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Identification of a four-miRNA signature predicts the prognosis of papillary thyroid cancer

Fan Y *et al*. Prognosis prediction of papillary thyroid cancer

Yang Fan, Zhou Yi-Li

Abstract

BACKGROUND

In recently diagnosed patients with thyroid cancer, papillary thyroid cancer (PTC), as the most common histological subtype, accounts for 90% of all cases. Although PTC is known as a relatively adolescent malignant disease, there still is a high possibility of recurrence in PTC patients with a poor prognosis. Therefore, new biomarkers are necessary to guide more effective stratification of PTC patients and personalize therapy to avoid overtreatment or inadequate treatment. Accumulating evidence demonstrates that microRNAs (miRNAs) have broad application prospects as diagnostic biomarkers in cancer.

AIM

To explore novel markers consisting of miRNA-associated signatures for PTC prognostication.

METHODS

We obtained and analyzed the data of 497 PTC patients from The Cancer Genome Atlas. The patients were randomly assigned to either a training or testing cohort.

RESULTS

We discovered 237 differentially expressed miRNAs in tumorous thyroid tissues compared with normal tissues, which contained 172 up-regulated and 65 down-regulated miRNAs. The evaluation of differently expressed miRNAs was conducted

using our risk score model. We then successfully generated a four-miRNA potential prognostic signature [risk score = (-0.001 × hsa-miR-181a-2-3p) + (0.003 × hsa-miR-138-5p) + (-0.018 × hsa-miR-424-3p) + (0.284 × hsa-miR-612)], which reliably distinguished patients from high and low risk with a significant difference in the overall survival (P < 0.01) and was effective in predicting the five-year disease survival rate with the area under the receiver operating characteristic curve of 0.937 and 0.812 in the training and testing cohorts, respectively. Additionally, there was a trend indicated that high-risk patients had shorter relapse-free survival, although statistical significance was not reached (P = 0.082) in our sequencing cohort.

CONCLUSION

Our results indicated a four-miRNA signature that has a robust predictive effect on the prognosis of PTC. Accordingly, we would recommend more radical therapy and closer follow-ups for high-risk groups.

Key Words: Papillary thyroid cancer; microRNA; Prognosis; Signature

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Core Tip: Thyroid cancer is the most prevalent endocrine malignancy in the world, and its incidence is rapidly rising. In this paper, an efficient and accurate prognostic prediction model for thyroid cancer was constructed, which is valuable for future clinical studies.

INTRODUCTION

Thyroid cancer is the most prevalent endocrine malignancy in the world, and its incidence is rapidly rising[1]. It ranks as the fifth most common cancer in female patients, and its incidence is approximately three times higher than in males in most

regions and populations[2,3]. Differentiated thyroid cancer derives from follicular epithelial cells; the main subtypes comprise papillary thyroid cancer (PTC), follicular thyroid cancer, and Hurthle cell carcinoma[4]. The most common histological subtype of thyroid cancer is PTC, which accounts for 90% of newly diagnosed thyroid cancers and has the best prognosis among all subtypes[4]. PTC usually behaves like an indolent disease in most patients and can be well controlled or cured using the appropriate surgical procedure or with the help of radioiodine. However, the recurrence rate of PTC remains high, and the dedifferentiation of PTC would potentially lead to invasiveness and a poor prognosis[5].

Given that PTC is a heterogeneous disease, optimal treatment for PTC patients has long been a heated controversy. While more aggressive treatment of cancer can reduce the recurrence of disease and mortality rates, it will also give rise to treatment-related complications[6]. To alleviate this dilemma, we need to improve risk stratification to identify patients with worse outcomes more accurately. Therefore, introducing new biomarkers as an advanced method in improving the overall survival (OS) of PTC patients is favored.

MicroRNAs (miRNAs) are types of noncoding, single-stranded RNA molecules consisting of approximately 18 to 25 nucleotides. The specific binding of miRNAs to the complementary mRNA can either facilitate mRNA degradation or prevent mRNA translation into protein[7]. Previous reports have suggested that miRNAs are essential in the tumorigenesis and progression of PTC[8,9]. Accumulating evidence has also demonstrated that miRNAs have broad application prospects, such as diagnostic biomarkers and therapeutic targets in cancer[10]. However, the limitations of existing studies include inadequate sample quantitation and limited comprehensive analyses on many PTC samples. With the help of The Cancer Genome Atlas (TCGA) database, we could investigate cancer-specific signatures, which contain large-scale miRNA expression data and prognostic survival data.

In this study, we utilize data from the TCGA database to conduct a comprehensive analysis and screen out differentially expressed miRNAs. We then assess the prognostic

value of these miRNAs using a risk score model. A panel of four miRNAs is generated as a prognostic signature, which is then tested in PTC patients. Such a practical tool has satisfying potential in stratifying PTC patients and individualized therapy to avoid overtreatment or inadequate treatment.

MATERIALS AND METHODS

Expression profiles collection

Level three miRNASeq datasets of 507 PTC and 58 normal samples and the corresponding clinical data of PTC patients were extracted from the TCGA database (http://cancergenome.nih.gov) on December 12, 2019[11]. The inclusion criteria of the studied samples were as follows: (1) The data contained both miRNA sequencing and clinical information; (2) the sample had prognosis information; and (3) the histological typing was PTC. A total of 497 PTC samples met our criteria and were selected for further analysis. The entire set was randomly separated into a training cohort (249 cases) and a test cohort (248 cases). The detailed baseline characteristics of the entire set are listed in Supplementary Table 1.

Identification of differentially expressed miRNA

An analysis of the global miRNA expression profile detected 2202 miRNAs. Then, the miRNA expression profiles were standardized using the R package of edgeR[12]. EdgeR was also utilized to sift out the differentially expressed miRNAs according to the following criteria: (1) Fold change (FC) > 2 for up- or down-regulation; and (2) false discovery rate (FDR) < 0.05. Based on the analysis of the differentially expressed miRNA, a volcano plot was produced with label colors that were determined by the filtering criteria.

Selection of candidate prognosis biomarkers

First, a univariate cox regression analysis was used to sift out each differently expressed miRNA that was related to patients' OS. Subsequently, these differently expressed

miRNAs with $P < 0.05$ were selected for the least absolute shrinkage and selection operator analysis (LASSO). The LASSO analysis created a more refined model by constructing a penalty function. Finally, we established general multivariate stepwise Cox regression models to identify which of the significant miRNAs was an independent predictor of prognosis.

Construction of the miRNA signature

MiRNAs that had a notable association with OS in the multivariate Cox regression analysis were utilized to construct the miRNA signature, which was used to estimate the prognostic risk score for each patient. The miRNA signature was built using the coefficients obtained from the Cox regression analysis. The standards were as follows: Risk score = (-0.001 × hsa-miR-181a-2-3p) + (0.003 × hsa-miR-138-5p) + (-0.018 × hsa-miR-424-3p) + (0.284 × hsa-miR-612). Subsequently, according to the same median risk score as the cutoff point, patients in both the training and testing cohorts were divided into the low-risk and high-risk groups. Next, the area under the curve (AUC) of the time-dependent ROC analysis was analyzed to reveal the predictive effect of the miRNA-based classifier and prognostic model. To make the prognostic miRNA signature more convenient in clinical practice, we also constructed a prognostic nomogram. Furthermore, a calibration curve was carried out to assess the consistency of model prediction and the actual outcome.

Functional analysis of the miRNA signature

The miRDB (http://www.mirdb.org/miRDB/) and TargetScan (http://www.targetscan.org/) were used for the prediction of target genes of four miRNAs. Furthermore, overlapping target genes from these two online analysis databases were analyzed using the functional enrichment analysis tool FunRich[13]. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were used to analyze the function of these target genes. These target genes of four miRNAs are listed in Supplementary Table 2.

Statistical analysis

The Mann-Whitney *U* test and the χ^2 test were used to analyze the associations of continuous and categorical variables between the training and testing cohorts, respectively. Survival analyses were compared using log-rank tests, while the Kaplan-Meier method was adopted to plot the survival curves. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (Chicago, IL, United States) and R version 3.6.1.

RESULTS

Baseline clinical characteristics of PTC patients

We extracted and investigated the data of 497 PTC patients from the TCGA database. The patients were randomly assigned to either the training or testing cohort. Table 1 demonstrates the detailed clinical characteristics (age, sex, vital status, stages, and T/N/M classification) of both cohorts, finding no significant differences between the two groups ($P > 0.05$).

Selection of differentially expressed miRNAs and candidate diagnostic biomarkers

To select significantly differentially expressed miRNAs in the 497 PTC tissues and 59 adjacent normal thyroid tissues (Figure 1), we performed a volcano plot to evaluate miRNA expression variation with the standard of FC > 2 or < 0.5, as well as FDR < 0.05. A total of 237 miRNAs were differentially expressed in the cancerous tissues compared with the normal tissues, including 172 up-regulated miRNAs and 65 down-regulated miRNAs. These 237 significantly differently expressed miRNAs were identified as potential prognostic biomarkers for PTC. To screen out the OS-related miRNAs, a univariate cox regression analysis was performed for these significantly differentially expressed miRNAs in the training cohort. Subsequently, we found that 13 miRNAs were distinctly associated with the OS of PTC (Table 2).

Construction of the miRNA prognostic signature

To construct the miRNA prognostic signature, these 13 miRNAs were further selected into the LASSO and multivariate cox regression analyses. The lambda value was set using lambda min, which is the value of lambda, to obtain the minimum mean cross-validated error. Four miRNAs with non-zero coefficients were defined. We finally managed to establish four miRNAs that had an independent prognostic effect for PTC in the training cohort based on the LASSO and Cox regression models (Table 3). To clearly reveal the weight of each weighting coefficient of miRNAs, a forest figure is presented in Supplementary Figure 1. We then chose the same median risk score in the above two independent cohorts as the cutoff point, classifying patients into the low-risk and high-risk groups. Figure 2 shows the distribution of the miRNA-based risk score, OS, and four miRNAs expression profiles of the training and testing cohorts. The Kaplan-Meier survival analysis indicated a much worse prognosis ($P < 0.001$) in the high-risk group (Figure 3A).

Next, we conducted a time-dependent ROC curve analysis to assess the performance of the four-miRNA signature in predicting the PTC prognosis. The AUC values of the four-miRNA signature at five years were 0.937 and 0.812 in the training and testing cohorts, respectively (Figure 3B). To make the prognostic miRNA signatures more convenient in clinical practice, a four-miRNA-based nomogram was established (Figure 4A). Furthermore, calibration plots of the four-miRNA-based prognostic model showed compactness in the training and testing cohorts for the 3- and 5-year survival rates, respectively, which indicated good calibration ability (Figure 4B).

The four-miRNA signature as an independent prognostic factor of OS

The predictive effect of the four-miRNA signature on OS considering the clinicopathological features was evaluated using the univariate and multivariate Cox regression analyses. The multivariate Cox regression analysis showed that the four-miRNA signature was an independent prognostic factor associated with the OS of PTC patients (Table 4).

Validation of the four-miRNA signature in the sequencing cohort

We performed whole-transcriptome sequencing of 19 paired-PTC tissue samples[14]. We obtained the expression of these four miRNAs and then calculated their risk score based on the four-miRNA signature in 19 PTC samples. Then, we chose the median risk score as the cutoff point, classifying patients into the low-risk and high-risk groups. We found that there was no significant difference in OS time between the high-risk and low-risk groups (P = 0.99). There was a trend indicated that high-risk patients had shorter relapse-free survival, although statistical significance was not reached. (P = 0.082, Figure 5).

Target prediction and function analysis

The target genes of the selected four miRNAs, hsa-miR-181a-2-3p, hsa-miR-138-5p, hsa-miR-424-3p, and hsa-miR-612, were predicted by TargetScan and miRDB. Then, the biological roles of the overlapped target genes were assessed using an enrichment analysis. The GO biological processes were mainly enriched in the regulation of nucleobase, nucleoside, nucleotide, and nucleic acid metabolism; transport; regulation of gene expression; epigenetics; and cell adhesion (Table 5). In addition, the KEGG pathways were remarkably enriched in the integrin family cell surface interactions, beta1 integrin cell surface interactions, and proteoglycan and syndecan-mediated signaling events (Table 6).

DISCUSSION

In the era of precision medicine, molecular biomarker-guided treatment and more accurate patient survival prediction are demanding a prompt solution. These efforts have been enormously successful in the field of PTC. With the increasing use of thyroid fine-needle aspiration cytology, the classification of indeterminate nodules is becoming more accurate. However, approximately 20% of nodules lack specific characteristics in cytology[15]. ThyroSeq v3 Genomic Classifier is a tool that includes a variety of thyroid

cancer-related point mutations, gene fusions, copy number variations, and gene expression alterations to achieve both high sensitivity and specificity in differentiating benign and malignant thyroid nodules sampled by FNA biopsy[16]. According to the latest research report, the ThyroSeq v3 demonstrated 94% sensitivity and 82% specificity of thyroid nodules with Bethesda III and IV cytology[17]. Moreover, a BRAF V600E mutation was reported in many studies associated with poorer clinicopathological outcomes of PTC[18]. Our previous studies showed that the co-existence of BRAF V600E and TERT promoter mutations was related to high-risk clinicopathological features of PTC[19].

With the advancement of sequencing technology and bioinformatics, we can obtain comprehensive DNA epigenetics, mRNA expression profiles, noncoding RNAs, and proteomics data. In the future, more molecular biomarker-based approaches will be developed based on different molecular data. As miRNAs are relatively stable and easily detected, they are promising biomarkers in the clinic[20-22]. In 2018, Liu *et al*[23] constructed a two-miRNA (hsa-miR-181a-2-3p and hsa-miR-138-1-3p) signature for a PTC prognosis assessment. The AUC value of the two-miRNA signature was 0.784. Additionally, Xiong *et al*[24] constructed another four-miRNA signature (hsa-miR-6843, hsa-miR-6730, hsa-miR-196a-2, and hsa-miR-206) as a potential prognostic biomarker in PTC. The AUC values of the four-miRNA signature were 0.886 and 0.882 in the training and testing cohorts, respectively. In this study, we analyzed large-scale miRNA sequencing data in the TCGA database and selected a total of 2203 miRNAs to provide a more comprehensive analysis. Consequently, we confirmed a four-miRNA signature that had a strong prognostic effect on the prognosis of PTC with relatively higher credibility. Although there was no statistical difference, we found a trend for shorter survival times in the high-risk group compared with the low-risk group in the sequencing cohort. This may be related to the inadequate sample size and short follow-up period.

It is widely recognized that miRNAs are pivotal regulators of gene expression in complex cellular processes, including cancer cell proliferation, metastasis, migration,

and apoptosis[25]. The four miRNAs found in this study may be potential oncogene or tumor suppressor genes in PTC and independent predictors of PTC prognosis. Among these four miRNAs, hsa-miR-181a-2-3p has been reported as a potential prognostic indicator of PTC. However, its specific function and molecular mechanism in PTC have not been reported[23], and the biological functions of the remaining miRNAs remain unclear.

He *et al*[26] analyzed the miRNA expression of peripheral blood between healthy people and lung cancer patients and found a significant difference in the hsa-miR-138-5p expression in two groups. Hsa-miR-424-3p may be a key miRNA for liver cancer, which was involved in telomere maintenance *via* telomerase, protein sumoylation, the histone mRNA metabolic process, and angiotensin maturation[27]. However, many studies suggest that the down-regulation of hsa-miR-612 was involved in a variety of signal pathways that affect the pathophysiology of gastric cancer, liver cancer, and ovarian cancer. However, its relationship with PTC remains unclear[28-30]. As a result, it is necessary to conduct additional *in vitro* and *in vivo* experiments investigations using these four miRNAs.

CONCLUSION

In conclusion, this study indicated that the four-miRNA signature could accurately predict the prognosis of PTC. More intensive treatment and closer follow-ups for high-risk PTC patients are recommended.

ARTICLE HIGHLIGHTS

Research background

Papillary thyroid cancer is a highly heterogeneous disease and therefore molecular markers need to be established to predict its prognosis.

Research motivation

The present study aims to explore novel markers consisting of microRNA (miRNA)-associated signatures for papillary thyroid cancer (PTC) prognostication.

Research objectives

To establish a practical tool has satisfying potential in stratifying PTC patients and individualized therapy to avoid overtreatment or inadequate treatment.

Research methods

In this study, a panel of four miRNAs is generated as a prognostic signature, which is then tested in PTC patients.

Research results

The panel of four miRNAs could reliably distinguished PTC patients from high and low risk with a significant difference in the overall survival.

Research conclusions

More intensive treatment and closer follow-ups for high-risk PTC patients are recommended.

Research perspectives

Our prognostic signature contributed to individualized therapy to avoid overtreatment or inadequate treatment.

Figure Legends

Figure 1 Volcano plot of 2202 miRNAs in papillary thyroid cancer patients. The red color indicates up-regulated expression, and the green color represents down-regulated expression. FDR: False discovery rate; FC: Fold change.

Figure 2 The distribution of the risk score, overall survival, and overall survival status and the heat map of the prognostic four-miRNA signature. A: The training cohort; B: Test cohort. The dotted line indicates the cutoff point of the median risk score, which is used to stratify patients into the low-risk and high-risk groups.

Figure 3 Kaplan-Meier curves of overall survival and time-dependent receiver operating characteristic curves of the 5-year survival rate for papillary thyroid cancer patients based on the four-miRNA signature. A: Training cohort; B: Test cohort. AUC: Area under the curve; ROC: Receiver operating characteristic.

Figure 4 Title. A: The prognostic nomogram based on the four-miRNA signature; B: Calibration plots of the four-miRNA-based prognostic model in the training and test cohorts of the 3-year survival rate; C: Calibration plots of the four-miRNA-based prognostic model in the training and test cohorts of the 5-year survival rate.

Figure 5 Title. A: Overall survival curves; B: Recurrence-free survival curves in the whole-transcriptome sequencing cohort.

Table 1 Clinical characteristic of 497 patients with papillary thyroid cancer

Variable	Train cohort (*n* = 249)	Test cohort (*n* = 248)	*P* value
Age			0.968
< 45	112	112	
≥ 45	137	138	
Sex			0.064
Male	75	57	
Female	174	193	
Vital status			0.617
Death	9	7	
Alive	240	241	
Stages			0.768
I	140	138	
II	28	23	
III	53	61	
IV	28	26	
T classification			0.302
T1	67	76	
T2	92	74	
T3	78	85	
T4	12	11	
Tx	0	2	
N classification			0.166
N0	107	121	
N1	120	99	
Nx	22	28	
M classification			0.584
M0	139	139	
M1	3	6	
Mx	107	103	

Table 2 Univariate cox regression analyses of microRNA were distinctly associated with overall survival of papillary thyroid cancer in train cohort

miRNA	*P* value	HR	Lower 95%CI	Upper 95%CI
hsa-miR-138-5p	0.0001	1.0024	1.0011	1.0036
hsa-miR-1179	0.0006	1.0120	1.0050	1.0191
hsa-miR-138-1-3p	0.0009	1.0280	1.0112	1.0451
hsa-miR-612	0.0064	1.3720	1.0929	1.7222
hsa-miR-7-2-3p	0.0077	1.0109	1.0028	1.0191
hsa-miR-146b-3p	0.0165	0.9999	0.9998	0.9999
hsa-miR-181a-2-3p	0.0177	0.9999	0.9998	0.9999
hsa-miR-146b-5p	0.0224	0.9999	0.9999	0.9999
hsa-miR-5682	0.0308	1.8605	1.0587	3.2696
hsa-miR-31-5p	0.0320	0.9952	0.9908	0.9995
hsa-miR-424-3p	0.0393	0.9790	0.9594	0.9989
hsa-miR-6842-3p	0.0437	0.9457	0.8959	0.9984
hsa-miR-4709-3p	0.0471	0.9702	0.9416	0.9996

CI: Confidence interval; HR: Hazard ratio; PTC: Papillary thyroid cancer.

Table 3 Multivariate cox regression analyses of microRNA were distinctly associated with overall survival of papillary thyroid cancer in train cohort

miRNA	Coefficient	*P* value	HR	Lower 95%CI	Upper 95%CI
hsa-miR-181a-2-3p	-0.001	0.0800	1.000	1.000	1.000
hsa-miR-138-5p	0.003	0.0001	1.003	1.001	1.004
hsa-miR-424-3p	-0.018	0.0590	0.982	0.964	1.001
hsa-miR-612	0.284	0.0242	1.329	1.038	1.702

CI: Confidence interval; HR: Hazard ratio; PTC: Papillary thyroid cancer.

Table 4 Univariate and multivariate cox regression analyses of the four miRNA signature and clinicopathologic factors in the entire set

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age (< 45 *vs* ≥ 45)	0.013 (0.000-0.756)	0.036	-	-
Stage (I/II *vs* III/IV)	0.141 (0.045-0.439)	0.001	-	-
Sex	2.029 (0.734-5.613)	0.173	-	-
Four miRNA signature (high risk *vs* low risk)	8.625 (1.956-38.03)	0.004	6.186 (1.405-27.24)	0.016

CI: Confidence interval; HR: Hazard ratio; PTC: Papillary thyroid cancer.

Table 5 The significant enriched Gene Ontology biological processes of target genes

Term	Count	Fold enrichment	*P* value
Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	291	1.228	< 0.001
Transport	127	1.247	0.005
Regulation of gene expression, epigenetic	12	2.171	0.008
Cell adhesion	12	2.653	0.001

Table 6 The significant enriched Kyoto Encyclopedia of Genes and Genomes pathways of target genes

Term	Count	Fold enrichment	*P* value
Integrin family cell surface interactions	149	1.265	< 0.001
Beta1 integrin cell surface interactions	147	1.273	< 0.001
Proteoglycan syndecan-mediated signaling events	146	1.267	< 0.001
PAR1-mediated thrombin signaling events	145	1.306	< 0.001
Thrombin/PAR pathway	145	1.305	< 0.001
VEGF and VEGFR signaling network	145	1.301	< 0.001
Alpha9 beta1 integrin signaling events	145	1.300	< 0.001
ErbB receptor signaling network	145	1.294	< 0.001
S1P pathway	145	1.294	< 0.001
TRAIL signaling pathway	145	1.277	< 0.001

PAR: Protease-activated receptor; VEGF: Vascular endothelial-derived growth factor; SIP: Sphingosine 1-phosphate; TRAIL: Tumour necrosis factor-related apoptosis-inducing ligand.

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