

A Prospective Evaluation of the Bedside Index for Severity in Acute Pancreatitis Score in Assessing Mortality and Intermediate Markers of Severity in Acute Pancreatitis

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OBJECTIVES: Our aim was to prospectively evaluate the ability of the bedside index for severity in acute pancreatitis (BISAP) score to predict mortality as well as intermediate markers of severity in a tertiary center.

METHODS: The BISAP score was evaluated among 397 consecutive cases of acute pancreatitis admitted to our institution between June 2005 and December 2007. BISAP scores were calculated on all cases using data within 24 h of presentation. The ability of the BISAP score to predict mortality was evaluated using trend and discrimination analysis. The optimal cutoff score for mortality from the receiver operating curve was used to evaluate the development of organ failure, persistent organ failure, and pancreatic necrosis.

RESULTS: Among 397 cases, there were 14 (3.5%) deaths. There was a statistically significant trend for increasing mortality ($P < 0.0001$) with increasing BISAP score. The area under the receiver operating curve for mortality by BISAP score in the prospective cohort was 0.82 (95% confidence interval: 0.70, 0.95), which was similar to that of the previously published validation cohort. A BISAP score ≥ 3 was associated with an increased risk of developing organ failure (odds ratio = 7.4, 95% confidence interval: 2.8, 19.5), persistent organ failure (odds ratio = 12.7, 95% confidence interval: 4.7, 33.9), and pancreatic necrosis (odds ratio = 3.8, 95% confidence interval: 1.8, 8.5).

CONCLUSIONS: The BISAP score represents a simple way to identify patients at risk of increased mortality and the development of intermediate markers of severity within 24 h of presentation. This risk stratification capability can be utilized to improve clinical care and facilitate enrollment in clinical trials.

Am J Gastroenterol 2009; 104:966–971; doi:10.1038/ajg.2009.28; published online 17 March 2009

INTRODUCTION

There is a need for a simple and clinically oriented severity scoring system that can predict mortality of acute pancreatitis within 24 h of presentation. Early recognition of severe disease would enable the clinician to consider more aggres-

sive interventions within a time frame that could potentially prevent adverse outcomes. Our group developed and validated the bedside index for severity in acute pancreatitis (BISAP) score (1). The score was developed using the Cardinal Health database, a large administrative database that records the

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The preliminary data for this study were presented as an oral presentation at the AGA Institute: Advances in Acute and Chronic Pancreatitis Session, Digestive Diseases Week, San Diego, 21 May 2008.

Received 28 June 2008; accepted 2 December 2008

demographic, clinical, and laboratory information on all hospital admissions primarily in the state of Pennsylvania.

The BISAP score is comprised of five variables: blood urea nitrogen >25 mg/dl, impaired mental status, systemic inflammatory response syndrome, age >60 years, and pleural effusion detected on imaging. One point is assigned for each variable within 24 h of presentation and added for a composite score of 0–5. We demonstrated earlier that BISAP scores of 3, 4, and 5 in the validation cohort of 18,256 patients corresponded to a mortality of 5.3, 12.7, and 22.5%, respectively (1).

The primary aim of this study was to evaluate the ability of BISAP score to predict mortality in a prospective cohort of acute pancreatitis patients from our institution. The secondary aim was to assess the ability of the BISAP score to predict which patients are at risk for intermediate markers of severity including the development of organ failure, persistent organ failure, and pancreatic necrosis.

METHODS

The demographic, clinical, laboratory, and radiologic data for all patients admitted or transferred to our institution with a diagnosis of acute pancreatitis between June 2005 and December 2007 were prospectively collected for this study. Up to 7 days of data for all patients were collected during the course of each patient’s hospitalization. Consent was obtained from all transferred patients to request all of their pertinent medical records from referring institutions. This study was approved by the Partners Healthcare Institutional Review Board.

Definitions

Acute pancreatitis was defined as two or more of the following: characteristic abdominal pain; serum amylase and/or lipase levels 3× the upper limit of normal; and/or a contrast-enhanced computed tomography (CT) of the abdomen within the first 7 days of hospitalization demonstrating changes consistent with acute pancreatitis. BISAP scores were calculated on all patients based on data obtained within 24 h of presentation (Table 1). Impaired mental status was assessed by a Glasgow Coma Scale score of < 15 within 24 h of presentation. Glasgow Coma Scale scores are routinely obtained at our institution at the time of triage in the emergency room and/or when the patient undergoes an initial assessment by the nursing staff on the general medical wards or intensive care unit. Systemic inflammatory

response syndrome was defined as ≥2 or more of the following: temperature of <36 or >38°C, P_aCO₂ <32 mmHg or respiratory rate >20 breaths/min, pulse >90 beats/min, and white blood cell count <4,000 or >12,000 cells/mm³ or >10% immature bands. The presence of a pleural effusion(s) was determined by a CT scan, chest radiograph, or abdominal ultrasound obtained within 24 h of presentation. Imaging obtained within 24 h of presentation at the hospital of origin for transferred patients was also collected and reviewed.

Organ failure was defined as a score of ≥2 in one or more of the three (respiratory, renal, and cardiovascular) out of the five organ systems initially described in the Marshall score (2,3) (Table 2). Organ failure scores were calculated for all patients during the first 72 h of hospitalization based on the most extreme laboratory value or clinical measurement during each 24 h period. Duration of organ failure was defined as transient (≤48 h) or persistent (>48 h) from the time of presentation.

A CT or MRI of the abdomen, obtained at any time in the first 7 days of hospitalization, was required to differentiate necrotizing from interstitial pancreatitis. All patients with a CT or MRI within the first 24 h in which necrosis could not be definitively ascertained (n=23) underwent a repeat scan within the first 7 days of hospitalization. All imaging studies were independently

Table 1. Individual components of the BISAP scoring system

BUN >25 mg/dl
Impaired mental status (Glasgow Coma Scale Score < 15)
SIRS
SIRS is defined as
two or more of the following:
(1) Temperature of <36 or >38°C
(2) Respiratory rate >20 breaths/min or P _a CO ₂ <32 mmHg
(3) Pulse >90 beats/min
(4) WBC <4,000 or >12,000 cells/mm ³ or >10% immature bands
Age >60 years
Pleural effusion detected on imaging
BISAP, bedside index for severity in acute pancreatitis; SIRS, systemic inflammatory response syndrome.
One point is assigned for each variable within 24 h of presentation and added for a composite score of 0–5.

Table 2. Criteria for organ failure based on Marshall scoring system

Organ system	Score				
	0	1	2	3	4
Respiratory (P _a O ₂ /F _i O ₂)	>400	301–400	201–300	101–200	<101
Renal (serum creatinine, mg/dl)	≤1.5	>1.5 to ≤1.9	>1.9 to ≤3.5	>3.5 to ≤5.0	>5.0
Cardiovascular (systolic blood pressure, mm Hg)	>90	<90, fluid responsive	<90, fluid unresponsive	<90, pH <7.3	<90, pH <7.2

reviewed by two radiologists (T.L.B. and K.J.M.), each blinded to the clinical information.

Statistical analysis

Categorical values were evaluated using χ^2 or Fisher's exact test. Trends were evaluated using the Cochran Armitage test. Discrimination of the BISAP score for predicting mortality was evaluated in the prospective cohort, using the area under the receiver operating curve (AUC). The receiver operating curve was examined for an optimal BISAP score for mortality prediction. The ability of this cutoff value to predict the development and duration of organ failure as well as pancreatic necrosis was then evaluated. Predicting the development of organ failure would require excluding patients with organ failure at or within 24 h of presentation as the BISAP score is also calculated within this time frame. As the calculation of the BISAP score is independent of obtaining a CT or magnetic resonance cholangiopancreatography (MRCP), it can be used to predict the presence or development of necrosis. A *P* value < 0.01 was chosen to be significant for all tests given the multiple testing conducted among the study cohort. All statistical calculations were carried out using SAS 9.1 (Cary, NC) and SPSS 15.0 (Chicago, IL).

RESULTS

The demographic, clinical characteristics, imaging results, and outcomes for all cases of acute pancreatitis in the prospective cohort from 2005 to 2007 are detailed in **Table 3**. There were a total of 339 patients, accounting for 397 hospitalizations (cases), over a 2.5-year period, with 14/397 (3.5%) deaths. There was an equal gender distribution. The high rate of post-endoscopic retrograde cholangiopancreatography (ERCP) and idiopathic acute pancreatitis (29.7%) and transferred cases (16%) reflects the referral nature of our institution. The median APACHE II score within 24 h of presentation was 7. Among the cases with organ failure, transient organ failure was observed in 53 (74%) and persistent organ failure was observed in 19 (26%).

Evaluation of mortality by BISAP scores

The distribution of cases and mortality by BISAP score in the prospective cohort is shown in **Figure 1**. There were 24.2, 42.3, 19.1, 11.1, 2.5, and 0.8% of cases with BISAP scores of 0–5, respectively, with corresponding mortality rates of 0, 2, 0, 9, 50, and 33%. The trend for increasing mortality with increasing BISAP score was statistically significant (*P* < 0.0001). The distribution of cases and mortality among the 230 cases admitted for their first episode of acute pancreatitis was also evaluated (**Figure 2**). The majority of deaths, 12 (5.2%), occurred in this group. The trend for increasing mortality with increasing BISAP score among these first episode cases was also statistically significant (*P* < 0.0001). The trends for mortality by BISAP score seen across all cases (*n* = 397) and among those admitted with their first episode of acute pancreatitis (*n* = 230) are similar to those of the validation cohort in the original study (1) (*P* < 0.0001).

Table 3. Demographics, clinical characteristics, imaging results, and outcomes of cases in prospective acute pancreatitis cohort (*n* = 397)

Demographics	
Male gender	195 (49)
Age	52 ± 16
BMI	27 ± 7
Transferred cases	64 (16)
Clinical characteristics	
APACHE II ≤ 24 h of presentation	7 (5, 11)
Etiology	
Gallstones	108 (27)
Alcohol	85 (21.4)
Idiopathic	60 (15.1)
Post-ERCP	58 (14.6)
Drug-induced	16 (4)
Hypertriglyceridemia	10 (2.5)
Number of prior episodes	
0	230 (57.9)
1	50 (12.6)
2	15 (3.8)
≥ 3	102 (25.7)
Imaging (<i>n</i> = 257)	
Necrotizing	36 (14%)
Interstitial	191 (74%)
Unenhanced CT	30 (12%)
Outcomes	
No organ failure (≤ 72 h)	325 (82%)
Any organ failure (≤ 72 h)	72 (18%)
Transient (≤ 48 h) organ failure	53 (74%)
Persistent (> 48 h) organ failure	19 (26%)
Deaths	14 (3.5%)

BMI, body mass index; CT, computed tomography.
Values are presented as number (%), median (Q1, Q3), or mean ± s.d.

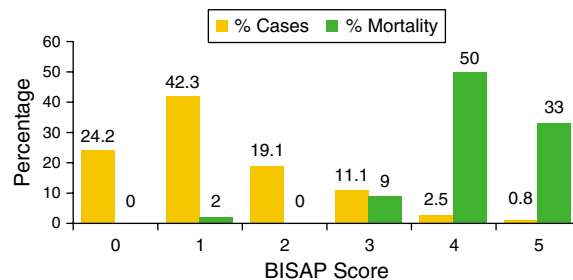


Figure 1. Distribution of cases (in yellow) and mortality (in green) by BISAP score in the prospective cohort (*n* = 397).

The AUC for mortality by BISAP score in both the prospective and validation cohorts was identical at 0.82 (Table 4). The AUC for mortality by APACHE II scores within 24 h of presentation in the prospective and validation cohorts was 0.88 and 0.83, respectively. However, the corresponding 95% confidence intervals, (0.77, 0.99) and (0.80, 0.85), overlap, suggesting no statistically significant difference between the APACHE II scores for the prospective and validation cohorts.

Evaluation of intermediate markers of severity

The receiver operating curve demonstrated a BISAP score of 3 as the optimal sensitivity and specificity threshold for mortality. In the prospective cohort, 18% of cases with a

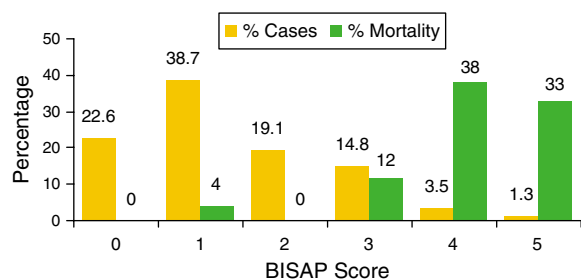


Figure 2. Distribution of cases (in yellow) and mortality (in green) by BISAP score among patients with their first episode of acute pancreatitis in the prospective cohort (n=230).

BISAP score of ≥ 3 died compared with 1% of cases with a BISAP score of < 3 ($P < 0.0001$). A BISAP score of ≥ 3 had a sensitivity of 71%, specificity of 83%, a positive predictive value of 17.5%, and a negative predictive value of 99% for mortality. This relationship was also seen in the prior validation cohort (1), with a 10-fold difference in mortality for cases with a BISAP score of ≥ 3 (7%) compared with those with < 3 (0.7%) ($P < 0.0001$). In the validation cohort, a BISAP score of ≥ 3 had a sensitivity of 50%, specificity of 91%, positive predictive value of 6% and negative predictive value of 99.2% for mortality.

We sought to further examine the ability of a BISAP score of < 3 vs. ≥ 3 to predict the development and persistence of organ failure, and pancreatic necrosis (Table 5). After excluding cases with documented organ failure within 24 h of presentation (n=52), we evaluated the ability of a BISAP score of ≥ 3 to predict the development of organ failure after the first 24 h of presentation. Cases with a BISAP score of ≥ 3 were 7.4 times more likely to develop organ failure than those with scores of < 3 ($P < 0.0001$). After including all cases with organ failure, we found that cases with a BISAP score of ≥ 3 were nearly 13 times more likely to develop persistent (> 48 h) organ failure than those with scores of < 3 ($P < 0.0001$). On the basis of those cases who underwent imaging (n=227), it was also noted that those with BISAP scores of ≥ 3 were nearly four times more likely to have pancreatic necrosis ($P = 0.0004$).

DISCUSSION

We have externally evaluated the ability of the BISAP score to predict mortality in a prospective cohort of cases with acute pancreatitis, irrespective of episode. This was demonstrated by the increasing mortality seen with increasing BISAP scores and high discrimination for mortality by AUC in the prospective cohort. A similar trend and discrimination for mortality has been observed in the validation cohort of our initial study of the BISAP score (1). A BISAP score of ≥ 3 was associated with higher mortality than scores of < 3 by receiver operating curve. Using this cutoff, we found high specificity and negative

Table 4. Discrimination of BISAP and APACHE II scores for mortality in the validation and prospective cohorts

	AUC of validation cohort 2004–2005 (n=18,256)	AUC of prospective cohort 2005–2007 (n=397)
BISAP	0.82 (0.79, 0.84)	0.82 (0.70, 0.95)
APACHE II	0.83 (0.80, 0.85)	0.88 (0.77, 0.99)

BISAP, bedside index for severity in acute pancreatitis.

Table 5. BISAP scores of ≥ 3 predict the development of organ failure, persistent organ failure, and necrosis in the prospective cohort of 397 cases

	Prospective cohort 2005–2007 (n=397)		OR (95% CI)	P value
	BISAP < 3 (n=340) (%)	BISAP ≥ 3 (n=57) (%)		
Organ failure ^a	4	23	7.4 (2.8, 19.5)	< 0.0001
Persistent organ failure	2	21	12.7 (4.7, 33.9)	< 0.0001
Necrosis ^b	12	34	3.8 (1.8, 8.5)	0.0004

BISAP, bedside index for severity in acute pancreatitis; CI, confidence interval; OR, odds ratio.

^aAll cases with organ failure within the first 24 h of presentation (n=52) were excluded for this analysis leaving a total of 310 cases with a BISAP score < 3 and 35 cases with a BISAP score ≥ 3 .

^bAnalysis based on all cases who underwent imaging with contrast-enhanced computed tomography or magnetic resonance cholangiopancreatography within the first 7 days of hospitalization (n=227). There were 186 cases with a BISAP score < 3 and 41 cases with a BISAP score ≥ 3 .

predictive value for mortality. We also found that BISAP scores of ≥ 3 predicted the development of organ failure, persistent organ failure, and pancreatic necrosis.

The BISAP score carries several important advantages over other prognostic scoring systems in acute pancreatitis. The first is that the score is simple to calculate, requiring only those vital signs, laboratories, and imaging that are commonly obtained at the time of presentation or within 24 h of presentation. The second is that the score was initially derived and tested using 36,248 cases of acute pancreatitis across 389 hospitals, reflecting the full spectrum of health-care delivery (1). This is in contrast to many other studies that have focused on smaller numbers of patients, primarily in tertiary referral centers, with predicted severe acute pancreatitis (4–8). The third is that the score predicts in-hospital mortality. There have also been prior studies that have proposed scoring systems for the prediction of mortality based on the collection of routine vital signs and laboratory data within 24 h of admission. Some of these studies developed their prognostic scoring systems using only patients with severe acute pancreatitis as defined by ≥ 2 criteria from the Japanese criteria for the grading of severity of acute pancreatitis (9), a mean APACHE II score of 11 (10), or only those patients in an intensive care unit (11). One study analyzed the blood of patients for the cytokine IL-6, which is not routinely collected in clinical practice (11). Other studies, although not restricting their inclusion criteria to patients with predicted severe acute pancreatitis, have limited their study populations by etiology (12–15) and/or first episode of acute pancreatitis (12,15,16). Both of these have the effect of limiting the generalizability of results seen in any one study. Also, the evidence from our study and others (17,18) suggests that the first episode is generally more severe than recurrent episodes of acute pancreatitis. Another study by Talamini *et al.* (19) examined the utility of a serum creatinine level of >2 mg/dl and a chest radiograph demonstrating pleural effusions and/or opacifications, obtained within 24 h of admission, in predicting prognosis as defined by mortality, the presence of pancreatic necrosis, and infected necrosis. The primary limitation of this study was the lack of discrimination analysis. It is quite possible that the AUC for mortality in this study, which employed only two prognostic variables, would be lower than that of ours and that of the APACHE II score.

The most widely used prognostic scoring system in acute pancreatitis, particularly for research purposes, remains the APACHE II score (20). However, it has several limitations. The APACHE II score was initially designed as an intensive care unit instrument and therefore contains many variables. The chronic health-profile portion of the score requires knowledge of patient history and medication details, which may not be available if the patient is unconscious, intubated, or transferred from an outside hospital with few medical records. The APACHE II score is also clinically cumbersome and difficult to remember for clinicians. Both the BISAP and APACHE II scores incorporate systemic inflammatory response syndrome, age, and Glasgow Coma Scale. However, with only the addition

of blood urea nitrogen and pleural effusion, the BISAP score has a discriminatory ability to predict mortality, which is equivalent to the APACHE II score.

In addition to an evaluation of mortality, an important finding of our study is that BISAP scores of ≥ 3 carry a 7.4- and 12.7-fold higher risk of developing organ failure and persistent organ failure, respectively, than those with scores of ≥ 3 . Organ failure has been shown to be a much stronger predictor of mortality than the extent of necrosis (21–23). Perez *et al.* (21) reported an overall mortality rate of 14% among 99 patients with pancreatic necrosis but found that the concomitant presence of organ failure at admission or during hospitalization was associated with a nearly 50% mortality rate. Rau *et al.* (23) noted a 19-fold increased risk of mortality among 230 patients with sterile necrosis, treated either operatively or conservatively, with multisystem (>2) organ failure. In addition to the presence of organ failure, the persistence of organ failure has been shown to be a major determinant of mortality in acute pancreatitis (24,25).

The strengths of our study include the following: (1) diagnosis of acute pancreatitis was not based on International Classification of Diseases (ICD)-9 coding but on a careful chart and imaging review as well as patient examination; (2) exhaustive efforts were made to collect all clinical and radiographic data from transferring institutions to ensure calculation of complete BISAP scores; and (3) the method of data collection enabled us to evaluate the relationships between the BISAP score and intermediate markers of severity such as organ failure and pancreatic necrosis. Large administrative databases usually are unable to evaluate these intermediate markers of severity as the data are either not collected or listed by ICD-9 codes, calling into question the reliability of the diagnosis.

The limitations of our study are the following. (1) The size of our cohort limits a more extensive evaluation of the ability of the BISAP score to predict organ failure and pancreatic necrosis using discrimination analysis. However, we were able to use this analysis to evaluate mortality, the primary aim of our study. (2) The Glasgow Coma Scale assessment used for the evaluation of impaired mental status is subject to interobserver variation. (3) Our study cohort was comprised of both admissions and transfers to a tertiary care center. However, it should be noted that the BISAP score was initially developed using hospital admissions from tertiary as well as community centers (1). A future prospective study of the BISAP score in a community center, ensuring that data on patients who are transferred out are analyzed with an intention to treat, would be useful to validate the generalizability of the score.

In summary, we have externally evaluated the ability of the BISAP score to predict mortality and intermediate markers of severity in a prospective cohort of cases with acute pancreatitis. In our opinion, the ability of the BISAP score to stratify patients at risk of mortality within 24 h of presentation will help improve clinical care and facilitate enrollment of appropriate patients with acute pancreatitis in future prospective trials.

CONFLICT OF INTEREST

Guarantor of the article: Vikesh K. Singh, MD, MSc.

Specific author contributions: Vikesh K. Singh: study design, data abstraction and collection, data analysis, and manuscript preparation; Bechien U. Wu: development of BISAP score, study design, and manuscript preparation; Thomas L. Bollen: evaluation of radiologic imaging; Kathryn Repas: data abstraction and collection; Rie Maurer: statistical analysis; Richard S. Johannes: development of BISAP score; Koenraad J. Mortele: evaluation of radiologic imaging; Darwin L. Conwell: study design and manuscript preparation; Peter A. Banks: development of BISAP score, study design, and manuscript preparation.

Financial support: This study was supported by a clinical research grant from the National Pancreas Foundation to Peter A. Banks (principal investigator) and Vikesh K. Singh (co-investigator).

Potential competing interests: None.

Study Highlights**WHAT IS CURRENT KNOWLEDGE**

- ✓ There are no simple clinical scoring systems in acute pancreatitis that can predict mortality based on routine laboratory and diagnostic testing within 24 h of presentation.
- ✓ Our earlier study demonstrated that the BISAP score could predict mortality within 24 h of presentation in a large retrospective cohort of acute pancreatitis patients.

WHAT IS NEW HERE

- ✓ An external evaluation of the BISAP score among a prospective cohort of acute pancreatitis confirmed its ability to predict mortality within 24 h of presentation.
- ✓ A BISAP score of ≥ 3 within 24 h of presentation also predicts the development of intermediate markers of severity.
- ✓ The BISAP score could be used to stratify patients by risk within 24 h of presentation for clinical care and future clinical studies.

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