

# Risk Factors for Acute Kidney Injury in Acute Pancreatitis: A 7-year Retrospective Analysis of Patients in a Large Tertiary Hospital

**Bingjun Yu**

First Affiliated Hospital of Nanchang University

**Wenhua He**

First Affiliated Hospital of Nanchang University

**Nonghua Lu** (✉ [lnonghua@ncu.edu.cn](mailto:lnonghua@ncu.edu.cn))

First Affiliated Hospital of Nanchang University <https://orcid.org/0000-0003-4373-551X>

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## Research article

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# Abstract

**Background** Acute kidney injury (AKI) is a serious complication of acute pancreatitis (AP) and causes a high risk of mortality. The aim of this study was to investigate the risk factors for AKI in patients in the early phase of AP.

**Methods** In this retrospective observational study, 1655 AP patients were divided into an AKI and a non-AKI group. Age, sex, BMI, APACHE II score, smoking history, hypertriglyceridaemia (HTG), alcohol abuse, biliary disease, organ failure, pancreatic necrosis and necrosis debridement were collected from the hospital record database.

**Results** 1036 males (62.6%) and 619 females (37.4%) were enrolled in this study. 1255 and 430 AP patients were included in the non-AKI and AKI groups, respectively. The mean age was  $45.90 \pm 11.73$  years. Hospital and intensive care unit (ICU) lengths of stay were  $18.13 \pm 43.26$  and  $31.53 \pm 72.47$  days, respectively. The incidence of organ failure and pancreatic necrosis were 25.0% and 32.2%, respectively. The morbidity of percutaneous catheter drainage (PCD) and operative necrosectomy (ON) was 10.9%, and the mortality among AP patients was 6.3%. HTG was identified as a risk factor for AKI in AP ( $P=0.001$ ). The incidence of organ failure ( $P=0.001$ ), pancreatic necrosis ( $P=0.001$ ) and necrosis debridement were greater in the AKI group than those in the non-AKI group.

**Conclusions** HTG is an independent risk factor for AKI in AP. AP patients with AKI have adverse outcomes such as high rates of organ failure, pancreatic necrosis, and necrosis debridement and longer hospital and ICU lengths of stay.

## Background

Acute pancreatitis (AP) is characterized by oedema, haemorrhage and necrosis caused by various mechanisms and is a potentially life-threatening disease due to the risk of organ failure [1, 2]. A study proposed that 20–25% of AP patients develop acute kidney injury (AKI), and that the total mortality among AP patients with AKI is nearly 25% [3, 4]. Thus, managing AP patients with AKI remains challenging. The pathogenesis and the exact mechanism of AP with AKI may involve the following processes: Firstly, cytokine cascades caused by systemic inflammatory response syndrome (SIRS) in the early phase of AP lead to the development of AKI [5–7]. Secondly, endotoxins and reactive oxygen species (ROS) also play key roles in the pathophysiology of AKI in AP patients. Thirdly, serum phospholipase A2 (PLA2) activity is related to renal tubular cell injury in AP patients [8–10]. All the above pathological processes of AKI may aggravate AP progression. Therefore, we hypothesized that identifying possible risk factors for AKI in AP patients can substantially reduce the complication and mortality rates associated with the disease.

To date, many studies [10] have proposed that hypoxaemia, a history of renal disease, abdominal compartment syndrome, and other conditions are associated with AKI in AP patients. However, the risk

factors for the development of AKI in the early phase of AP have not been well defined. Thus, the causal relationships between such risk factors and AKI in AP patients must be investigated.

In general, AKI may emerge within a few hours after AP onset, and cytokines act as triggers in the course of AKI in AP [11]. The seriousness of AKI in AP patients cannot be overlooked. Obesity, diabetes, body mass index (BMI) and hypertriglyceridaemia (HTG) are often complicated by AP and are closely related to renal diseases [12–14]. Hence, the relationship between these factors and AKI in AP patients is a reasonable consideration.

The aims of our study were to verify risk factors in the early phase of AP-related AKI and to clarify the relationship between prognostic factors and AKI based on prospectively collected AP patient data.

## Methods

### Patient data

This was a large retrospective study with patient data from the AP database of the First Affiliated Hospital of Nanchang University, which was approved by the ethics committee (database approval number: 2011001). From January 1, 2012, to December 31, 2018, 1655 patients who presented with AP were identified in our AP database in the department of digestion of the First Affiliated Hospital of Nanchang University. Patients younger than 18 years or older than 80 years was excluded from the study. The exclusion criteria are listed in Figure 1. We recorded clinical data such as age, sex, a history of smoking and drinking alcohol, diabetes, hypertension, a history of renal diseases, complications, the severity of AP during hospitalization, death, the length of stay in hospital after AP onset and body mass index (BMI) on admission. Weight in kilograms divided by height in square metres was measured as the BMI ( $\text{kg}/\text{m}^2$ ). Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated based on patient data.

### Diagnosis and definitions

The total population was divided into two groups: the AKI group and the non-AKI group. The early phase of AP with AKI was defined as within 7 d after AP onset. AKI was defined as an absolute increase in serum creatinine greater than 0.3 mg/dl ( $\geq 26.4 \mu\text{mol}/\text{l}$ ) and a percentage increase in serum creatinine greater than 50% (1.5-fold from baseline) within 48 hours [15]. AP was diagnosed based on the 2012 revised Atlanta classification criteria [11]. Biliary disease was defined as 1 or more gallstones or bile duct dilation and laboratory results indicative of obstructive jaundice [16], alcohol abuse was defined as the consumption of more than 80 g of alcohol per day for at least 5 years [17,18], and HTG was defined as a serum Triglyceride(TG) level on admission greater than 11.3 mmol/L or greater than 5.65 mmol/L with lactescent serum before AP onset [18,19]. The 2012 revision of the Atlanta Acute Pancreatitis Diagnostic and Classification Criteria was used to classify AP severity. Organ failure was defined according to the modified Marshall Scoring System [11]. Pancreatic necrosis was diagnosed by contrast-enhanced computed tomography (CECT) based on diffuse enlargement of the pancreatic or peripancreatic volume,

blurred edges surrounding the pancreas, mild enhancement of the oedema area after enhanced scanning, and no enhancement of necrotic areas [20,21]. Mortality was defined as death during hospitalization. These definitions are shown in Supplementary table 1.

## Statistical analyses

Statistical comparisons of the two groups were performed using the  $\chi^2$  test.  $P < 0.05$  was considered statistically significant and two-tailed Fisher's exact test was used. SPSS version 21 was used for all analyses. We expressed continuous variables as the mean (SEM) or as the median with the interquartile range, and normally distributed data were analysed by a 2-tailed t test, whereas non-normally distributed data were tested by the Mann-Whitney U test. Risk factors and odds ratios (ORs) were examined using multivariate logistic regression analysis. Subsequently, variables with a P value  $< 0.2$  on univariate analysis were entered into a multivariable Cox regression to identify independent predictors.

## Results

### Baseline characteristics of the patients

A total of 1655 patients were admitted within 72 hours of AP onset and 1225 patients were included in the non-AKI group, while 430 patients were included in the AKI group. Overall, 1036 males (62.6%) and 619 females (37.4%) were enrolled. The mean age of all the AP patients was  $45.90 \pm 11.73$  years. The hospital length of stay ( $18.13 \pm 43.26$  vs  $31.53 \pm 72.47$  days) and intensive care unit (ICU) length of stay ( $0.87 \pm 3.78$  vs  $7.63 \pm 14.16$  days) in days in the AKI group were longer than those in the non-AKI group ( $P=0.001$ ). The incidence rates of organ failure and pancreatic necrosis were 25.0% and 32.2%, respectively. The morbidity rate of percutaneous catheter drainage (PCD) and operative necrosectomy (ON) was 10.9%, and the mortality rate among the AP patients was 6.3%. Detailed data of the patients' conditions are listed in Tables 1, 2, 3 and 4.

APACHE II scores ( $6.75 \pm 4.24$  in the non-AKI group vs  $9.16 \pm 5.54$  in the AKI group) and the severity of AP differed between the non-AKI group and the AKI group, as shown in Supplementary table 2. A total of 196 patients (45.7%) developed AKI in the first 24 h, 111 patients (25.9%) were diagnosed with AKI in the following 24 hours, and 122 patients (28.4%) developed AKI on the third day. These details are listed in Supplementary table 3.

### Risk factors among the AP patients with AKI

In the univariate analysis, 5 factors had a P value  $< 0.2$ , including age (OR, 1.000; 95% confidence interval [CI], 1.000-1.001;  $P=0.115$ ), BMI (OR, 1.007; 95%CI, 0.999-1.105,  $P=0.109$ ), diabetes (OR, 1.279; 95%CI, 0.930-1.758,  $P=0.131$ ), HTG (OR, 7.715; 95%CI, 5.792-9.493,  $P=0.001$ ) and biliary diseases (OR, 1.270; 95%CI, 1.212-1.344,  $P=0.001$ ). These 5 risk factors were subjected to multivariate logistic regression analysis. The P values showed that HTG (OR, 6.556; 95%CI, 4.817-8.923,  $P=0.001$ ) was a significant risk factor for AP with AKI. Detailed data of the patients' conditions are listed in Tables 1 and 2.

## **The incidence rates of complications and debridement of necrosis among the AP patients**

Univariate and multivariate logistic regression analyses were applied to AP complications and the results showed that AP patients with AKI experienced more complications and required more interventions. In the multivariate logistic regression analyses, the P value for organ failure, pancreatic necrosis and debridement of necrosis was 0.001 (OR, 17.605; 95%CI, 11.828-26.205), 0.001 (OR, 2.276; 95%CI, 1.539-3.366) and 0.001 (OR, 2.286; 95%CI, 1.701-4.761) respectively. Detailed patient data are listed in Tables 3 and 4.

## **The incidence of mortality among the AP patients**

The mortality of AP was also examined by logistic regression analysis. The results showed no significant difference in mortality between the AKI and non-AKI groups (OR, 1.150; 95%CI, 0.651-2.029; P=0.631), as shown in Table 4.

## **Discussion**

The AP has a wide range of mortality depending on its severity. AKI is one of the most common complications in AP patients and has a dramatic impact on clinical outcome in the course of AP. AKI is known to often occur in the early phase of AP, especially within the first week of AP onset and is closely related to increased mortality rate, costs and days of hospitalization. In this study, the results show that most AKIs are diagnosed within the first 48 hours, and the injury of renal function is even earlier. As most patients have experienced AKI on admission, it is necessary for us to investigate the predictive factors for AKI in the early phase of AP.

In previous study, HTG was proposed to be an aetiological factor of AP several years ago [22–24] and HTG-associated AP is a potentially fatal disease with high mortality and complication rates [25]. Although the exact pathogenesis of HTG-associated AP is not clearly defined, it may be associated with toxic damage to acinar cells [26, 27]. The contribution of HTG to all AP aetiologies varies in different studies. Twenty years ago, Fortson et al. reported that HTG accounted for 1.3–3.8% of the aetiology of AP [28], while a multi-centre study in Taiwan showed that HTG-associated AP accounted for 12.3% of all AP cases [29]. Another study performed by Jieshou Li also reported that HTG is a risk factor for AP [30], and that the different range of HTG may be related to the outcomes in the early phase of AP with AKI [31]. An animal experimental model of AP also showed that high levels of HTG in mice (ApoCIII<sup>tg</sup>) can accelerate kidney damage during the course of AP, especially severe HTG levels [32]. The above studies indicate that HTG is an important risk factor when predicting the occurrence of AKI in AP patients and plays a critical role in influencing the progression of AP. These results are similar to those in our study indicating that HTG is an independent risk factor for AKI in the early phase of AP, with a prevalence of HTG of 38.3% among the entire population and a prevalence as high as 49.2% in the AKI group.

Although HTG is a well-recognized cause of AP [33], it is not responsible for all these patients as etiology. Havel [24] reported that a high level of free fatty acids (FFAs) is a potential cause for AP, which is caused

by the hydrolysis of TG by pancreatic lipase. We hypothesize that the mechanism of AKI development in the early phase of AP involves the following processes: Pancreatic lipase hydrolyses excess TG in serum, leading to the accumulation of FFAs, which are damaging to organ function. The FFAs may directly impair the renal parenchyma and cause high levels of pancreatic enzymes in the glomerulus, which can lead to aggravation of renal function damage. This mechanism can explain why HTG accounts for a substantial proportion of AP cases with AKI and why AKI occurs very early in most cases. This hypothesis can explain why hypertriglyceridemia takes a great proportion of patients with AKI and why AKI occurs so early in most cases.

The AP patients with HTG may have chronic kidney disease such as glomerulosclerosis. This is a neglected problem as relevant tests are seldom taken when AP is the primary illness. We suppose that patients presenting with AKI in the early phase of AP have a special physiology that can be described as a “time bomb”, then leads to the progression of AP. Pre-existing metabolic disorders such as diabetes, chronic kidney disease and hypertension are responsible for the severity of AP. Hence, identifying AP patients with a high risk for AKI is important. Physicians should focus more on risk factors in AP patients.

The role of HTG in governing the course of AP is controversial [34, 35]. In recent years, studies have shown that HTG is related to the severity of AP and accentuates acute necrotizing pancreatitis [36–38]. In our study, we also found that HTG was an independent risk factor for AKI in AP patients and aggravated the severity of the disease and pancreatic necrosis. The revised Atlanta classification indicates that cytokine cascades resulting in SIRS are established during the development of organ failure of AKI in AP patients [11]. SAP begins with SIRS in the early phase, which is obviously significant in patients with organ failure. As it is very clear that cytokines are directly responsible for organ failure in SIRS and sepsis. it is reasonable to bring inflammation and organ failure together in SAP[5, 39, 40]. Our results may be a potential supplementary to this widely accepted opinion of AKI in the early phase of AP.

The APACHE II is an assessment tool for AP that contains a variety of indicators, including creatinine and HTG. In clinical practice, APACHE II scores are often used as a general measure to evaluate AP. Study have evidenced that APACHE II scores can predict the severity of AP with 100% accuracy [41]. In this study, the results show that the APACHE II score in the AKI group was significantly higher than that in the non-AKI group. Hence, the APACHE II score may also reflect the severity of the AP with AKI. However, we should also collect SIRS scores and RANSON scores for comparison with APACHE II scores in future research.

A previous study reported that severe HTG is usually associated with high mortality in AP patients with AKI and reflects a poor prognosis. In our study, the mortality rate in the AKI group was higher than that in the non-AKI group [42, 43], but no significant different was found between the two groups. We speculated that the reasons for this finding are the small number of cases of mortality among the AP patients that difficult to establish statistical analysis. In addition, the AP patients with AKI usually had longer hospital stays and ICU stays in this study. More importantly, these patients also had higher rates of pancreatic necrosis and debridement of necrosis (PCD and/or ON). According to the above results, we know that AP

patients with AKI can easily progress to a serious state. Therefore, It is important to identify patients with high risk for AKI. Physicians should pay more attention to patients with SAP.

## Strengths And Limitations

This study has several strengths. This is the first large-sample study to explore risk factors for the development of AKI in the early phase of AP. Our data show that a change in HTG is an independent risk factor for AKI in AP. Finally, The results in this study provide good guidance for further clinical work.

Several limitations exist in this study. Firstly, this is a retrospective observational study which does not absolutely imply causality between HTG and AKI. Therefore, a prospective study is needed to address the role of HTG in AKI with AP patients. Secondly, There are a little bias of the results in this study because we excluded 281 patients with a history of diabetes, kidney disease, or hypertension which would substantially impact serum creatinine levels.

## Conclusion

AKI is a complication of the early phase of AP and HTG is an independent risk factor for this complication. We speculate that accumulation of FFAs and cytokines in renal tissue may be an underlying mechanism. AP patients with AKI have adverse outcomes such as high rates of organ failure, pancreatic necrosis, and debridement of necrosis (PCD and/or ON) and long hospital and ICU stays.

## Abbreviations

Hypertriglyceridaemia: HTG. Acute pancreatitis: AP. Reactive oxygen species: ROS. Acute kidney injury: AKI. Phospholipase A2: PLA2. Severe acute pancreatitis: SAP. Body mass index: BMI. Acute respiratory distress syndrome: ARDS. Odds ratio: OR. Confidence interval: CI. Mild acute pancreatitis: MAP. Moderate severe acute pancreatitis: MSAP. Wild-type: WT. Systemic inflammatory response syndrome: SIRS. Acute Physiology and Chronic Health Evaluation II: APACHE II. Intensive care unit: ICU

## Declarations

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**Authors' contributions:** YuBingjun conceived the study; Wenhua He and Nonghua Lu participated in the study design; YuBingjun collected the data; YuBingjun, Wenhua He performed the statistical analyses; YuBingjun drafted the manuscript; and Nonghua Lu edited and reviewed the manuscript. All of the authors have read and approved the final manuscript.

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**Availability of data and materials:** The data enrolled and analyzed in our study are not publicly available due to appropriate protection of patient personal information but are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate:** The study was approved by the ethics committee of the First Affiliated Hospital of Nanchang University (database approval number: 2011001) prior to data collection. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This study is a retrospective analysis, it did not include any human trial, and as such no informed consent from patients was needed.

**Consent for publication:** Not applicable.

**Competing interests:** The authors declare no potential conflicts of interest. No writing assistance was provided in the production of this manuscript.

**Patient and public involvement** Patients were not involved in the design of this research study.

**Author details:** <sup>1</sup> Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China. <sup>2</sup>Department of cardiothoracic surgery, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

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## Tables

Table 1. The basic characteristics of the study population

	All patients (N=1655)	Non-AKI (N=1225)	AKI (N=430)	P value
<b>Age</b>	45.90±11.73	45.89±11.76	45.92±11.68	0.96 <sup>a</sup>
<b>Sex</b>				
Male	1036(62.6%)	768 (62.7%)	268(62.3%)	0.908 <sup>b</sup>
Female	619(37.4%)	457 (37.3%)	162(37.7%)	
<b>BMI</b>	24.67±12.60	24.35±10.72	25.60±16.84	0.079 <sup>a</sup>
<b>Diabetes</b>				
Yes	208(12.6%)	145(11.8%)	63(14.7%)	0.078 <sup>b</sup>
No	1447(87.4%)	1080(88.2%)	367(85.3%)	
<b>Biliary disease</b>				
Yes	840(50.8%)	701(57.2%)	114(26.5%)	0.001 <sup>b</sup>
No	815(49.2%)	524(42.8%)	316(73.5%)	
<b>Alcohol abuse</b>				
Yes	384(23.2%)	278(22.7%)	106(24.7%)	0.408 <sup>b</sup>
No	1271(76.8%)	947(77.3%)	324(75.3%)	
<b>Hypertriglyceridaemia</b>				
Yes	634(38.3%)	322(26.3%)	312(72.6%)	0.001 <sup>b</sup>
No	1021(61.7%)	903(73.7%)	118(27.4%)	
<b>Hypertension</b>				
Yes	304(18.4%)	228(18.6%)	76(17.7%)	0.718 <sup>b</sup>
No	1351(81.6%)	997(81.4%)	354 (82.3%)	
<b>History of renal diseases</b>				
Yes	161(9.7%)	112(9.1%)	49(11.4%)	0.337 <sup>b</sup>
No	1493(90.2%)	1112(90.8%)	381(88.6%)	
<b>History of smoking</b>				
Yes	364(22.0%)	269(22.0%)	95(22.1%)	0.946 <sup>b</sup>
No	1291(78.0%)	956(78.0%)	335(77.9%)	

Note \* a: t test, comparison between the training group and validation group; b: Chi-squared test, comparison between the training group and validation group.

Abbreviations: AKI, Acute kidney injury; PCD, Percutaneous catheter drainage; ON, Operative necrosectomy.

Table 2. Univariate and multivariate Cox regression analyses of risk factors in AP patients

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
<b>Age</b>	1.000(1.000-1.001)	0.115	1.009(0.998-1.020)	0.017
<b>Sex</b>				
Male	Reference			
Female	1.016(0.810-1.274)	0.892		
<b>BMI</b>	1.007(0.999-1.015)	0.109	1.005(0.997-1.014)	0.242
<b>Diabetes</b>				
No	Reference		Reference	
Yes	1.279(0.930-1.758)	0.131	1.369(0.960-1.953)	0.083
<b>Biliary disease</b>				
No				
Yes	1.270(1.212-1.344)	0.001	0.794(0.576-1.094)	0.159
<b>Alcohol abuse</b>				
No	Reference			
Yes	1.114(0.862-1.441)	0.408	0.900(0.676-1.199)	0.472
<b>Hypertriglyceridaemia</b>				
No	Reference		Reference	
Yes	7.715(5.792-9.493)	0.001	6.556(4.817-8.923)	0.001
<b>Hypertension</b>				
No	Reference			
Yes	0.939(0.703-1.253)	0.668		
<b>History of renal diseases</b>				
No	Reference			
Yes	0.986(0.920-1.056)	0.688		
<b>History of smoking</b>				
No	Reference			
Yes	1.008(0.773-1.314)	0.954		

Table 3. Characteristics of the patients: complications, interventions, stay time, and death

	All patients (n=1655)	Non-AKI (n=1225)	AKI (n=430)	P value
<b>Organ failure (ARDS and/or shock)</b>				
Yes	413(25.0%)	90(7.3%)	322(74.9%)	0.001 <sup>b</sup>
No	1242(75.0%)	1135(92.7%)	108(25.1%)	
<b>Pancreatic necrosis</b>				
Yes	533(32.2%)	211(17.2%)	107(24.9%)	0.001 <sup>b</sup>
No	1122(67.8%)	1014(82.8%)	323(75.1%)	
<b>Debridement of necrosis (PCD and/or ON)</b>				
Yes	181(10.9%)	42(3.4%)	139(32.3%)	0.001 <sup>b</sup>
No	1474(89.1%)	1183(96.6%)	291(67.7%)	
<b>Mortality</b>				
Yes	104(6.3%)	29(2.4%)	75(17.4%)	0.001 <sup>b</sup>
No	1551(93.7%)	1196(97.6%)	355(82.6%)	
<b>Hospital length of stay in days</b>	21.61±52.8	18.13±43.26	31.53±72.47	0.001 <sup>a</sup>
<b>ICU length of stay in days</b>	2.62±8.45	0.87±3.78	7.63±14.16	0.001 <sup>a</sup>

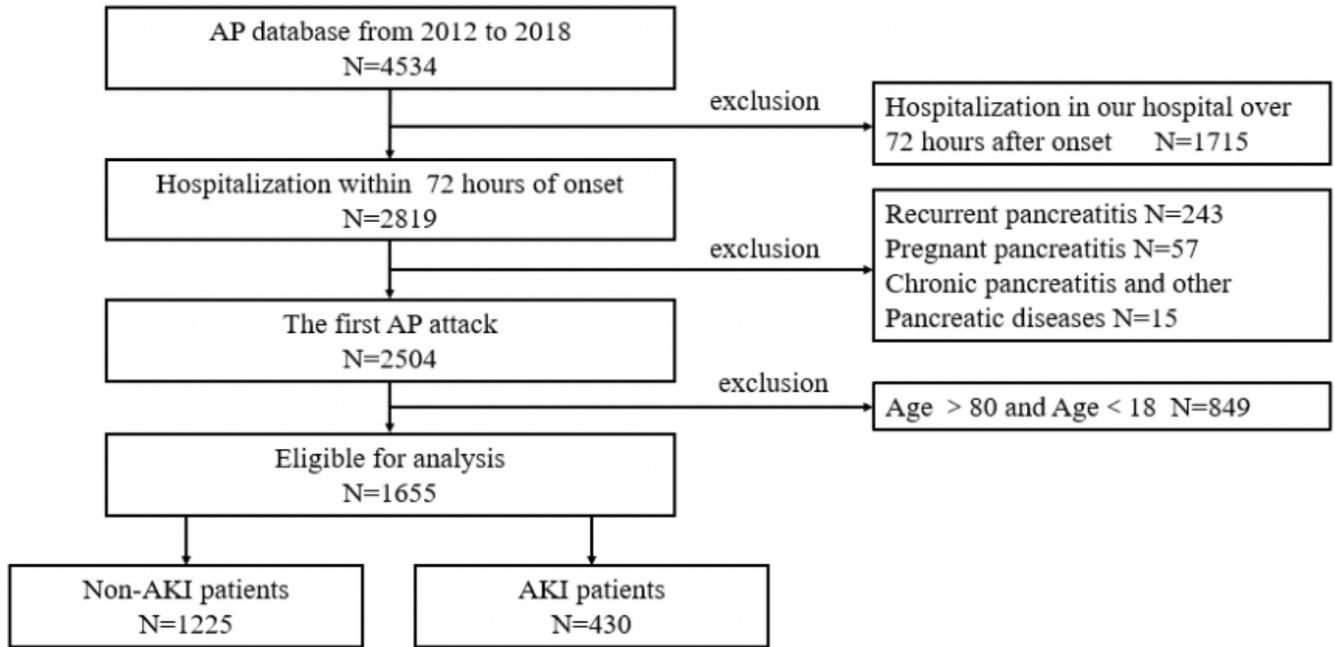
Note \* a: t test, comparison between the training group and validation group; b: Chi-squared test, comparison between the training group and validation group.

Abbreviations: AKI, Acute kidney injury; PCD, Percutaneous catheter drainage; ON, Operative necrosectomy; ARDS, Acute respiratory distress syndrome.

Table 4. Univariate and multivariate Cox regression analyses of prognostic factors in AP patients

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
<b>Organ failure (ARDS and/or shock)</b>				
No	Reference		Reference	
Yes	38.069(28.023-51.716)	0.001	17.605(11.828-26.205)	0.001
<b>Pancreatic necrosis</b>				
No	Reference		Reference	
Yes	14.328(11.008-18.650)	0.001	2.276(1.539-3.366)	0.001
<b>Debridement of necrosis (PCD and/or ON)</b>				
No	Reference		Reference	
Yes	13.454(9.310-19.442)	0.001	2.286(1.701-4.761)	0.001
<b>Mortality</b>				
No	Reference		Reference	
Yes	8.713(5.585-13.592)	0.001	1.150(0.651-2.029)	0.631
<b>Hospital length of stay in days</b>	1.005(1.002-1.007)	0.001		
<b>ICU length of stay in days</b>	1.206(1.168-1.244)	0.001		

## Figures



**Figure 1**

Study flowchart

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalTables.docx](#)