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

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Abstract

Background: This study aimed to investigate the predictive value of long non-coding RNA intersectin 1-2 (Inc-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. Inc-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: Inc-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, Inc-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, Inc-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: Inc-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

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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 IncRNAs, long non-coding RNA intersectin 1-2 (Inc-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 Inc-ITSN1-2 in SAP remained to be clarified. This study was aimed to explore Inc-ITSN1-2 in SAP patients and its predictive value for SAP risk, as well as investigate the correlation of Inc-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.5 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: (a) 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°C) to collect plasma. After collection, the plasma samples were stored at −80°C until further measurement. The relative expression of Inc-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−ΔΔCt.
formula. GAPDH was set as the internal reference. Primers (5′-3′): Inc-ITSN1-2 forward primer: TTAGTCTGTTCCAGGCTGCCATAA, reverse primer: GCTTGCTGCTTACATCTCTTG; GAPDH forward primer: GAGTCCACTGCGCTTTCAC, reverse primer: ATCTTGAGGGCTGTGTCACTTCT.

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. 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 patients, 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
Inc-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: 0.939; 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, IncRNAs receive great attention for their biological function and regulation in physiopathological processes. In AP, studies have disclosed that several IncRNAs serve as regulator of disease progression. For example, IncRNA forhead box F1 adjacent non-coding developmental regulatory RNA (IncRNA Fendrr) promotes apoptosis in AP cell model by directly binding to annexin A2. Moreover, IncRNA 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. In a clinical study, it is found that IncRNA H19 expression is elevated in AP patients compared to HCs, and in SAP patients compared to MAP patients.

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

For Inc-ITSN1-2, limited information about its role in inflammation-related disease is found, just a few studies have been performed, which reveal that Inc-ITSN1-2 correlates with increased risk of RA and sepsis; however, no study has been done to explore the function of Inc-ITSN1-2 in predicting SAP until now. In this study, we discovered an elevated expression of Inc-ITSN1-2 in SAP patients compared with MSAP, MAP patients, and HCs; meanwhile, Inc-ITSN1-2 presented with potential in predicting increased risk of SAP. These results could be explained by that Inc-ITSN1-2 was closely related to inflammation activity (mentioned below) in AP patients, and the overexpression of Inc-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, Inc-ITSN1-2 was increased in SAP patients and it presented good predictive value for increased SAP risk.

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

![Figure 1](image1.png)

**Figure 1** Expression of Inc-ITSN1-2 and its predictive value for SAP risk. A, Difference of Inc-ITSN1-2 in SAP patients compared to MSAP patients, MAP patients, and HCs. B, Discrimination of SAP patients from MSAP patients by Inc-ITSN1-2. C, Discrimination of SAP patients from MAP patients by Inc-ITSN1-2. D, Discrimination of SAP patients from HCs by Inc-ITSN1-2. Comparisons of Inc-ITSN1-2 between groups were conducted by Dunn’s multiple comparisons test. Predictive value of Inc-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.
with disease activity score in 28 joints, erythrocyte sedimentation rate and CRP in RA patients, 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, 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 CRP is one of the most common inflammatory indicators; therefore, lnc-ITSN1-2 was positively correlated with CRP in AP patients. (b) lnc-ITSN1-2 might increase systemic 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.

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

| Items            | SAP patients (N = 60) | P value | Correlation coefficient (r) | MSAP patients (N = 60) | P value | Correlation coefficient (r) | MAP patients (N = 60) | 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.
(c) The inflammation and organ failure were more severe in SAP patients, thereby exacerbated the correlation of Inc-ITSN1-2 with CRP and disease severity assessments, and the specific mechanism needed further investigation.

For the prognosis value of Inc-ITSN1-2, several researches reveal that Inc-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. In line with the previous study, we disclosed that Inc-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 Inc-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 Inc-ITSN1-2 might be a potential predictive factor for in-hospital mortality in AP patients. These data could be explained by that Inc-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 Inc-ITSN1-2 for in-hospital mortality in MAP patients was unclear. (c) The underlying mechanisms of the interaction of Inc-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 Inc-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, Inc-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 Inc-ITSN1-2 might be a potential biomarker for discrimination of SAP to improve the prognosis of SAP patients.

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REFERENCES
1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144(6):1252-1261.
2. Satoh K, Shimosegawa T, Masamune A, et al. Nationwide epidemiological survey of acute pancreatitis in Japan. Pancreas. 2011;40(4):503-507.
3. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. Nat Rev Gastroenterol Hepatol. 2010;7(3):131-145.
4. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-111.
5. Johnson CD, Besselink MG, Carter R. Acute pancreatitis. BMJ. 2014;349:g4859.
6. Wu BU, Banks PA. Clinical management of patients with acute pancreatitis. Gastroenterology. 2013;144(6):1272-1281.
7. Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. Gut. 2005;54(Suppl 3):iii1-iii9.
8. Landahl P, Ansari D, Andersson R. Severe acute pancreatitis: gut barrier failure, systemic inflammatory response, acute lung injury, and the role of the mesenteric lymph. Surg Infect (Larchmt). 2015;16(6):651-656.
9. Zerem E. Treatment of severe acute pancreatitis and its complications. *World J Gastroenterol*. 2014;20(38):13879-13892.

10. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet*. 2009;10(3):155-159.

11. Akhade VS, Pal D, Kanduri C. Long noncoding RNA: genome organization and mechanism of action. *Adv Exp Med Biol*. 2017;1008:47-74.

12. Liao K, Xu J, Yang W, et al. The research progress of LncRNA involved in the regulation of inflammatory diseases. *Mol Immunol*. 2018;101:182-188.

13. Zeng Q, Wu J, Yang S. Circulating IncRNA ITS1-2 is upregulated, and its high expression correlates with increased disease severity, elevated inflammation, and poor survival in sepsis patients. *J Clin Lab Anal*. 2019;33(4):e22836.

14. Xuming Gong XF, Zhang Z, Cai Q, et al. Circulating Inc-ITSN1-2 expression presents a high value in diagnosis of rheumatoid arthritis and correlates with disease activity. *Int J Clin Exp Pathol*. 2017;10(10):10451-10458.

15. Xu Y, Shao B. Circulating IncRNA IFNG-AS1 expression correlates with increased disease risk, higher disease severity and elevated inflammation in patients with coronary artery disease. *J Clin Lab Anal*. 2018;32(7):e22452.

16. Tenner S, Baillie J, DeWitt J, et al. College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9):1400-1415; 1416.

17. Zhao D, Ge H, Ma B, et al. The interaction between ANXA2 and IncRNA Fendrr promotes cell apoptosis in caerulein-induced acute pancreatitis. *J Cell Biochem*. 2019;120(5):8160-8168.

18. Wang L, Zhao X, Wang Y. The pivotal role and mechanism of long non-coding RNA B3GALT5-AS1 in the diagnosis of acute pancreatitis. *Artif Cells Nanomed Biotechnol*. 2019;47(1):2307-2315.

19. Baojun Li LH, Yuanxin Sun. Expression of long non-coding RNA H19 in serum in patients with acute pancreatitis and its clinical significance. *J Clin Hepatol*. 2017;3(33):492-496.

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