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PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 24(3): 292-298 (2024)
DOI: 10.31901/24566322.2024/24.03.892

Clinical Value of Mir-320a Combined with HMGB1 in Diagnosis and Prognosis of Severe Acute Pancreatitis Complicated with Sepsis

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KEYWORDS HMGB1. Interleukin-6 (IL-6). microRNA-320a. Severe Acute Pancreatitis. Sepsis

ABSTRACT Severe acute pancreatitis (SAP) often leads to sepsis in severe cases. This study investigated the clinical potential of combining miR-320a with HMGB1 in diagnosing and predicting the prognosis of SAP complicated with sepsis (SAP-CS). Serum levels of miR-320a were found to be decreased, while HMGB1 levels were increased in patients with SAP-CS. The combination of miR-320a and HMGB1 showed promise in diagnosing SAP-CS (AUC = 0.9634, sensitivity = 90.70%, specificity = 93.02%). Specifically, miR-320a levels were downregulated and HMGB1 levels were elevated in patients with a poor prognosis. Furthermore, the low miR-320a group had a worse prognosis, and miR-320a, HMGB1, and IL-6 were independent factors influencing poor prognoses. Therefore, miR-320a combined with HMGB1 has the potential to be a clinical indicator for diagnosing and predicting the prognosis of SAP-CS.

INTRODUCTION

Severe acute pancreatitis (SAP) is a condition characterized by acute abdominal pain, severe symptoms, and high mortality rates. It involves severe inflammatory damage to the pancreatic tissue, leading to impaired pancreatic function and an uncontrolled inflammatory response (Zhang et al. 2021; Jacobs et al. 2022). During the progression of SAP, the systemic inflammatory response can induce sepsis and multiple organ failure (Yeh et al. 2018). SAP complicated with sepsis (SAP-CS) is indicative of disease severity and is a significant contributor to patient mortality. Currently, there is no definitive "gold standard" for diagnosing and predicting the prognosis of SAP-CS, apart from clinical monitoring and severity scoring. Therefore, it is crucial to identify and treat patients promptly using new approaches and predict their potential prognostic outcomes.

Many reports have claimed that microRNAs (miRNAs), a class of RNAs with no coding function, may be involved in the development of various diseases and various life activities by regulating gene expression (Shi et al. 2020; Song et al. 2022; Wang et al. 2023). For example, Shao et al. described in a recent report that high expression of miR-155-5p aggravated SAP-related intestinal barrier injuries by mediating SOCS1 and NLRP3 (Shao et al. 2023). Moreover, in a study by Zheng et al., miR-127-5p was reported to be associated with sepsis-induced acute lung injury (Zheng et al. 2023). Additionally, miR-320a, which is located on chromosome 8p21.3, belongs to the miR-320 family and is implicated in the progression of various diseases (Li et al. 2023). Collectively, existing studies have consistently reported decreased expression of miR-320a in melanoma, where it influences cellular activity by binding to PBX3. Consequently, downregulation of miR-320a is expected to be a prognostic oncogenic factor in non-small cell lung

Funding: This study was funded by 2022 Municipal Science and Technology Development Special Fund Competitive Allocation Program [No 2022A01122].
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cancer (Fu et al. 2020; Khandelwal et al. 2021). In addition, miR-320a downregulated has been observed in osteoarthritis, suggesting its potential as a therapeutic target for patients (Mao and Zhang 2023). However, investigations into miR-320a in SAP-CS remain sparse.

HMGB1 is a protein that binds to nuclear chromatin, and its abnormal expression or release can lead to excessive activation of the inflammatory response or dysfunction of immune regulation (Giovannini et al. 2017). Elevated levels of HMGB1 have been observed in inflammatory conditions such as SAP and sepsis, and suppressing HMGB1 has shown potential to improve multi-organ injuries and patient prognoses (Yang et al. 2017; Deng et al. 2022). Notably, HMGB1 was confirmed to be a direct target of miR-320a in tumors (Lv et al. 2017; Li et al. 2020). Given these findings, the researchers became interested in exploring the potential role of miR-320a combination with HMGB1 in SAP-CS.

In this study, patients with SAP-CS were enrolled and divided into good and poor prognosis groups. By observing and comparing the differences in miR-320a and HMGB1 levels, the researchers aimed to explore the diagnostic and prognostic value of miR-320a combined with HMGB1. The outcomes of this research could serve as a foundational reference for clinical treatment strategies and the identification of biomarkers.

MATERIAL AND METHODS

Inclusion of Study Subjects

Patients with SAP-CS of 86 cases treated in the Second Affiliated Hospital of Guangdong Medical University from February 2022 to December 2023 were included as the target subjects. The group consisted of 45 men and 41 women, with an average age of 65.88 ± 8.82 years. Another group of 86 healthy patients exhibiting normal vital signs during physical examination was selected as the control group during the same period. This group comprised 52 men and 34 women, with a mean age of 65.29 ± 9.97 years.

The enrolled patients met the diagnostic criteria for severe acute pancreatitis as formulated by the Chinese Medical Association, as well as the definition of sepsis outlined in the international guidelines for sepsis management of sepsis (Yan et al. 2022; Shuanglian et al. 2023). These patients exhibited abdominal pain consistent with severe acute pancreatitis and imaging changes indicative of pancreatitis on enhanced CT scans. Additionally, they had imaging evidence of sepsis. Patients with comorbid malignancies, diabetes mellitus, hypertension, or autoimmune diseases were excluded from the study.

The study received approval from the hospital ethics committee, and all participants provided informed consent.

Detection and Prognosis of Clinical Indicators in Patients

Fasting venous blood samples were drawn from the patients and healthy subjects. The samples were centrifuged, and the upper layer of serum was decanted into a new centrifuge tube and stored in a freezer at -20°C for measurement. Serum levels of procalcitonin (PCT), C-reactive protein (CRP), inflammatory factors (IL-6, IL-10, IL-17), HMGB1, heparin-binding protein (HBP), and glycoprotein 2 (GP-2) in patients with SAP-CS were detected using ELISA kit. APACHE-II scores were calculated based on the patients' baseline conditions and clinical manifestations, with higher scores indicating a more serious condition.

All patients received systemic treatment and were followed up for 30 days. A good prognosis was defined as a return to normal or greatly improved physical function, while a poor prognosis was indicated by disease progression or death.

Detection of miR-320a Levels

Total RNA was extracted from serum samples using TRIzol reagent (Sigma, USA), and the quality of the obtained RNA were determined. The miRNA cDNA first-strand Synthesis Kit (TIANGEN, China) was used for miRNA reverse transcription experiments. The resulting cDNA was used as the reaction template, and amplification experiments were conducted according to the instructions provided with the miRNA fluorescence quantitative detection Kit (TIANGEN, China). PCR reactions were performed on an ABI StepOnePlus Real-Time qPCR system (Thermo Fisher Scientific, USA), with three parallel experiments set up for each group. The cycling parameters were as follows: incubation at 95°C for 10 min, 40 cycles of 95°C for 15 s, 60°C for 60 s, and extension at 72 °C for 10 min.

miR-320a expression was calculated by 2-??Ct method, with U6 serving as an internal control.

Statistical Methods

Statistical analysis was conducted by SPSS 22.0 and GraphPad Prism 9.0 software. Measurement data were presented as mean ± standard deviation (SD). The diagnostic value of miR-320a and HMGB1 in patients with SAP-CS was assessed using ROC curve. The patients' prognoses were determined based on overall survival and represented using a Kaplan-Meier curve. In addition, binary logistic regression analysis was employed to evaluate the risk factors associated with poor prognoses in patients with SAP-CS. $P < 0.05$ was considered statistically significant.

RESULTS

Analysis of General Information in the Included Sample

An equal number of healthy individuals and patients with SAP-CS were included. There were no significant differences in age ($P = 0.685$), gender ($P = 0.284$), or BMI ($P = 0.515$) between the two groups. However, PCT, CRP, IL-6, IL-10, IL-17, HMGB1, HBP, and GP-2 levels were markedly enhanced in the patient group compared to the healthy control group, and the difference was statistically significant ($P < 0.001$) in Table 1.

Expression of Serum miR-320a and HMGB1

Serum miR-320a was found to be downregulated in patients with SAP-CS, as verified by RT-qPCR method ($P < 0.001$, Fig. 1A), when compared to healthy individuals. Conversely, elevated levels of HMGB1 were observed in patients using ELISA method ($P < 0.001$, Fig. 1B). These findings suggest a potential association between abnormal levels of miR-320a and HMGB1 and the occurrence of SAP-CS.

Potential of miR-320a and HMGB1 for Diagnosing SAP Complicated with Sepsis

ROC curve analysis elucidated that the AUC for predicting SAP-CS was 0.8806 (95% CI: 0.8255 - 0.9358) for miR-320a and 0.9210 (95% CI: 0.8779 - 0.9642) for HMGB1, with sensitivities of 91.86 per-

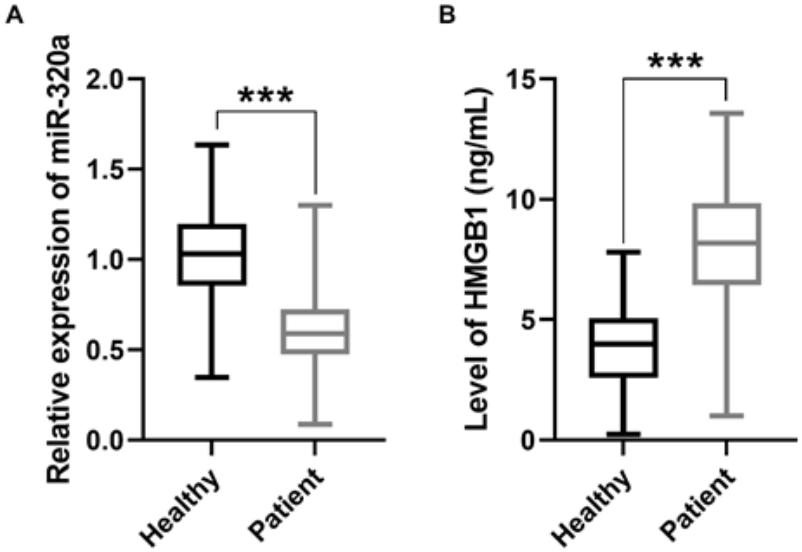

Fig. 1. Expression of miR-320a and HMGB1 in the included samples. (A) Serum miR-320a expression was downregulated in patients with SAP-CS compared to healthy controls. (B) HMGB1 levels were elevated in patients. (* $P < 0.001$)**

Table 1: Baseline information of study subjects

Indicators	*Healthy (n = 86)*	*Patient (n = 86)*	*P-value*
Age (years)	65.88 ± 8.82	65.29 ± 9.97	0.685
Gender (male/female)	45/41	52/34	0.284
BMI (kg/m^2)	22.91 ± 2.23	23.19 ± 3.22	0.515
APACHE-II score	-	18.77 ± 2.57	-
PCT (ng/mL)	0.03 ± 0.01	19.08 ± 4.82	< 0.001
CRP (mg/L)	5.08 ± 1.79	66.38 ± 11.94	< 0.001
IL-6 (pg/mL)	11.24 ± 3.15	149.44 ± 11.67	< 0.001
IL-10 (pg/mL)	12.68 ± 3.29	30.53 ± 5.73	< 0.001
IL-17 (pg/mL)	15.43 ± 3.95	239.70 ± 23.35	< 0.001
HMGB1(ng/mL)	3.94 ± 1.57	8.04 ± 2.34	< 0.001
HBP (ng/mL)	7.09 ± 1.71	18.71 ± 4.14	< 0.001
GP-2 (pmol/L)	0.77 ± 0.25	59.94 ± 9.96	< 0.001

BMI: body mass index; APACHE II score: acute physiology and chronic health evaluation II score; PCT: procalcitonin; CRP: C-reactive protein; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-17: Interleukin-17; HMGB1: High mobility group box protein 1; HBP: Heparin-binding protein; GP-2: Glycoprotein 2.

cent and 83.72 percent, and specificities of 81.40 percent and 89.53 percent, respectively ($P < 0.0001$, Fig. 2A and 2B, Table 2). Combining miR-320a and HMGB1 yielded a higher predictive value, with an AUC of 0.9634 (95% CI: 0.9378-0.9889), sensitivity of 90.70 percent, and specificity of 93.02 percent in distinguishing between healthy subjects and patients ($P < 0.0001$, Fig. 2C, Table 2).

Table 2: Diagnostic value of miR-320a and HMGB1 in severe acute pancreatitis combined with sepsis

Indicators	*miR-320a*	*HMGB1*	*combined*
AUC	0.8806	0.9210	0.9634
Standard error	0.0281	0.0220	0.0130
95% CI	0.8255-0.9358	0.8779-0.9642	0.9378-0.9889
Sensitivity	91.86%	83.72%	90.70%
Specificity	81.40%	89.53%	93.02%
P value	< 0.0001	< 0.0001	< 0.0001

Prognostic Analysis

Patients with SAP-CS were categorized into the good (n = 45) and poor prognosis group (n = 41) according to their prognoses. RT-qPCR experiments confirmed that miR-320a expression was downregulated in the poor prognosis group ($P < 0.001$, Fig. 3A). In addition, ELISA assay experiments showed that HMGB1 levels were enhanced in the poor prognosis group compared with patients in the good prognosis group ($P < 0.001$, Fig. 3B).

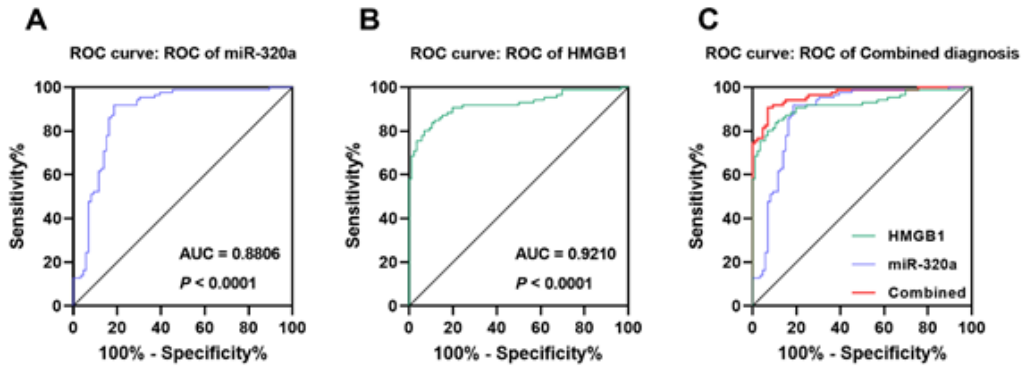

Fig. 2. The predictive significance of miR-320a and HMGB1 in identifying patients with SAP-CS. (A) ROC analysis showed that the AUC of miR-320a in the diagnosis of patients was 0.8806. (B) ROC analysis showed that the AUC of HMGB1 in the diagnosis of patients was 0.9210. (C) The combined diagnosis of miR-320a and HMGB1 holds high value in predicting SAP-CS. (*$P < 0.001$)**

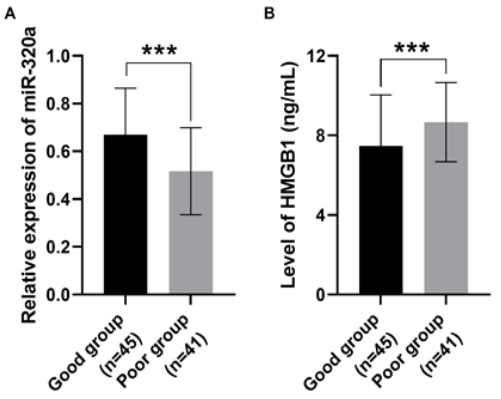

Fig. 3. Expression of miR-320a and HMGB1 in the good and poor prognosis groups. (A-B) The expression of miR-320a was decreased in the poor prognosis group, while HMGB1 levels were increased. (*$P < 0.001$)**

Kaplan-Meier survival curves were constructed based on patients' survival outcomes within 30 days of systemic therapy. The mean value of miR-320a expression in patients was used as the cutoff point to categorize the included patients into a low miR-320a group (n = 44) and a high miR-320a group (n = 42). Figure 4 depicts the significantly reduced survival of patients in the low miR-320a group compared to the high miR-320a group ($P = 0.0224$). Furthermore, binary logistic regression analyses were performed with patients' clinical indicators as variables. The results showed that miR-320a, HMGB1, and IL-6 ($P = 0.010$, $P = 0.025$ and $P = 0.042$) were unfavorable indicators for a poor prognosis in patients with SAP-CS (Table 3).

Table 3: Binary Logistic regression analysis of adverse prognostic factors in patients with severe acute pancreatitis complicated with sepsis

Indicators	*OR*	*95% CI*	*P value*
Age	0.543	0.188 - 1.567	0.259
Gender	0.743	0.250 - 2.205	0.592
BMI	2.005	0.674 - 5.968	0.211
PCT	1.036	0.366 - 2.935	0.947
CRP	1.208	0.390 - 3.736	0.743
IL-6	3.381	1.045 - 10.946	0.042
IL-10	1.503	0.541 - 4.179	0.434
IL-17	0.931	0.315 - 2.758	0.898
HMGB1	0.252	0.076 - 0.838	0.025
HBP	0.531	0.186 - 1.515	0.237
GP-2	0.816	0.284 - 2.339	0.705
miR-320a	3.975	1.385 - 11.413	0.010

BMI: body mass index; PCT: procalcitonin; CRP: C-reactive protein; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-17: Interleukin-17; HMGB1: High mobility group box protein 1; HBP: Heparin-binding protein; GP-2: Glycoprotein 2.

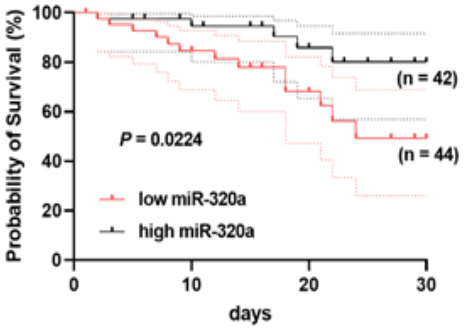

Fig. 4. Kaplan-Meier analysis of survival in patients with SAP-CS within 30 days ($P = 0.0224$)

DISCUSSION

SAP-CS is a critical condition that requires urgent intervention and treatment. SAP can result in the destruction of pancreatic tissues and bacterial infection, which can further lead to the development of sepsis and patient death. A study has indicated that the main reason for sepsis emergence is bacterial translocation following damage to the intestinal barrier (Zhang et al. 2023). With an understanding of SAP and advancements in nursing technology, the incidence of SAP patients has reduced. However, the mortality rate of SAP patients remains around 30 percent, with sepsis being the key factor in patient deaths (Shi et al. 2021). Therefore, discovering new biological factors holds significant value in evaluating and predicting patient outcomes.

In this study, a total of 86 patients with SAP-CS and a corresponding number of healthy individuals were enrolled. After collecting and analyzing the clinical data, the expression of PCT, CRP, IL-6, IL-10, IL-17, HMGB1, HBP, and GP-2 in patients was obviously higher than that in the healthy control group. Some studies have proposed that serum CRP and PCT levels, as well as APACHE-II scores, have high application value in evaluating the severity and prognosis of SAP patients (Bao and Ge 2022). Similarly, elevations in inflammatory factors such as HMGB1, HBP and GP-2 have also been reported to be elevated in SAP, serving as effective parameters for assessing SAP (Wen et al. 2020; Shu et al. 2021; Zhong et al. 2022). This aligns with the findings of the current research.

It is known that dysregulation of miRNA expression is commonly associated with disease pro-

gression and pathological processes. In this study, it was observed that serum miR-320a was lowly expressed in patients with SAP-CS and in a group with poor prognoses compared to a group with good prognoses. This implicates that miR-320a may be involved in the process of SAP-CS and that down-regulation of miR-320a may be responsible for poor prognoses in patients. Combined with the report by Amira Mohamed et al., miR-320a expression was reduced in metabolic syndrome and its ability to assess disease progression (Abd El-Jawad et al. 2022). Additionally, elevated miR-320a has been found to affect the growth and activity of trophoblast cells by targeting the inflammatory factor IL-4, thereby influencing the occurrence and development of preeclampsia (Xie et al. 2019). Taken together, miR-320a may mediate the progression of SAP-CS by regulating the inflammatory response. HMGB1 is secreted extracellularly by immune cells in response to injury or stimulation, which participates in various pathological processes such as immunity and inflammation in the body (Wang et al. 2022). In patients with SAP-CS, HMGB1 levels were elevated, particularly in the group with poor prognoses. This suggests that higher levels of HMGB1 are associated with worsened patient conditions and unfavorable prognostic outcomes. Existing evidence also supports the possibility that decreasing HMGB1 levels in the body may enhance the survival of patients with SAP and sepsis (J. Yang et al. 2022a; K. Yang et al. 2022b).

In the current study, the ROC results indicated that both miR-320a and HMGB1 demonstrated high sensitivity and specificity in diagnosing SAP-CS, and the combination of miR-320a and HMGB1 had even better diagnostic efficacy. In addition, Kaplan-Meier curves and logistic regression analyses illustrated that low expression of miR-320a and high levels of HMGB1 and IL-6 were risk factors associated with poor prognoses in patients with SAP-CS. The above suggests that both miR-320a and HMGB1 may serve as potential biomarkers for the diagnosis and prognosis of SAP-CS. Interestingly, Lu et al. proposed that HMGB1 is a downstream target of miR-320a in HCC and that miR-320a affects tumor cell metastasis by regulating HMGB1 expression (Lv et al. 2017). Therefore, the relationship between miR-320a and HMGB1 in SAP-CS warrants further investigation in future studies.

CONCLUSION

In conclusion, decreased serum miR-320a expression and increased HMGB1 expression are closely correlated with a poor prognosis in SAP-CS. Furthermore, the combination of miR-320a and HMGB1 may assist in identifying SAP-CS. These findings present new markers for diagnosing and predicting outcomes in patients and provide additional medical evidence for the clinical management of patients undergoing anti-inflammatory treatment.

RECOMMENDATIONS

In subsequent studies, more patient samples need to be included for further analysis, and the pathological mechanisms of miR-320a and HMGB1 in SAP-CS need to be deeply investigated.

REFERENCES

Abd El-Jawad AM, Ibrahim IH, Zaki ME et al. 2022. The potential role of miR-27a and miR-320a in metabolic syndrome in obese Egyptian females. *J Genet Eng Biotechnol*, 20: 75.

Bao Y, Ge W 2022. Correlation between serum levels of PTX-3, SIL-2R, inflammatory markers, and APACHE II scores in patients with severe acute pancreatitis. *Medicine (Baltimore)*, 101: e31252.

Deng C, Zhao L, Yang Z et al. 2022. Targeting HMGB1 for the treatment of sepsis and sepsis-induced organ injury. *Acta Pharmacol Sin*, 43: 520-528.

Fu G, Lu, J, Zheng Y et al. 2020. MiR-320a inhibits malignant phenotype of melanoma cells via targeting PBX3. *J Buon*, 25: 2071-2077.

Giovannini S, Tinelli G, Biscetti F et al. 2017. Serum high mobility group box-1 and osteoprotegerin levels are associated with peripheral arterial disease and critical limb ischemia in type 2 diabetic subjects. *Cardiovasc Diabetol*, 16: 99.

Jacobs R, Wise RD, Myatchin I et al. 2022. Fluid management, intra-abdominal hypertension and the Abdominal Compartment Syndrome: A narrative review. *Life (Basel)*, 12.

Khandelwal A, Sharma U, Barwal TS et al. 2021. Circulating miR-320a acts as a tumor suppressor and prognostic factor in non-small cell lung cancer. *Front Oncol*, 11: 645475.

Li M, Qu L, Chen F et al. 2020. Propofol upregulates miR-320a and reduces HMGB1 by downregulating ANRIL to inhibit PTC cell malignant behaviors. *Pathol Res Pract*, 216: 152856.

Li Y, Gu F, He Y et al. 2023. MicroRNA in adenoid cystic carcinoma (Review). *Int J Oncol*, 62.

Lv G, Wu M, Wang M et al. 2017. miR-320a regulates high mobility group box 1 expression and inhibits invasion and metastasis in hepatocellular carcinoma. *Liver Int*, 37: 1354-1364.

Mao J, Zhang L 2023. MiR-320a upregulation improves IL-1β-induced osteoarthritis via targeting the DAZAP1 and MAPK pathways. *J Orthop Surg Res*, 18: 541.
Shao Y, Li Y, Jiang Y et al. 2023. Circulating exosomal miR-155-5p contributes to severe acute pancreatitis-associated intestinal barrier injury by targeting SOCS1 to activate NLRP3 inflammasome-mediated pyroptosis. *Faseb J*, 37: e23003.
Shi J, Hu C, Zhou Y et al. 2020. MicroRNA profiling in paired left and right eyes, lungs, and testes of normal mice. *Mol Ther Nucleic Acids*, 21: 687-695.
Shi N, Sun GD, Ji YY et al. 2021. Effects of acute kidney injury on acute pancreatitis patients' survival rate in intensive care unit: A retrospective study. *World J Gastroenterol*, 27: 6453-6464.
Shu W, Wan J, Yang X et al. 2021. Heparin-binding protein levels at admission and within 24 h are associated with persistent organ failure in acute pancreatitis. *Dig Dis Sci*, 66: 3597-3603.
Shuanglian Y, Huiling Z, Xunting L et al. 2023. Establishment and validation of early prediction model for hypertriglyceridemic severe acute pancreatitis. *Lipids Health Dis*, 22: 218.
Song Q, Chen P, Wu SJ et al. 2022. Differential expression profile of micrornas and tight junction in the lung tissues of rat with mitomycin-C-induced Pulmonary Veno-Occlusive Disease. *Front Cardiovasc Med*, 9: 746888.
Wang S, Guan YG, Zhu YH et al. 2022. Role of high mobility group box protein 1 in depression: A mechanistic and therapeutic perspective. *World J Psychiatry*, 12: 779-786.
Wang X, Xing Y, Wang Y et al. 2023. Association of microRNA gene polymorphisms with recurrent spontaneous abortion: An updated meta analysis. *Exp Ther Med*, 25: 179.
Wen Y, Sun HY, Tan Z et al. 2020. Abdominal paracentesis drainage ameliorates myocardial injury in severe experimental pancreatitis rats through suppressing oxidative stress. *World J Gastroenterol*, 26: 35-54.
Xie N, Jia Z, Li L 2019. miR 320a upregulation contributes to the development of preeclampsia by inhibiting the growth and invasion of trophoblast cells by targeting interleukin 4. *Mol Med Rep*, 20: 3256-3264.
Yan X, Li Y, Liu J et al. 2022. Serial changes in left ventricular myocardial deformation in sepsis or septic shock using three-dimensional and two-dimensional speckle tracking echocardiography. *Front Cardiovasc Med*, 9: 925367.
Yang J, Tang X, Wu Q et al. 2022a. Heparin protects severe acute pancreatitis by inhibiting HMGB-1 active secretion from macrophages. *Polymers (Basel)*, 14.
Yang K, Fan M, Wang X et al. 2022b. Lactate promotes macrophage HMGB1 lactylation, acetylation, and exosomal release in polymicrobial sepsis. *Cell Death Differ*, 29: 133-146.
Yang R, Tenhunen J, Tonnessen TI 2017. HMGB1 and histones play a significant role in inducing systemic inflammation and multiple organ dysfunctions in severe acute pancreatitis. *Int J Inflam*, 2017: 1817564.
Yeh CH, Hsieh LP, Lin MC et al. 2018. Dexmedetomidine reduces lipopolysaccharide induced neuroinflammation, sickness behavior, and anhedonia. *PLoS One*, 13: e0191070.
Zhang C, Li G, Lu T, et al. 2023. The interaction of microbiome and pancreas in acute pancreatitis. *Biomolecules*, 14.
Zhang Y, Shao F, Guan Z et al. 2021. Overexpression of miR-99a Alleviates intestinal mucosal barrier injury in rats with severe acute pancreatitis *J Interferon Cytokine Res*, 41: 72-80.
Zheng XL, Gu WJ, Zhang F et al. 2023. Exosomal miR-127-5p from BMSCs alleviated sepsis-related acute lung injury by inhibiting neutrophil extracellular trap formation *Int Immunopharmacol*, 123: 110759.
Zhong J, Liao J, Zhang R et al. 2022. Reduced plasma levels of RGM-A predict stroke-associated pneumonia in patients with acute ischemic stroke: A prospective clinical study *Front Neurol*, 13: 949515.

Paper received for publication in March, 2024
Paper accepted for publication in May, 2024