

Aberrant blood cell division cycle 42 expression and its correlation with disease severity, inflammation and mortality risk in patients with acute pancreatitis

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Abstract. Cell division cycle 42 (CDC42) can inhibit inflammation by regulating the activity of macrophage and T cells, which contributes to the pathophysiology of acute pancreatitis (AP). Therefore, CDC42 may have application as a potential biomarker for AP. The present study aimed to explore this possibility. Peripheral blood mononuclear cells (PBMCs) were collected from 149 patients with AP and 50 healthy controls (HCs). Subsequently, CDC42 expression in the PBMCs was measured using RT-qPCR; C-reactive protein (CRP), TNF- α and IL-6 in the serum of patients with AP were measured using ELISA. Meanwhile, Mann-Whitney U test, Kruskal-Wallis test, and Spearman's rank correlation test were performed on the data. The CDC42 expression levels were lower in patients with AP compared with those in HCs ($P < 0.001$). CDC42 expression was declined in patients with moderate-severe AP (MSAP) vs. patients with mild AP (MAP) ($P = 0.029$), and in patients with severe AP (SAP) vs. patients with MAP ($P = 0.004$). CDC42 expression correlated negatively with the Ranson's score ($P < 0.001$), APACHE II score ($P = 0.011$) and SOFA score ($P < 0.001$) in patients with AP. CDC42 expression also correlated negatively with CRP ($P < 0.001$) and TNF- α ($P = 0.004$) levels but not with IL-6 levels ($P = 0.177$). Furthermore, CDC42 expression was lower in deceased patients with AP vs. AP survivors ($P < 0.001$) and in deceased patients with SAP vs. SAP survivors ($P = 0.026$). CDC42 had good potential in predicting mortality from AP, with AUC of 0.829 and a 95% CI of 0.731-0.927, and it also had certain potential in predicting mortality from SAP

and MSAP, with AUC (95% CI) of 0.794 (0.616-0.973) and 0.757 (0.558-0.956), respectively. In conclusion, data from the present study suggest that lower CDC42 expression levels correlate with higher disease susceptibility, disease severity, inflammation, and mortality risk in patients with AP.

Introduction

Acute pancreatitis (AP) is an inflammatory condition that is characterized by the autodigestion, edema, bleeding and even necrosis of pancreatic tissues (1). Over the past number of decades, AP has been observed to be one of the most prevalent gastrointestinal conditions leading to hospitalization in China, USA and Japan (1-3). Furthermore, AP incurs considerable financial burden on the patients and healthcare system, with costs of >\$2 billion attributed to it annually in the USA alone (4). Despite developments in the diagnosis (including laboratory tests, electrocardiography and chest radiography) and treatment (including early fluid resuscitation, antibiotics and nutritional support) strategies of AP (1,2,5), rates of morbidity and mortality from AP remain high, with the morbidity of ~60,000 and mortality of ~50,000 in the USA alone in 2021 (6,7). In addition, local or systemic complications, such as pancreatic abscess and acute respiratory failure, adversely affect the quality of life of patients with AP (1-3,5). Due to these remaining obstacles in the management of AP, exploring potential novel biomarkers for ameliorating this condition is of importance.

Cell division cycle 42 (CDC42) has the capacity to modulate several biological processes, including cytoskeleton organization, membrane trafficking, cell migration and adhesion (8,9). Of note, a number of studies have previously reported that CDC42 can inhibit systemic inflammation by regulating the activity of macrophages and T cells (10-13). It has been suggested that CDC42 can promote M2 macrophage polarization to suppress inflammation (12,13). In addition, CDC42 has been found to inhibit the differentiation of T helper (Th)17 cells whilst promoting that of Th2 cells and regulatory T cells (Tregs), in turn suppressing inflammation (10,11). Previous studies have also reported that CDC42 can regulate the pathophysiology of AP (14,15). Based on these previous

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findings aforementioned, it was speculated that CDC42 may serve as a potential prognostic biomarker for AP. However, this concept remains poorly understood.

Therefore, the aim of the present study was to explore the possible association between CDC42 expression and the disease characteristics of AP and inflammation, in addition to its predictive value for mortality risk in patients with AP.

Materials and methods

Subjects. Between January 2018 and May 2021, a total of 149 patients with AP (aged 23-77, male:female ratio, 3.8:2) in the Affiliated Nanhua Hospital, University of South China Hunan, China were consecutively enrolled into the present study. The enrollment criteria were as follows: i) Confirmed as AP according to the 2016 Revised Atlanta Classification for Acute Pancreatitis (16); ii) aged >18 years; iii) enrollment within 24 h of diagnosis; and iv) ability to provide informed consent and provide a peripheral blood (PB) sample. The exclusion criteria were as follows: i) Diagnosed with pancreatic cancer or other hepatobiliary malignancies; ii) accompanied with autoimmune diseases or hematological malignancies; iii) received radiotherapy or chemotherapy within 180 days; and iv) being pregnant or lactating.

Within the same time period, 50 age- and sex-matched healthy individuals (aged 35-65, male:female ratio, 3:2) were also enrolled into the present study as healthy controls (HCs). The health status of HCs was checked when they came to the Affiliated Nanhua Hospital, University of South China Hunan, China for physical examination. The recruitment criteria for HCs were as follows: i) No history of pancreatitis; ii) no history of hepatobiliary diseases; iii) no history of malignant diseases; and iv) normal biochemical indices.

The present study was approved by the Institutional Review Board of the Affiliated Nanhua Hospital, University of South China (approval no. 2017-136) and written informed consent was obtained from all subjects or their guardians.

Collection of data. Demographic and clinical characteristics of patients with AP were recorded following physical examination. AP severity was classified in accordance with the 2016 Revised Atlanta Classification for Acute Pancreatitis (16), which included mild AP (MAP), moderate-severe AP (MSAP) and severe AP (SAP). The Ranson's, Acute Pathologic and Chronic Health Evaluation II (APACHE II) (17) and Sequential Organ Failure Assessment (SOFA) (18) scores of the patients with AP were also evaluated ordinally within 24 h from hospitalization. All patients with AP were closely followed up until either they succumb to the disease in hospital or are discharged from the hospital, where in-hospital mortality was recorded. Age and sex of all individuals in the HC group were recorded following health examination.

Collection of blood samples. PB (10 ml) from all individuals was collected by venipuncture within 24 h from admission or enrollment. Following collection, half of the blood samples were kept at room temperature (37°C) for >0.5 h and then centrifuged at 4°C, 1,170 x g for 10 min to separate the serum and the supernatant was collected by discarding the pellet. The serum was used immediately for cytokine determination. PB

mononuclear cells (PBMCs) were isolated immediately from the other half of the PB sample using Ficoll-Paque density gradient centrifugation. Briefly, PB sample diluted with phosphate buffered saline (PBS) was gently layered over an equal volume of Ficoll-Paque PLUS (cat. no. 17144002; Cytiva) in a Falcon tube and centrifuged for 20 min at 400 x g (20°C). Then four layers formed, each containing different cell types. The second white layer which contained PBMCs was gently removed using a Pasteur pipette and added to PBS to wash off any remaining platelets.

Reverse transcription-quantitative PCR (RT-qPCR). RT-qPCR was performed to quantitatively measure the expression of CDC42 in the PBMCs. Briefly, total RNA was extracted using a QIAamp RNA Blood Mini kit (Qiagen China Co., Ltd.) and reverse-transcribed using PrimeScript™ RT reagent kit (Perfect Real Time; Takara Biotechnology Co., Ltd.). The reverse transcription was performed at 42°C for 15 min. qPCR was performed using SYBR® Premix DimerEraser™ (Takara Biotechnology Co., Ltd.). The reactions of qPCR were incubated in 96-well optical plates (95°C, 5 min), followed by 30 cycles (94°C for 30 sec, 55°C for 1 min and 72°C for 1 min). The specific primers used for qPCR were as follows: CDC42 forward, 5'-GCCCCGTGACCTGAAGGCTGTCA-3' and reverse, 5'-TGCTTTTAGTATGATGCCGACACCA-3'. GAPDH was used as an internal control: forward, 5'-AAGGTGAAGGTCGGAGTCA-3' and reverse, 5'-GGAAGATGGTGATGGGATTT-3' (19). CDC42 expression was calculated using the $2^{-\Delta\Delta Cq}$ method (20).

ELISA. The levels of CRP in the serum of patients with AP and HCs were measured using a Human C-Reactive Protein ELISA kit (cat. no. CYT298; Merck KGaA). The levels of TNF- α and IL-6 in the serum of patients with AP were measured using a Human TNF- α Quantikine ELISA kit (cat. no. DTA00C; R&D Systems, Inc.) and Human IL-6 ELISA kit (cat. no. LS-F29154; LifeSpan BioSciences, Inc.). All processes were performed according to the manufacturers' protocols.

Statistical analysis. Statistical analysis was performed using the SPSS 26.0 software (IBM Corp.) and figures were plotted using GraphPad Prism 7.01 software (GraphPad Software, Inc.). Continuous data were displayed with mean \pm standard deviation (SD) and median with interquartile range (IQR) as appropriate. Categorical data were displayed as numbers (percentage). Differences in demographics, clinical features and biochemical indexes among subjects were assessed using unpaired Student's t-test, χ^2 test, Mann-Whitney U test, Kruskal-Wallis test and one-way analysis of variance. Multiple comparisons were performed by Dunn post hoc test with Bonferroni correction. Correlation between CDC42 expression and the level of inflammatory cytokines or disease assessment indicators were evaluated using the Spearman's rank correlation test. Receiver operating characteristic (ROC) curve analysis was used to investigate the efficacy of CDC42 expression for the evaluation of AP severity. Univariate logistic regression analysis was used to assess factors associated with in-hospital mortality, then all potential factors were included in the multivariate logistic regression analysis with step forward method by SPSS 26.0 software (IBM Corp.).

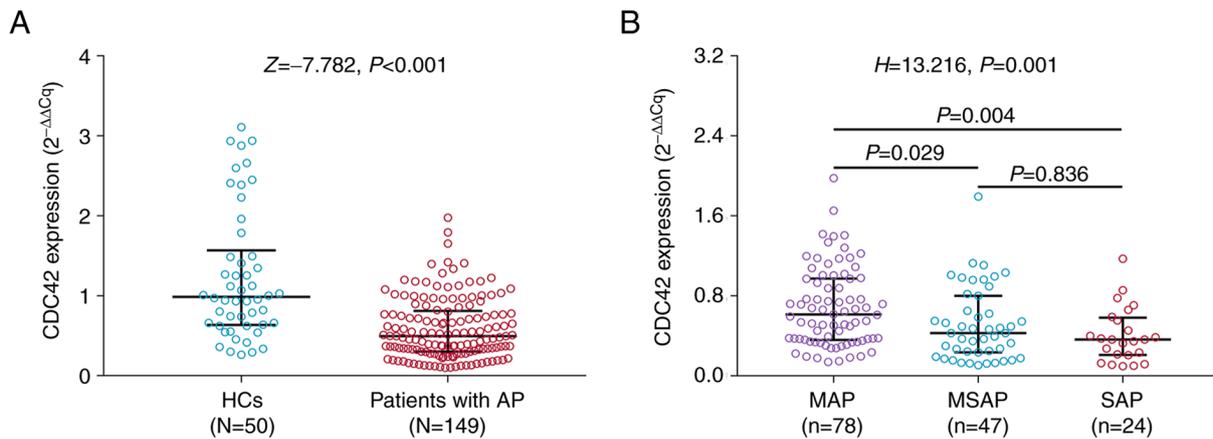


Figure 1. CDC42 expression in patients with AP. (A) Comparison of CDC42 expression between individuals in the HC group and patients with AP. (B) Comparison of CDC42 expression between patients with MAP vs. MSAP, patients with MSAP vs. SAP, and patients with MAP vs. SAP. CDC42, cell division cycle 42; AP, acute pancreatitis; HC, healthy controls; MAP, mild AP; MSAP, moderate-severe AP; SAP, severe AP.

$P < 0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of HCs and patients with AP. The group of patients with AP consisted of 51 (34.2%) women and 98 (65.8%) men with a mean age of 52.5 ± 13.9 years. The 50 HCs consisted of 20 (40.0%) women and 30 (60.0%) men with a mean age of 51.7 ± 9.4 years (Table I). Furthermore, the median CRP level in patients with AP [55.1 (31.7-91.3)] was significantly higher compared with that in HCs [3.2 (1.2-4.6); $P < 0.001$; Table I]. In terms of the Ranson's, APACHE II and SOFA scores, patients in the SAP groups scored the highest, followed by the MSAP and the MAP groups (all $P < 0.001$). However, no differences in age or sex could be identified between the AP and HC groups (Table I). Regarding the Ranson's, APACHE II and SOFA scores in patients with AP, they were found to be 2.0 (1.0-3.0), 7.0 (4.0-11.0) and 2.0 (1.0-4.0), respectively. The in-hospital mortality incidence was 12 (8.1%) in patients with AP (Table I).

Patients with AP were further classified into those with MAP (n=78), MSAP (n=47) and SAP (n=24) according to the 2016 Revised Atlanta Classification for Acute Pancreatitis (16). Comparative analysis revealed no difference in age, sex and etiology among patients with MAP, MSAP and SAP, whilst significant differences were identified in other characteristics (all $P < 0.001$; Table I). Furthermore, the incidence of in-hospital mortality was the highest in patients with SAP (29.2%), followed by patients with MSAP (10.6%) and was the lowest in patients with MAP (0.0%; $P < 0.001$; Table I).

CDC42 in HCs and patients with AP. The levels of CDC42 expression was significantly lower in patients with AP [0.495 (0.302-0.811)] compared with those in the HC group [0.985 (0.635-1.569); $P < 0.001$; Fig. 1A]. Furthermore, CDC42 expression was declined in patients with MSAP [0.429 (0.236-0.801)] compared with patients with MAP [0.614 (0.359-0.974)] ($P = 0.029$); moreover, CDC42 expression was decreased in patients with SAP [0.364 (0.210-0.582)] compared with patients with MAP [0.614 (0.359-0.974)] ($P = 0.004$); while no difference in CDC42 expression was

found between patients with MSAP and patients with SAP ($P = 0.836$; Fig. 1B). However, no changes in CDC42 expression could be observed among patients with AP of different etiologies ($P = 0.292$; Fig. S1).

Correlation between CDC42 and each of the disease assessment indicators tested in patients with AP. The Ranson's, APACHE II and SOFA scores were recorded in each patient with AP, which revealed that CDC42 was negatively correlated with the Ranson's ($r = -0.338$; $P < 0.001$), APACHE II ($r = -0.207$; $P = 0.011$) and SOFA ($r = -0.379$; $P < 0.001$) scores (Fig. 2A-C).

Correlation between CDC42 and each of the inflammatory indices in patients with AP. The levels of CRP, TNF- α and IL-6 were measured using ELISA to evaluate the degree of inflammation in patients with AP, which revealed that CDC42 was negatively correlated with CRP ($r = -0.295$; $P < 0.001$) and TNF- α ($r = -0.238$; $P = 0.004$; Fig. 3A and B). However, no correlation could be found between CDC42 expression and IL-6 levels ($r = -0.111$; $P = 0.177$; Fig. 3C).

Correlation between CDC42 expression and mortality risk in patients with AP. CDC42 expression was found to be significantly decreased in patients who succumbed to AP [median (IQR): 0.226 (0.124-0.372)] compared with that in survivors of AP [median (IQR), 0.531 (0.332-0.878); $P < 0.001$; Fig. 4A]. Furthermore, subgroup analysis was performed in patients with SAP, MSAP and MAP. CDC42 expression was significantly reduced in patients who succumbed to SAP [median (IQR), 0.216 (0.118-0.364)] compared with that in survivors of SAP [median (IQR), 0.400 (0.279-0.684); $P = 0.026$; Fig. 4B). However, no change in CDC42 expression was observed between patients who succumbed to MSAP and survivors of MSAP ($P = 0.062$; Fig. 4C). In addition, since there were no in-hospital deaths among patients with MAP, it was not possible to compare CDC42 expression between MAP survivors and those who succumbed to MAP (Fig. 4D). Multivariate logistic regression model analysis revealed that higher CDC42 expression was independently associated with reduced mortality in patients with AP [odds ratio, 0.002; 95% confidence interval (CI), 0.001-0.274; $P = 0.013$; Table S1].

Table I. Characteristics of HCs and patients with AP.

Items	HCs (n=50)	Patients with AP (n=149)	Statistic (t/ χ^2 /Z)	P-value	MAP (n=78)	MSAP (n=47)	SAP (n=24)	Statistic (F/ χ^2 /H)	P-value
Age (years), mean \pm SD	51.7 \pm 9.4	52.5 \pm 13.9	-0.487	0.627	53.5 \pm 12.5	50.2 \pm 15.1	53.8 \pm 15.6	0.946	0.391
Sex, N (%)			0.543	0.461				0.729	0.694
Female	20 (40.0)	51 (34.2)			26 (33.3)	15 (31.9)	10 (41.7)		
Male	30 (60.0)	98 (65.8)			52 (66.7)	32 (68.1)	14 (58.3)		
CRP (mg/l), median (IQR)	3.2 (1.2-4.6)	55.1 (31.7-91.3)	-10.546	<0.001	39.2 (20.9-57.3)	71.5 (55.2-120.8)	91.4 (50.0-188.4)	43.314	<0.001
Etiology, N (%)			-	-				11.349	0.078
BAP	-	73 (49.0)			32 (41.0)	25 (53.2)	16 (66.7)		
HTGAP	-	49 (32.9)			31 (39.7)	13 (27.7)	5 (20.8)		
AAP	-	10 (6.7)			3 (3.8)	6 (12.8)	1 (4.2)		
Others	-	17 (11.4)			12 (15.4)	3 (6.4)	2 (8.3)		
Ranson's score, mean \pm SD	-	2.0 (1.0-3.0)	-	-	1.0 (1.0-1.0)	3.0 (2.0-4.0)	3.5 (3.0-5.0)	112.684	<0.001
APACHE II score, mean \pm SD	-	7.0 (4.0-11.0)	-	-	5.0 (3.0-7.0)	11.0 (8.0-16.0)	11.5 (7.0-20.8)	69.920	<0.001
SOFA score, mean \pm SD	-	2.0 (1.0-4.0)	-	-	1.0 (1.0-1.0)	3.0 (2.0-4.0)	5.5 (4.0-7.0)	95.265	<0.001
TNF- α (pg/ml), median (IQR)	-	67.5 (39.4-108.2)	-	-	54.2 (28.1-79.5)	98.6 (60.1-141.7)	92.6 (59.8-197.5)	33.028	<0.001
IL-6 (pg/ml), median (IQR)	-	39.2 (22.5-62.9)	-	-	25.6 (14.8-43.1)	52.4 (34.9-76.0)	52.1 (28.7-112.9)	31.366	<0.001
Treatment, N (%)			-	-				33.556	<0.001
Conservative therapy	-	121 (81.2)			73 (93.6)	37 (78.7)	11 (45.8)		
Laparotomy	-	15 (10.1)			0 (0.0)	6 (12.8)	9 (37.5)		
Percutaneous drainage	-	13 (8.7)			5 (6.4)	4 (8.5)	4 (16.7)		
In-hospital mortality, No. (%)	-	12 (8.1)	-	-	0 (0.0)	5 (10.6)	7 (29.2)	21.703	<0.001

HCs, health controls; AP, acute pancreatitis; MAP, mild acute pancreatitis; MSAP, moderate-severe acute pancreatitis; SAP, severe acute pancreatitis; CRP, C-reactive protein; IQR, inter-quartile range; BAP, biliary acute pancreatitis; HTGAP, hypertriglyceridemia acute pancreatitis; AAP, alcohol-induced acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

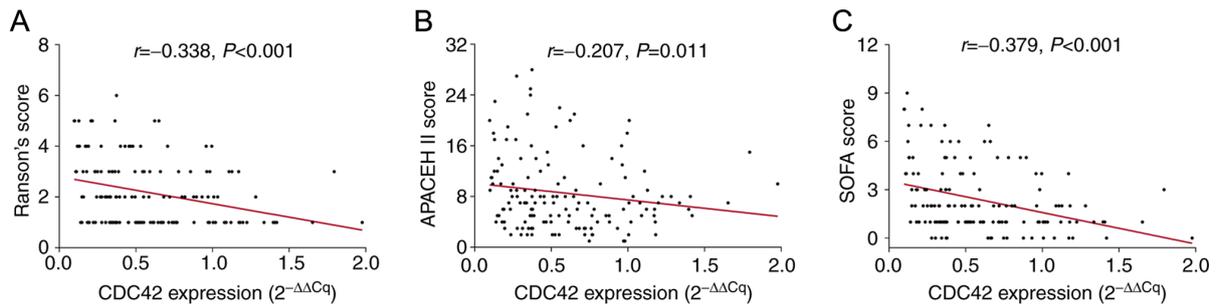


Figure 2. Correlation between CDC42 and disease severity scores of patients with AP. Correlation between CDC42 expression and (A) Ranson's, (B) APACHE II and (C) SOFA scores of patients with AP. CDC42, cell division cycle 42; AP, acute pancreatitis; APACHE II, acute Pathologic and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

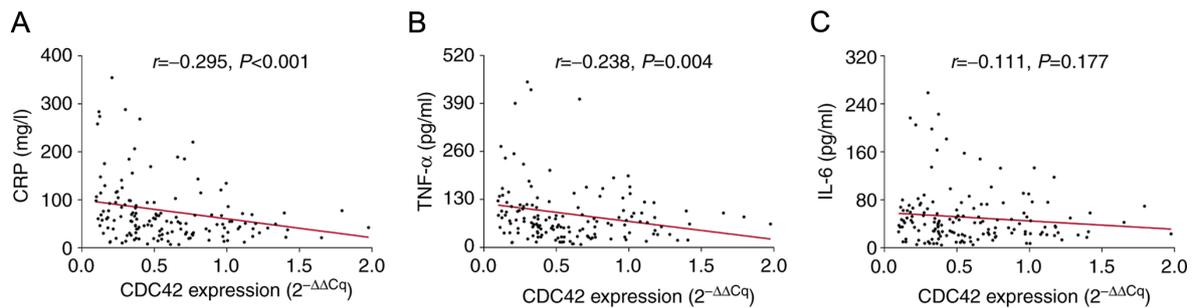


Figure 3. Correlation between CDC42 and the inflammation indices in patients with AP. Correlation between CDC42 expression and (A) CRP, (B) TNF- α and (C) IL-6 in patients with AP. CDC42, cell division cycle 42; AP, acute pancreatitis; CRP, C-reactive protein.

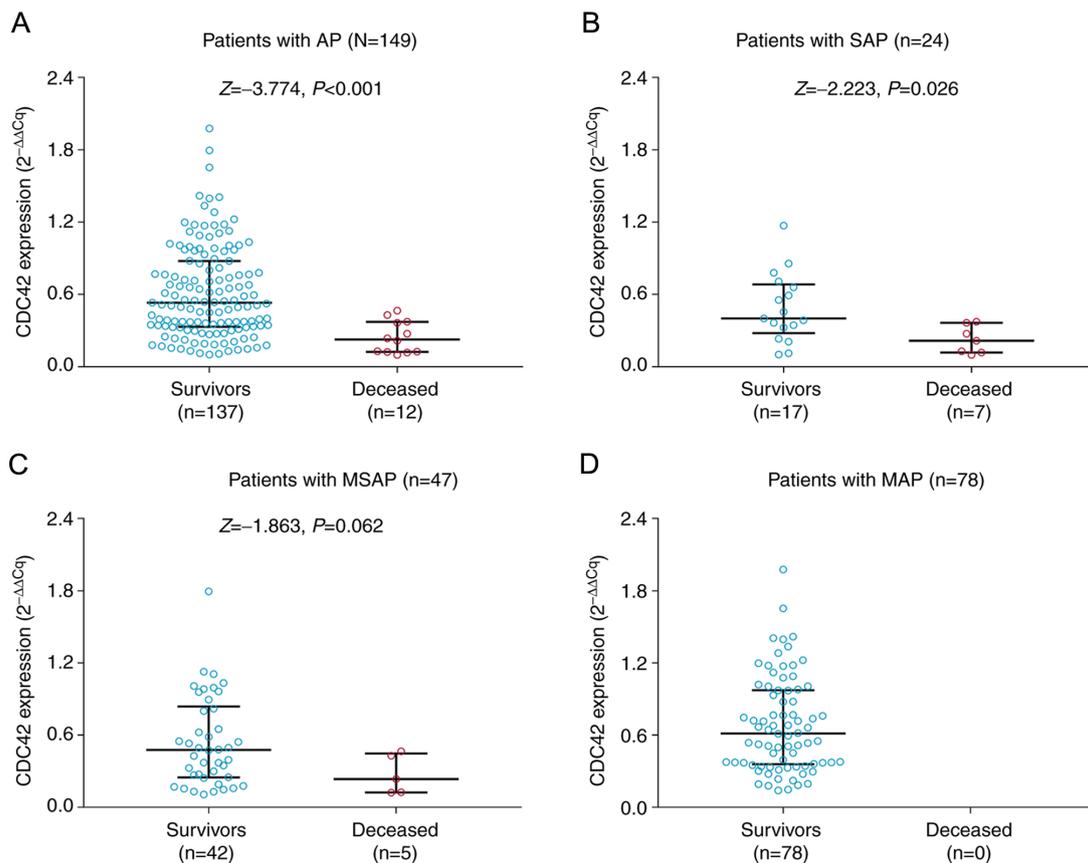


Figure 4. CDC42 expression in surviving and deceased patients with AP. Comparison of CDC42 expression in (A) surviving and deceased patients with AP, (B) in surviving patients with SAP and patients who succumbed to SAP, (C) in surviving patients with MSAP and patients who succumbed to MSAP and (D) in surviving patients with MAP and patients who succumbed to MAP. CDC42, cell division cycle 42; AP, acute pancreatitis; MAP, mild AP; MSAP, moderate-severe AP; SAP, severe AP.

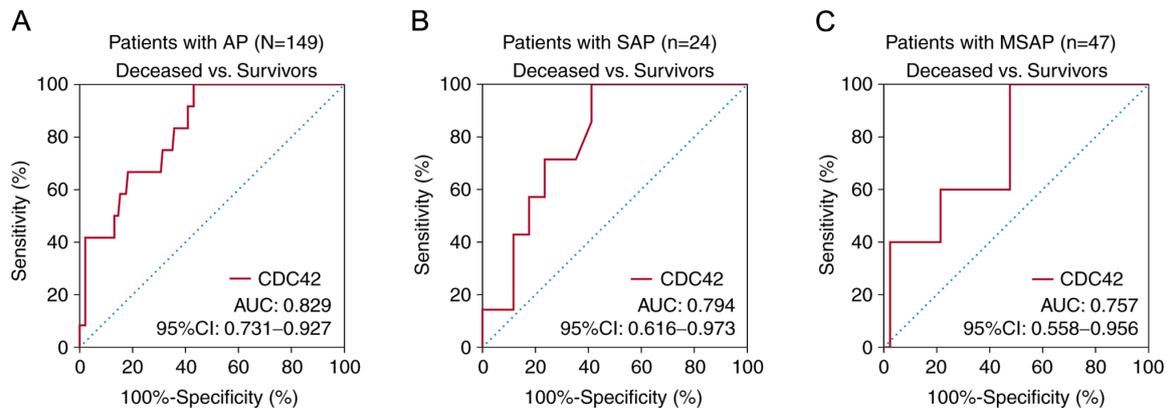


Figure 5. Ability of CDC42 to predict the severity and mortality of AP. The ability of CDC42 to predict mortality from (A) AP, (B) SAP and (C) MSAP was assessed using receiver operating characteristics. CDC42, cell division cycle 42; AP, acute pancreatitis; MSAP, moderate-severe AP; SAP, severe AP; AUC, area under the curve; CI, confidence interval.

Subsequent receiver operating characteristic analysis found that CDC42 had good potential in predicting mortality from AP, with area under the curve (AUC) of 0.829 and a 95% confidence interval (CI) of 0.731-0.927 (Fig. 5A). In addition, CDC42 had certain potential in predicting mortality from SAP and MSAP, with AUC (95% CI) of 0.794 (0.616-0.973) and 0.757 (0.558-0.956), respectively (Fig. 5B and C). In terms of the prognostic value of Ranson's score (Fig. S2A), APACHE II score (Fig. S2B) and SOFA score (Fig. S2C) in patients with AP, they also had potential in predicting mortality from AP, with AUC (95% CI) of 0.941 (0.898-0.985), 0.843 (0.722-0.965) and 0.931 (0.882-0.981), respectively.

Discussion

CDC42 has been found to be dysregulated in a number of inflammatory disorders. For instance, CDC42 expression is decreased in patients with Crohn's disease compared with that in the healthy population (21). In addition, several studies have reported that CDC42 can regulate a variety of cellular functions in the pancreas, including glucose-induced insulin secretion and actin cytoskeletal dynamics (15,22-24). However, information regarding the potential role of CDC42 in AP is limited. Therefore, the present study evaluated the expression of CDC42 in patients with AP and HCs, which revealed that CDC42 expression is decreased in patients with AP compared with that in HCs. A possible reason for this could be that CDC42 can inhibit systemic inflammation by promoting M2 macrophage polarization, in addition to suppressing the differentiation of Th17 cells whilst enhancing that of Th2 cells and Tregs (11-13). Since AP is characterized as a systemic inflammatory response syndrome (25), CDC42 expression was decreased in patients with AP compared with that in HCs.

The correlation between CDC42 and disease severity in AP has not been previously reported. To explore this issue, patients with AP were classified into the MAP, MSAP and SAP categories according to disease severity. It was subsequently discovered that CDC42 expression was the lowest in patients with SAP, followed by patients with MSAP and the highest in patients with MAP. A possible reason for this may be that

organ failure was associated with in MSAP and SAP (1,26). Furthermore, CDC42 could prevent multiorgan dysfunction, with reported effects including the alleviation of intestinal injury through regulating F-actin cytoskeleton in AP (27-29). Therefore, CDC42 expression was the lowest in patients with SAP. Furthermore, the Ranson's, APACHE II and SOFA scores of patients with AP were evaluated within 24 h from hospitalization, where it was found that CDC42 expression was negatively correlated with these scores. A potential explanation for this may be that CDC42 could inhibit inflammation and suppress multiple organ failure through several pathways such as protein kinase B signaling (27-29), which could have led to the decline in the AP assessment scores. In addition, CDC42 was found to be negatively correlated with inflammatory indices of patients with AP, which could be explained by the following: i) CDC42 could restrain the differentiation of Th1, potentially leading to a subsequent decline in TNF- α levels (11); and ii) CDC42 could suppress inflammation by promoting the polarization of M2 macrophages in AP (12,13).

Mortality rates of AP continue to increase, particularly in patients with SAP (1,30). Therefore, exploring biomarkers for predicting mortality risk is in urgent demand to improve the outcome of AP. Currently, the main methods of predicting mortality risk in AP include bedside index for severity in acute pancreatitis scoring system and neutrophil-to-lymphocyte ratio at 48 h, whose measurement parameters are relatively complicated (31,32). To identify an accurate and simple approach for predicting mortality risk, differences in CDC42 expression between patients who succumbed to AP, SAP and MSAP and those who survived were evaluated. It was found that lower levels of CDC42 expression predicted higher mortality risks in all patients with AP, SAP and MSAP. A potential explanation for this may be that CDC42 could reduce pancreatic injury by regulating intestinal epithelial cell cytoskeleton turnover, which could have enhanced survival in patients with AP (15). Therefore, data from the present study suggest that CDC42 expression was able to predict in-hospital mortality from AP. This finding suggested that CDC42 may serve as a potential predictor of mortality risk for AP.

The present study had several limitations: i) The included patients were from a single center, which may have led to the

limited generalizability of the present findings; ii) the role of CDC42 in the regulatory mechanism of AP should be explored further to investigate the therapeutic value of CDC42 in AP; iii) the clinical value of CDC42 in patients with chronic pancreatitis should be investigated further; iv) RT-qPCR was used for the quantitative analysis of CDC42 expression in the present study, whilst the protein expression of CDC42 should be evaluated in the future studies; v) the levels of TNF- α and IL-6 in the serum from HCs should be detected in a future study for comparison between patients with AP and HCs; vi) the number of MSAP and SAP patients was relatively small, which should be enlarged in the future; and vii) the correlation of CDC42 expression with disease assessment and inflammation in patients with AP with different severities should be explored in a further study.

In conclusion, lower CDC42 expression levels were found to be correlated with higher disease susceptibility, disease severity, inflammation and mortality risk in patients with AP, suggesting that monitoring CDC42 expression can be used for the management of AP.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JY and XL conceived and designed the study. XY contributed to data acquisition of patients. HW contributed to the PCR and ELISA. LD and NF performed the statistical analysis and figures plotted. JY performed statistical analysis and critically revised the manuscript. JY and XL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by Institutional Review Board of the Affiliated Nanhua Hospital, University of South China (approval no. 2017-136; Hengyang, China). The written informed consent was obtained from all subjects or their guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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