

## Original Article

# Octreotide acetate combined with somatostatin upregulates miR-1291 and downregulates miR-331-3p in patients with cirrhosis and upper gastrointestinal bleeding

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**Abstract:** Objective: This study aimed to explore the efficacy of octreotide acetate combined with somatostatin (OA + SS) for the treatment of patients with cirrhosis and upper gastrointestinal bleeding (UGIB). Methods: A total of 118 patients with cirrhosis and UGIB in our hospital were enrolled from June 2018 to September 2019. Fifty-seven were treated with OA alone (Group A) whereas 61 were treated with OA + SS (Group B). Results: The therapeutic effects, inflammatory cytokines, liver function indices, and relative expression levels of miR-1291 and miR-331-3p were then observed. Compared with the patients in Group A, those in Group B had lower post-treatment inflammatory cytokine levels ( $P < 0.05$ ), better post-treatment liver function indices ( $P < 0.05$ ), lower incidences of adverse reactions ( $P < 0.05$ ), and a higher total effective rate ( $P < 0.05$ ). The OA + SS treatment group had upregulated miR-1291 and downregulated miR-331-3p ( $P < 0.05$ ). Conclusion: OA + SS therapy is safe and effective for the treatment of patients with cirrhosis and UGIB.

**Keywords:** Octreotide acetate, somatostatin, patients with cirrhosis with upper gastrointestinal bleeding, miR-1291, miR-331-3p

## Introduction

Liver cirrhosis (LC) represents the final histological change in various chronic liver diseases [1]. Because patients with LC have a high risk of acquiring bacterial infections, which causes systemic inflammation and may lead to organ failure and chronic hepatic failure, they have a high risk of short-term death [2]. LC and its complications are the major causes of morbidity and mortality at the community level [3]. One such complication, upper gastrointestinal bleeding (UGIB) [4], is due to the rupture and bleeding of varicose veins formed in the esophagus [5].

Octreotide acetate (OA), which can control the flow of blood through the portal veins and the liver, is usually combined with other drugs and presents a low incidence of adverse reactions [6]. Somatostatin (SS), a regulatory peptide

that acts as an endogenous inhibitory regulator of the secretory and proliferative responses of target cells, is released either in large quantities from the storage pool of secretory cells or in small quantities from activated immune and inflammatory cells and is widely distributed in the brain and the peripheral blood [7].

microRNAs (miRNAs), which are noncoding RNA molecules, can regulate gene expression through various mechanisms [8] and seem to participate in almost all biological processes [9]. In addition to playing a pivotal role in regulating many physiological and pathological processes, miRNAs may act as good candidates for the early detection of various diseases or as prognostic biomarkers [10]. The miRNAs miR-1291 and miR-331-3p have been shown to exhibit abnormal manifestations in a variety of diseases. According to previous studies, miR-1291 is downregulated in pancreatic cancer

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**Table 1.** Primer sequences

	Upstream primers (5'-3')	Downstream primers (5'-3')
miR-1291	TGGCCCTGACTGAAGACCA	CAGTGCCTGTCGTGGAGT
miR-331-3p	CACAACCTCGAGAACGTACAGAAGGCTCCAGAAATG	TGAAGATCTGAAGGATTAACCAACCAATTTTTCG
U6	CTCGCTTCGGCAGCACCA	AACGCTTCACGAATTTGCGT

specimens, and its restoration inhibits the tumorigenesis of pancreatic cancer cells [11, 12]. Similarly, miR-331-3p is downregulated in colorectal cancer, and its overexpression inhibits cell proliferation [13]. These findings indicate that miR-1291 and miR-331-3p have effects on cellular biological mechanisms.

In this study, the efficacy of OA combined with SS (hereinafter OA + SS) for the treatment of patients with cirrhosis and UGIB and its effects on miR-1291 and miR-331-3p were explored.

## Materials and methods

### General information

In total, 118 patients with cirrhosis and UGIB in our hospital were enrolled from June 2018 to September 2019. Of these patients, 57 were treated with OA alone (Group A) and 61 were treated with OA + SS (Group B). This study was approved by the Medical Ethics Committee of Handan Central Hospital. The patients and their families were informed of the study and signed informed consent forms.

### Inclusion and exclusion criteria

The inclusion criterion was a diagnosis of LC with active bleeding found by endoscopy or persistent red blood found in nasogastric tube aspirates [14]. The exclusion criteria were mental disorders, allergy to the drugs used in this study, and severe hepatic and renal insufficiency.

### Methods

(1) Sample collection: Postoperative venous blood (5 mL) was obtained from the patients before and after treatment, allowed to stand for 20 min, and then centrifuged in a centrifuge (10×g at 4°C for 15 min; Beijing BMH Instruments Co., Ltd., Beijing, China) to separate the serum. The serum samples were quickly frozen in liquid nitrogen and stored at -80°C for later use.

(2) Treatment methods: The patients in both groups received routine treatment upon admission, with their various signs monitored and venous access established. The blood of the patients was enriched appropriately according to the rate of hemorrhage. The patients in Group A were administered OA (0.1 mg dissolved in 20 mL of 0.9% normal saline, cat. No B2582, BioVision, Inc. US) via an intravenous drip at 25 µg/h for 12 h each day for a total of 3 days. Those in Group B were first intravenously injected with 0.25 mg of SS (cat. No 38916-34-6, GenScript Biotech Corporation, US) and then administered OA (0.1 mg dissolved in 20 mL of 0.9% normal saline) via an intravenous drip at 25 µg/h for 12 h each day for 3 days.

(3) miRNA detection: Total RNA was extracted from the serum sample according to the instructions of the mirVana™ miR Isolation Kit (Shanghai Huzhen Industrial Co., Ltd., Shanghai, China). The concentration and purity of the extracted RNA were detected using an ultraviolet spectrophotometer (Clix Science Instruments, Shanghai, China). cDNA was synthesized from the RNA by using reverse transcriptase and oligonucleotides according to the operating instructions of the manufacturer. The reverse transcription reaction system (20 µL) comprised buffer (4 µL), reverse transcriptase (2 µL), total RNA (2 µL), and RNase-free water (12 µL). The reaction was carried out in a water bath at 42°C for 1 h and then at 95°C for 5 min. PCR amplification was then carried out, using the synthesized cDNA as a template and U6 as the internal reference gene. The primer sequences used were designed by He Peng (Shanghai) Biotechnology Co., Ltd. (Shanghai, China) (Table 1). miR-1291 and miR-331-3p were quantitatively detected on a real-time fluorescence quantitative PCR system (Nanjing ZhongkeBio Medical Technology Co., Ltd., Nanjing, China) according to the instructions provided with the miRNA RT-qPCR detection kit (Genetimes Technology, Inc., Shanghai,

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**Table 2.** General information ( $\bar{x} \pm sd$ ) [n (%)]

Categories	Group A (n=57)	Group B (n=61)	t/ $\chi^2$ value	P value
Gender			0.996	0.318
Male	36 (63.16)	33 (54.10)		
Female	21 (36.84)	28 (45.90)		
Age (Years)	66.32 $\pm$ 6.35	67.14 $\pm$ 6.22	0.708	0.480
Body weight (kg)	65.44 $\pm$ 6.11	66.21 $\pm$ 6.24	0.676	0.500
Height (cm)	168.43 $\pm$ 7.34	167.25 $\pm$ 6.79	0.907	0.366
Place of residence			0.928	0.335
Countryside	34 (59.65)	31 (50.82)		
City	23 (40.35)	30 (49.18)		
Educational history			0.351	0.553
Below senior high school	33 (57.89)	32 (52.46)		
Above senior high school	24 (42.11)	29 (47.54)		
Nationality			1.409	0.235
Han	48 (84.21)	46 (75.41)		
Ethnic minorities	9 (15.79)	15 (24.59)		
Economic level			0.048	0.826
Poor	11 (19.30)	13 (21.31)		
Well-off	31 (54.38)	29 (47.54)		
Rich	15 (26.32)	19 (31.15)		
History of drinking			0.133	0.714
Yes	41 (71.93)	42 (68.85)		
No	16 (28.07)	19 (31.15)		
History of smoking			1.125	0.288
Yes	39 (68.42)	36 (59.01)		
No	18 (31.58)	25 (40.98)		
Obesity			0.389	0.532
Yes	35 (61.40)	34 (55.74)		
No	22 (38.60)	27 (44.26)		
Doing exercises			0.487	0.485
Yes	27 (47.37)	25 (40.98)		
No	30 (52.63)	36 (59.02)		
Staying up			0.552	0.457
Yes	26 (45.61)	32 (52.46)		
No	31 (54.39)	29 (47.54)		

China). The PCR system (20  $\mu$ L) comprised the upstream primer (0.4  $\mu$ L), downstream primer (0.4  $\mu$ L), and Taq DNA polymerase (0.5  $\mu$ L), and enough ddH<sub>2</sub>O to make up the final volume. The reaction conditions were pre-denaturation at 95°C for 30 s, followed by 40 cycles of 95°C for 5 s and 60°C for 30 s. Each experimental well had two replicates, and three repeated experiments were carried out. The relative expression level of the miRNAs was calculated using the 2<sup>- $\Delta\Delta$ CT</sup> method.

test. A value of  $P < 0.05$  indicated a statistically significant difference.

### Results

#### Comparison of general information

There was no difference between Groups A and B in terms of general information, such as self-condition and basic symptoms ( $P > 0.05$ , **Table 2**).

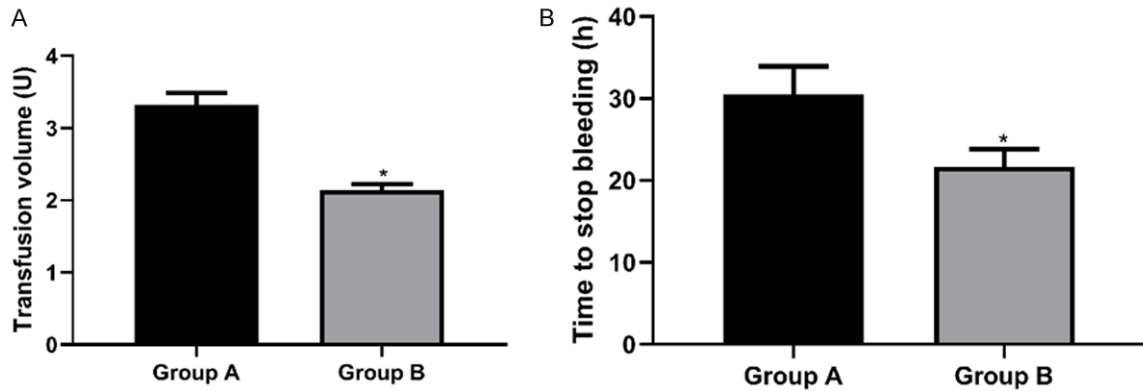
#### Outcome measures

(1) The serum levels of interleukin 6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) before and after treatment were detected using an enzyme-linked immunosorbent assay (Suzhou ELSBIO Biotechnology Co., Ltd., Suzhou, China). (2) The efficacy of each treatment was determined on the basis of the patient's symptoms [15]. "Markedly effective" indicated that the symptoms had basically disappeared and the bleeding had stopped. "Effective" indicated that the symptoms had been relieved, but the bleeding did not stop completely. "Ineffective" indicated that the symptoms were not relieved.

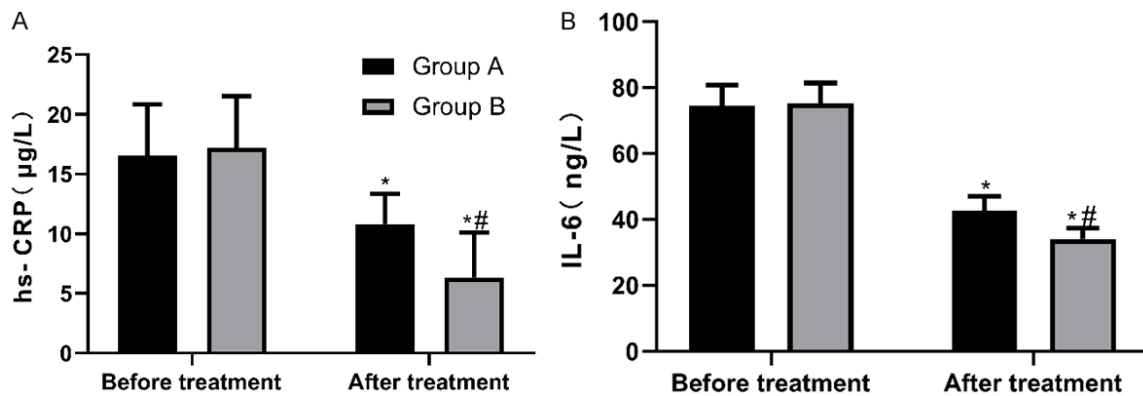
#### Statistical methods

SPSS 21.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses of the data. GraphPad Prism 8.0 (GraphPad Software Inc. US) was employed to prepare figures. The comparison of the measurement data (presented as the  $\bar{x} \pm SD$ ) between groups was analyzed using the  $t$  test, whereas the comparison of the count data [represented by n (%)] was analyzed with the Chi-square

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**Figure 1.** Comparison of blood transfusion volumes and hemostasis times. A. The blood transfusion volume in Group B was shorter than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with Group A. B. The hemostasis time in Group B was shorter than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with Group A.



**Figure 2.** Comparison of inflammatory cytokines before and after treatment. A. There was no difference in the pre-treatment hs-CRP levels between Groups A and B ( $P > 0.05$ ). After the treatment, the levels in the two groups were significantly reduced ( $P < 0.05$ ), with the level in Group B being significantly lower than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with the same group before treatment. #Indicates  $P < 0.05$  when compared with Group A. B. There was no difference in the pre-treatment IL-6 levels between Groups A and B ( $P > 0.05$ ). After the treatment, the levels in the two groups were significantly reduced ( $P < 0.05$ ), with the level in Group B being significantly lower than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with the same group before treatment. #Indicates  $P < 0.05$  when compared with Group A.

### Comparison of blood transfusion volume and hemostasis time

The blood transfusion volume was  $3.32 \pm 0.17$  U in Group A and  $2.14 \pm 0.08$  U in Group B. The hemostasis time was  $30.46 \pm 3.44$  h in Group A and  $21.68 \pm 2.13$  h in Group B. The blood transfusion volume and hemostasis time in Group B were significantly better than those in Group A ( $P < 0.05$ , **Figure 1**).

### Comparison of inflammatory cytokines

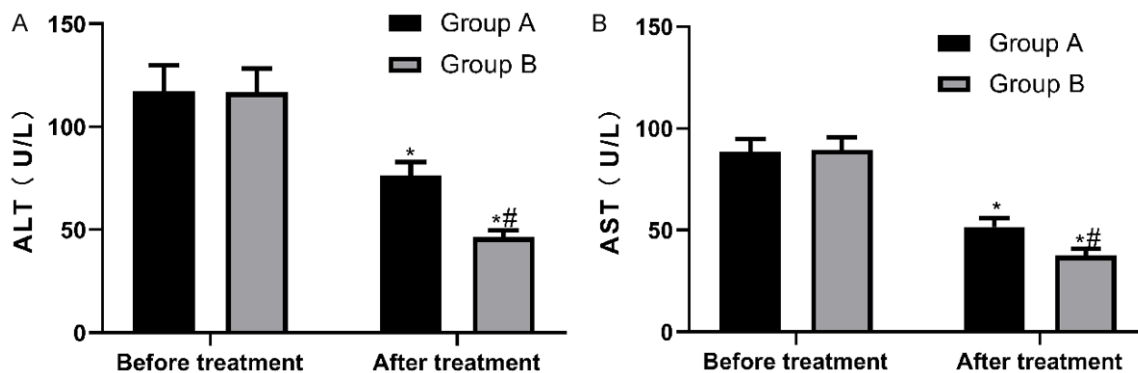
The pre- and post-treatment hs-CRP levels were respectively  $16.58 \pm 4.27$  µg/L and  $10.83 \pm 2.51$  µg/L in Group A, and  $17.21 \pm 4.33$  µg/L

and  $6.35 \pm 3.75$  µg/L in Group B. The pre- and post-treatment IL-6 levels were respectively  $74.42 \pm 6.38$  µg/L and  $42.68 \pm 4.28$  µg/L in Group A, and  $75.25 \pm 6.13$  µg/L and  $34.16 \pm 3.20$  µg/L in Group B. Generally, the inflammatory cytokine levels in Group B were significantly lower than those in Group A after the treatment ( $P < 0.05$ , **Figure 2**).

### Comparison of liver function before and after treatment

The pre- and post-treatment ALT levels were respectively  $117.32 \pm 12.48$  U/L and  $76.25 \pm 6.54$  U/L in Group A, and  $116.65 \pm 11.69$  U/L and  $116.65 \pm 11.69$  U/L in Group B. The pre-

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**Figure 3.** Comparison of liver function indices before and after treatment. A. There was no difference in the pre-treatment ALT levels between Groups A and B ( $P > 0.05$ ). After the treatment, the levels in the two groups were significantly reduced ( $P < 0.05$ ), with the level in Group B being significantly lower than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with the same group before treatment. #Indicates  $P < 0.05$  when compared with Group A. B. There was no difference in the pre-treatment AST levels between Groups A and B ( $P > 0.05$ ). After the treatment, the levels in the two groups were significantly reduced ( $P < 0.05$ ), with the level in Group B being significantly lower than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with the same group before treatment. #Indicates  $P < 0.05$  when compared with Group A.

**Table 3.** Comparison of adverse reactions [n (%)]

Adverse reactions	Group A (n=57)	Group B (n=61)	$\chi^2$ value	$P$ value
Mild abdominal pain	4 (7.02)	1 (1.64)	-	-
Dizziness	3 (5.26)	0 (0.00)	-	-
Fever	2 (3.51)	1 (1.64)	-	-
Vomiting	2 (3.51)	0 (0.00)	-	-
Arrhythmia	3 (5.26)	2 (3.28)	-	-
Palpitation and chest tightness	2 (3.51)	1 (1.64)	-	-
Total incidence	16 (28.07)	5 (8.20)	7.955	0.004

**Table 4.** Comparison of efficacy [n (%)]

	Group A (n=57)	Group B (n=61)	$t/\chi^2$ value	$P$ value
Markedly effective	14 (24.56)	29 (47.54)	-	-
Effective	25 (43.86)	28 (45.90)	-	-
Ineffective	18 (31.58)	4 (6.56)	-	-
Total effective rate	39 (68.42)	57 (93.44)	12.161	0.011

and post-treatment AST levels were respectively  $88.45 \pm 6.31$  U/L and  $51.57 \pm 4.28$  U/L in Group A, and  $89.39 \pm 6.22$  U/L and  $37.41 \pm 3.62$  U/L in Group B. Overall, the liver function indices in Group B were significantly better than those in Group A ( $P < 0.05$ , **Figure 3**).

### Comparison of adverse reactions and treatment efficacy

The incidence of adverse reactions in Group B was significantly lower than that in Group A ( $P < 0.05$ , **Table 3**). The total effective rate of the

treatments was significantly higher in Group B than in Group A ( $P < 0.05$ , **Table 4**).

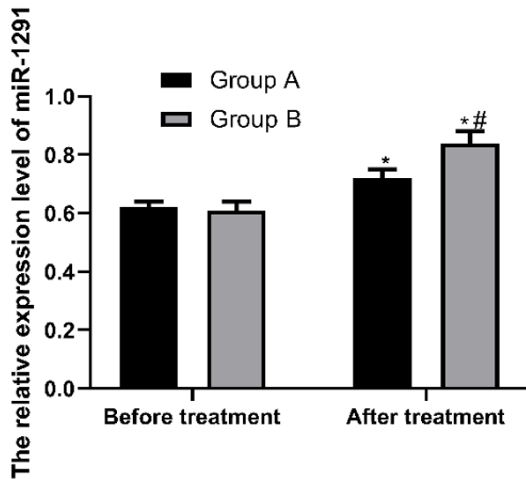
### Relative miR-1291 and miR-331-3p expression levels before and after treatment

The relative miR-1291 expression levels in Group A were  $0.62 \pm 0.02$  and  $0.72 \pm 0.03$  before and after treatment, respectively, whereas those in Group B were  $0.61 \pm 0.03$  and  $0.84 \pm 0.04$ . The relative expression level of miR-1291 was elevated by the combination treatment (**Figure 4**). The relative expression levels of miR-331-3p in Group A were  $1.87 \pm 0.13$  and  $1.65 \pm 0.09$  before and after treatment, respectively, whereas those in Group B were  $1.88 \pm 0.11$

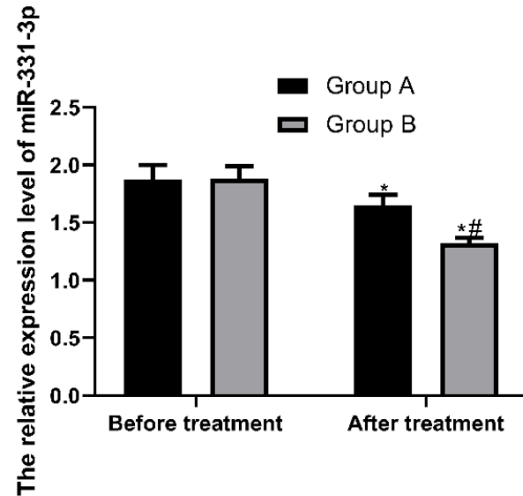
and  $1.32 \pm 0.05$ . The results indicated that the relative expression level of miR-331-3p had been significantly reduced by the combination treatment (**Figure 5**). The relative expression levels of miR-1291 and miR-331-3p were closely correlated with the clinical features of LC ( $P < 0.05$ , **Table 5**).

### Discussion

Chronic and low-grade inflammation is a pathway through which social and behavioral variables exert long-term effects on health, with



**Figure 4.** Relative miR-1291 expression levels before and after treatment. Before the treatment, there was no significant difference in the relative expression levels of miR-1291 between Groups A and B ( $P > 0.05$ ). After the treatment, the levels in the two groups were significantly increased ( $P < 0.05$ ), with the level in Group B being significantly higher than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with the same group before treatment. #Indicates  $P < 0.05$  when compared with Group A.



**Figure 5.** Relative miR-331-3p expression levels before and after treatment. Before the treatment, there was no significant difference in the relative expression levels of miR-331-3p between Groups A and B ( $P > 0.05$ ). After the treatment, the levels in the two groups were significantly increased ( $P < 0.05$ ), with the level in Group B being significantly higher than that in Group A ( $P < 0.05$ ). Note: \*Indicates  $P < 0.05$  when compared with the same group before treatment. #Indicates  $P < 0.05$  when compared with Group A.

IL-6 and CRP being the two most commonly used biomarkers of the inflammatory condition [16]. As a pleiotropic cytokine that plays a central role in the comprehensive immune defense network against infection, IL-6 functions through classical or anti-signaling pathways to produce different immune responses to different types of infection [17]. This cytokine is crucial for maintaining homeostasis of the dynamic processes in liver cells and acts as an effective mitogen for those cells, inducing liver regeneration and liver metabolic function [18]. As an acute reactant, hs-CRP expression is known to be increased in chronic liver diseases and spontaneous bacterial peritonitis; thus, its level can be used as an alternative prognostic marker for patients with cirrhosis and spontaneous bacterial peritonitis [19]. Our results showed that the inflammatory cytokine levels were lower and the liver function indices were better in the patients in Group B, suggesting that OA + SS therapy has a good curative effect. The continuous activation of inflammation leads to adverse pathophysiological reactions, which is possibly the reason for the lower incidence of adverse reactions in this experiment. A similar study had revealed that the combina-

tion of OA and SS could significantly improve the recovery of leukocytes, blood glucose, and blood calcium and reduce the occurrence of complications in patients with non-metastatic castration-resistant prostate cancer [20]. These studies collectively indicate that the combination treatment causes fewer adverse reactions and is effective for inflammation control.

miRNAs, which are important regulators of gene expression [21], achieve their effects by binding to and preventing the translation of mRNAs [22]. Some miRNAs have significant effects on the development, progression, and treatment of diseases, functioning as oncogenes or tumor suppressor genes in various cancers [23]. According to a previous study, miR-1291 is a biologically relevant regulator of glypican-3 gene expression in liver cancer cells and acts by silencing the endoplasmic reticulum stress sensor inositol-requiring transmembrane kinase/endoribonuclease 1 $\alpha$  [24]. Meanwhile, because the serum miR-331-3p level is significantly increased in patients with hepatocellular carcinoma, it acts as a diagnostic and prognostic biomarker for the disease

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**Table 5A.** Correlation between relative miR-1291 expression level and clinical features

	n	miR-1291		$\chi^2$	P
		High expression (48)	Low expression (70)		
Age (Years)				1.677	0.195
≤ 60	40	13	27		
> 60	98	35	43		
Gender				1.244	0.264
Male	69	31	38		
Female	49	17	32		
Bleeding volume (mL)				12.761	0.001
≤ 800	87	27	60		
> 800	31	21	10		
Classification [16]				31.742	< 0.001
A	46	33	13		
B	58	10	48		
C	14	5	9		

**Table 5B.** Correlations between relative expression levels of miR-1291 and miR-331-3p and clinical features

	n	miR-331-3p		$\chi^2$	P
		High expression (67)	Low expression (51)		
Age (Years)				0.078	0.779
≤ 50	40	22	18		
> 50	98	45	33		
Gender				0.197	0.656
Male	69	38	31		
Female	49	29	20		
Bleeding volume (mL)				23.161	< 0.001
≤ 800	87	38	49		
> 800	31	29	2		
Classification				29.982	< 0.001
A	46	12	34		
B	58	46	12		
C	14	9	5		

[25, 26]. LC creates an environment in which hepatocytes become cancerous [27] and is considered to be the end stage of chronic liver diseases that may lead to hepatocellular carcinoma [28]. Therefore, we suspected that miR-1291 and miR-331-3p play a pathogenic role in the progression of LC. In this study, the OA + SS treatment, with its high liver function improvement effects, also upregulated miR-1291 and downregulated miR-331-3p, suggesting that these two miRNAs may be pathogenic factors

and that the changes in their expression may significantly benefit patients with cirrhosis and UGIB. However, there is as yet no clear indication that the combination treatment regulates the two miRNAs; this topic is worthy of further research.

Although we proved that the additional use of SS was effective for the treatment of patients with cirrhosis and UGIB, our study still had some shortcomings. We did not investigate the mechanism underlying the efficacy of OA + SS in our patient cohort or study the effects of the combination treatment on miR-1291 and miR-331-3p in depth. We will continue to explore these aspects in the future. Nevertheless, in summary, OA + SS therapy, which effectively upregulates miR-1291 and downregulates miR-331-3p, is safe and effective for the treatment of patients with cirrhosis and UGIB.

### Disclosure of conflict of interest

None.

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