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Clinical value of serum miR-214-3p expression in the diagnosis of type 2 diabetes mellitus and prediction of its chronic complications

Meng Ding[1†], Siyu Yang[2†], Junli Li[3], Lie Ma[4], Cunyou Xiong[5] and Jie Zhang[6*]

Abstract

Background The majority of diabetes cases fall into type 2 diabetes mellitus (T2DM), which is prone to chronic complications that have a long-term impact on patients. The aim of this study was to investigate the diagnostic potential of miR-214-3p in T2DM and its predictive value for chronic complications, providing a novel biomarker for the disease.

Methods A total of 156 patients with T2DM and 80 non-T2DM individuals were included. Serum miR-214-3p levels were measured by real-time reverse transcription quantitative PCR (RT-qPCR). The correlation of miR-214-3p with hemoglobin A1c (HbA1c) and low-density lipoprotein cholesterol (LDL-C) was analyzed by Spearman's rank correlation. The clinical value of miR-214-3p in T2DM was evaluated using the receiver operating characteristic (ROC) curve and logistic regression analysis.

Results The serum levels of miR-214-3p were decreased in T2DM patients compared to non-T2DM individuals. A negative correlation was identified between miR-214-3p expression and the levels of HbA1c and LDL-C. miR-214-3p could effectively differentiate T2DM patients from non-T2DM individuals with the area under ROC curve (AUC) of 0.884. Patients with low miR-214-3p expression had a higher incidence of chronic complications. The AUC for miR-214-3p in differentiating between T2DM patients with and without complications was 0.832. Low expression of miR-214-3p was a risk factor linked to the development of chronic complications in patients with T2DM.

Conclusion Serum miR-214-3p was downregulated in T2DM and could differentiate T2DM patients from non-T2DM individuals. miR-214-3p was a promising biomarker for predicting the chronic complications of T2DM.

Keywords miR-214-3p, Type 2 diabetes mellitus, Diagnosis, Chronic complications

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Background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease accounting for over 90% of all diagnosed cases of diabetes [1]. As a consequence of the aging population and lifestyle changes, the incidence of T2DM shows an upward trend on a global scale [2]. The disease is primarily characterized by insulin resistance and a relative decrease in insulin secretion, which results in an imbalance in the body's metabolism of carbohydrates [3]. The accuracy of traditional tests, such as the 2-hour oral glucose tolerance test (OGTT) and fasting blood glucose (FBG), is affected by the timing of blood collection in the diagnosis of T2DM. Several factors, including the duration of fasting, recent eating, excessive exercise, stress, and sleep deprivation, can influence the results of these tests [4]. Consequently, new effective diagnostic tools need to be explored. Abnormal glucose metabolism and the prolongation of the disease will result in a variety of complications, including but not limited to cardiovascular disease, renal disease, neuropathy, and so on [5–7]. Diabetes mellitus and its resulting chronic complications have the potential to significantly impair patients' quality of life. It is therefore imperative that strategies be developed to reduce the incidence of chronic complications among patients with T2DM. There is a pressing need for a comprehensive understanding of the risk factors associated with chronic complications of T2DM, which is essential for the development of targeted interventions.

The involvement of microRNAs (miRNAs) in the regulation of a variety of biological processes has led to a significant amount of research being conducted in this area [8]. Previous studies have indicated that the dysregulation of miRNAs is linked to T2DM and its complications [9–11]. For example, evidence has demonstrated that the miR-103 family functions as a pivotal regulator of glucose homeostasis in T2DM and possesses a high diagnostic value as a biomarker for T2DM [12]. Moreover, it has been demonstrated that serum miR-23a-3p levels are markedly diminished in individuals with T2DM, exhibiting a correlation with the severity of diabetic kidney disease [13]. Avgeris and colleagues reported the dysregulation of miR-214-3p in patients with T2DM by constructing miRNA expression profiles and real-time quantitative PCR (RT-qPCR) assays [14]. A study conducted by Pang et al. discovered that miR-214-3p was effective in mitigating neurological impairment and pathological alterations in diabetic rats [15]. Another study indicated that miR-214-3p was downregulated in diabetic mice and was linked to cardiac fibrosis [16]. Consequently, it is postulated that miR-214-3p may be linked to the development of T2DM and its associated complications. At present, the clinical value of miR-214-3p in T2DM remains unclear.

In this study, the clinical value of serum miR-214-3p expression in T2DM was investigated by data analysis, providing new ideas for the diagnosis of T2DM and the prediction of its chronic complications.

Materials and methods

Study population

A total of 156 patients with newly diagnosed T2DM between 2020 and 2021 from the Yantai Mountain Hospital were selected as study subjects. Inclusion criteria: ①complete clinical data; ② meet the diagnostic criteria of T2DM [17]: typical symptoms (polydipsia, polyphagia, polyuria, and weight loss), random plasma glucose ≥ 11.1 mmol/L or FBG ≥ 7.0 mmol/L or 2-hour OGTT ≥ 11.1 mmol/L; and ③ age 20–80 years old. Exclusion criteria: ① women who are pregnant or lactating; ② patients with acute complications of diabetes; ③ patients with severe cardiac, hepatic, pulmonary, or renal insufficiency; ④ patients with malignant tumors or severe infections; and ⑤ patients with severe mental illness. In the same period, a total of 80 healthy individuals who underwent a medical examination at this hospital were selected as the non-T2DM group. This study was approved by the Ethics Committee of the hospital. All study subjects gave informed consent.

General information (age, sex, height, weight, and blood pressure) and laboratory findings (blood glucose, lipids, and glycated hemoglobin) were collected from all study participants.

Evaluation of chronic complications

A three-year follow-up was conducted on all T2DM patients to investigate the occurrence of complications. Cardiovascular diseases were diagnosed regarding the relevant diagnostic criteria of Expert consensus on the management of diabetic patients with cardiovascular diseases [18], combined with clinical assessment of the cardiac and peripheral vascular systems, electrocardiogram, and vascular ultrasonography. The diagnosis of diabetic kidney disease was dependent upon urinary albumin excretion rate, estimated glomerular filtration rate, and so on, with reference to the KDIGO clinical practice guideline [19]. Diabetic neuropathy was diagnosed with reference to the relevant criteria of the American Diabetes Association [20], combined with history taking, neurological examination, nerve conduction velocity test, and quantitative sensory test. Diabetic retinopathy was diagnosed with reference to the clinical guideline published by the American Academy of Ophthalmology [21], in conjunction with fundus examination and fluorescein fundus angiography. Patients with T2DM who developed chronic complications were included in the complication group and the rest were included in the non-complication group.

Table 1 Clinical characteristics of the study population

Characteristic	Non-T2DM group ($n=80$)	T2DM group ($n=156$)	*P* value
Age (years)	53.83 ± 8.32	54.43 ± 10.42	0.629
Sex (male, %)	49 (61.25)	89 (57.05)	0.536
BMI (kg/m^2)	23.45 ± 2.91	23.99 ± 2.44	0.130
DBP (mmHg)	74.84 ± 7.70	76.73 ± 9.66	0.129
SBP (mmHg)	118.30 ± 12.22	119.50 ± 13.02	0.495
FBG (mmol/L)	5.09 ± 0.83	9.23 ± 1.46	< 0.001
Triglyceride (mmol/L)	1.18 ± 0.28	1.88 ± 0.53	< 0.001
TC (mmol/L)	4.22 ± 0.68	5.01 ± 1.17	< 0.001
HDL-C (mmol/L)	1.39 ± 0.20	1.19 ± 0.28	< 0.001
LDL-C (mmol/L)	2.46 ± 0.33	2.93 ± 0.45	< 0.001
HbA1c (%)	5.04 ± 0.50	7.44 ± 1.00	< 0.001

Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c

Determination of serum miR-214-3p expression

Fasting venous blood was collected from all subjects on admission and subsequently centrifuged at 3000 r/min for 5 minutes in order to determine serum miR-214-3p expression. Total RNA was extracted using TRI reagent (Sigma-Aldrich, Germany) and then transcribed into cDNA using PrimeScript RT reagent Kit (TaKaRa, Japan). The reverse transcription primer for miR-214-3p is: 5'- GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACACTGCC-3'. RT-qPCR was conducted using PowerUp SYBR Green Master Mix (Applied Biosystems, USA) on the ViiA 7 Real-Time PCR System (Applied Biosystems). Cycle threshold (Ct) values are listed in the Supplementary tables S1 and S2. The relative levels of serum miR-214-3p were calculated using the $2^{-\Delta\Delta Ct}$ method [22] with U6 as the internal reference. The forward and reverse primers of miR-214-3p were 5'-GCGACAGCAGGCACAGACA-3' and 5'-AGTGCAGGGTCCGAGGTATT-3', respectively. Three independent experiments were conducted and three replicates were set up for each test.

Statistical analysis

Data processing was performed using SPSS 22.0 software and GraphPad 8.0. Normally distributed data were expressed as mean ± standard deviation, and Student's t-test was used for comparison between the two groups. Data that did not fit the normal distribution were expressed as median with interquartile range and analyzed using a non-parametric test. Categorical variables were expressed as numbers (n) with percentages (%), and comparisons between groups were made using the Chi-Squared test. The correlation of miR-214-3p with hemoglobin A1c (HbA1c) and low-density lipoprotein cholesterol (HDL-C) was analyzed using Spearman's rank correlation. The value of miR-214-3p in identifying patients with different statuses was evaluated by the receiver operating characteristic (ROC) curve. Multivariate logistic regression was used to evaluate the risk factors for chronic complications in patients with T2DM. Differences were statistically significant at $P<0.05$.

Results

Serum miR-214-3p expression was downregulated in T2DM

The current study enrolled T2DM patients ($n=156$) and non-T2DM individuals ($n=80$) to investigate the clinical value of miR-214-3p in T2DM. Comparison of the clinical data revealed statistically significant differences in the levels of FBG, HbA1c, triglyceride, total cholesterol (TC), HDL-C, and LDL-C between individuals with and without T2DM (Table 1). miR-214-3p expression was reduced in the serum of T2DM patients compared to the non-T2DM individuals (Fig. 1A). ROC curve showed that miR-214-3p could distinguish between non-T2DM populations and T2DM patients with the AUC of 0.884 (Fig. 1B). Furthermore, the expression of miR-214-3p was

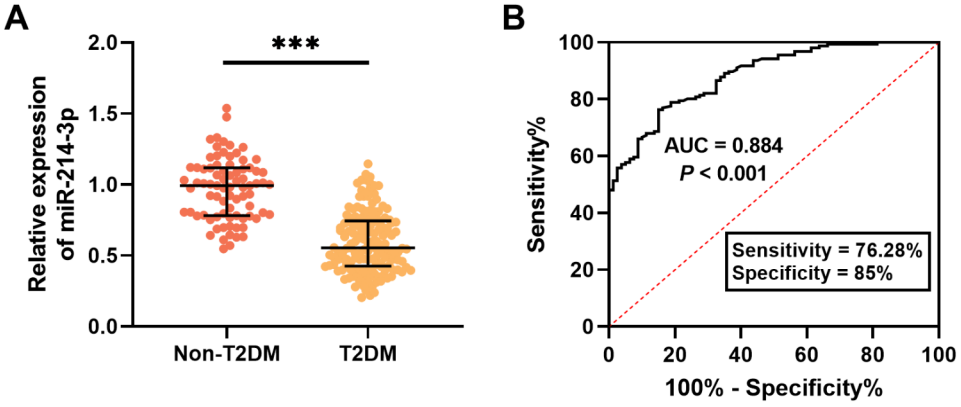

Fig. 1 miR-214-3p was associated with T2DM. (**A**) The expression of miR-214-3p was reduced in the serum of patients with T2DM. (**B**) The level of miR-214-3p could distinguish between non-T2DM individuals and patients with T2DM. ***$P<0.001$

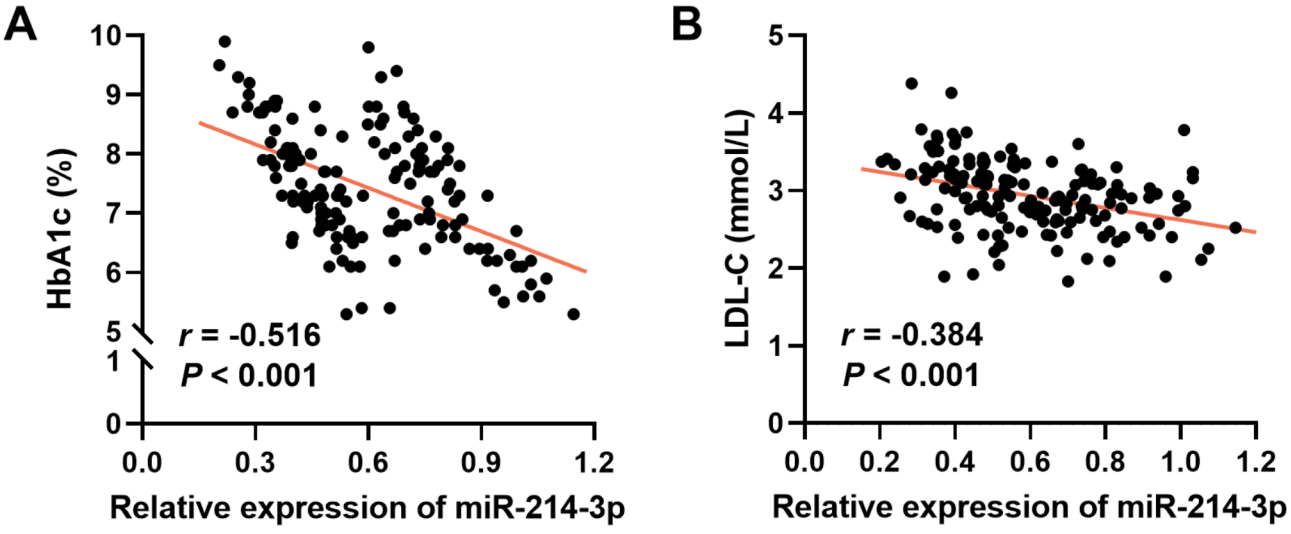

Fig. 2 miR-214-3p was adversely correlated with the levels of HbA1c (**A**) and LDL-C (**B**) in patients with T2DM

Table 2 Correlation between miR-214-3p expression and chronic complications

Complication	miR-214-3p expression		*P* value
	Low (*n* = 84)	High (*n* = 72)	
Diabetic kidney disease	15	6	0.013
Cardiovascular disease	12	5	0.032
Diabetic retinopathy	10	3	0.020
Diabetic neuropathy	6	1	0.032

adversely correlated with the levels of HbA1c (r = -0.516, Fig. 2A) and LDL-C (r = -0.384, Fig. 2B) (both $P < 0.001$).

miR-214-3p expression was related to T2DM complications

Of the 156 patients with T2DM, 54 patients developed at least one chronic complication, including 21 cases of diabetic kidney disease, 17 cases of cardiovascular disease, 13 cases of diabetic retinopathy, and 7 cases of diabetic neuropathy (Table 2). miR-214-3p was downregulated in patients within the complication group in comparison to the non-complication group (Fig. 3A). Furthermore, the association between miR-214-3p and the development of complications was investigated. All T2DM patients were classified into two groups according to the mean level of

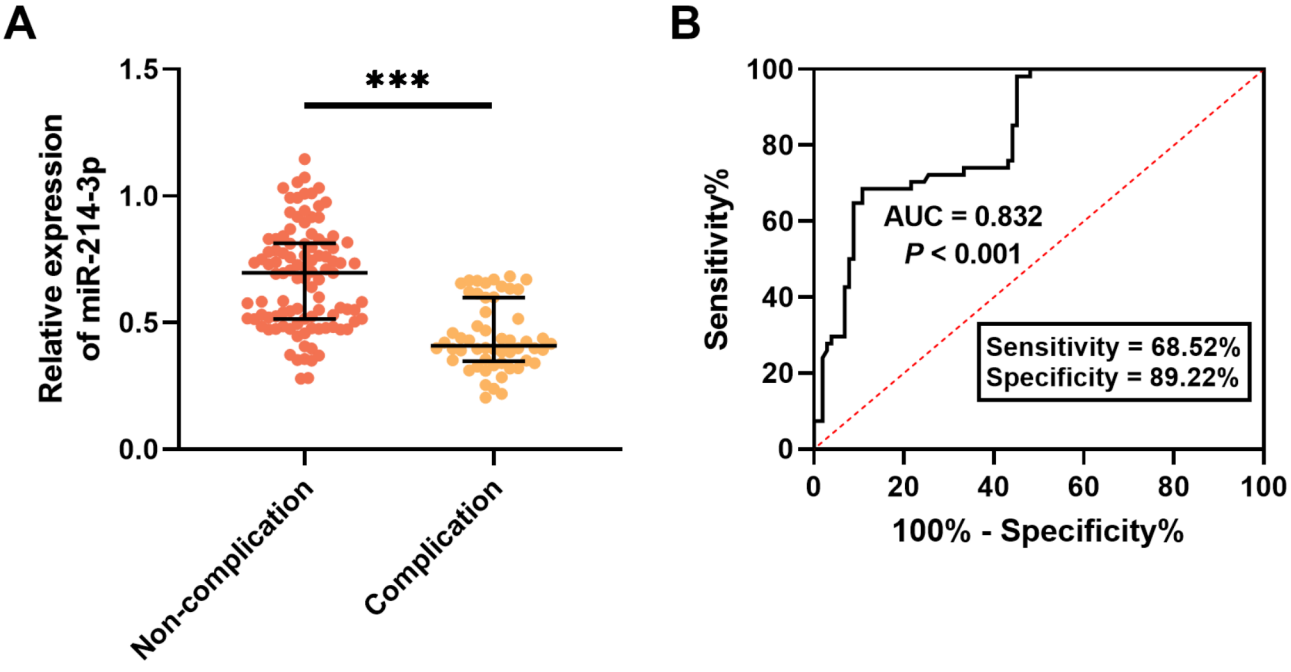

Fig. 3 (**A**) The expression of miR-214-3p was lower in T2DM patients with complications than in those without complications. (**B**) The level of miR-214-3p could differentiate between T2DM patients with and without complications. ***$P < 0.001$

Table 3 Clinical characteristics of T2DM patients with and without complications

Characteristic	Non-complication group ($n=102$)	Complication group ($n=54$)	*P* value
Age (years)	53.41 ± 9.81	56.35 ± 11.33	0.094
Sex (male, %)	60 (58.82)	29 (53.70)	0.539
BMI (kg/m^2)	23.75 ± 2.39	24.45 ± 2.50	0.092
DBP (mmHg)	75.74 ± 9.52	78.61 ± 9.74	0.077
SBP (mmHg)	118.33 ± 12.77	121.70 ± 13.33	0.124
FBG (mmol/L)	9.08 ± 1.38	9.51 ± 1.58	0.082
Triglyceride (mmol/L)	1.86 ± 0.55	1.92 ± 0.48	0.479
TC (mmol/L)	4.92 ± 1.05	5.16 ± 1.36	0.272
HDL-C (mmol/L)	1.21 ± 0.26	1.14 ± 0.29	0.135
LDL-C (mmol/L)	2.84 ± 0.43	3.11 ± 0.44	< 0.001
HbA1c (%)	7.27 ± 0.97	7.76 ± 0.99	0.003

Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c

miR-214-3p in serum: the low-expression ($n=84$) and the high-expression ($n=72$) groups. The prevalence of complications was higher in low miR-214-3p expression group ($P<0.05$, Table 2). In addition, the level of miR-214-3p effectively differentiated T2DM patients with and without complications with the AUC of 0.832 (Fig. 3B).

miR-214-3p was a risk factor linked to T2DM complications

Clinical indices such as LDL-C and HbA1c showed notable differences between the non-complication and complication groups (Table 3). Multivariate logistic regression revealed that miR-214-3p [odds ratio (OR) = 0.273, 95% confidence interval (CI): 0.122–0.610, $P=0.002$], LDL-C (OR = 2.559, 95% CI: 1.132–5.786, $P=0.024$), and HbA1c (OR = 2.773, 95% CI: 1.274–6.034, $P=0.010$) were risk factors related to complications in patients with T2DM (Fig. 4).

Discussion

The prevalence of T2DM is on the rise globally with economic development and changes in people's lifestyles [23]. Despite the heightened focus on T2DM, the etiology and pathogenesis of the disease remain incompletely understood [24]. As the disease progresses, patients with T2DM are at an elevated risk of developing chronic complications. Such conditions not only impact the quality of life of those affected but also result in increased

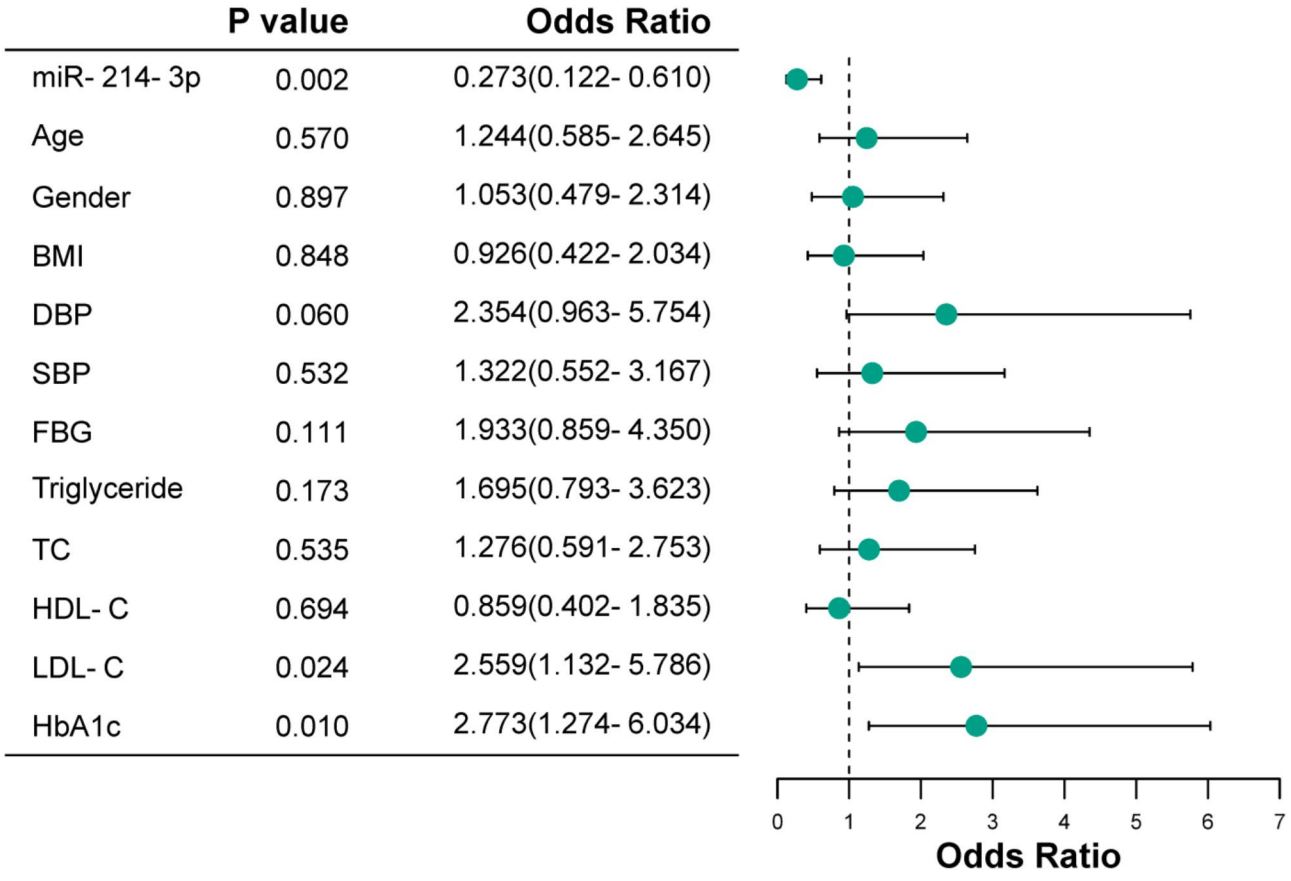

Fig. 4 The expression of miR-214-3p served as a risk factor for the development of complications in patients with T2DM

consumption of medical resources and heightened social and economic burdens [25, 26]. Timely diagnosis and assessment of T2DM were beneficial for the treatment of the disease and the prevention of chronic complications.

Numerous studies have indicated that miRNAs act as regulators in the pathological mechanisms of diabetes and are associated with the onset and progression of the disease [27]. For instance, miR-210 levels are increased in serum samples from patients with T2DM and correlate with disrupted lipid metabolism [28]. Another study discovered that miR-31 delayed the progression of T2DM in vivo, improved glucolipid metabolism, and was protective against vascular injury in T2DM mice [29]. It has been reported that miR-214-3p is a dysregulated miRNA in peripheral blood samples from patients with T2DM compared to subjects without the disease [14]. Nevertheless, the clinical utility of miR-214-3p in T2DM remains poorly understood. Here, the blood glucose and lipid indices of individuals with T2DM exhibited notable abnormalities in comparison to those of non-T2DM individuals, suggesting that the patient's glucose and lipid metabolism was disrupted. miR-214-3p was downregulated in the serum of T2DM patients. Additionally, the level of miR-214-3p effectively differentiated T2DM patients from the non-T2DM population. These findings indicate that miR-214-3p may act as a promising biomarker for T2DM and its potential role in the development of T2DM.

Patients with diabetes are in a state of chronic hyperglycemia, which is susceptible to tissue and organ damage [30]. T2DM is closely related to the lesions of the organism's macrovascular and microvascular systems, leading to chronic complications. This is the main cause of poor outcomes in T2DM patients, resulting in kidney failure, blindness, amputation, and even death [31, 32]. The level of HbA1c is an important indicator of blood glucose status over the past 2–3 months and has been included in the diagnostic criteria as an important test [33]. Furthermore, some clinical studies have identified HbA1c as a critical factor in the pathogenesis of microvascular complications, neuropathy, and cardiovascular disease in patients with T2DM [34–36]. It has been found that LDL-C is closely linked to chronic complications in T2DM patients, and lowering LDL-C is beneficial in delaying complications [37]. The present study revealed a negative correlation between miR-214-3p and the levels of HbA1c and LDL-C in patients with T2DM, indicating a potential association between miR-214-3p and the complications of T2DM. Among the 156 T2DM patients who were studied, 54 developed at least one complication. These complications included cardiovascular disease, diabetic kidney disease, diabetic neuropathy, and diabetic retinopathy. miR-214-3p expression was decreased in T2DM patients with complications and was strongly related to the development of chronic complications. This suggests that T2DM patients with lower miR-214-3p levels may be more prone to chronic complications.

Previously, miR-214-3p was identified as a potential regulator of diabetic complications [38]. One study has indicated that miR-214-3p exerts a suppressive effect on neuronal pyroptosis and autophagy in diabetic mice, thereby exerting neuroprotective effects [39]. In a recent study, Zhang and colleagues revealed that miR-214-3p exerts a regulatory effect on renal inflammation and kidney injury in diabetic mice [40]. The current study further unveiled that miR-214-3p exhibited the capacity to differentiate between T2DM patients with and without chronic complications. Subsequent analysis demonstrated that low miR-214-3p expression was a risk factor linked to complications of T2DM. Accordingly, the monitoring of miR-214-3p levels has the potential to be a valuable tool for the early detection of chronic complications in patients with T2DM in the clinical setting. Furthermore, there were notable differences in the levels of LDL-C and HbA1c between T2DM patients with and without chronic complications. The analysis also demonstrated that LDL-C and HbA1c are risk factors for the development of chronic complications in patients with T2DM, which is consistent with previous studies [41]. The timely detection of changes in these associated factors could facilitate more effective prevention and control of chronic complications, thus improving patient outcomes.

However, the relatively modest sample size and the potential for selection bias among the patient cohort may restrict the clinical generalizability of these findings. It is crucial to conduct further research with a larger sample size to validate the findings of the study and enhance their potential for clinical application. A study revealed that U6 is not an optimal internal reference for serum or plasma miRNA studies [42]. However, the unstable expression of U6 in these bodily fluids may be attributable to its susceptibility to alteration in certain pathological conditions. To date, this phenomenon has not been documented in diabetic patients. This study lacked the detailed information regarding the antidiabetic treatment that patients received. To control for relevant confounders, the potential impact of treatment regimens should be considered in future studies. Additionally, the involvement of miRNAs in disease progression is typically through the regulation of downstream gene expression and related signaling pathways. Consequently, further investigation is required to elucidate the direct targets and downstream mechanisms of miR-214-3p in T2DM.

Conclusion

In conclusion, the findings of this study disclosed that miR-214-3p expression was decreased in patients with T2DM, indicating that miR-214-3p may serve as a promising biomarker for this disease. Furthermore, low expression of miR-214-3p was identified as a risk factor related to the development of complications in individuals with T2DM.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01916-1.

Supplementary Material 1

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Author contributions
Conceptualization, J.L. L., L.M., C.Y. X.; Data curation, J.L. L., L.M., C.Y. X.; Formal analysis, M. D., S.Y. Y, J.L. L., L.M., J. Z.; Investigation, J.L. L., L.M.; Methodology, J.L. L., L.M., C.Y. X.; Project administration, C.Y. X.; Resources, J.L. L., L.M.; Software, J.L. L., L.M.; Supervision, C.Y. X.; Validation, M. D., S.Y. Y, J.L. L., L.M., J. Z.; Visualization, J.L. L., L.M.; Roles/Writing - original draft, J.L. L., L.M.; Writing - review & editing, C.Y. X., M. D., S.Y. Y, J. Z.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Yantai Mountain Hospital before the study began. The written informed consent has been obtained from the participants involved.

Consent for publication
Not applicable.

Conflict of interest
There is no conflict of interest in this study.

Clinical trial number
Not Applicable.

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