Received: 27 January 2022 | Revised: 8 March 2022 | Accepted: 9 March 2022

DOI: 10.1002/jcla.24358

RESEARCH ARTICLE

WILEY

Clinical value of serum miR-320-3p expression in predicting the prognosis of sepsis-induced acute kidney injury

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Abstract

Background: For investigating the expression of miR-320-3p in children with sepsis-induced acute kidney injury (AKI) and its prognostic value.

Methods: A total of 142 patients were grouped into a survival group (n = 95) and death group (n = 47), which was based on their 28-day survival. Serum degrees of miR-320-3p, neutrophil gelatinase-associated lipid carrier protein (NGAL) and kidney injury molecule-1 (KIM-1) were detected. The Acute Physiology and Chronic Health scoring system II (APACHE II) marks were recorded. Target gene forecast and functional enrichment discussion of miR-320-3p were performed, and a protein–protein interaction (PPI) network diagram was plotted by applying bioinformatics methods. Multivariate logistic regression, ROC curve and Pearson correlation analysis were applied.

Results: The death group showed greatly higher serum levels of miR-320-3p, KIM-1 and APACHE II scores than the survival group ($p < 0.01$). Multivariate logistic regression analysis showed that levels of miR-320-3p, NGAL, KIM-1 and APACHE II scores were independent risk elements for death in sepsis children with AKI ($p < 0.01$). According to ROC curve analysis, the region under the curve (0.963, 95% CI: 0.908–0.996) of miR-320-3p, NGAL, KIM-1 levels and APACHE II scores combined to forecast the death of kids suffering from sepsis and AKI were the biggest. According to correlation analysis, the expression degree of serum miR-320-3p in the death group was positively correlated with NGAL, KIM-1 and APACHE II scores (all $p < 0.01$).

Conclusions: The expression level of serum miR-320-3p in children with sepsis-induced AKI was significantly increased, and the combination of NGAL, KIM-1 and APACHE II scores has good value for prognosis prediction in children.

KEYWORDS
acute kidney injury, children, miR-320-3p, prognostic prediction, sepsis

Jian Ji and Hong Luo contributed equally to this work, and they should be considered as co-first authors.

1 | INTRODUCTION

As one of the most common and serious complications in the growth of kids suffering from sepsis, acute kidney injury (AKI) is a serious threat to children's life and health. Unfortunately, little is known about the epidemiology of the disease and we do not accurately know its incidence and mortality, which may be derived from a lack of concerted epidemiology of criteria between sepsis criteria and AKI.[1] The pathogenesis of sepsis complicated with AKI has not been fully studied, and is generally believed to be caused by multiple factors, including renal haemodynamic changes, ischaemia reperfusion injury, direct inflammatory injury, coagulation and vascular endothelial cell dysfunction. Previous studies have shown that degrees of neutrophil gelatinase-related lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) grew rapidly in AKI patients. This increase is associated with the appearance and growth of AKI, and can be adopted as a biological marker reflecting renal function impairment in early AKI. MicroRNA (miRNA), as a new type of gene regulatory molecule, widely takes part in regulating various biological processes including cell proliferation, apoptosis and immune inflammatory response, and exerts a significant effect on the occurrence, growth and prognosis of kidney diseases.[2] Some researchers have found abnormal expression of miR-320-3p in renal injury diseases; thus, it may be a new biomarker for diagnosing and treating renal ischaemia-reperfusion injury.[3] The prognosis of critically ill patients is commonly evaluated by applying the Acute Physiology and Chronic Health scoring system II (APACHE II). Therefore, this study analysed the prognostic value of miR-320-3p, NGAL, KIM-1 and APACHE II scores in the serum of children with sepsis complicated with AKI, with the aim of providing a basis for the prognostic evaluation and targeted therapy of children with sepsis complicated with AKI.

2 | MATERIALS AND METHODS

2.1 | Research objects

A total of 142 children with sepsis-induced AKI, including 88 males and 54 females, aged from 11 months to 13 years (6.12 ± 1.70), were enrolled in the Affiliated Children's Hospital of Soochow University from January 2018 to December 2020. The study's inclusion criteria were as follows: diagnosis of sepsis was on the basis of expert consensus on diagnosing and treating septic shock in kids (2015 version) [5], and the diagnostic standards for AKI were based on KDIGO Clinical Practice Guidelines for Acute Kidney Injury 2012.[4] Exclusion standards: (1) Patients with a history of chronic kidney disease, kidney surgery, recent contrast examination and use of nephrotoxic drugs; (2) malignant tumours, diseases of the blood system, chronic liver diseases and autoimmune diseases. According to the survival or death of the 142 children 28 days after hospitalization, they were grouped into a 'survival' group of 95 and a 'death' group of 47. Patients' age, sex, body mass index, infection site, heart rate, respiration, APACHE II mark and other basic information were saved upon admission.

2.2 | Research methods

Observation indicators for miR-320-3p detection: the collection of 3 ml of venous blood from all the children was made on the day of onset and placed in a centrifugal tube without anticoagulant. The serum was isolated by centrifugation and stored in a low-temperature refrigerator at −80°C for testing. Real-time fluorescence quantitative polymerase chain reaction (RT-PCR) was performed with the ABI 7,500 fluorescence quantitative PCR instrument (Thermo Scientific). The kit of RNA extraction: Invitrogen TRIzol (Thermo Scientific). The assay system was 20 μl: TaqMan MicroRNA Assay 1.00 μl, cDNA 1.33 μl, TaqMan 2 × Universal PCR Master Mix 10.00 μl and ddH_2O 7.67 μl. The amplification conditions were shown below: predenaturation at 95°C for 10 min, denaturation at 95°C for 15 s and renaturation at 60°C for 60 s for 45 cycles. With U6 as the internal reference, the $2^{-\triangle\triangle Ct}$ approach was adopted to calculate the relative expression level of miR-320-3p, where $\triangle Ct$ =the target gene of Ct-CTU6. In addition, the collection of 3 ml of fasting venous blood was made, followed by placement in a centrifuge tube without anticoagulant and a 37°C water bath for 30 min, centrifugal at a centrifugation radius of 13.5 cm and at 1836 *g* for 10 min. The separated serum was stored at −80°C for examination. The degrees of NGAL and KIM-1 were determined by enzyme-associated immunoassay (ELISA). American R&D Company offered the reagents.

2.3 | Bioinformatics analysis

Target gene forecast and functional enrichment discussion: Target genes of miR-320-3p were forecast based on three online databases: miRWalk (http://mirwalk.umm.uni-heidelberg.de/), miRDB (http://mirdb.org/) and Targetscan (http://www.targetscan.org/vert_71/), and a Venn diagram was used to intersect the target genes. GO enrichment discussion and KEGG signalling pathway enrichment discussion were performed on the obtained target genes using the DAVID 6.8 online tool. Protein–protein interaction network: Target gene interaction analysis was conducted with the online tool STRING (https://cn.string-db.org/) and visualized by utilizing Cytoscape software (version 3.9.0). Ten hub genes were screened using CytoHubba plug-in.

2.4 | Statistical methods

SPSS 19.0 statistical software was used for analysis. A normality test was performed on all continuous variables. Measurement data meeting normal distribution were shown by (x ± S), and comparison between groups was made by a group *T* test. The χ^2 test was used to compare the data groups. The risk elements of death in children were analysed by multivariate logistic regression with sepsis complicated with AKI. The value of serum miR-320-3p, NGAL, KIM-1 and APACHE II scores in forecasting the prognosis of kids suffering from sepsis complicated with AKI was analysed by drawing the receiver operating characteristic (ROC) curve. An area under the curve (AUC) comparison was performed using a Z test. Correlation analysis was

conducted with a Pearson correlation analysis; $p < 0.05$ was of statistical significance.

3 | RESULTS

3.1 | Clinicopathological characteristics of patients

No obvious diversity was shown in gender, age, body mass index, infection site, heart rate and respiration, and between the death group and the survival group for AKI children ($p > 0.05$). The APACHE II scores of the two groups were greatly varied ($p < 0.05$) (Table 1).

3.2 | Expression level and multivariate logistic regression analysis

The death group showed greatly higher serum miR-320-3p, NGAL and KIM-1 levels than the survival group ($p < 0.01$) (Table 2). According to multiple logistic regression analysis, miR-320-3p, NGAL, KIM-1 and APACHE II were independent risk elements for death in kids suffering from sepsis complicated with AKI (Table 3).

3.3 | Predictive value of serum miR-320-3p, NGAL, Kim-1 and APACHE II scores

The optimal cut-off values of the serum miR-320-3p, NGAL, Kim-1 and APACHE II scores for predicting death in children with sepsis complicated with AKI were 1.05, 442.30 mg/L, 23.15 μg/L and 19.50 points respectively. The region under the curve (0.963, 95% CI: 0.908–0.996) of the four items combined, to forecast the death of kids suffering from sepsis complicated with AKI, was significantly higher than that of single scores of miR-320-3p (0.860, 95% CI: 0.802–0.918), NGAL (0.854, 95% CI: 0.793–0.914), KIM-1 (0.817, 95% CI: 0.761–0.885) and APACHE II (0.792, 95% CI: 0.734–0.853), and its sensitivity and specificity were 97.5% and 91.0% (Figure 1) respectively.

3.4 | Correlation analysis

Based on Pearson correlation analysis, the serum miR-320-3p expression degree was related with NGAL in the death group ($r = 0.882$, $p < 0.01$) positively (Figure 2). The expression level of miR-320-3p in serum of the death group was related to KIM-1 ($r = 0.847$, $p < 0.01$) positively (Figure 3), and the expression level of miR-320-3p in serum of the death group was positively related to the APACHE II score ($r = 0.790$, $p < 0.01$) (Figure 4).

3.5 | Bioinformatics analysis

Target gene prediction: 17,169, 1,045 and 841 target genes were identified from miRWalk, miRDB and Targetscan, respectively, and a total of 370 target genes were finally obtained by taking the intersection using a Venn diagram (Figure 5).

Functional enrichment analysis: According to the outcomes of GO enrichment analysis (Figure 6), the biological process (BP) involved in the target genes includes: positive control of transcribing from RNA polymerase II promoter; negative control of transcribing from RNA polymerase II promoter; positive control of transcription, DNA–templated; transcription from RNA polymerase II promoter and transcription, DNA–templated. The cell component (CC) contains nucleoplasm, membrane, cytoplasm, nucleus and cytosol. Protein binding, calcium ion binding, transcription element activity,

TABLE 1 Comparison of clinical data

Parameters	Survival group ($n = 95$)	Death group ($n = 47$)	p
Gender (male/female)	57/38	31/16	0.702
Age (year)	6.35 ± 1.80	5.90 ± 1.42	0.246
BMI (kg/m^2)	17.80 ± 2.48	17.46 ± 2.30	0.524
Infection site [n (%)]			0.406
Pulmonary infection	42 (44.2)	23 (48.9)	
Abdominal infection	20 (21.1)	12 (25.5)	
Skin soft-tissue infection	12 (12.6)	4 (8.5)	
Urinary system infection	3 (3.2)	1 (2.1)	
Intracranial infection	5 (5.3)	4 (8.5)	
Blood-borne infection	13 (13.7)	3 (6.4)	
Heart rate (times/min)	116.20 ± 6.27	118.36 ± 7.15	0.702
Breathe (times/min)	24.65 ± 3.18	25.42 ± 3.37	0.443
APACHE II score	16.40 ± 4.75	25.60 ± 6.20	<0.001

Abbreviations: APACHE II, acute physiology and chronic health scoring system II; BMI, body mass index.

TABLE 2 Serum levels of miR-320-3p, NGAL and KIM-1

Group	*n*	miR-320-3p	NGAL (mg/L)	KIM-1 (μg/L)
Survival group	95	0.61 ± 0.15	290.35 ± 30.26	16.70 ± 3.14
Death group	47	1.52 ± 0.56	558.62 ± 52.47	28.12 ± 6.05
p		<0.001	<0.001	<0.001

Abbreviations: KIM-1, kidney injury molecule-1.NGAL, neutrophil gelatinase-related lipid carrier protein.

TABLE 3 Multivariate logistic regression analysis of risk factors for death in children with sepsis complicated with AKI

Factor	*β*	SE	Wald	OR (95% CI)	*p*
miR-320-3p	0.985	0.504	10.368	2.357 (1.516–5.117)	<0.001
NGAL	1.405	0.992	9.874	3.105 (1.964–6.822)	<0.001
KIM-1	0.905	0.280	5.316	1.942 (1.248–3.506)	0.002
APACHE II score	0.813	0.238	5.112	1.714 (1.205–3.118)	0.008

Abbreviations: AKI, Acute kidney injury; APACHE II, acute physiology and chronic health scoring system II; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-related lipid carrier protein.

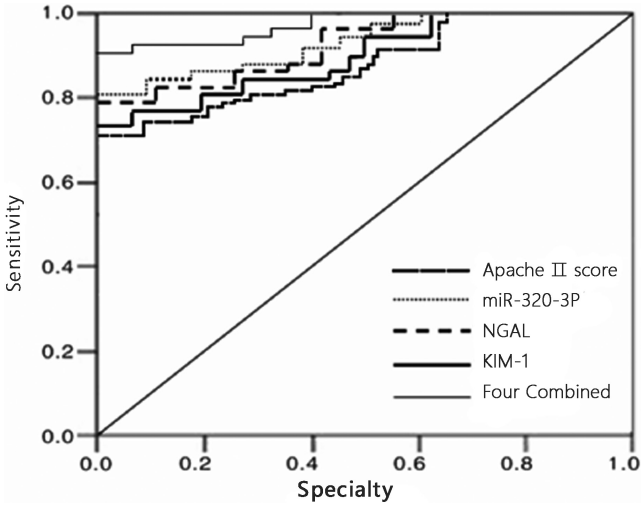

FIGURE 1 Receiver operating characteristic curve of four indicators for the diagnosis of sepsis-induced acute kidney injury

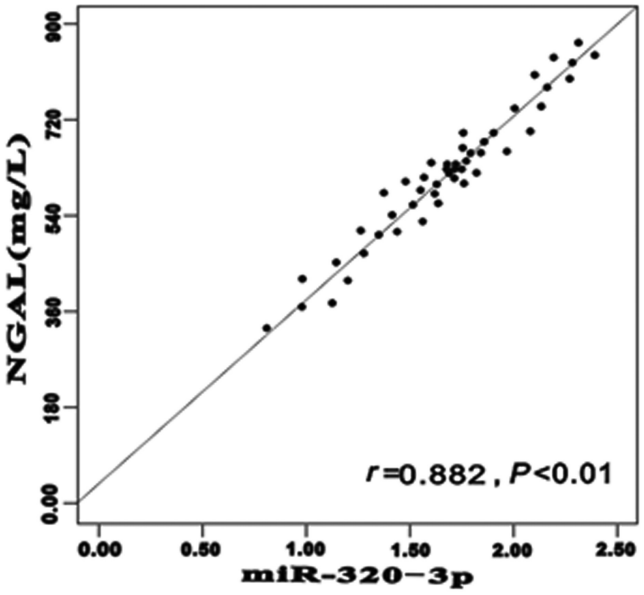

FIGURE 2 Correlation between miR-320-3p expression level and NGAL in the death group of sepsis-induced acute kidney injury. NGAL, neutrophil gelatinase-related lipid carrier protein

sequence–given DNA binding, sequence–given DNA binding; DNA bindings are enriched in the molecular function (MF). The outcomes of KEGG signalling pathway enrichment analysis (Figure 7) suggest that the target genes may be involved in processes such as transcriptional misregulation in cancer, the sphingolipid signalling pathway, signalling pathways controlling pluripotency of stem cells, rap1 signalling pathway, protein processing in endoplasmic reticulum, mTOR signalling pathway, focal adhesion, oestrogen signalling pathway, axon guidance, AMPK signalling pathway, and so on.

Protein–protein interaction network: The PPI obtained based on the STRING database includes 370 nodes and 580 edges (Figure 8A). After visualization using Cytoscape software (version 3.9.0), 10 hub genes (PTEN, PIK3CA, MAPK1, CDK6, PIK3R1, FOXM1, CDH2, BMI1, COMMD3-BMI1 and HSPA4) were screened with the CytoHubba plug-in, using the MCC algorithm. The larger the diameter of the target gene protein, the stronger the protein's interaction with other proteins (Figure 8B).

4 | DISCUSSION

Acute kidney injury is one of the common complications of sepsis patients, and the clinical changes in serum creatinine and urine output are commonly used as the evaluation index for judging the prognosis of AKI. However, serum creatinine's sensitivity and specific degrees are poor, and urine is also affected by factors such as diuretics and urinary tract obstruction. Thus, both methods cannot timely and accurately reflect the renal injury situation, and are unable to meet clinical needs. Therefore, it is particularly important to find a clinical laboratory indicator for early and accurate assessment of AKI prognosis. NGAL is a small molecular weight secretory protein found in activated neutrophils, which can

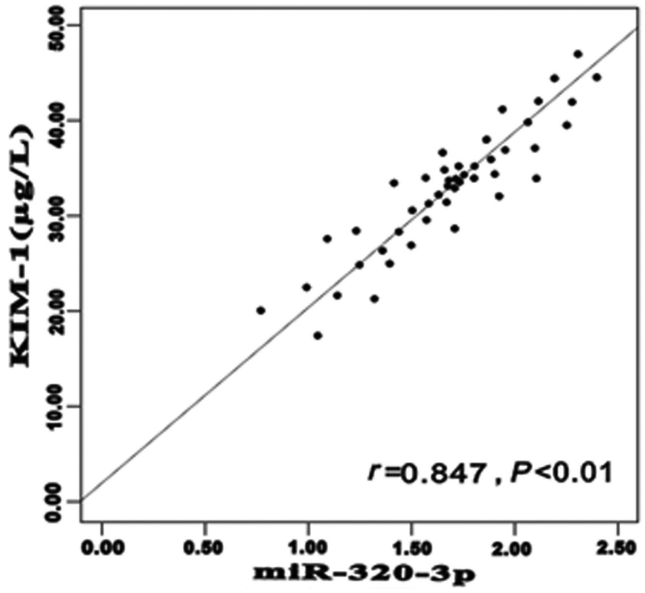

FIGURE 3 Correlation between miR-320-3p expression level and KIM-1 in the death group of sepsis-induced acute kidney injury. KIM-1, kidney injury molecule-1

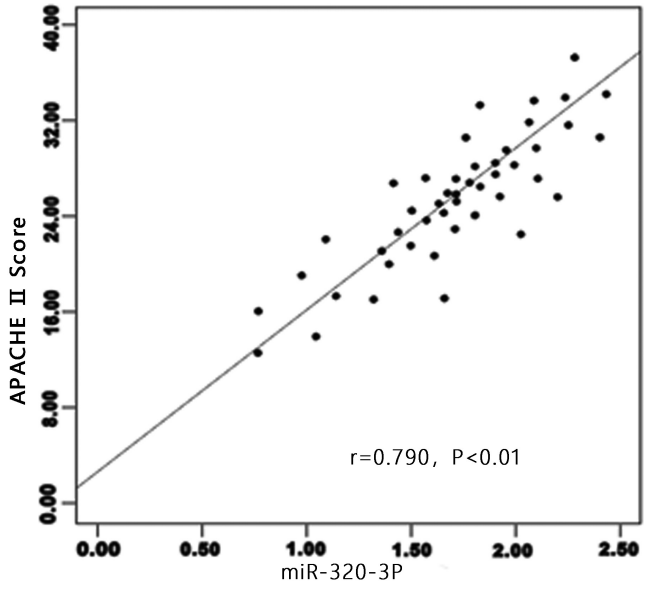

FIGURE 4 Correlation between miR-320-3p expression level and APACHE II in the death group of sepsis-induced acute kidney injury. APACHE II, acute physiology and chronic health scoring system II

show the extent of kidney injury directly; and urinary NGAL can be greatly grown in the early phase of AKI.[5] As is a transmembrane glycoprotein of renal proximal convoluted tubule epithelial cells, KIM-1 is rarely expressed in normal renal tissues but highly expressed in renal proximal convoluted tubule epithelial cells after injury; it thus has certain predictive significance for renal injury.[6] miRNAs are a category of endogenous single-chain noncoding RNA molecules made up of 18–25 nucleotides in length, which produce cell damage by affecting various pathological processes or signalling pathways such as cell ischaemia and hypoxia, cell differentiation, proliferation, metabolism and apoptosis, and thus participate in the regulation of AKI.[7,8] Past researches have indicated that miRNA is abnormally expressed in AKI and exerts a significant effect on its appearance and growth; it thus provides new ideas for early intervention in the progression of AKI, and will act as a new biomarker for early diagnosis and prognosis assessment of AKI.[9]

As far as we know, this is the first study which investigates miR-320-3p expression in AKI. Previous research on miR-320-3p has focused on pulmonary hypertension, ischaemia/reperfusion injury and muscle wasting in obesity.[10–12] In this study, the death group showed greatly higher the levels of serum miR-320-3p, NGAL, KIM-1 and the APACHE II mark than the survival group, suggesting that the levels of serum miR-320-3p, NGAL and KIM-1 are related to the severity of sepsis complicated with AKI, and may take part in the appearance and growth of AKI. Similarly, Hu X M et al. displayed that serum NGAL and KIM-1 extents were significantly grown in the death group, and the combined detection of the two tests had good predictive value for neonatal renal injury with sepsis at 28d. Zhang et al.[13] showed that miRNA significantly increased in sepsis complicated with AKI, reflecting the severity of the disease. The higher the miRNA level, the higher the mortality of sepsis patients; and thus it may become a new diagnostic marker and therapeutic target for AKI.

In this study, multivariate logistic regression analysis displayed that increased degrees of miR-320-3p, NGAL, KIM-1 and APACHE II scores were independent risk elements for death in kids suffering from sepsis complicated with AKI. Previously, Lin et al. showed that increased miRNA expression level is an independent risk element for AKI in sepsis patients, which can be used as an early predictor of AKI, and has predictive value for the prognosis and survival rate of patients with sepsis complicated with AKI.[14] Fan et al.[15] observed that in patients with severe infectious AKI, high levels of NGAL and KIM-1 were associated with the mortality risk score, which has important guiding value for the diagnosis, treatment and prognosis prediction of patients with AKI. Wu et al.[16] showed that the higher the APACHE II score, the higher the risk of death of patients with sepsis, and that the APACHE II score has good value in forecasting the prognosis of patients suffering from sepsis.

This research applied ROC curve analysis: the combined prediction of the serum miR-320-3p, NGAL, KIM-1 and APACHE II scores had the largest area under the curve (0.960, 95% CI: 0.905–0.994) for the death of children with sepsis complicated with AKI, with high sensitivity and specificity. According to correlation analysis, the expression level of serum miR-320-3p in the death group was positively correlated with NGAL, KIM-1 and APACHE II scores, further suggesting that the combined detection of miR-320-3p with NGAL, KIM-1 and APACHE II scores could help predict the death of children with sepsis complicated with AKI. Zheng et al.[17] found that serum miRNA expression levels vary in different stages and times of renal ischaemia reperfusion injury, which is related to the severity of

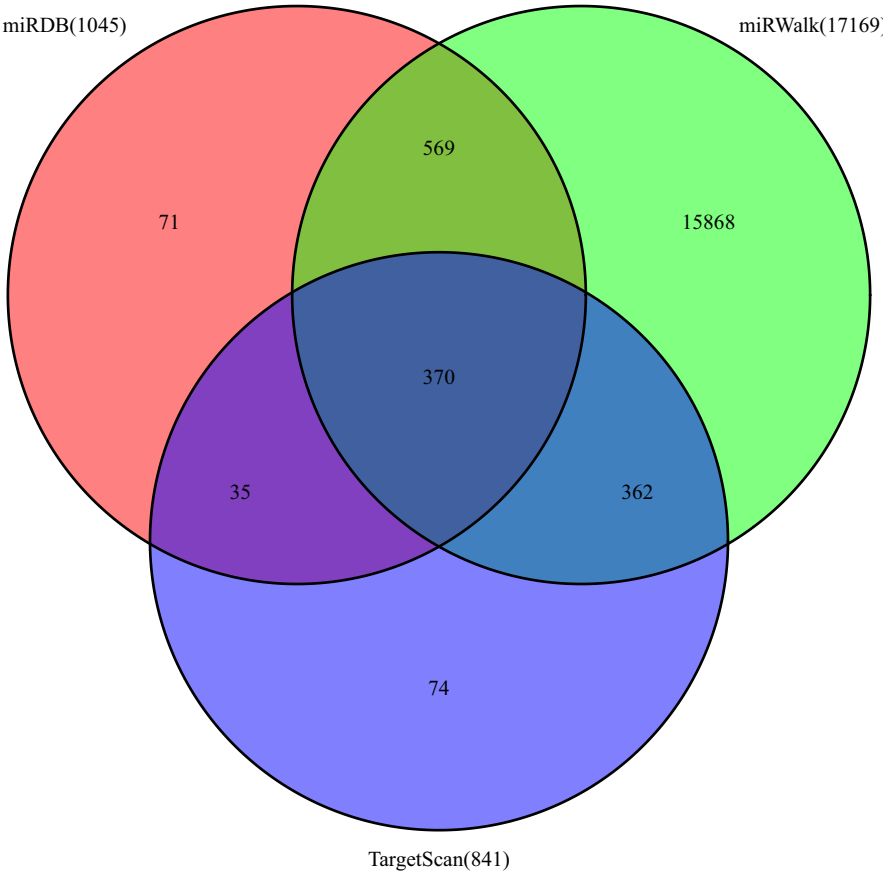

FIGURE 5 Venn diagram representing the number of common target genes

AKI, and will become a new tool for the diagnosis, classification and prognosis of AKI. Other researches have indicated that the grown expression level of serum MiR-146a is related to the severity and prognosis of patients suffering from sepsis complicated with AKI, and miRNA combined with the APACHE II score has a high value in forecasting the 28-day death of patients with sepsis complicated with AKI.

In this study, there were 370 target genes of miR-320-3p identified, and several of them, including NRP1, SEMA3A and PTEN, have been experimentally confirmed to take part in the pathogenesis of sepsis-associated acute kidney injury. NRP1 is a neuropilin protein. It has been shown that miR-128-3p can promote the inflammatory response to sepsis-related acute kidney injury by inhibiting the expression of NRP1.[18] Regulating the miR-199a-5p/NRP1 axis can reduce the degree of inflammation in sepsis-associated acute kidney injury, and therefore may be a new target for sepsis treatment.[19,20] SEMA3A is a member of the signalling protein family as an important regulator taking part in cellular immune responses. Studies have found that the inhibition of SEMA3A significantly improved sepsis-induced immunosuppression,[21] and that SEMA3A could exacerbate the inflammatory response by driving apoptosis of renal tubular epithelial cells in acute kidney injury.[22] PTEN is an oncogene with the potential to improve the inflammatory response. Multiple studies have demonstrated that PTEN can interact with multiple miRNAs to modulate the severity of sepsis-related acute kidney injury.[23–26] For instance, MiR-22-3p can inhibit sepsis-induced acute kidney injury by targeting PTEN, and miR-205 can attenuate sepsis-induced renal injury by stopping the activity of the HMGB1/PTEN signalling pathway. MiR-214 can inhibit autophagy by regulating the PTEN/AKT/mTOR signalling pathway, thereby mitigating acute kidney injury caused by sepsis. PTEN can be a target of miRNA-186 to alleviate sepsis-induced renal injury. Therefore, according to the above findings, we speculate that miR-128-3p may interact with target genes and affect the growth of sepsis-induced acute kidney injury.

In conclusion, this study found that serum miR-320-3p expression level is significantly increased in kids suffering from sepsis complicated with AKI; it is an independent risk element for death in such cases, and is expected to be used as a biological indicator for prognosis prediction. NGAL, KIM-1 and APACHE II scores are of good value for prognosis prediction in children with sepsis complicated with AKI.

ACKNOWLEDGEMENT

We sincerely thank some students from People's Hospital of Suzhou for helping us in data collection and collation.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

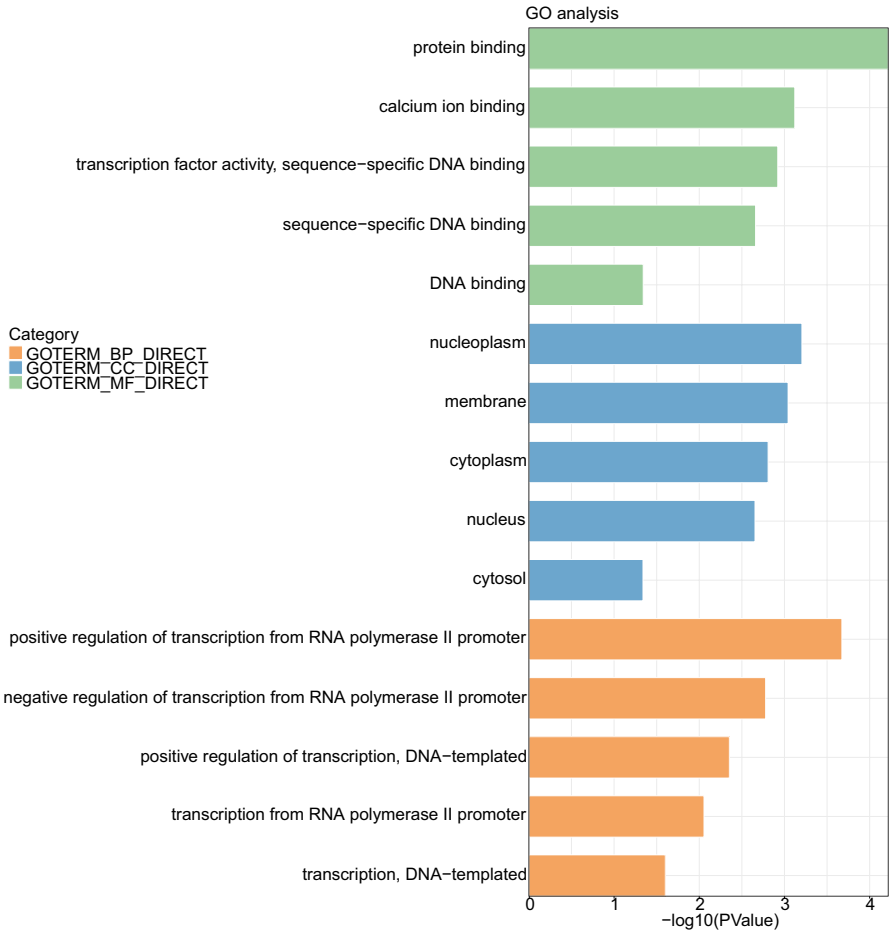

FIGURE 6 GO enrichment analysis of the target genes

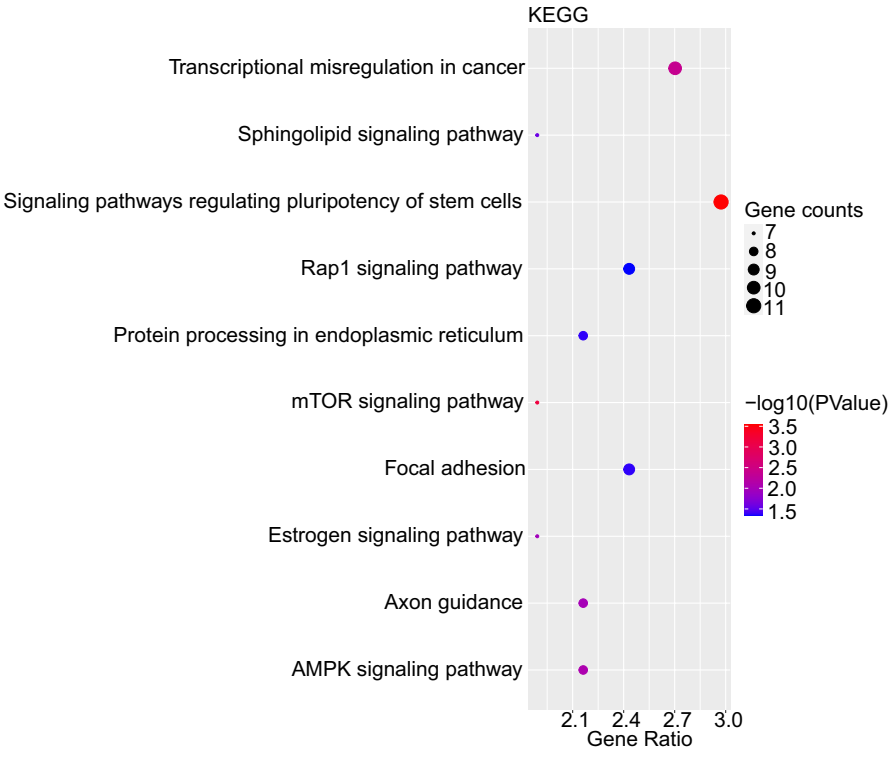

FIGURE 7 KEGG pathway enrichment analysis of the target genes

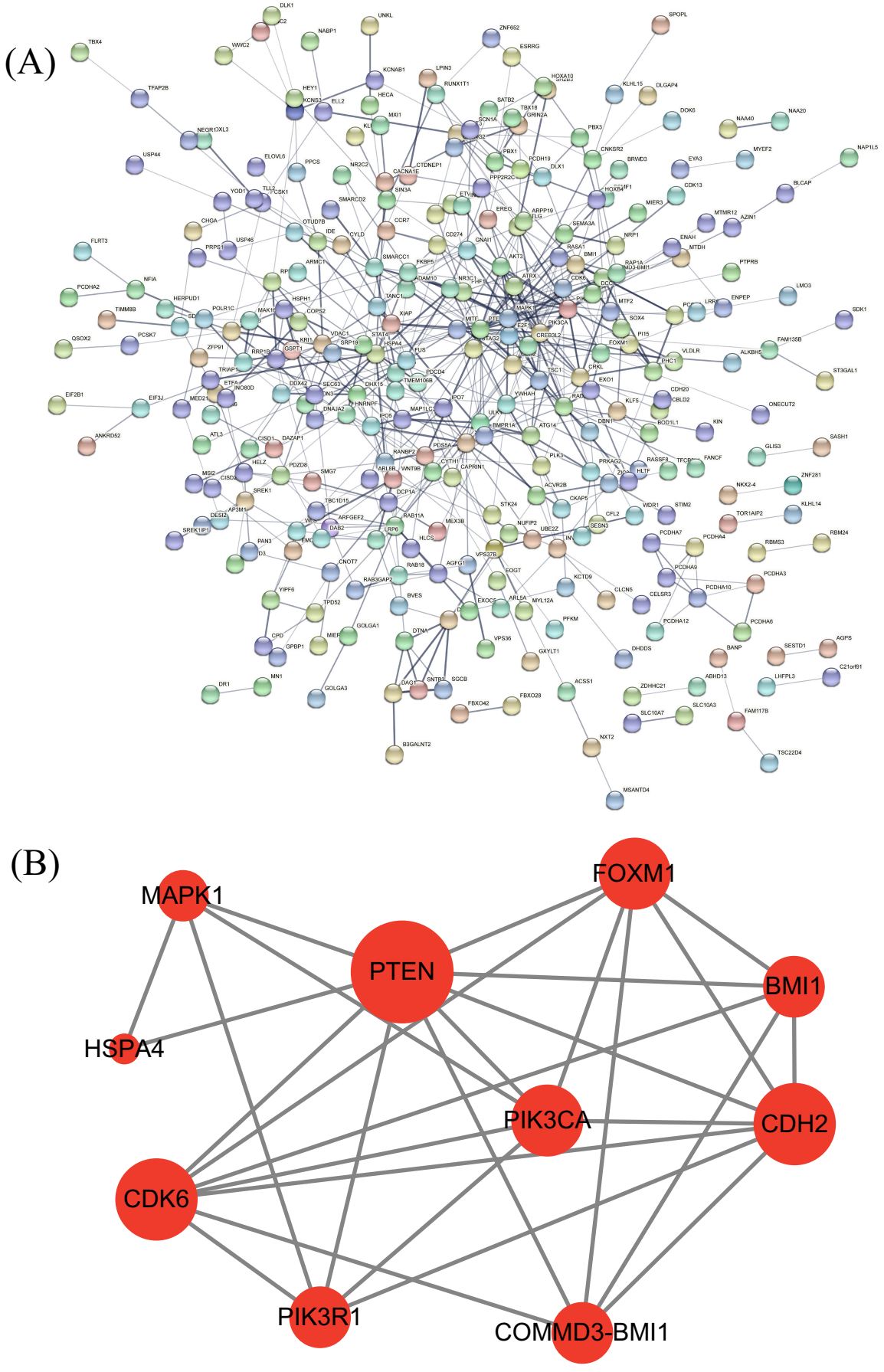

FIGURE 8 Protein–protein interaction network for the target genes generated using STRING. (A) The PPI network of the target genes. (B) The PPI network of 10 hub genes

AUTHOR CONTRIBUTIONS

Jian Ji formed the idea of the research, assessed the included patients and drafted the manuscript. Hong Luo performed bioinformatics analysis and drafted the manuscript. Jufen Shi was involved in imaging and revised the manuscript. Jian Ji and Jufen Shi involved in collection of the cases, performed the statistical analysis and revised the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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How to cite this article: Ji J, Luo H, Wang Q, Shi J. Clinical value of serum miR-320-3p expression in predicting the prognosis of sepsis-induced acute kidney injury. *J Clin Lab Anal*. 2022;36:e24358. doi:10.1002/jcla.24358