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Review Article

Clinical and prognostic significance of SMAD3 and miR-346 in severe sepsis

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Abstract: Objective: To explore the clinical and prognostic significance of SMAD3 and miR-346 in severe sepsis. Methods: Patients with sepsis after surgery in the Second Hospital of Shandong University from March 2017 to March 2019 were enrolled as a research group, and healthy individuals after surgery in the hospital during the same period were enrolled as a control group. The expression of SMAD3 and miR-346 in all participants in the two groups was determined, and the expression before and after treatment was analyzed. In addition, the diagnostic value of SMAD3 and miR-346 in different degrees of sepsis was also analyzed, and the influence of both of them on the prognosis of patients with sepsis was evaluated. Results: The SMAD3 expression in the research group before treatment was higher than that in the control group ($P<0.05$), and the miR-346 level in the research group before treatment was lower than that in the control group ($P<0.05$). While after treatment, the SMAD3 expression in the research group was significantly decreased ($P<0.05$), and miR-346 expression in the group was significantly increased ($P<0.05$). SMAD3 and miR-346 have good diagnostic value for sepsis diagnosis and different degrees of sepsis, and they are strongly linked to the prognosis of patients with sepsis ($P<0.05$). Conclusion: SMAD3 is highly expressed in sepsis while miR-346 is poorly expressed in sepsis, and both of them have good diagnostic value in determining sepsis and are strongly linked to the prognosis of patients with sepsis. Therefore, they may be excellent indicators for the diagnosis and treatment of sepsis in the future.

Keywords: Sepsis, SMAD3, miR-346, prognosis

Introduction

Sepsis is a systemic inflammatory response syndrome caused by infection, which has been clinically confirmed to be associated with bacteria and has a highly infectious foci [1]. Its incidence is as high as 270/100,000 [2]. As a serious disease with high fatality rate, sepsis shows a gradually increasing incidence annually [3]. Due to excessive inflammatory reactions, patients with severe sepsis are prone to suffer from disorders of various bodily systems, and may even suffer from septic shock in severe cases; which further aggravates the disease and even brings about multiple organ dysfunction, seriously compromising the patients' life and health [4]. According to statistics, with a mortality rate higher than that of myocardial infarction, sepsis has become the main cause of death of patients except for those with heart diseases in intensive care units [5]. Due to the high morbidity and mortality of sepsis, domestic scientists and clinicians have been committed to exploring more effective diagnosis and treatment methods for it [6]. With the continuous deepening of research and the development of medical technology in recent years, remarkable progress has been made in anti-infection treatment and organ function support technology, but the underlying pathogenesis of sepsis is still under investigation, and its mortality is still high [7]. In the face of the increasingly serious clinical challenges brought by sepsis, finding an effective, convenient, and accurate marker becomes a hot topic in clinical research.

TGF-β1 is an important immune and inflammatory regulator, with crucial regulatory function in the occurrence, progression, and regression of immune inflammatory reactions [8]. In the pathway of TGF-β1 in exerting inflammatory regula-

tory function, SMAD3 is the key protein that determines the effect of TGF-β1 [9]. According to research, SMAD3 can regulate the homeostasis of the immune system by regulating inflammatory cells such as macrophages and T lymphocytes [10]. MiRNA is a non-coding microRNA with a length of about 18-25 nucleotides, which plays a crucial regulatory role in cell growth, differentiation, proliferation, and apoptosis [11]. It has been found that MiRNA is essential for a variety of diseases and related to the pathogenesis of many diseases [12]. According to references, miR-346 is involved in the chronic inflammation process by regulating IL-18 [13]. At present, the role of miR-346 in sepsis remains unclear, and there are few studies on SMAD3 in sepsis. However, both SMAD3 and miR-346 are involved in the inflammatory response, so we speculated that they may also participate in the development and progression of sepsis. Therefore, this study explored the clinical and prognostic significance of SMAD3 and miR-346 in severe sepsis, with the goal of providing novel ideas and methods for future clinical diagnosis and treatment of sepsis.

Materials and methods

General materials

Patients with sepsis after surgery in the Second Hospital of Shandong University from March 2017 to March 2019 were enrolled as a research group, and healthy individuals after surgery in the hospital during the same period were enrolled as a control group. A total of 112 sepsis patients admitted to The Second Hospital of Shandong University were enrolled as a research group, and 96 healthy individuals in physical examination were included. This experiment was approved by the Ethics Committee of The Second Hospital of Shandong University, and it was carried out with informed consent signed by all research participants, and it is in line with the Declaration of Helsinki.

Inclusion and exclusion criteria

The inclusion criteria of the research group: Patients meeting the clinical manifestation of sepsis and diagnosed with sepsis by the Second Hospital of Shandong University [14], patients who had not received hormone and immune preparation before admission, patients who received follow-up treatment in The Second Hospital of Shandong University after diagnosis, patients with detailed case data, patients willing to cooperate with the investigation, and those who had not received any adjuvant treatment before admission.

The exclusion criteria of the research group: Patients with comorbid tumors, cardio-cerebrovascular diseases, chronic diseases, mental diseases or autoimmune diseases, patients with organ failure, hepatic or renal insufficiency or drug allergy, long-term bedridden patients due to physical disability, patients unable to take care of themselves, patients transferred midway to The Second Hospital of Shandong University, and those who died during treatment.

Determination methods

Polymerase chain reaction (PCR) was employed to determine SMAD3 and miR-346 as follows: Fasting venous blood (5 mL) was sampled from each participant, let stand at room temperature for 30 min, and then centrifuged at 4000 rpm/min for 10 min for usage of the upper serum. Total RNA was extracted from the collected serum with an EasyPure miRNA Kit (ER601-01, TransGen Biotech, Beijing, China), and the concentration, purity, and integrity of the total RNA were determined using ultraviolet spectrophotometer and agarose gel electrophoresis. Subsequently, the total RNA was reversely transcribed into cDNA using a TransScript Green miRNA Two-Step qRT-PCR SuperMix (AQ202-01, TransGen Biotech, Beijing, China) according to the kit instructions for PCR amplification assay. The qPCR amplification system consisted of 20 μL total volume containing 1 μL cDNA, 0.4 μL upstream and downstream primers, 10 μL 2×TransTaq® Tip Green qPCR SuperMix, 0.4 μL Passive Reference Dye (50X), and ddH2O added to adjust the volume. The amplification conditions were as follows: Pre-denaturation at 94°C for 30 s, followed by 40 cycles of denaturation at 94°C for 5 s, and annealing and extension at 60°C for 30 s. Three replicate wells were set for each sample, and the experiment was repeated three times. The data in this assay were analyzed using 2-ΔΔc. The upstream primer of SMAD3: 5'-GTCAACAAGTGGTGGCCTGTG-3'; downstream primer: 5'-GTGTGGAGCAACATGTGGAACTCTA-3'; upstream primer of miR-346: 5'-GAGTGCCTGCCTCTCTGTTG-3'; downstream primer: 5'-GAGCAGCTCTGCCCAGG-3'.

Table 1. Comparison of general data between the two groups [n (%)]

	The research group (n=112)	The control group (n=96)	t/χ^2	*P*-value
Age (Y)	48.7±8.2	49.1±7.6	0.363	0.717
BMI (KG/cm^2)	24.62±2.84	24.78±3.38	0.371	0.711
Sex			0.121	0.728
Male	65 (58.04)	58 (60.42)		
Female	47 (41.96)	38 (39.58)		
Smoking history			0.386	0.534
Yes	57 (50.89)	53 (55.21)		
No	55 (49.11)	43 (44.79)		
Drinking history			0.079	0.779
Yes	62 (55.36)	55 (57.29)		
No	50 (44.64)	41 (42.71)		
Exercise habit			1.391	0.238
Yes	48 (42.86)	49 (51.04)		
No	64 (57.14)	47 (48.96)		
Place of residence			0.016	0.900
Urban area	86 (76.79)	73 (76.04)		
Rural area	26 (23.21)	23 (23.96)		
Nationality			0.272	0.602
Han nationality	99 (88.39)	87 (90.63)		
Minority nationality	13 (11.61)	9 (9.38)		
Family medical history			0.518	0.472
Yes	33 (29.46)	24 (25.00)		
No	79 (70.54)	72 (75.00)		

Outcome measures

Main outcome measures: The expression of SMAD3 and miR-346 in all participants in the two groups was determined, and their expression in the participants in the research group before and after treatment and participants in the control group was analyzed. In addition, the diagnostic value of SMAD3 and miR-346 in sepsis was evaluated, and the influence of each one on the prognosis of patients with sepsis was analyzed.

Secondary outcome measures: The diagnostic value of SMAD3 and miR-346 in different degrees of sepsis was analyzed.

Statistical analyses

The obtained data were statistically analyzed using SPSS 22.0, and illustrated into required figures using Graphpad 7. Enumeration data were expressed as rate, and compared between groups using the chi-square test, and measurement data were expressed as the mean ± standard deviation, and compared between groups using the t test. Data in normal distribution were analyzed using the t test and data not in a normal distribution were analyzed using the rank sum test. The diagnosis efficiency was analyzed using receiver operating characteristic (ROC) curves, and the survival rate was calculated using the Kaplan-Meier method, and compared using the Log-rank test. *P*<0.050 indicates a significant difference.

Results

Comparison of general data

There was no significant difference between the two groups in age, body mass index (BMI), sex, smoking history, drinking history, exercise habits, place of residence, nationality, and familial diseases (all *P*>0.050) **Table 1**.

Expression of SMAD3 and miR-346 before treatment

The SMAD3 expression in the research group before treatment was higher than that in the control group (P<0.05), and the miR-346 expression in the research group before treatment was lower than that in the control group (P<0.05) **Figure 1**.

Expression of SMAD3 and miR-346 in the research group before and after treatment

Comparison of SMAD3 and miR-346 expression in the research group before and after treatment revealed that after treatment, the SMAD3 expression in the research group significantly decreased, while miR-346 significantly increased (both P<0.05). **Figure 2**.

Diagnostic value of SMAD3 and miR-346 in sepsis

ROC curve analysis revealed that when the cut-off value was 25.710, the sensitivity and speci-

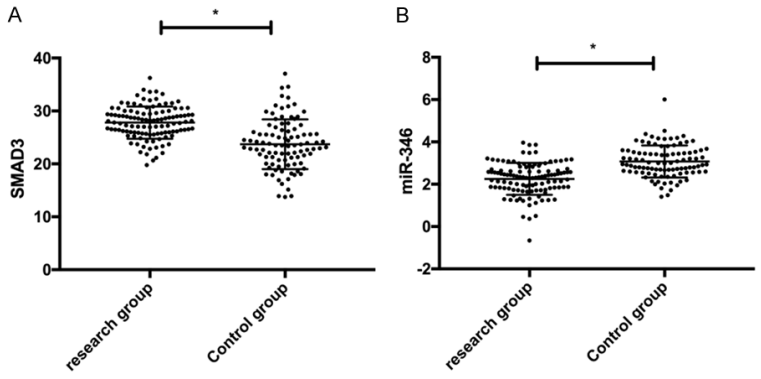

Figure 1. Expression of SMAD3 and miR-346 before treatment. A. Expression of SMAD3 in the two groups. B. Expression of miR-346 in the two groups.

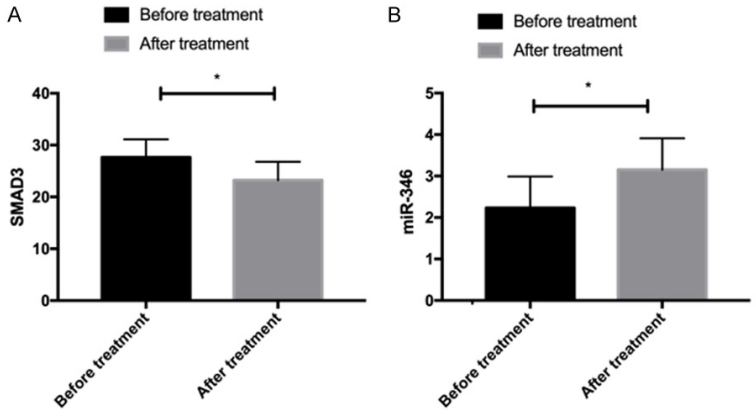

Figure 2. Expression of SMAD3 and miR-346 in the research group before and after treatment. A. Expression of SMAD3 in the research group before and after treatment. B. Expression of miR-346 in the research group before and after treatment.

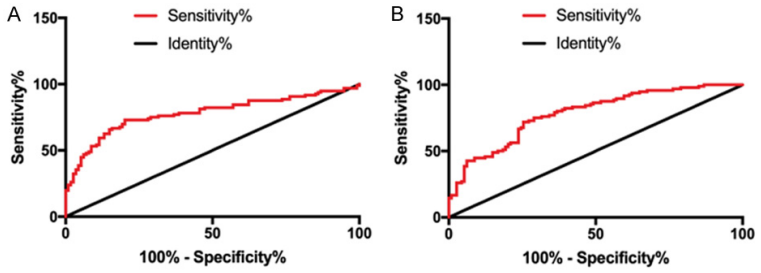

Figure 3. Diagnostic value of SMAD3 and miR-346 in sepsis. A. ROC curve of SMAD3 in diagnostic value for sepsis. B. ROC curve of miR-346 in diagnostic value for sepsis.

ficity of SMAD3 for sepsis diagnosis were 72.92% and 78.95%, respectively. When the cut-off value was 2.678, the sensitivity and specificity of miR-346 for sepsis diagnosis were 70.83% and 74.56%, respectively. **Figure 3** and **Table 2**.

Diagnostic value of SMAD3 and miR-346 in different degrees of sepsis

Patients in the research group were divided into patients with sepsis (n=78) and those with sepsis shock (n=36). ROC curves showed that when the cut-off was 27.510, the sensitivity and specificity of SMAD3 in diagnosing the deterioration from sepsis to sepsis shock in the research group were 88.89% and 76.92%, respectively. When the cut-off was 2.172, the sensitivity and specificity of miR-346 in diagnosing the deterioration were 86.11% and 67.95%, respectively **Figure 4** and **Table 3**.

Effects of SMAD3 and miR-346 on the prognosis of patients with sepsis after treatment

The patients were divided into a high SMAD3 expression group (SMAD3>23.23, n=68) and a low SMAD3 expression group (SMAD3≤23.23, n=46), and a high miR-346 expression group (miR-346>3.15, n=61) and a low miR-346 expression group (miR-346≤3.15, n=53) according to the expression of SMAD3 and miR-346. It was found that the prognosis of the low SMAD3 expression group was superior to that of the high SMAD3 expression group (P=0.004), and the prognosis of high miR-346 expression group was superior to that of the low miR-346 group (P=0.005) **Figure 5**.

Discussion

Sepsis is a prevalent clinical malignant disease, which poses a serious threat to patients in intensive care units [15]. It often occurs in patients with severe diseases such as severe burns and multiple injuries and patients after surgery [16], and it is also common in patients

Table 2. Diagnosis efficiency of SMAD3 and miR-346 in sepsis

	SMAD3	MiR-346
AUC	0.778	0.784
Std.Error	0.034	0.031
95% CI	0.712~0.845	0.723~0.845
cut-off	<25.710	>2.678
Sensitivity (%)	72.92	70.83
Specificity (%)	78.95	74.56
Youden index (%)	51.87	45.39
P-value	<0.001	<0.001

with chronic diseases such as diabetes mellitus, chronic obstructive bronchitis, leukemia, aplastic anemia, and anemia [17]. Sepsis can be caused by infection in any body part, and it is clinically common in pneumonia, peritonitis, urinary system infections, etc. [18]. The main pathogenesis of sepsis is a severe systemic inflammatory reaction caused by infection, which can result in shock and multiple organ damage and failure [19], seriously threading the life safety of patients. Therefore, there is an urgent need to find clinical potential biomarkers of sepsis. This study explored the clinical value of SMAD3 and miR-346 in severe sepsis, We have not carried out a more in-depth study to explore the exact mechanism of SMAD3 and miR-346 on sepsis, but we have preliminarily confirmed through experiments that the two are closely related to the development and progression of sepsis, and have verified through relevant experiments that SMAD3 and miR-346 have extremely high application value in the diagnosis, treatment, and prognosis of sepsis; which is of great significance for sepsis which still lacks effective observation indicators and markers. In the future, clinical determination of SMAD3 and miR-346 will help to find effective and timely intervention for sepsis in patients and improve their prognosis. In addition, based on the in-depth analysis on the mechanism of influence of SMAD3 and miR-346 on sepsis in our study, we suspected that both factors have great application prospects as therapeutic targets for sepsis.

The results of this study showed that SMAD3 was highly expressed in patients with sepsis, while miR-346 was lowly expressed, suggesting that SMAD3 and miR-346 may be involved in the development and progression of sepsis. In addition, previous studies have confirmed the increase of SMAD3 in cancer [20], and a significant decrease of miR-346 in hepatocellular carcinoma tissues [21], which also supports the results of this study. MicroRNAs (miRNAs) are small non-coding RNA molecules, which mainly regulate gene expression at the post-transcriptional level by base pairing with the 3'-untranslated region of the target mRNA, and mRNA degradation or translation inhibition [22]. MiRNA is a key regulatory factor affecting the immune response of immune cell maturation, proliferation, differentiation, and activation, antibody secretion, and release of inflammatory mediators [23]. MiR-346 is a recently discovered miRNA. Wang S and others have pointed out that miR-346 is abnormally expressed in inflammatory intestinal diseases, and Kempinska-Podhorodecka A and others [25] have verified that miR-346 is involved in the development and progression of primary cholangitis [24]. Cholangitis may clinically give rise to sepsis [26]. Sepsis is a systemic inflammatory syndrome caused by bacterial infection of various pathogenic microorganisms, so we speculated that miR-346 may also play a role in influencing the inflammatory response in sepsis. However, the mechanism of miR-346 was not determined because the basic experiment was not carried out in this study. SMAD3 is a key protein that determines the effect of TGF-β1, and TGF-β1 is a key immune and inflammatory regulator, with important regulatory functions in the development, progression, and regression of immune inflammatory responses [27]. One study has verified that TGF-β1 can inactivate mononuclear macrophages and inhibit the production of TNF-α and IL-1, thus exerting a powerful inflammatory inhibitory effect [28]. Some animal studies have revealed that SMAD3 gene-deleted mice showed an increase in the activation of T cells and mucosal immunity [29]. Furthermore, some studies have confirmed the close relationship between SMAD3 and the development and progression of septicemia and the participation of SMAD3 in septicemia [30], which further confirmed our results. Additionally, we evaluated the changes of SMAD3 and miR-346 expression in the research group before and after treatment, finding that after treatment, the SMAD3 expression in the research group significantly decreased, while miR-346 significantly increased, which also confirmed our above results. In addi-

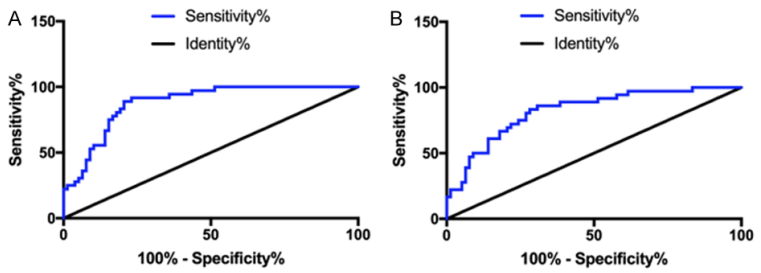

Figure 4. Diagnostic value of SMAD3 and miR-346 in patients of different degrees of sepsis. A. ROC curve of SMAD3 in diagnosing the deterioration from sepsis to sepsis shock. B. ROC curve of miR-346 in diagnosing the deterioration from sepsis to sepsis shock.

Table 3. Diagnosis efficiency of SMAD3 and miR-346 in different degrees of sepsis

	SMAD3	MiR-346
AUC	0.879	0.824
Std.Error	0.031	0.041
95%CI	0.818~0.941	0.744~0.904
cut-off	>27.510	<2.172
Sensitivity (%)	88.89	86.11
Specificity (%)	76.92	67.95
Youden index (%)	65.81	54.06
P-value	<0.001	<0.001

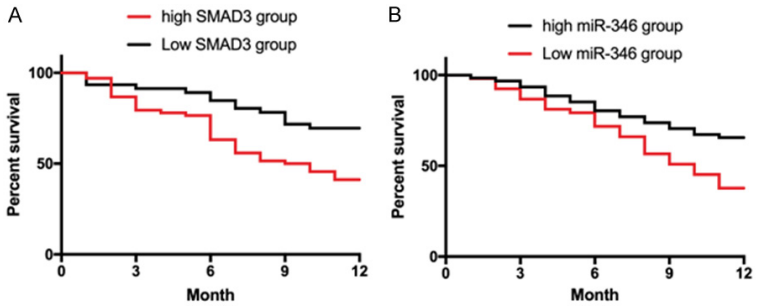

Figure 5. Prognostic survival curves of SMAD3 and miR-346 in patients with sepsis. A. One-year prognostic survival curves of the high SMAD3 expression group and the low SMAD3 expression group. B. One-year prognostic survival curves of the high miR-346 expression group and the low miR-346 expression group.

tion, it was found through analysis on the diagnostic value of SMAD3 and miR-346 in sepsis that both had a good prediction effect on the occurrence of sepsis, which also suggests that they can be used as screening indexes for sepsis in future clinical practice to improve the diagnosis rate of sepsis. Compared with traditional disease diagnosis methods, SMAD3 and miR-346 have the advantages of providing detection convenience, intuitive detection results, and requiring no clinicians' previous judgment experience for analysis of pathological results. Moreover, peripheral blood samples can be kept for a long time, which is conducive to clinical reexamination at any time. We further analyzed the diagnostic value of SMAD3 and miR-346 in different degrees of sepsis, and found that SMAD3 and miR-346 also had good diagnosis efficiency on patients from sepsis to septic shock, which implies that we can use the two as indicators to detect the progression of sepsis to understand the development of the disease. Finally, we assigned the patients to a high SMAD3 expression group and a low SMAD3 expression group, and a high miR-346 expression group and a low miR-346 expression group according to the expression of SMAD3 and miR-346, finding that the prognosis of the low SMAD3 expression group was superior to that of the high SMAD3 expression group, and the prognosis of high miR-346 expression group was superior to that of the low miR-346 group. The results revealed that SMAD3 and miR-346 were also closely related to the prognosis of patients, suggesting that clinical monitoring of SMAD3 and miR-346 can help clinicians to judge the recovery and prognosis of patients in the future.

This study aimed to explore SMAD3 and miR-346 in patients with sepsis. However, due to the limited experimental conditions, there are still some deficiencies. For instance, the research period is short, which makes it impossible to evaluate the influences of SMAD3 and miR-346 on the long-term prognosis of patients with sepsis. In addition, the study lacks the support of *in vitro* experiments, so the mechanism of SMAD3 and miR-346 affecting sepsis is still

not completely clear. Moreover, we have not analyzed the correlation between SMAD3 and miR-346. We will conduct more in-depth experiments as soon as possible to verify our point of view, and conduct more comprehensive analysis on the application of SMAD3 and miR-346 in sepsis to improve experimental results.

Conclusion

SMAD3 is highly expressed in sepsis, and miR-346 is poorly expressed in it, and both of them have good diagnostic value in sepsis and are strongly linked to the prognosis of septic patients. Therefore, they may be excellent indicators for the diagnosis and treatment of sepsis in the future.

Disclosure of conflict of interest

None.

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