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META ANALYSIS

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Dysregulated expression of long noncoding RNAs serves as diagnostic biomarkers of type 2 diabetes mellitus

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Abstract

Purpose Long noncoding RNAs (LncRNAs) are widely investigated in various diseases as a novel type of biomarkers. We aimed to elucidate the diagnostic values of lncRNAs in patients with type 2 diabetes mellitus (T2DM).

Methods We comprehensively searched PubMed, Web of Science, EMBASE, CBM, Scopus, and the Cochrane Library databases from the inception to 3 January 2019. Studies concerning the association between lncRNAs expression and diagnostic outcomes in type 2 diabetes mellitus patients were included. We employed pooled odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate diagnostic parameters.

Results Seven relevant studies were eligible in our study. The pooled results showed that lncRNAs performed the area under the curve (AUC) of 0.73 (95%Cl: 0.69–0.77), with sensitivity of 0.71 (95%Cl: 0.64–0.77) and specificity of 0.66 (95%Cl: 0.60–0.71) in discriminating type 2 diabetes from healthy controls. As for prediabetes, lncRNAs conducted AUC of 0.75 with 76% sensitivity and 64% specificity. Moreover, subgroup analysis based on expression levels of lncRNAs, sample sizes, and specimen of eligible studies were further performed.

Conclusions This study indicates that lncRNAs may serve as promising indicators for diagnostic evaluation of T2DM patients.

Keywords Long noncoding RNA · Type 2 diabetes mellitus · Diagnosis · Meta-analysis.

Introduction

Diabetes mellitus comprises of a series of metabolic disorders featured by abnormally high glucose level in blood. Among all the diabetes cases, around 90% is type 2 diabetes mellitus (T2DM) [1]. T2DM develops because of insulin resistance of human organs and insufficient secretion of insulin from pancreatic β-cells [2]. Patients with T2DM may proceed with severe long-term complications including heart, kidney, retinopathy, and foot problems that increase the risk of mortality [3]. The pathogenesis of diabetes has been widely investigated and multifactors including smoking, diet, genetic, and environmental factors may contribute to it [4]. Although great progression has been made in the diagnosis and treatment of T2DM, the outcome of this chronic disease is still unsatisfied. Therefore, novel biomarkers were warranted for early detection of this disease.

Long noncoding RNAs (LncRNAs), composed of over 200 nucleotides but without the ability of protein coding, are a novel type of functional noncoding RNAs [5, 6]. LncRNAs are known to be of great importance in diverse biological activities of cell differentiation, proliferation, metabolism, genomic regulation, and immune function [7, 8]. Nowadays, the close association between lncRNAs and progression of numerous diseases has been widely researched [9–11]. Whereas, the abnormal expression and function of lncRNAs in regulation of glucose homeostasis and T2DM remain largely unknown [12–14]. Therefore, we undertook a meta-analysis to gain a comprehensive understanding of the diagnostic values of lncRNAs in T2DM patients.

Supplementary information The online version of this article (https://doi.org/10.1007/s12020-019-02015-7) contains supplementary material, which is available to authorized users.

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Materials and methods

Data search strategy

A systematic literature search was conducted in online databases of PubMed, Web of Science, EMBASE, CBM, Scopus, and the Cochrane Library databases from the inception to 3 January 2019. We developed the search strategy in terms of the following terms: ("lncRNA" or "long noncoding RNA") and ("diabetes" or "diabetes mellitus" or "Type 2 diabetes mellitus" or "T2DM"). To avoid omitting any eligible studies, we also searched the references of all the related articles. We contacted the authors of certain studies if the articles and data were not available. The inclusion criteria in this study were as follows: (a) case–control study or cohort study; (b) patients with definite diagnosis of T2DM; (c) evaluating the relationship between lncRNAs expression and risk of T2DM; (d) the total number of sample, area under the curve (AUC), sensitivity, and specificity were available and/or data on dysregulated lncRNAs were available. Whereas, studies (a) not relevant to lncRNAs or T2DM; or (b) the subject was not human; or (c) the article was not a comparative study; or (d) had multiple duplicate data; or (e) were reviews, animal experiments, and case reports were excluded from this study. To avoid bias and ensure the reliability of test results, we didn't include a minimum specificity- and/or sensitivity acceptance-value in our meta-analysis.

Data extraction and quality assessment

Two investigators (Weiyue Zhang and Juan Zheng) evaluated the eligibility of all the included studies and they extracted the relevant data independently. A third investigator (Lulu Chen) was consulted to resolve disagreements. For each eligible study, the following information was extracted independently: (1) author, publication year, lncRNA type, disease, case load, specimen source, and method for detection; (2) upregulated or downregulated expression role of lncRNAs; (3) in diagnostic analysis, we also collected the sensitivity, specificity, AUC, and so on. The quality of our work was evaluated and recommended as high quality (scores ≥ 7) according to the Newcastle-Ottawa Scale (Supplementary Table S1). The approach of our work was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Statistical analysis

Stata version 14.0 was utilized to conduct the statistical analysis. Pooled odds ratios with 95% confidence intervals were calculated to characterize diagnostic parameters including sensitivity, specificity, AUC, and so on. According to the statistical principle, only homogeneous data can be used for the statistics of multiple studies. If the differences between these studies are too great, quantitative results cannot be combined. Therefore, it is of great importance to perform the heterogeneity test in the meta-analysis. The heterogeneity between studies was evaluated by the I^2 statistic. The I^2 statistic describes the percentage of the inter-research variations in total variation (including intra-research variations and residual sampling error). No significant heterogeneity across the eligible studies was suggested if I^2 statistic was <50% [15]. Pooled analysis was performed using the fixed effect model, but when the heterogeneity was significant, random effects model was employed. Subgroup analyses were undertaken to explore possible sources of heterogeneity. Publication bias was evaluated mainly using the Deeks' funnel plot and was suggested to be significant if the two-tailed P-value was <0.05.

Results

Literature search and study selection

The flow diagram (Fig. 1) exhibited the study selection procedure. Our online database searches yielded 267 potential articles, amongst which 195 were excluded through abstract evaluation. Therefore, the full text of the rest 72 articles was evaluated. During the evaluation, another 65 studies were excluded for the following reasons: 27 were excluded for having no relation to lncRNAs or T2DM, 21 studies were reviews or animal experiments, 11 were of no diagnostic outcomes reported, and 6 were of lacking data for analysis. In total, seven eligible studies were ultimately included in our meta-analysis [16–22].

Characteristics of studies

Table 1 summarized the included studies. LncRNAs were all extracted from blood specimens in these studies. In addition, quantitative real time polymerase chain reaction (qRT-PCR) was utilized to measure the expression of lncRNAs. As indicated by Table 1, three kinds of lncRNAs were upregulated and eight were downregulated. Eleven types of lncRNAs were evaluated as biomarkers for T2DM, while three for prediabetes. The sensitivity, specificity, and AUC were also collected for diagnosis analyses. Besides, the quality scores of all included researches were evaluated according to NOS. The scores ranged from 7 to 8, suggesting the researches were with high quality (Supplementary Table 1). Furthermore, we collected the population distribution information of included studies (Supplementary Table 2).

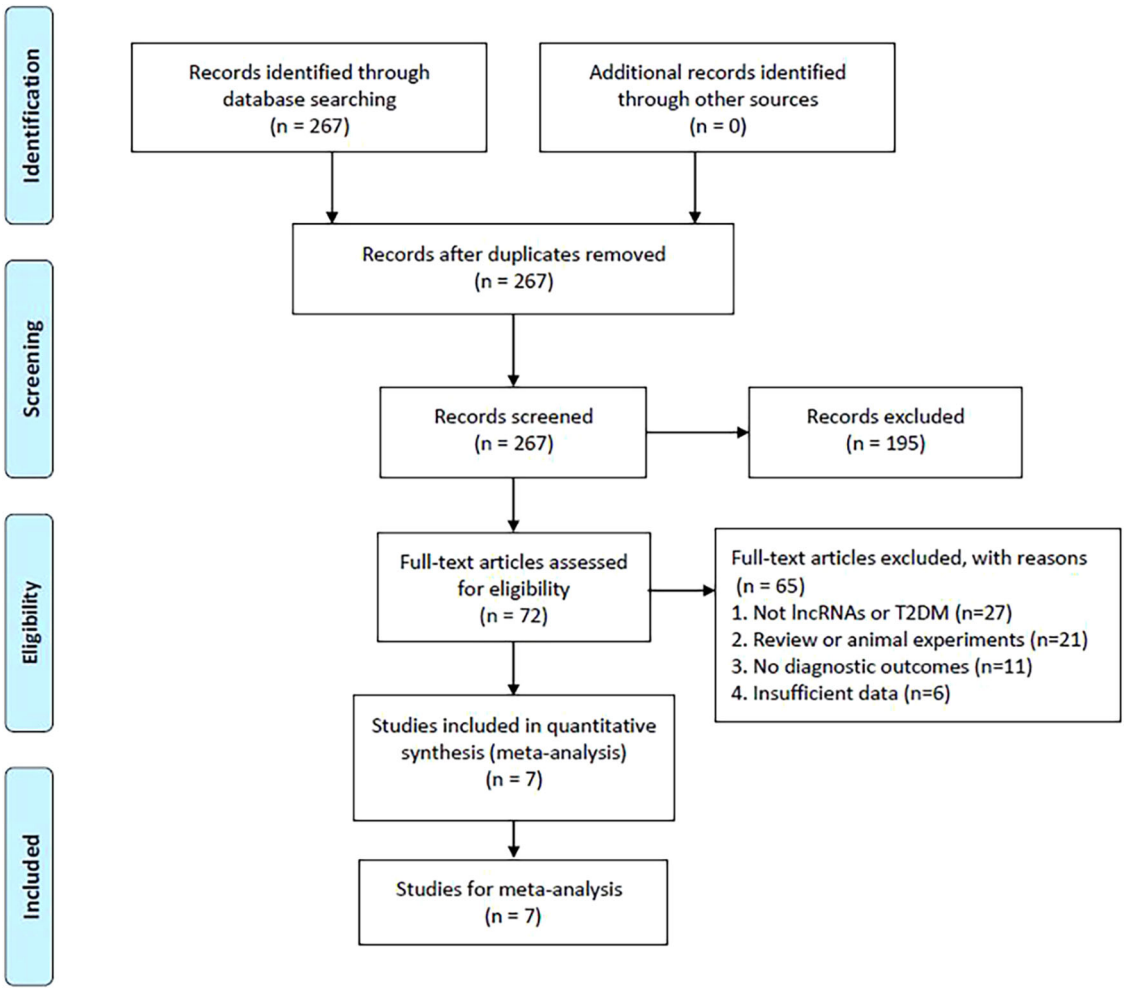

Fig. 1 Flowchart of the study selection process

Meta-analysis for diagnostic values of lncRNAs in T2DM

These seven articles including eleven types of lncRNAs in T2DM were in the present study. We undertook meta-analysis of sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR), overall diagnostic odds ratio (DOR), and summary receiver operator characteristics (SROC) for lncRNAs. A random effect model was utilized for meta-analysis with significant heterogeneity ($I^2 > 50\%$). Forest plots of sensitivity and specificity of lncRNAs for diagnosing T2DM were displayed (Fig. 2a, b). Furthermore, the values of summary estimates were listed below: sensitivity 0.71 (95%CI 0.64–0.77); specificity 0.66 (95%CI 0.60–0.71); PLR 2.10 (95%CI 1.80–2.40); NLR 0.44 (95%CI 0.36–0.54); and DOR 5.0 (95%CI 3.0–6.0). Moreover, an SROC curve (Fig. 2c) was performed with the AUC of 0.73 (95%CI 0.69–0.77). To sum up, lncRNAs were indicated to have a relatively high diagnostic efficacy for T2DM.

Meta-analysis for diagnostic values of lncRNAs in prediabetes

In this study, three articles with three types of lncRNAs in prediabetes patients were incorporated. Forest plots were performed to evaluate the sensitivity and specificity of lncRNAs for diagnosing prediabetes (Fig. 3a, b). Since the heterogeneity ($I^2 < 50\%$) was not significant, we performed a fixed effect model. The summary estimates for lncRNAs in prediabetes were as below: sensitivity 0.76 (95%CI 0.62–0.86); specificity 0.64 (95%CI 0.51–0.75); PLR 2.10 (95%CI 1.50–2.80); NLR 0.38 (95%CI 0.24–0.59); and DOR 6.0 (95%CI 3.0–10.0). We further calculated the AUC 0.75 (95%CI 0.71–0.78) with a SROC curve (Fig. 3c). Therefore, lncRNAs also showed a relatively high diagnostic accuracy for prediabetes.

Table 1 Main characteristics of included studies

Study	Year	LncRNA	Disease type	Sample size		Specimen	Method	Regulation	Diagnostic power		
				Case	Control				Sen	Spe	AUC
Omidvar et al.	2018	lncRNA VIM-AS1	T2DM	100	100	PBMCs	qRT-PCR	Downregulated	0.561	0.684	0.630
Omidvar et al.	2018	lncRNA CTBP1-AS2	T2DM	100	100	PBMCs	qRT-PCR	Downregulated	0.587	0.753	0.680
Saeidi et al.	2018	lncRNA LY86-AS1	T2DM	100	98	PBMCs	qRT-PCR	Downregulated	0.646	0.798	0.747
Saeidi et al.	2018	lncRNA HCG27_201	T2DM	100	98	PBMCs	qRT-PCR	Downregulated	0.556	0.750	0.645
Mansoori et al.	2018	lncRNA LINC00523	T2DM	100	98	PBMCs	qRT-PCR	Downregulated	0.814	0.611	0.743
Mansoori et al.	2018	lncRNA LINC00994	T2DM	100	98	PBMCs	qRT-PCR	Downregulated	0.813	0.535	0.666
Wang et al.	2018	lncRNA CASC2	T2DM	296	56	Blood	qRT-PCR	Downregulated	0.662	0.482	0.632
Yin et al.	2017	lncRNA GAS5	T2DM	10	30	Blood	qRT-PCR	Downregulated	0.700	0.600	0.741
Carter et al.	2015	lncRNA GAS5	T2DM	47	49	Blood	qRT-PCR	Downregulated	0.851	0.673	0.810
Li et al.	2017	lncRNA ENST00000550337.1	T2DM	64	60	Blood	qRT-PCR	Upregulated	0.750	0.650	0.732
Li et al.	2017	lncRNA ENST 00000550337.1	Prediabetes	63	60	Blood	qRT-PCR	Upregulated	0.750	0.650	0.712
Li et al.	2017	lncRNA TCONS_ 00007244	T2DM	20	20	Blood	qRT-PCR	Upregulated	0.750	0.650	0.712
Li et al.	2017	lncRNA TCONS_ 00007244	Prediabetes	20	20	Blood	qRT-PCR	Upregulated	0.650	0.750	0.692
Li et al.	2017	lncRNA TCONS_ 00000886	T2DM	20	20	Blood	qRT-PCR	Upregulated	0.850	0.600	0.700
Li et al.	2017	lncRNA TCONS_ 00000886	Prediabetes	20	20	Blood	qRT-PCR	Upregulated	0.900	0.500	0.687

T2DM type 2 diabetes mellitus, *PBMCs* peripheral blood mononuclear cells, *qRT-PCR* quantitative real time polymerase chain reaction, *Sen* sensitivity, *Spe* specificity, *AUC* area under the ROC curve

Subgroup analysis based on expression level of lncRNAs

To detect the source of heterogeneity for diagnostic values of lncRNAs in T2DM, we performed subgroup analysis according to abnormal expression of lncRNAs. In our study, eight types of lncRNAs were recognized as downregulated and three were upregulated. As for downregulated lncRNAs, forest plots were conducted to assess the sensitivity and specificity of lncRNAs for diagnosing T2DM (Fig. 4a, b). We employed a random effect model since the heterogeneity ($I^2 > 50\%$) was significant. The results were sensitivity 0.69 (95%CI 0.61–0.76), specificity 0.66 (95% CI 0.60–0.72), and AUC 0.73 (95%CI 0.69–0.76) with a SROC curve (Fig. 4c). Whereas, no significant heterogeneity ($I^2 < 50\%$) was detected as for upregulated lncRNAs. Upregulated lncRNAs showed a relatively high diagnostic efficacy for T2DM with sensitivity 0.77 (95%CI 0.68–0.84), specificity 0.64 (95%CI 0.54–0.73), and AUC 0.77 (95%CI 0.73–0.80) (Fig. 4e–g).

Subgroup analysis based on sample sizes

Further subgroup analysis based on sample sizes was performed to investigate possible sources of heterogeneity. All the studies enrolled in our work were divided into two groups by T2DM case number (<100 or ≥100 cases). As for studies with sample size <100, forest plots were conducted for assessing the sensitivity and specificity of lncRNAs for diagnosing T2DM (Fig. 5a, b). The fixed effect model was utilized since there was no significant between-study heterogeneity ($I^2 < 50\%$). The results were sensitivity 0.79 (95%CI 0.79–0.79), specificity 0.64 (95%CI 0.64–0.64), and AUC 0.78 (95%CI 0.75–0.82) with a SROC curve (Fig. 5c). Whereas, the summary outcomes for sample size ≥100 were sensitivity 0.67 (95%CI 0.59–0.74), specificity 0.67 (95%CI 0.59–0.74), and AUC 0.72 (95%CI 0.68–0.76) (Fig. 5e–g). In this case, we performed the random effect model because of the significant heterogeneity ($I^2 > 50\%$).

Subgroup analysis based on specimen

Further subgroup analysis based on specimen was performed to investigate possible sources of heterogeneity. All the studies enrolled in our work were divided into two groups by PBMCs and blood specimen in T2DM case. As for studies with PBMCs, forest plots were conducted for assessing the sensitivity and specificity of lncRNAs for diagnosing T2DM (Fig. 6a, b). The random effect model was utilized since there was significant between-study

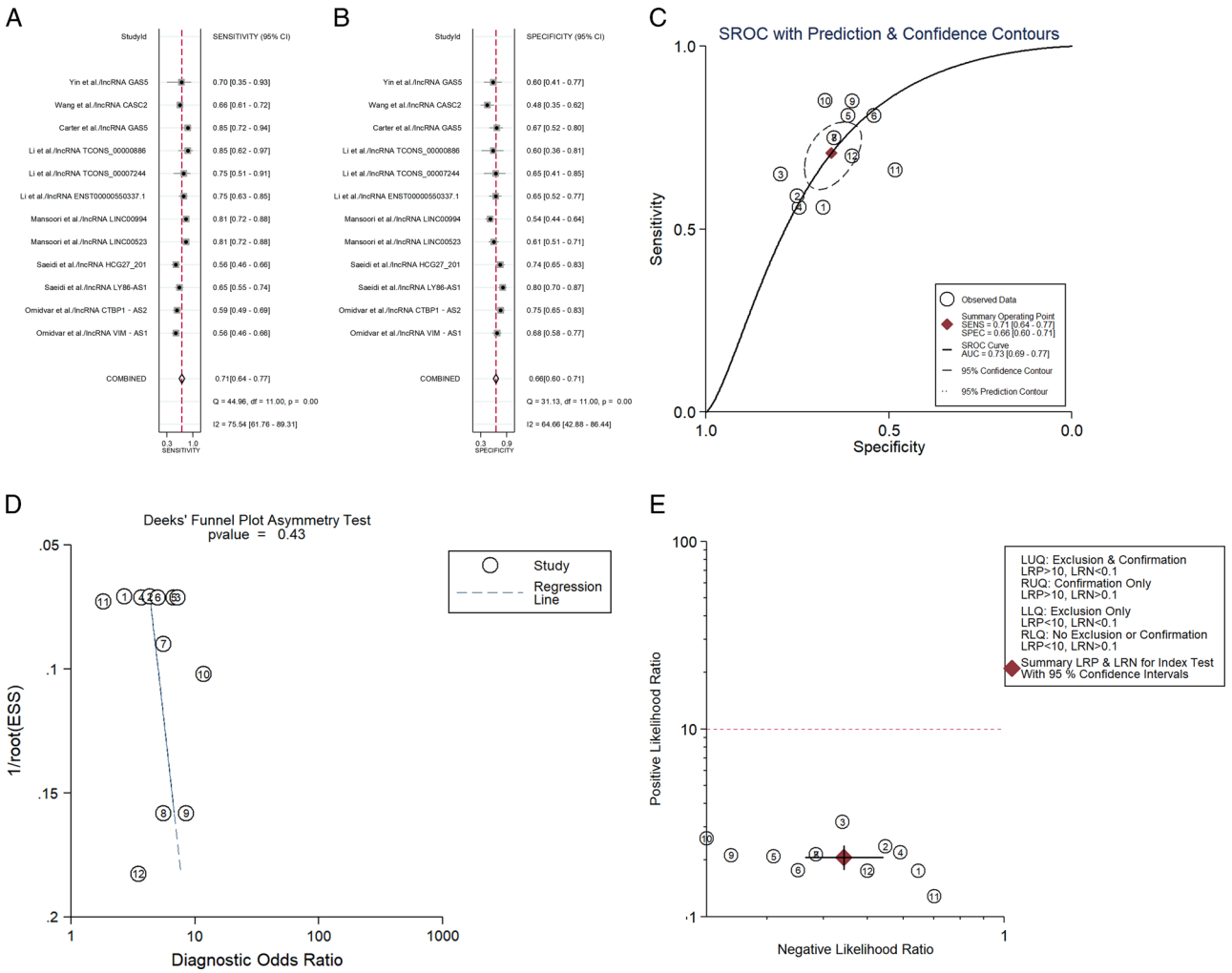

Fig. 2 **a**, **b** Forest plots for sensitivity and specificity of lncRNAs for diagnosing T2DM; **c** The summary receiver operator characteristic (SROC) curve; **d** Deeks' funnel plot asymmetry tests; **e** Two-dimensional graph of positive/negative likelihood ratio

heterogeneity ($I^2 > 50\%$). The results were sensitivity 0.67 (95%CI 0.57–0.76), specificity 0.69 (95%CI 0.62–0.76), and AUC 0.74 (95%CI 0.70–0.77) with a SROC curve (Fig. 6c). Furthermore, the summary outcomes for blood specimen were sensitivity 0.75 (95%CI 0.67–0.82), specificity 0.61 (95%CI 0.53–0.68), and AUC 0.73 (95%CI 0.69–0.77) (Fig. 6e–g) with random effect model.

Publication bias and sensitivity analysis

In the present meta-analysis, the funnel plot indicated that no evidence of publication bias existed (Supplementary Fig. 1). We also quantitatively performed Deeks' funnel plot asymmetry tests [23] to assess the publication bias of the studies incorporated in our meta-analysis. The results of the tests failed to identify any evidence of publication bias in our analyses (Figs. 2d, 3d, 4d, 4h, 5d, 5h, 6d, and 6h), thus excluding the possibility of publication bias. Moreover, two-dimensional graph of positive/negative likelihood ratio were shown in Fig. 2e. Furthermore, the sensitivity analysis, performed by omitting one study at a time, did not recognize any outlier (Supplementary Fig. 2).

Discussion

The burden of T2DM has been aggravated by diagnosis after the occurrence of preventable complications of the disease [24], which can be lowered by taking early preventive measures in people with high risk. However, current risk models perform suboptimally in predicting individual diabetes risk [25], leading to the need of new biomarkers to improve the current golden standard to enable earlier detection of T2DM.

The critical roles of lncRNAs expression in human diseases were recently widely recognized, while in the case of

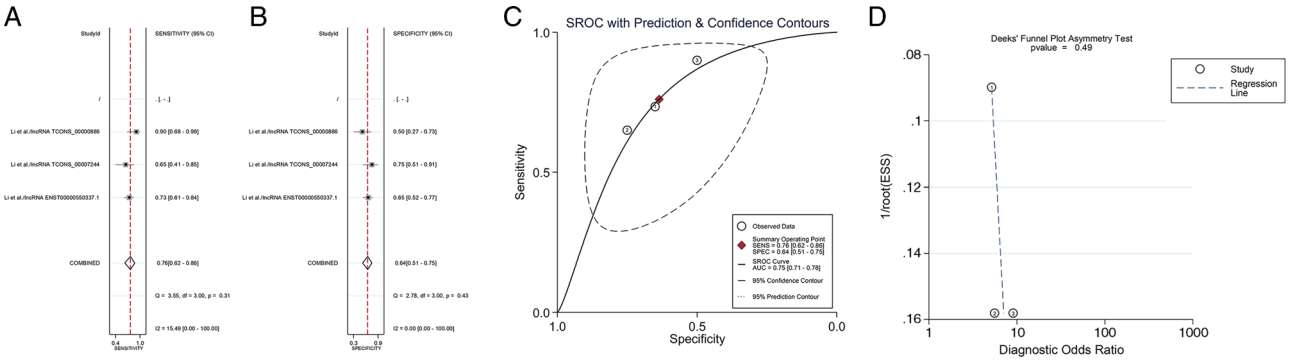

Fig. 3 **a**, **b** Forest plots for sensitivity and specificity of lncRNAs for diagnosing prediabetes; **c** The summary receiver operator characteristic (SROC) curve; **d** Deeks' funnel plot asymmetry tests

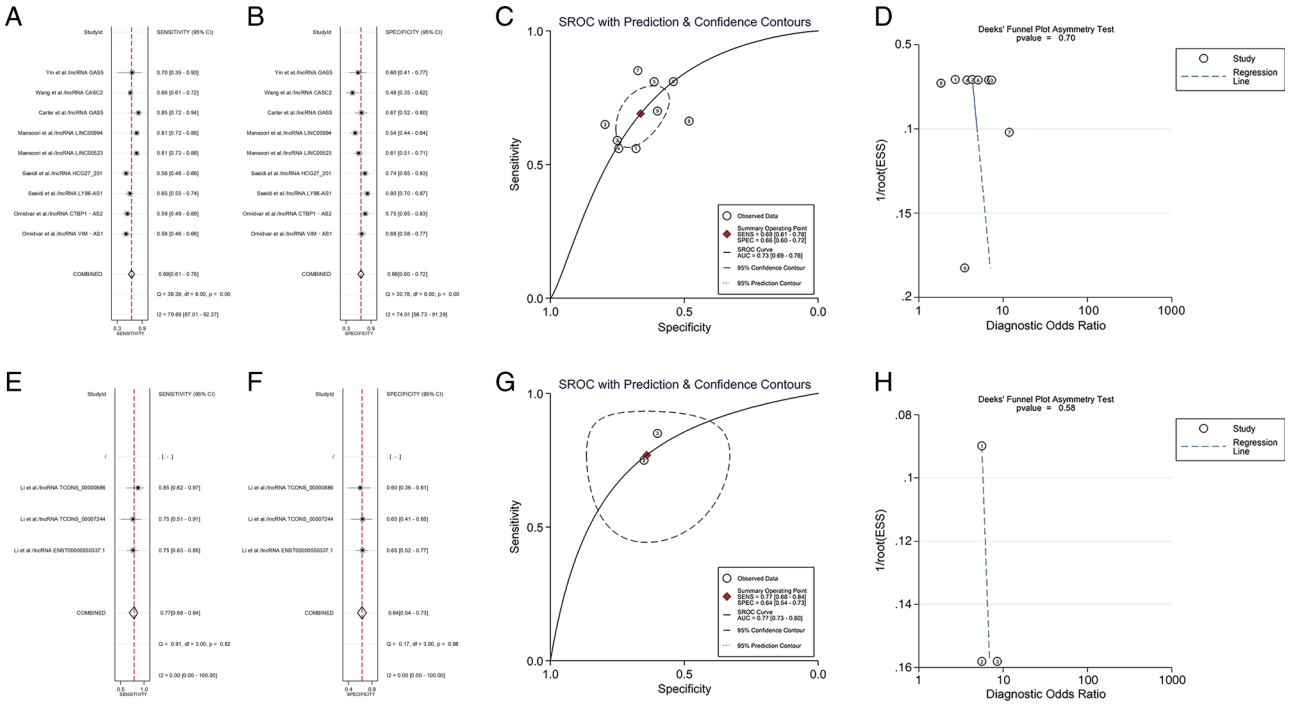

Fig. 4 **a**, **b** Forest plots for sensitivity and specificity of downregulated lncRNAs for diagnosing T2DM; **c** The summary receiver operator characteristic (SROC) curve; **d** Deeks' funnel plot asymmetry tests; **e**, **f** Forest plots for sensitivity and specificity of upregulated lncRNAs for diagnosing T2DM; **g** The summary receiver operator characteristic (SROC) curve; **h** Deeks' funnel plot asymmetry tests

T2DM, we failed to identify any related meta-analysis about the role of lncRNAs expression. Our present work, however, revealed a significant association between abnormal lncRNAs expression and its diagnostic values in T2DM patients. Seven relevant studies in all were finally incorporated in our study. As for diagnostic features, lncRNAs showed a relatively high diagnostic accuracy for T2DM or prediabetes. Further subgroup analysis based on expression level of lncRNAs or sample sizes were conducted, the pooled outcomes remained consistent for the diagnostic values of lncRNAs in T2DM.

The pancreatic islet enjoys a central part in the pathophysiology of diabetes [26, 27]. Ding et al. firstly demonstrated that lncRNA H19 may participate in transgenerational transmission of gestational diabetes mellitus which gives rise to impaired islet function [28]. Researchers further identified tissue-specific and dynamically regulated abnormally expressed lncRNAs in pancreatic beta-cells of T2DM [29].

Among all the human organs, liver is critical in maintaining glucose or lipid homeostasis of the whole body by utilizing and producing glucose. As for high-fat diet-fed

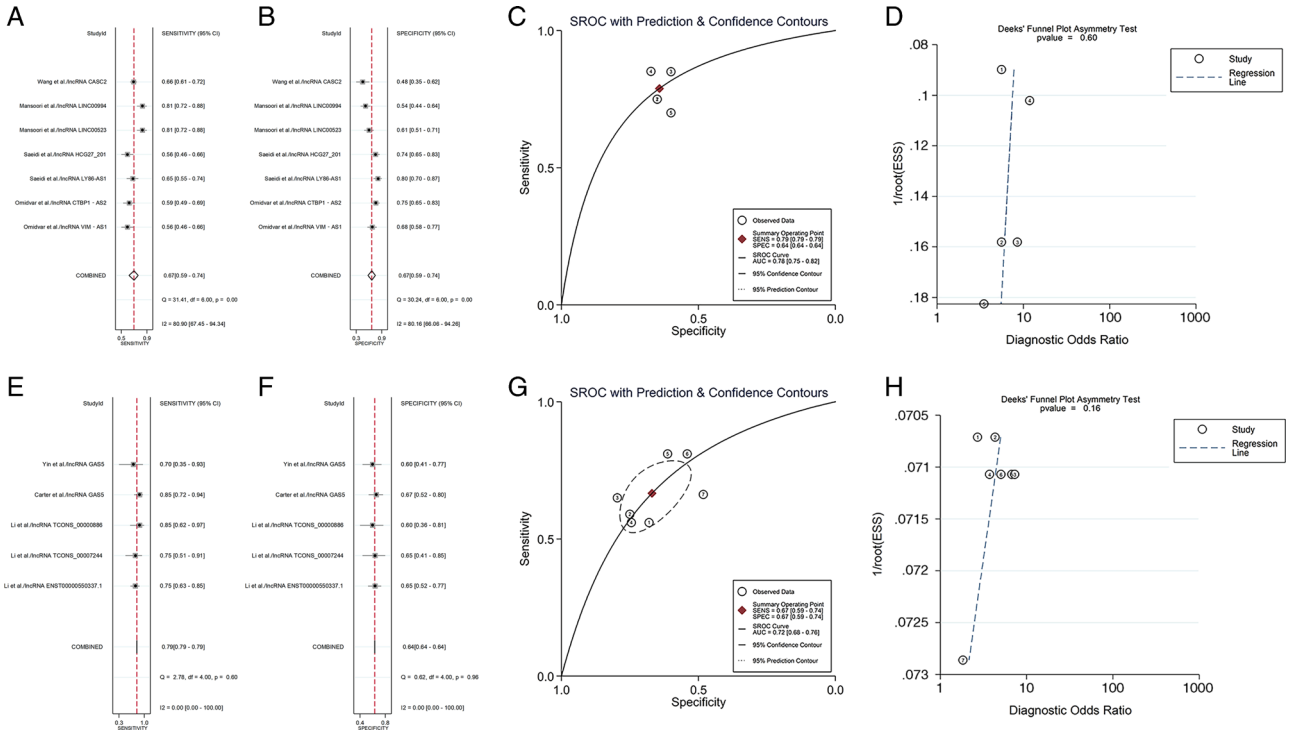

Fig. 5 **a**, **b** Forest plots for sensitivity and specificity of sample size <100; **c** The summary receiver operator characteristic (SROC) curve; **d** Deeks' funnel plot asymmetry tests; **e, f** Forest plots for sensitivity and specificity of sample size ≥100; **g** The summary receiver operator characteristic (SROC) curve; **h** Deeks' funnel plot asymmetry tests

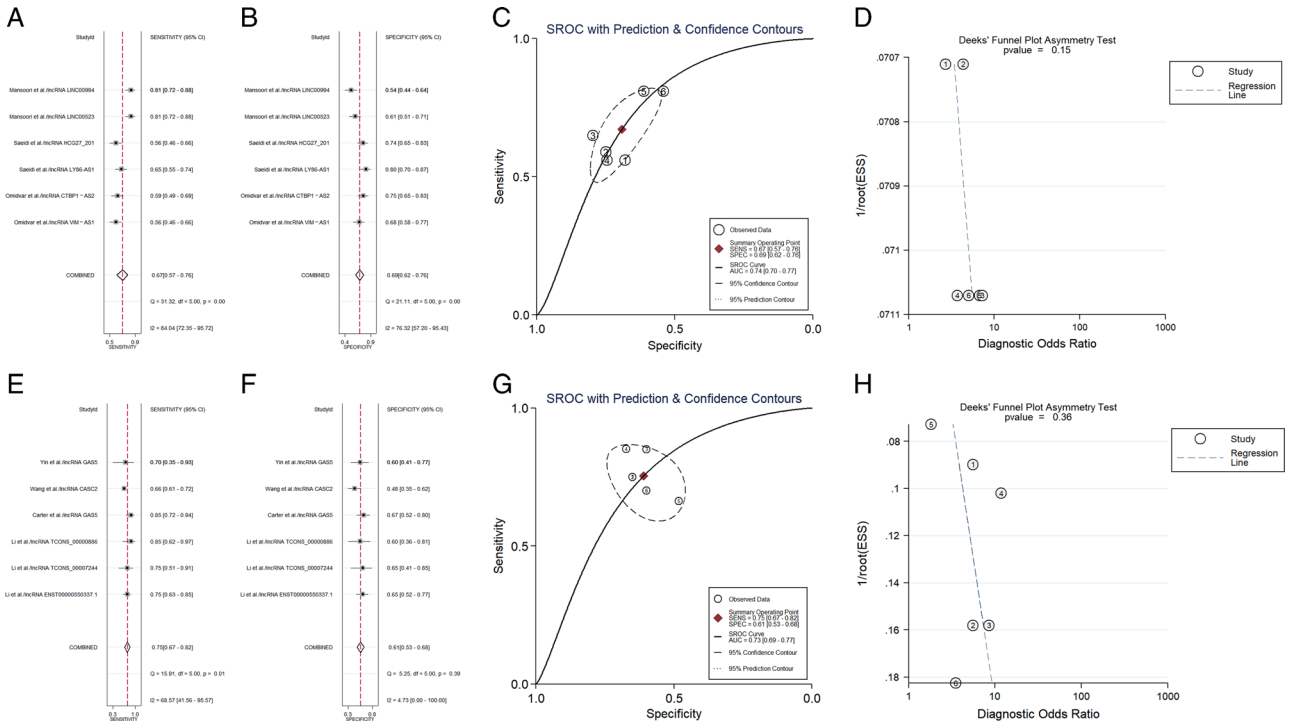

Fig. 6 **a**, **b** Forest plots for sensitivity and specificity of PBMCs specimen; **c** The summary receiver operator characteristic (SROC) curve; **d** Deeks' funnel plot asymmetry tests; **e**, **f** Forest plots for sensitivity and specificity of blood specimen; **g** The summary receiver operator characteristic (SROC) curve; **h** Deeks' funnel plot asymmetry tests

mice and ob/ob mice model, increased lncRNA MEG3 in hepatocytes may result in elevated hepatic gluconeogenesis with hepatic insulin resistance [30].

LncRNAs play a remarkable role not only in major metabolic tissues like pancreatic islet and liver during the pathogenesis of diabetes, but also in diabetic complications. Upregulated expression of lncRNA PVT1 during diabetic nephropathy may result in increased fibrosis because of extracellular matrix proteins accumulation in renal cells [31]. Altered expression of lncRNAs MALAT1 [32] and MEG3 [33] are shown to be related with diabetic retinopathy. These researches indicated the immense potential of lncRNAs as biomarkers for the pathogenesis and development of diabetes. Moreover, lncRNAs are suggested to be a perfect candidate for therapeutic intervention because researches have exhibited the beneficial role of normalizing lncRNA levels in diverse diseased status.

Our study has demonstrated the suitability of lncRNAs as a type of diagnostic biomarker for T2DM. Whereas, further meta-regression or subgroup analysis based on age, gender, and lncRNA types were warranted to be performed. Since the cell or tissue samples from patients with dysregulated expressions of lncRNAs can be easily accessed, the measurement can be done economically and conveniently. Besides, the chemical structure of lncRNAs could maintain its stability under various conditions. In brief, lncRNAs were promising biomarkers in early diagnosis of T2DM with notable advantages.

The sensitivity analysis utilized to explore potential sources of heterogeneity identified no outliers. During our subgroup analyses, we found that differences in lncRNAs expression, sample size, and specimen may account for the significant heterogeneity. Furthermore, the Deeks' funnel plot asymmetry test failed to find any publication bias in studies for diagnostic analysis. In spite of the reliability of our work, more relevant researches are warranted to corroborate our findings.

However, our current meta-analysis still had some limitations. Firstly, subgroup analysis by lncRNA types were not performed because of the limited number of studies. Secondly, functional studies are required to clarify the underlying mechanisms of lncRNAs regulating the pathogenesis of diabetes. Thirdly, the relatively small number of subjects might lead to insufficient statistical power. Fourthly, lncRNAs were extracted from different biological specimen with PBMCs or blood. Although subgroup analysis showed that the conclusion of our study remained consistent, it would be better to extract lncRNAs from the same specimen. Finally, diagnostic values of lncRNAs expression for T2DM with several long-term complications such as coronary artery disease, chronic renal failure, or diabetic retinopathy were needed to be further investigated.

With the aim to identify the function of lncRNAs in T2DM as mentioned in our second limitation, more approaches are warranted in the future to establish the role and function of the lncRNA biomarkers. Firstly, because of the relatively small sample size, additional laboratory and clinical studies should be undertaken with larger numbers of participants, different ethnicity and disease duration to get the epidemiological data. In the process, RNA-Seq technology and genome databases are needed. Secondly, regulating the expression of lncRNAs with plasmid or virus transfection or shRNA in cells and animal level to obtain a better understanding of the roles of lncRNAs in the pathogenesis of T2DM. Thirdly, lncRNAs were proved to be with miRNA response elements that could be modulated by microRNAs (miRNAs). Thus, lncRNAs could act as competing endogenous RNAs (ceRNAs) to communicate with messenger RNAs (mRNAs) through competing for shared miRNAs. Experimental evidence suggested that dysregulated expressions of crucial lncRNAs in the ceRNA network have large effects on the development of numerous diseases. Therefore, lncRNA–miRNA–mRNA ceRNA networks could be established in the onset of T2DM to clarify the underlying mechanism of lncRNAs. Finally, the aforementioned studies also inspired us to focus on the role of lncRNAs expression in pancreatic islet and liver during T2DM development [26, 27, 29, 30].

With more relevant studies included, we will update this meta-analysis to clarify the problems above.

Conclusions

In summary, our meta-analysis demonstrated a remarkable association between abnormal lncRNA expression and diagnostic outcomes in T2DM cases. Moreover, lncRNAs might be a promising biomarker and therapeutic target for T2DM. In the future, we advocate more researches in this field to be done to investigate the effect of lncRNAs on T2DM.

Authors' contributions Study conception and design: Z.W.Y., Z.J. and C.L.L. Acquisition of data: Z.W.Y., Z.J., H.X. and C.L.L. Analysis of data: Z.W.Y., Z.J. Paper drafting: Z.W.Y., C.L.L. Critical appraisal of paper: C.L.L. All the authors have approved the final paper to be published.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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