

Criteria for the diagnosis and severity stratification of acute pancreatitis

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Abstract

Recent diagnostic and therapeutic progress for severe acute pancreatitis (SAP) remarkably decreased the case-mortality rate. To further decrease the mortality rate of SAP, it is important to precisely evaluate the severity at an early stage, and initiate appropriate treatment as early as possible. Research Committee of Intractable Diseases of the Pancreas in Japan developed simpler criteria combining routinely available data with clinical signs. Severity can be evaluated by laboratory examinations or by clinical signs, reducing the defect values of the severity factors. Moreover, the severity criteria considered laboratory/clinical severity scores and contrast-enhanced computed tomography (CE-CT) findings as independent risk factors. Thus, CE-CT scans are not necessarily required to evaluate the severity of acute pancreatitis. There was no fatal case in mild AP diagnosed by the CE-CT severity score, whereas case-mortality rate in those with SAP was 14.8%. Case-mortality of SAP that fulfilled both the laboratory/clinical and the CE-CT severity criteria was 30.8%. It is recommended, therefore, to perform CE-CT examination to clarify the prognosis in those patients who were diagnosed as SAP by laboratory/clinical severity criteria. Because the mortality rate of these patients with SAP is high, such patients should be transferred to advanced medical units.

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Key words: Severe acute pancreatitis; Severity score; Scoring system; Prognostic factors; Case-mortality

Core tip: The new severity criteria of acute pancreatitis (AP) consist of two independent prognostic factors; laboratory and/or clinical severity scores and contrast-enhanced computed tomography (CE-CT) findings. Mortality rate of severe acute pancreatitis (SAP) that

satisfied both laboratory/clinical and CE-CT severity criteria was as high as 30.8%. It is recommended to perform CE-CT examination in those patients who were diagnosed as SAP by laboratory/clinical severity criteria. Patients who fulfill both severity criteria should be transferred to advanced medical units. The revised criteria are extremely useful to detect SAP at an early stage of AP.

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INTRODUCTION

Acute pancreatitis (AP) involves various clinical features from mild cases with only transient abdominal symptoms to severe fatal cases. It is important to identify patients with AP who are at risk for developing persistent organ failure early in the course of the disease^[1]. Because case-mortality rate of severe AP (SAP) at the survey conducted by the Research Committee of Intractable Diseases of the Pancreas (RCIDP) supported by the Japanese Ministry of Health, Labour and Welfare was as high as 30%^[2], SAP has been designated as an intractable disease by the Japanese Ministry of Health and Welfare since 1990, and the cost of treatment for SAP is paid in full by the government^[3]. With the start of the medical expense payment system for patients with SAP, the RCIDP established the criteria for the diagnosis and severity stratification of AP. The severity scoring system was revised and the 2002 version was developed in 2002 (JPN criteria 2002)^[1,4-6].

The criteria 2002 were complicated and composed of 18 items of prognostic factors; 5 clinical sign items, 10 blood test items, computed tomography (CT) findings, the presence of systemic inflammatory response syndrome (SIRS) and age^[1,4-6]. The attending physician cannot remember all or even most of the factors. Moreover, these numerous parameters are not available soon enough or not available as the routine laboratory tests at all hospitals. There is a possibility, therefore, that incomplete examinations or defect values of the prognostic factors underestimated the severity of AP, resulting in insufficient and inadequate treatment of the disease, and aggravated AP^[1]. There is another possibility that incomplete severity evaluation of AP overlooked the predicted serious cases to transfer to medical institutions with the high-level medical facilities and intensive care.

To decrease the mortality rate of the SAP, it is important to precisely evaluate the severity early in the disease and initiate appropriate treatment as early as possible^[7-9]. The Ranson^[10] and the modified Glasgow (Imrie) scores^[11] represent a major advantage in the evaluation of

the disease severity in AP but require 48 h of data collection before the severity can be evaluated. Thereafter, several clinical scoring systems such as acute physiology and chronic health evaluation (APACHE II) score systems^[12-15], SIRS^[16], bedside index for severity in acute pancreatitis (BISAP)^[17] and harmless acute pancreatitis score (HAPS)^[18,19] for evaluating AP have been developed, but these methods to predict the development of SAP are complicated, cumbersome, and insufficiently sensitive^[20]. Recently a web-based consultative process involving multiple international pancreatic societies revised and updated the Atlanta classification of AP^[21-23]. Severity of the disease is classified as mild, moderate, and severe by the absence or presence of organ failure and local or systemic complications. Moderately SAP has transient organ failure of < 2 d, while SAP is defined by the presence of persistent organ failure for ≥ 2 d. Although the revised Atlanta classification of AP is simple and will help the clinician to predict the outcome of patients with AP, it is unable to differentiate between moderately SAP and SAP before 48 h after onset. It is expected, therefore, to develop simpler severity scoring system with routinely available data that predicts outcome, the system that clinicians can use at the bedside.

PROBLEM OF THE PREVIOUS JPN CRITERIA FOR THE DIAGNOSIS AND STRATIFICATION OF THE SEVERITY

JPN clinical criteria for the diagnosis of AP proposed in 2002 are (1) acute abdominal pain and tenderness in the upper abdomen; (2) elevated pancreatic enzyme levels in serum, urine or ascitic fluid; and (3) ultrasonographic (US) or radiologic abnormalities characteristic of AP^[1,4-6]. When at least two of the above conditions are present, then excluding other pancreatic and acute abdominal diseases of different causes can make the diagnosis of AP. Acute exacerbation of chronic pancreatitis is also included in this category. When diagnosis is confirmed by surgery and/or autopsy, the event has to be duly recorded^[1,4-6].

The JPN severity criteria 2002 consisted of 5 clinical sign items (shock, respiratory failure, mental disturbance, severe infection, hemorrhagic diathesis), 10 blood test items [base excess (BE), hematocrit (Ht), blood urea nitrogen (BUN) or creatinine, calcium concentration (Ca), fasting blood glucose, arterial oxygen saturation (PaO₂), lactate dehydrogenase (LDH), total protein, prothrombin time (PT), and platelet count], and CT findings. In cases with severity scores ≥ 2 points, SIRS and an age over 70 had to be added to the prognostic factors^[1,4-6]. These items of prognostic factors were all scored as severity scores, 1 or 2 points for each positive factor, and the highest possible total score was 27 points. However, blood glucose level, serum total protein concentrations and Ht are inappropriate for the prognostic factors after the initiation of the treatment of the disease because initial fluid resuscitation might have an influence on the

measurement value of these laboratory data. In addition, the severity criteria had redundant prognostic factors indicating similar clinical condition such as shock and the decrease in BE, and dyspnea and fall of PaO₂. Bleeding tendency, platelet counts and PT also indicate similar clinical condition. Moreover, the clinical signs such as severe infection that rarely develops within 48 h after disease onset were implicated in the severity criteria. The severity criteria included CT grade by the non-enhanced plain CT scan as one of the prognostic factors. Plain CT scans can evaluate peripancreatic inflammatory changes, but are unable to identify pancreatic necrosis that is closely associated with various complications and prognosis^[21,24-26].

Usefulness of the JPN criteria 2002 for severity stratification was evaluated in 1131 consecutive patients with AP that had been admitted to high specific or intensive therapy units of the affiliated research group hospitals from January 1 1995 to December 31 1998 (survey 1998; before the establishment of the JPN criteria 2002), and in 1768 patients who visited the hospitals in the year 2003 (survey 2003; from January 1 to December 31; after the establishment of the criteria in 2002)^[1,4-6]. The results revealed that the severity score have almost the same value for assessment as the APACHE II score and the Ranson score^[4].

In survey 1998, case-fatality rate of mild, moderate and SAP was 0.2%, 1.6% and 13.8%, respectively, whereas it was 0.1%, 0.7% and 9.0%, respectively, in survey 2003^[1,4-6]. The case-mortality rate of mild and moderate AP was quite low, and there was little clinical significance to differentiate moderate from mild AP. The case-mortality rate of SAP at stage 2 (3.7%) was low compared with that at stage 3 (25.4%) in survey 2003^[1,4-6]. Therefore, it was inappropriate to classify these patients at stage 2 as SAP and identify as applicants for the medical expense payment system^[3].

Although the previous severity criteria classified prognostic factors into 2 groups; each of the items in the first group has 2 points, while that in the second group is 1^[1,4-6], there is no significant difference in case mortality between these 2 groups with different prognostic scores. JPN severity criteria 2002 were complicated and included several prognostic factors which cannot be measured at outpatient clinic or emergency room, especially at night. In addition, multiple scoring systems of the severity criteria were very cumbersome to use and they suffer from their complexity^[1,4-6]. Indeed, 56% of 1768 clinical records of AP in survey 2003 had defect values of more than 3 items of 11 laboratory examinations. Especially, BE was measured in only 25.1%, and PT and PaO₂ were measured in only 38.3% and 38.7%, respectively^[1]. These results indicate that even if we can diagnose the patient as AP, in the presence of many defect values a correct stage classification is difficult, and it is very likely that we underestimate the severity.

Because CT grade was included as one of the prognostic factors^[1,4-6], it was required to perform CT examination repeatedly to precisely evaluate the severity and

stage of AP. However, it is unacceptable to perform CT examination repeatedly^[27], and thus one of the prognostic factors remains as a defect value. In addition, there are many hospitals that cannot perform CT examination and laboratory tests such as PT, especially at night. This might be one of the reasons for many defect values in the clinical records of AP^[1].

NEW DIAGNOSTIC CRITERIA OF AP

JPN diagnostic criteria of AP are revised taking into account of the recent progress of imaging studies and laboratory examinations of pancreatic enzymes. The revised clinical criteria for the diagnosis of AP are (1) acute pain and tenderness in the upper abdomen; (2) elevated pancreatic enzyme levels in blood and/or urine; and (3) ultrasound (US), CT or magnetic resonance imaging (MRI) abnormalities of the pancreas characteristic of AP^[1]. When at least two of the above conditions are present, the diagnosis of AP can be made by excluding other pancreatic and acute abdominal diseases of other causes than pancreatitis. Acute exacerbation of chronic pancreatitis is included in this category.

Measurement of pancreatic enzyme levels in serum has been generally adopted in clinical practice, whereas those in ascitic fluid and urine are rarely determined. Since, however, recent studies have demonstrated that urinary strip tests for trypsinogen activation peptide (TAP) and trypsinogen-2 provide a reliable early diagnosis of AP^[28-35], the revised diagnostic criteria included the elevation of the pancreatic enzymes in serum and/or urine, excluding that in ascitic fluid. It is well known, however, that some patients with AP, mostly alcoholic etiology, show normoamylasemia^[28], and that serum amylase level rises only slightly in many patients with acute exacerbations of chronic alcoholic pancreatitis^[36]. Moreover, serum amylase level seldom rises in AP caused by hyperlipidemia^[37,38] and in those with pancreatic insufficiency^[39]. In addition, the elevation of serum amylase level is only transient and declines within 3 d after onset of AP^[28,40]. On the other hand, abnormally high values of serum lipase persist for longer period than that of serum amylase and are observed even in cases of alcohol-induced pancreatitis^[41]. Although a recent case report of AP has demonstrated that serum amylase and lipase remain normal throughout the acute phase of AP in a man with pancreatic insufficiency and cystic fibrosis^[39], serum lipase is considered to be a more reliable diagnostic marker of AP than serum amylase. Therefore, the revised diagnostic criteria recommend determining pancreatitis specific enzymes in serum and/or urine such as pancreatic-type amylase^[42,43] and lipase^[44].

The new diagnostic criteria require the presence of clear findings indicating AP by imaging studies such as US, CT and MRI. US can visualize pancreatic enlargement, inflammatory changes around the pancreas, and abnormal findings associated with AP such as the presence of ascitic fluid and gallstones. US examination can

Table 1 Laboratory/clinical criteria for grading the severity of acute pancreatitis

No.	Laboratory/clinical criteria
1	Base excess ≤ -3 mEq/L or shock (systolic blood pressure ≤ 80 mmHg)
2	PaO ₂ ≤ 60 mmHg (room air) or respiratory failure (artificial respiratory ventilation)
3	BUN ≥ 40 mg/dL or creatinine ≥ 2.0 mg/dL or oliguria (urinary volume ≤ 400 mL/d after hydration)
4	LDH: More than twice higher than the upper limit of normal (≥ 700 IU/L)
5	Serum total Ca ≤ 7.5 mg/dL
6	Platelet count $\leq 1 \times 10^5/\text{mm}^3$
7	CRP ≥ 15 mg/dL
8	Positive score of SIRS criteria ≥ 3
9	Age ≥ 70 yr

One point for each positive factor. Severe acute pancreatitis: total scores ≥ 3 points. BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; SIRS: Systemic inflammatory response syndrome; CRP: C-reactive protein.

be performed repeatedly at bedside. CT provides clear local images without being affected by the adipose tissue in the abdominal wall and abdominal cavity^[14,45]. CT findings of an enlarged pancreas, inflammatory changes around the pancreas and fluid collections are useful marker for the diagnosis of AP. Thus, CT is the most important imaging procedures for the diagnosis of AP^[46-48]. MRI scanning can also visualize the enlargement of the pancreas and the inflammatory changes around the pancreas^[49,50].

SEVERITY CRITERIA OF AP BY MULTIPLE-SCORING SYSTEM

Following the correct diagnosis of AP, severity stratification should be performed promptly and repeatedly, in particular for the first 48 h after the onset of the disease^[1]. Early recognition of severe disease and application of appropriate therapy require vigilance as decisions regarding management need to be made shortly after admission.

The revised severity score put the redundant factors that show similar clinical conditions together into one, and deleted the unclear clinical signs. Since the new severity criteria combined laboratory data with clinical signs, the severity of AP can be evaluated by one of these findings. BE can be substituted by shock (systolic blood pressure less than 80 mmHg), PaO₂ by respiratory failure (artificial respiratory ventilation), and BUN or creatinine by oliguria (urinary volume less than 400 mL/d after hydration). Thus, SAP can be properly diagnosed by reducing underestimation of severity by the defect values (Table 1).

Among several serum biochemical markers that have been developed for severity stratification of AP, C-reactive protein (CRP) remains the most useful^[19,32,51-54]. Although its increase delays, peaking not earlier than 72 h after the onset of symptoms, it is accurate and widely available. According to United Kingdom guidelines for the man-

Table 2 Contrast-enhanced computed tomography criteria for grading the severity of acute pancreatitis

Contrast-enhanced computed tomography criteria	Scores
Extension of extrapancreatic inflammatory changes	
Anterior pararenal extraperitoneal space	0 point
Root of the mesocolon	1 point
Beyond inferior renal pole	2 points
Unenhanced area in the pancreatic parenchyma (Divide the pancreas into 3 areas for expediency, head, body and tail)	
Limited to one area or peripancreatic area	0 point
Extend over 2 areas	1 point
More than 2 areas	2 points

Severe acute pancreatitis: total computed tomography severity scores ≥ 2 points.

agement of AP^[55] and the Working Party of the Program Committee of the Bangkok World Congress of Gastroenterology 2002^[56], CRP ≥ 15 mg/dL is adopted as a prognostic factor. Moreover, Gardner *et al.*^[57] have demonstrated that an age above 70 years is an independent risk factor for mortality in patients admitted with SAP. Based on these previous studies, the new severity criteria included CRP and age of the patient. In spite of these changes, the new severity criteria that employ routinely available data are simple and easy to remember.

Since the contrast-enhanced CT (CE-CT) is the mainstay of imaging patients with AP and recommended for the evaluation of the severity of AP^[20,24-27,34,35,49], the revised severity criteria included the CE-CT findings of the presence and extent of pancreatic necrosis, and the extent of peripancreatic inflammatory changes (Table 2). The revised Atlanta classification provided precise definitions of CE-CT findings, including peripancreatic necrosis, walled-off-necrosis and pseudocyst^[21,22]. Although the revised Atlanta classification suggested that pancreatic necrosis can rarely be identified accurately during the first several days of hospitalization, CE-CT findings help us to decide special measures such as continuous regional arterial infusion (CRAI) of protease inhibitors and antibiotics, and continuous hemodiafiltration (CHDF)^[58-60]. Once it is thought that contrast medium exacerbates pancreatitis^[61-63], but denied by another studies^[64,65]. Since, however, there is a possibility that intravenous contrast media extend pancreatic necrosis and exacerbate renal impairment^[61-63], vigorous intravenous hydration for the purpose of intravascular resuscitation is important during and after CE-CT examination. Attending physicians must aware of the possibility that the contrast medium aggravates renal dysfunction associated with SAP.

The new severity criteria considered laboratory/clinical symptoms and radiographic features of CE-CT scans as independent risk factors. Indeed, Leung *et al.*^[14] have demonstrated that CT severity index is a useful tool in assessing the severity and outcome of AP, and superior to Ranson score^[10] and APACHE II scoring system^[12-15] in predicting AP outcome. Thus, the CE-CT is not necessarily required to evaluate the severity of the patients with AP. Preliminary study revealed that the case-fatality

Table 3 Verification of the revised severity criteria

Total severity score (points)	Revised severity criteria	Criteria 2002
0	66	77
1	51	31
2	18	15
3	11 (1)	9
4	4	7
5	4 (2)	6
6	2 (1)	3 (1)
7	0	2 (1)
8	0	0
9	0	1
10	0	2 (2)
11	0	2
12	0	1
Total	156 (4)	156 (4)

Results shown are number of patients. Number in parenthesis indicates patients died of acute pancreatitis. The same patients with acute pancreatitis were evaluated by the revised criteria and by the criteria 2002. Total severity score of the revised criteria ≥ 3 points, while that of the criteria 2002 ≥ 2 points was diagnosed as severe acute pancreatitis.

Table 5 Relationship between the laboratory/clinical and the contrast-enhanced computed tomography severity scores

Total CE-CT severity score (points)	Total laboratory/clinical severity score (points)							Total
	0	1	2	3	4	5	6	
0	0	0	0	0	0	0	0	0
1	56	40	13	5	1	0	0	115
2	3	5	2	1	0	2 (1)	1 (1)	14 (2)
3	2	1	1	3 (1)	3	2 (1)	1	13 (2)
Total	61	46	16	9 (1)	4	4 (2)	2 (1)	142 (4)

Results shown are number of patients. Number of patients died of acute pancreatitis is indicated in parenthesis. In these 142 patients, laboratory/clinical and contrast-enhanced computed tomography (CE-CT) examinations were evaluated at the same time.

in patients with the CE-CT severity score 1 was 3.3%, while that in those with severity score 2 and 3 points was 21.9% and 33.3%, respectively. Thus, the severity scores of CE-CT ≥ 2 points was defined as SAP (Table 2).

Analysis of case records of 1337 consecutive patients with AP in survey 2003^[1,5,6] in that more than 5 items of 9 prognostic factors of the new severity criteria were recorded revealed that case-fatality rate of patients with severity score point 0 and point 1 was nearly the same (0.2% *vs* 0.7%), whereas that of patients with severity score 2 and 3 points was greatly different (2.6% *vs* 11.1%). Thus, the new criteria divided the severity of AP into mild (severity score ≤ 2 points) and SAP (severity score ≥ 3 points). Based on this classification, case-mortality rate of mild AP and SAP was 0.83% (9/1183) and 19.5% (30/154), respectively.

VERIFICATION OF THE NEW SEVERITY CRITERIA

Usefulness of the new severity criteria was prospectively

Table 4 Relationship between the revised laboratory/clinical or contrast-enhanced computed tomography severity score and incidence of organ failure

Total severity score (points)	Incidence of organ failure	
	Laboratory/clinical	CE-CT
0	1.5%	0.0%
1	7.8%	4.3%
2	5.5%	42.9%
3	36.4%	46.2%
4	50.0%	-
5	75.0%	-
6	100.0%	-

Total number of patients evaluated by laboratory/clinical examinations was 156, whereas contrast-enhanced computed tomography (CE-CT) severity score was evaluated in 142 of these 156 patients at the same time.

studied in 156 patients with AP. CE-CT severity score was evaluated in 142 of these 156 patients at the same time with laboratory examinations. Overall case-mortality of 156 patients with AP was 2.6%, and was similar to that reported in nationwide survey in 2003^[1,5,6]. Although some survey sheets had defect data of laboratory examinations, most frequently BE (defect value 41.0%) and PaO₂ (defect value 41.0%), these data were substituted by clinical signs of shock (defect value 0%) and respiratory failure (defect value 0%), respectively. Therefore, the severity score could be precisely calculated even if these laboratory data were defect values.

The revised severity criteria (Table 1) identified 13.5% of these 156 patients with AP as SAP, whereas 30.8% were diagnosed as SAP if the criteria 2002 were adopted. Case-mortality of SAP diagnosed by the revised criteria was 19.1%, whereas that by the criteria 2002 was only 8.3% due to large number of patients who are diagnosed as SAP (Table 3). The validity of the revised classification was further revealed by the incidence of complications of organ failure. Complications of organ failure were far greater in patients with SAP than in those with mild AP (Table 4). These results clearly indicate that the patients with SAP diagnosed by the revised criteria are suitable as applicants for the medical expense payment system^[3].

Since the new severity criteria consider laboratory data/clinical symptoms, and the CE-CT severity score as independent risk factors, SAP can be diagnosed either by the laboratory/clinical severity criteria or by the CE-CT severity criteria. There was no fatal case of mild AP diagnosed by the laboratory/clinical severity score regardless of CT severity score. Similarly, there was no fatal case of mild AP diagnosed by the CE-CT severity score regardless of laboratory/clinical severity scores (Table 5). Case-mortality rate of patients with SAP diagnosed by the laboratory/clinical severity score was 21.1%, whereas that in those diagnosed by the CE-CT severity score was 14.8%. Case fatality of SAP that fulfilled both laboratory/clinical (severity score ≥ 3 points) and CE-CT severity criteria (severity score ≥ 2 points) was as high as 30.8%. It is recommended, therefore, to perform CE-CT examination to clarify the prognosis in patients who were diagnosed as SAP by laboratory/clinical severity score. Because the

mortality rate of these patients with SAP was high, such patients should be transferred to advanced medical units with physicians specializing in intensive care, endoscopic treatment, radiological intervention, and biliary-pancreatic surgery^[1,5,6].

CONCLUSION

The new severity criteria consist of laboratory examinations combined with clinical symptoms and the CE-CT severity score. The laboratory and/or clinical symptoms and the CE-CT findings are independent risk factors. SAP can be diagnosed either by the severity score alone, or by the CE-CT findings alone. Mortality rate of SAP that fulfilled both laboratory/clinical and CE-CT severity criteria was high. It is recommended, therefore, to perform CE-CT examination in those patients who were diagnosed as SAP by laboratory/clinical severity criteria. Patients with SAP who fulfill both severity criteria should be transferred to advanced medical units. The revised criteria are extremely useful to detect SAP at an early stage of AP.

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