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Predictive value of long non-coding RNA intersectin 1-2 for occurrence and in-hospital mortality of severe acute pancreatitis

Jun Li[1] | Xiaofen Bu[2] | Xuanlan Chen[1] | Peng Xiong[1] | Zhen Chen[3,4] | Li Yu[1]

[1]Department of Intensive Care Unit, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2]Department of General Practice, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[3]Department of Emergency, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[4]Department of Evidence-based medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Correspondence
Li Yu, Department of Intensive Care Unit, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, NO.26, Shengli Street, Wuhan 430014, China.
Email: luyunzhongj2t@163.com

Zhen Chen, Department of Emergency and Department of Evidence-based medicine, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, NO.26, Shengli Street, Wuhan 430014, China.
Email: chen90501765@163.com

Abstract

Background: This study aimed to investigate the predictive value of long non-coding RNA intersectin 1-2 (lnc-ITSN1-2) for severe acute pancreatitis (SAP) risk, and its correlation with disease severity and in-hospital mortality in SAP patients.

Methods: Plasma samples from 60 SAP, 60 moderate-severe acute pancreatitis (MSAP) and 60 mild acute pancreatitis (MAP) patients were collected within 24 hours, and plasma samples from 60 age and gender-matched healthy controls (HCs) were collected when enrollment. Lnc-ITSN1-2 was detected by reverse transcription-quantitative polymerase chain reaction. In AP patients, disease severity was evaluated and in-hospital deaths were recorded.

Results: Lnc-ITSN1-2 was increased in SAP patients compared with MSAP, MAP patients, and HCs, and it is well-discriminated SAP patients from MSAP patients (area under curve (AUC): 0.699, 95% confidence interval (CI): 0.605-0.792), MAP patients (AUC: 0.862, 95% CI: 0.798-0.926), and HCs (AUC: 0.958, 95% CI: 0.925-0.990). For disease severity, lnc-ITSN1-2 was positively correlated with Ranson's score, acute pathologic and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, and C-reactive protein (CRP) in SAP patients, MSAP patients, and MAP patients; meanwhile, the correlation coefficients were highest in SAP patients. Furthermore, lnc-ITSN1-2 displayed a good predictive value for increased in-hospital mortality in SAP (AUC: 0.803, 95% CI: 0.673-0.933) and MSAP (AUC: 0.854, 95% CI: 0.752-0.956) patients, which was similar with several common prognostic factors (including Ranson's score, APACHE II score, SOFA score, and CRP).

Conclusion: Lnc-ITSN1-2 might be a potential biomarker for discrimination of SAP to improve the prognosis of SAP patients.

KEYWORDS

disease severity, in-hospital mortality, long non-coding RNA intersectin 1-2, predictive factor, severe acute pancreatitis

Li and Bu contributed equally to this work.

1 | INTRODUCTION

Acute pancreatitis (AP), defined as inflammation of the pancreas where self-digestion occurs due to incorrect activation of trypsin, is one of the most frequent gastrointestinal causes for hospital admission, whose incidence rate ranges from 130 to 450 per million population.[1-3] According to the occurrence of organ failure and complications, AP is further classified into severe acute pancreatitis (SAP), moderate-severe acute pancreatitis (MSAP), and mild acute pancreatitis (MAP).[4] For AP patients, the majority of them (approximately 80%) are diagnosed as MAP and MSAP, while nearly 20% of them are diagnosed as SAP that is characterized by persisting single or multiple organ failure for more than 48 hours and systemic inflammation.[5-7] Although several organizations have released approaches for the management of AP and many AP patients (particularly MSAP and MAP patients) recover within a few days, the prognosis of SAP patients is not satisfying with the mortality rate of 15%-30%.[8,9] Therefore, it is vital to screen for novel potential biomarkers to predict the occurrence and mortality of SAP, thereby further achieving improvement of prevention, management, and prognosis for SAP patients.

Long non-coding RNAs (lncRNAs) are a group of non-protein coding RNAs with more than 200 nucleotides, and some of them show a close relationship to inflammation.[10-12] Among these lncRNAs, long non-coding RNA intersectin 1-2 (lnc-ITSN1-2) (NONCODE gene ID NONHSAG032726.2), located on chromosome 21 with a length of 451 bp, is reported to be correlated with increased disease risk, enhanced inflammation, and elevated disease severity in several inflammatory-related diseases (such as sepsis, rheumatoid arthritis (RA), and coronary artery disease (CAD)).[13-15]

To the best of our knowledge, the role of lnc-ITSN1-2 in SAP remained to be clarified. This study was aimed to explore lnc-ITSN1-2 in SAP patients and its predictive value for SAP risk, as well as investigate the correlation of lnc-ITSN1-2 with disease severity and in-hospital mortality in SAP patients.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 60 SAP patients, 60 MSAP patients, and 60 MAP patients were consecutively enrolled between January 2016 and June 2019 from the Central Hospital of Wuhan. All patients were diagnosed as AP based on a combination of symptoms, physical examination, and focused laboratory values according to the 2012 revision of the Atlanta Classification of acute pancreatitis.[4] The inclusion criteria of SAP patients were as follows: (a) AP patients with persistent single or multiple organ failure (>48 hours); (b) age ≥ 18 years. The inclusion criteria of MSAP patients were as follows: (a) AP patient with transient organ failure (organ failure that resolves within 48 hours) or local or systemic complications in the absence of persistent organ failure; (b) age ≥ 18 years. The inclusion criteria of MAP patients were as follows: (a) AP patients had no organ failure and no local or systemic complications; (b) age ≥ 18 years. The exclusion criteria of SAP, MSAP, and MAP patients were as follows: (s) history of or complicated with hematologic malignancies or solid tumors; (b) complicated with severe infection (eg, human immunodeficiency virus or human cytomegalovirus) or autoimmune disease (eg, rheumatoid arthritis or systemic lupus erythematosus); (c) complicated with other gastrointestinal inflammatory diseases (eg, Crohn's disease); (d) treated with antibiotics within one month before admission; and (e) pregnant or lactating woman. In addition, from May 2019 to July 2019, 60 healthy subjects whose age and gender-matched with AP patients were enrolled as healthy controls (HCs) in this study. All HCs had no history of pancreatic or bile duct diseases or obvious abnormalities in biochemical index. This study was approved by the Ethics Committee of the Central Hospital of Wuhan and was conducted according to the Declaration of Helsinki. All participants or their guardians signed the informed consents before enrollment.

2.2 | Data collection

The clinical characteristics including age, gender, and C-reactive protein (CRP) level were recorded for all participants. And the etiology of AP such as biliary acute pancreatitis (BAP), alcohol-induced acute pancreatitis (AAP), and hypertriglyceridemia-induced acute pancreatitis (HTGAP) was assessed with reference to abdominal ultrasound or biochemical indexes. The assessment of severity and organ dysfunction for AP patients was conducted within 48 hours after admission, which was evaluated using Ranson's score, acute pathologic and chronic health evaluation II (APACHE II) score, and sequential organ failure assessment (SOFA) score.

2.3 | Sample collection

For AP patients, the peripheral blood samples were collected within 24 hours after admission, and the peripheral blood samples of HCs were collected after enrollment. Then, the peripheral blood samples were immediately centrifuged at 1500 *g* for 20 minutes (4℃) to collect plasma. After collection, the plasma samples were stored at −80°C until further measurement. The relative expression of lnc-ITSN1-2 in plasma was detected by reverse transcription-quantitative polymerase chain reaction (RT-qPCR).

2.4 | RT-qPCR

Total RNA extraction was conducted using TRIzol™ Reagent (Invitrogen). Reverse transcription was performed using an iScript™ cDNA Synthesis Kit (Bio-Rad) according to the manufacturer's instructions. qPCR was conducted using THUNDERBIRD® SYBR® qPCR Mix (Toyobo) following the manufacturer's guidance. The relative expression of lncRNA was calculated by the $2^{-\Delta\Delta Ct}$

formula. GAPDH was set as the internal reference. Primers (5′-3′): lnc-ITSN1-2 forward primer: TTAGTCTGTTCAGGCTGCCATAA, reverse primer: GCTTGCTCACTTGCTATCTCTTG; GAPDH forward primer: GAGTCCACTGGCGTCTTCAC, reverse primer: ATCTTGAGGCTGTTGTCATACTTCT.

2.5 | Treatment and follow-up

Acute pancreatitis patients' treatments such as conservative therapy, percutaneous drainage, or laparotomy were conducted according to clinical status and American College of Gastroenterology guideline: management of acute pancreatitis.[16] The routine follow-up was performed for patients during hospital treatment, which was lasted until they were died in the hospital or discharged from hospital. In-hospital mortality was calculated based on the number of deaths during follow-up. And patients were further divided into in-hospital deaths and survivors.

2.6 | Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical variables were displayed as count and percentage. Comparison among groups was determined by one-way analysis of variance (One-way ANOVA), chi-squared test, or Kruskal-Wallis H test, and multiple comparisons were determined by Dunn's test. Comparison between two groups was determined by the Wilcoxon rank-sum test. Correlation between two continuous variables was analyzed by Spearman's rank correlation test. The performance of variables in discriminating SAP from MSAP, MAP, and HCs or in predicting in-hospital mortality was assessed by receiver operating characteristic (ROC) curve and the area under the curve (AUC) with 95% confidence interval (CI). Statistical analysis was performed using SPSS 22.0 (IBM), and figure was plotted using GraphPad Prism 7.01 (GraphPad software). *P* value < .05 was considered significant.

3 | RESULTS

3.1 | Clinical characteristics of AP patients and HCs

For demographic characteristics, the mean age of SAP patients, MSAP patients, MAP patients, and HCs were 59.8 ± 13.9 years, 56.3 ± 14.1 years, 56.0 ± 12.6 years, and 58.6 ± 13.5 years, respectively. No difference was found in age (*P* = .345) and gender (*P* = .631) among SAP patients, MSAP patients, MAP patients, and HCs. For clinical characteristics, Ranson's score, APACHE II score, SOFA score, and CRP level were highest in SAP patients, followed by MSAP patients, and then MAP patients (All *P* < .001), whereas no difference was found in etiology among SAP patients, MSAP patients, and MAP patients (*P* = .470). As to treatment, the proportion of patients receiving conservative treatment, percutaneous drainage, and laparotomy was different among SAP patients, MSAP patient,s and MAP patients (*P* < .001). The detailed clinical characteristics of AP patients and HCs were shown in Table 1.

3.2 | Lnc-ITSN1-2 expression and its predictive value for SAP risk

Lnc-ITSN1-2 was increased in SAP patients compared with MSAP patients (*P* = .009), MAP patients (*P* < .001), and HCs (*P* < .001) (Figure 1A). Meanwhile, ROC curves revealed that lnc-ITSN1-2 well-distinguished SAP patients from MSAP patients with AUC of 0.699 (95% CI: 0.605-0.792) (Figure 1B), from MAP patients with AUC of 0.862 (95% CI: 0.798-0.926) (Figure 1C), and from HCs patients with AUC of 0.958 (95% CI: 0.925-0.990) (Figure 1D).

3.3 | Correlation of lnc-ITSN1-2 with disease severity in AP patients

In SAP patients, lnc-ITSN1-2 was positively correlated with Ranson's score (r = 0.519, *P* < .001), APACHE II score (r = 0.370, *P* = .004), SOFA score (r = 0.492, *P* < .001), and CRP (r = 0.469, *P* < .001). In MSAP patients, lnc-ITSN1-2 was also positively correlated with Ranson's score (r = 0.515, *P* < .001), APACHE II score (r = 0. 412, *P* = .001), SOFA score (r = 0.302, *P* = .019), and CRP (r = 0.403, *P* = .001). In MAP patients, lnc-ITSN1-2 was positively correlated with Ranson's score (r = 0.255, *P* = .049), APACHE II score (r = 0.290, *P* = .024), SOFA score (r = 0.278, *P* = .031), and CRP (r = 0.352, *P* = .006) as well (Table 2). Regarding from the correlation coefficients, it was revealed that the correlation between lnc-ITSN1-2 and disease severity was stronger in SAP patients compared to that in MSAP patients and MAP patients.

3.4 | Predictive value of lnc-ITSN1-2 for in-hospital mortality in AP patients

There were 14 (23.3%) in-hospital deaths and 46 (76.7%) survivors in SAP patients, 3 (5.0%) in-hospital deaths, and 57 (95.0%) survivors in MSAP patients, while 0 (0.0%) in-hospital deaths and 60 (100.0%) survivors in MAP patients (Figure 2A). In SAP patients, lnc-ITSN1-2 was increased in in-hospital deaths compared with survivors (*P* < .001) (Figure 2B), and it showed a good predictive value for increased in-hospital mortality (AUC: 0.803, 95% CI: 0.673-0.933) (Figure 2C). In MSAP patients, lnc-ITSN1-2 was increased in in-hospital deaths compared with survivors (*P* = .037) (Figure 2D), and it presented good predictive value for in-hospital mortality (AUC: 0.854, 95% CI: 0.752-0.956) as well (Figure 2E). However, no in-hospital death occurred in MAP patients; therefore, it was unable to evaluate the predictive value of lnc-ITSN1-2 for in-hospital mortality in these patients. Notably, data revealed that the predictive value of

TABLE 1 Clinical characteristics among SAP patients, MSAP patients, MAP patients, and HCs

Items	SAP patients (N = 60)	MSAP patients (N = 60)	MAP patients (N = 60)	HCs (N = 60)	*P* value
Age (years), mean ± SD	59.8 ± 13.9	56.3 ± 14.1	56.0 ± 12.6	58.6 ± 13.5	.345
Gender, No. (%)					
Female	24 (40.0)	20 (33.3)	24 (40.0)	27 (45.0)	.631
Male	36 (60.0)	40 (66.7)	36 (60.0)	33 (55.0)	
Etiology, No. (%)					
BAP	33 (55.0)	31 (51.7)	23 (38.4)	-	.470
AAP	4 (6.7)	7 (11.7)	5 (8.3)	-	
HTGAP	17 (28.3)	18 (30.0)	24 (40.0)	-	
Others	6 (10.0)	4 (6.6)	8 (13.3)	-	
Ranson's score, mean ± SD	3.7 ± 1.0	1.9 ± 0.7	1.2 ± 0.5	-	<.001
APACHE II score, mean ± SD	14.5 ± 6.8	6.6 ± 3.0	4.3 ± 2.0	-	<.001
SOFA score, mean ± SD	6.7 ± 2.0	4.4 ± 1.5	2.0 ± 0.6	-	<.001
CRP (mg/L), median (IQR)	148.8 (101.3-190.3)	95.6 (68.9-147.0)	43.2 (26.6-59.5)	3.5 (1.3-4.6)	<.001
Treatment, No. (%)					
Conservative	35 (58.3)	48 (80.0)	57 (95.0)	-	<.001
Percutaneous drainage	6 (10.0)	6 (10.0)	3 (5.0)	-	
Laparotomy	19 (31.7)	6 (10.0)	0 (0.0)	-	

Note: Comparison was determined by one-way analysis of variance (One-way ANOVA), chi-squared test, or Kruskal-Wallis H test.

Abbreviations: AAP, alcohol-induced acute pancreatitis; AP, acute pancreatitis; APACHE II, acute pathologic and chronic health evaluation II; BAP, biliary acute pancreatitis; CRP, C-reactive protein; HCs, healthy controls; HTGAP, hypertriglyceridemia-induced acute pancreatitis; IQR, interquartile range; MAP, mild acute pancreatitis; MSAP, moderate-severe acute pancreatitis; SAP, severe acute pancreatitis; SD, standard deviation; SOFA, sequential organ failure assessment.

lnc-ITSN1-2 for in-hospital mortality was similar to that of common prognosis factors (including Ranson's score, APACHE II score, SOFA score, and CRP) for in-hospital mortality. In detail, in MSAP patients, Ranson's score (AUC: 0.836; 95% CI: 0.708-0.965), APACHE II score (AUC: 0.800; 95% CI: 0.672-0.928), SOFA score (AUC: 0.783; 95% CI: 0.653-0.914), and CRP (AUC: 0.731; 95% CI: 0.576-0.887) presented with good predictive values for increased in-hospital mortality (Figure 3A); meanwhile, in MSAP patients, Ranson's score (AUC: 0.930; 95% CI: 0.856-1.000), APACHE II score (AUC: 0.947; 95% CI: 0.885-1.000), SOFA score (AUC: 0.959; 95% CI: 0.880-1.000), and CRP (AUC: 0.743; 95% CI: 0.594-0.891) well-predicted enhanced in-hospital mortality (Figure 3B).

4 | DISCUSSION

In this study, we found the following: (a) Lnc-ITSN1-2 was highly expressed in SAP patients compared with MSAP, MAP patients, and HCs, and it showed good predictive value for increased SAP risk. (b) Lnc-ITSN1-2 correlated positively with disease severity in SAP, MSAP, and MAP patients, and the correlation coefficient was highest in SAP patients. (c) Lnc-ITSN1-2 displayed a good predictive value for in-hospital mortality in SAP and MSAP patients, which was similar to that of several common predictive factors (including CRP level, Ranson's score, APACHE II score, and SOFA score).

Recently, lncRNAs receive great attention for their biological function and regulation in physiopathological processes.[11] In AP, studies have disclosed that several lncRNAs serve as regulator of disease progression.[17-19] For example, lncRNA forkhead box F1 adjacent non-coding developmental regulatory RNA (lncRNA Fendrr) promotes apoptosis in AP cell model by directly binding to annexin A2.[17] Moreover, lncRNA Beta-1,3-Galactosyltransferase 5 antisense 1 (B3GALT5-AS1) expression is decreased in AP patients, and in vitro study reveals that it alleviates apoptosis in AP cell model via the regulation of microRNA-203/nuclear factor, interleukin 3 regulated axis and via the inhibition of nuclear factor-kappa B pathway.[18] In a clinical study, it is found that lncRNA H19 expression is elevated in AP patients compared to HCs, and in SAP patients compared to MAP

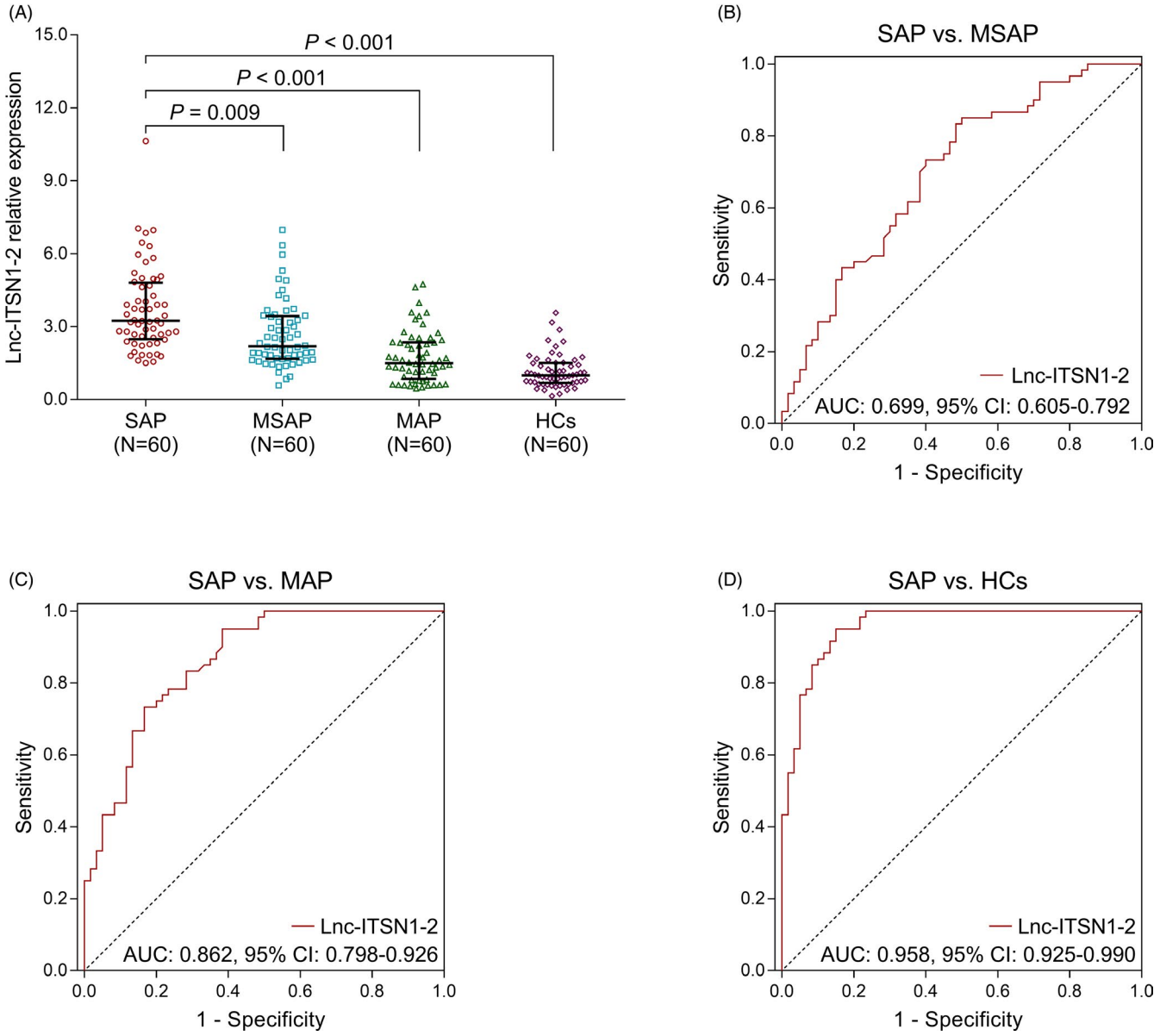

FIGURE 1 Expression of lnc-ITSN1-2 and its predictive value for SAP risk. A, Difference of lnc-ITSN1-2 in SAP patients compared to MSAP patients, MAP patients, and HCs. B, Discrimination of SAP patients from MSAP patients by lnc-ITSN1-2. C, Discrimination of SAP patients from MAP patients by lnc-ITSN1-2. D, Discrimination of SAP patients from HCs by lnc-ITSN1-2. Comparisons of lnc-ITSN1-2 between groups were conducted by Dunn's multiple comparisons test. Predictive value of lnc-ITSN1-2 for SAP risk was evaluated by conducting ROC curve. *P* value < .05 was considered significant. Lnc-ITSN1-2, long non-coding RNA intersectin 1-2; SAP, severe acute pancreatitis; MSAP, moderate-severe acute pancreatitis; MAP, mild acute pancreatitis; HCs, healthy controls; ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval

patients.[19] Collectively, these studies suggest that several lncRNAs play pivotal roles in AP and might contribute to the prevention and treatment of AP.

For lnc-ITSN1-2, limited information about its role in inflammation-related disease is found, just a few studies have been performed, which reveal that lnc-ITSN1-2 correlates with increased risk of RA and sepsis; however, no study has been done to explore the function of lnc-ITSN1-2 in predicting SAP until now.[13,14] In this study, we discovered an elevated expression of lnc-ITSN1-2 in SAP patients compared with MSAP, MAP patients, and HCs; meanwhile, lnc-ITSN1-2 presented with potential in predicting increased risk of SAP. These results could be explained by that lnc-ITSN1-2 was closely related to inflammation activity (mentioned below) in AP patients, and the overexpression of lnc-ITSN1-2 might increase the secretion of pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6, IL-8, and IL-17), thereby elevated systematic inflammation, promoted the likelihood of multiple organ failure, and increased SAP risk in AP patients. Therefore, lnc-ITSN1-2 was increased in SAP patients and it presented good predictive value for increased SAP risk.

As to the correlation of lnc-ITSN1-2 with disease severity, one previous study displays that lnc-ITSN1-2 is positively correlated

TABLE 2 Correlation of lnc-ITSN1-2 with disease severity in SAP patients, MSAP patients, and MAP patients

	Lnc-ITSN1-2					
	SAP patients (N = 60)		MSAP patients (N = 60)		MAP patients (N = 60)	
Items	*P* value	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)
Ranson's score	<.001	.519	<.001	.515	.049	.255
APACHE II score	.004	.370	.001	.412	.024	.290
SOFA score	<.001	.492	.019	.302	.031	.278
CRP	<.001	.469	.001	.403	.006	.352

Note: Correlation was determined by Spearman's rank correlation test.

Abbreviations: APACHE II, acute pathologic and chronic health evaluation II; CRP, C-reactive protein; MAP, mild acute pancreatitis; MSAP, moderate-severe acute pancreatitis; SAP, severe acute pancreatitis; SOFA, sequential organ failure assessment.

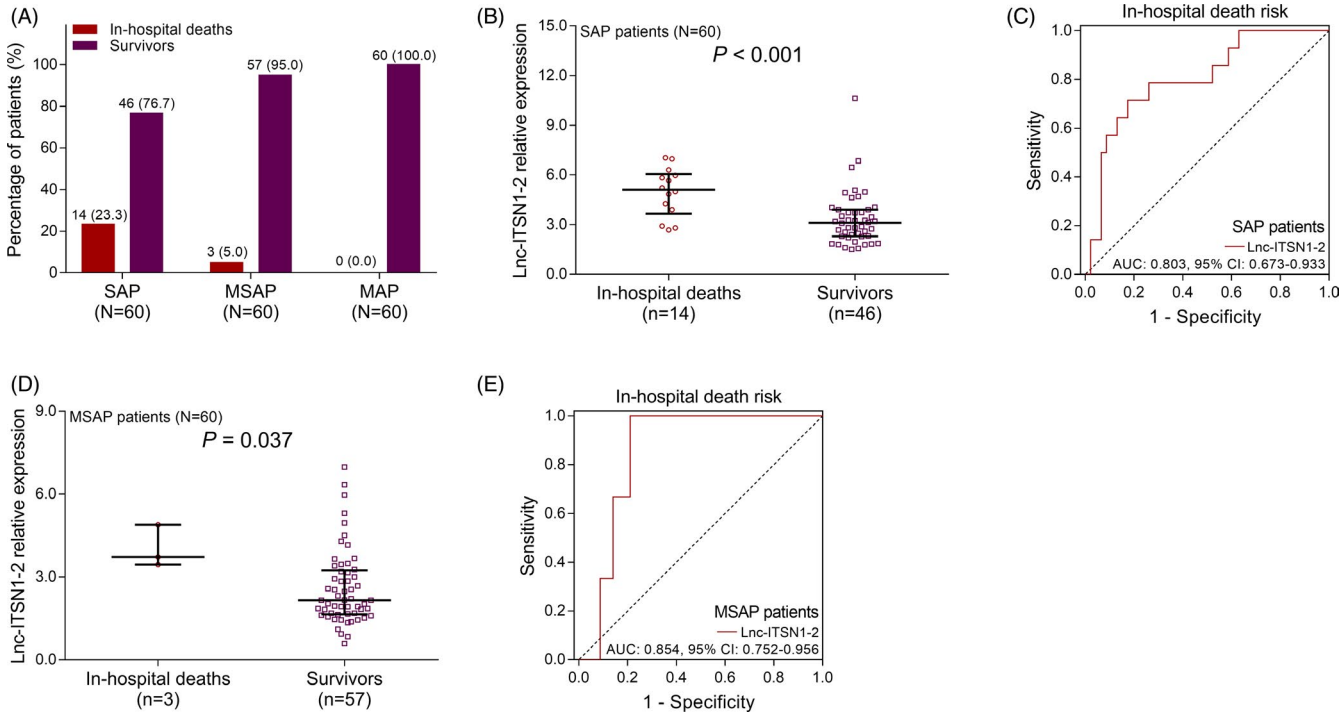

FIGURE 2 Lnc-ITSN1-2 in in-hospital deaths and its predictive value for in-hospital mortality in AP patients. A, Percentage of in-hospital deaths and survivors in SAP, MSAP, and MAP patients. B, Comparison of lnc-ITSN1-2 between in-hospital deaths and survivors in SAP patients. C, Predictive value of lnc-ITSN1-2 for in-hospital mortality in SAP patients. D, Comparison of lnc-ITSN1-2 between in-hospital deaths and survivors in MSAP patients. E, Predictive value of lnc-ITSN1-2 for in-hospital mortality in MSAP patients. Comparison of lnc-ITSN1-2 between groups was conducted by the Wilcoxon rank-sum test. Predictive value of lnc-ITSN1-2 for in-hospital risk was evaluated by conducting ROC curve. *P* value < .05 was considered significant. Lnc-ITSN1-2, long non-coding RNA intersectin 1-2; SAP, severe acute pancreatitis; MSAP, moderate-severe acute pancreatitis; MAP, mild acute pancreatitis; ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval

with disease activity score in 28 joints, erythrocyte sedimentation rate and CRP in RA patients,[14] and another study discloses that lnc-ITSN1-2 is positively associated with APACHE II score, CRP, and pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6, IL-8, and IL-17) in sepsis patients,[13] indicating a close relationship between lnc-ITSN1-2 and increased inflammation activity. However, a little was known about the role of lnc-ITSN1-2 in AP patients. In this study, we found that increased lnc-ITSN1-2 was correlated with enhanced Ranson's score, APACHE II score, SOFA score, and CRP in SAP, MSAP, and MAP patients; moreover, the correlation coefficients were highest in SAP patients. Possible explanations for these data might be that (a) Lnc-ITSN1-2 may enhance inflammation in AP patients (mentioned above), and CPR is one of the most common inflammatory indicators; therefore, lnc-ITSN1-2 was positively correlated with CPR in AP patients. (b) Lnc-ITSN1-2 might increase systematic inflammation, subsequently induced multiple organ failures. Thus, it was positively associated with disease severity assessments (Ranson's score, APACHE II score, and SOFA score) in AP patients.

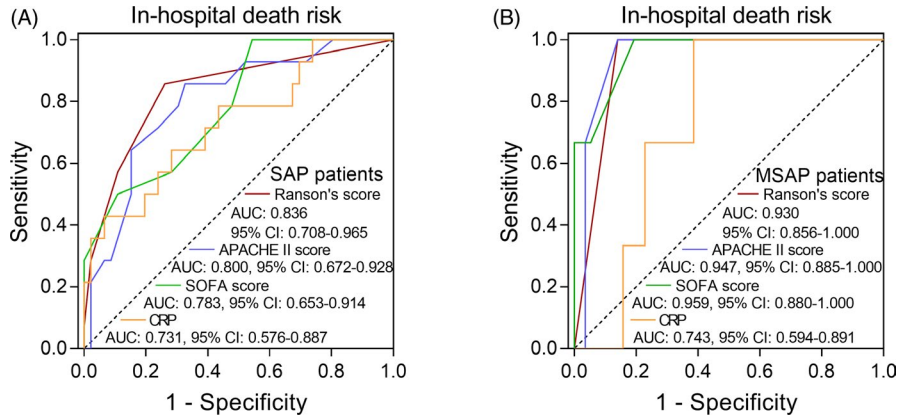

FIGURE 3 Predictive value of Ranson's score, APACHE II score, SOFA score, and CRP for in-hospital mortality in AP patients. A, Predictive value of Ranson's score, APACHE II score, SOFA score, and CRP for in-hospital mortality in SAP patients. B, Predictive value of Ranson's score, APACHE II score, SOFA score, and CRP for in-hospital mortality in MSAP patients. Predictive value of Ranson's score, APACHE II score, SOFA score, and CRP for in-hospital mortality in SAP and MSAP patients was evaluated by conducting ROC curve. SAP, severe acute pancreatitis; MSAP, moderate-severe acute pancreatitis; ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval; APACHE II, acute pathologic and chronic health evaluation II; SOFA, sequential organ failure assessment; CPR, C-reactive protein

(c) The inflammation and organ failure were more severe in SAP patients, thereby exacerbated the correlation of lnc-ITSN1-2 with CRP and disease severity assessments, and the specific mechanism needed further investigation.

For the prognosis value of lnc-ITSN1-2, several researches reveal that lnc-ITSN1-2 is elevated in non-survivors (patients died within 30 days of follow-up) compared with survivors (patients survived within 30 days of follow-up), and it distinguishes survivors from non-survivors in sepsis patients.[13] In line with the previous study, we disclosed that lnc-ITSN1-2 was increased in in-hospital deaths compared to survivors among SAP and MSAP patients, and it predicted the enhanced risk of in-hospital death. More importantly, the predictive value of lnc-ITSN1-2 for in-hospital mortality was similar with several common predictive factors (such as Ranson's score, APACHE II score, SOFA score, and CRP) in SAP and MSAP patients, indicating that lnc-ITSN1-2 might be a potential predictive factor for in-hospital mortality in AP patients. These data could be explained by that lnc-ITSN1-2 might enhance systematic inflammation and multiple organ failures to increase disease severity (above-mentioned), thereby elevated in-hospital mortality in AP patients.

Although we found some interesting results, there were several limitations to this study. (a) In the present study, we only enrolled 60 cases in each group, which might cause poor statistical power. Further study with a larger sample size should be done to verify the results. (b) There was no in-hospital death in MAP patients; therefore, the predictive value of lnc-ITSN1-2 for in-hospital mortality in MAP patients was unclear. (c) The underlying mechanisms of the interaction of lnc-ITSN1-2 with inflammation in SAP were not explored, which could be further investigated. (d) This study was single-centered, which might cause selection bias, and a multi-centered study could be conducted in the future. (e) The dynamic change of lnc-ITSN1-2 in SAP, MSAP, and MAP patients at different timepoints during treatment was not investigated in this study, which could be conducted in the future.

To conclude, lnc-ITSN1-2 is overexpressed in SAP patients, and it exhibits a good predictive value for increased SAP risk; meanwhile, it correlated with enhanced disease severity and predicted higher in-hospital mortality in SAP patients. These findings suggested that lnc-ITSN1-2 might be a potential biomarker for discrimination of SAP to improve the prognosis of SAP patients.

ORCID

Li Yu https://orcid.org/0000-0003-1209-4254

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