Prognosis in acute pancreatitis

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Since the original Ranson criteria were published more than 30 years ago,[1] few topics have engendered as much sustained interest as the prediction of outcome in acute pancreatitis. Acute pancreatitis is a common cause for admission to hospital, accounting for more than 200 000 admissions in the United Stated annually.[2] Although most patients with acute pancreatitis will recover without sequelae, between 10% and 20% will have a more complicated clinical course with a higher risk of morbidity and mortality.[3]

This review provides a summary of recent developments in early risk assessment in acute pancreatitis, emphasizing the parameters that may be useful in the management of this condition. The evidence underpinning this review is primarily based on findings from recently published observational cohort studies. Although not a systematic review, this article will focus on risk assessment strategies that have been externally validated in the literature.

How can prognosis be determined?

The two most common approaches to determining prognosis in acute pancreatitis are use of a clinical scoring system and measurement of specific laboratory tests. These prognostic markers should not be confused with the actual measures of severity that are used to classify the degree of illness a patient has. Measures of severity in acute pancreatitis were defined in the Atlanta classification system. These include either local complications (e.g., necrosis and acute collection of fluid) or persistent organ failure (e.g., shock, respiratory failure or renal insufficiency).[4]

When evaluating prognosis in acute pancreatitis, it is also important to consider the outcome that one is trying to predict and when such a prediction should be made. Most studies that evaluate prediction methods in acute pancreatitis have focused on death as the outcome of interest because it is a well-defined, clinically significant outcome. However, recent data from the US National Center for Health Statistics suggest that overall mortality has declined over the past several

decades, with estimates ranging from 1%–5%.[5] This has led to increased debate over whether death remains the most appropriate outcome to use when predicting the outcome of acute pancreatitis.

With respect to the timing of prediction, it is now clear that the first 24 hours after admission to hospital are critical. In a retrospective cohort study conducted across 159 intensive care units (ICUs) in the United Kingdom, 75% of patients with acute pancreatitis who required intensive care were transferred to the ICU within the first 72 hours of admission to hospital, with a median time-to-transfer of 24 hours after admission.[6] To be of the greatest value to clinicians, predictions of outcome should be accurately and reliably applied as early as possible, preferably during the first 24 hours of admission to hospital. A prediction tool should also have a high level of sensitivity; underestimating the severity of pancreatitis can have life-threatening consequences.

Scoring systems

The most widely used index for early risk stratification is the Acute Physiology and Chronic Health Examination (APACHE) II.[7] Although more recent iterations of this scoring system have been developed, the advantages of the APACHE II are its familiarity, objective nature, and ability to be calculated at any time during a patient's stay in hospital. This scoring system has been widely validated for predicting death in acute pancreatitis. Most practice guidelines recommend a cut-off score of more than eight points at admission for prediction of severe disease, although several prospective observational studies have shown that specificity can be increased by raising the threshold to 10 points or more at admission (specificity 66%–81%).[8,9]

Use of the APACHE II in clinical practice has

KEY POINTS

- An accurate determination of prognosis during the early management of acute pancreatitis is an important opportunity for intervention.
- Both clinical scoring systems and individual laboratory tests can be used to help predict outcome during the early phase of illness.
- Recent attention has focused on optimizing routine tests to help guide resuscitation efforts.

several important limitations, such as the requirement for multiple parameters and the need for an online calculator (versions of which are widely available on the Internet). As a result, several additional scoring systems have been developed for bedside application. The modified Glasgow score was developed in the mid-1980s.[10] This scoring system, which incorporates seven routine laboratory tests, as well as the patient's age, has been widely validated for the prediction of outcome in acute pancreatitis. Although simpler to use than the original Ranson criteria, the modified Glasgow score was similarly designed to be calculated 48 hours after admission to hospital. As previously noted, this may miss a potentially important therapeutic window.

A more recent scoring system developed for use during the first 24 hours of admission to hospital is the Bedside Index of Severity in Acute Pancreatitis (BISAP).[3] This score was derived using data from a population of 17 992 patients and validated on a population of 18 256 patients in the United States. This five-factor scoring system (Box 1) was shown to have similar accuracy to the APACHE II for predicting death (area under the receiver operating characteristic [ROC] curve 0.82) in the initial retrospective study and in several subsequent prospective cohort studies.[11,12] The BISAP is a simplified scoring system that can be easily applied in the earliest phases of acute pancreatitis to help identify which patients have an increased risk of death.

There has been interest in determining to what extent the development of systemic inflammatory response syndrome alone (Box 2) can be used to determine prognosis in acute pancreatitis.[13–15] This four-factor syndrome, diagnosed on the basis of vital signs and the leukocyte count, first emerged from the literature on sepsis.[16] Although the presence of the syndrome during the first 24 hours of admission to hospital has high sensitivities for predicting organ failure (85%) and death (100%), it lacks specificity for severe disease (41%). Specificity is increased with the duration of the syndrome, such that per-sistent systemic inflammatory response syndrome (i.e., longer than 48 hours) has been linked with adverse outcomes that include organ dysfunction and death.[14]

Laboratory tests

A key advantage of using laboratory tests to determine prognosis is the potential to monitor a patient's initial response to treatment. For patients with acute pancreatitis, initial treatment primarily consists of fluid resuscitation. Several routine laboratory tests have been proposed as possible predictors of outcome: serum hematocrit, serum creatinine and blood urea nitrogen levels. Results of several small single-centre studies in the late 1990s and early 2000s suggested that an elevated hematocrit or "hemoconcentration" at admission was a predictor of pancreatic necrosis.[17,18] Unfortunately, the accuracy of hematocrit as a prognostic indicator of necrosis was not confirmed in several subsequent external validation studies.[19–21] More recently, attention has focused on early changes in serum creatinine levels.[22]

Recent data suggest that serial measurement of blood urea nitrogen levels is the most useful routine laboratory test for determining risk of death. In a large retrospective cohort study conducted at 69 US hospitals, the levels of blood urea nitrogen at admission and during the first 24 hours of a patient's stay in hopital were found to be more accurate predictors of death than other routine laboratory tests (leukocyte count and glucose, hemoglobin and creatinine levels),[23] with an area under the ROC curve similar to that of the APACHE II. The prognostic accuracy of serial measurement of blood urea nitrogen levels has since been validated using data from three independent prospective cohort studies.[24]

Several markers of systemic inflammation have also been studied as potential biomarkers to help predict the outcome of acute pancreatitis. The most widely available and well studied is the acute-phase reactant, C-reactive protein. Several

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Box 1: Scoring system for Bedside Index of Severity in Acute Pancreatitis (BISAP)[3]

Score one point for each of the following criteria:

- Blood urea nitrogen level > 8.9 mmol/L
- Impaired mental status
- Systemic inflammatory response syndrome is present (see Box 2)
- Age > 60 yr
- Pleural effusion on radiography

A score of more than three indicates an increased risk of death.

Box 2: How to determine if systemic inflammatory response syndrome is present[13,14]

Systemic inflammatory response syndrome is present if two or more of the following criteria are met:

- Heart rate > 90 beats/min
- Respiration rate > 20 breaths/min or partial pressure of carbon dioxide is < 32 mm Hg
- Body temperature < 36°C or > 38°C
- Leukocyte count < 4 or > 12 $\leftrightarrow$ 10⁹/L, or > 10% immature neutrophils (bands)

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observational studies have shown that C-reactive protein levels peak on day three after the start of symptoms and have their greatest prognostic value 48 hours after the start of symptoms.[25] Unfortunately, this timeline limits the usefulness of measuring C-reactive protein levels during the initial treatment phase of acute pancreatitis.

Procalcitonin, polymorphonuclear elastase, and interleukins 6 and 8 have each been shown to have a high degree of accuracy in several prospective observational cohort studies.[25] Although potentially valuable for investigational purposes, none of these parameters is widely available for routine clinical use in North America.

Markers of protease activation have also been extensively studied as early predictors of outcome in acute pancreatitis. The most well established is urine trypsinogen-activation peptide,

which has been shown to be both an accurate and reliable early prognostic indicator.[26] Unfortunately, this test is not commercially available.

Which tools are most helpful in clinical practice?

A summary of the aforementioned risk-stratification tools and biomarkers in acute pancreatitis is presented in Table 1. Although complex scoring systems such as the APACHE II are well suited to research purposes, a more simplified approach such as the BISAP is more likely to be helpful in routine clinical practice. In addition, serial measurement of blood urea nitrogen levels can be useful not only to rapidly identify patients at increased risk of death, but also to

Table 1: Tools for determining prognosis in acute pancreatitis

Tool	Use	Advantages	Disadvantages
Clinical scoring system			
Ranson[1]	At admission (five criteria) or after 48 h (six criteria)	Well-established	Requires 48 h to complete; no longer as useful in routine practice
Modified Glasgow[2]	Eight factors measured over 48 h	Straightforward calculation	Requires 48 h to complete, limiting its use in routine practice
APACHE II[7]	Chronic health score and 12 physiologic measurements	Widely validated instrument; can be done at any time	Cumbersome; not all parameters routinely collected
BISAP[3,11,12]*†	All five factors measured over 24 h	Straightforward calculation; can be done any time during initial 24 h	Static measurement (does not incorporate changes over time)
SIRS[13–15]*‡	Four factors measured at any time	High sensitivity	Lacks specificity unless syndrome persists > 48 h
Laboratory test			
Blood urea nitrogen*	Level > 7.14 mmol/L at admission or increase in level over 24 hr	Accurate, inexpensive and widely available	May reflect several disease processes
Serum creatinine*	Increase during initial 48 h associated with necrosis	Routine test; widely available	Uncertain whether findings can be extrapolated to earlier time points
C-reactive protein	Level > 143 nmol/L at 48 h has high level of accuracy for prediction of severe outcome	Widely validated biomarker; widespread availability	Peaks 48 h after onset of illness
Inflammatory biomarkers (procalcitonin, polymorphonuclear elastase, and interleukins 6 and 8)	Higher levels associated with severe outcome	High degree of accuracy in the early phase of disease	Not widely available; peak early in the course of disease
Urine trypsinogen-activation peptide	Urine spot measurement	High accuracy 24 h after symptom onset; validated for clinical use	Not commercially available

Note: APACHE = Acute Physiology and Chronic Health Examination, BISAP = Bedside Index of Severity in Acute Pancreatitis, SIRS = Systemic Inflammatory Response Syndrome.
*Most useful in routine clinical practice.
†See Box 1 for definition.
‡See Box 2 for definition.

potentially help guide initial fluid resuscitation efforts. Box 3 provides an example of how these tools might be used.

Gaps in knowledge

The Atlanta classification system that provided a consensus definition of severe acute pancreatitis in 1992 is currently being revised. The original system established a useful framework for researchers to evaluate prognostic factors in acute pancreatitis, but many of the criteria are now outdated. The revised criteria will incorporate our improved understanding of the nature of local complications seen in acute pancreatitis, such as the distinction between a pseudocyst and an acute necrotic collection. The revised Atlanta classification system will also formally recognize appropriate measures of severity during specific phases of illness.

Another scoring system for predicting outcome in acute pancreatitis, the Pancreatitis Outcome Prediction (POP) score, was developed using data from a retrospective cohort of 2462 patients at the time of admission to the ICU. The POP score is a good predictor of death among patients with severe acute pancreatitis (area under the ROC curve 0.84).[6] However, this score has yet to be validated prospectively.

Further research is needed to help guide early resuscitation and treatment strategies in acute pancreatitis. Although current practice guidelines universally recommend agressive fluid resuscitation,

limited data is available to support these recommendations. Moreover, the type of fluid used in resuscitation may be important in terms of mitigating systemic inflammation. Finally, the potential role of early pharmacologic treatment for prevention of complications in acute pancreatitis remains an area that is markedly understudied.

Conclusion

Recent advances in determining prognosis for acute pancreatitis have centred on methods that can help guide resuscitation efforts during the crucial phase of illness (i.e., the first 24 hours after admission to hospital). Scoring systems such as the BISAP can be useful to identify patients most likely to benefit from a targeted fluid resuscitation protocol. In addition, serial measurement of routine laboratory tests such as blood urea nitrogen may help track a patient's progress during early resuscitation. Studies are currently underway that will help determine whether such objective approaches to initial management can lead to improved outcomes for patients with acute pancreatitis.

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Box 3: Applying the tools in clinical practice

A 71-year-old man with a long-standing history of alcohol consumption presents to the emergency department with sudden onset of pain in his upper abdomen that extends to his back. Physical examination shows tachycardia (heart rate 115 beats/min) and tenderness in the epigastrium. A diagnosis of acute pancreatitis is confirmed by laboratory investigations that show elevated serum lipase levels (2770 IU/L; upper limit of normal, 60 IU/L). Further laboratory investigations show leukocytosis (leukocyte count 15×10^9/L), a hematocrit of 47% and mild elevation in the blood urea nitrogen level (8.9 mmol/L; upper limit of normal, 7.85 mmol/L).

Based on these results, the patient has a BISAP score of at least three points (blood urea nitrogren level > 8.9 mmol/L, presence of systemic inflammatory response, age > 60 yr), placing him in a high-risk category.

For patients with a BISAP score of three or more, one implements a targeted fluid resuscitation protocol modeled after the Surviving Sepsis Campaign.[27] In this protocol, one administers a volume challenge of 20 mL/kg of crystalloid solution as a bolus infusion, followed by 3 mL/kg of continuous infusion for six to eight hours. Further fluid adjustments are then made according to the changes in blood urea nitrogen levels and other clinical parameters (e.g., urine output, tachycardia).

The impact of this strategy on systemic inflammation is being evaluated in the context of a randomized-controlled trial (trial of intravenous goal-directed early fluid resuscitation [TIGER], www.clinicaltrials.gov trial no. NCT00853515).

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