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Invited Article

Use of Prognostic Markers in The Management of Acute Pancreatitis

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ABSTRACT

Management of acute pancreatitis (AP) is tailored by its severity, which is defined at 48 hr by the revised Atlanta or determinant-based classification. However, using these classifications, it is probably too late to offer any treatment that might change natural course of AP. The best markers for ruling out severe AP within the first day are APACHE II score. Marker that can rule-out pancreatic necrosis in case imaging study could not be done is C-reactive protein (CRP) <150 mg/L after 3 days. Markers that help indicate infected pancreatic necrosis in case fine needle aspiration could not be performed is procalcitonin ≥ 3.5 ng/mL (rule-in) and CRP <430 mg/L (rule-out).

Key words : acute pancreatitis, infected pancreatic necrosis, markers, pancreatic necrosis, prognosis

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BACKGROUND

Acute pancreatitis (AP) is an inflammatory condition of the pancreas with variable degree of local and systemic complications[1]. Most of the patients (80-85%) have mild and uneventful outcomes with almost zero mortality rate (mild AP), while 15-20% experience either local complications (pancreatic necrosis, walled-off necrosis or acute pseudocyst) or systemic complications (organ failure), which are now classified as moderate to severe AP and carries 10-30% mortality[2].

Determinants of Mortality of AP

It is now clear that there are 2 major determinants of the mortality of AP, which are the presence of persistent organ failure (POF) and infected pancreatic necrosis (IPN)[3]. Overall, the presence of POF carries 30% mortality and the presence of IPN had 20% mortality[3]. Mortality according to the combination of these 2 determinants from the systematic review by Petrov, *et al*[3] are shown in Table 1.

Definition of the severity of AP

Currently, there are 2 standard classifications of AP; the revised Atlanta classification 2012[1] and determinant-based classification 2012[4]. Detail of each classification is presented in Table 2. The revised Atlanta classification classifies AP in to 3 groups i.e. mild, moderate and severe, while determinant-based classification tops up the severe group with critical group. The main differences of the determinant-based classi-

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Table 1. Mortality according to the presence or absence of the 2 main determinants of AP[3].

Determinants		Mortality (%)
Persistent organ failure	**Infected pancreatic necrosis**	
Absent	Absent	0
Absent	Present	10
Present	Absent	20
Present	Present	40

Table 2. The Revised Atlanta classification[1] and the determinant-based classification[4].

	Revised Atlanta classification		
Determinants	**Severity**		
	Mild	**Moderate**	**Severe**
Organ failure	Absent	Transient (<48 hours)	Persistent (≥48 hours)
	and	*or*	
Local complications	Absent	Present	Present or absent

	Determinant-based classification			
Determinants	**Severity**			
	Mild	**Moderate**	**Severe**	**Critical**
Organ failure	Absent	Transient (<48 hours)	Persistent (≥48 hours)	Persistent (≥48 hours)
	and	*or*	*or*	*and*
Local complications	Absent	Sterile pancreatic necrosis	Infected pancreatic necrosis	Infected pancreatic necrosis

fication from the revised Atlanta classification are that the former emphasizes the difference between sterile pancreatic necrosis (SPN) and IPN, while the latter does not. Hence, POF with IPN is classified as critical, while in the revised Atlanta classification remains classifying as severe. Second point is the definition of moderate AP. In the revised Atlanta classification, moderate AP is defined by transient organ failure (TOF) or the presence of pancreatic necrosis without POF, however, the determinant-based classification defined moderate AP as having TOF or SPN only. The presence of IPN is severe at least but becomes critical if POF is present. Nevertheless, a recent large comparative study showed that both classifications are well-comparable and equivalent[5].

How common is the severe AP?

In the past, using the previous Atlanta classification[6], the reported prevalence of severe AP (SAP) is around 15-20% of all AP. However, most of the recent reports using the revised Atlanta classification demonstrated that haft to two-third of the previously diagnosed SAP would become moderate AP. Thus, the prevalence of SAP (*i.e.* the presence of POF) in the recent reports is approximately 5-15%, moderate AP in 10-15% and mild AP in 70-85%[7, 8].

USE OF THE PROGNOSTIC MARKERS IN THE MANAGEMENT OF AP

Markers of SAP

Importance

According to the standard definition of severity of AP mentioned above, which are now the gold standards, it requires at least 48 hr to define. To accurately predict which patient will eventually have SAP since

admission or no later than 48 hr is very important for many reasons[9]. First, it helps physician triage severe patients, who need aggressive monitoring, investigation and treatment. Second, it helps utilize our limited resources appropriately. Last, the management of SAP is different from mild AP in many ways *e.g.* aggressive intravenous fluid (4-5 L within the first 24 hr[10], preferring lactate ringer solution[11]), early enteral feeding within 48 hr[12], imaging study at day 5-7 days to look for local complications[1] and giving potential new treatments in the future.

The 3 key characteristics of any desirable marker for SAP are as follows:

1. It must take shortest time to complete, preferably at admission or no later than 24 hr. This lies on the basic pathophysiology of AP (Figure 1)[13] that, immediately after the onset of AP, cytokine production begins, OF progressively develops and reaches its peak and no longer reversible after 60 hr from onset. Thus, the therapeutic window for any treatment to prevent or reverse OF is narrow and probably no more than 48 hr after the diagnosis. Using the revised Atlanta or determinant-based definition of SAP to pick up SAP patients is too late and we, therefore, need markers that can rule in or rule out SAP at admission or within 24 hr after admission.

2. It must have either high positive (PPV) or negative predictive value (NPV). The reports of sensitivity, specificity, accuracy or area under the curve (AUC) of any marker for SAP, which are commonly seen in the literature, are not as useful as the report of PPV or NPV. In fact, the best should be the report of likelihood ratio positive (LR+) or negative (LR-) because these will allow physicians to calculate the post-test probability of SAP according to the prevalence of SAP in their own settings[14]. The appropriate minimal PPV and NPV for markers of SAP are unknown but it has been proposed that the PPV and NPV should be >75% and >98%, respectively[14, 15]. These mean that if test is positive, the chance of SAP should be more than 3 in 4. Over-diagnosis of patient as SAP for one-fourth seems to be acceptable. In contrast, one should not miss any SAP, thus, if test is negative, the allowable chance of missing SAP must be <2%.

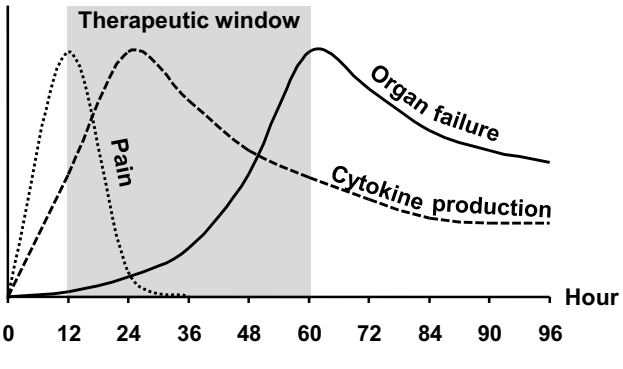

Figure 1. Natural course of the cytokine production, development of organ failure in severe acute pancreatitis and the therapeutic window (adapted from Ref 13)

3. It must be available, easy to use and inexpensive. This is important because there have been more than hundreds of markers of SAP published in the literature so far. Many have stood out of time due to the availability, easiness to use, low cost and the good performance, whereas many faded away rapidly due to the high cost, unavailability and unfeasibility of the tests.

Which marker are candidates?

There are 2 types of prognostic markers of SAP, *i.e.* clinical (including laboratory) markers and imaging study (computed tomography [CT] or magnetic resonance imaging [MRI]). Although there have been plenty of studies showing that imaging studies are valuable for early severity assessment of AP, they are costly and carry potential risks from radiation or contrast media exposures. Recently, a large comparative study by Bollen, et al confirmed that clinical scoring systems are as good as imaging study[8], thus, clinical markers should be the mainstay tools, while imaging study should be preserved for patients predicted to have SAP by these clinical markers only and prefers being done later after 5th -7th day[1].

Based on the desirable characteristics mentioned above, some of the potential prognostic markers for SAP which are primarily available and inexpensive are shown in Table 3.

According to the Table 3, the best prognostic markers for SAP seem to be the APACHE II score[20] and d-dimer[18]. Anyhow, since there is only 1 study on d-dimer, the reproducibility is uncertain. Admission systemic inflammatory response syndrome (SIRS)[21], Bedside Index for Severity of Acute Pancreatitis (BISAP)[22], Japanese Severity Score (JSS)[23] and serum creatinine can be alternatives although the NPV are not as satisfying as APACHE II score. However, it

Table 3. The potential prognostic markers for SAP and their characteristics.

	Predictive within 24 hr	Sensitivity (%)	Specificity (%)	PPV (%)*	NPV (%)*
SIRS[16]	Yes	69	63	15	96
Ranson score[16]	No	66	82	26	96
Glasgow score[16]	No	78	82	28	98
APACHE II score[16]	Yes	84	58	19	98
BISAP[16]	Yes	54	82	23	95
JSS[16]	Yes	53	90	32	95
Hematocrit[17]	Yes	60	75	18	96
BUN[16]	Yes	59	83	25	96
Creatinine[16]	Yes	77	62	15	97
D-dimer[18]	Yes	90	89	42	99
C-reactive protein[16]	No	66	88	30	96
ESR[19]	No	86	57	15	98

APACHE II, Acute Physiologic And Chronic Health Evaluation; BISAP, Bedside Index for Severity of Acute Pancreatitis; ESR, erythrocyte sedimentation rate; JSS, Japanese severity score; NPV, negative predictive value; PPV, positive predictive value; SIRS, systemic inflammatory response syndrome
*The PPV and NPV shown here are calculated from the LR+ and LR- based on recent systematic review by Yang, *et al*[16] or from individual studies using the estimated pre-test probability of SAP (*i.e.,* persistent organ failure) 10%.

should be emphasize that the overall benefit of these markers is to rule-out SAP when they are absent due to the high NPV. In another word, if tests are negative, patients likely have mild AP.

How to use these markers clinically?

After the diagnosis of AP, apply APACHE II score or look for SIRS, BISAP, JSS or elevated serum creatinine. If these prognostic scores are low (APACHE II <8, BISAP <3 or JSS <3), normal serum creatinine and SIRS is absent, treat patients as mild AP with confidence. On the other hand, if these scores are higher than the respectively cut-off points or there is SIRS, treat patients as SAP at first, though we realize that most patients will eventually turn out to be mild or moderate. Then, re-evaluate patients again at 48 hr after admission using the "gold standard" revised Atlanta[1] or determinant-based classification[4] to finally define the patients (Figure 2).

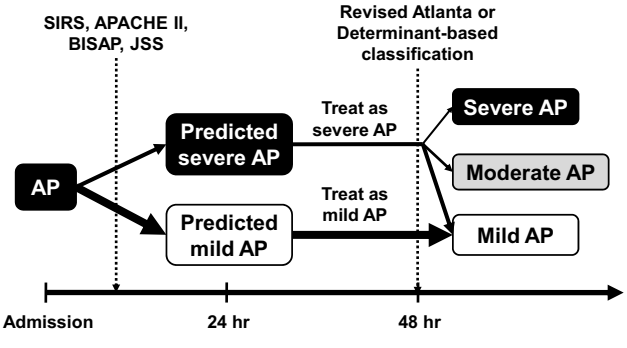

Figure 2. The use of prognostic markers of severe acute pancreatitis to treat patient (AP, acute pancreatitis; APACHE II, Acute Physiologic and Chronic Health Evaluation; BISAP, Bedside Index for Severity of Acute Pancreatitis; JSS, Japanese severity score; MAP, mild acute pancreatitis; SIRS, systemic inflammatory response syndrome).

Markers of pancreatic necrosis

Importance

The presence of necrotizing pancreatitis or pancreatic necrosis (PN) is a well-known factor contributing to the morbidity and mortality and presented in approximately 20% of patients with AP. Therefore, imaging study to search for PN is a standard recommendation in patients with clinically SAP or those who fail to improve within 3-5 days[24, 25]. CT scan is the investigation of choice and the recommended timing is after 5-7 days[1]. However, there are some situations, when CT scan may not be able to perform, *e.g.,* unstable patients or patients with acute kidney injury. In these cases, although, MRI may be an alternative[26, 27], it has not gained acceptance and does not

solve the problem of unstable patients. Thus, if there is marker that can accurately predict PN, it would remarkably help. Although ones may argue that to discover PN during the first 1-2 weeks of AP may not change any management because the only potential difference in the management is probably the antibiotic prophylaxis, of which the benefit is no longer believed[28].

Which marker are candidates?

Some of the reports of markers for predicting SAP also evaluated the role in predicting PN. However, markers that are potential are hematocrit[17,29,30], serum creatinine[30,31] and C-reactive protein (CRP)[32-34] as summarized in Table 4.

From Table 4, it is clear that hematocrit is not good enough to either rule-in or rule-out PN. Serum creatinine had promising high PPV in 1 study[30] but was not confirmed by a larger subsequent study[31]. So far, studies of CRP seem to be most consistent. All studies showed that CRP had a very high NPV (95-98%) to rule-out PN, particularly when it was measured after the third day. Using a cut-off of 150 mg/L seems to be reasonable because it is the well-known cut-off level used for predicting SAP[6].

How to use these markers clinically?

In patients with SAP or those who fail to improve after 3-5 days of conservative treatment, contrast-enhanced CT scan should be performed. In case CT could not be done due to any reason and the presence of PN impacts management, CRP should be measured. If CRP is <150 mg/L, PN is very unlikely. However, if CRP is ≥ 150 mg/L, the chance of having PN is around 50%. Thus, patients may be treated as PN first until CT can finally be done to verify the presence of PN.

Markers of infected pancreatic necrosis

Importance

The presence of IPN is another determinant of mortality in AP besides POF[3]. When PN is discovered during the course of SAP, effort should be put to diagnose whether this PN is infected or sterile, especially in very ill patients because IPN carries 3-fold mortality rate compared to SPN and IPN is the main indication for interventions i.e., percutaneous catheter drainage, endoscopic necrosectomy or surgery[24,25]. Diagnosis of IPN is difficult since the clinical manifestation may not be distinguishable from SPN. Currently, the only 2 ways to diagnose IPN are the presence of gas in the necrotic area seen by CT scan or by percutaneous fine needle aspiration (FNA). However, there are some circumstances, when pancreatic gas is absent and FNA is not available, while the patients deteriorate. In this situation, surgery may be an option because whether the PN is infected or sterile, surgical debridement may help the patients. Nevertheless, current trend of the treatment of SPN is to avoid surgery (if possible) or postpone surgery to after 4 wk[24,25]. Thus, the presence of markers to help diagnose or rule-out IPN is of importance.

Which marker are candidates?

So far, 2 markers have been shown in more than one study to have potential role in the diagnosis of IPN[16]. They are serum procalcitonin (PCT) and CRP. Systematic review of the performance of these 2 markers[16] is shown in Table 5. CRP ≥ 430 mg/L has a very high NPV (98%), thus, is suitable for rule-out IPN. In contrast, PCT ≥ 3.5 ng/mL has high PPV (92%), therefore, may be used to diagnose or rule-in IPN.

Table 4. Potential markers for pancreatic necrosis and their characteristics.

	Sensitivity (%)	Specificity (%)	PPV (%)*	NPV (%)*
Admission hematocrit >44%[17, 29, 30]	56-72	62-84	26-68	85-88
Peak Cr >1.8 mg/dL (<48 hr)[30]	41	99	93	82
Peak Cr >2 mg/dL (<48 hr)[31]	14-23	95-97	41-50	87-89
CRP >110 mg/L (Day 3)[32]	94	65	57	96
CRP >140 mg/L (Day 3)[33]	83	84	56	95
CRP >150 mg/L (Day 3)[34]	82	88	53	98

Cr, creatinine; CRP, C-reactive protein; PPV, positive predictive value; NPV, negative predictive value
*The PPV and NPV shown here are calculated from the LR+ and LR- from individual studies, using the estimated pre-test probability of pancreatic necrosis 20%.

Table 5. Potential markers for IPN and their characteristics.

	Sensitivity (%)	Specificity (%)	PPV (%)*	NPV (%)*
CRP ≥ 430 mg/L	90	89	70	98
PCT ≥ 3.5 ng/mL	50	99	92	90

*The PPV and NPV shown here are calculated from the LR+ and LR- based on recent systematic review by Yang, *et al*[16] using the estimated pre-test probability of IPN in patients who have PN 20%.

How to use these markers clinically?

In patients with PN, who have multi-organ failure or deteriorate, CT should be repeated to look for pancreatic gas that indicates IPN. Then percutaneous FNA should be performed[24,25]. If FNA cannot be done, check CRP or PCT, depended on which is available. CRP < 430 mg/L likely favors SPN and conservative treatment should be continued and CRP may be repeated in 1 week if the patient condition persists. If PCT is ≥ 3.5 ng/mL, begin step-up approach for a suspicious IPN by referring, performing percutaneous catheter drainage, endoscopic necrosectomy (if feasible) or surgical debridement[24,25].

Conclusion

Various clinical and laboratory markers are useful in the management of AP. Immediately after diagnosing AP, apply APACHE II score or alternatives e.g. SIRS, BISAP, JSS or serum creatinine to classify patient as mild AP (low score or absent of these markers) and SAP (high score) and treat patient accordingly. After 48 hr, re-classify patients using gold standard revised Atlanta or determinant-based classification. In patient with SAP, whose CT scan cannot be done at day 5-7 for any reason, CRP <150 mg/L likely rule-out NP with confidence and treat patient with CRP ≥ 150 mg/L as having PN until being proven finally by CT scan. When PN patient deteriorates, CT shows no gas and FNA cannot be done, use CRP <430 mg/L or PCT ≥ 3.5 ng/mL to rule-out and rule-in IPN, respectively.

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