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CIRCULATING miR-216a-5p, miR-375 AND miR-551b-5p AS POTENTIAL BIOMARKERS FOR EARLY SEVERITY STRATIFICATION IN ACUTE PANCREATITIS

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ABSTRACT

Background: Acute pancreatitis (AP) is an inflammatory disease that can range from an uncomplicated form to severe one with organ failure and a significant rise in mortality. Recognizing patients who will experience severe forms of the disease at an early stage is not always possible with standard biochemical tests and clinical scoring systems. Researchers are now turning to microRNAs (miRNAs) as potential biomarkers due to their stability in circulation and involvement in inflammatory processes. The present study aims to assess the levels of circulating miR-216a-5p, miR-375, and miR-551b-5p and their association with AP severity.

Methods: It is suggested that a prospective case-control study was carried out on 50 subjects, of which 40 were found to have acute pancreatitis (AP), while the remaining 10 were healthy. Patients were divided into two groups: those with mild cases (low-risk group, n=20) and those with severe cases (high-risk group, n=20) depending on the severity of the illness. miRNA was isolated from the blood plasma with the use of miRNeasy Serum/Plasma Advanced kit, and cDNA was synthesized from the samples. Additionally, qPCR was used to measure the relative quantity of miRNAs, which was calculated using the 2^-ΔΔCt method. The results were analyzed using statistical tests with the threshold set at $P<0.05$.

Results: The circulating expression of miR-216a-5p was significantly increased in high-risk acute pancreatitis (AP) patients than that in the control group ($P = 0.0004$) and low-risk group ($P = 0.026$). Moreover, the expression of miR-551b-5p was notably down-regulated in high-risk patients in contrast to the low-risk group ($P = 0.020$). In addition, miR-375 showed an upward tendency in high-risk patients, but the difference was not statistically significant ($P = 0.065$).

Conclusion: Circulating miR-216a-5p and miR-551b-5p demonstrated strong associations with the severity of acute pancreatitis. Moreover, these microRNAs can be considered potential non-invasive biomarkers for the early risk stratification of acute pancreatitis. Although miR-375 was shown to possess limited diagnostic accuracy, further investigations, including multi-center trials, are necessary to confirm the results and determine the role of microRNAs in acute pancreatitis management.

KEYWORDS: Acute pancreatitis; microRNA; miR-216a-5p; miR-375; miR-551b-5p; biomarkers; quantitative real-time PCR.

1. INTRODUCTION

Acute pancreatitis (AP) is one of the most frequent gastrointestinal emergencies worldwide. This condition is characterized by an acute inflammation of the pancreas, caused by the self-digestion of the organ due to the enzymes' activation [1–3]. Most often, this disease is mild and passes on its own; however, in 15–20% of cases, it can lead to severe acute pancreatitis (SAP), which is associated with a high risk of pancreatic necrosis, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, and death [1–4]. It is vital to identify patients with an increased risk of developing SAP at an early stage in order to provide the adequate treatment [2,4].

The diagnosis of AP is usually based on the symptoms, such as abdominal pain, increased levels of amylase/lipase in the blood, and radiological imaging [1,5]. However, these diagnostic measures are not sufficient to determine the severity of pancreatitis. Moreover, most of the commonly used scoring systems, such as Ranson's criteria, APACHE II, BISAP, and CT Severity Index, require multiple laboratory tests or radiological imaging, which can be unavailable in the early stages of the disease [1,5–7]. Therefore, there is a need to find new biomarkers that can predict the severity of AP at the early stages of the disease and allow for taking the adequate measures timely [7].

MicroRNAs (miRNAs) are short endogenous non-coding RNAs consisting of approximately 18–25 nucleotides that regulate the expression of genes by binding to complementary messenger RNA (mRNA) and causing either mRNA degradation or inhibition of its translation [8,9]. These molecules participate in the regulation of various

physiological processes, such as inflammation, cell death, immune response, cell proliferation, and others [8–10]. miRNAs are stable in body fluids due to their protection by membranes of exosomes, proteins, and lipoproteins; therefore, they can be used as potential biomarkers for the diagnosis and prognosis of many diseases, including cancer and inflammatory conditions [10–12].

The altered levels of miRNAs were reported in patients with AP, which makes these molecules a promising tool for the diagnosis and prognosis of this disease [11–13]. In particular, miR-216a-5p is a pancreas-specific miRNA that is involved in the regulation of exocrine function and is upregulated in response to the acinar injury [13,14]. Another miRNA, miR-375, is essential for the proper endocrine function of the pancreas Finally, miR-551b-5p is involved in the regulation of inflammatory response and immune cell activity; however, the role of this miRNA in AP has not been sufficiently studied. Therefore, the levels of these miRNAs can serve as a potential biomarker for the early diagnosis of AP and prediction of its severity [15].

MicroRNAs were chosen based on the available literature reporting their role in pancreatic injury, inflammation, and disease progression. MiR-216a-5p is a pancreas-enriched microRNA that is rapidly released into the circulation upon acinar cell injury and has been described as a sensitive biomarker of acute pancreatic damage [13,14]. MiR-375 is another pancreatic tissue-enriched microRNA reported to play a role in the endocrine function of the pancreas and inflammatory response; however, its diagnostic value seems to be inconsistent in acute pancreatitis. The reason for choosing miR-551b-5p was due to the fact that it was recently shown to be involved in inflammatory response and immunity [15]. Therefore, the authors decided to evaluate the diagnostic and prognostic value of these three circulating microRNAs in patients with acute pancreatitis.

Therefore, the present study was designed to assess the circulating levels of miR-216a-5p, miR-375, and miR-551b-5p in patients diagnosed with acute pancreatitis and explore their diagnostic and prognostic significance for the disease severity.

2. METHODOLOGY

2.1 Study Design and Participants

This is a prospective case-control study done in the Department of Surgery and Department of Biochemistry, JSS Medical College and Hospital, Mysuru, India. There were 50 patients (40 patients with acute pancreatitis and 10 healthy volunteers). Patients with AP were divided into low-risk and high-risk groups. The study was carried out on patients with acute pancreatitis who met the diagnostic criteria and presented within 72 hours of symptom onset [1,2,16]. The study was approved by the Institutional Ethics Committee, JSS Medical College, Mysuru (reference number: IEC no.) and informed consents were taken from all participants.

2.2 Sample Collection

Five milliliters of peripheral venous blood was collected from the participants in EDTA vacutainer tubes before therapy. The samples were centrifuged at 2500 rpm for 10 minutes, and the supernatant was stored at -80C until analysis [10].

2.3 Isolation of Circulating miRNA

Total RNA including miRNA was isolated from the study samples using QIA serum/plasma advanced kit (QIAGEN, Hilden, Germany) as per the manufacturer's instructions and stored at -80C. Complementary DNA (cDNA) was synthesized from the isolated RNA using Taqman advanced miRNA cDNA synthesis kit (Applied Biosystems, Thermo Fisher Scientific, USA) as per the manufacturer's instructions and stored at -20C.

2.4 Quantitative Real-Time PCR

Expression of miR-216a-5p, miR-375, and miR-551b-5p was estimated using DyNAmo colorflash SYBR green qPCR kit (Thermo scientific, USA) following the manufacturer's instructions. PCRs were run on a real-time PCR instrument. The reactions were carried out in duplicates, and miR-191-5p was taken as an endogenous control. Relative expressions were calculated using the 2^-ΔΔCt method and were represented as the fold change compared to the control group [17].

2.5 Statistical Analysis

The Statistical analysis was done using GraphPad prism version 10.0 (or SPSS version XX if that's the one you used). All statistical analysis was done using GraphPad Prism version 10.0. Shapiro-Wilk test was used to check normality, and data were expressed as mean ± SD or median (IQ) for continuous variables. Analysis of variance (ANOVA) with Tukey's post-hoc test or Kruskal-Wallis test followed by Dunn's post-hoc test was used to compare miRNA expressions between the groups. A 95% CI was reported if applicable, and p-value <0.05 was taken as statistically significant.

3. RESULTS

3.1 Study Population

A total of 50 participants were enrolled in the present study, comprising 40 patients with acute pancreatitis (AP) and 10 healthy controls. Patients with AP were stratified into low-risk (n = 20) and high-risk (n = 20) groups according to the CT Severity Index (CTSI). The demographic and clinical characteristics of the study population are summarized in Table 1.

Table 1. Distribution of study participants

Study Group	Number of Participants (n)	Description
Healthy Controls	10	Individuals without any known pancreatic disease, inflammatory disorders, or systemic illness.
Low-Risk Acute Pancreatitis	20	Patients diagnosed with AP presenting with mild clinical features and without radiological indicators of severe disease.
High-Risk Acute Pancreatitis	20	Patients diagnosed with AP exhibiting clinical and radiological features suggestive of severe disease based on severity scoring systems.

3.2 Baseline Demographic and Clinical Characteristics

The demographic and clinical characteristics of patients with acute pancreatitis are summarized in Table 2. Patients in the high-risk group exhibited higher BMI, CT severity scores, serum amylase, and serum lipase levels compared with the low-risk group. The majority of participants in both groups were males, and the most common etiologies included biliary pancreatitis, ethanol-induced pancreatitis, and acute unspecified pancreatitis.

Table 2: Baseline demographic and clinical characteristics of patients with acute pancreatitis

Characteristic	Low-risk AP (n = 20)	High-risk AP (n = 20)
Age (years)	25 – 68	23 – 63
Sex (Male/Female)	16/4	17/3
BMI (kg/m²)	22.9–32.4	32.8–38.0
CT Severity Index	2 – 4	6 – 10
Serum amylase (U/L)	180 – 590	320 – 1450
Serum lipase (U/L)	420 – 920	1320 – 2200
Major etiologies	Gallstone, alcohol-induced, unspecified pancreatitis	Gallstone, alcohol-induced, unspecified pancreatitis

3. 3 Expression of miR-216a-5p

The relative expression of miR-216a-5p was significantly elevated in patients with acute pancreatitis compared with healthy controls, with the highest expression observed in the high-risk group (Figure 1). No statistically significant difference was observed between healthy controls and low-risk patients (P = 0.135). However, expression was significantly higher in high-risk patients than in healthy controls (P = 0.026), and a highly significant increase was observed between healthy controls and high-risk patients (P = 0.0004). These findings indicate a positive association between circulating miR-216a-5p expression and disease severity.

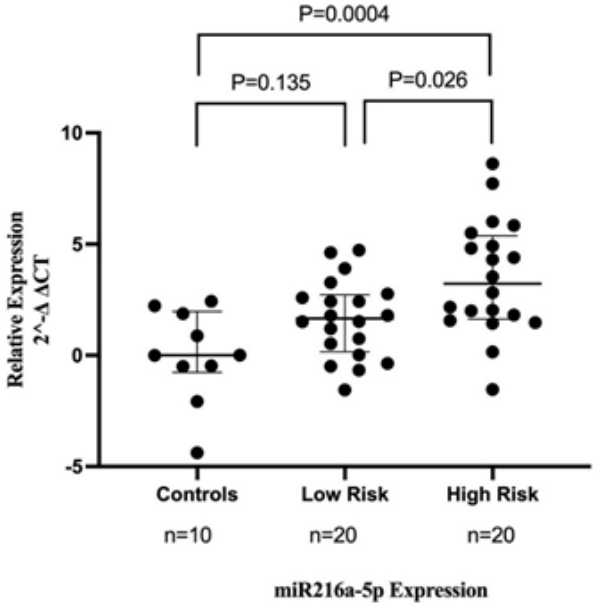

Figure 1. Relative expression of circulating miR-216a-5p among healthy controls, low-risk acute pancreatitis, and high-risk acute pancreatitis patients.

3.4 Expression of miR-375

Expression analysis of miR-375 demonstrated a tendency toward increased expression in patients with acute pancreatitis compared with healthy controls. However, no statistically significant differences were observed between healthy controls and low-risk patients (P = 0.533), healthy controls and high-risk patients (P = 0.301), or between low-risk and high-risk patients, although the latter comparison showed a trend toward significance (P = 0.065). These findings suggest that miR-375 is not significantly associated with disease severity in the present

study.

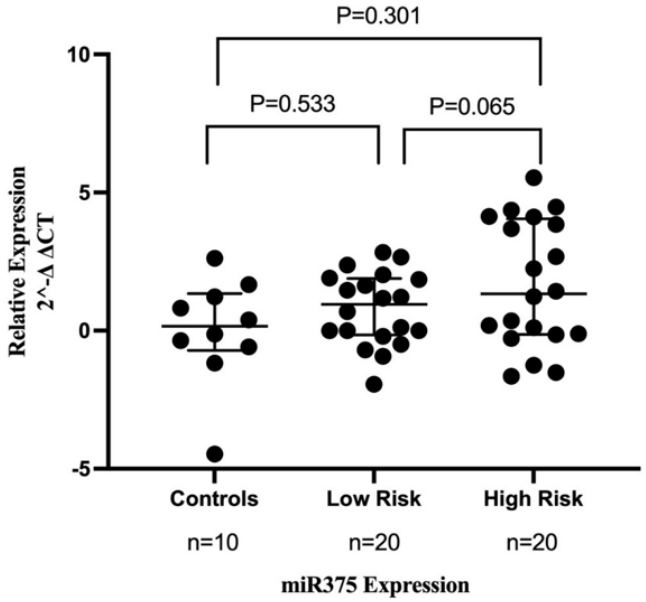

Figure 2. Relative expression of circulating miR-375 among healthy controls, low-risk acute pancreatitis, and high-risk acute pancreatitis patients.

3.5 Expression of miR-551b-5p

The expression of miR-551b-5p decreased progressively with increasing disease severity (Figure 3). Although the difference between healthy controls and low-risk patients did not reach statistical significance (P = 0.098), expression was significantly lower in high-risk patients than in low-risk patients (P = 0.020). No statistically significant difference was observed between healthy controls and high-risk patients (P = 0.693), possibly due to variability within the control group. Overall, these findings suggest that reduced circulating miR-551b-5p expression is associated with severe acute pancreatitis.

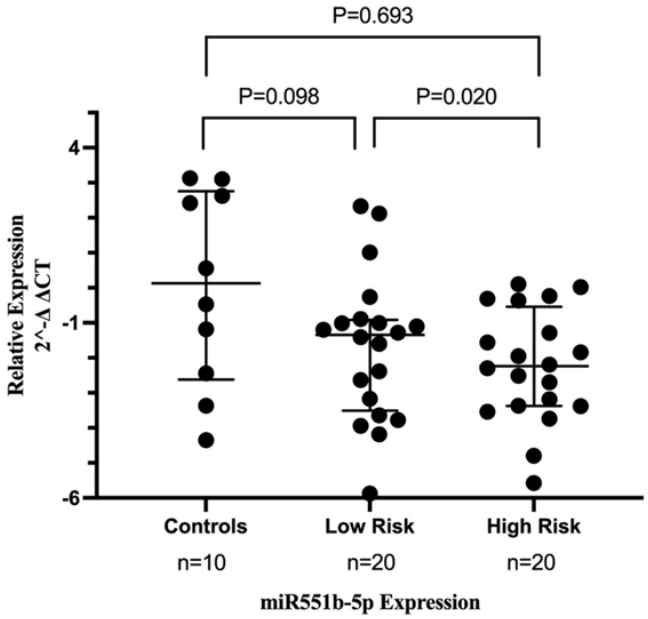

Figure 3. Relative expression of circulating miR-551b-5p among healthy controls, low-risk acute pancreatitis, and high-risk acute pancreatitis patients.

3.6 Summary of Differential miRNA Expression

Among the three investigated circulating microRNAs, miR-216a-5p demonstrated a significant increase in expression with increasing disease severity, whereas miR-551b-5p showed a significant reduction in expression among patients with severe acute pancreatitis. In contrast, miR-375 exhibited only a modest increase in expression that did not reach statistical significance. These findings indicate that miR-216a-5p and miR-551b-5p may have greater potential as circulating biomarkers for severity assessment in acute pancreatitis than miR-375.

Table 3. Summary of circulating miRNA expression patterns

miRNA	Expression Pattern	Statistical Significance	Interpretation

miR-216a-5p	Increased with disease severity	Significant	Potential biomarker for severe AP
miR-375	Mild increase	Not significant	Limited diagnostic utility
miR-551b-5p	Decreased with disease severity	Significant between severity groups	Potential severity-associated biomarker

4. DISCUSSION

Acute pancreatitis (AP) is a complex disease, varying from mild self-limiting forms to severe acute pancreatitis developing necrosis, multi-organ failure, and fatal conditions [1,2]. The challenge is to determine early those patients who will develop a severe form of the disease because the existing scales and tests for assessing the severity of AP are complicated by too many factors [3,7]. However, scientists are actively studying various ways to identify biomarkers for diagnosing and predicting the course of AP. The question under study was the use of microRNA (miR) for early diagnosis and disease prediction [11].

MiR-216a-5p, miR-375, and miR-551b-5p contents were analyzed in the patients with diagnosed AP. It was found that miR-216a-5p levels were significantly higher in patients with severe AP than in healthy controls and mild AP patients. Moreover, the level of miR-216a-5p increased gradually depending on the severity of the disease. These results suggest that miR-216a-5p is involved in the pathogenesis of AP and can be used for early prediction of a severe disease course. Researchers have revealed that miR-216a is a marker of pancreatic damage since mainly this miRNA is found in the acinar cells of the pancreas [13,14,18]. When these cells rupture, their content is released into the bloodstream, and its level increases, indicating damage. Researchers found similar results – an increase in miR-216a in patients with severe AP, which suggests that this miRNA can be a reliable predictor of severe disease. In addition, they emphasize that miR-216a turned out to be one of the first markers of damage to the pancreas [14,19].

MiR-375 levels were only moderately increased compared to the control, but the difference was not statistically significant. This miRNA is highly expressed in the endocrine tissues of the pancreas and plays an essential role in regulating its function, and in particular in the development of beta-cells and the process of insulin secretion. Besides, miR-375 is involved in the inflammatory response regulation process [15,20]. Some researchers have found that in patients with severe AP, the level of miR-375 was higher compared to those with mild disease. However, other studies failed to find any association between miR-375 and AP. The reason for no significant results in our study could be a small sample size or the heterogeneity of the study groups. It is possible that the different stages of the disease or the predominance of exocrine or endocrine tissues involvement was not considered in the study [14,21].

An interesting finding of our study was that miR-551b-5p levels decreased significantly with increased AP severity. Few studies have so far examined the association between miR-551b-5p and AP. However, some reports suggest that this miRNA is involved in the regulation of the inflammatory response and cell stress processes [22,23]. Thus, decreased levels of miR-551b-5p can be associated with impaired anti-inflammatory protective mechanisms contributing to the development of severe AP. These findings indicate the potential of using miR-551b-5p as a severity predictor in patients with AP.

The clinical findings of our study showed that patients with high CTSI scores had significantly higher levels of serum amylase and lipase and higher BMI compared to patients with a low score [1,3,24]. Increased serum amylase and lipase levels are associated with severe disease due to their active release from damaged pancreatic cells into the bloodstream. Moreover, there is evidence that BMI is positively correlated with the severity of AP [24,25]. However, the clinical use of these indicators is limited by their insufficient accuracy in predicting the disease course and rapid normalization after the acute episode. In addition, microRNA molecules are more stable in the blood serum than enzymes, ensuring more accurate test results [10,11].

The strength of our study is that miR-216a-5p, miR-375, and miR-551b-5p contents were quantified using qPCR in patients with mild and severe AP. Besides, the patients were divided into two groups depending on the CTSI score, which made it possible to compare the miR levels between these groups. In addition, we included the control group of healthy volunteers in our study.

However, the small sample size was the main limitation of the study since it was conducted at one medical site with a relatively small number of patients. Another limitation was that miRNA levels were measured only once for each patient. Further research is needed to explore in detail the potential of the miRNAs tested for predicting the course of AP. In addition, future studies should examine the mechanisms by which miR-216a-5p, miR-375, and miR-551b-5p affect the development of AP [1,11].

Overall, the present findings indicate that circulating miR-216a-5p and miR-551b-5p are promising biomarkers for the early severity stratification of acute pancreatitis. Integration of these circulating microRNAs with established clinical and radiological scoring systems may improve early risk assessment and facilitate timely therapeutic intervention. However, validation in larger multicenter cohorts is essential before routine clinical implementation.

5. CONCLUSION

The current study proved that microRNAs could be valuable non-invasive biomarkers for the diagnosis and

determination of acute pancreatitis severity. According to the results, miR-216a-5p was increased while miR-551b-5p decreased in patients with severe cases of illness, while miR-375 was not significantly different between the groups. Thus, miR-375 seems to be a poor biomarker for pancreatitis. The study also found that changes in microRNA levels were associated with the CT Severity Index and increased pancreatic enzyme levels in high-risk patients.

MiR-216a-5p and miR-551b-5p could be used as biomarkers alongside standard clinical, biochemical, and imaging procedures for acute pancreatitis to identify patients with severe forms of the disease. The research is limited by the fact that it used a sample from a single center and had a small size. More research is needed to confirm the results and determine the diagnostic accuracy of miR-216a-5p and miR-551b-5p in larger populations. Multicenter studies with greater sample sizes are necessary to evaluate the role of microRNAs in acute pancreatitis severity and collect sufficient data for constructing a ROC curve.

Overall, the current paper proved the clinical significance of miR-216a-5p and miR-551b-5p in the progression of acute pancreatitis. By identifying biomarkers, researchers could predict the development of a severe form of the disease and help physicians provide appropriate treatment for patients. Therefore, the study can be considered valuable as it suggests using microRNAs as non-invasive and accurate methods for acute pancreatitis diagnosis and prognosis.

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Conflict of Interest:
The authors declare no conflict of interest.

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Ethical Approval Statement
The study protocol was approved by the Institutional Ethics Committee, JSS Medical College and Hospital, Mysuru (IEC Approval No. JSS/MC/PG/234/2023–24). Written informed consent was obtained from all participants.

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