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Potential Diagnostic Markers of Diabetic Retinopathy: Serum LncRNA MIAT, HOTTIP, SNHG16

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Purpose: To study the expression and diagnostic ability of the long noncoding RNAs (lncRNAs) MIAT, HOTTIP, and SNHG16 in serum of patients with diabetic retinopathy.

Methods: A total of 70 healthy controls and 195 patients with Type 2 Diabetes (T2D) were collected. T2D patients include 65 patients with Nondiabetic retinopathy (NDR), 65 patients with Nonproliferative diabetic retinopathy (NPDR) and 65 patients with Proliferative diabetic retinopathy (PDR). The relative expression of MIAT, HOTTIP and SNHG16 in participant serum was measured through Real-time fluorescence quantitative polymerase chain reaction to compare the differential expression between the groups. *t* test, Mann–Whitney *U*-test, Pearson's chi-square test and the receiver operating characteristic (ROC) curve were used to analyze the expression of these LncRNAs and their diagnostic ability for DR.

Results: We compare the healthy control group with T2D group, healthy control group with NDR group, NDR group with DR (NPDR +PDR) group, and NPDR group with PDR group. When NDR group was compared with the healthy control group, there was no difference between MIAT ($p>0.05$)and HOTTIP ($p>0.05$), only the relative expression of SNHG16($p<0.05$) was different and it's ROC curve had identification significance. In the remaining inter-group comparisons, the differences in the expression of MIAT ($p<0.05$), HOTTIP ($p<0.05$) and SNHG16 ($p<0.05$) were statistically significant, and their ROC curves were all had identification significance.

Conclusion: These findings prove that serum LncRNA MIAT, HOTTIP and SNHG16 may be used as potential markers to monitor the progress of DR.

Keywords: LncRNA MIAT, HOTTIP, SNHG16, diabetic retinopathy, type 2 diabetes

Introduction

Diabetic retinopathy (DR) is the most common ocular complication of diabetic patients, and it is a series of fundus lesions caused by long-term retinal microvascular and nerve dysfunction. The global prevalence rate is about 35%, and the low vision or even blindness it causes has a serious impact on the quality of life of patients.[1,2] Nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) are two main clinical forms. Effective treatment of DR must be achieved through early diagnosis, and early treatment can prevent serious vision loss or even blindness.[3] In recent years, with the extensive application of sequencing technology in retina research, it has been proven that noncoding RNA is closely related to the occurrence and development of DR.[4] Whether these noncoding RNAs can be used as auxiliary diagnostic factors for DR and whether they can be used as potential therapeutic targets deserves our investigation.

Long noncoding RNA (lncRNA) is a type of ncRNA with a transcript length of more than 200 nt that plays an important role in many vital activities, such as dose compensation, epigenetic regulation, cell cycle regulation and cell

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differentiation regulation.[5,6] LncRNAs have been confirmed to be widely involved in the regulation of retinal gene expression.[7] In the DR model, numerous lncRNAs showed abnormal expression.[8] These abnormally expressed lncRNAs may serve as potential biomarkers for the diagnosis and prognosis prediction of DR and become effective therapeutic targets.[5] At present, some studies have found that LncRNA OGRU, MALAT1, HOTAIR, etc. may be used as potential diagnostic markers of DR.[9] The serum levels of these LncRNAs were obviously different between normal population and DR population, but the researchers only compared the normal population and DR population, and did not make further comparison according to the classification of DR.

Myocardial infarct-associated transcript (MIAT), an important heart-related lncRNA with a length of 30,051 bp, is located on chromosome 22q12.1, it involved in the biological processes of genome imprinting, chromatin modification and transcription activation.[10] Researchers have proven that serum MIAT expression in T2D patients is significantly higher than that in the healthy population.[11] The distal HOXA transcript (HOXA transcript at the distal tip, HOTTIP) is a lncRNA with 3764 nucleotides encoded by the genomic region at the 5' end of the HOXA locus, which plays an important role in the transmission of signals from higher-order chromosomal configuration to chromatin code.[12] The expression of HOTTIP in the retina was significantly upregulated in a high glucose environment.[13] Small nucleolar RNA host gene 16 (SNHG16) is an LncRNA located at position 17q25.1 of the human chromosome region, which was first reported in neuroblastoma.[14] It was found that the content of SNHG16 in serum of diabetic retinopathy patients was significantly higher than that of normal people.[15]

At present, there are few studies on the correlation between lncRNAs and DR. We compared the expression differences of MIAT, HOTTIP and SNHG16 in the plasma of DR patients in different stages to explore whether MIAT, HOTTIP and SNHG16 can be used as potential reference indicators for the diagnosis and evaluation of DR progression.

Methods

Patients and Study Design

The study was reviewed and approved by the Suining Central Hospital Research Ethics Committee (KYLLKS20230126) and in compliance with the principles of the Helsinki Declaration. This study has been registered in China Clinical Trial Registration Center (ChiCTR2300078659).Written informed consent was obtained from the participants, and the study was authorized to publish all the information related to the research.

Medical records were analysed for patients who first presented from January 2021 to December 2023. Calculate sample size using GPower software with Effect size d set to 0.5, α err prob set to 0.05, Power set to 0.8, Allocation ratio N2/N1 set to 1, and the calculated sample size of each group was at least 64 cases. A total of 70 healthy controls and 195 patients with type 2 diabetes (T2D) were included. The T2D patients included 65 patients with Non-DR (NDR) and 130 patients with DR (65 patients with NPDR and 65 patients with PDR). The diagnoses of NDR, NPDR and PDR were confirmed by fundus fluorescein angiography and were jointly diagnosed by three ophthalmologists who had worked for more than five years. T2D patients have a history of more than three years and use oral drugs or insulin to control blood sugar. No medical history of hypertension, cerebral infarction and cardiac infarction, no or occasional smoking, and no medical history of ocular tumour, ocular trauma and intraocular surgery. Some of the patients participating in the study were treated with retinal laser and/or intravitreal anti-VEGF injection, and some underwent vitrectomy. Plasma collection was completed before the patients received specialist treatment. Participants were between 44 and 76 years of age, and were both male and female.

Extraction of Serum LncRNA and Determination of Its Expression Level

Extract 4 mL from the collected venous blood of elbow, 3500 r/min, centrifuge for 10 min with an effective radius of 10cm, and store the separated serum in the refrigerator at −80°C for inspection. Trizol reagent (Thermo Fisher Scientific Shier Technology Co., Ltd.) was used to extract total RNA from serum, and the concentration and purity of total RNA were detected by ultraviolet spectrophotometer. The A260 /A280 was 1.8–2.0, which could be used for downstream experiments. Using PrimeScript RT polymerase (Thermo Fisher Scientific Shier Technology Co., Ltd)., 2μg of total RNA

was reverse transcribed into cDNA. cDNA was used as a template for routine polymerase chain reaction, and the expression levels of LncRNA MIAT, HOTTIP and HEIH were detected by Real-time PCR. Real-time polymerase chain reaction (PCR) used 20 μL of responder lines: TB Green Premix ex Taq II (TLI RNase H Plus) (2×) 10 μ l, ROX Reference Dye or Dye II (50×) 0.4 μ l, cDNA(50 ng /μL) 2 μL, and upstream and downstream primers (10 μmol /L) 0.8 μL each. Reaction conditions: 95°C, 30s; 95°C, 5s; 60°C, 34s, 40 cycles. β-actin was used as the reference gene, and the primers used in this study were designed by Primer 5.0 primer design software: MIAT-F:5'-GCAC CTTG AGTG ATCAAGCAG-3',MIAT-R:5'-TGGCAGCATCCGCGACACACAGG-3';HOTTIP-F:5"-TACGCGTATTCTTAAGCAAT -3',HOTTIP-R:5'-ACCCGTCACCGAAGAGAGTC-3';SNHG16-F:5′-CCCAAGCTTGCGTTCTTTTCGAGGTCG GC-3′, SNHG16-R:5′-CCGGAATTCTGACGGTAGTTTCCCAAGTT-3′; β-actin-F: 5'-CTCCTCCTGGCTGT-3', β-actin-R: 5'-GCTGTCATCTCCTTCC-3'. All conditions were strictly carried out according to the detection system, and the expression level of these LncRNAs was quantitatively analyzed by 2-$^{\Delta\Delta}$CT method.

Statistical Analysis

The statistical software used was SPSS 22.0 (SPSS Inc., Chicago, IL), and $P < 0.05$ indicated statistical significance. Measurement data are expressed as the mean±standard deviation (± s). A *t* test was used for data conforming to a normal distribution, and the Mann–Whitney *U*-test was used for data not conforming to a normal distribution. Enumeration data were expressed as numbers and compared using Pearson's chi-square test. The area under the receiver operating characteristic (ROC) curve (AUC) was used to analyse the predictive value of MIAT, HOTTIP, SNHG16 and their combination for DR in the diagnosis.

Results

Clinical Baseline Information for Participants

Clinical baseline comparisons among the healthy control group (70 people), the NDR group (65 people), the NPDR group (65 people), and the PDR group (65 people) (Table 1). Compared with T2D group, there are differences in HbA1c ($P < 0.05$), triglyceride ($P < 0.05$), diabetes duration ($P < 0.05$) and medical duration ($P < 0.05$) in control group. Compared with NDR group, there were differences in HbA1c ($P <0.05$), diabetes course ($P<0.05$) and medication time ($P <0.05$) in the control group. NPDR and PDR groups differ in Creatinine ($P<0.05$).

Expression of MIAT, HOTTIP and SNHG16 in Serum

The relative expression levels of MIAT ($P<0.05$), HOTTIP ($P<0.05$) and SNHG16 ($P<0.05$) in the T2D group were significantly higher than those in the healthy control group. Only SNHG16 in the NDR group ($P<0.05$) had an increased relative expression level compared with that in the healthy control group. The relative expression levels of MIAT

Table 1 Comparison of Clinical Data of Participants in Each Group

	Total (n=265)	Controls (n=70)	NDR (n=65)	NPDR (n=65)	PDR (n=65)	p^a	p^b	p^c	p^d
Male/Female	86/74	32/38	19/11	14/16	21/9	0.072	0.106	0.648	0.067
Age(years)	60.500±10.426	63.33±11.41	60.500±12.276	58.167±11.339	60.000±9.602	0.454	0.688	0.791	0.759
HbA1C	6.525±1.452	4.522±0.946	6.945±0.771	6.958±0.814	7.763±0.845	**0.000**	**0.001**	0.392	0.166
Cholesterol	5.598±1.180	5.022±0.862	5.210±1.198	6.203±1.073	5.957±1.378	0.172	0.761	0.163	0.737
Triglyceride	2.305±0.858	1.627±0.695	2.328±0.481	2.635±0.563	2.633±1.242	**0.021**	0.070	0.460	0.998
BMI	24.192±2.026	23.217±1.812	25.200±1.708	24.883±2.623	23.467±1.500	0.179	0.080	0.329	0.277
GPT (U/L)	35.850±9.917	31.200±10.159	39.600±11.866	34.400±7.956	38.400±10.164	0.236	0.264	0.565	0.508
Creatinine (mmol/L)	84.100±26.372	73.200±17.712	76.400±13.795	73.600±15.534	113.200±33.752	0.298	0.758	0288	**0.044**
LDL(mmol/L)	2.825±0.725	2.696±0.577	2.666±0.855	2.860±0.897	3.078±0.701	0.658	0.950	0.499	0680
Diabetes duration(years)	6.200±4.607	0	6.200±1.934	8.800±2.168	9.800±4.438	**0.000**	**0.000**	0.79	0.663
Medication duration(years)	5.250±4.128	0	4.800±1.924	7.400±2.075	8.800±4.086	**0.000**	**0.001**	0.053	0.514

Notes: The statistically significant parts were represented by bold fonts. [a]Comparison between control group and T2D(NDR, NPDR, PDR) group. [b]Comparison between control group and NDR group. [c]Comparison between NDR group and DR(NPDR, PDR) group. [d]Comparison between NPDR group and PDR group.
Abbreviations: GPT, Glutamic-pyruvic transaminase; LDL, low-density lipoprotein.

Table 2 Relative Expression of Serum MIAT, HOTTIP and HEIH in Each Group

	Controls	T2D	NDR	NPDR	PDR	p^a	p^b	p^c	p^d
MIAT	1.381±0.622	2.035±0.872	1.560±0.630	2.016±0.725	2.529±0.962	**0.000**	0.192	**0.000**	**0.023**
HOTTIP	0.993±0.529	1.758±0.965	1.174±0.574	1.711±0.743	2.388±1.099	**0.000**	0.102	**0.000**	**0.007**
HEIH	0.982±0.519	2.072±1.162	1.278±0.647	1.865±0.847	3.073±1.129	**0.000**	**0.024**	**0.000**	**0.000**

Notes: The statistically significant parts were represented by bold fonts. [a]Comparison between control group and T2D(NDR, NPDR, PDR) group. [b]Comparison between control group and NDR group. [c]Comparison between NDR group and DR(NPDR, PDR) group. [d]Comparison between NPDR group and PDR group.

(P<0.05), HOTTIP (P<0.05) and SNHG16 (P<0.05) in the DR (NPDR+PDR) group were higher than those in the NDR group. The relative expression levels of MIAT (P<0.05), HOTTIP (P<0.05) and SNHG16 (P<0.05) in the PDR group were higher than those in the NPDR group. Their expressions were shown in Table 2.

The Expression Changes of MIAT, HOTTIP and SNHG16 with the Progression of DR

With the progression of DR, the relative expression of MIAT in patient serum gradually increased (Figure 1a). There was no significant difference between the NDR group and the healthy control group (P = 0.102), the difference between the NPDR group and NDR group was statistically significant (P = 0.003), the difference between the PDR group and NPDR group was statistically significant (P=0.00). With the progression of DR, the relative expression of HOTTIP in patient serum gradually increased (Figure 1b). There was no significant difference between the NDR group and the control group (P=0.192), the difference between the NPDR group and NDR group was statistically significant (P=0.012), the difference between the PDR group and NPDR group was statistically significant (P=0.000). With the progression of DR, the relative expression of SNHG16 in patient serum gradually increased (Figure 1c). There was significant difference between NDR group and control group (P=0.024), the difference between the NPDR group and NDR group was statistically significant (P=0.004), the difference between the PDR group and NPDR group was statistically significant (P=0.007).

Diagnostic Ability of Serum MIAT, HOTTIP and SNHG16 in DR

Diagnostic Value of Distinguishing the Healthy Control Group from the T2D Group

MIAT was distinguishable between the healthy control group and T2D group. The AUC of the ROC curve was 0.717, 95% CI was 0.639–0.795, P=0.000, cut-off point was 1.635, sensitivity was 0.689, and specificity was 0.643. HOTTIP was distinguishable between the healthy control group and the T2D group. The AUC of the ROC curve was 0.764, 95% CI was 0.690–0.838, P=0.000, cut-off point was 1.428, sensitivity was 0.622 and specificity was 0.843. SNHG16 was distinguishable between the healthy control group and the T2D group. The AUC of the ROC curve was 0.797, 95% CI was 0.730–0.865, P=0.000, cut-off point was 1.596, sensitivity was 0.611, and specificity was 0.886. The combined levels of MIAT, HOTTIP and SNHG16 were distinguishable between the healthy control group and T2D group. The

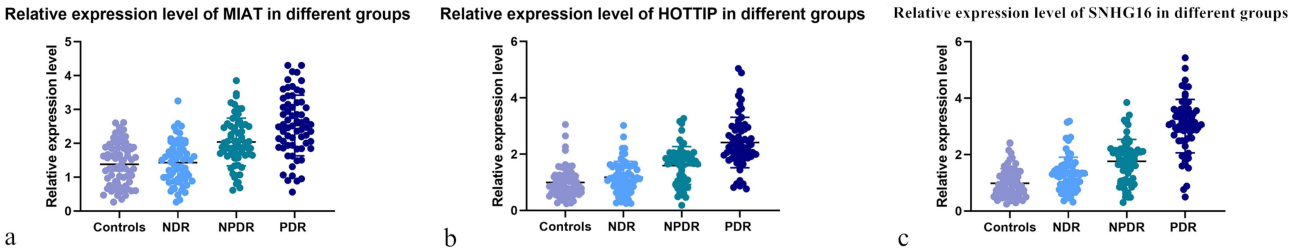

Figure 1 With the progress of DR, the expression of MIAT, HOTTIP and HEIH. (**a**) With the progression of DR, the relative expression of MIAT in patient serum gradually increased. (**b**) With the progression of DR, the relative expression of HOTTIP in patient serum gradually increased. (**c**) With the progression of DR, the relative expression of SNHG16 in patient serum gradually increased.

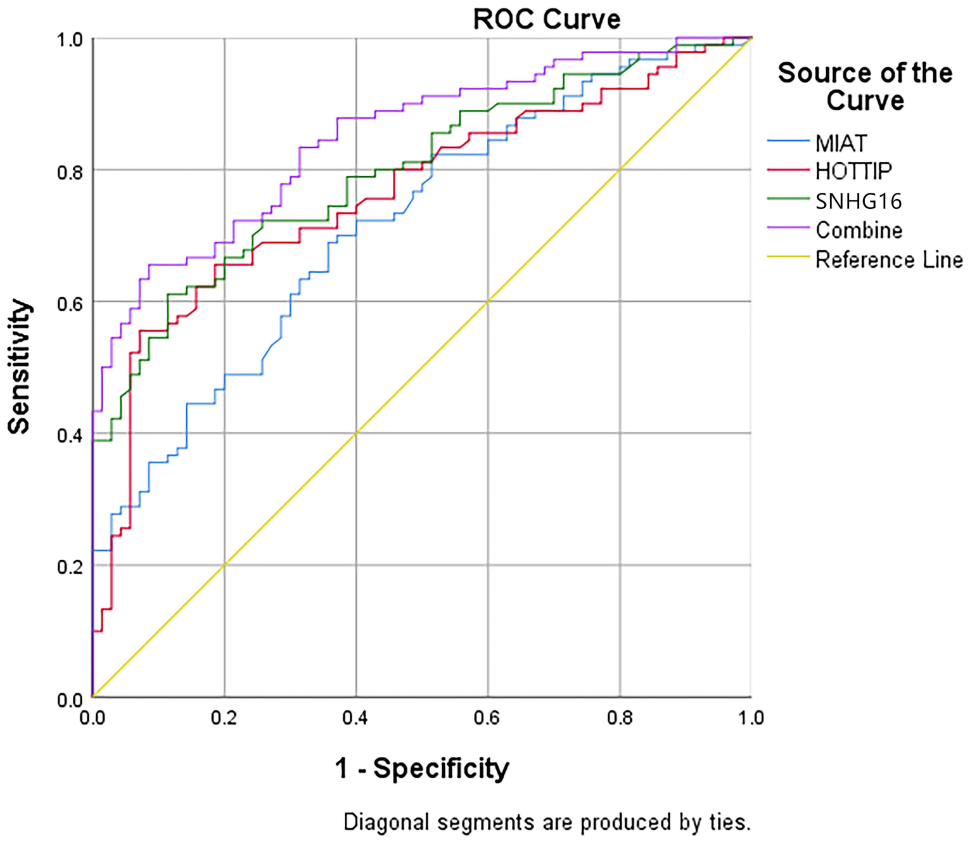

Figure 2 ROC curve for distinguishing healthy control group and T2D group. MIAT, HOTTIP, SNHG16 and their combinations can be used to distinguish the control group from T2D group.

AUC of the ROC curve was 0.849, 95% CI was 0.792–0.907, *P*=0.000, cut-off point was 0.680, sensitivity was 0.633, and specificity was 0.929, as shown in Figure 2.

Diagnostic Value of Distinguishing the Healthy Control Group from the NDR Group

MIAT was not distinguishable between the healthy control group and the NDR group. The AUC of the ROC curve was 0.570, the 95% CI was 0.452–0.687, *P*=0.272, the cut-off point was 1.046, the sensitivity was 0.833, and the specificity was 0.345. HOTTIP was not distinguishable between the healthy control group and the NDR group. The AUC of the ROC curve was 0.604, the 95% CI was 0.478–0.729, *P*=0.102, the cut-off point was 1.116, the sensitivity was 0.533, and the specificity was 0.686. SNHG16 was distinguishable between the healthy control group and the NDR group. The AUC of the ROC curve was 0.643, the 95% CI was 0.525–0.762, *P*=0.024, the cut-off point was 1.265, the sensitivity was 0.611, and the specificity was 0.886. The combined levels of MIAT, HOTTIP and SNHG16 were distinguishable between the healthy control group and NDR group. The AUC of the ROC curve was 0.680, 95% CI was 0.569–0.790, *P*=0.005, cut-off point was 0.261, sensitivity was 0.767 and specificity was 0.586, as shown in Figure 3.

Diagnostic Value of Distinguishing the NDR Group from the DR (NPDR, PDR) Group

MIAT was distinguishable between the NDR group and DR group. The AUC of the ROC curve was 0.752, the 95% CI was 0.648–0.856, *P*=0.000, the cut-off point was 1.846, the sensitivity was 0.700, and the specificity was 0.767. HOTTIP was distinguishable between the NDR group and DR group. The AUC of the ROC curve was 0.791, 95% CI was 0.696–0.886, *P*=0.000, cut-off point was 1.627, sensitivity was 0.717, and specificity was 0.967. SNHG16 was distinguishable between the NDR group and DR group. The AUC of the ROC curve was 0.803, the 95% CI was 0.713–0.894, *P*=0.000, the cut-off point was 1.379, the sensitivity was 0.717, and the specificity was 0.833. The

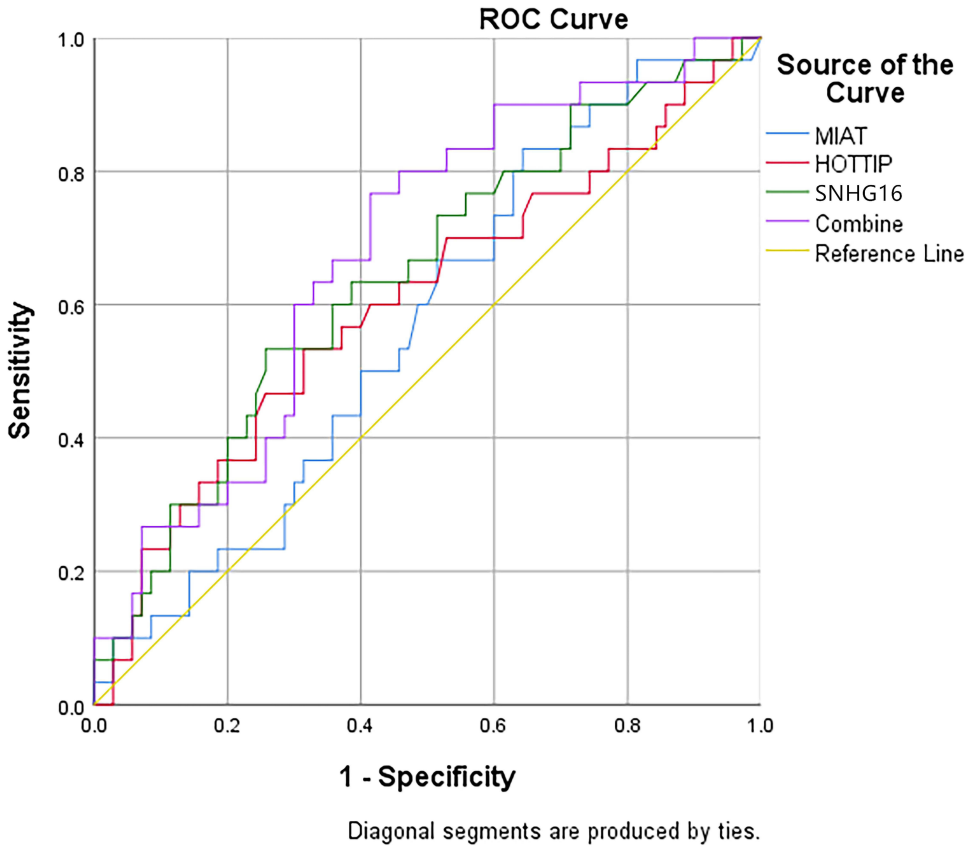

Figure 3 ROC curve for distinguishing healthy control group and NDR group. MIAT and HOTTIP are not used to distinguish the control group from NDR group, but SNHG16 and combined diagnosis can be used to distinguish the control group from NDR group.

combined levels of MIAT, HOTTIP and SNHG16 were distinguishable between the NDR group and DR group. The AUC of the ROC curve was 0.874, 95% CI was 0.800–0.949, *P*=0.000, cut-off point was 0.620, sensitivity was 0.800 and specificity was 0.867, as shown in Figure 4.

Diagnostic Value of Distinguishing the NPDR Group from the PDR Group

MIAT was distinguishable between the NPDR group and the PDR group. The AUC of the ROC curve was 0.668, the 95% CI was 0.530–0.807, *P*=0.025, the cut-off point was 2.101, the sensitivity was 0.667, and the specificity was 0.658. HOTTIP was distinguishable between the NPDR group and the PDR group. The AUC of the ROC curve was 0.693, the 95% CI was 0.560–0.826, *P*=0.010, the cut-off point was 1.859, the sensitivity was 0.700, and the specificity was 0.567. SNHG16 was distinguishable between the NPDR group and the PDR group. The AUC of the ROC curve was 0.804, the 95% CI was 0.689–0.919, *P*=0.000, the cut-off point was 2.485, the sensitivity was 0.800, and the specificity was 0.767. The combined levels of MIAT, HOTTIP and SNHG16 were distinguishable between the NPDR group and the PDR group. The AUC of the ROC curve was 0.840, 95% CI was 0.733–0.947, *P*=0.000, cut-off point was 0.486, sensitivity was 0.867 and specificity was 0.767, as shown in Figure 5.

Discussion

LncRNAs are located in the nucleus or cytoplasm. They are not involved in the coding of proteins, but they can affect the function of adjacent coding genes by regulating gene expression on chromosomes.[16] Study has shown that multiple lncRNAs in the DR model of the retina are abnormally expressed.[17] We expect to find lncRNA markers related to the progression of DR that can be easily detected in blood, saliva or urine and provide a reference for the diagnosis and treatment of DR.

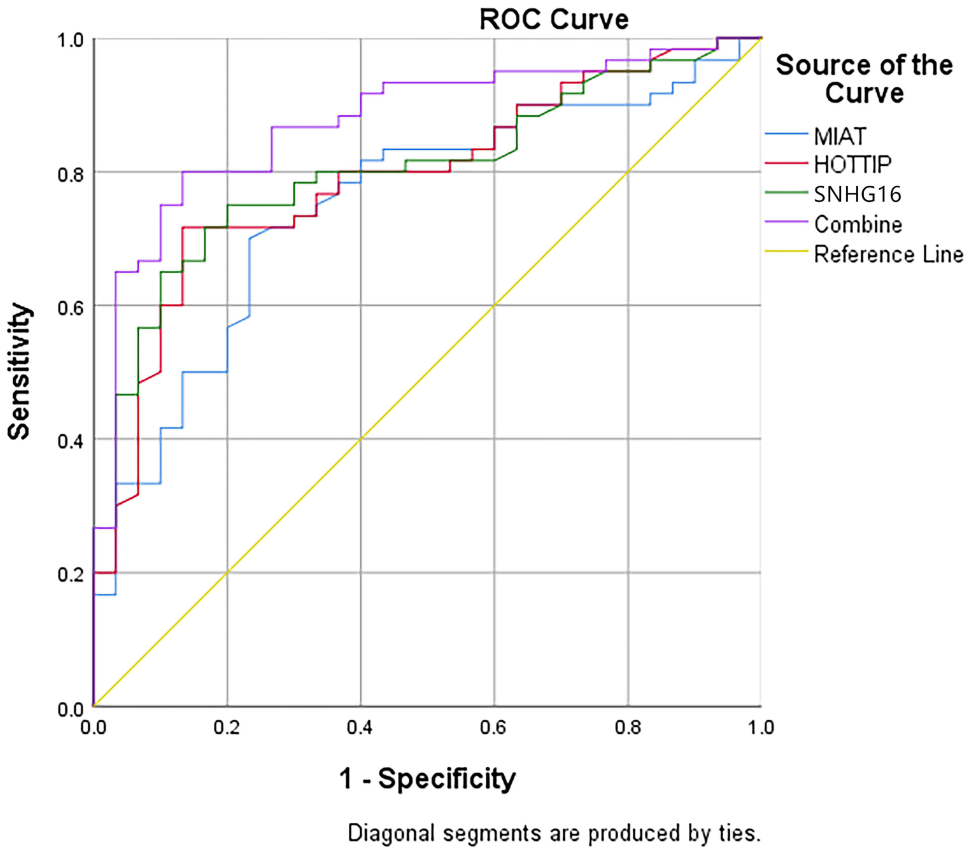

Figure 4 ROC curve for distinguishing NDR group and DR (NPDR+PDR) group. MIAT, HOTTIP, SNHG16 and their combinations can be used to distinguish the NDR group from DR (NPDR+PDR) group.

Our study observed the expression of MIAT, HOTTIP and SNHG16 in the serum of patients with different degrees of DR. The results showed that the relative expression levels of MIAT and HOTTIP increased with the progression of DR, but only after T2D patients developed DR (NPDR and PDR) were the expression levels in the next stage statistically significant compared with those in the previous stage. In SNHG16, not only was the expression level in the next stage after the appearance of DR statistically significant compared with the previous stage, but the NDR group was also statistically significant compared with the healthy control group. In addition, compared with the healthy control group, the relative expression levels of MIAT, HOTTIP and SNHG16 in T2D patients were significantly increased, and the difference was statistically significant. Combined with the above results, it can be seen that the expression of these lncRNAs in the serum of diabetic patients was higher than that of healthy people, the expression gradually increased with the progression of DR, and these lncRNAs were directly proportional to the severity of DR. These markers can be stably detected in human serum, which can be used as potential reference materials for detecting the progress of DR.[18]

Our findings was different from the findings of Biswas S et al[19] who thought that there was no significant difference in serum MIAT expression between the healthy control group and PDR patients. We analyze that this may be due to differences in sample size and the conditions set when selecting participants.

MIAT is a regulator of microvascular function, and its upregulation significantly aggravates retinal microvascular dysfunction and induces an increase in the expression of vascular endothelial growth factor (VEGF).[20] MIAT can reduce cell viability by activating the transforming growth factor-β1 signalling pathway,[21] and activation of the transforming growth factor-β1 signalling pathway can promote the development of diabetic retinopathy.[22,23] The expression of MIAT is positively correlated with proinflammatory cytokines (IL-1β and IL-6), and the increased expression of MIAT aggravates the inflammatory response in the retina.[24] MIAT knockdown inhibits luminal formation, migration, and

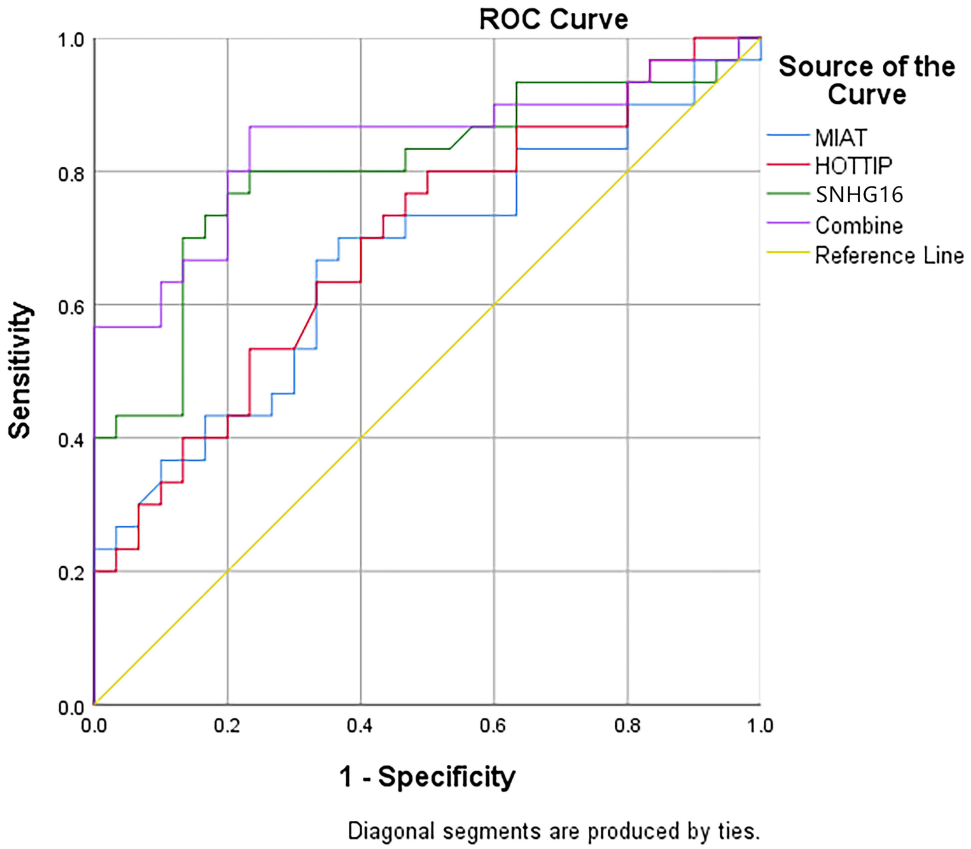

Figure 5 ROC curve for distinguishing NPDR group and PDR group. MIAT, HOTTIP, SNHG16 and their combinations can be used to distinguish the NPDR group from PDR group.

proliferation of retinal endothelial cells, improves diabetic retinal microvascular dysfunction in vivo, and reduces apoptosis by regulating serine/threonine kinase 1 phosphorylation.[25] HOTTIP can promote the apoptosis of retinal endothelial cells through the P38/MAPK signalling pathway and can also upregulate the levels of inflammatory factors (intercellular adhesion molecule-1 and VEGF) in the retina, thus promoting the progression of DR. Inhibition of the expression of HOTTIP can reduce the visual function decline and retinal cell apoptosis caused by a high glucose environment.[12] Under high glucose conditions, the expression of SNHG16 increases, which promotes dysfunction of retinal microvascular endothelial cells and accelerates the progression of diabetic retinopathy by activating the NF kB and PI3K/AKT pathways.[26] Inhibition of SNHG16 expression can reduce pathological angiogenesis in high glucose environment.[27] In summary, the increased expression of MIAT, HOTTIP and SNHG16 is closely related to the progression of DR.

We assessed the diagnostic value of serum LncRNA for DR severity using the ROC curve. Serum MIAT, HOTTIP, SNHG16 and combined diagnosis can be used to distinguish the healthy control group from the T2D group, and the AUC increases when combined diagnosis is used. Serum SNHG16 and combined diagnosis can be used to distinguish the healthy control group from the NDR group, and the AUC increases with combined diagnosis. Serum MIAT, HOTTIP, SNHG16 and combined diagnosis can be used to distinguish the NDR group from the DR group, and the AUC increases with combined diagnosis. Serum MIAT, HOTTIP, SNHG16 and combined diagnosis can be used to distinguish the NPDR group from the PDR group, and the AUC increases with combined diagnosis. These results indicated that these lncRNAs had certain reference significance for the diagnosis of DR. The diagnostic abilities of SNHG16 and combined diagnosis for all levels of DR were stronger than those of MIAT and HOTTIP.

Conclusion

In summary, the relative expression of MIAT, HOTTIP and SNHG16 in the serum of diabetic patients gradually increased with the aggravation of DR, which proved that these lncRNAs were closely related to the progression of DR, and at the same time, these lncRNAs could be used as potential screening and staging evaluation markers of DR. However, there are relatively few samples in the current research cohort, and further restricting the blood parameters of participants can make the analysis results between LncRNAs and DR more accurate.

Data Sharing Statement

Relevant clinical data of subjects can be obtained by contacting the correspondent author.

Disclosure

The authors report no conflicts of interest in this work.

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