

Diagnostic value of miR-155 for acute lung injury/acute respiratory distress syndrome in patients with sepsis

Journal of International Medical Research

48(7) 1–9

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DOI: 10.1177/0300060520943070

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Zhou-Feng Wang¹, Yu-Min Yang² and Heng Fan² 

Abstract

Objective: We aimed to investigate the diagnostic value of microRNA-155 (miR-155) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) in patients with sepsis.

Methods: In this prospective study, we used Spearman correlation analysis to investigate relationships between miR-155 expression and inflammatory factors, oxygenation ratio (PaO₂/FiO₂), and ALI/ARDS score, and used area under the receiver operating characteristic curve (AU-ROC) to evaluate miR-155's diagnostic accuracy for ALI/ARDS in patients with sepsis.

Results: In total, 156 patients with sepsis were enrolled in our study, of which 41 had ALI and 32 had ARDS. miR-155 expression in plasma of patients with sepsis and ALI/ARDS was significantly higher than that of patients with sepsis but no ALI/ARDS. The miR-155 level in patients with sepsis and ALI/ARDS was positively correlated with interleukin (IL)-1 β and tumor necrosis factor (TNF)- α levels and ALI/ARDS score, but negatively correlated with PaO₂/FiO₂. The AU-ROC of plasma miR-155 for diagnosis of sepsis with ALI/ARDS was 0.87, and plasma miR-155, IL-1 β , and TNF- α had high sensitivity and specificity for the diagnosis of sepsis with ALI/ARDS.

Conclusion: miR-155 is highly expressed in plasma of patients with septic ALI/ARDS; it is positively correlated with lung function and can be used for early diagnosis.

Keywords

miR-155, acute lung injury, sepsis, acute respiratory distress syndrome, prognosis, PaO₂/FiO₂ ratio

Date received: 18 January 2020; accepted: 26 June 2020

¹Department of Respiratory and Critical Care, Ningbo First Hospital Longshan Hospital Medical and Health Group, Ningbo, Zhejiang Province, P. R. China

²Department of Intensive Care Unit, Ningbo First Hospital, Ningbo, Zhejiang Province, P. R. China

Corresponding author:

Heng Fan, Department of Intensive Care Unit, Ningbo First Hospital, No. 59 Liuting Road, Ningbo, Zhejiang Province, 315000, P.R. China.
Email: peterbenny@163.com



Introduction

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) refers to a sudden decline in lung gas exchange function caused by various non-cardiac pathogenic factors such as sepsis, harmful gas inhalation, radiation and chemotherapy, trauma, shock, and severe pancreatitis, among others.¹ Sepsis is a leading cause of death in intensive care unit (ICU) patients, and the lungs are the earliest affected organs.² The incidence of ALI/ARDS in patients with sepsis is 40% to 60%, and the mortality ranges from 35% to 40%.³ The main clinical manifestations of patients with septic ALI/ARDS are refractory hypoxemia and respiratory distress.

An important feature of septic ALI/ARDS is pulmonary edema, an increase in pulmonary vascular endothelial permeability leading to an increase in extravascular lung water, causing refractory hypoxemia. The severity of pulmonary edema is closely related to the prognosis of patients with septic ALI/ARDS, which is associated with high mortality.⁴ In the case of sepsis, various inflammatory factors and mediators are released and activated in large quantities, and the imbalance between inflammatory and anti-inflammatory factors damages lung tissue and promotes the development of ALI/ARDS.⁵

Identifying new biomarkers of ALI/ARDS for early diagnosis and treatment is an important approach to improve the prognosis of patients with sepsis. Studies on the relationship between microRNAs (miRNAs) and tumors have become a hot topic in the medical community. With deepening research into miRNAs, many studies have confirmed that miRNAs are involved in the occurrence and development of ALI. A recent study showed that miR-155 can be secreted into the blood of patients with sepsis through the Ang-2-Tie-2 pathway.⁶ Another study indicated that miR-155 can

be used as a novel biomarker to predict mortality and outcomes in patients with septic ALI/ARDS.⁷ Therefore, detecting the expression of miRNAs in plasma samples of patients with sepsis may help identify key factors for predicting ALI. In the present study, we investigated the relationship between miR-155 expression and the levels of inflammatory factors and lung function loss in patients with sepsis, and to determine the diagnostic value of miR-155.

Materials and methods

Inclusion and exclusion criteria

We conducted a prospective cohort study, and enrolled 156 patients with sepsis who were admitted to the ICU Center of Ningbo First Hospital from September 2016 to August 2019. Inclusion criteria were as follows: (1) adults (age >18 years) admitted to our ICU center; (2) diagnosed with sepsis before enrollment;⁸ and (3) had complete data during hospitalization and follow-up. Exclusion criteria were as follows: (1) length of ICU stay <24 hours; (2) pregnancy or lactation; or (3) patients with other serious illnesses or complications such as cardiothoracic surgery, severe liver or kidney dysfunction, acute coronary syndrome, malignant tumor, or autoimmune disease. The study met the requirements of medical ethics, and was approved by the hospital medical ethics committee. All patients or their family members provided written informed consent.

Related definitions and grouping

The diagnostic criterion for sepsis was life-threatening organ dysfunction caused by host dysregulation of infection, consistent with the diagnostic criteria of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).⁸

Diagnosis of ALI/ARDS was in line with the diagnostic criteria of the 2012 New Berlin Definition.⁹ We used the standard from Peek et al.¹⁰ for ALI/ARDS score, and divided sepsis patients into three groups according to oxygenation index (ratio of arterial oxygen partial pressure to fractional inspired oxygen; $\text{PaO}_2/\text{FiO}_2$): >300 for the sepsis with no ALI/ARDS group; 200 to 300 for the sepsis with ALI group; <200 for the sepsis with ARDS group. All patients with ALI/ARDS underwent mechanical ventilation based on the ARDSNET ventilator regulations established in the 2004 guidelines for the treatment of severe sepsis and sepsis shock.^{2,10}

Detection of inflammatory factors and miR-155

Blood was collected from septic patients within 24 hours after enrollment and centrifuged at $845 \times g$ for 5 minutes; the supernatant was stored in a refrigerator at -80°C . We used ELISA to measure interleukin (IL)- 1β and tumor necrosis factor (TNF)- α levels in plasma. Total RNA of plasma was extracted by TRIzol reagent (BOSD Co., Wuhan, China). We used real-time quantitative-PCR (RT-qPCR) to detect miR-155 expression in plasma samples. The primer sequences for miR-155 were (forward) 5'-CCTGCACTCAGGGCTGCCAACACT-3' and (reverse) 5'-GGCATCATTGCCGCACGAATCAGC-3'. We performed RT-qPCR of miR-155 by TaqMan advanced miRNA system (Invitrogen Co., Shanghai, China) and used U6 small nuclear RNA as an internal reference to calculate the $2^{-\Delta\Delta\text{Ct}}$ value.

Clinical data collection

We collected detailed clinical data from patients with sepsis, including age, sex, primary disease, blood gas analysis results, $\text{PaO}_2/\text{FiO}_2$, lung injury score, renal

function, liver function, electrolytes, length of ICU and hospital stays, acute physiology and chronic health evaluation (APACHE II) score, 28-day mortality, and hospital mortality.

Statistical methods

We used SPSS version 23.0 software (IBM Corp., Armonk, NY, USA) to perform statistical analysis on the data. Descriptive data were expressed as mean \pm standard deviation or percentage as appropriate. We used the *t* test to compare differences between the two groups for measurement data and the Chi-square test for count data. We used Spearman correlation analysis to investigate the relationship between miR-155 expression and levels of inflammatory factors, $\text{PaO}_2/\text{FiO}_2$ ratio, and ALI/ARDS score, and used the area under the receiver operating characteristic curve (AU-ROC) to evaluate the diagnostic accuracy of miR-155. $P < 0.05$ was considered statistically significant.

Results

General characteristics of patients

A total of 156 patients with sepsis were enrolled in our study, of which 41 (26.3%) had sepsis with ALI and 32 (20.5%) had sepsis with ARDS. The details of patients with sepsis are shown in Table 1. There were no significant differences in age, sex, body mass index, or source of infection between groups. However, patients with septic ALI had significantly higher APACHE II score and arterial blood lactate, significantly decreased lung function, increased length of ICU and hospital stays, and increased 28-day mortality and hospital mortality compared with patients with sepsis without ALI/ARDS. Moreover, compared with patients with septic ALI, patients with septic ARDS

Table 1. General characteristics of patients with sepsis.

Variable	Sepsis, no ALI/ARDS (n = 83)	Sepsis and ALI (n = 41)	Sepsis and ARDS (n = 32)
Age (years)	59.2 ± 8.7	61.6 ± 9.3	62.0 ± 8.9
Sex (male/female)	37/46	19/22	14/18
Body mass index (kg/m ²)	25.7 ± 4.8	26.4 ± 4.6	28.5 ± 5.2
APACHE II score	16.3 ± 3.1	21.6 ± 5.2***	22.8 ± 5.7
PaO ₂ /FiO ₂ ratio	321.9 ± 21.8	241.8 ± 13.2**	141.2 ± 7.6####
Arterial blood lactate (mg/dL)	1.8 ± 0.6	2.3 ± 0.9***	2.9 ± 1.1###
Mechanical ventilation			
Mechanical ventilation days	3.1 ± 1.6	7.9 ± 2.1***	8.6 ± 2.4
FiO ₂ (%)	34.2 ± 6.9	42.6 ± 7.9*	43.1 ± 8.2
Tidal volume (mL)	504.2 ± 37.6	521.7 ± 41.2	539.4 ± 42.6
PEEP (cm H ₂ O)	4.7 ± 2.1	7.5 ± 3.5***	8.4 ± 3.6#
Cdyn (mL/mbar)	201.4 ± 49.2	143.2 ± 35.8***	102.6 ± 26.5###
ALI/ARDS score	1.1 ± 0.2	3.2 ± 0.8***	5.6 ± 1.3###
Infected site (n)			
Lung	27 (32.5%)	12 (29.2%)	7 (21.9%)
Urinary tract	11 (13.3%)	6 (14.6%)	4 (12.5%)
Abdominal cavity	36 (43.4%)	16 (39.0%)	13 (40.6%)
Blood flow	4 (4.8%)	3 (7.4%)	3 (9.4%)
Skin soft tissue	5 (6.0%)	4 (9.8%)	5 (15.6%)
Length of ICU stay (days)	7.2 ± 3.8	12.4 ± 4.9***	16.7 ± 5.1#
Length of hospital stay (days)	11.6 ± 4.8	21.3 ± 6.1***	24.1 ± 6.9#
28-day mortality	7 (8.4%)	16 (39.0%)*	18 (56.3)
Hospital mortality	7 (8.4%)	19 (46.3%)*	21 (65.6%)

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; APACHEII, Acute Physiologic and Chronic Health Evaluation II; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP, positive end expiratory pressure; Cdyn, dynamic compliance of lung; ICU, intensive care unit. **p* < 0.05, ***p* < 0.01, ****p* < 0.001 vs. Septic no-ALI; #*p* < 0.05, ###*p* < 0.01, ####*p* < 0.001 vs. Septic ALI.

had increased APACHE II score and arterial blood lactate and a more severe degree of lung injury.

Level of plasma miR-155 in patients with septic ALI/ARDS

To investigate the expression of inflammatory factors in patients with septic ALI/ARDS, we used ELISA to detect the levels of IL-1β and TNF-α. Plasma levels of IL-1β and TNF-α were significantly higher (*p* < 0.001) in patients with septic ALI than in patients with sepsis but no ALI or ARDS. The levels of IL-1β and

TNF-α in plasma of patients with septic ARDS were significantly higher (*p* < 0.001) than those of patients with septic ALI (Figure 1a, b). We used RT-qPCR to detect the expression of miR-155 in patients with sepsis. Expression of miR-155 was 1.3 (±0.2)-fold higher in patients with septic ALI than in those with sepsis without ALI/ARDS, and the difference between the two groups was significant (*p* < 0.001) (Figure 1c). In addition, expression of miR-155 in patients with septic ARDS was significantly higher (*p* < 0.001) than that of patients with septic ALI (Figure 1c).

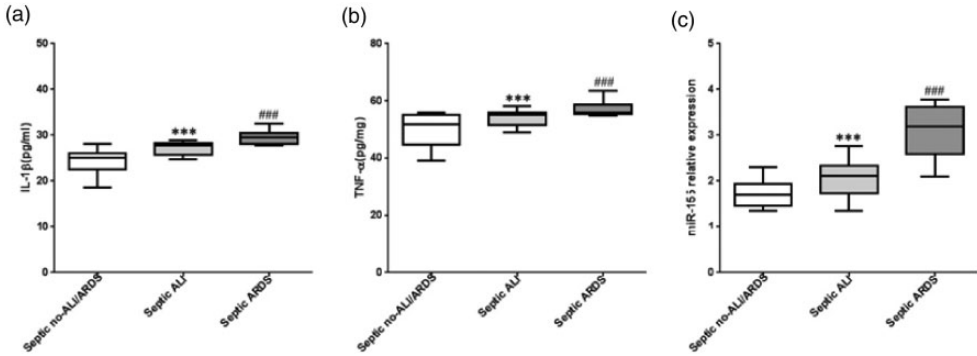


Figure 1. Boxplots showing expression of IL-1 β , TNF- α , and plasma miR-155 in patients with septic ALI/ARDS. (a) Level of IL-1 β in the plasma of patients with sepsis; (b) level of TNF- α in the plasma of patients with sepsis; (c) expression of plasma miR-155 in patients with sepsis. The box indicates the middle 50%, the line indicates the median, and the whiskers indicate the range of values. *** $p < 0.001$ vs. patients with sepsis but no ALI/ARDS; #### $p < 0.001$ vs. patients with sepsis and ALI.

IL-1 β , interleukin-1 β ; TNF- α , tumor necrosis factor- α ; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Correlation between miR-155 and pulmonary function

To investigate the relationship between miR-155 expression and levels of inflammatory factors, PaO₂/FiO₂ ratio, and ALI/ARDS score in patients with septic ALI/ARDS, we used Spearman correlation analysis to determine the relationships among them. Expression of miR-155 in patients with septic ALI/ARDS was positively correlated with the levels of IL-1 β ($r = 0.402$, $p < 0.001$; Figure 2a) and TNF- α ($r = 0.478$, $p < 0.001$; Figure 2b). Expression of miR-155 in patients with septic ALI/ARDS was negatively correlated with pulmonary function index PaO₂/FiO₂ ratio ($r = -0.680$, $p < 0.001$; Figure 2c) but positively correlated with ALI/ARDS score ($r = 0.775$, $p < 0.001$; Figure 2d).

Use of plasma miR-155 to predict septic ALI/ARDS

To clarify the accuracy of plasma miR-155 expression in the diagnosis of patients with septic ALI/ARDS, we used the AU-ROC to determine the correlation between them.

The AU-ROC of plasma miR-155 for the prediction of septic ALI/ARDS is shown in Figure 3. We found that the AU-ROC for diagnosis of septic ALI/ARDS was 0.89 for plasma IL-1 β , 0.80 for plasma TNF- α , and 0.87 for plasma miR-155. We also tested the sensitivity, specificity, and threshold levels of miR-155, IL-1 β , TNF- α , and arterial blood lactate. We found that plasma miR-155, IL-1 β , and TNF- α , but not arterial blood lactate, could be used to predict development of septic ALI/ARDS (Table 2).

Discussion

The etiology and pathogenesis of ALI is complex; its mortality rate is >40%, and the quality of life of patients is severely affected.¹¹ ALI has become one of the most difficult issues in the study of critical care. Sepsis is a systemic inflammatory response syndrome caused by infection, which leads to multiple organ dysfunction.¹² The lungs are among the most vulnerable target organs in patients with sepsis, prone to ALI, and severe patients

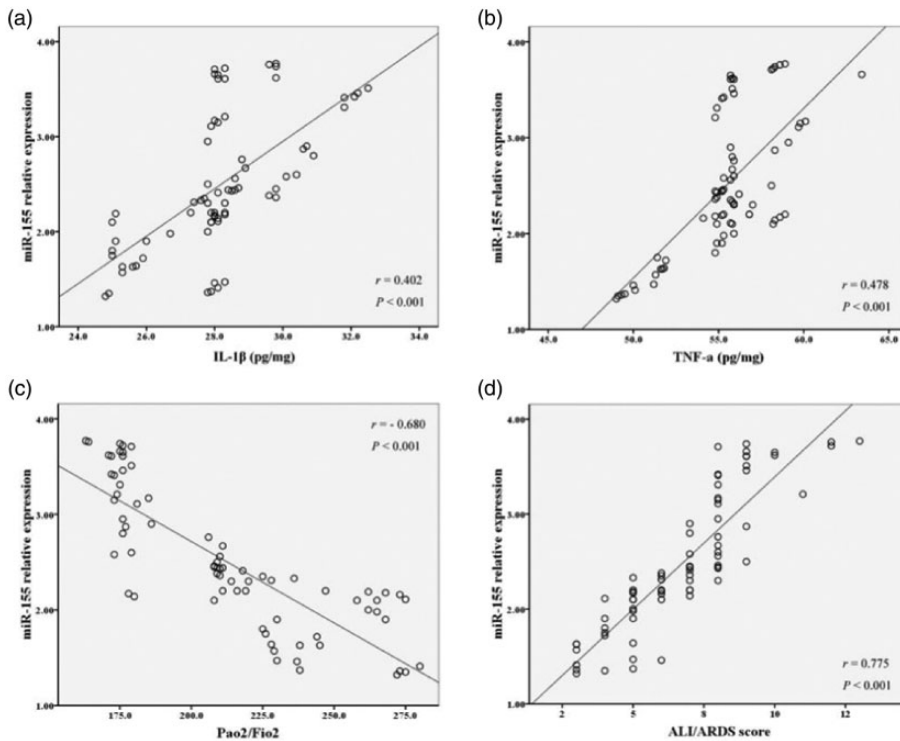


Figure 2. Correlations between miR-155 expression and pulmonary function in patients with ALI/ARDS. (a) correlation between miR-155 expression and IL-1 β level; (b) correlation between miR-155 expression and TNF- α level; (c) correlation between miR-155 expression and PaO₂/FiO₂ ratio; (d) correlation between miR-155 expression and ALI/ARDS score.

IL-1 β , interleukin-1 β ; TNF- α , tumor necrosis factor- α ; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

can develop into ARDS.^{13,14} The pathogenesis of sepsis-associated ALI has not been fully elucidated, but it is clear that an inflammatory cell-mediated uncontrolled inflammatory response is key in its pathogenesis, including TNF- α and IL-1 β as potent pro-inflammatory factors.¹⁵ However, neutrophils are the main effector cells in sepsis and bacterial infection, and it is necessary to understand their role in patients with ALI/ARDS or sepsis.¹⁶ We collected detailed clinical data of patients with sepsis and detected plasma levels of IL-1 β and TNF- α . Levels of IL-1 β and TNF- α were significantly higher in patients with septic ALI than in those with sepsis

without ALI/ARDS. Moreover, the expression of IL-1 β and TNF- α was significantly higher in plasma of patients with septic ARDS than in patients with septic ALI.

In recent years, studies have found that miRNAs are closely related to the development and prognosis of lung diseases, including lung pneumonia, lung cancer, and pulmonary fibrosis.¹⁷ MicroRNAs are small noncoding gene expression regulators, with highly conserved, endogenous single-stranded RNA; miRNAs degrade or suppress expression by binding to the 3' untranslated region of the target gene. Wang et al.¹⁸ showed that miR-155 expression is significantly increased in

lipopolysaccharide-induced ALI, and *IL6* mRNA expression was increased in wild-type mice but significantly decreased in miR-155 knockout mice. Rao et al.¹⁹ analyzed the miRNA expression profile of mice exposed to staphylococcal enterotoxin B in ALI and found that miR-155 was increased significantly.

In the present study, we used Spearman correlation analysis to determine relationships between miR-155 expression and inflammatory factors, PaO₂/FiO₂ ratio, and ALI/ARDS score. We found that expression of miR-155 in patients with

septic ALI/ARDS was positively correlated with expression of IL-1 β and TNF- α . Thus, we hypothesized that miR-155 could regulate the expression of various cytokines, including inflammatory factors, by binding to target genes. We found that expression of miR-155 in patients with septic ALI/ARDS was negatively correlated with the pulmonary function index PaO₂/FiO₂ ratio but positively correlated with ALI/ARDS score. Our results confirmed that expression of miR-155 is positively correlated with lung function and disease severity in patients with sepsis ALI/ARDS, and thus can be used as an important predictor of prognosis.

Early diagnosis of ALI/ARDS in patients with sepsis is key to timely intervention and improved survival. Han et al.⁷ detected the expression of miR-155 by RT-qPCR, and suggested that miR-155 can be used as an important predictor of mortality in patients with septic ALI/ARDS. There are many indicators for clinical diagnosis of ALI/ARDS in patients with sepsis, such as oxygenation index, ventilator setting parameters, and computed tomography. However, most of these indicators lack specificity and sensitivity and are susceptible to multiple factors. In our study, we used the AU-ROC to determine the accuracy of plasma miR-155 expression in the diagnosis of patients with septic ALI/ARDS. Plasma miR-155 had high sensitivity and specificity for diagnosis of ALI/ARDS in patients

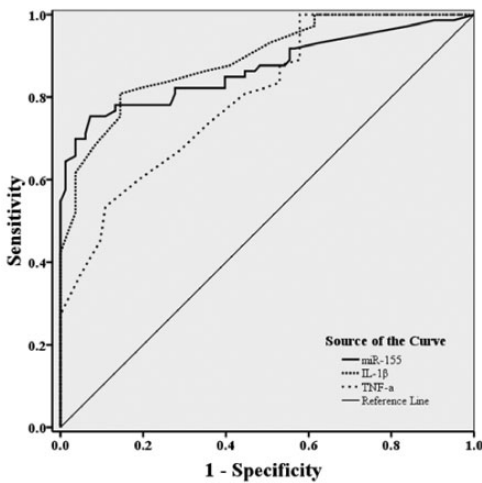


Figure 3. Use of plasma miR-155 for prediction of septic ALI/ARDS.

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Table 2. Plasma miR-155 for predicting the development of septic ALI/ARDS.

Variable	AU-ROC	95% CI	p-value	Threshold value	Sensitivity (%)	Specificity (%)
Plasma miR-155	0.87	0.81–0.93	<0.001	1.43	95.9	77.1
Plasma IL-1 β (pg/mL)	0.89	0.84–0.94	<0.001	24.8	90.1	62.7
Plasma TNF- α (pg/mL)	0.80	0.73–0.87	0.001	49.8	89.8	69.3
Lactate (mg/dL)	0.47	0.41–0.53	0.56	–	–	–

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; AU-ROC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; IL-1 β , interleukin-1 β ; TNF- α , tumor necrosis factor- α .

with sepsis, suggesting that miR-155 could be used as an important indicator.

Our study had the following limitations. First, it was a single-center prospective study with a limited sample number. Second, patients with sepsis often have multiple complications, and lung injury may not be the only complication. We excluded patients with sepsis who had more serious diseases. Third, we only studied samples collected at the time of diagnosis of the disease, so the results might be affected by factors such as regional climate, diet, or life-style, among others. Fourth, when analyzing relevant data, we did not consider other factors affecting the patient, such as mild liver or renal disease.

In conclusion, although this experimental and clinical study adds to our understanding of the occurrence and development of ALI/ARDS patients with sepsis, the underlying mechanism is not fully elucidated. We confirmed that miR-155 is highly expressed in patients with septic ALI/ARDS and high expression is positively correlated with worse pulmonary function. Thus, miR-155 can be used for early diagnosis, and targeted therapy for miR-155 should be the main direction of future research.

Declaration of conflicting interest


The authors declare that there is no conflict of interest.

Funding

This research was supported by Zhejiang Provincial Natural Science Foundation of China (under grant no. LQ18H150001), the Zhejiang Provincial Medical and Health Science Fund of China (under grant no. 2020KY815), and the Cixi Agricultural and Social Development Project (under grant no. CN2019035). The funding sources had no role in study design, data collection, data analysis, data interpretation, writing of the

report, or decision to submit the manuscript for publication.

ORCID iD

Heng Fan  <https://orcid.org/0000-0003-4519-1130>

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