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Endothelial progenitor cells in peripheral blood may serve as a biological marker to predict severe acute pancreatitis

Xiao-Qin Ha, Yue-Juan Song, Hong-Bin Zhao, Wei-Wei Ta, Hong-Wei Gao, Qiang-Sheng Feng, Ju-Zi Dong, Zhi-Yun Deng, Hong-Yan Fan, Jun-Hua Peng, Zhi-Hua Yang, Yong Zhao

AIM
To investigate the significance of endothelial progenitor cells (EPCs) in predicting severe acute pancreatitis (SAP).

METHODS
We recruited 71 patients with acute pancreatitis (AP) and excluded 11 of them; finally, cases of mild acute pancreatitis (MAP) (n = 30) and SAP (n = 30), and healthy volunteers (n = 20) were internalized to investigate levels of EPCs, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibrinogen (FIB)
and white blood cells (WBC) in peripheral blood.

RESULTS
The levels of TNF-α, WBC, FIB and CRP were higher both in SAP and MAP cases than in healthy volunteers (P < 0.05, all). Interestingly, the level of EPCs was higher in SAP than MAP (1.63% ± 1.47% vs 6.61% ± 4.28%, P < 0.01), but there was no significant difference between the MAP cases and healthy volunteers (1.63% ± 1.47% vs 0.55% ± 0.54%, P > 0.05). Receiver operating characteristics curve (ROC) showed that EPCs, TNF-α, CRP and FIB were significantly associated with SAP, especially EPCs and CRP were optimal predictive markers of SAP. When the cut-off point for EPCs and CRP were 2.26% and 5.94 mg/dL, the sensitivities were 90.0% and 73.3%, and the specificities were 83.3% and 96.7%. Although, CRP had the highest specificity, and EPCs had the highest sensitivity and highest area under the curve value (0.93).

CONCLUSION
Data suggest that EPCs may be a new biological marker in predicting SAP.

Key words: Severe acute pancreatitis; Marker; Endothelial progenitor cells

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Core tip: Endothelial progenitor cells (EPCs) may be used as a novel biological marker to predict the severity of acute pancreatitis (AP) considering the relation between endothelial cells and EPCs. We compared five markers, and concluded that EPCs had the highest area under the curve value (0.93) and Youden index (0.8), sensitivity (90.0%) and specificity (83.3%). EPCs may represent a new biological marker for predicting severe AP at the early stage.


INTRODUCTION
Acute pancreatitis (AP) is a frequent disease. Mild acute pancreatitis (MAP) is easy to treat and the cure rate is high. Although severe acute pancreatitis (SAP) accounts for only 15%-30% of AP cases, it has a high rate of multiple complications and a fatality rate of 5% to 70%[11]. The treatment strategy for SAP is different than that for MAP. The major treatment for MAP is conservative, while SAP requires enhanced monitoring and comprehensive care that includes enteral/abenteric nutrition support, antibiotics, or endoscopic sphincterotomy. Lack of accurate or timely evaluation of AP will lead to excessive medical treatments and a higher fatality rate. Therefore, correct appraisal of the severity of AP is key to clinical decision-making.

It is difficult to evaluate the severity of AP at the early stage. Over the past decade, only 19% of AP cases were graded accurately and only 67% of SAP cases received special therapy in the intensive care unit[2]. AP has a complex etiology, and disease progression does not always match clinical manifestations.

With the development of diagnostic tools - such as the Acute Physiology And Chronic Health Evaluation-II (APACHE-II) scoring system, Ranson criteria, the Balthazar scoring system, and the gold standard, contrast-enhanced computed tomography (CECT)[3,4] - the ability to accurately predict the severity and clinical outcome of AP patients can be up to 80%[3]. However, these methods are inconvenient to use and have limited clinical value[6-8].

The Ranson score focuses primarily on biochemical disturbances and must be completed more than 48 h after admission. The APACHE-II score focuses on physiologic variables. APACHE-II and Balthazar scoring can be done within the first 24 h, but the scores are based on a high number of variables, and the methods are not easily mastered. CECT also has several limitations; for example, iodinated contrast medium is contraindicated in some patients and carries the risk of nephrotoxicity. In addition, it usually requires patient transport to another hospital site.

Serum biochemical detection is objective, exact, economical, and enables real-time monitoring. Levels of tumor necrosis factor-alpha (TNF-α), white blood cell (WBC) count, C-reactive protein (CRP), and fibrinogen (FIB) all can predict SAP, yet endothelial progenitor cells (EPCs) may be a new biological marker.

Other biomarkers
Serum amylase (S-Amy) and urinary glandular amylase (U-Amy) play an important role in the final diagnosis of AP. However, the level of S-Amy in SAP may be lower than that in MAP due to extensive necrosis and calcification of the pancreas, which leads to consumption of S-Amy[9]. Therefore, it cannot be used to predict SAP exactly.

However, data show that other biomarkers, including CRP[10] and TNF-α[11], are significantly related to the severity and prognosis of AP. As a non-specific acute phase protein, CRP induces endothelial cell dysfunction, impairs vessel walls, and promotes inflammatory reactions. In addition, a certain level of CRP may impair the number and function of EPCs by depressing the expression of endothelial nitric oxide synthase mRNA[12].
In AP, TNF-α promotes a cascade of inflammatory factors, such as IL-6 and IL-1. These are produced by neutrophils and macrophages that infiltrate pancreatic tissue. IL-1 promotes aggregation of WBCs and apoptosis of pancreatic acinar cells[13].

Leukocyte-endothelial interaction and microcirculation disorder may be central to the start of AP progression[14]. In addition, both TNF-α and EPCs can promote apoptosis of pancreatic acinar cells by inducing the release of caspase-3 protease, thereby affecting the prognosis of AP[15,16]. At a certain level, TNF-α also induces premature aging of high proliferation EPCs by modulating the p38 mitogen-activated protein kinase pathway[17].

Various inflammatory mediators are produced and result in damage to cells and tissues. Highly coagulated blood also leads to microcirculation disorders and disseminated intravascular coagulation[18]. Activation of the coagulation and fibrinolytic systems cause other serious outcomes.

Damage to endothelial cells (ECs) is a key factor in systemic inflammatory mediator reactions and secondary organ injury; EPCs sustain ECs. During the embryonic period, EPCs differentiate from the outer layer of the blood-island[19]. Postnatal EPCs derive mainly from umbilical cord blood, bone marrow and peripheral blood[20].

Today, CD34+CD133+VEGFR+ cells, which are involved in neovascularization associated with angiogenic and vasculogenic mechanisms[21,22], are widely considered as EPCs[23]. As such, EPCs can also be used to predict progression or prognosis of cardiovascular diseases and tumors[24-26]. In AP, activated proteases, neutrophils and inflammatory mediums cause widespread damage to ECs, eventually leading to dysfunction of the endothelial barrier that activates coagulation and causes capillary leaks.

As stated above, damaged ECs are a critical factor in systemic inflammatory mediator reactions and secondary organ injury[27]. Previous studies report that impaired or apoptotic ECs are repaired through hyperplasia and lateral movement of peripheral mature ECs. However, in 1997, Asahara et al[28] first discovered that CD34+ hematopoietic stem cells were capable of differentiating into ECs and incorporating into sites of neovascularization in vitro.

The apoptotic bodies of ECs damaged in AP were shown to mobilize EPCs into peripheral blood from bone marrow, and to promote the proliferation and differentiation of EPCs[29]. These progressions were also shown to be mediated by inflammatory cells, e.g., WBCs and macrophages, and inflammatory factors such as TNF-α, CRP and interleukin-8 (IL-8).

The purpose of this study was to investigate the significance of EPCs in predicting SAP.

MATERIALS AND METHODS

Patient recruitment
From September 2010 to October 2011, a total of 71 AP patients (38 women and 33 men; aged 22-80 years, median age of 50 years) were recruited within 24 h from the time of admission. The diagnosis of AP was made according to at least two of the following three criteria: (1) abdominal pain characteristic of AP; (2) S-Amy and/or lipase ≥ 3 times the upper limit of normal; and (3) characteristic findings of AP on a computed tomography (CT) scan. Informed consent was obtained from the patients and ethics approval was obtained from the Institutional Research Ethics Committee.

Reports show that in tumor patients, EPCs mobilize from bone marrow into peripheral blood; besides, age and chemotherapy also affect the number of EPCs. So, exclusion criteria included any of the following: age > 80 years, a diagnosis of cancer or hematological proliferative disease under treatment, current steroid or chemotherapy for any reason, normal findings on amylase and lipase testing, failure to find changes associated with pancreatitis on CT examination, and unavailable complete blood counts or medical records. Eleven patients with AP were excluded according to these criteria.

Patients with pancreatitis were classified as the SAP group (7 women, 13 men; median age of 57 ± 16 years) if they had organ failure, a Ranson score ≥ 3, an APACHE-II score ≥ 8, a class D or E Bathazar score, or a CT severity index ≥ 4. The remainder were classified as the MAP group (11 women, 9 men; median age of 47 ± 20 years)[9].

After MAP and SAP had been diagnosed according to Chinese criteria[9], all patients received conventional treatments. Early prediction of SAP (according to EPCs, TNF-α, WBC, CRP, FIB and other criteria) was made within 24 h after admission. The control group consisted of 20 healthy volunteers (9 women and 11 men; median age of 47 years), and all of the AP patients were volunteers. In addition to the informed consent and ethics approval cited above, this study was also approved by ethics committee of Lanzhou Military Command General Hospital of the People’s Liberation Army. Again, written informed consent was obtained from every subject.

Methods
We obtained blood samples from healthy volunteers and AP patients within 24 h after admission. Blood samples for cytofluorimetric analysis were processed within 12 h, whereas plasma samples were stored at -20 °C until used for other analyses.

Flow cytometric analysis
A total of 200 microliters of peripheral blood collected in ethylene diaminetetraacetic acid (EDTA)-containing tubes was incubated for 30 min at 4 °C with 5 μL of FITC-anti-CD34 and PE-anti-CD133. After red cell lysis, the samples were centrifuged and the pellets resuspended in 1 mL PBS buffer. Cells (1 × 10⁵) were acquired by flow cytometer (FACSCalibur; Becton Dickinson).
The severe acute pancreatitis group was taken as the positive group and MAP as the negative group to predict SAP, perhaps due to distortions from drugs. According to ANOVA test, MAP: Mild acute pancreatitis; SAP: Severe acute pancreatitis.

### Table 1  Analysis of diagnostic value

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>EPCs, %</th>
<th>TNF-α, pg/mL</th>
<th>WBCs, 10^9/L</th>
<th>FIB, g/L</th>
<th>CRP, mg/dL</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>YI</th>
<th>AUC</th>
</tr>
</thead>
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<tr>
<td>2.26</td>
<td>90.0%</td>
<td>83.3%</td>
<td>0.73</td>
<td>0.926</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.12</td>
<td>80.0%</td>
<td>80.0%</td>
<td>0.60</td>
<td>0.790</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.88</td>
<td>83.3%</td>
<td>63.3%</td>
<td>0.47</td>
<td>0.704</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.85</td>
<td>66.7%</td>
<td>76.7%</td>
<td>0.43</td>
<td>0.749</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.94</td>
<td>73.3%</td>
<td>96.7%</td>
<td>0.70</td>
<td>0.859</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

EPCs: Endothelial progenitor cells; TNF-α: Tumor necrosis factor-alpha; WBC: White blood cells; FIB: Fibrinogen; CRP: C-reactive protein.

### Table 2  Basic characteristics of the three groups

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Control group</th>
<th>MAP group</th>
<th>SAP group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Average years of age</td>
<td>47.65 ± 15.14</td>
<td>48.17 ± 16.85</td>
<td>54.97 ± 15.35</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>10/10</td>
<td>14/16</td>
<td>17/13</td>
</tr>
</tbody>
</table>

There was no significant difference in ages or sex among the three groups according to ANOVA test.

### RESULTS

#### Comparison of characteristics of SAP, MAP and control groups

The box plot shows that the distribution of data (i.e., EPCs, TNF-α, WBC, FIB and CRP) in each group was asymmetrical (Figure 2). Furthermore, there were different levels of the characteristics among the three groups. Though, the level of EPCs in the control and MAP groups was similar, there was a significant difference between the MAP and SAP groups.

ANOVA showed that there was no significant difference in age or sex among the three groups. In the SAP, MAP and control groups, the serum levels of TNF-α, WBC, FIB and CRP decreased sequentially; differences were significant (P < 0.05, all). The level of EPCs was higher in the SAP group compared with the MAP group (P < 0.01), but there was no significant difference between the MAP and SAP groups (P = 0.21) (Tables 2 and 3, Figure 3).

#### Correlations between the five markers

Correlations between the five biomarkers were positive (P < 0.01, all). EPCs had the closest correlation with TNF-α (r = 0.721, P = 0.00) (Table 4, Figure 4).

#### Diagnostic value of EPCs, TNF-α, WBC, FIB and CRP

The optimal cut-off values of EPCs, TNF-α, FIB and CRP were 2.26%, 103.12 pg/mL, 5.85 g/L and 5.94 mg/dL, respectively. A comparison of AUCs showed AUC-EPCs (0.93) > AUC-CRP (0.86) > AUC-TNF-α (0.79) > AUC-FIB (0.75) (P < 0.01, all). Although AUC-WBC was 0.704 (AUC > 0.70), WBC 8.98 × 10^9 could not be used to predict SAP, perhaps due to distortions from drugs.
EPCs may serve as a marker for severe AP, followed by CRP. Besides the highest AUC value (0.93) and YI (0.73), EPCs also had the highest sensitivity (90%), while CRP had the highest specificity (96.7%). In serial tests, the YI of combinations including EPCs was higher than that of other combinations without EPCs. EPCs combined with CRP had the highest specificity (99.4%). Combining more markers did not improve diagnostic value according to YI.

**DISCUSSION**

Systemic inflammatory response syndrome and multiple organ dysfunction syndrome induced by various inflammatory mediators are lethal factors in AP. Inflammation and imbalance of coagulation are
two keys to these pathologic processes. Therefore, inflammatory and coagulation factors may serve as biological markers to predict the severity and prognosis of AP.

**New biological maker to predict SAP**
EPCs have a close relation with the endothelial system, and may be antigen-presenting cells\(^{[31]}\). That means EPCs may contribute to the processes of AP, and may be a potential marker to predict the severity and prognosis of AP at the early stage. This investigation supports that hypothesis.

Data indicate that the normal level of EPCs in peripheral blood range from 0% to 0.05% of circulating mononuclear cells\(^{[32,33]}\). We found that the mean level of EPCs in peripheral blood of the control, MAP and SAP patients were 0.55% ± 0.54%, 1.63% ± 1.47% and 6.61% ± 4.28%, respectively. The difference between the MAP and SAP groups was significant \((P < 0.01)\). However, the level of EPCs in the control and MAP groups was similar. Furthermore, the control group level of EPCs (mean of 0.55% ± 0.54%, range of 0% to 0.16%) was higher than reported. This may be attributed to national, altitude and other factors.

EPCs also had positive correlations with the other four markers in AP patients and controls \((P < 0.01, \text{all})\).

According to AUC value and YI, EPCs and CRP appeared to be optimal biomarkers for predicting SAP. Although CRP had the highest specificity (96.7%), EPCs had the highest sensitivity (90.0%) and highest AUC value (0.93) compared with the other five markers. CRP is produced by the liver after the stimulation of IL-6 and other hormones so that the peak of CRP appears 24-48 h later than IL-6; as well,
CRP as a feasible biological marker to predict SAP

CRP impairs the repairing effect of EPCs and leads to the dysfunction of ECs, finally resulting in progression of AP. This investigation showed that CRP has a positive correlation with EPCs that may be attributable to the peripheral blood level of CRP. CRP is accurate, cost-effective and popular. Therefore, it could be used as a significant independent biological marker.[35,36] The World Congress of Gastroenterology also suggests that CRP might be an independent risk factor for SAP. If CRP is > 150 mg/L in 72 h, it suggests SAP and the occurrence of complications. The Congress’ Report[37] included that the sensitivity, specificity, positive predictive value (PV+) and negative predictive value (PV-) of CRP were 86%, 87%, 75% and 93%, respectively. This investigation indicates that CRP > 5.94 mg/dL (59.4 mg/L) within 24 h after admission suggests SAP. Furthermore, at this cut-off value, the sensitivity, specificity, PV+ and PV- of CRP were 73.3%, 96.7%, 95.7% and 78.4%, respectively.

CRP is produced later in the progress of AP, with the peak sustained in only 24 h. That the optimal cut-off level is lower than reported, may be attributed to different patient admission times.

Value of TNF-α and FIB is still in dispute

TNF-α rose rapidly at the early stage of AP, and it had a negative correlation with the rate of decay and the severity of AP. This investigation indicated that TNF-α, with a significant AUC value (AUC-TNF-α > 0.7), can be used as a marker to predict SAP at the early stage.

Since coagulation function disorder also occurs in the early stage of SAP, markers of coagulation function can also be used to predict the severity of AP. FIB is the most important coagulation factor, with the highest normal serum level of 2-4 g/L. Reports suggest that progressive change indicates poor prognosis. This investigation found that FIB > 5.85 g/L may predict SAP with a respective sensitivity and specificity of 66.7% and 76.7%.

According to the AUC value and YI, both TNF-α and FIB seemed to have lower diagnostic value than EPCs or CRP. Furthermore, WBC could be easily modified by anti-inflammatory drugs, such as aspirin, making it an unlikely biomarker to identify SAP or MAP.

In this investigation, we first proposed that EPCs may be used as a novel biological marker to predict the severity of AP considering the relation between ECs and EPCs. We compared five markers, and concluded that EPCs had the highest AUC value (0.93) and YI.
(0.8), sensitivity (90.0%) and specificity (83.3%). According to the YI, combination of CRP with EPCs would improve diagnostic value. Data suggest that EPCs may be a new biological marker in predicting SAP at the early stage.

COMMENTS

Background
Acute pancreatitis (AP) is a frequent disease. Mild acute pancreatitis is easy to treat and the cure rate is high. Although severe acute pancreatitis (SAP) accounts for only 15%-30% of AP cases, it has a high rate of multiple complications and a fatality rate of 5% to 70%. Lack of accurate or timely evaluation of AP will lead to excessive medical treatments and a higher fatality rate. Therefore, correct appraisal of the severity of AP is key to clinical decision-making. Data show that biomarkers, including C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), are significantly related to the severity and prognosis of AP. As a non-specific acute phase protein, CRP induces endothelial cell dysfunction, impairs vessel walls and promotes inflammatory reactions. In addition, a certain level of CRP may impair the number and function of endothelial progenitor cells (EPCs) by depressing the expression of endothelial nitric oxide synthase. The purpose of this study was to investigate the significance of EPCs in predicting SAP.

Research frontiers
EPCs have a close relation with the endothelial system, and may be antigen-presenting cells. That means that EPCs may contribute to the processes of AP, and may be a potential marker to predict the severity and prognosis of AP at the early stage.

Innovations and breakthroughs
In this investigation, the authors first proposed that EPCs may be used as a novel biological marker to predict the severity of AP, considering the relation between ECs and EPCs. The authors compared five markers, and concluded that EPCs had the highest AUC value (0.93) and Youden index (YI) (0.8), as well as the highest sensitivity (90.0%) and the second highest specificity (83.3%) from among five markers evaluated. According to the YI, combination of CRP with EPCs will improve diagnostic value. Furthermore, this investigation showed that EPCs had positive correlations with the four other markers in AP patients.

Applications
This study suggests that EPCs may be used as a new biological marker in predicting SAP at the early stage.

Terminology
EPCs may be used as a novel biological marker to predict the severity of AP considering the relation between ECs and EPCs. The authors compared five markers, and concluded that EPCs had the highest AUC value (0.93) and YI (0.8), sensitivity (90.0%) and specificity (83.3%). EPCs may be a new biological marker in predicting SAP at the early stage.

Peer-review
This article relooks at whether EPCs may be used as a novel biological marker to predict the severity of AP, considering the relation between ECs and EPCs. Compared with five markers, the authors concluded that EPCs had the highest AUC value (0.93) and YI (0.8), sensitivity (90.0%) and specificity (83.3%). So, EPCs may be useful as a new biological marker in predicting SAP at the early stage.

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