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# Prediction of mortality and organ failure based on coagulation and fibrinolysis markers in patients with acute pancreatitis

## A retrospective study

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**Abstract**

This study explored the predictive value of coagulation and fibrinolysis markers with acute pancreatitis (AP)-related mortality and organ failure.

We retrospectively reviewed and analyzed coagulation and fibrinolysis markers and clinical outcomes of the patients with AP.

A total of 273 patients with AP were enrolled, 7 patients died and 28 patients suffered from organ failure. Uni- and multivariate logistic regression identified the differences of all of the coagulation and fibrinolysis markers as risk factors for AP-related mortality. The differences of APTT value, TT value, D-dimmer level, FDP level, and AT III level were risk factors for organ failure. Furthermore, the OR of the differences of platelet, PT, APTT, TT, fibrinogen, D-dimmer, FDP, and AT III was substantially improved by grouping with intervals of $10 \times 10^9$/L, 2 seconds, 5 seconds, 3 seconds, 0.5 g/L, 3 mg/L FEU, 5 mg/L and 10%, respectively. The risk of mortality can increase up to 1.62, 5.17, and 5.60 fold for every $10 \times 10^9$/L, 2 seconds and 5 seconds of increase in platelet, PT and APTT, respectively. There is approximate 2-fold increase in risk of organ failure for every 2 seconds of TT increase. In receiver operating characteristic analysis, there is no difference in the predictive power of bedside index for severity in acute pancreatitis (BISAP) with them in mortality or organ failure.

In patients with AP, the dynamic changes of coagulation and fibrinolysis markers are good predictors for AP-related mortality and organ failure, especially platelet, PT and APTT in mortality and TT in organ failure.

**Abbreviations:** AP = acute pancreatitis, APTT = activated partial thromboplastin time, AT III = antithrombin III, AUC = an area under the curve, BISAP = bedside index for severity in acute pancreatitis, FDP = fibrin/fibrinogen degradation products, FIB = Fibrinogen, OR = odds ratio, PT = prothrombin time, ROC = receiver operating characteristic, TT = thrombin time.

**Keywords:** acute pancreatitis, coagulation, fibrinolysis, mortality, organ failure, prediction

## 1. Introduction

Acute pancreatitis (AP) is a common acute abdominal disease characterized by acute upper abdominal pain and increased serum levels of pancreatic enzymes.[1] The condition leads to more than 220,000 hospitalizations annually in the US.[2] Approximately 15% to 20% of patients die from this disease in the intensive care unit.[3] Therefore, identified risk factors for mortality and organ failure in patients with AP as early as possible may improve prevention and early treatment, thereby improving prognosis. The potential risk factors to be identified should be valid before and after admission, even after in-hospital treatment has begun.

The most common consequence of AP is systemic inflammation reaction, which is characterized by high circulating levels of pro- and anti-inflammatory cytokines,[4] and hypercoagulation leading to microvascular thrombosis.[5,6] Several studies have demonstrated that microvessel changes are significant events in the progression of AP and that coagulative disorders are related to AP severity.[7,5] However, despite increasing evidence suggests an important role of the coagulation system in AP,[8,9] meaningful studies on the clinical value of parameters of the coagulation system in predicting mortality and organ failure are still scarce.[10,11] Therefore, in the present study, we retrospectively reviewed records of patients with AP at our hospital to identify coagulation and fibrinolysis markers for adverse outcomes.

## 2. Material and methods

### 2.1. Patients

This retrospective study included a consecutive series of patients admitted for AP at West China Hospital of Sichuan University

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CL and XZ contributed equally to this work.

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without treatment before admission between April 1, 2016 and December 31, 2017. In accordance with the revised Atlanta Classification *(2012)*,[12] patients were diagnosed with AP when they presented with 2 or more of the following: abdominal pain consistent with AP, serum levels of amylase and/or lipase ≥3 times the upper limit of normal, or characteristic features on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography. Patients were excluded when they in these conditions:

1. admitting >72 hours after onset,
2. suffering from malignant tumor,
3. taking anticoagulants,
4. suffering from organ failure, such as renal failure (glomerular filtration rate (GFR) <15 ml/min/1.73 $m^3$), respiratory system dysfunction (PaO2 < 60 mmHg when breathing air), severe heart failure [New York Heart Association (NYHA) class IV] and other diagnosed organ failure, or
5. incomplete information. This study was approved by the Ethics Committee of Sichuan University. We have followed the strobe checklist for case-control studies.

### 2.2. Data collection

The authors independently extracted data on patient characteristics and clinical variables (including laboratory data and outcomes) from the hospital central database. The coagulation and fibrinolysis markers of admission were measured within 2 hours of admission as standard procedure at our hospital. The coagulation and fibrinolysis markers including platelet number, PT, APTT, and TT values, as well as fibrinogen (FIB), AT III, FDP and D-dimmer levels. All of the markers were performed every 1 to 2 days thereafter or assayed at the discretion of the attending physician.

The platelet number was determined in the Sysmex XE5000 hematology analyzer (Sysmex, Japan), and the other coagulation and fibrinolysis markers were measured in the Sysmex CS 5100 automatic coagulation analyzer (Sysmex, Japan).

### 2.3. Outcomes

The primary outcome was all-cause mortality during hospitalization. Secondary outcome was organ failure during hospitalization, including diagnosed acute kidney injury, respiratory failure and other organ failure diagnosed by physician. Acute kidney injury was defined as an increase in serum creatinine of ≥0.3 mg/dl (≥26.4 μmol/L) within 48 hours or an increase in serum creatinine to 1.5 times baseline.[14] Patients were diagnosed with respiratory failure when they had hypoxemia and/or hypercapnia, that is, arterial oxygen pressure <60 mmHg and/or arterial carbon dioxide pressure >50 mmHg while breathing air.[15]

### 2.4. Statistical analysis

Index-time curves of coagulation and fibrinolysis markers were plotted to determine the maximum or minimum of indices. Time is the number of days that it takes to reach the maximum or minimum values of particular markers during hospitalization. For PT, APTT, TT, FDP, and D-dimmer, the maximum values obtained during hospitalization were used to calculate the difference to the value in admission. For platelet, FIB and AT III, the minimum values obtained during hospitalization were used to calculate the difference to the value in admission. The differences of the coagulation and fibrinolysis markers would be used for later logistic analysis and receiver operating characteristic (ROC). The differences of platelet, PT, APTT and TT, FIB, AT III, FDP, and D-dimmer were substantially grouped by intervals of $10 \times 10^9$/L, 2 seconds, 5 seconds, 3 seconds, 0.5 g/L, 3 mg/L FEU, 5 mg/L and 10%, which would be used for later logistic analysis.

Data for continuous variables were reported as mean ± standard deviation if they showed a normal distribution based on Shapiro-Wilk tests. Skewed continuous data were reported as median (interquartile range, IQR) and analyzed using the rank sum test. Data for categorical variables were expressed as percentages, and inter-group differences were analyzed by chi-squared or Fisher exact tests. Backward univariate and multivariate logistic regression analyses were performed to assess the independent risk for both mortality and organ failure. In order to control confounding bias, multivariate logistic analysis was adjusted by age, gender and BMI. The odds ratio (OR) represents the predicted change in risk per unit increase in the predictor.

To compare the predictive power of bedside index for severity in acute pancreatitis (BISAP) and each of the differences of the coagulation and fibrinolysis markers in mortality and organ failure, the AUC were calculated and compared, respectively.

All statistical analyses were performed using SPSS 19.0 (IBM, Chicago, IL) and MedCalc 15.2.2 (Mariakerke, Belgium). In all analyses, $P < .05$ was considered significant.

## 3. Result

Of the 731 potentially eligible patients, 458 were excluded because of admitting >72 hours after onset (n=402), suffering from malignant tumor (n=4), taking anticoagulants (n=5), renal failure (n=2) and incomplete information (n=45) (Fig. 1). A total of 273 patients with AP were involved in our study, 7 patients died and 28 patients suffered from organ failure (acute kidney injury, n=5; respiratory failure, n=21; acute kidney injury and respiratory failure, n=2). Baseline characteristics and the coagulation and fibrinolysis markers of the patients are shown in Table 1. A total of 167 (61%) patients were men. The patients' mean age was 48 years old, BMI was 25.5 and median hospitalization day was 10. There were no significant differences in age, gender, and body mass index between the 2 groups in mortality and organ failure (Table 1). The cause of AP was not possible to determine definitively in most of our sample because of the short disease course: the disease was related to food or was not linked to any obvious cause in 251 patients (92%), it was linked to cholangitis in 3 patients (1%), and it was related to alcohol in the remaining 19 patients (7%).

### 3.1. Coagulation and fibrinolysis markers at admission

Patients who died have higher levels of D-dimmer (Table 1). In univariate analysis, higher levels of D-dimmer (OR 1.19, 95%CI 1.01–1.39; $P=.034$) was associated with death. D-dimmer at admission (adjusted OR 1.20, 95%CI 1.02–1.42; $P=.026$) was independent risk factor for death under multivariate regression (Table 2).

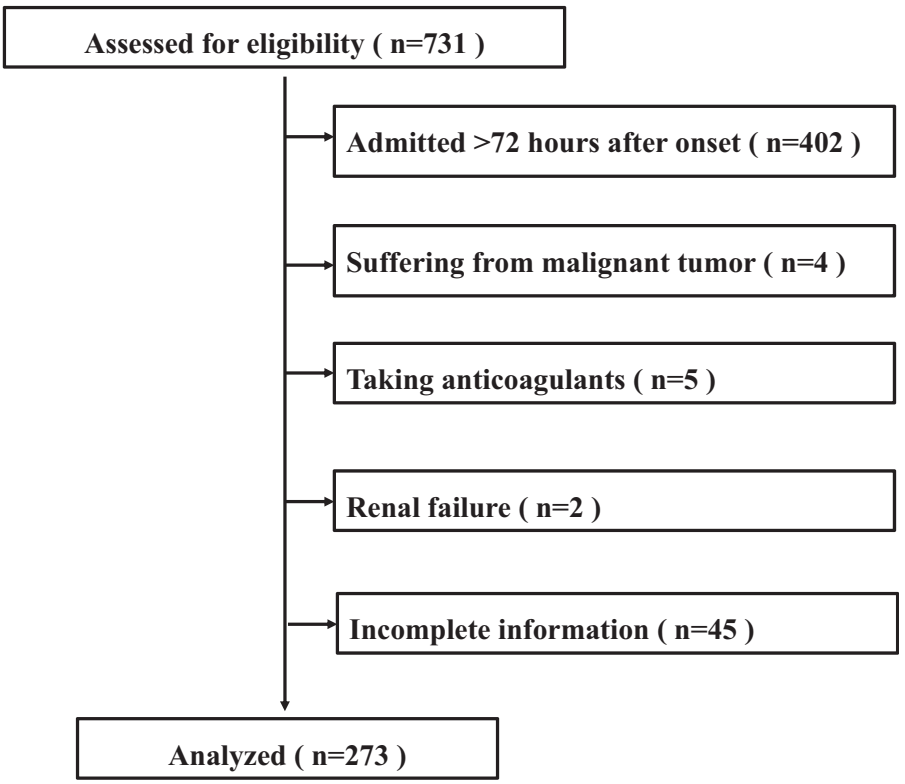


**Figure 1.** Flow diagram of patients.

Patients who suffered from organ failure have higher levels of PT, APTT, D-dimmer and FDP (Table 1), as well as lower level of AT III. In univariate and multivariate analysis, higher levels of APTT (adjusted OR 1.07, 95%CI 1.02–1.12; $P=.003$), D-dimmer (adjusted OR 1.17, 95%CI 1.05–1.32; $P=.006$) and FDP (adjusted OR 1.04, 95%CI 1.00–1.08; $P=.036$) were independent risk factors for organ failure (Table 2).

### 3.2. Coagulation and fibrinolysis markers during hospitalization

The minimum of platelet, FIB and AT III, as well as the maximum of PT, APTT, TT, D-dimmer, and FDP during hospitalization were analyzed. Patients who died had lower platelet, FIB and AT III. Patients who died also had higher D-dimmer and FDP (Table 1). The minimum or maximum of markers in mortality often appeared on 1 to 3 days after admission, which were later than them in survivor (0–1 day) (Table 1). It suggests that the deterioration of coagulation and fibrinolysis function is associated with death. The minimum of platelet, FIB and AT III, as well as the maximum of PT, APTT, D-dimmer, and FDP during hospitalization were found to be associated with death in univariate analysis. Furthermore, platelet, AT III, PT, APTT, D-dimmer, and FDP during hospitalization were identified as independent risk factors for mortality under multivariate regression (Table 2). FIB during hospitalization was excluded when adjusted by age, gender, and BMI (Table 2).

Patients who suffered from organ failure had lower platelet, FIB and AT III, as well as higher APTT, D-dimmer, and FDP (Table 1). The minimum of platelet and AT III, as well as the maximum of PT, APTT, TT, D-dimmer, and FDP during hospitalization were found to be associated with morbidity in univariate analysis. All of them were identified as independent risk factors for morbidity under multivariate regression (Table 2).

### 3.3. Changing of coagulation and fibrinolysis markers in mortality

The differences between the maximum or minimum during hospitalization and the value of admission were calculated and showed significant difference in dead and survivor (Table 1). It suggests that coagulation and fibrinolysis function continued to worsen in dead. In multivariate regression, the differences of platelet, PT, APTT, TT, FIB, D-dimmer, FDP, and AT III were found to be risk factors of death (Table 3).

ROC curve analysis showed the AUC of the differences of platelet, PT, APTT, FIB, FDP, and AT III were range from 0.73 to 0.87 in mortality (Table 4). The AUC of platelet, PT and APTT reach up to 0.87, 0.81, and 0.85, which show good predictive value of mortality. There is no difference in the power of predicting mortality among coagulation markers platelet ($P=.818$), PT ($P=.496$), APTT ($P=.777$), FIB ($P=.234$), FDP ($P=.356$) and AT III ($P=.263$) with BISAP.

All of the markers were grouped for further clinical application. Platelet, PT, APTT, TT, FIB, D-dimmer, FDP, and AT III were substantially grouped by intervals of $10\times10^9$/L, 2 seconds, 5 seconds, 3 seconds, 0.5 g/L, 3 mg/L FEU, 5 mg/L, and 10%, respectively. Risk of mortality increased in a stepwise with increasing of the values of coagulation and fibrinolysis markers (Table 3), especially the risk of mortality increase up to 1.62, 5.17 and 5.60 fold for every $10\times10^9$/L, 2 seconds and 5 seconds of increase in platelet, PT and APTT, respectively.

**Table 1**

**Demographic features of patients*.**

| Variables | Total | Mortality | | *P* value | Morbidity | | *P* value |
|---|---|---|---|---|---|---|---|
| | | Yes (n=7) | No (n=266) | | Yes (n=28) | No (n=245) | |
| Demographic features | | | | | | | |
| Age, yr | 48.2±14.6 | 58.0±8.1 | 48.0±14.7 | .073 | 52.3±13.4 | 47.8±14.7 | .121 |
| Male, n (%) | 167 (61.2)% | 2 (29%) | 165 (62%) | .073 | 13 (46%) | 154 (63%) | .091 |
| Body Mass Index, kg/m$^2$ | 25.5±3.66 | 24.5±4.1 | 25.5±3.7 | . 499 | 24.8±4.4 | 25.6±3.6 | .310 |
| BISAP | 2±1 | 3±1 | 1±1 | <.001 | 2±1 | 1±1 | <.001 |
| Coagulation – fibrinolysis markers | | | | | | | |
| PLT | | | | | | | |
| $PLT_{ad}$ ($10^9$/L) | 176.74±74.84 | 196.29±94.92 | 176.22±74.39 | .485 | 166.43±67.63 | 177.91±75.65 | .443 |
| $PLT_{min}$ ($10^9$/L) | 142.12±57.10 | 69.00±52.89 | 144.05±56.02 | .001 | 119.39±57.69 | 144.72±56.57 | .026 |
| ΔPLT ($10^9$/L) | 23 (0,44.5) | 79 (64,151) | 22 (0,42) | .001 | 33 (0,74) | 22 (0,42) | .191 |
| Time†-ΔPLT (d) | 0 (0,1) | 3 (1,9) | 1 (0,2) | .003 | 2 (0,3) | 1 (0,1) | .033 |
| PT | | | | | | | |
| $PT_{ad}$ (s) | 12.4±1.46 | 12.3±1.6 | 12.4±1.5 | .846 | 13.0±1.9 | 12.3±1.4 | .036 |
| $PT_{max}$ (s) | 13.1±2.5 | 19.2±12.0 | 12.9±1.5 | .215 | 15.0±6.3 | 12.9±1.5 | .085 |
| ΔPT (s) | 0 (0,0.9) | 2.6 (0.6,10.1) | 0 (0,0.9) | .001 | 0 (0,0.98) | 0 (0,0.90) | .194 |
| Time†-ΔPT (d) | 0 (0,1) | 1 (1,3) | 0 (0,1) | .004 | 0 (0,1) | 0 (0,1) | .954 |
| APTT | | | | | | | |
| $APTT_{ad}$ (s) | 29.9±7.2 | 26.8±3.7 | 30.0±7.3 | .241 | 34.9±14.3 | 29.4±5.7 | .050 |
| $APTT_{max}$ (s) | 32.2±9.1 | 50.5±30.2 | 31.8±7.3 | .153 | 40.9±19.6 | 31.2±6.2 | .015 |
| ΔAPTT (s) | 0 (0,2.2) | 11.1 (2.5,33.1) | 0 (0,1.9) | <.001 | 0 (0,5.0) | 0 (0,2) | .342 |
| Time†-ΔAPTT (d) | 0 (0,1) | 1 (1,17) | 0 (0,1) | <.001 | 0 (0,1) | 0 (0,1) | .777 |
| TT | | | | | | | |
| $TT_{ad}$ (s) | 18.6±6.5 | 19.3±2.1 | 18.6±6.5 | .784 | 22.4±19.3 | 18.2±1.7 | .262 |
| $TT_{max}$ (s) | 19.0±6.5 | 20.8±2.2 | 19.0±6.6 | .470 | 23.3±19.1 | 18.5±1.9 | .202 |
| ΔTT (s) | 0 (0,0) | 1.4 (0,3.3) | 0 (0,0) | .011 | 0 (0,1.4) | 0 (0,0) | .006 |
| Time†-ΔTT (d) | 0 (0,0) | 1 (0,3) | 0 (0,0) | .014 | 0 (0,2) | 0 (0,0) | .051 |
| FIB | | | | | | | |
| $FIB_{ad}$ (g/L) | 4.14±1.77 | 3.68±2.00 | 4.15±1.77 | .493 | 3.94±1.49 | 4.16±1.81 | .534 |
| $FIB_{min}$ (g/L) | 3.93±1.73 | 2.45±0.87 | 3.97±1.73 | .003 | 3.57±1.56 | 3.98±1.74 | .243 |
| ΔFIB (g/L) | 0 (0,0) | 0.48 (0,1.9) | 0 (0,0) | .002 | 0 (0,0.44) | 0 (0,0) | .006 |
| Time†-ΔFIB (d) | 0 (0,0) | 0 (0,12) | 0 (0,0) | .017 | 0 (0,3) | 0 (0,0) | <.001 |
| D-dimmer | | | | | | | |
| $D\text{-dimmer}_{ad}$ (mg/LFEU) | 2.11±2.67 | 4.46±2.58 | 2.04±2.65 | .018 | 3.67±3.51 | 1.92±2.50 | .001 |
| $D\text{-dimmer}_{max}$ (mg/LFEU) | 3.29±4.64 | 9.23±5.25 | 3.13±4.52 | .001 | 7.73±8.82 | 2.76±3.52 | .006 |
| ΔD-dimmer (mg/L FEU) | 0 (0,0.29) | 2.04 (0,10.3) | 0 (0,0.25) | .035 | 0.63 (0,5.61) | 0 (0,0.85) | <.001 |
| Time†-ΔD-dimmer (d) | 0 (0,1) | 1 (0,8) | 0 (0,1) | .058 | 0.5 (0,6.8) | 0 (0,1) | .003 |
| FDP | | | | | | | |
| $FDP_{ad}$ (mg/L) | 6.21±7.53 | 11.33±6.82 | 6.07±7.51 | .068 | 9.69±8.46 | 5.80±7.32 | .009 |
| $FDP_{max}$ (mg/L) | 9.31±11.87 | 30.17±22.14 | 8.74±11.0 | .043 | 19.45±18.74 | 8.09±10.16 | .004 |
| ΔFDP (mg/L) | 0 (0,0.55) | 15.6 (0,31.5) | 0 (0,0.33) | .001 | 2.4 (0,14) | 0 (0,0) | <.001 |
| Time†-ΔFDP (d) | 0 (0,1) | 3 (0,6) | 0 (0,1) | .042 | 1 (0,6) | 0 (0,0) | <.001 |
| AT III | | | | | | | |
| $AT\ III_{ad}$ (%) | 84.4±15.8 | 73.2±21.8 | 84.7±15.5 | .056 | 76.9±18.6 | 85.3±15.2 | .007 |
| $AT\ III_{min}$ (%) | 80.2±16.3 | 53.1±26.5 | 80.9±15.4 | <.001 | 68.0±20.6 | 81.6±15.2 | .002 |
| ΔAT III (%) | 0 (0,3.1) | 24.3 (0,33.2) | 0 (0,1.6) | .002 | 0.25 (0,12.35) | 0 (0,1.25) | .013 |
| Time†-ΔAT III (d) | 0 (0,1) | 1 (0,3) | 0 (0,1) | .030 | 0.5 (0,2.8) | 0 (0,0) | .001 |
| Hospitalization days (d) | 10 (7,14) | 13 (4,41) | 10 (7,14) | .328 | 17 (11,19.8) | 9 (7,13.5) | <.001 |

AP = acute pancreatitis, APTT = activated partial thromboplastin time, AT III = antithrombin III, AUC = an area under the curve, BISAP = bedside index for severity in acute pancreatitis, FDP = fibrin/fibrinogen degradation products, FIB = Fibrinogen, OR = odds ratio, PT = prothrombin time, ROC = receiver operating characteristic, TT = thrombin time.

* Ad=at admission, max=maximum, min=minimum.

† time, hospitalization days since authors are taking the minimum and maximum values of specific laboratory tests.

### *3.4. Changing of coagulation and fibrinolysis markers in organ failure*

The differences of TT, FIB, D-dimmer, FDP, and AT III were shown difference in organ failure. In univariate and multivariate regression, the differences of APTT, TT, D-dimmer, FDP, and AT III were found to be risk factors of organ failure (Table 3).

ROC curve analysis showed the AUC of the differences of TT, D-dimmer, FDP, and AT III were range from 0.62 to 0.71, which are similar with BISAP (AUC 0.71) (Table 4). There is no difference in the power of predicting organ failure among TT ($P$=.174), D-dimmer ($P$=.580), FDP ($P$=.991) and AT III ($P$=.143) with BISAP. But their predictive values of organ failure were worse than mortality.

After grouping, risk of organ failure increased in a stepwise with increase of the values of PT, TT, fibrinoge, D-dimmer, FDP, and AT III, especially the risk of organ failure increase up to 2.13 fold for every 2 seconds of increase in TT value. (Table 3)

**Table 2**

**Univariate and multivariate logistic regression for coagulation and fibrinolysis markers in AP-related mortality and morbidity.**

| | Mortality | | | | Morbidity | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted† | | Unadjusted | | Adjusted* | |
| | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| BISAP | 4.67 (1.88,11.57) | .001 | 3.86 (1.59,9.35) | .003 | 2.15 (1.48,3.11) | <.001 | 2.03 (1.39,2.96) | <.001 |
| $PLT_{ad}$ | 1.00 (0.99,1.01) | .485 | 1.01 (1.00,1.02) | .071 | 1.00 (0.99,1.00) | .442 | 1.00 (0.99.1.01) | .605 |
| $PLT_{min}$ | 0.96 (0.94,0.98) | <.001 | 0.97 (0.95,0.99) | .003 | 0.99 (0.98,1.00) | .027 | 0.99 (0.98,1.00) | .037 |
| $PT_{ad}$ | 0.95 (0.56,1.62) | .845 | 0.82 (0.43,1.6) | .553 | 1.28 (1.01,1.62) | .040 | 1.24 (0.97,1.60) | .092 |
| $PT_{max}$ | 1.57 (1.13,2.17) | .007 | 1.62 (1.15,2.29) | .006 | 1.40 (1.13,1.74) | .003 | 1.37 (1.09,1.71) | .006 |
| $APTT_{ad}$ | 0.88 (0.74,1.05) | .162 | 0.84 (0.69,1.03) | .093 | 1.07 (1.03,1.12) | .002 | 1.07 (1.02,1.12) | .003 |
| $APTT_{max}$ | 1.07 (1.03,1.12) | .001 | 1.08 (1.03,1.13) | .001 | 1.08 (1.04,1.13) | <.001 | 1.08 (1.04,1.13) | <.001 |
| $TT_{ad}$ | 1.01 (0.94,1.09) | .791 | 0.99 (0.75,1.30) | .936 | 1.18 (0.96,1.46) | .115 | 1.20 (0.97,1.50) | .099 |
| $TT_{max}$ | 1.02 (0.96,1.08) | .519 | 1.02 (0.94,1.10) | .623 | 1.28 (1.07,1.53) | .006 | 1.31 (1.09,1.57) | .004 |
| $FIB_{ad}$ | 0.84 (0.52,1.37) | .495 | 1.04 (0.63,1.74) | .870 | 0.93 (0.74,1.17) | .533 | 0.97 (0.75,1.25) | .815 |
| $FIB_{min}$ | 0.35 (0.14,0.89) | .028 | 0.41 (0.17,1.04) | .060 | 0.86 (0.67,1.11) | .244 | 0.88 (0.67,1.15) | .341 |
| $D\text{-dimmer}_{ad}$ | 1.19 (1.01,1.39) | .034 | 1.20 (1.02,1.42) | .026 | 1.18 (1.06,1.32) | .003 | 1.17 (1.05,1.32) | .006 |
| $D\text{-dimmer}_{max}$ | 1.12 (1.03,1.22) | .007 | 1.13 (1.03,1.23) | .006 | 1.17 (1.08,1.26) | <.001 | 1.16 (1.08,1.26) | <.001 |
| $FDP_{ad}$ | 1.05 (0.99,1.11) | .098 | 1.04 (0.99,1.11) | .148 | 1.05 (1.01,1.09) | .019 | 1.04 (1.00,1.08) | .036 |
| $FDP_{max}$ | 1.06 (1.03,1.10) | <.001 | 1.06 (1.03,1.10) | .001 | 1.05 (1.03,1.08) | <.001 | 1.05 (1.02,1.08) | <.001 |
| AT $III_{ad}$ | 0.97 (0.93,1.00) | .060 | 0.98 (0.93,1.02) | .335 | 0.97 (0.95,0.99) | .010 | 0.98 (0.95,1.00) | .058 |
| AT $III_{min}$ | 0.94 (0.90,0.97) | <.001 | 0.94 (0.90,0.97) | .001 | 0.96 (0.94,0.98) | <.001 | 0.96 (0.94,0.98) | .001 |

APTT = activated partial thromboplastin time, AT III = antithrombin III, BISAP = bedside index for severity in acute pancreatitis, FDP = fibrin/fibrinogen degradation products, FIB = Fibrinogen, OR = odds ratio, PT = prothrombin time, TT = thrombin time.

* adjusted by age, gender and BMI.

## 4. Discussion

Here, we performed detailed retrospective analysis of patients treated for AP at our hospital. We found that the level of D-dimmer at admission, as well as the minimum of platelet and AT III, and the maximum of PT, APTT, D-dimmer, and FDP during hospitalization are associated with increased AP-related mortality and organ failure. In addition to these markers, APTT and FDP at admission, as well as the maximum of TT are also associated with organ failure. Furthermore, the differences of all of the coagulation and fibrinolysis markers were found to be risk factors for AP-related mortality. The differences of APTT, TT, D-dimmer, FDP and AT III were risk factors for organ failure. The OR of them was substantially improved by grouped. The risk of mortality can increase up to 1.62, 5.17, and 5.60 fold for every $10 \times 10^9$/L, 2 seconds, and 5 seconds of increase in platelet, PT and APTT, respectively. There is approximate 2-fold increase in risk of organ failure for every 2 seconds of TT increase. In receiver

**Table 3**

**Univariate and multivariate logistic regression to assess the association between the change of coagulation – fibrinolysis markers and AP-related mortality and morbidity*.**

| | | Mortality | | | | Morbidity | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Unadjusted | | Adjusted† | | Unadjusted | | Adjusted† | |
| | | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| ΔPLT | Difference value | 1.01 (1.01,1.02) | <.001 | 1.02 (1.01,1.02) | .001 | 1.00 (1.00,1.01) | .180 | 1.00 (1.00,1.01) | .234 |
| | Grouped by $10^*10^9$/L | 1.48 (1.18,1.87) | .001 | 1.62 (1.21,2.17) | .001 | 1.10 (0.98,1.23) | .097 | 1.09 (0.97,1.23) | .163 |
| ΔPT | Difference value | 1.69 (1.21,2.35) | .002 | 1.73 (1.23,2.44) | .002 | 1.26 (0.99,160) | .063 | 1.26 (0.99,1.61) | .064 |
| | Grouped by 2 s | 4.73 (2.10,10.68) | <.001 | 5.17 (2.11,12.63) | <.001 | 1.69 (1.05,2.70) | .029 | 1.67 (1.03,2.70) | .038 |
| ΔAPTT | Difference value | 1.16 (1.08,1.25) | <.001 | 1.30 (1.10,1.54) | .002 | 1.05 (1.01,1.10) | .030 | 1.06 (1.01,1.11) | .029 |
| | Grouped by 5 s | 3.38 (1.90,6.03) | <.001 | 5.60 (2.27,13.82) | <.001 | 1.34 (0.95,1.90) | .101 | 1.38 (0.97,1.96) | .077 |
| ΔTT | Difference value | 1.68 (1.12,2.50) | .012 | 1.76 (1.16,2.66) | .008 | 1.45 (1.09,1.92) | .010 | 1.47 (1.10,1.95) | .008 |
| | Grouped by 3 s | 2.98 (1.27,6.99) | .012 | 3.41 (1.40,8.30) | .007 | 2.03 (1.16,3.55) | .014 | 2.13 (1.20,3.76) | .009 |
| ΔFIB | Difference value | 2.28 (1.37,3.81) | .002 | 2.53 (1.45,4.42) | .001 | 1.36 (0.87,2.12) | .180 | 1.35 (0.86,2.12) | .193 |
| | Grouped by 0.5 g/L | 1.45 (1.08,1.94) | .013 | 1.58 (1.14,2.19) | .006 | 1.27 (1.02,1.59) | .033 | 1.29 (1.03,1.61) | .028 |
| ΔD-dimmer | Difference value | 1.14 (1.02,1.28) | .019 | 1.15 (1.02,1.28) | .020 | 1.19 (1.09,1.31) | <.001 | 1.19 (1.09,1.31) | <.001 |
| | Grouped by 3 mg/L FEU | 1.81 (1.21,2.70) | .004 | 1.85 (1.21,2.84) | .004 | 1.63 (1.26,2.10) | <.001 | 1.63 (1.26,2.12) | <.001 |
| ΔFDP | Difference value | 1.09 (1.04,1.14) | <.001 | 1.09 (1.04,1.14) | .001 | 1.07 (1.03,1.11) | <.001 | 1.07 (1.03,1.10) | <.001 |
| | Grouped by 5 mg/L | 1.74 (1.27,2.36) | <.001 | 1.67 (1.20,2.32) | .002 | 1.5 (1.24,1.82) | <.001 | 1.48 (1.21,1.80) | <.001 |
| ΔAT | Difference value | 1.08 (1.03,1.12) | <.001 | 1.09 (1.04,1.14) | <.001 | 1.04 (1.01,1.07) | .011 | 1.05 (1.01,1.08) | .007 |
| | Grouped by 10% | 2.58 (1.47, 4.53) | .001 | 3.10 (1.63,5.88) | .001 | 1.58 (1.13,2.19) | .007 | 1.66 (1.18,2.32) | .003 |

AP = acute pancreatitis, APTT = activated partial thromboplastin time, AT III = antithrombin III, FDP = fibrin/fibrinogen degradation products, FIB = Fibrinogen, OR = odds ratio, PT = prothrombin time, ROC = receiver operating characteristic, TT = thrombin time.

* ΔPLT, $PLT_{ad}-PLT_{min}$; ΔPT,$PT_{max}-PT_{ad}$; ΔAPTT, $APTT_{max}-APTT_{ad}$; ΔTT, $TT_{max}-TT_{ad}$; ΔFIB,$FIB_{ad}-FIB_{min}$; ΔD-dimmer, $D\text{-dimmer}_{max}-D\text{-dimmer}_{ad}$; ΔFDP, $FDP_{max}-FDP_{ad}$; ΔATIII, AT $III_{ad}$−AT $III_{min}$.

† adjusted by age, gender, and BMI.

**Table 4**

**ROC analysis for BISAP and coagulation and fibrinolysis markers in predicting AP-related mortality and morbidity.**

| Variables | Mortality | | Mortality | |
|---|---|---|---|---|
| | AUC (95% CI) | *P* value | AUC (95% CI) | *P* value |
| BISAP score | 0.89 (0.81, 0.97) | <.001 | 0.71 (0.61, 0.82) | <.001 |
| ΔPLT | 0.87 (0.74, 1.00) | .001 | 0.58 (0.45, 0.71) | .169 |
| ΔPT | 0.81 (0.63, 0.99) | .005 | 0.56 (0.44, 0.68) | .298 |
| ΔAPTT | 0.85 (0.68, 1.00) | .001 | 0.54 (0.42, 0.67) | .465 |
| ΔTT | 0.71 (0.47, 0.94) | .063 | 0.62 (0.50, 0.74) | .046 |
| ΔFIB | 0.73 (0.49, 0.96) | .042 | 0.60 (0.48, 0.72) | .080 |
| ΔD-dimmer | 0.69 (0.45, 0.93) | .085 | 0.68 (0.56, 0.80) | .002 |
| ΔFDP | 0.78 (0.56, 0.99) | .012 | 0.71 (0.60, 0.82) | <.001 |
| ΔATIII | 0.77 (0.55, 0.99) | .015 | 0.62 (0.50. 0.73) | .047 |

APTT = activated partial thromboplastin time, AT III = antithrombin III, BISAP = bedside index for severity in acute pancreatitis, FDP = fibrin/fibrinogen degradation products, FIB = Fibrinogen, OR = odds ratio, PT = prothrombin time, TT = thrombin time.

*ΔPLT, $PLT_{ad}-PLT_{min}$; ΔPT, $PT_{max}-PT_{ad}$; ΔAPTT, $APTT_{max}-APTT_{ad}$; ΔTT,$TT_{max}-TT_{ad}$; ΔFIB, $FIB_{ad}-FIB_{min}$; ΔD-dimmer, $D\text{-}dimmer_{max}-D\text{-}dimmer_{ad}$; ΔFDP, $FDP_{max}-FDP_{ad}$; ΔATIII,$AT\ III_{ad}-AT\ III_{min}$.

operating characteristic analysis, there is no difference in the predictive power of BISAP with them.

A lot of models and risk factors have been built to predict AP-related mortality or severe classification. The Acute Physiology and Chronic Health Evaluation (APACHE II)[15] assesses three sets of variables using weighted scoring and objectively discriminates uncomplicated, complicated and fatal attacks within a few hours of admission to hospital. But the score remains difficult to implement in the clinic because of the amount of clinical data required and the complexity of the calculations. Wu[16] subsequently reported a scoring system called BISAP for predicting AP-related mortality. The system was also cumbersome for widespread clinical use. Although, the APACHE II and BISAP scores have been confirmed as superior for severity prediction in recent systematic reviews.[17] These scoring system are of little value in daily clinical practice.[18] More concise predictors should be found.

Previous work on AP has focused on risks associated with surgery[19,20] and drug treatment,[21,22] as well as epidemiology, genetic risk factors[24] and disease mechanisms, such as the role of interleukin,[24,25] levels of arterial blood gases[26] and C-reactive protein.[27] These studies have not, however, clarified risk factors for serious morbidities following AP. These parameters are not routinely analyzed at admission in most hospitals.

The initial phase of AP is the activation of pancreatic proteases, which is followed by activation of local inflammatory cells and various inflammatory mediators.[24,25] Prolonged or excessive inflammatory reaction of patients with AP is the most common consequence.[26] Proinflammatory cytokines activate the vascular endothelium, which triggers migration of leukocytes into tissues, reduces the endothelial antithrombogenic by reducing the internalization and degradation of thrombomodulin,[11] as well as adhesiveness and aggregation of platelet number increasing,[28] which decreases anticoagulation, inhibits fibrinolysis, and stimulates the coagulation pathway and the formation of fibrin and microvascular thrombi.[29] These coagulative abnormalities results in thrombosis in small vessels, even disseminated intravascular coagulation (DIC), which is often associated with mortality and organ failure through its bleeding tendency and disturbance of tissue microcirculation, that leads to a rapid increase of coagulation and fibrinolysis.[30] This statement leads to the increase of PT, APTT, TT, FDP, and D-dimmer, as well as the decrease of platelet, FIB and AT III. A series of studies show that the levels of coagulation and fibrinolysis markers were associated with severity and prognosis of AP.[28,31–33]

In the present study, OR was significantly improved by calculating the differences of platelet, PT, APTT, TT, FIB, D-dimmer, FDP, and AT III. It suggests dynamic monitoring coagulation and fibrinolysis markers will be more helpful for predicting AP-related mortality and organ failure. Their predictive powers are similar to BISAP.

The current study was conducted in a single center with a relatively small sample, which may create bias. Another limitation is that we did not take into account some inflammation factors, such as C-reactive protein[27] and interleukin-6[24]; or arterial blood gases, which have been shown to be useful predictors of mortality in AP,[26] because they were not routinely analyzed at admission in our hospital.

In conclusion, the present study demonstrates that the dynamic changes of coagulation and fibrinolysis markers are good predictor for AP-related mortality and organ failure, especially platelet, PT and APTT in mortality and TT in organ failure. The difference of them is reasonable good predictor of mortality and organ failure in AP patients. Based on the result of our study, further investigation of coagulation and fibrinolysis markers in more patients seems to be more constructive.

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## Author contributions

JZ conceived and designed the study; CNL, XFZ, SC, LQL, QL, JM and SLY collected data; CNL and XFZ collated and analyzed the data; XFZ, CNL and JZ drafted the manuscript, CNL and JZ revised the manuscript. All authors approved the final version of the manuscript.

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