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Longitudinal change in microRNA-130a expression and its correlation with the risk of developing major adverse cardiovascular and cerebral events in patients undergoing continuous ambulatory peritoneal dialysis

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Abstract

Background: MicroRNA-130a (miR-130a) regulates angio-cellular dysregulation, atherosclerosis, and cardiocerebral injuries, serving as a biomarker for major adverse cardiovascular and cerebral events (MACCE) in several chronic diseases. However, its clinical application in patients with end-stage renal disease (ESRD) undergoing continuous ambulatory peritoneal dialysis (CAPD), who are at a high risk of developing MACCE, has not been reported. Therefore, this study aimed to explore this aspect.

Methods: miR-130a expression in peripheral blood mononuclear cells obtained from 50 healthy controls (HCs) at recruitment and 257 ESRD patients undergoing CAPD at month (M)0, M12, M24, and M36 was determined by reverse transcription-quantitative polymerase chain reaction. ESRD patients undergoing CAPD were followed up until MACCE occurred or M36. Then, MACCE were recorded, and MACCE-free survival was calculated.

Results: miR-130a expression was significantly lower in ESRD patients undergoing CAPD than in HCs ($p < 0.001$). In addition, miR-130a expression significantly decreased from M0 to M36 in ESRD patients undergoing CAPD ($p < 0.001$). Moreover, miR-130a expression at M0, M12, and M24 was significantly lower in patients with MACCE than in those without MACCE (all $p < 0.05$). Furthermore, high miR-130a expression at M0, M12, and M36 was significantly correlated with prolonged MACCE-free survival in ESRD patients undergoing CAPD (all $p < 0.05$), and high miR-130a expression at M0 was an independent factor for improved MACCE-free survival ($p = 0.015$; hazard ratio (HR) (95% confidential interval): 0.456 (0.243–0.857)).

Conclusion: miR-130a expression decreases continuously with disease progression in patients with ESRD undergoing CAPD. Additionally, this expression is negatively correlated with MACCE risk in these patients.

KEYWORDS
continuous ambulatory peritoneal dialysis, end-stage renal disease, longitudinal change, major adverse cardiovascular and cerebral events, miR-130a

1 | INTRODUCTION

End-stage renal disease (ESRD) is diagnosed when the estimated glomerular filtration rate falls below 15 ml/min/1.73 m^2. It is an irreversible kidney disease that is complicated with comorbidities, resulting in high morbidity and mortality among patients.[1–3] In terms of treatments for ESRD, peritoneal dialysis (PD) is a useful strategy to reduce the levels of uremic toxins[4–6]; however, ESRD patients undergoing PD are at a high risk of developing major adverse cardiovascular and cerebral events (MACCE).[1,7–9] According to previous studies, the prevalence of MACCE in ESRD patients undergoing PD is approximately 15%.[10,11] Unfortunately, with the prolonged duration of PD, ESRD patients undergoing continuous ambulatory PD (CAPD) might more frequently experience MACCE due to the disruption of the equilibrium between pro-coagulation and anticoagulation activities and subsequent thrombosis, leading to increased hospitalization and mortality.[1,10] Therefore, identifying biomarkers to determine the risk of developing MACCE in ESRD patients undergoing CAPD is crucial to provide optimized treatment strategies and improve their survival.

Several studies have reported that microRNA-130a (miR-130a) exerts myocardial-protective and neuroprotective effects in vitro and in vivo.[12,13] For example, in in vivo conditions, miR-130a relieves neuronal injury and facilitates neuronal brain tissue growth by downregulating phosphatase and tensin homologous protein (PTEN) expression and upregulating the phosphatidylinositol 3-hydroxy kinase (PI3K) and protein kinase B (Akt) signaling pathways in rats with intracerebral hemorrhage.[14] In addition, miR-130a alleviates human coronary artery endothelial cell injury by inhibiting PTEN expression and activating the PI3K/Akt/endothelial nitric oxide synthase signaling pathway.[13] To date, studies on the correlation of miR-130a with the risk of developing MACCE are limited, and their findings have been controversial. One study reported that miR-130a predicts low MACCE risk in patients with unprotected left main coronary artery disease (ULMCAD) who undergo coronary artery bypass grafting (CABG),[15] whereas another study showed no correlation between miR-130a expression and MACCE risk in CAD patients.[16] However, whether miR-130a expression is associated with MACCE risk in ESRD patients undergoing CAPD remains unclear.

This study aimed to evaluate miR-130a expression during a 3-year follow-up period and the correlation of miR-130a expression with the development of MACCE in ESRD patients undergoing CAPD.

2 | METHODS

2.1 | Subjects

Two hundred and fifty-seven ESRD patients who underwent CAPD in the hospital between May 2015 and December 2017 were consecutively recruited in this prospective study. The recruitment criteria for patients were as follows: (i) diagnosed with ESRD, (ii) underwent CAPD for more than 3 years, (iii) aged more than 18 years, (iv) volunteered to participate in the study and willing to provide peripheral blood mononuclear cells (PBMCs) for use in the study, and (v) able to complete the study follow-up. The exclusion criteria for the patients were as follows: (i) history of kidney surgery; (ii) underwent hemodialysis; (iii) complications with peritonitis, tunnel tract, or exit-site infection in the preceding 8 weeks or during CAPD; (iv) complications with cardiovascular and cerebrovascular diseases; (v) complications with solid tumors or hematological malignancies; and (vi) pregnant or lactating women. During the same period, 50 healthy subjects were enrolled in the study as healthy controls (HCs). The exclusion criteria for patients with ESRD were also appropriate for HCs. This study was approved by the institutional review board of Taizhou First People's Hospital, and all subjects signed informed consent forms.

2.2 | Collection of data and samples

For data collection, the clinical characteristics of ESRD patients were recorded, including demographic characteristics, vital signs, biochemical indexes, and previous treatment information. Peripheral blood samples of ESRD patients were collected at the baseline (M0) and 12 months (M12), 24 months (M24), and 36 months (M36) after enrollment to isolate PBMCs; miR-130a expression in the PBMCs was evaluated by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay. In addition, PBMCs from HCs were isolated at their recruitment, and miR-130a expression in their PBMCs was assessed using RT-qPCR.

2.3 | RT-qPCR assay

To determine miR-130a expression, RT-qPCR assays were conducted. Briefly, total RNA was extracted from PBMCs using the QIAamp RNA Blood Mini Kit (Qiagen), followed by reverse transcription into cDNA using PrimeScript™ RT reagent Kit (Perfect Real Time) (Takara). Subsequently, qPCR was conducted using KOD SYBR® qPCR Mix (Toyobo) to quantify miR-130a expression, calculated by the $2^{-\Delta\Delta Ct}$ method with U6 as an internal reference.[17] The primers used in qPCR were designed according to a previous study.[18]

2.4 | Follow-up

All patients were followed up until MACCE occurred or up to M36. During follow-up, MACCE occurrence was recorded for further analysis. MACCE included acute coronary syndrome (ACS), stable angina pectoris requiring transient ischemic attack, target vessel revascularization, ischemic stroke, death or hospitalization due to cardiovascular disease, and cerebrovascular disease.[19] In the present study, all patients who were hospitalized due to ACS, stroke, or other cardiovascular and cerebrovascular diseases and died due to rescue failure were regarded as death due to cardiovascular and cerebrovascular

diseases. Patients who were lost during follow-up were analyzed using the last observation carried forward (LOCF) method. MACCE-free survival was defined as the date from recruitment to the date of MACCE occurrence during the 36-month follow-up.

2.5 | Statistical analysis

The Mann–Whitney *U*-test was used to determine the difference in miR-130a expression between the two groups. The Wilcoxon signed rank sum test was used to compare miR-130a expression at different time points. Repeated measures of miR-130a expression were analyzed using the Friedman test. Survival analysis was performed using the Kaplan–Meier curve and determined using the log-rank test. Factors affecting MACCE-free survival were determined by multivariate Cox proportional hazards regression analyses using the forward stepwise method. A two-sided p value < 0.05 was considered statistically significant. SPSS software (version 19.0; IBM Corp.) and GraphPad Prism 7.02 (GraphPad Software Inc.) were used to perform statistical analyses and prepare charts.

3 | RESULTS

3.1 | Study flow

In total, 285 patients with ESRD who underwent CAPD were screened for eligibility in this study, 28 of which were excluded. Peripheral blood samples from the remaining 257 patients eligible for recruitment were collected at M0. During the first year of follow-up, 24 patients were lost. At M12, peripheral blood samples of the remaining 233 patients were collected. During the second year of follow-up, 27 patients were lost. Peripheral blood samples of the remaining 206 patients were collected at M24. During the third year of follow-up, 16 patients were lost. At M36, peripheral blood samples of the remaining 190 patients were collected. Finally, 190 (73.9%) patients completed the 36-month follow-up, and all 257 patients were included in the analysis using the LOCF method (Figure 1).

3.2 | Clinical characteristics of ESRD patients

The mean age was 56.2 ± 10.6 years, and females and males comprised 31.9% and 68.1% of the total patients, respectively (Table 1). The median (interquartile range (IQR)) values of systolic and diastolic blood pressure were 137.0 (128.0–152.0) mmHg and 83.0 (77.0–89.0) mmHg, respectively. The median (IQR) levels of C-reactive protein (CRP) and fasting blood glucose (FBG), which are biochemical indexes, were 4.8 (2.8–7.8) mg/L and 5.7 (4.4–7.1) mmol/L, respectively. The mean level of low-density lipoprotein cholesterol (LDL-C) was 2.7 ± 0.6 mmol/L. The median (IQR) PD duration (PDD) was 62.0 (48.0–79.0) months, and the mean value of clearance multiplied by treatment time and divided by the urea distribution volume was 1.9 ± 0.4. More detailed information on the demographic characteristics and other biochemical indexes are presented in Table 1.

3.3 | miR-130a expression in ESRD patients and HCs

miR-130a expression was significantly lower in ESRD patients than in HCs ($p < 0.001$). The median (IQR) miR-130a levels in ESRD patients at the baseline and HCs were 0.485 (0.207–0.916) and 0.995 (0.435–1.330), respectively (Figure 2).

3.4 | Change in miR-130a expression in ESRD patients from M0 to M36

miR-130a expression significantly decreased from M0 to M36 in ESRD patients undergoing CAPD ($p < 0.001$). The median (IQR) miR-130a levels in ESRD patients at M0, M12, M24, and M36 were 0.485 (0.207–0.916), 0.450 (0.200–0.836), 0.407 (0.181–0.708), and 0.340 (0.159–0.582), respectively (Figure 3).

3.5 | miR-130a expression in ESRD patients with or without MACCE

miR-130a expression at M0, M12, and M24 was significantly lower in ESRD patients undergoing CAPD with MACCE than in those without MACCE (all $p < 0.05$) (Figure 4A–C). However, no significant difference in miR-130a expression at M36 was found between the two groups of ESRD patients ($p = 0.145$) (Figure 4D).

3.6 | Correlation of miR-130a expression with accumulating MACCE-free survival in ESRD patients

According to the median miR-130a levels at each visit, miR-130a expression was divided into high and low expression at M0, M12, M24, and M36. As such, miR-130a levels at M0, M12, and M36 were significantly correlated with prolonged MACCE-free survival in ESRD patients undergoing CAPD (all $p < 0.05$) (Figure 5A,B,D), but a significant correlation between miR-130a expression at M24 and MACCE-free survival was not observed ($p = 0.052$) (Figure 5C).

To explore factors affecting MACCE-free survival, multivariate Cox proportional hazard regression analyses were performed, and the findings are shown in Table 2. High miR-130a expression at M0 was an independent factor for better MACCE-free survival ($p = 0.015$; hazard ratio (HR) (95% confidential interval (CI)): 0.456 (0.243–0.857)), whereas advanced age ($p = 0.003$; HR (95% CI): 2.642 (1.391–5.015)), high body mass index ($p = 0.001$; HR (95% CI): 3.148 (1.605–6.175), prolonged PDD ($p < 0.001$; HR (95% CI): 3.944 (2.031–7.659)), high CRP levels ($p = 0.002$; HR (95% CI): 2.899 (1.492–5.632)), high FBG levels ($p < 0.001$, HR (95% CI): 3.411

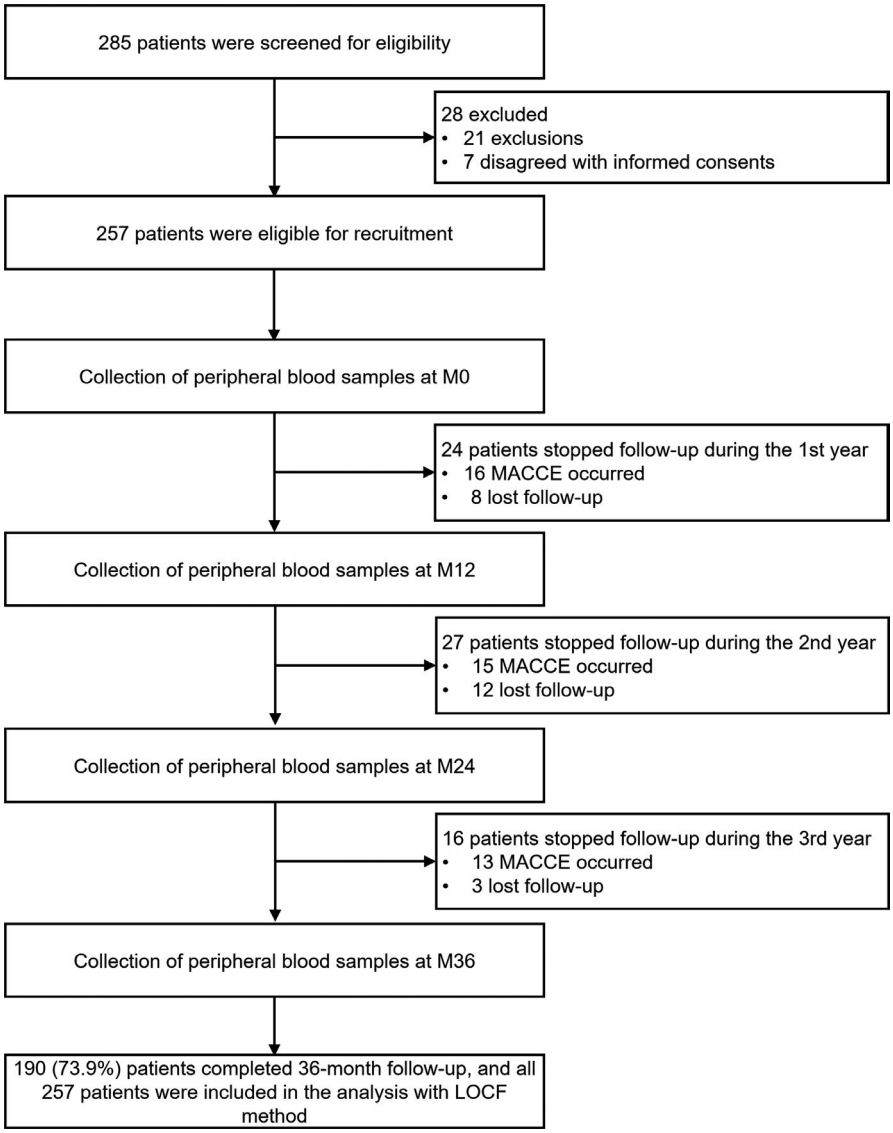


FIGURE 1 Flow chart of the present study comprising a cohort of ESRD patients. ESRD, end-stage renal disease; LOCF, last observation carried forward; M, month; MACCE, major adverse cardiovascular and cerebral events

(1.731–6.723)), and high LDL-C levels ($p = 0.019$, HR (95% CI): 2.107 (1.131–3.926)) were independent factors for poor MACCE-free survival (Table 2).

Moreover, no significant difference in Kt/V [clearance (K) multiplied by treatment time (t) and divided by the urea distribution volume (V)] was found between ESRD patients with and without MACCE ($p = 0.889$) (Figure S1A); no significant correlation was found between Kt/V and MACCE-free survival ($p = 0.359$) (Figure S1B).

4 | DISCUSSION

miR-130a is abnormally expressed in chronic kidney disease (CKD), although some studies have reported contradictory findings.[20,21] For example, one study showed that miR-130a expression is upregulated in the urine of CKD patients.[20] Another study showed that the expression of miR-130a is low in the large extracellular vesicles of CKD patients.[21] However, to the best of our knowledge, no previous study has determined miR-130a expression in patients with ESRD. The current study showed that miR-130a expression was lower in ESRD patients undergoing CAPD than in HCs. In addition, miR-130a expression decreased with the increase in the follow-up period for ESRD patients undergoing CAPD. The possible reasons for this decrease in expression could be as follows: (1) miR-130a protects against renal injury through multiple signaling pathways, such as the PI3K/AKT, Wnt, nuclear factor kappa-B (NF-κB), and transforming growth factor-β1 (TGF-β1)/Smad pathways[22,23]; thus, miR-130a expression is negatively associated with renal damage. Moreover, patients with ESRD display severe kidney damage. Therefore, miR-130 expression was downregulated in ESRD patients. (2) With the increase in follow-up duration, ESRD patients exhibit severely impaired renal function, and decreased miR-130a expression is correlated with severe renal injury in these patients.[22,23] Therefore, miR-130a expression decreased with the increase in follow-up period in ESRD patients. Previous studies have also reported that other miRNAs, such as miR-133b, are correlated with nephropathy and cerebral or cardiovascular events.[24–26] Therefore, further studies

TABLE 1 Characteristics of ESRD patients undergoing CAPD

Characteristics	ESRD patients (*N* = 257)
Demographic characteristics	
Age (years), mean ± SD	56.2 ± 10.6
Gender, No. (%)	
Female	82 (31.9)
Male	175 (68.1)
BMI (kg/m^2), mean ± SD	21.7 ± 2.7
Smoke, No. (%)	51 (19.8)
Drink, No. (%)	44 (17.1)
Vital signs	
SBP (mmHg), median (IQR)	137.0 (128.0–152.0)
DBP (mmHg), median (IQR)	83.0 (77.0–89.0)
Biochemical indexes	
HB (g/L), mean ± SD	103.3 ± 14.5
WBC (×10^9/L), mean ± SD	7.8 ± 2.2
Platelet (×10^9/L), mean ± SD	211.7 ± 57.0
CRP (mg/L), median (IQR)	4.8 (2.8–7.8)
Scr (μmol/L), median (IQR)	919.9 (770.6–1099.7)
SUA (μmol/L), mean ± SD	414.1 ± 73.9
Ca (mmol/L), mean ± SD	2.2 ± 0.2
P (mmol/L), median (IQR)	1.6 (1.3–1.9)
FBG (mmol/L), median (IQR)	5.7 (4.4–7.1)
ALB (g/L), mean ± SD	38.8 ± 6.1
TG (mmol/L), median (IQR)	1.6 (1.0–2.4)
TC (mmol/L), mean ± SD	4.7 ± 1.0
LDL-C (mmol/L), mean ± SD	2.7 ± 0.6
HDL-C (mmol/L), median (IQR)	1.0 (0.9–1.2)
PDD (months), median (IQR)	62.0 (48.0–79.0)
Kt/*V*, mean ± SD	1.9 ± 0.4

Abbreviations: ALB, albumin; BMI, body mass index; Ca, calcium; CAPD, continuous ambulatory peritoneal dialysis; CRP, C-reactive protein; DBP, diastolic blood pressure; ESRD, end-stage renal disease; FBG, fasting blood glucose; HB, hemoglobin; HDL-C, high density lipoprotein cholesterol; IQR, interquartile range; *Kt*/*V*, clearance (K) multiplied by treatment time (t) and divided by the urea distribution volume (V); LDL-C, low-density lipoprotein cholesterol; P, phosphorus; PDD, peritoneal dialysis duration; SBP, systolic blood pressure; Scr, serum creatinine; SD, standard deviation; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

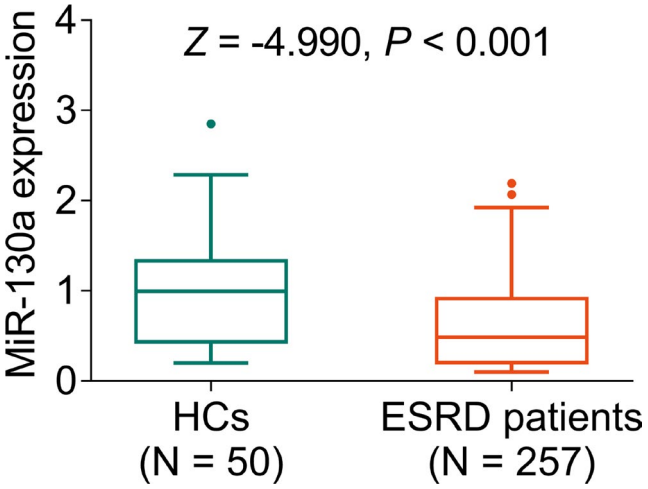
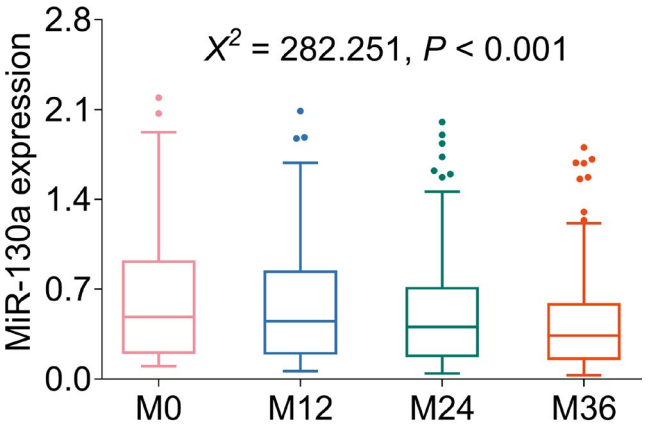


FIGURE 2 Comparison of miR-130a levels between ESRD patients at the baseline and HCs. ESRD, end-stage renal disease; HCs, healthy controls; M, month; miR-130a, microRNA-130a



	Z	*P* value
M36 vs. M0	-12.040	< 0.001
M24 vs. M0	-10.741	< 0.001
M12 vs. M0	-6.722	< 0.001
M36 vs. M12	-10.729	< 0.001
M36 vs. M24	-7.340	< 0.001
M24 vs. M12	-8.770	< 0.001

FIGURE 3 Longitudinal change in miR-130a expression during follow-up in ESRD patients. ESRD, end-stage renal disease; M, month; miR-130a, microRNA-130a

could be conducted to explore whether miR-133b could serve as a biomarker for MACCE in patients with ESRD undergoing CAPD.

In terms of the correlation of miR-130a expression with the risk of developing MACCE in patients, in a previous study, miR-130a expression was found to be associated with low MACCE occurrence in ULMCAD patients undergoing CABG[15]; in contrast, another study showed that miR-130a cannot predict the risk of developing MACCE in CAD patients.[16] However, to the best of our knowledge, no previous study has determined miR-130a expression to monitor the risk of developing MACCE in ESRD patients undergoing CAPD. The present study revealed that high miR-130a expression was correlated with low MACCE risk and prolonged MACCE-free survival in ESRD patients, which can be attributed to the fact that miR-130a plays a myocardial-protective and neuroprotective role in ESRD patients. High miR-130a levels alleviated cardiac dysfunction and cerebral damage by modulating the PTEN/PI3K/AKT axis[27,28] or targeting the X-linked inhibitor of apoptosis protein[12] to prolong MACCE-free survival in ESRD patients.

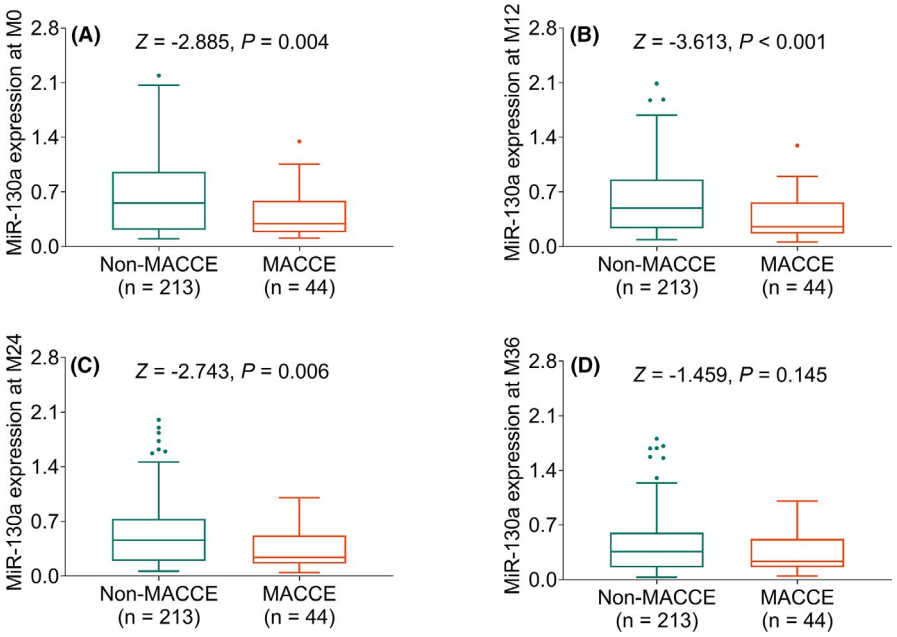


FIGURE 4 Comparison of miR-130a levels between ESRD patients with and without MACCE occurrence. miR-130a levels between ESRD patients with and without MACCE occurrence at M0 (A), M12 (B), M24 (C), and M36 (D). ESRD, end-stage renal disease; M, month; MACCE, major adverse cardiovascular and cerebral events; miR-130a, microRNA-130a

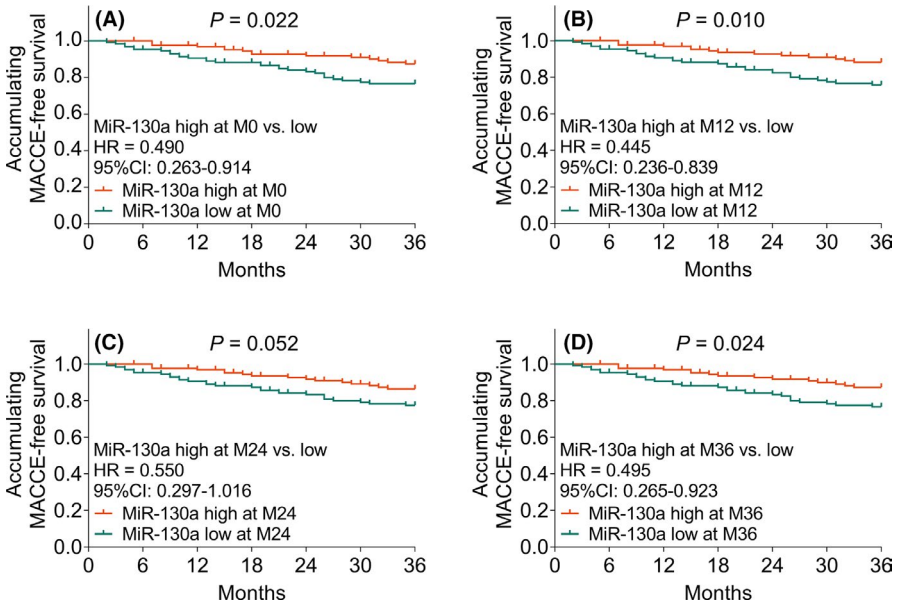


FIGURE 5 Association of miR-130a levels with MACCE-free survival in ESRD patients. Association of miR-130a levels with MACCE-free survival at M0 (A), M12 (B), M24 (C), and M36 (D) in ESRD patients. ESRD, end-stage renal disease; M, month; MACCE, major adverse cardiovascular and cerebral events; miR-130a, microRNA-130a

TABLE 2 Factors affecting MACCE-free survival by Cox's proportional hazards regression analysis

	Multivariate Cox's regression analysis			
			95% CI	
Items	*p* Value	HR	Lower	Higher
MiR–130a (M0) high vs. low	0.015	0.456	0.243	0.857
Age high vs. low	0.003	2.642	1.391	5.015
BMI high vs. low	0.001	3.148	1.605	6.175
PDD high vs. low	<0.001	3.944	2.031	7.659
CRP high vs. low	0.002	2.899	1.492	5.632
FBG high vs. low	<0.001	3.411	1.731	6.723
LDL-C high vs. low	0.019	2.107	1.131	3.926

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; FBG, fasting blood glucose; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiovascular and cerebral events; MiR, microRNA; PDD, peritoneal dialysis duration.

Although miR-130a is implicated in MACCE and can clinically predict the occurrence of MACCE,[15] previous studies have not explored whether miR-130a plays a similar role as a biomarker in ESRD patients. The highlights of the present study were as follows: the study cohort comprised ESRD patients undergoing CAPD because their PDD is prolonged, and since these patients have a high risk of developing MACCE, the evaluation of the predictive value of miR-130a for MACCE risk in ESRD patients was facilitated. Notably, in the current study, we conducted a 3-year follow-up and investigated the changes in miR-130a expression at each visit to facilitate the better monitoring of MACCE risk and assess MACCE-free survival in ESRD patients undergoing CAPD.

Nonetheless, there were several limitations in this study. First, the sample size was small, leading to low statistical power, and therefore, further studies with large sample sizes should be conducted in the future. Second, the molecular mechanisms through which miR-130a regulates the development of MACCE in ESRD patients remain to be explored. Third, the follow-up period in this study was only 36 months. Further studies with long follow-up durations should be conducted in the future.

To be conclusive, miR-130a expression decreases continuously with the disease course in patients with ESRD undergoing CAPD. Interestingly, its expression was negatively correlated with the risk of developing MACCE in these patients.

ACKNOWLEDEGMENT

None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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