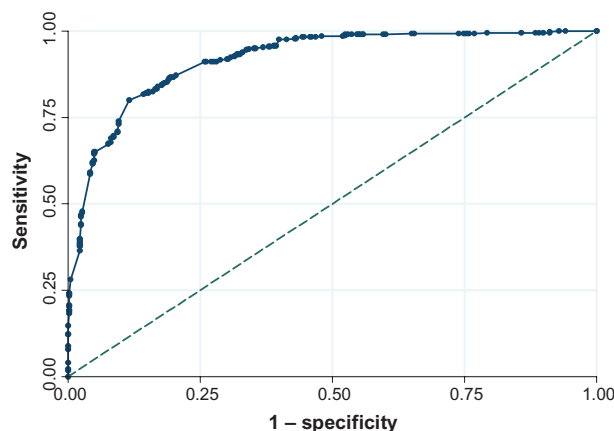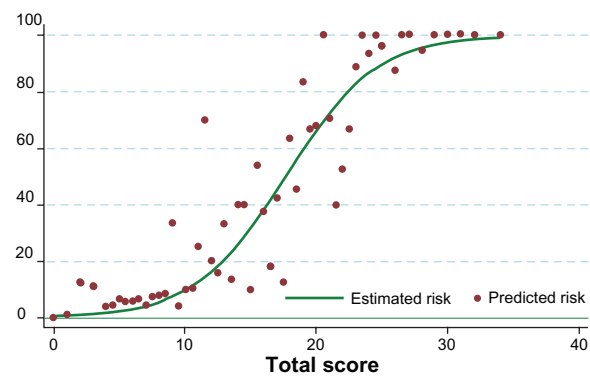

Figure 1 Receiver operating characteristic curve of risk for peptic ulcer perforation predicted by risk scoring (curved line) and a 50% chance prediction (diagonal line).
Note: Area under receiver operating characteristic curve = 0.9173.

Table 4 Distribution of risk for perforation among patients with peptic ulcer perforation and nonperforation

Risk level	PUP (%)	PUNP (%)	LR	95% CI of LR	P value
Low (<10.5)	13 (10.16%)	43 (76.79%)	0.13	0.07–0.23	<0.001
Medium (11–21)	66 (51.56%)	2 (3.57%)	14.44	3.66–56.89	<0.001
High (≥21.5)	49 (38.28%)	11 (19.64%)	1.95	1.10–3.46	0.013

Abbreviations: CI, confidence interval; LR, likelihood ratio; PUNP, peptic ulcer nonperforation; PUP, peptic ulcer perforation.

study, using total scores to calculate risk, predicted PUP with an accuracy of 91.73% – a slight reduction from the unscored regression analysis which yielded an accuracy of 94.46%.

The combined results of studies suggest that the diagnostic indicators of patients are related to the multifactorial pathogenesis of peptic ulcer complications.[6] Older age groups and males were more likely to experience PUP last century, but that is now changing. In England, PUP most commonly affects young women.[18] In addition, the incidence of PUP across many countries has shown that a marked prognostic factor was patient history of peptic ulcer,[10,11,13,16,19] and the literature suggests a continuing increase in the use of nonsteroidal antiinflammatory drugs.[1,20]

Delayed treatment of peptic ulcer patients who are referred from other hospitals with severe signs and symptoms may progress to gastrointestinal perforation. PUP at the anterior surface of the stomach is indicated by sudden intense abdominal pain. Posterior wall penetration leads to tenderness and guarding, which regularly radiates abdominal pain to the back. These variables reduce survival, increase poor clinical outcomes, and lengthen hospitalization.[6]

It is appreciated that complications arising from perforation (eg, peritonitis) and mortality rates increase with delayed diagnosis. Higher rates of lethal outcomes in PUP emergency operations have been observed.[17]

The diagnostic indicators score in the current study may also be used to classify patients with an increased likelihood of experiencing PUP in the future. The diagnostic indicators score might be useful for clinicians and nurses in developing countries in preparing for surgery. However, external validation of the scoring scheme will need to be applied to a different setting of PUP patients. This validation will be essential before any real use in applications such as clinical decision making and evaluation reviews of clinicians.

Additionally, the prediction rule is implemented as part of a critical pathway so that a hospital or clinic has procedures and policies established for how to manage patients identified as high or low risk for disease, which impact clinical outcomes. Therefore, the more intensively the prediction rule is implemented, the more benefits will occur. As a result, the risk of PUP may be predicted by a simplified score using eight predictors. Because of this, the risk score can accurately identify patients with low, moderate, and high risk.

Based on routine and intensive care in high-risk groups, the simplified prediction may bring some benefit, even though several studies have suggested that *Helicobacter pylori* colonizes the stomach and induces chronic gastritis and a long-lasting inflammation of the stomach.[19–29] Additionally, *H. pylori* bacterium was first reported in the stomach and, along with acid secretion, can damage the tissue of the stomach and duodenum.[22] *H. pylori* causes inflammation and can develop into gastric and duodenal ulcer.[22,23] *H. pylori* infection mutates host glycosylation and influences the pattern of putative colonization that is associated with lifetime risk of gastric perforation.[22] Studies have shown that *H. pylori* is etiologically linked to stomach cancer,[24–27] and a study from India has shown that *H. pylori* infection is less common in more developed Asian nations.[24] Gastric cancer is common among ethnic Chinese with East Asian genotype.[25] *H. pylori* plays an important role in the pathogenesis of peptic ulcer disease, distal gastric adenocarcinoma, and gastric lymphoma in the United Kingdom and Hong Kong.[26,27] Importantly, the exact role that *H. pylori* plays could not be established in the present study for two reasons. Firstly, during the 4-year study period (2005–2008), the *H. pylori* test was not well known in Thailand and was rarely ordered by doctors in cases of perforation. Secondly, about 70% of the patients required urgent or emergent surgery. Therefore, *H. pylori* was not detected in these patients.

A study from the 1950s found that the ABO blood group was associated with gastric diseases, and gastric cancer was found to be associated with blood group A in 1969.[29] Villalobos et al demonstrated that blood type O was associated with peptic ulcer in 1990.[30] The correlation between blood type A and gastric cancer has been confirmed and researchers have also confirmed that blood group O has a higher risk of peptic ulcers than those with other blood groups.[31] However, the ABO blood group variable was not used in the current analysis, as testing for blood type is not part of routine laboratory investigation and is therefore rarely noted in the medical records. Only subgroups who receive a blood transfusion are tested for blood type.

Study strengths and weaknesses

A strength of this study was that the simplified clinical prediction included predictor variables obtained from patient history, examination, and simple diagnostic tests, which can assist in making diagnosis appropriate management strategies.

A weakness of this study was that the retrospectively reviewed medical records were sometimes incomplete in regard to the patient's lifestyle (eg, stress) and laboratory investigation (eg, glucocorticoids and ABO blood groups). These variables are major contributing factors to peptic ulcers and are interrelated to perforation.

Conclusion

This risk score might be relevant for clinicians and nurses to support them in early detection and treatment of patients who are at high risk for PUP. Consequently, the scoring scheme needs to be externally validated in independent patients who are undergoing PUP.

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Disclosures

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