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DIAGNOSING NAFLD IN DIABETIC PATIENTS WITH cirCRNA CDR1as: AN ANALYSIS OF EFFICACY AND CORRELATION WITH GLUCOSE METABOLISM

DIJAGNOSTIFIKOVANJE NAFLD KOD DIJABETIČARA POMOĆU circRNA CDR1as: ANALIZA EFIKASNOSTI I KORELACIJE SA METABOLIZMOM GLUKOZE

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Summary

Background: To explore the expression characteristics and diagnostic efficacy of circRNA CDR1as, as well as its correlation with glucose metabolism disorders in patients with diabetes mellitus (DM) complicated by non-alcoholic fatty liver disease (NAFLD), to provide a novel target for precision diagnosis and treatment.
Methods: From May 2024 to April 2025, 74 DM patients complicated by NAFLD (research group) and 71 patients with uncomplicated DM (control group) were included. Serum CDR1as levels were detected by quantitative reverse transcription polymerase chain reaction (qRT-PCR), fasting insulin (FINS) by chemiluminescence, fasting blood glucose (FPG) by a blood glucose meter, and glycosylated haemoglobin (HbA1c) by high-performance liquid chromatography (HPLC). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. The diagnostic efficacy of CDR1as was evaluated by receiver operating characteristic (ROC) curves, and the correlation between CDR1as and glucose metabolism indexes was analysed.
Results: CDR1as was expressed at an elevated level (29.90% greater) in the research group than in controls

Kratak sadržaj

Uvod: Cij je bio da se ispitaju karakteristike ekspresije i dijagnostička efikasnost circRNA CDR1as, kao i njihova povezanost sa poremećajima metabolizma glukoze kod pacijenata sa dijabetes melitusom (DM) komplikovanom nealkoholnom masnom bolešću jetre (NAFLD), u cilju obezbeđivanja novog ciljanog pristupa preciznoj dijagnostici i terapiji.
Metode: Od maja 2024. do aprila 2025. obuhvaćena su 74 pacijenta sa DM komplikovanim NAFLD (grupa ispitanika) i 71 pacijent sa nekoplikovanim DM (kontrolna grupa). Nivoi CDR1as u serumu su određeni pomoću kvantitativne reverzne transkripcione lančane reakcije (qRT-PCR), nivo insulina natašte (FINS) hemiluminiscencijom, glikemija natašte (FPG) pomoću glukometra, a glikozilirani hemoglobin (HbA1c) tečnom hromatografijom visokih performansi (HPLC). Izračunat je indeks insulinske rezistencije (HOMA-IR). Dijagnostička efikasnost CDR1as procenjena je pomoću ROC krivih, a povezanost između CDR1as i parametara metabolizma glukoze je analizirana korelacionom analizom.
Rezultati: Ekspresija CDR1as je bila povišena (za 29,90%) u grupi ispitanika u poređenju sa kontrolnom grupom

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(P<0.05). In diagnosing NAFLD in DM cases, CDR1as showed an area under the ROC curve (AUC) of 0.781 (sensitivity 64.86%, specificity 80.28%). In stratified analysis, CDR1as exhibited superiority in diagnosing moderate and severe steatosis (S2/S3), with AUCs of 0.829 and 0.878, respectively. HOMA-IR, FINS, FPG, and HbA1c, all of which were higher in the research group compared to controls (P<0.05), showed a positive correlation with CDR1as. Treatment induced a decline in CDR1as expression (P<0.05), with higher levels observed in patients with poor prognosis compared with those with favourable outcomes (P<0.05). According to ROC curve analysis, the AUC of CDR1as in predicting prognosis was 0.747, with 57.14% sensitivity and 84.78% specificity.

Conclusions: This study establishes CDR1as as a promising non-invasive biomarker for NAFLD diagnosis in diabetic patients, with particular utility for stratifying disease severity. The strong correlation with glucose metabolism parameters underscores its potential as a monitoring tool for metabolic dysfunction.

Keywords: circRNA CDR1as, non-alcoholic fatty liver disease (NAFLD), diabetes mellitus (DM), diagnostic biomarker, glucose metabolism disorders

(P<0,05). U dijagnostici NAFLD kod pacijenata sa DM, CDR1as je pokazala površinu ispod ROC krive (AUC) od 0,781 (senzitivnost 64,86%, specifičnost 80,28%). U stratifikovanoj analizi, CDR1as je pokazala najbolju efikasnost u dijagnostici umerenog i teškog steatoznog oštećenja (S2/S3), sa AUC vrednostima od 0,829 i 0,878. HOMA-IR, FINS, FPG i HbA1c, koji su bili viši u grupi ispitanika u odnosu na kontrolnu (P<0,05), pokazali su pozitivnu korelaciju sa CDR1as. Nakon terapije došlo je do pada ekspresije CDR1as (P<0,05), pri čemu su viši nivoi zabeleženi kod pacijenata sa lošijom prognozom u poređenju sa onima sa povoljnim ishodom (P<0,05). Prema ROC analizi, AUC vrednost CDR1as u predviđanju prognoze iznosila je 0,747, sa senzitivnošću 57,14% i specifičnošću 84,78%.

Zaključak: Ova studija identifikuje CDR1as kao obećavajući neinvazivni biomarker za dijagnostiku NAFLD kod pacijenata sa dijabetesom, posebno koristan za stratifikaciju težine bolesti. Njena snažna povezanost sa parametrima metabolizma glukoze ukazuje na potencijalnu ulogu u praćenju metaboličkog poremećaja.

Ključne reči: circRNA CDR1as, nealkoholna masna bolest jetre (NAFLD), dijabetes melitus (DM), dijagnostički biomarker, poremećaji metabolizma glukoze

Introduction

Diabetes mellitus (DM), one of the most prevalent metabolic diseases worldwide, leads to complications that have become a significant public health issue threatening human health (1). Non-alcoholic fatty liver (NAFLD), the most common extrahepatic complication of DM, is diagnosed in approximately 50–70% of all DM cases, with both conditions sharing the core pathological mechanism of insulin resistance (IR) (2). Without timely intervention, NAFLD can progress to non-alcoholic steatohepatitis (NASH), liver fibrosis, and even cirrhosis, significantly increasing all-cause mortality (3). However, the early diagnosis of NAFLD still faces challenges: although liver biopsy is the gold standard, its invasiveness limits its clinical popularisation (4); imaging (e.g., ultrasound, magnetic resonance imaging [MRI]) is insensitive to early steatosis (5); serological indicators (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) show insufficient specificity (6). Consequently, the search for highly sensitive, non-invasive biomarkers to enable early screening and risk stratification of NAFLD in DM patients holds significant clinical value.

In recent years, circular ribonucleic acids (circRNAs) have emerged as a hotspot in the study of metabolic diseases due to their stable structure and strong tissue specificity (7). As sponge molecules or transcription regulators of microRNAs (miRNAs), circRNAs are widely involved in pathological processes such as glycolipid metabolism and inflammatory reaction (8). Of these, CDR1as (cerebellar degeneration-related protein 1 antisense RNA) is a highly conserved circRNA implicated in diseases such as type 2 DM and atherosclerosis (9, 10). Animal experiments suggest that CDR1as may affect glycolipid homeostasis by regulating insulin signalling pathways, such as the PI3K/AKT axis, and key lipid-metabolism genes (e.g., SREBP-1c) (11). Accumulating evidence indicates that CDR1as plays regulatory roles in metabolic diseases. For instance, it promotes cardiomyocyte apoptosis in diabetic cardiomyopathy via the Hippo signalling pathway (10) and is associated with mild cognitive impairment in type 2 diabetes through α-synuclein-mediated mechanisms (11). These findings suggest broad involvement of CDR1as in diabetes-related complications. However, its expression characteristics, diagnostic efficacy, and relationship with glucose metabolism in DM complicated with NAFLD remain to be characterised.

Currently, exploration of circRNA biomarkers for NAFLD in DM patients primarily focuses on single-cohort or mechanism validation (12), lacking a systematic evaluation of CDR1as's diagnostic value. Meanwhile, the correlation between CDR1as and glucose metabolism indicators (e.g., glycated haemoglobin [HbA1c], fasting plasma glucose [FPG], and homeostasis model assessment of IR [HOMA-IR]) remains unclear, which limits its clinical translation potential. In this study, a case-control design was used to analyse differences in serum CDR1as expression between DM patients with NAFLD and uncomplicated DM cases, to evaluate its diagnostic efficacy for NAFLD, and to explore the intrinsic relationship between CDR1as and glucose metabolism disorders by combining glucose metabolism parameters. This marks the first systematic exploration of the diagnostic value of CDR1as for NAFLD in the DM population, breaking through the limitations of traditional markers. Additionally, it reveals the quantitative correlation between CDR1as and glucose metabolism indexes, providing a new theoretical basis for »glucose control-

NAFLD intervention«. Verification of CDR1as as a reliable diagnostic biomarker would pave the way for a refined early screening strategy for NAFLD in diabetic patients, thereby decreasing the need for invasive tests. Research into its correlation with glucose metabolism will also provide a target for delaying NAFLD progression through enhanced glucose management, ultimately improving the quality of life of DM patients and reducing the risk of long-term liver disease-related adverse events.

Materials and Methods

Sample size estimation

This study is a diagnostic trial. The primary endpoint is the diagnostic efficacy (sensitivity and specificity) of serum circRNA CDR1as for diagnosing NAFLD in DM. Referring to similar circRNA diagnostic studies (13) and assuming higher CDR1as expression in the DM+NAFLD group than in the uncomplicated DM group (effect size $d=1.0$, $\alpha=0.05$, $\beta=0.2$), the sample size was calculated using the two-independent-samples t-test formula. The calculation indicated a minimum of 60 cases per group, which was adjusted to 66 per group to accommodate a 10% dropout rate.

Research participant selection and grouping

The research participants comprised DM patients with NAFLD and uncomplicated DM, admitted between May 2024 and April 2025. NAFLD was diagnosed via abdominal ultrasonography (Logic E9, GE Healthcare) based on the following criteria: hepatorenal echo contrast, deep attenuation of the ultrasound signal, and vascular blurring. Steatosis severity was graded as S1 (mild, 5–33% hepatocyte involvement), S2 (moderate, 34–66%), and S3 (severe, >66%) according to the guidelines of the American Association for the Study of Liver Diseases Inclusion criteria: 18–70 years old; a DM diagnosis (FPG≥7 mmol/L, 2-hour postprandial blood glucose (2hPG) ≥11.1 mmol/L, or HbA1c ≥6.5%) (14); informed consent for the present study with provision of the consent form. Exclusion criteria: special DM types (type 1 DM, gestational DM, etc.); alcoholic liver disease; viral hepatitis; severe cardiac and renal insufficiency; pregnant or lactating women; use of medications that may significantly affect circRNA expression, including insulin sensitisers (e.g., metformin), lipid-lowering drugs (e.g., statins), or hepatoprotective agents within 3 months before enrollment; malignant tumours or severe infections. 74 DM patients with NAFLD (research group) and 71 uncomplicated DM cases (control group) were screened for inclusion.

Sample collection

Elbow vein blood (4 mL) was collected from patients upon admission. After 30 minutes of standing at room temperature and centrifugation, the serum was isolated for testing in our hospital's laboratory.

Laboratory tests

CDR1a detection: 200 μL of serum was added to 1 mL of TRIzol and vigorously shaken for 15s. Then, 200 μL of chloroform was added, and the mixture was vortexed for 1 minute. The mixture was left at room temperature for 2–3 minutes. Following centrifugation (12,000×g, 15 min, 4 °C), the upper aqueous phase was transferred to a new tube. Next, an equal volume of isopropanol was added to precipitate RNA. RNA concentration and purity were measured using a NanoDrop 2000 (Thermo Fisher), with A260/A280 ratios maintained between 1.8 and 2.0. The mixture was left to stand at -20 °C for 30 minutes, then centrifuged (12,000×g for 10 minutes). The supernatant was discarded, and the precipitate was washed with 75% ethanol, then dried and dissolved in 20 μL of RNase-free water. The RNA samples were then treated with RNase R (incubated at 37 °C for 15 min, 3 U/μg RNA) to remove linear RNAs and enrich circRNAs. Subsequently, cDNA was synthesised by reverse transcription and amplified. The reaction conditions are: 95 °C for 15 seconds → 60 °C for 1 minute → 95 °C for 15 seconds. The CDR1as-specific primers were as follows: F: 5′-ATGGAGACCGCAGCTTCTC-3′; R: 5′-GCTTCTGCCTCC-AGGTCTT-3′. The primers for GAPDH were: F: 5′-GGAGCGAGATCCCTCCAAAAT-3′, R: 5′-GGCTGTTGTCATACTTCTCATGG-3′. The relative expression level was calculated using the $^{2\text{-}\Delta\Delta}$Ct method.

Glucose metabolism detection: FPG and HbA1c were measured with a blood glucose meter, with results automatically displayed after the sample was loaded into the instrument. FINS measurement employed chemiluminescence immunoassay. The sample (diluted 10 times) was added to the reaction cup and incubated for 15 minutes. After washing, a luminescent substrate was added. The relative light unit (RLU) was measured, and the standard curve was used to calculate the insulin concentration. HOMA-IR was calculated based on the detection results of FPG and FINS.

Assessment of prognosis

Prognosis was evaluated at 6 months: a favourable prognosis was defined as ALT reduction ≥50% and improvement in steatosis by ≥1 grade on ultrasound; a poor prognosis was defined as ALT increase or progression of steatosis.

Quality control

Table I Comparison of clinical baseline data.

Projects		Control group n=71	Research group n=74	Statistical t or χ^2	P
Age (years old)		64.38±5.62	65.95±5.87	1.640	0.103
Sex	male	42 (59.15)	50 (67.57)	1.106	0.293
	female	29 (40.85)	24 (32.43)		
BMI (kg/m^2)		22.13±1.61	23.59±1.86	5.055	<0.001
Smoking	yes	32 (45.07)	38 (51.35)	0.573	0.449
	no	39 (54.93)	36 (48.65)		
Drinking alcohol	yes	10 (14.08)	14 (18.92)	0.613	0.434
	no	61 (85.92)	60 (81.08)		
Duration of DM (years)		9.15±3.01	8.39±2.73	1.600	0.112
Family history of NAFLD	yes	16 (22.54)	22 (29.73)	0.970	0.325
	no	55 (77.46)	52 (70.27)		
Registered permanent residence	urban	48 (67.61)	55 (74.32)	0.795	0.373
	rural	23 (32.39)	19 (25.68)		

The Ethics Committee of our hospital has approved this study. NAFLD was independently evaluated by two senior doctors (double-blinded interpretation of imaging results). The collection, processing, and qRT-PCR detection of serum samples were performed by trained technicians, with the coefficient of variation of repeated tests maintained at <5%.

Statistical methods

Data were imported into SPSS 26.0 for statistical analysis. Continuous variables were presented as mean ± standard deviation ($\bar{x}\pm s$). Normality was assessed using the Shapiro-Wilk test. Between-group comparisons were performed using an independent-samples t-test for normally distributed data and a Mann-Whitney U-test for non-normally distributed data. Categorical variables, expressed as percentages (%), were analysed using the χ^2 test. Pearson's correlation coefficient (r) was used to evaluate the relationship between CDR1as and blood glucose parameters. Diagnostic performance was assessed using receiver operating characteristic (ROC) curves, calculating the area under the curve (AUC), sensitivity, specificity, and 95% confidence interval (CI). A P-value <0.05 was considered statistically significant.

Results

Comparability analysis of research participants

When comparing baseline data between the research and control groups, we found no significant differences in age, sex, or DM course (P>0.05), confirming group comparability. However, the research group had a higher BMI than controls (P<0.05; *Table I*).

Diagnostic efficacy of CDR1as for NAFLD

The results showed a 29.90% elevation in serum CDR1as expression in the research group compared to the control group (2.52±0.61 vs. 1.94±0.48, P<0.05). Through ROC curve analysis, it was found that when CDR1as was greater than 2.30, the sensitivity for diagnosing NAFLD in DM patients was 64.86% and the specificity was 80.28% (AUC=0.781, P<0.05, *Figure 1*).

Diagnostic performance of CDR1as in discriminating NAFLD steatosis grades

The level of CDR1as increased significantly with the aggravation of NAFLD steatosis, especially in S3 patients (P<0.05). Stratified diagnostic analysis showed that CDR1as demonstrated sufficient diagnostic efficacy for S2 and S3 NAFLD (P<0.05), with diagnostic AUCs of 0.829 and 0.878, respectively (P<0.05; *Figure 2*).

Relationship between CDR1as and glucose metabolism

Compared with controls, patients in the research group exhibited higher HOMA-IR, FINS, FPG, and HbA1c (P<0.05). The results of the corre-

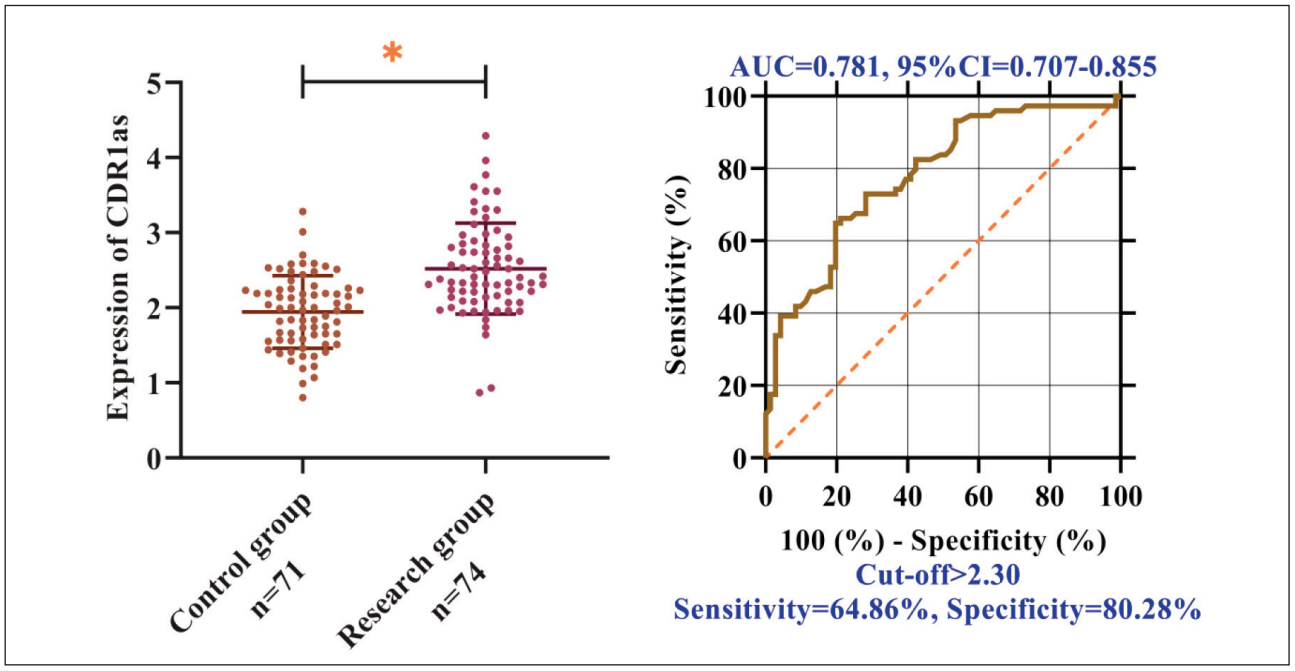

Figure 1 Diagnostic ROC Curves of CDR1as for NAFLD in DM patients.
* indicates P<0.05.

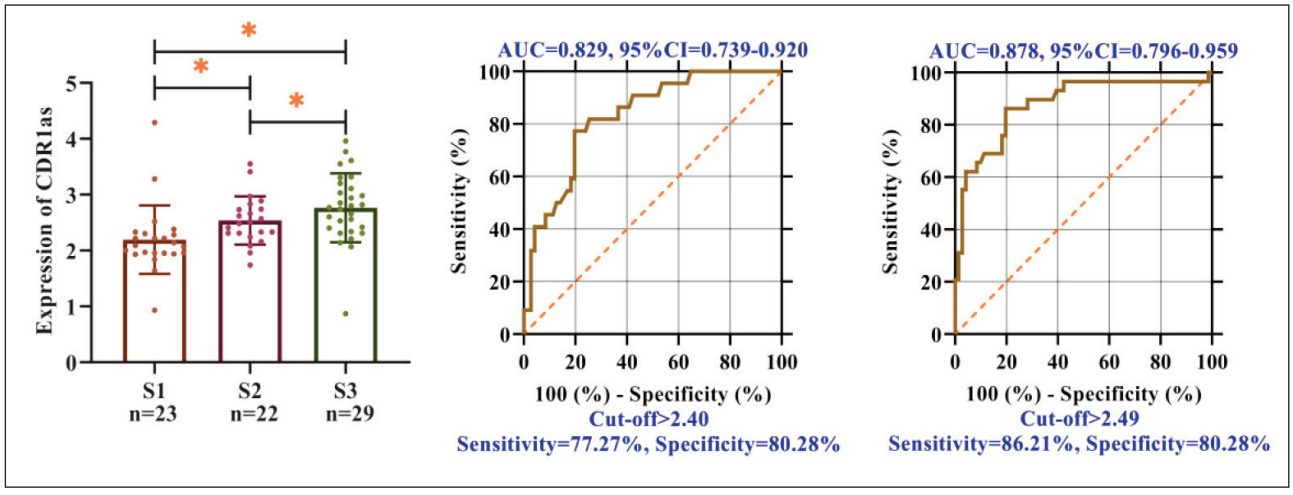

Figure 2 CDR1as expression levels in different steatosis grades.
* indicates P<0.05.

lation coefficient analysis indicated a positive correlation between CDR1as and HOMA-IR, FINS, FPG, and HbA1c in the research group (P<0.05; *Figure 3*).

Association of CDR1as with patient prognosis

The research group showed a 13.10% decline in serum CDR1as expression from baseline following the intervention (P<0.05). The 6-month follow-up survey of patients in the research group revealed a favourable prognosis in 46 cases and a poor prognosis in 28. Through comparison, we identified higher post-treatment CDR1as expression in patients with unfavourable outcomes (P<0.05). According to the ROC curve, CDR1as had a sensitivity of 57.14% and a specificity of 84.78% for predicting poor prognosis in DM patients with NAFLD when the post-treatment serum level was greater than 2.18 (AUC=0.747, P<0.05, *Figure 4*).

Discussion

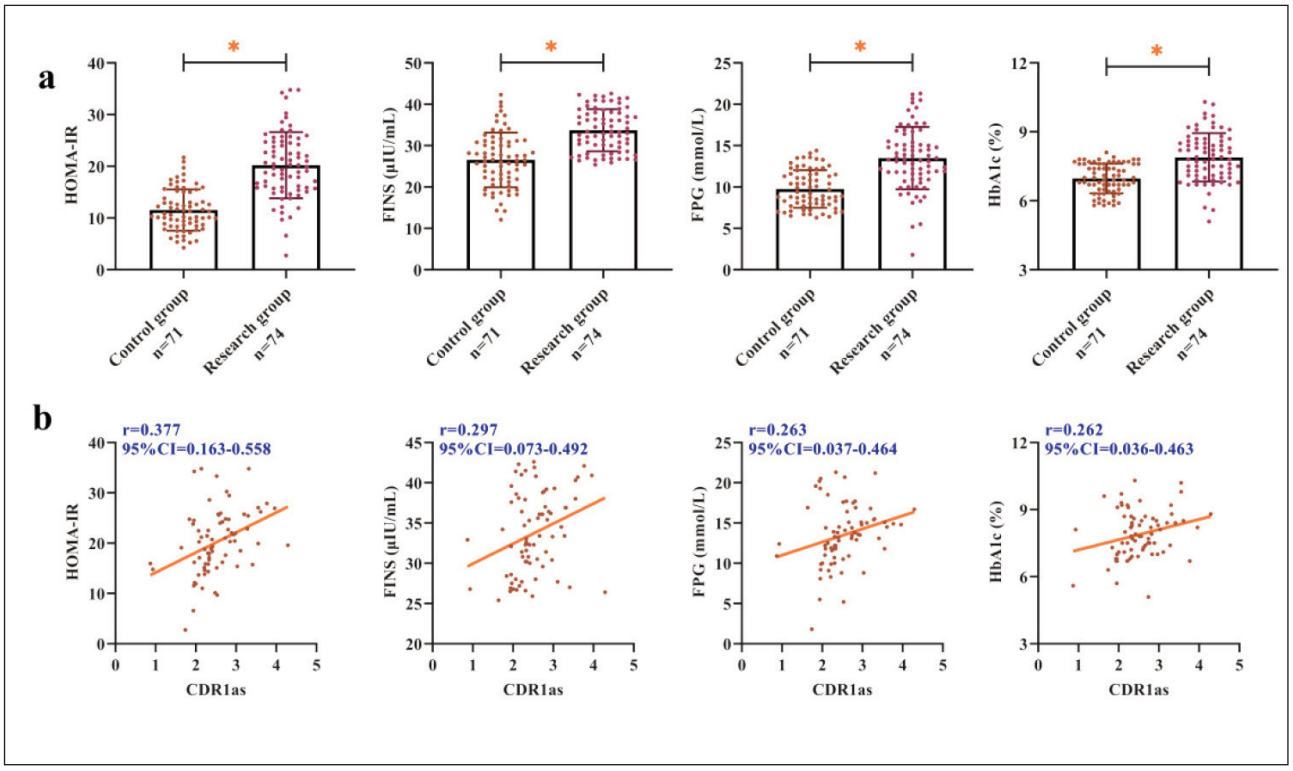

Figure 3 Correlation between CDR1as and glucose metabolism parameters.

a) Comparison of glucose metabolism parameters between the study group and the control group. b) correlation analysis of CDR1as with HOMA-IR, FINS, FPG, and HbA1c. * indicates P<0.05.

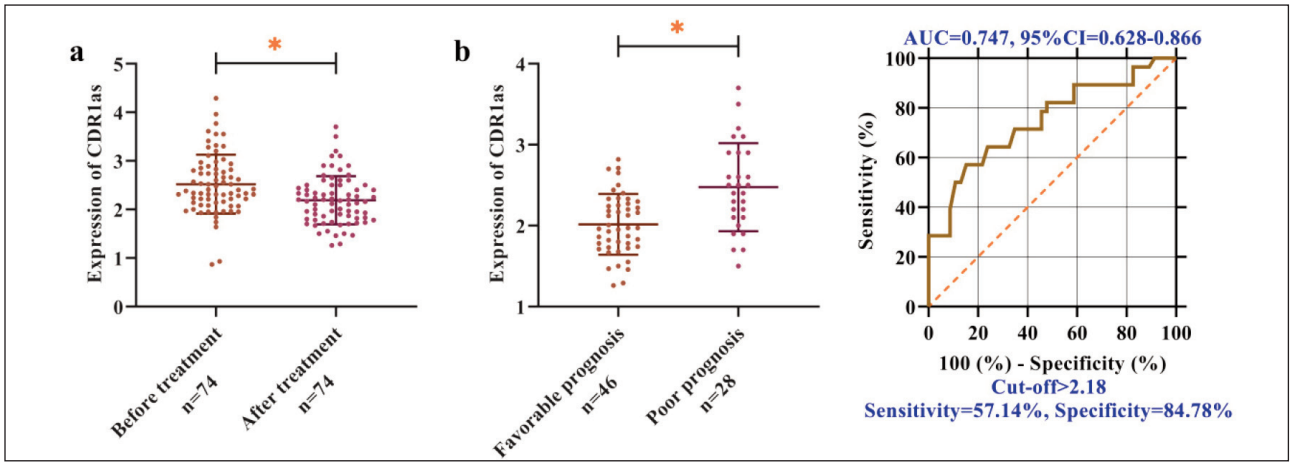

Figure 4 Prognostic ROC curve of CDR1as in DM patients with NAFLD.

a) Changes in CDR1as before and after treatment. b) Diagnostic efficacy of CDR1as for poor prognosis. * indicates P<0.05.

This study provides the first comprehensive assessment of circRNA CDR1as, exploring its diagnostic potential and biological roles in patients with DM and NAFLD. The results indicated a 29.90% elevation in serum CDR1as expression in DM patients with NAFLD compared to uncomplicated DM cases. Moreover, CDR1as expression correlated positively with the degree of NAFLD steatosis, with the highest levels identified in grade S3 patients. As determined by receiver operating characteristic (ROC) curve analysis, CDR1as exhibited an AUC of 0.781 for NAFLD diagnosis, with 64.86% sensitivity and 80.28% specificity. Its diagnostic utility was even more pronounced for moderate and severe steatosis (S2/S3), with AUCs achieving 0.829 and 0.878, respectively.

Furthermore, CDR1as was positively correlated

with glucose metabolism disorders (HOMA-IR, FINS, TG, LDL-C). Its expression decreased by 13.10% post-treatment in the research group, and high expression was associated with unfavourable outcomes (AUC=0.747). Therefore, CDR1as is not only a potential diagnostic marker for NAFLD in DM patients, but may also participate in disease progression by regulating IR and lipid metabolism, providing a new molecular target for the »glycemic control-NAFLD intervention« approach (15).

We hypothesise that CDR1as, as a sponge for miR-7, may alleviate miR-7–mediated inhibition of IRS-1/PI3K signalling, thereby exacerbating insulin resistance (15). miR-7 inhibits insulin signalling by targeting the 3'UTR region of insulin receptor substrate 1 (IRS-1) and phosphoinositide 3-kinase (PI3K) (16). Therefore, the overexpression of CDR1as may release miR-7 via sponge effects, leading to decreased IRS-1/PI3K pathway activity and, consequently, increased HOMA-IR and lipid synthesis. However, this mechanism requires validation in future functional studies. In addition, CDR1as may promote the secretion of inflammatory factors (e.g., TNF-α, IL-6) through modulation of the nuclear factor-κB (NF-κB) axis (17) or accelerate the fibrosis process by activating hepatic stellate cells via the miR-29b-3p/transforming growth factor-β (TGF-β) axis (18). This might also be the mechanism by which CDR1as promotes NAFLD progression and steatosis.

Subsequently, ROC curve analysis demonstrated the good diagnostic performance of CDR1as for NAFLD. We hypothesise that the following three factors underlie these advantages: ① CDR1as is highly expressed in the liver, while traditional indexes like ALT are greatly affected by muscle injury or drugs (19). CDR1as is highly expressed in liver tissue, as demonstrated by RNA-seq data from the Human Protein Atlas (20), which may explain its superiority over non-specific markers like ALT. ② The long half-life of serum circRNAs (up to 48 hours) and their insensitivity to changes in temperature and pH values have eliminated the volatility issue of traditional markers such as CRP. ③ Unlike conventional indicators, which only reflect the indirect consequences of liver damage, CDR1as expression is closely related to the core pathological mechanisms of NAFLD (HOMA-IR, SREBP-1c, etc.) because it directly participates in IR and lipid metabolism regulation. It is worth noting that the pathogenic role of CDR1as is tissue-specific. Meanwhile, the diagnostic value of CDR1as in NAFLD steatosis grading showed a gradient difference, possibly due to the increase in the volume and quantity of lipid droplets in hepatocytes with the worsening of fatty degeneration, which leads to aggravated cell membrane tension and mechanical damage that promotes CDR1as release into the blood through vesicle secretion or cell necrosis (21). Additionally, CDR1as demonstrated excellent diagnostic efficacy for moderate-to-severe steatosis (S2/S3). This gradient effect may be attributed to increased hepatocyte damage in advanced disease stages. More severe steatosis leads to greater circRNA release into circulation, thereby enhancing detectability. For mild steatosis (S1), the pathological changes are relatively localised. The circulating CDR1as level may be diluted by other circRNAs or serum proteins, thereby reducing diagnostic sensitivity. For patients at the S3 level, however, liver inflammation and fibrosis have significantly increased, leading to CDR1as levels far exceeding the detection threshold. These results also suggest the potential of CDR1as as a dynamic monitoring indicator for disease progression. For example, CDR1as could guide stratified management, e.g., levels >2.30 may identify patients requiring intensified glycemic monitoring or earlier pharmacologic intervention, while levels <2.18 might allow for routine follow-up.

Although CDR1as shows good diagnostic performance, its clinical application still needs careful interpretation. For instance, although CDR1as is highly expressed in the liver, does its circulating level truly reflect the liver's pathological state? Evidence shows that circRNAs have a half-life of up to 48 hours in the blood and are susceptible to phagocytosis by macrophages or degradation by nucleases (22), which may lead to inconsistencies between detection results and local liver expression. In addition, the causal relationship between CDR1as and NAFLD is yet to be defined. Furthermore, an increase in CDR1as may result from NAFLD (e.g., hepatocyte injury-induced release) or serve as a driving factor in disease progression (e.g., aggravating steatosis by regulating metabolic pathways). In the future, the causal direction of this phenomenon needs to be verified using Mendelian randomisation studies or intervention experiments (e.g., adeno-associated virus-mediated CDR1as knockout).

In addition, this study still has many limitations to address. For example, the single-centre design may introduce selection bias, particularly because dietary patterns in our region (a high-carbohydrate, high-fat diet) differ from those in other populations, potentially affecting both NAFLD prevalence and CDR1as expression patterns. Future multicenter collaborations are needed to expand sample sizes and include diverse ethnic groups to verify universality. Second, although the correlation between CDR1as and IR was initially revealed, the direct downstream targets (e.g., the phosphorylation level of IRS-1) regulated by CDR1as have not been verified. Basic experiments (such as hepatocyte overexpression/knockout CDR1as models) need to be carried out urgently to clarify the molecular mechanism. The correlational nature of our findings cannot distinguish whether CDR1as overexpression drives NAFLD progression or merely reflects hepatocyte injury-related release. Mendelian randomisation studies are needed to clarify causality. Finally, uncorrected factors that may

affect the results, such as unmeasured indicators of iron metabolism (e.g., serum ferritin) or intestinal microbiota diversity, could influence the accuracy of the results. Although BMI differences are inherent to NAFLD, its potential independent effect on CDR1as expression represents a confounding factor. Future studies should adjust for BMI in multivariate models.

Conclusion

CircRNA CDR1as, which is upregulated in DM patients with NAFLD, shows favourable diagnostic performance for NAFLD in this population. Meanwhile, it can serve as a new biomarker for stratified management of NAFLD in DM patients. In the future, research efforts should focus on molecular mechanisms, longitudinal follow-up, and cross-ethnic validation to facilitate the transformation of CDR1as from a laboratory discovery to a precise diagnostic tool.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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