Original Article

Competing endogenous RNA network for esophageal cancer progression

Saihua Chen[#], Guanjun Ju[#], Jianmei Gu, Minxin Shi, Yilang Wang, Xiaodan Wu, Qing Wang, Liyun Zheng, Ting Xiao, Yihui Fan

Department of Thoracic Surgery, Tumor Hospital Affiliated to Nantong University & Nantong Tumor Hospital, Nantong, China

Contributions: (I) Conception and design: S Chen, G Ju; (II) Administrative support: None; (III) Provision of study materials or patients: L Zheng, Y Fan, M Shi; (IV) Collection and assembly of data: J Gu, Y Wang, T Xiao; (V) Data analysis and interpretation: X Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yihui Fan. Department of Thoracic Surgery, Tumor Hospital Affiliated to Nantong University & Nantong Tumor Hospital, 30 Tongyang North Road, Pingchao, Tongzhou, Nantong 226361, China. Email: fanyihui1987@sina.com.

Background: Esophageal cancer (ESCA) constitutes one of the most common cancers worldwide. The identification of potential biomarkers is important to improving the diagnostic accuracy and treatment efficiency for patients with ESCA. In this study, we aimed to identify biomarkers related to ESCA progression through a comprehensive analysis of long non-coding RNAs (lncRNAs), microRNA (miRNAs), and mRNA expression profiles in ESCA.

Methods: Differentially expressed lncRNAs, miRNAs, and mRNAs (DElncRNAs, DEmiRNAs, and DEmRNAs, respectively) in ESCA samples compared with normal controls were obtained. A competing endogenous RNA (ceRNA) network consisting of interacting DElncRNAs, DEmiRNAs, and DEmRNAs was constructed using a combination of the miRCode and TargetScan databases. Relationships between RNAs in the ceRNA network and overall survival in patients with EC were explored through another independent ESCA dataset from The Cancer Genome Atlas.

Results: A total of 1,014 DElncRNAs, 3,677 DEmRNAs, and 35 DEmiRNAs were identified in ESCA samples compared with normal samples. Functional enrichment analysis indicated that the DEmRNAs were involved in cell activity, inflammatory response, and oxygen metabolism-related biological processes. A ceRNA network containing 5 DEmiRNAs, 582 DEmRNAs and 764 DElncRNAs was obtained. In the survival analysis, 39 genes were found to be significantly associated with overall survival in patients with EC, including *GOLGA7*, *NFYB*, *TOP1*, and *TMTC3*.

Conclusions: Our study constructed a ceRNA network for ESCA for the first time, which will be helpful for the disease's diagnosis and treatment.

Keywords: Esophageal cancer (ESCA); lncRNA; miRNA; competing endogenous RNA network (ceRNA network); overall survival

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Introduction

Esophageal cancer (ESCA) is one of the most common cancers worldwide, and a spectacular rise in its incidence has been observed in Western countries over the last four decades (1,2). Barrett's esophagus is a precursor to ESCA, which sees the replacement of normal esophageal squamous epithelium with columnar epithelia and goblet cells (3). There are several therapeutic approaches for ESCA, among which endoscopic mucosal resection (for early ESCA and precancerous lesions)

and radiotherapy are the most common (4). However, due to metastasis, the 5-year survival rate of patients with ESCA is low, standing at only 18.3% (5). Therefore, understanding the mechanisms of ESCA progression is critical to improving the prognosis of patients with this disease.

Long non-coding RNAs (lncRNAs) are noncoding RNAs exceeding 200 nucleotides in length. LncRNAs bind microRNAs (miRNAs/miRs) and act as miRNA sponges, reducing their regulatory abilities (6). Alterations in lncRNA expression profiles are associated with the progression of many diseases, including cancer. For instance, the lncRNA H19 was found to sponge miR-138 and miR-200a to promote epithelial-mesenchymal transition (EMT) in colorectal cancer (7). Kallen *et al.* also discovered let-7 binding sites in lncRNA H19, which indicates that this lncRNA may influence let-7 regulatory functions (8). Further, Wu *et al.* reported that the lncRNA PAGBC could suppress miR-133b and miR-511 function and promote gallbladder tumorigenesis (9). Several studies about lncRNAs in ESCA have also been conducted. For instance, Xu *et al.* described the ability of lncRNA HOTAIR to sponge miR-148a and promote EMT in ESCA (10). In their study, Li *et al.* quantified the expression levels of the lncRNA UCA1 in ESCA through quantitative real-time PCR , finding it to be a poor prognostic indicator (11). Another study demonstrated that lncRNA PEG10 could inhibit ESCA cell proliferation and invasion, and promote apoptosis (12).

As small non-coding RNAs, miRNAs can down-regulate the expression of mRNAs by inhibiting their translation (13). miRNA abundance can also be influenced by other types of RNA, including lncRNAs, containing tandem repeats of miRNA response elements (MREs) (14). Interactions between MRE-containing RNAs, miRNAs and mRNAs form the competing endogenous RNA (ceRNA) network. An aberrant ceRNA network can result in many diseases, including cancer (15-17). Numerous studies have focused on the roles of ceRNA networks in cancers such as bladder (18), breast (19), and gastric (20) cancer. Research of ceRNA networks is critical to understanding the progression of diseases; however, no such study has been conducted for ESCA.

In this study, we conducted a comprehensive analysis of lncRNA, miRNA, and mRNA expression profiles in ESCA using Gene Expression Omnibus (GEO). A ceRNA network was constructed based on the miRCode and TargetScan databases. From another independent ESCA dataset, several prognostic genes were obtained. This study aimed to identify potential biomarkers for ESCA in order to improve the early diagnosis and treatment of patients with the disease. We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4478).

Methods

Microarray datasets

ESCA lncRNA and mRNA expression profiles were downloaded from GEO (https://www.ncbi.nlm.nih.gov/geo/) (accession No. GSE89102). Five ESCA tissues and five adjacent non-tumor tissues were included. The Agilent-045997 Arraystar human lncRNA microarray V3 (GPL16596) platform was used to profile the expression of lncRNAs and mRNAs in the tissues. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The Affiliated Tumor Hospital of Nantong University (No. 2020811521).

Microarray analysis

Raw microarray data were imported into R programming software and quartile normalization was conducted. Differentially expressed lncRNAs and mRNAs (DElncRNAs and DEmRNAs, respectively) in the ESCA samples compared with the normal samples were identified using the limma package (21), with the thresholds of adjusted $P<0.05$ and $|\log2(\text{fold change})| >1$.

Functional enrichment analysis

To investigate the biological processes involved in ESCA progression, we conducted functional enrichment analysis of DEmRNAs through DAVID (the Database for Annotation, Visualization and Integrated Discovery, https://david.ncifcrf.gov/) (22). Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways meeting the criterion of $P<0.05$ were screened out.

ceRNA network analysis

To identify the miRNAs with which the DElncRNAs interact, the miRCode database (http://www.mircode.org/) (23) was searched for predicted lncRNA-miRNA pairs. Besides, an ESCA miRNA expression profile dataset

(containing three ESCA samples and three normal samples) was obtained from GEO (accession no. GSE71043), to identify differentially expressed miRNAs (DEmiRNAs) in ESCA compared with normal samples. Consistent with the analysis of DElncRNA and DEmRNA expression, only miRNAs meeting the criteria of adjusted P<0.05 and |log2(fold change)| >1 were considered as differentially expressed. Then, interactions between DElncRNAs and DEmiRNAs were obtained. Targets of DEmiRNAs were screened using the TargetScan database (http://www.targetscan.org/vert_71/) (24), and only DEmRNAs were included in the ceRNA network. Finally, the DElncRNA-DEmiRNA-DEmRNA ceRNA network was obtained and visualized with the Cytoscape software (25).

Survival analysis

The associations of RNAs contained in the ceRNA network with ESCA prognosis were explored in the ESCA dataset from The Cancer Genome Atlas (TCGA, https://cancergenome.nih.gov/). ESCA samples were divided into two groups based on the median expression value of a specific gene, and the log-rank test was used to test the survival difference between the two groups.

Results

DElncRNAs and DEmRNAs

A total of 1,014 DElncRNAs (531 down-regulated and 483 up-regulated) and 3,677 DEmRNAs (1,408 down-regulated and 2,269 up-regulated) were identified in ESCA samples compared with normal samples. Supervised clustering of the 10 samples based on the DElncRNAs and DEmRNAs was conducted. As shown in *Figure 1A*,*1B*, ESCA and normal samples could be distinguished by DElncRNAs and DEmRNAs, respectively. *Figure 1C*,*1D* show scatter plots of lncRNA and mRNA expression profiles, respectively; down-regulated and up-regulated genes are represented by red and blue dots, respectively, while the black dots represent non-differentially expressed genes.

Enriched functions

The functions of the top 1,000 most significant DEmRNAs were analyzed with DAVID . Based on the threshold of P<0.05, 65 GO terms and 6 KEGG pathways were significantly enriched in DEmRNAs. *Figure 2* show the top 20 most significantly enriched GO terms and all of the significantly enriched KEGG pathways. The DEmRNAs were closely associated with biological processes related to cell activity and oxygen metabolism.

ceRNA network

A total of 35 DEmiRNAs were identified in ESCA samples compared with normal samples. *Table 1* shows the full list of DEmiRNAs and their corresponding P value and log2(fold change). By using a combination of the miRCode and TargetScan databases, we obtained a ceRNA network containing 5 DEmiRNAs, 582 DEmRNAs, and 764 DElncRNAs. *Figure 3* depicts the ceRNA network, with red, green, and blue circles representing DEmiRNAs, DEmRNAs, and DElncRNAs, respectively.

Identification of ESCA prognostic genes

The ESCA dataset from TCGA was used to identify prognostic biomarkers in ESCA from the ceRNA network. A total of 39 genes were found to be significantly associated with survival of ESCA; these 39 genes and their corresponding P values and hazard ratios are shown in *Table 2*. *Figure 4* depicts Kaplan-Meier curves based on the expression of *GOLGA7*, *NFYB*, *TOP1*, and *TMTC3*. The high expression of each of these genes was associated with a poor prognosis.

Discussion

As the ninth most common cancer in the world, ESCA affects more than 450,000 people each year, and its incidence is increasing spectacularly (26). Although several therapeutic methods exist for ESCA (26-28), a lack of understanding of the disease's mechanisms means its 5-year survival rate is still low. In this study, we conducted—for the first time—a ceRNA network analysis for ESCA and identified several prognostic genes, which could be helpful for the diagnosis and treatment of patients with the disease.

In this study, the ceRNA network was restricted to DElncRNAs, DEmiRNAs, and DEmRNAs specific to ESCA. Studies have shown that miR-191, miR-144, and miR-93 interacted with DElncRNAs and could regulate DEmRNAs. All five of these miRNAs have been proved to be deregulated in ESCA. For instance, through quantitative real-time PCR, Ansari *et al.* reported that miR-93 was down-regulated in human ESCA compared with normal

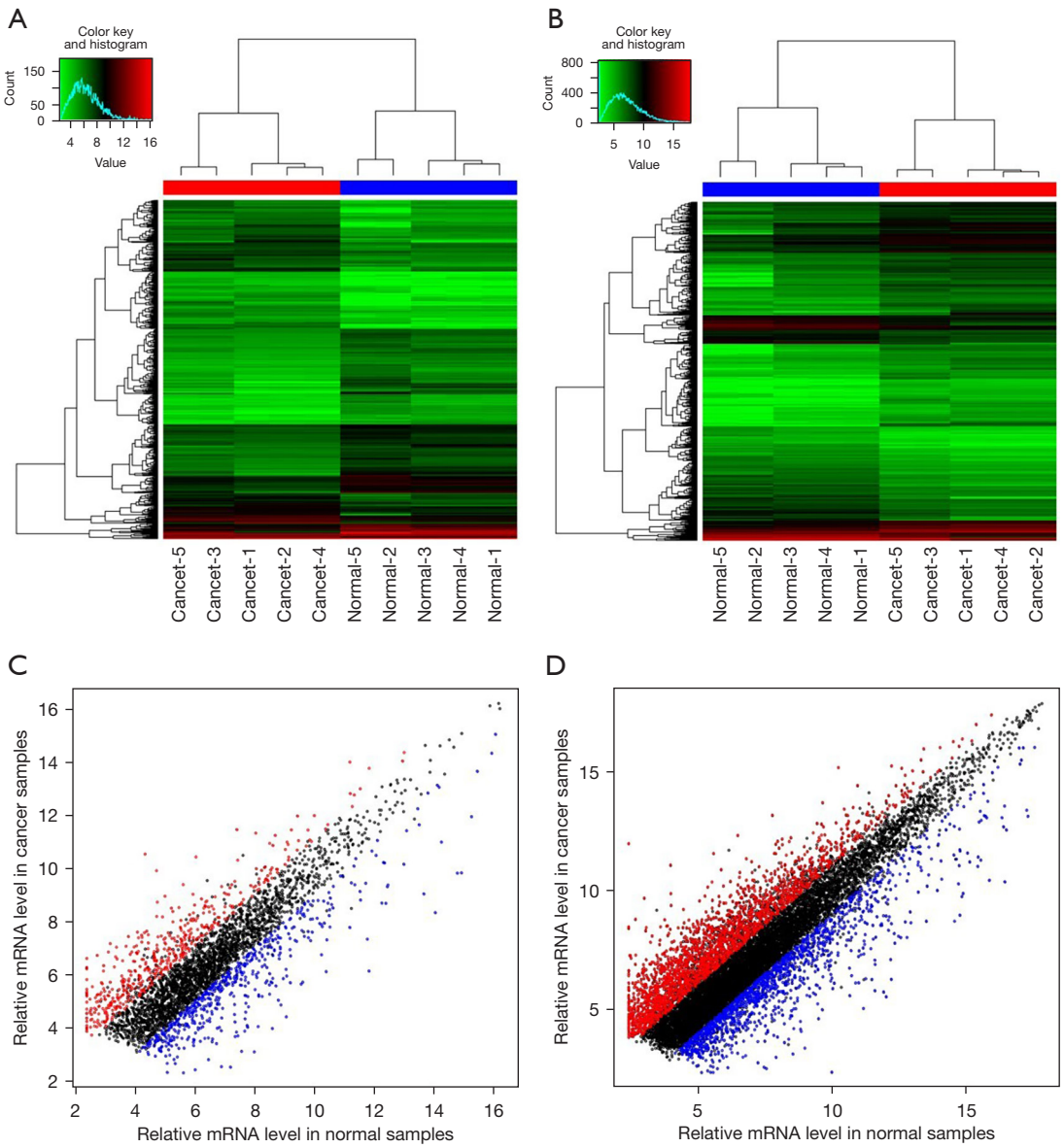

Figure 1 LncRNA and mRNA microarray analysis. (A,B) Supervised clustering of samples based on DElncRNAs and DEmRNAs, respectively. Rows and columns represent genes and samples, respectively; color gradient from green to red indicates increasing expression values; barcode at the top of the heatmap indicates different groups of samples, with blue and red indicating control and esophageal cancer samples respectively. (C,D) Scatter plots of lncRNA and mRNA expression profiles. Blue and red dots represent down-regulated and up-regulated genes, respectively; black dots represent non-differentially expressed genes. DElncRNAs, differentially expressed lncRNAs; DEmRNAs, differentially expressed miRNAs.

samples (29), while Cui *et al.* concluded that miR-93 could desensitize ESCA to radiotherapy (30). In Shao *et al.*'s study, miR-144 was proved to inhibit ESCA proliferation and metastasis via inhibiting cyclooxygenase-2 (31). As for miR-191, Gao *et al.* demonstrated that its up-regulation promoted cell proliferation and invasion and was predictive of a poor prognosis in ESCA (32). All of these studies suggest the reliability of the miRNAs contained in the ceRNA network for the diagnosis and treatment of ESCA.

The DEmRNAs in ESCA tissues were found to be

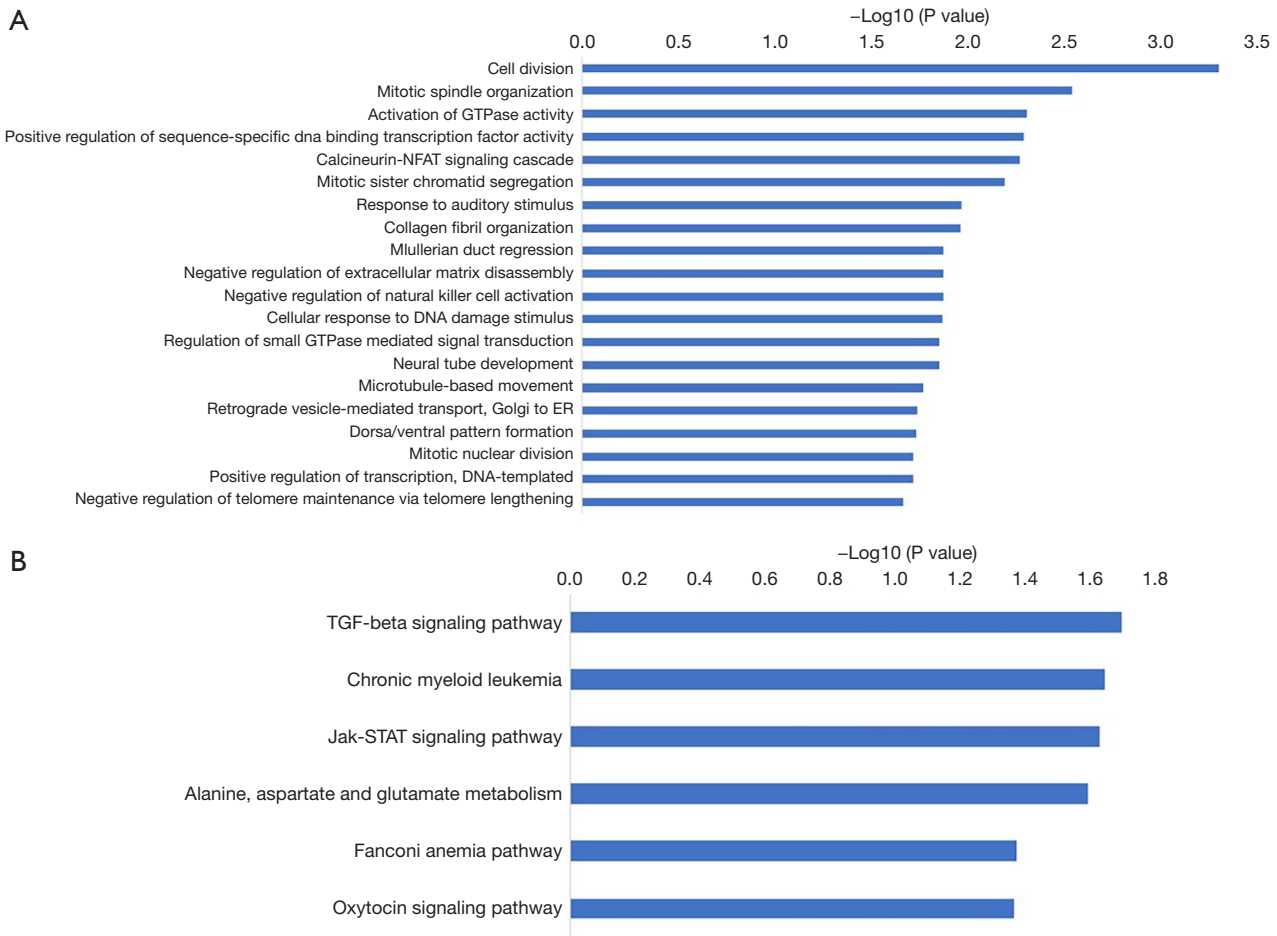

Figure 2 Functional enrichment analysis of DEmRNAs. (A) The top 20 significantly enriched GO pathways of DEmRNAs; (B) all significantly enriched KEGG pathways of DEmRNAs. DEmRNAs, differentially expressed miRNAs; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

significantly associated with cell activity and energy metabolism. Furthermore, the oxytocin signaling pathway, which has not been reported to be associated with ESCA, was also enriched in the DEmRNAs. Oxytocin has been proposed as a potential therapeutic agent for cancer (33), and the involvement of oxytocin-related proteins in cancer progression has also been evidenced. In Cassoni *et al.*'s study (34), nonapeptide oxytocin was found to play an important role in regulating cell proliferation and down-regulating the oxytocin receptor, thus indicating potential roles of oxytocin in primary tumors.

Thirty-nine genes in the ceRNA network were found to be significantly associated with ESCA prognosis. High TMTC3 expression was found to be linked to a poor prognosis of ESCA in this study (*Figure 4*). TMTC3 encodes a protein belonging to the transmembrane and tetratricopeptide repeat-containing protein family, which is mainly expressed in the skin and esophagus. TMTC3 is associated with reticulum stress response and is necessary for bronchial smooth muscle and alveolar myofibroblast development (35,36). No studies to date have focused on TMTC3 in ESCA, and its role in the disease still needs to be explored. Of the 39 prognostic genes in the ceRNA network, FBOX30 was identified as having the most significant association with ESCA prognosis (P=0.00137). FBOX30 encodes a member of F-box protein family and is most highly abundant in the endometrium . Mutation of FBOX30 is associated with the progression of nasopharyngeal carcinoma (37). The results of our study suggest that FBOX30 might also have potential value in

Table 1 Full list of DEmRNAs in ESCA samples compared with normal samples

miRNA ID	Log2FC	P value
let-7d	1.83	2.31E-07
miR-3911	3.02	1.26E-06
miR-144	5.03	5.50E-05
miR-1914	3.25	1.23E-04
miR-15a	4.99	2.10E-04
miR-16	6.34	2.83E-04
miR-93	3.1	1.16E-03
miR-4665	–1.93	1.35E-03
let-7i	1.74	1.39E-03
miR-1290	1.67	1.53E-03
miR-5196	3.29	2.25E-03
miR-107	3.04	2.34E-03
miR-130a	5.73	4.13E-03
miR-106b	4.4	4.34E-03
miR-23a	3.88	5.54E-03
miR-191	–2.43	7.14E-03
miR-19b	4.19	8.68E-03
miR-1238	–3.01	9.44E-03
miR-6069	–2.61	9.50E-03
miR-4721	3.3	1.05E-02
miR-25	4.06	1.13E-02
miR-4433	–2.83	1.20E-02
miR-185	3.2	1.34E-02
miR-21	2.5	1.34E-02
miR-130b	3.44	1.81E-02
miR-1228	–2.29	1.95E-02
miR-937	–1.73	2.10E-02
miR-1234	–2.24	2.44E-02
miR-451a	4.19	2.82E-02
miR-20a	2.32	2.85E-02
miR-3676	–2.43	3.13E-02
miR-6508	–3.4	3.44E-02
miR-6515	–2.41	3.47E-02
miR-345	2.41	4.43E-02
miR-3648	–2.22	4.96E-02

Log2FC represents log2(fold change). ESCA, esophageal cancer. DEmRNAs, differentially expressed miRNAs.

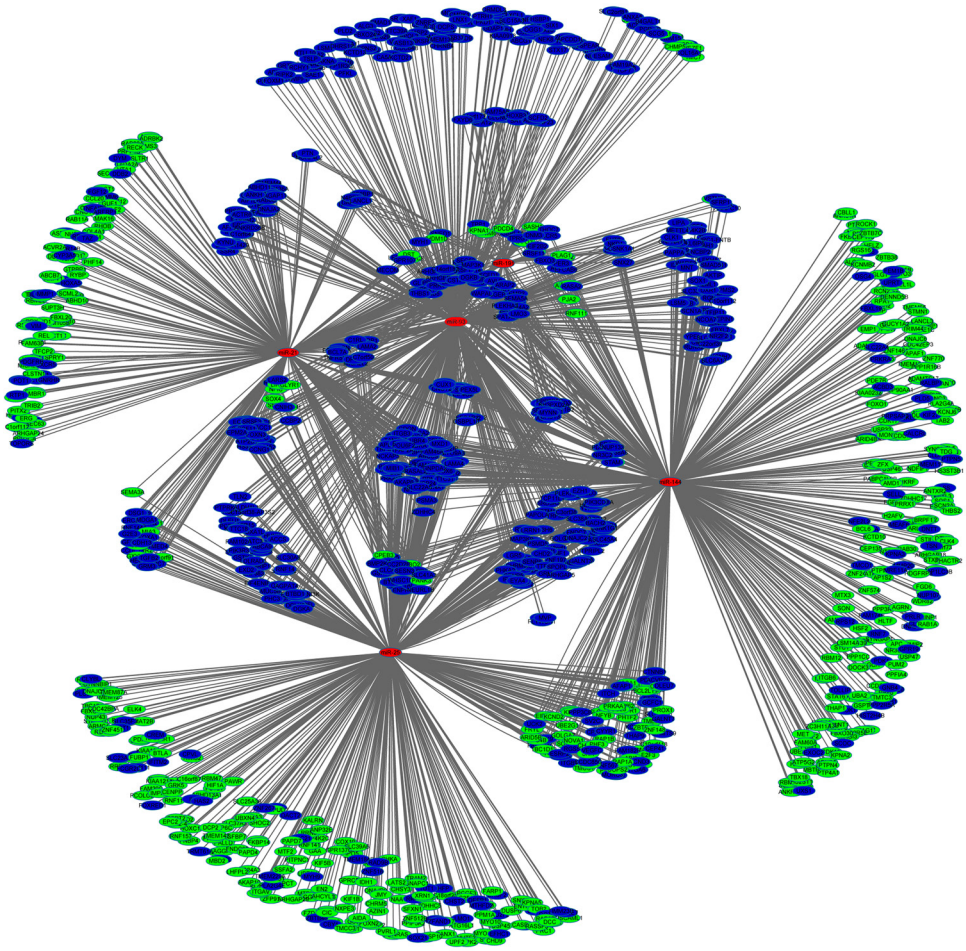

Figure 3 CeRNA network consisting of DElncRNAs, DEmiRNAs, and DEmRNAs. Red, blue, and green circles represent miRNAs, lncRNAs, and mRNAs, respectively. CeRNA, competing endogenous RNA; DElncRNAs, differentially expressed lncRNAs; DEmiRNAs, differentially expressed miRNAs; DEmRNAs, differentially expressed miRNAs.

ESCA for diagnosis and as a treatment target.

In conclusion, for the first time, we conducted a comprehensive analysis of lncRNA, miRNA, and mRNA expression profiles in ESCA and identified several significant known and novel prognostic biomarkers. Our findings could aid in improving the early diagnosis and

Table 2 Genes from the ceRNA network significantly associated with ESCA prognosis

Gene	P value	HR
FBXO30	0.001372	1.035714
PPP3R1	0.002612	1.111111
NCOA3	0.004158	0.965517
NFYB	0.004324	0.78
CCNE2	0.004354	1.111111
GOLGA7	0.004698	0.78125
CREB1	0.004975	1.035714
TOP1	0.005199	0.583333
IRS2	0.005324	0.9
RGS16	0.006564	0.9
ABCB7	0.009548	0.676471
HLTF	0.011359	0.965517
UBXN4	0.012267	0.965517
CHST7	0.015632	0.965517
LSM14A	0.019227	0.965517
EIF5A2	0.019846	0.83871
RCN2	0.020843	0.78125
SNAPC1	0.021467	1.478261
GCLM	0.021503	1.035714
CDC42EP3	0.024927	1.192308
NEDD4	0.025207	0.83871
KCNJ6	0.027246	0.810867
FAM60A	0.028846	0.676471
TDG	0.029623	0.9
CDK19	0.030387	0.83871
DCP2	0.031228	0.9
NKRF	0.034102	0.83871
TRIM23	0.034606	1.308132
TMTC3	0.035199	0.73
MAGI3	0.0363	1.111111
CXCL10	0.036416	0.965517
STMN1	0.039097	1.28
CYB5R4	0.042334	0.676471
MBTPS2	0.042671	0.78125
NDFIP1	0.043983	0.727273

Table 2 (*continued*)

Table 2 (*continued*)

Gene	P value	HR
VTA1	0.044488	0.676471
MAT2B	0.045206	0.9
RRN3	0.045968	1.035714
PHF6	0.048985	0.9

CeRNA, competing endogenous RNA; ESCA, esophageal cancer; HR, hazard ratio.

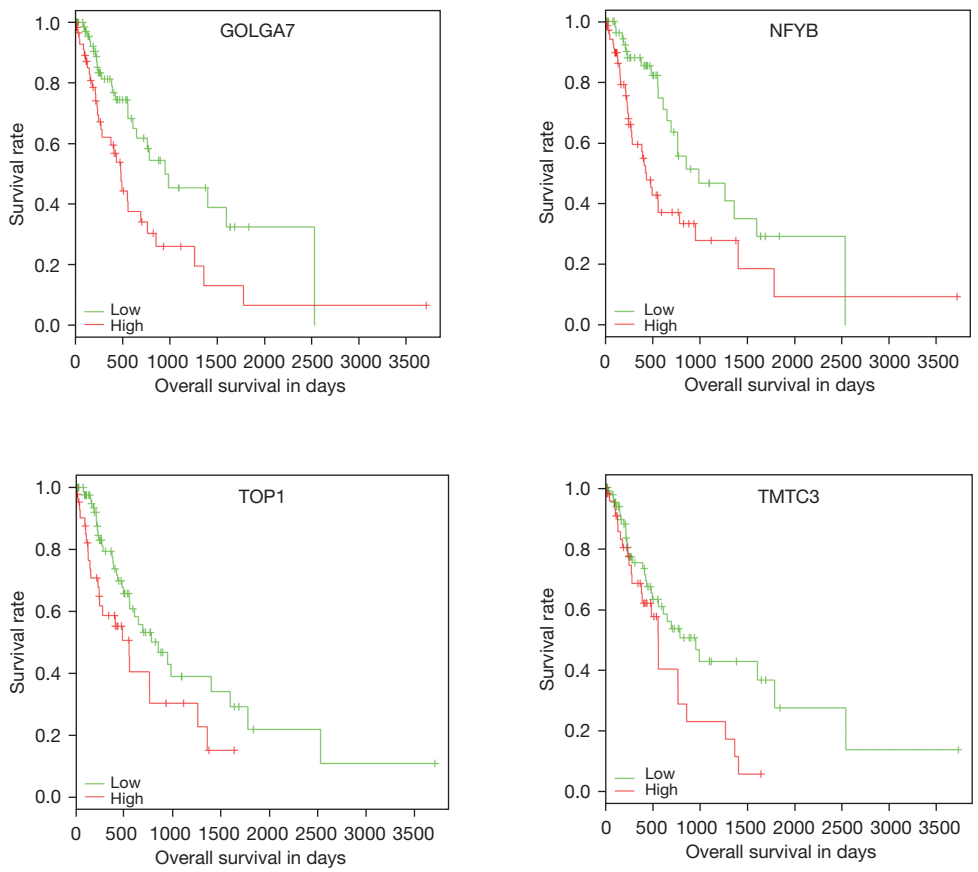

Figure 4 Kaplan-Meier survival curves for genes significantly associated with ESCA prognosis. Samples were divided into two groups based on the median expression value of a specific gene. Green and red lines represent samples with lower and higher expression values, respectively; plus sign represents a censored value. ESCA, esophageal cancer.

treatment of ESCA.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-4478). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The Affiliated Tumor Hospital of Nantong University (No. 2020811521).

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