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Original Research Article

# ExplORRNet: An interactive web tool to explore stage-wise miRNA expression profiles and their interactions with mRNA and lncRNA in human breast and gynecological cancers

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ABSTRACT

*Background:* MicroRNAs (miRNAs) are key regulators of gene expression that have been implicated in gynecological and breast cancers. Understanding the cancer stage-wise expression patterns of miRNAs and their interactions with other RNA molecules in cancer is crucial to improve cancer diagnosis and treatment planning. Comprehensive web tools that integrate data on the transcriptome, circulating miRNAs, and their validated targets to derive beneficial conclusions in cancer research are lacking.

*Methods:* Using the Shiny R package, we developed a web tool called ExplORRNet that integrates transcriptomic profiles from The Cancer Genome Atlas and miRNA expression data derived from various sources, including tissues, cell lines, exosomes, serum, and plasma, available in the Gene Expression Omnibus database. Differential expression analyses between normal and tumor tissue samples as well as different stages of cancer, accompanied by gene enrichment and survival analyses, can be performed using specialized R packages. Additionally, a miRNA-messenger RNA (mRNA)-long non-coding RNA (lncRNA) networks are constructed to identify regulatory modules.

*Results:* Our tool identifies cancer stage-wise differentially regulated miRNAs, mRNAs, and lncRNAs in gynecological and breast cancers. Survival analysis identifies miRNAs associated with patient survival, and functional enrichment analysis provides insights into dysregulated miRNA-related biological processes and pathways. The miRNA–mRNA–lncRNA networks highlight interconnected regulatory molecular modules driving cancer progression. Case studies demonstrate the utility of the ExplORRNet for studying gynecological and breast cancers.

*Conclusion:* ExplORRNet is an intuitive and user-friendly web tool that provides a deeper understanding of dysregulated miRNAs and their functional implications in gynecological and breast cancers. We hope our ExplORRNet tool has potential utility among the clinical and basic researchers and will be beneficial to the entire cancer genomics community to encourage and facilitate mining the rapidly growing public databases to progress the field of precision oncology. The ExplORRNet is available at https://mirna.cs.ut.ee.

## 1. Introduction

MicroRNAs (miRNAs) are small non-coding RNA (ncRNA) molecules consisting of 20–22 nucleotides. miRNAs have emerged as key regulators of gene expression in various cellular processes and a wide range of diseases [1,2]. miRNAs regulate gene expression by binding to the 3′UTR region of the target mRNA sequence [3]. This binding may lead to the translational repression or degradation of the target mRNA [4]. Moreover, miRNAs form a complex network with their target genes

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**Nomenclature**

| | |
|---|---|
| ExplORRNet | **E**xplorer of **O**ncology-**R**elevant mi**R**NA-mRNA-lncRNA **N**etwork |
| DEmiRNAs | Differentially regulated miRNAs |
| c-miRNAs | circulating miRNAs |
| TCGA | The Cancer Genome Atlas |
| GEO | Gene Expression Omnibus |
| UCEC | Uterine corpus endometrial carcinoma |
| UCS | Uterine carcinosarcoma |
| CESC | Cervical squamous cell carcinoma and endocervical adenocarcinoma |
| OV | Ovarian serous cystadenocarcinoma |
| BRCA | Breast invasive carcinoma |
| GDC | Genomics Data Commons |
| FIGO | Federation of Gynecology and Obstetrics |
| AJCC | American Joint Committee on Cancer |
| CRAN | The Comprehensive R Archive Network |
| HPA | The Human Protein Atlas |
| HP | Human Phenotype Ontology |
| WP | WikiPathways |
| DEcircmiR | Differentially regulated c-miRNAs |

in the pelvic region, including the uterus/endometrium, ovaries, cervix, vulva, and vagina, and breast cancer pose a significant health burden to women worldwide [9]. Aberrant expression of miRNAs in the above-mentioned cancers is of pathological importance because it influences critical aspects, such as the proliferation, survival, metastasis, and chemoresistance of tumors as well as the tumor microenvironment [9]. Altered miRNA expression has been associated with cancerous tissues, cancer metastasis, and various stages and subtypes of cancer [10]. Consequently, miRNAs have emerged as potential diagnostic and prognostic markers for gynecological cancers and their subtypes.

Notably, miRNAs often engage in crosstalk with other ncRNAs, such as long ncRNAs (lncRNAs), resulting in intricate molecular interactions. These interactions, called triplets (miRNA–mRNA–lncRNA interactions), can disrupt gene expression patterns and contribute to tumorigenesis [11]. lncRNAs and miRNAs together control the expression of mRNAs, which can also affect the expression of ncRNAs [11]. These lncRNAs are called competing endogenous RNAs (ceRNAs). The networks formed by ceRNAs involve specific binding sites, leading to the regulation of miRNA abundance and activity and subsequent gene repression. These ceRNA networks have been implicated in cancer progression [12,13].

Microarray and high-throughput techniques, such as RNA sequencing, have facilitated the study of miRNAs, revealing multiple mature miRNA sequences arising from a single pre-miRNA [14]. These miRNA variants, called isomiRs, exhibit sequence substitutions, insertions or deletions, non-templated additions at the 3′ end, and variations in 5′ and/or 3′ cleavage. Recent evidence suggests that isomiRs are not randomly distributed, implying their potential regulatory and functional significance [14]. IsomiRs are biologically relevant partners and downstream effectors, thereby exerting profound control over biological pathways [5]. Dysregulation of miRNAs has been implicated in the tumorigenesis of different types of cancers [6–8].

Breast cancer and gynecological cancers originating from the organs

**Table 1**
Clinical data fields for the five cancer types. Bcr_patient_barcode field was used to identify common samples in all three data types (miRNA/mRNA/lncRNA) from miRNAseq and RNASeq datasets. Stage_event_clinical_stage field was used to annotate patients with clinical stage information. Here, Stage IA, IA1, IA2, IB, IC are defined as Stage I. Stage II, IIA, IIA1, IIA2, IIB, IIC are defined as Stage II. Stage III, IIIA, IIIB, IIIC, IIIC1, IIIC2 are defined as Stage III. Stage IV, IVA, IVB are defined as Stage IV.

| Clinical data | TCGA-UCEC | TCGA-UCS | TCGA-CESC | TCGA-OV | TCGA-BRCA |
|---|---|---|---|---|---|
| bcr_patient_barcode | N = 596 | N = 65 | N = 315 | N = 590 | N = 1174 |
| vital_status | Alive:548, Dead:48 | Alive:31, Dead:34 | Alive:254, Dead:61 | Alive:284, Dead:303 | Alive:1062, Dead:112 |
| days_to_last_followup | Min: −13.0<br>Median: 404.0<br>Max: 5691.0<br>NA: 49 | Min: 0.0<br>Median: 497.0<br>Max:2841.0<br>NA: 33 | Min: 0.0<br>Median: 186.0<br>Max:5957.0<br>NA:61 | Min: 0.0<br>Median: 809.0<br>Max:5481.0<br>NA: 72 | Min: −7.0<br>Median: 360.0<br>Max:7067.0<br>NA: 112 |
| days_to_death | Min: 50.0<br>Median: 548.5<br>Max. :3251.0<br>NA: 548 | Min: 0.0<br>Median: 444.5<br>Max. :3115.0<br>NA: 31 | Min: 14.0<br>Median: 582.0<br>Max. :4086.0<br>NA: 254 | Min: 8.0<br>Median:1021.0<br>Max. :4624.0<br>NA: 288 | Min: 0<br>Median:1223<br>Max. :4456,<br>NA:1062 |
| age_at_initial_pathologic_diagnosis | Min:31.00<br>Median:64.00<br>Max:90.00 | Min. :51.00<br>Median:69.00<br>Max. :90.00 | Min. :20.00<br>Median:47.00<br>Max. :88.00 | Min. :26.00<br>Median:59.00<br>Max. :89.00 | Min. :26.00<br>Median:59.00<br>Max. :90.00 |
| stage_event_clinical_stage | Stage I: 2, Stage IA:155, Stage IB:136, Stage IC: 24 | Stage IA:11, Stage IB:7, Stage IC: 1 | Stage I: 5, Stage IA1, Stage IA1: 1, Stage IA2: 1, Stage IB: 38, Stage IB1: 78, Stage IB2: 38 | Stage I: 0 | NA |
| | Stage II: 26, Stage IIA: 6, Stage IIB: 12 | Stage II: 2, Stage IIA: 1, Stage IIB: 1 | Stage II: 5, Stage IIA: 9, Stage IIA1: 5, Stage IIA2: 7, Stage IIB: 40 | Stage IIA: 3, Stage IIB: 5, Stage IIC: 20 | NA |
| | Stage III: 2, Stage IIIA: 35, Stage IIIB: 4, Stage IIIC: 34, IIIC1: 23, IIIC2: 20 | Stage III: 2, Stage IIIA: 2, Stage IIIB: 1, Stage IIIC: 4<br>Stage IIIC1: 4, Stage IIIC2: 5 | Stage III: 1, Stage IIIA: 3, Stage IIIB: 40 | Stage IIIA: 7, Stage IIIB: 22, Stage IIIC: 352 | NA |
| | Stage IV: 3, Stage IVA: 3, Stage IVB: 19 | Stage IVB:9 | Stage IVA: 9, Stage IVB 13 | Stage IV: 79 | NA |
| stage_event_pathologic_stage | NA | NA | NA | NA | Stage I: 86, Stage IA: 78<br>Stage II: 5, Stage IIA: 339, Stage IIB: 243<br>Stage III: 2, Stage IIIA: 147, Stage IIIB: 23, Stage IIIC: 62<br>Stage IV: 13 |

**Table 2**
Sample number in each group for the five cancer types.

| Cancer | Normal | Stage I | Stage II | Stage III | Stage IV | Stage information |
|---|---|---|---|---|---|---|
| TCGA-UCEC | 35 | 341 | 51 | 130 | 29 | Clinical staging system |
| TCGA-UCS | – | 21 | 5 | 20 | 10 | Clinical staging system |
| TCGA-CESC | 3 | 162 | 69 | 45 | 21 | Clinical staging system |
| TCGA-OV | – | 1 | 21 | 292 | 57 | Clinical staging system |
| TCGA-BRCA | 113 | 182 | 627 | 249 | 20 | Pathological staging system |

that cooperate with canonical miRNAs and target pathways involving functionally related genes [14]. The heterogeneity of miRNA isoforms, in terms of length and sequence, can lead to modifications in the seed sequence, resulting in a shift in the targetome [15].

MiRNAs are detected in extracellular body fluids, including exosomes, macrovesicles, and apoptotic bodies, either alone or in complex with AGO2 proteins. Notably, these circulating miRNAs (c-miRNAs) have been implicated in oncogenic mechanisms and serve as promising non-invasive biomarkers for cancer [16,17]. For example, miRNA expression patterns in the serum of patients with ovarian cancer have been shown to differentiate between high- and low-risk groups [18]. The presence of miR-1290 in the serum exosomes of patients with epithelial ovarian cancer holds potential as a biomarker for distinguishing malignant from benign ovarian neoplasms [19].

Databases, such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO), are publicly available for the identification of miRNA biomarkers in cancer. Bioinformatics and statistical tools play crucial roles in the functional analysis of miRNA biomarkers, including target prediction, functional enrichment analysis, and survival analysis [20]. Numerous R packages and web tools have been developed for the functional prediction and annotation of miRNA targets in various tissue contexts, cell types, and pathological conditions [21]. Publicly available resources containing transcriptomic profiles of gynecological cancer patients and cell lines offer valuable opportunities for exploring and identifying potential biomarkers, thereby enhancing therapeutic approaches, and facilitating early-stage diagnosis. Although several web tools are available for miRNA analysis, more specific insights into breast and gynecological cancers are needed, enabling the stage-wise exploration of dysregulated RNA networks. To address this issue, we present ExplORRNet, an R Shiny based web interface designed to facilitate the exploration of miRNA, lncRNA, and mRNA expression profiles in gynecological cancers and breast cancer. The latter was included as a

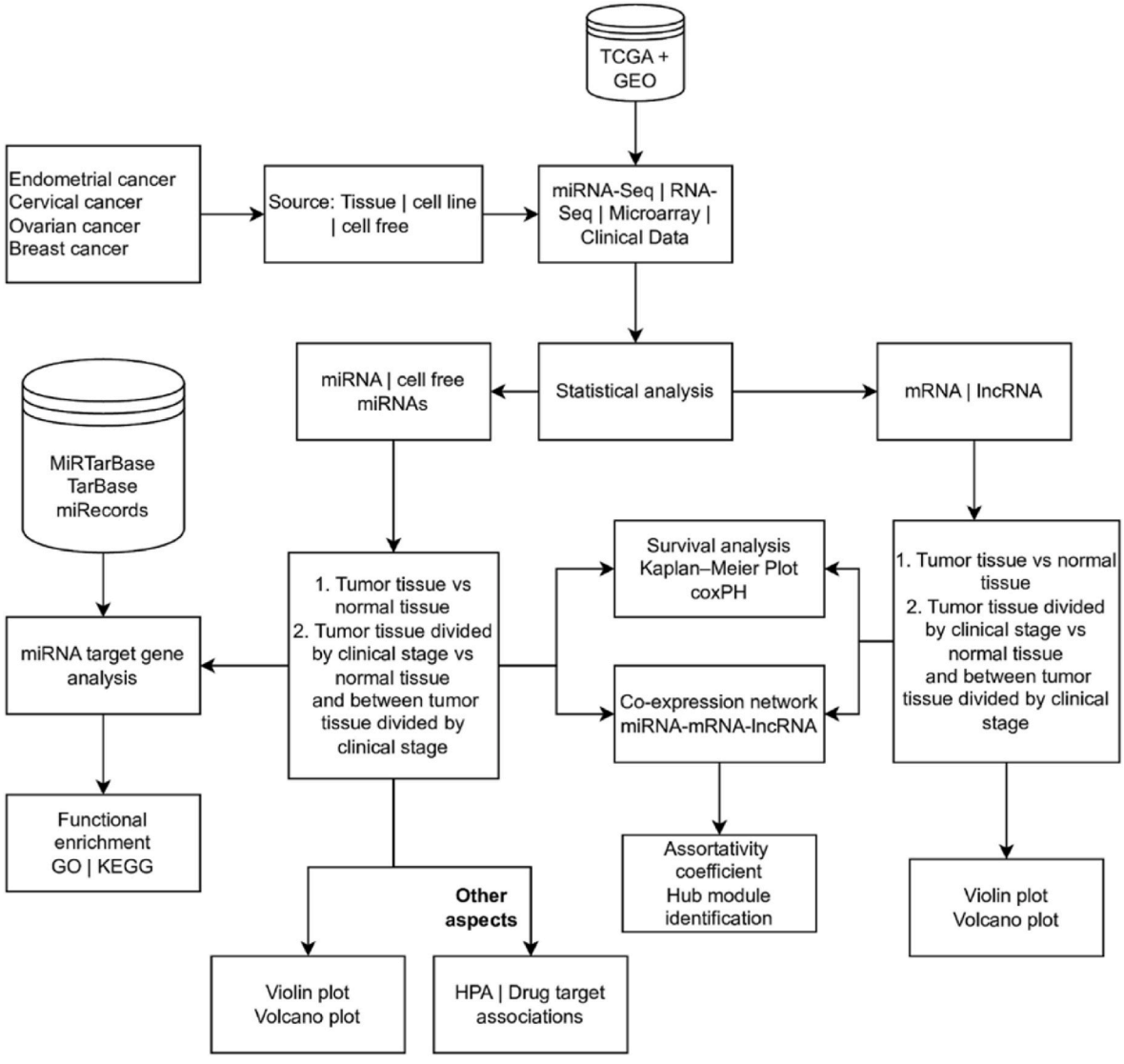



**Fig. 1.** Schematic representation depicting user interface and functionality of ExplORRNet.

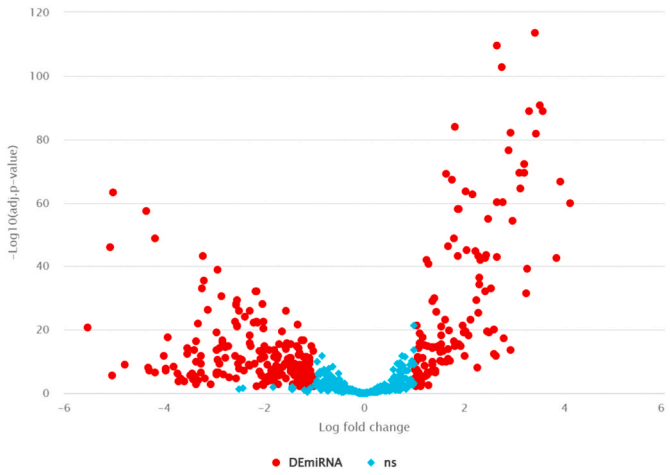



**Fig. 2.** An example of the Volcano plot showing DEmiRNAs between the normal and tumor samples of TCGA-UCEC. The red points are DEmiRNAs, and the blue points indicate the non-significant set of miRNAs (p-value = 0.01 & | Log2FC| = 1).

predominant women-specific cancer, which shares similarities in hormonal regulation [22] and risk factors [23] with gynecological cancers. Our tool utilizes data from TCGA and GEO, offering a user-friendly and interactive platform for investigating RNA expression patterns in gynecological cancers and breast cancer in tissue, extracellular space, and cell lines. Thus, our integration of patient-derived cancer profiles and cell line data enhances the comprehensiveness of our analyses, contributing to a deeper understanding of cancer biology and potential therapeutics.

## 2. Materials and methods

We used transcriptomic profiles consisting of 2504 samples from five cancers, including uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), ovarian serous cystadenocarcinoma (OV), and breast invasive carcinoma (BRCA), from the TCGA program available on the Genomic Data Commons Data Portal (GDC) (https://portal.gdc.cancer.gov/). Next, the raw read counts of miRNA isoform and RNA expression for the above-mentioned tumors and matched normal samples were downloaded. RNA expression data were grouped into protein-coding genes and long non-coding gene expression.

Furthermore, the clinical data (as outlined in Table 1) for the selected cancers was acquired by downloading XML files from the GDC web portal.

To download the transcriptome profiles and clinical data of the above-mentioned patients with cancer, we used the R package, TCGAbiolinks. Genes in the RNA-seq data were annotated using the Bioconductor R package biomaRt (v 2.54.1).

Gynecological cancer samples were staged using the Federation of Gynecology and Obstetrics (FIGO) system, and breast cancer samples were staged using the TNM (Tumor, Node, Metastasis) system maintained by the American Joint Committee on Cancer (AJCC). This categorization enabled pairwise differential analyses between tumor and normal tissues and among different cancer stages (I–IV). We created sample groups for miRNA isoform and RNA-Seq (protein-coding genes and lncRNA expression) for pairwise differential expression analysis (Table 2).

To identify the expression patterns of circulating miRNAs in patients with gynecological and breast cancer, we collected datasets from the GEO database. We used combinations of search terms to identify the datasets from GEO, such as "Circulating miRNAs/microRNAs and cancer," "Circulating miRNAs/microRNAs and gynecological cancer," "Extracellular miRNA/microRNAs and cancer/endometrial cancer/ovarian cancer/cervical cancer," "Exosome and microRNAs and cancer," "Plasma and microRNAs/miRNAs and cancer," and "Serum miRNAs/microRNAs and cancer."

Based on these search terms, we gathered datasets for endometrial, ovarian, cervical, and breast cancers. We included 1710 samples for expressions of c-miRNA and miRNA in tissues and cell lines.

### 2.1. Preprocessing and differential expression analysis

High-throughput sequencing counts of miRNA isoform data and protein-coding and lncRNA expression data collected from the GDC data portal were normalized using the calcNormFactors function from the

**Table 3A**
Targets of hsa-mir-106b-5p in TCGA-UCEC.

| Accession | miRNA ID | Target Symbol | TargetEntrez | Target Ensembl | Experiment | Support Type | Pubmed ID |
|---|---|---|---|---|---|---|---|
| MIMAT0000680 | hsa-miR-106b-5p | BCL2L2 | 599 | ENSG00000129473 | PAR-CLIP | Functional MTI (Weak) | 23446348 |
| MIMAT0000680 | hsa-miR-106b-5p | TMPO | 7112 | ENSG00000120802 | CLASH | Functional MTI (Weak) | 23622248 |
| MIMAT0000680 | hsa-miR-106b-5p | ZNF532 | 55205 | ENSG00000074657 | PAR-CLIP | Functional MTI (Weak) | 22012620 |
| MIMAT0000680 | hsa-miR-106b-5p | MIDN | 90007 | ENSG00000167470 | PAR-CLIP//HITS-CLIP | Functional MTI (Weak) | 21572407 |
| MIMAT0000680 | hsa-miR-106b-5p | WDR53 | 348793 | ENSG00000185798 | HITS-CLIP | Functional MTI (Weak) | 23313552 |
| MIMAT0000680 | hsa-miR-106b-5p | SERF1B | 728492 | ENSG00000205572 | PAR-CLIP | Functional MTI (Weak) | 22012620 |
| MIMAT0004672 | hsa-miR-106b-3p | PTEN | 5728 | ENSG00000171862 | qRT-PCR//Western blot | Functional MTI | 28288092 |

**Table 3B**
Targets of hsa-let-7f-5p, hsa-let-7f-3p in TCGA-OV.

| Accession | miRNA ID | Target Symbol | Target Entrez | Target Ensembl | Experiment | Support Type | Pubmed ID |
|---|---|---|---|---|---|---|---|
| MIMAT0000067 | hsa-let-7f-5p | ADH5 | 128 | ENSG00000197894 | PAR-CLIP | Functional MTI (Weak) | 26701625 |
| MIMAT0000067 | hsa-let-7f-5p | NUCB2 | 4925 | ENSG00000070081 | PAR-CLIP | Functional MTI (Weak) | 23592263 |
| MIMAT0000067 | hsa-let-7f-5p | RRM2 | 6241 | ENSG00000171848 | PAR-CLIP | Functional MTI (Weak) | 21572407 |
| MIMAT0000067 | hsa-let-7f-5p | SP1 | 6667 | ENSG00000185591 | CLASH | Functional MTI (Weak) | 23622248 |
| MIMAT0000067 | hsa-let-7f-5p | ZBTB5 | 9925 | ENSG00000168795 | PAR-CLIP | Functional MTI (Weak) | 23592263 |
| MIMAT0000067 | hsa-let-7f-5p | RAD18 | 56852 | ENSG00000070950 | PAR-CLIP | Functional MTI (Weak) | 21572407 |
| MIMAT0000067 | hsa-let-7f-5p | ZNF611 | 81856 | ENSG00000213020 | HITS-CLIP | Functional MTI (Weak) | 23706177 |
| MIMAT0000067 | hsa-let-7f-5p | MTSS2 | 92154 | ENSG00000132613 | CLASH | Functional MTI (Weak) | 23622248 |
| MIMAT0000067 | hsa-let-7f-5p | C5orf51 | 285636 | ENSG00000205765 | PAR-CLIP | Functional MTI (Weak) | 23446348 |
| MIMAT0004482 | hsa-let-7b-3p | NRBF2 | 29982 | ENSG00000148572 | PAR-CLIP | Functional MTI (Weak) | 20371350 |

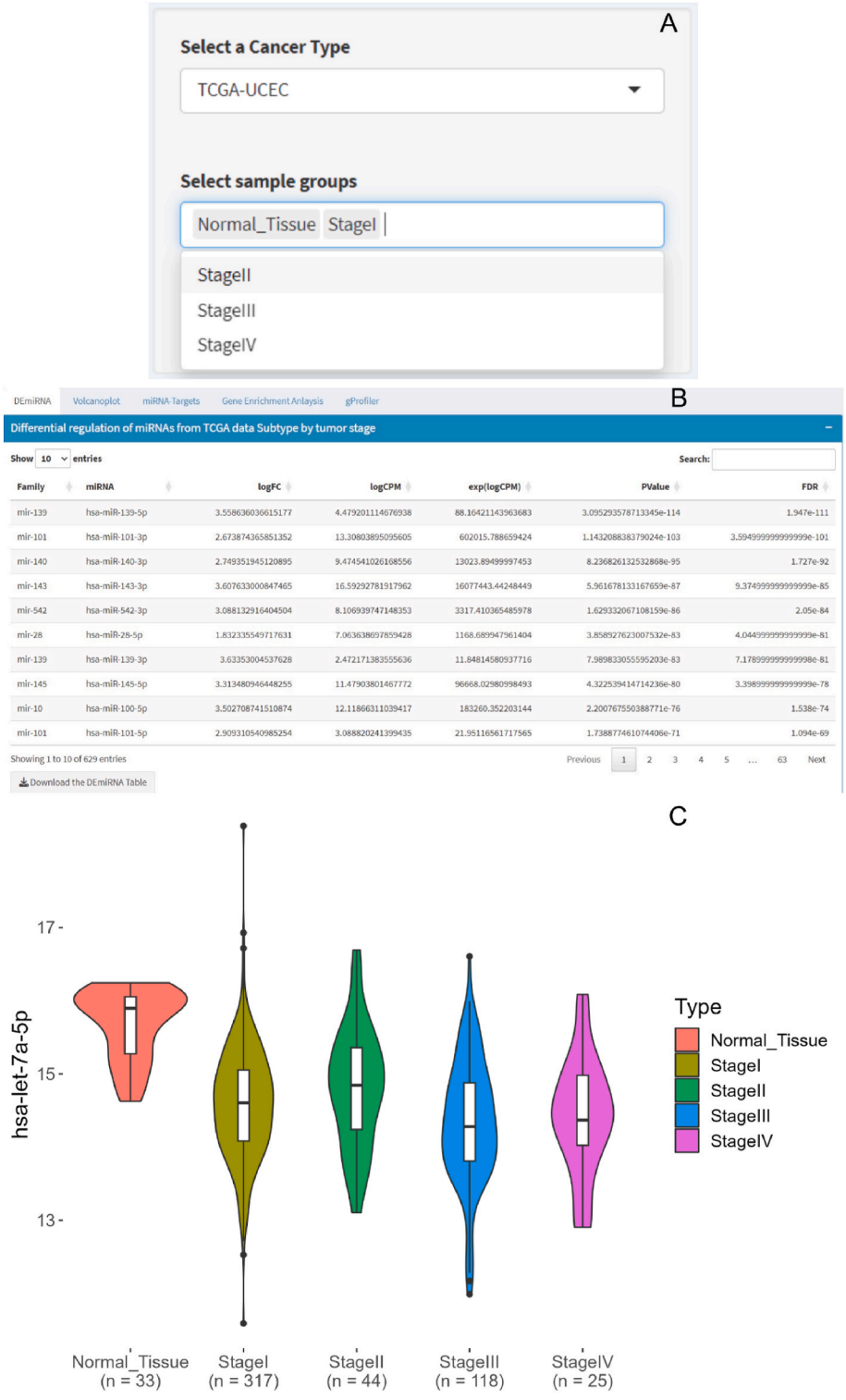



**Fig. 3.** Pairwise DEmiRNA analysis between the normal and tumor samples grouped by clinical stage (Stage I to IV). (A) Option to select cancer type and sample group to get DEmiRNAs. Here the normal sample group is compared against clinical stage I group. (B) Table of DEmiRNAs after selecting the normal sample groups and clinical stage I group. (C) Violin plot of has-let-7a-5p expression in TCGA-UCEC. Number of samples per group is denoted by 'n' in the bracket.

Bioconductor R package edgeR (v 3.40.2), and the filterByExpr function from the edgeR package was used to filter the lowly expressed miRNAs, genes, and lncRNAs to exclude them from differential expression analysis. We used glmFit and glmLRT functions from the edgeR package to identify differentially regulated miRNAs, protein-coding genes, and lncRNAs. p-values were adjusted using a false discovery rate (FDR) correction. Raw Affymetrix microarrays from the GEO datasets were normalized and background-corrected using the rma() function from the Bioconductor R package affy (v 1.50.0). Raw data from the Agilent microarrays were normalized and background-corrected using the Bioconductor R package limma (v 3.28.14). Log2-transformed data were then fitted to a linear model using the lmFit() function in limma (v 3.28.14).

Interactive volcano plots of the differential expression of miRNAs

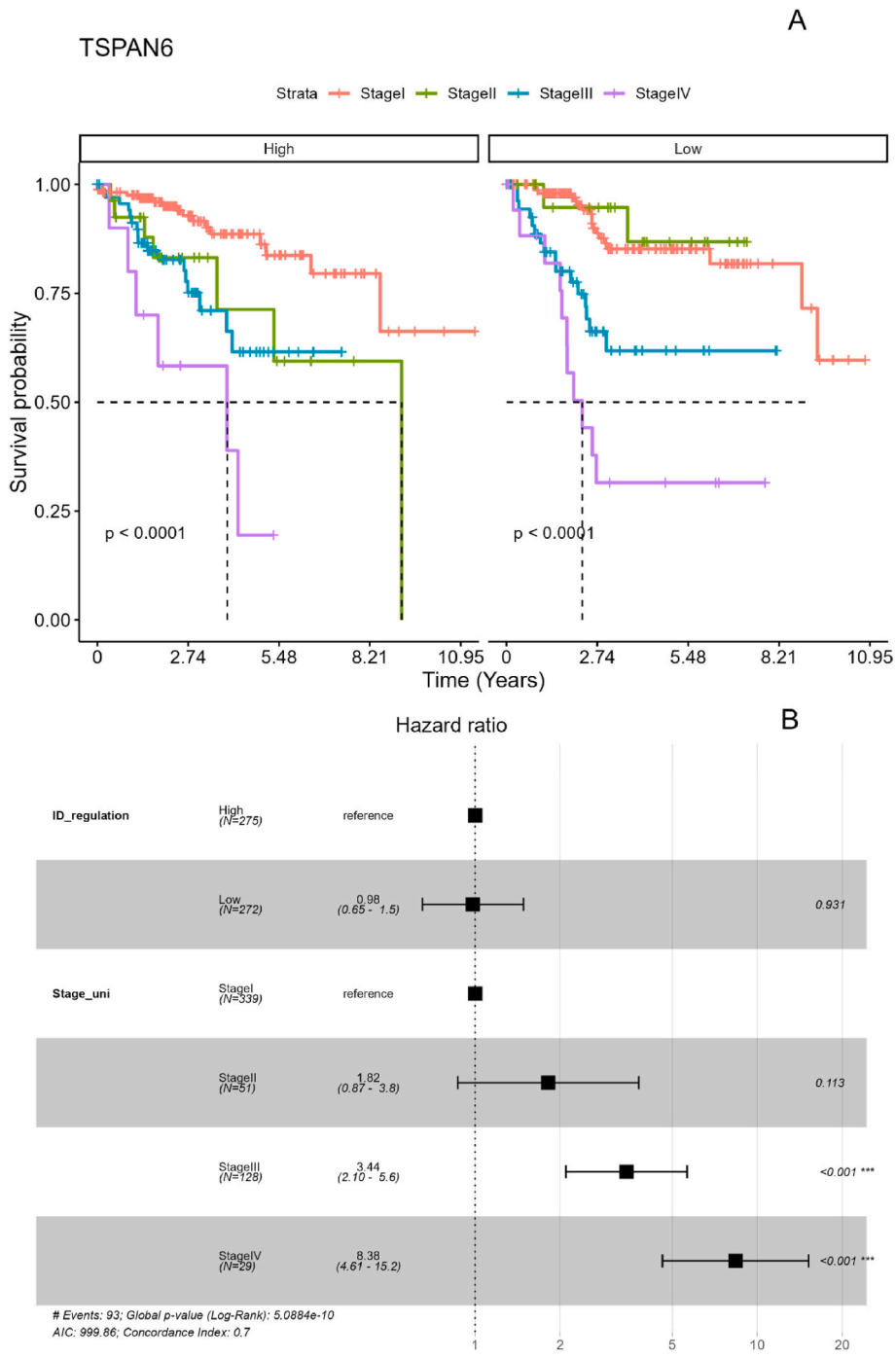



**Fig. 4.** Kaplan-Meier (A) and forest plot (B) for the gene *TSPAN6* showing connection to the patient survival in different clinical stages in TCGA-UCEC.

(DEmiRNAs), protein-coding genes, and lncRNAs were created using the CRAN R package highcharter (v 0.9.4).

### 2.2. Survival analysis

The survival curve was fitted for each miRNA expression, and a Kaplan–Meier plot (KM-plot) was created. The log-rank test using the survdiff() function was used to determine the survival difference between the high and low expression of each miRNA. The univariate Cox proportional hazard model was fitted using the CRAN R package survival (v 3.4–0), and the ggsurvplot() and ggforest() functions from the CRAN R package survminer (v 0.4.9) were used to plot the KM-plot and forest plots, respectively.

For protein-coding genes and lncRNAs, survival analysis was performed analogously.

### 2.3. Collection of validated miRNA targets

Experimentally validated lists of targets of differentially regulated miRNAs were collected from three validated miRNA target databases: miRecords [24], miRTarBase [25,26], and TarBase [27]. The Bioconductor R package multiMiR (v 1.18.0) [28] was used to download


**Fig. 5.** The co-expression network of miRNA-mRNA-lncRNA in TCGA-UCEC was generated from the cancer stage-wise analysis panel. (A) Options to select cancer type, comparison groups, and selection of cutoff values (p-value, log2FC, and correlation cutoff). (B) Co-expression network generated for TCGA-UCEC from DEmiRNAs, DEGs, and DElncRNAs selected by cutoff values (p-value = 0.01, |log2FC| = 1 & correlation cutoff = 0.75). (C) Edge table showing the connections of has-miR-449b-3p. The edge table contains the log2FC of miRNA (−3.63) and connected genes (FOXN4 = −2.52, CDC20B = −3.73 & AZU1 = −1.68).

data from the three databases using default parameters.

### 2.4. Functional annotations: pathway and GO enrichment analyses

Differentially regulated miRNA target genes generated from the miRNA target panel were used as inputs for GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses. The enrichGO and enrichKEGG functions of the Bioconductor R package clusterProfiler [29] (v 4.4.4) and the gost function of the CRAN R package gProfiler2 [30] (v 0.2.1) were used for functional enrichment analysis. The top enriched terms were visualized as a dotplot function using the Bioconductor R package enrichplot (v 1.18.3).

### 2.5. miRNA–mRNA–lncRNA network and hub module identification

To construct miRNA–mRNA–lncRNA network, we first calculated the Pearson correlation coefficients between differentially regulated miRNAs, mRNAs, and lncRNAs. Next, the miRNA–mRNA–lncRNA

**Table 4**
Table of tool comparison with other existing tools.

| Tool Name | Pan-Cancer | miRNA expression pattern exploration | miRNA Target and interactions | Functional annotations | Network | Survival | mRNA and lncRNA |
|---|---|---|---|---|---|---|---|
| ExplORRNet | No: BRCA, UCEC, UCS, CESC & OV | Pairwise: stages of cancer types | Validated targets & interactions: mRNA and lncRNA. | GO, KEGG & HPA | miRNA-mRNA-lncRNA network (correlation between differentially regulated biomolecules.) | CoxPH and log rank test, KM-plot for each biomolecule. | yes |
| miRNACancerMap (Tong, Ru, and Zhang 2018) | yes | Normal- tumor, subtype | yes | yes | Yes | no | no |
| miR-TV (Pan and Lin 2020) | yes | Normal-tumor | Predicted targets | no | No | no | Yes (miRNA target) |
| miRTissue (Fiannaca et al., 2018) | Yes | Normal-tumor | miRNA-target interactions in human tissues | yes | PPI network- drug target identification | no | no |
| OMCD (OncoMir cancer Database) (Sarver et al., 2018) | Yes (10000 cancer patients) | Normal-tumor, tumor-tumor & control-control | no | no | No | no | no |
| OncoMir (Wong et al., 2018) | yes | normal,-tumor, stage, grade, | Yes: miRNA-target correlation | no | No | Overall survival, miRNA-based survival signature | no |
| UALCAN (Chandrashekar et al., 2017) | yes | normal.-tumor, stage | yes | no | No | yes | yes |
| OncoLnc (Anaya 2016) | yes | yes | no | no | No | yes | yes |

correlation matrix with correlation coefficient $|r| > 0.5$ was used to create a network graph using the CRAN R package igraph (v 1.4.1). The Fastgreedy network community identification method was used to identify hub networks from the co-expression network of miRNA–mRNA–lncRNAs. The CRAN R package visNetwork (v 2.1.0) was used to visualize the co-expression networks.

### 2.6. miRNA-drug associations and Human Protein Atlas pathology data

Experimentally supported miRNAs and their drug associations present in gynecological and breast cancers were collected from the NoncoRNA DB [31]. In total, 672 associations were included. From The Human Protein Atlas (HPA), we collected the pathology data to explore miRNA target gene protein expression and their relevance in cancer prognosis.

### 2.7. Tool implementation

The Shiny R package was used to build the web application. A Docker image of the Shiny application was created to host the application on the public domain.

## 3. Results

### 3.1. Tool interface

ExplORRNet enables the exploration of miRNA or gene expression profiles from TCGA datasets for gynecological cancers and breast cancer tissues, as well as circulating miRNA expression profiles from blood, serum, plasma, and exosome, as shown in Fig. 1.

Users can select cancer types from the following options: TCGA-BRCA, TCGA-UCEC, TCGA-UCS, TCGA-CESC, and TCGA-OV. The DEmiRNAs and genes (coding and long non-coding genes) can also be explored by cancer subtypes defined according to the clinical staging systems of the given cancer type.

The sidebar panel of the tool interface has three sections for exploring the miRNAs, mRNAs, and lncRNAs. Each section is further categorized into two parts. The first part enables the exploration of differential expression between normal and tumor tissues. The second part enables the interactive selection of groups of samples according to the clinical stage of cancer to perform pairwise differential expression between the stages (or between normal tissue and any cancer stage).

Violin plots of miRNA or gene expression can be generated by selecting the miRNA/mRNA/lncRNA ID from the list, as shown in Supplementary Figs. S1A, S1C, and S1E. miRNA/mRNA/lncRNA expression in cancer stages can be visualized from the cancer stage-wise analysis tab, as shown in Supplementary Figs. S1B, S1D, and S1F. Supplementary Fig. S1G shows a violin plot for c-miRNA expression in the GEO dataset GSE178629.

### 3.2. miRNA/mRNA/lncRNA differential expression analysis

After data preprocessing, the DEmiRNAs are calculated on the tool interface and output as a table along with information regarding the miRNA family, logCPM, exp(logCPM), fold change value, p-value, and adjusted p-value (Supplementary Fig. S2). DEmiRNAs can be visualized as a volcano plot, and the p-values and $\log_2$ fold-change cutoff values can be adjusted by user choice, as shown in Fig. 2. Similar to miRNAs, differential expression analysis can also be performed for mRNAs and lncRNAs in gynecological and breast cancers by comparing the expression between normal and tumor tissues or the tumor tissue divided by clinical stages. Volcano plots of mRNA/lncRNA profiles can also be generated.

### 3.3. Extraction of miRNA target genes

Validated targets for the differentially regulated miRNAs (adjusted p-value $\leq 0.05$, $|\log \text{fold change}| > 0.5$) were obtained from the miRTarBase, miRecords, and TarBase databases using the multiMiR package. For any selected differential expression comparison, a validated miRNA target gene table will be generated from the three databases, as shown in Supplementary Figs. S3A and S3B. Tables 3A and 3B lists the target genes in TCGA-UCEC and TCGA-OV.

### 3.4. Gene ontology and pathway enrichment analysis of target genes of DEmiRNAs

This tool also provides functional annotations of miRNA target genes. Significantly enriched biological processes, cellular components, molecular functions, and KEGG pathways of the target genes of DEmiRNAs are plotted in the form of a dot plot, as shown in Fig. 8A- Fig. 8D. Furthermore, other biologically relevant proteins from the Human

**Table 5**
miRNA regulation in TCGA-UCEC.

| miRNA | Family | upregulation | downregulation | reference |
|---|---|---|---|---|
| has-mir-497-5p/3p | mir-497 | Normal Tissue<br>Normal tissue<br>Clinical stage I<br>Clinical stage II | Tumor tissue<br>Clinical stage I, II, III, IV<br>III, IV<br>III, IV | [37] |
| hsa-miR-23b-3p/5p | mir-23 | Normal Tissue<br>Normal Tissue | Tumor tissue<br>Clinical stage I, II, III, IV | [38] |
| hsa-miR-125b-5p | mir-10 | Normal Tissue<br>Normal Tissue | Tumor Tissue<br>Clinical stage I, II, III, IV | |
| hsa-miR-199a-3p | mir-199 | Normal Tissue<br>Normal Tissue | Tumor Tissue<br>Clinical stage I, II, III, IV | [38] |
| hsa-miR-221-3p | mir-221 | Normal Tissue<br>Normal Tissue | Tumor Tissue<br>Clinical stage I, II, III, IV | [38] |
| hsa-miR-451a | mir-451 | Normal Tissue<br>Normal Tissue | Tumor Tissue<br>Clinical stage I, II, III, IV | [39] |
| hsa-miR-363-3p | mir-363 | Tumor tissue<br>Clinical stage I, II, III, IV<br>Clinical stage IV<br>Clinical stage IV<br>Clinical stage IV | Normal Tissue<br>Normal tissue<br>Clinical stage I<br>Clinical stage II<br>Clinical stage III | [39] |
| hsa-miR-940 | mir-940 | Tumor Tissue<br>Clinical stage I, II, III, IV | Normal Tissue<br>Normal Tissue | [39] |
| hsa-miR-1301-3p/5p | mir-1301 | Tumor Tissue<br>Clinical stage I, II, III, IV | Normal Tissue<br>Normal Tissue | [39] |
| hsa-miR-18a-3p/5p | mir-17 | Tumor Tissue<br>Clinical Stage I, II, III, IV<br>III | Normal Tissue<br>Normal Tissue<br>SI | [40] |
| hsa-miR-18a-3p | mir-17 | Tumor Tissue<br>Clinical Stage I, II, III, IV<br>Clinical stage III<br>Clinical stage IV | Normal Tissue<br>Normal Tissue<br>Clinical stage I<br>Clinical stage SI | [40] |
| hsa-miR-18b-3p/5p | mir-17 | Tumor Tissue<br>Clinical Stage I, II, III, IV | Normal Tissue<br>Normal Tissue | [40] |
| hsa-miR-449c-5p | mir-449 | Tumor tissue<br>Clinical Stage I, II, III, IV | Normal Tissue<br>Normal Tissue | [40] |
| hsa-miR-1224-5p | mir-1224 | Tumor Tissue<br>Clinical Stage I, II, III, IV<br>Clinical stage I, II | Normal Tissue<br>Normal Tissue<br>Clinical stage III | [40] |
| hsa-miR-424-5p | mir-322 | Normal Tissue<br>Normal Tissue | Tumor Tissue<br>Clinical Stage I, II, III, IV | [40] |
| has-mir-101-3p/5p | mir-101 | Normal Tissue | Tumor Tissue | [41,42] |
| hsa-miR-106b-5p/3p | mir-17 | Tumor Tissue<br>Clinical Stage I, II, III, IV | Normal Tissue<br>Normal Tissue | [42,43] |
| hsa-miR-944 | mir-944 | Tumor Tissue<br>Clinical stage I, II, III, IV | Normal Tissue<br>Normal Tissue | [42,44] |

**Table 6**
miRNA regulation in TCGA-OV.

| miRNA | Family | upregulation | downregulation | reference |
|---|---|---|---|---|
| hsa-miR-19b-3p/1-5p | mir-19 | Clinical stage II | Clinical stage III, IV | [45–47] |
| hsa-let-7f-5p | let-7 | Clinical stage II | Clinical stage III, IV | |
| hsa-let-7b-3p | let-7 | Clinical stage II | Clinical stage III | |
| hsa-miR-323a-3p | mir-154 | Clinical stage III | Clinical stage IV | |
| hsa-miR-323b-3p | mir-154 | Clinical stage III | Clinical stage IV | |
| hsa-miR-128-3p | mir-128 | Clinical stage II | Clinical stage IV | |
| hsa-miR-486-3p | mir-486 | Clinical stage II | Clinical stage III, IV | |
| hsa-miR-98-5p | let-7 | Clinical stage II | Clinical stage III, IV | |
| hsa-miR-34a-5p | mir-34 | Clinical stage II | Clinical stage III | [47,48] |
| hsa-miR-34c-3p/5p, hsa-miR-34b-3p | mir-34 | Clinical stage III, IV | Clinical stage II | [47,48] |

Phenotype Ontology (HP), Human Protein Atlas (HPA), miRNAs, Reactome pathways, transcription factor (TF), and WikiPathways (WP) are generated using the gProfiler2 package, as shown in Supplementary Fig. S7.

### 3.5. Pairwise DEmiRNA analysis and visualization

Based on the classification by the clinical staging of the cancer type, users can opt for pairwise comparisons from the provided options, and the tool performs a differential expression analysis. The respective visualizations, as well as the DEmiRNA target gene information and enrichment analysis, are generated similarly as above. The option to select any two groups of samples for DEmiRNA analysis and DEmiRNA table as well as the has-let-7a-5p expression is visualized in the violin plot are shown in Fig. 3A- 3C respectively.

### 3.6. c-miRNA expression in gynecological and breast cancers

c-miRNA expression microarray and high-throughput sequencing data were collected from the GEO database. miRNA levels in blood plasma and serum and exosomal miRNA expression in gynecological and breast cancers were used. Similar to solid tumor tissue expression analysis, the expression patterns of miRNAs in the blood circulation, plasma, and serum of patients with gynecological and breast cancers can be explored and visualized as volcano or violin plots, as shown in Supplementary Figs. S4A-S4C. Target genes of differentially regulated circulating miRNAs (DEcircmiRs) are extracted from databases, including miRecords, miRTarBase, and TarBase, similar to those from TCGA data. Moreover, GO and KEGG pathway enrichment analyses for

**Table 7**
miRNA regulation in TCGA-BRCA.

| miRNA | Family | upregulation | downregulation | reference |
|---|---|---|---|---|
| hsa-miR-497-5p | mir-497 | Normal Tissue | Tumor Tissue, Clinical Stage I, II, III, IV | [49] |
| hsa-miR-200c-5p/3p | mir-8 | Tumor Tissue, Clinical Stage I, II, III, IV | Normal Tissue | |
| hsa-miR-141-5p/3p | mir-8 | Tumor Tissue, Clinical Stage I, II, III, IV | Normal Tissue | |
| hsa-miR-224-3p/5p | mir-224 | Normal Tissue | Tumor Tissue, Clinical Stage I, II, III, IV | [55] |
| | | Clinical stage II | Clinical Stage I | |
| hsa-miR-210-3p | mir-210 | Tumor Tissue, Clinical Stage I, II, III, IV | Normal Tissue | |
| | | Clinical Stage II, IV | Clinical Stage I | |
| hsa-miR-130a-3p | mir-130 | Normal Tissue | Tumor Tissue, Clinical Stage I, II, III, IV | |
| hsa-miR-30a-5p | mir-30 | Tumor Tissue, Clinical Stage I, II | Normal Tissue | [56] |
| hsa-miR-126-5p/3p | mir-126 | Normal Tissue | Tumor Tissue, Clinical Stage I, II, III, IV | |
| hsa-miR-140-3p | mir-140 | Normal Tissue | Tumor Tissue, Clinical Stage I, II, III, IV | |
| hsa-miR-206 | mir-1 | Normal Tissue | Clinical Stage I, II, III, IV | |
| | | Clinical stage II | Clinical Stage III | |
| hsa-miR-335-5p/3p | mir-335 | Normal Tissue | Clinical Stage I, II, III, IV | |

the target genes are also performed for DEcircmiRs, similar to Supplementary Figs. S3A and S3B.

### 3.7. Survival analysis

The overall patient survival probability as a KM-plot and a forest plot as a Cox proportional hazard model can be generated for miRNA/gene expression and the clinical staging of cancer types. miRNA/gene expression is separated into two groups: high and low expression, according to the median expression value in the selected cancer types (Fig. 4).

### 3.8. miRNA–mRNA–lncRNA co-expression analysis and hub network identification

A co-expression network comprising DEmiRNAs, differentially expressed genes, and differentially expressed lncRNAs was generated using a correlation matrix. The user interface enables the selection of cutoff values for the minimum correlation coefficient (ranging from −1 to −0.5 or 0.5 to 1), adjusted p-values by FDR (ranging from 0.001 to 0.05), and log2-fold change (ranging from −2 to −0.5 or 0.5 to 2). Only the edges satisfying the selected cutoff values were used to construct the network. To identify the hub module, the Fastgreedy method from the igraph package is applied. Each hub is represented by a unique color as shown in Fig. 5B and 7A.

The assortativity coefficient of the network, which measures the tendency of nodes to connect with similar or dissimilar nodes, is calculated after the hub module identification. A network with an assortativity coefficient (R) > 1 exhibits a tendency for hubs to connect with each other. A coefficient of <1 indicates a disassortative network in which hubs tend to avoid linking. An assortativity coefficient of zero represents a neutral network where nodes connect with an expected random probability. A visual representation of the network panel is shown in Fig. 5A–C.

### 3.9. Other aspects

miRNA and drug target association outputs can be generated using the tool interface, enabling users to explore miRNAs and their drug target associations for selected cancers, as shown in Supplementary Fig. S5. Users can select a specific cancer type from the drop-down list (including endometrium, ovary, cervix, and breast cancer tissues). Using the HPA database, the tool generates validated miRNA target genes and related pathological data. Additionally, a separate link to the HPA platform is provided in the table, which enables users to further explore selected proteins, as shown in Supplementary Fig. S6.

### 3.10. Comparing ExplORRNet with features and capabilities of existing tools

Compared to other web tools, ExplORRNet offers specialized features for BRCA, UCEC, UCS, CESC, and OV cancers, enabling the exploration of miRNA expression patterns at different cancer stages (Table 4). Moreover, our tool provides validated targets and interactions involving mRNA and lncRNAs, along with functional annotations, such as GO, KEGG, and HPA. Furthermore, users can construct comprehensive miRNA–mRNA–lncRNA networks that uncover correlations between differentially regulated biomolecules. Additionally, ExplORRNet performs survival analysis using CoxPH, log-rank tests, and KM-plots.

Other tools such as miRNACancerMap [10] focus on normal-vs-tumor miRNA expression, miR-TV [21] predicts miRNA targets, and miRTissue [32] offers miRNA-target interactions in human tissues, incorporating protein–protein interaction networks. In contrast, OMCD [33] covers various cancers but lacks miRNA targets, networks, and survival analyses. However, OncoMir [34] considers factors such as a normal tumor, stage, and grade and examines miRNA-target correlations and survival signatures. Similarly, UALCAN [35] analyzes normal tumor miRNA expression, functional annotations, survival, and target genes. Finally, OncoLnc [36] explores miRNA expression, survival, mRNA, and lncRNA analysis. Considering its specialized focus, validated targets, functional annotations, comprehensive networks, and survival analysis capabilities, ExplORRNet is a valuable addition to existing web tools.

### 3.11. Case studies

#### 3.11.1. Exploration of differentially regulated miRNAs in TCGA-UCEC, TCGA-OV, and TCGA-BRCA

Using the miRNA option in the sidebar panel of ExplORRNet, we analyzed miRNA expression levels in TCGA-UCEC, TCGA-OV, and TCGA-BRCA across tumor tissues and four tumor stages. In TCGA-UCEC, seven miRNAs (has-mir-497-5p/3p, hsa-miR-23b-3p/5p, hsa-miR-125b-5p, hsa-miR-199a-3p, hsa-miR-221-3p, hsa-miR-424-5p, and has-mir-101-3p/5p) were downregulated at higher tumor stages (SIII and SIV) compared to normal tissue or lower tumor stages (SI and SII) (Table 5). Conversely, six miRNAs (hsa-miR-363-3p, hsa-miR-940, hsa-miR-1301-3p/5p, hsa-miR-18a/b-3p/5p, hsa-miR-449c-5p, and hsa-miR-1224-5p) were upregulated in tumor tissues compared to normal tissues (Table 5). These findings are consistent with those of multiple studies using TCGA datasets and other repositories [37–44]. In TCGA-OV, we also observed characteristic regulation patterns consistent with previous reports [45–47] Pairwise comparisons between the clinical stages of ovarian tumor tissues revealed the downregulation of hsa-miR-19b-3p/1-5p, hsa-let-7f-5p, hsa-let-7b-3p, hsa-miR-128-3p, hsa-miR-98-5p, and hsa-miR-34a-5p in stages III and IV, whereas hsa-miR-323a-3p and hsa-miR-323b-3p were downregulated in stage IV (Table 6). Conversely, hsa-miR-34c-3p/5p and hsa-miR-34b-3p

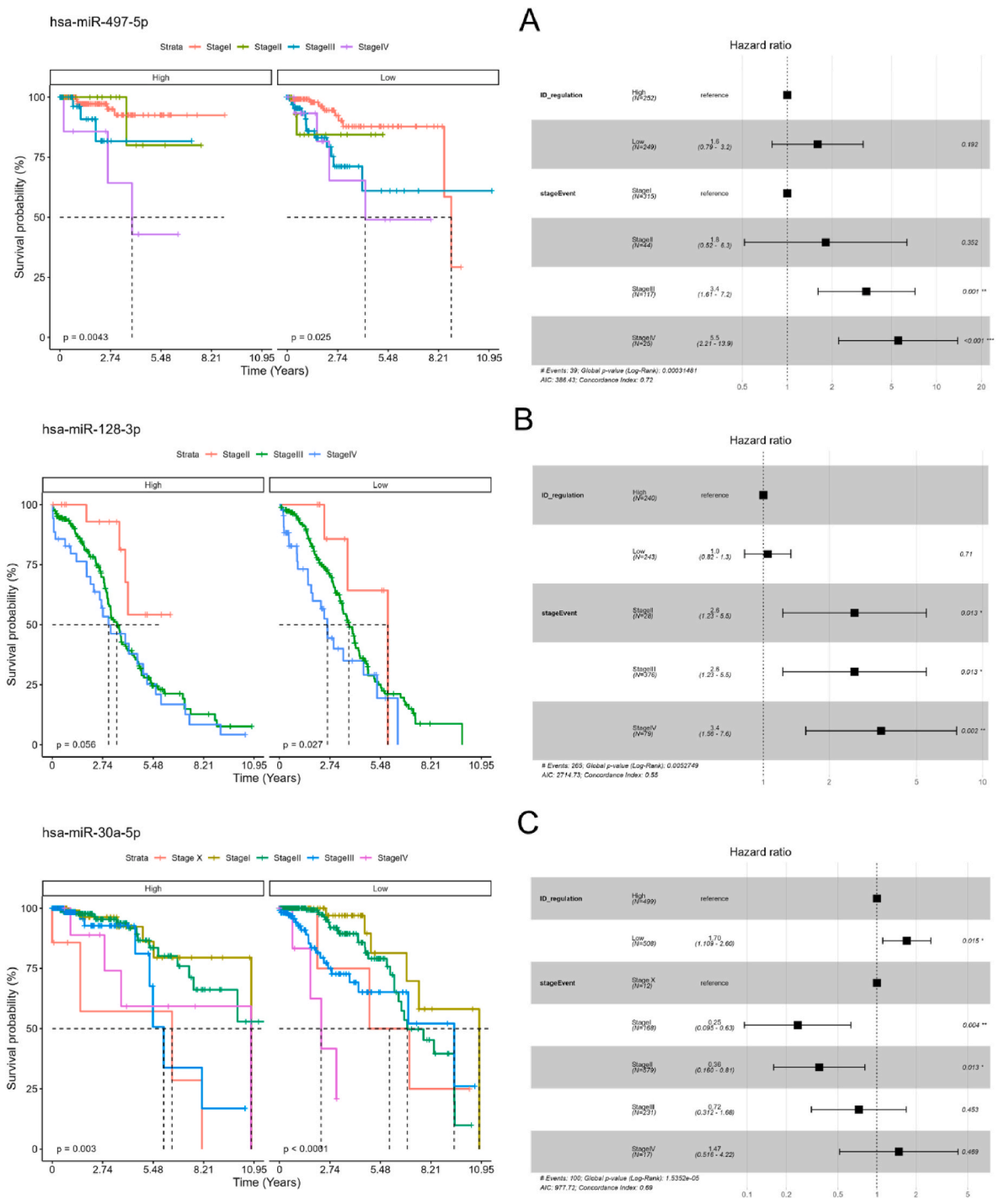


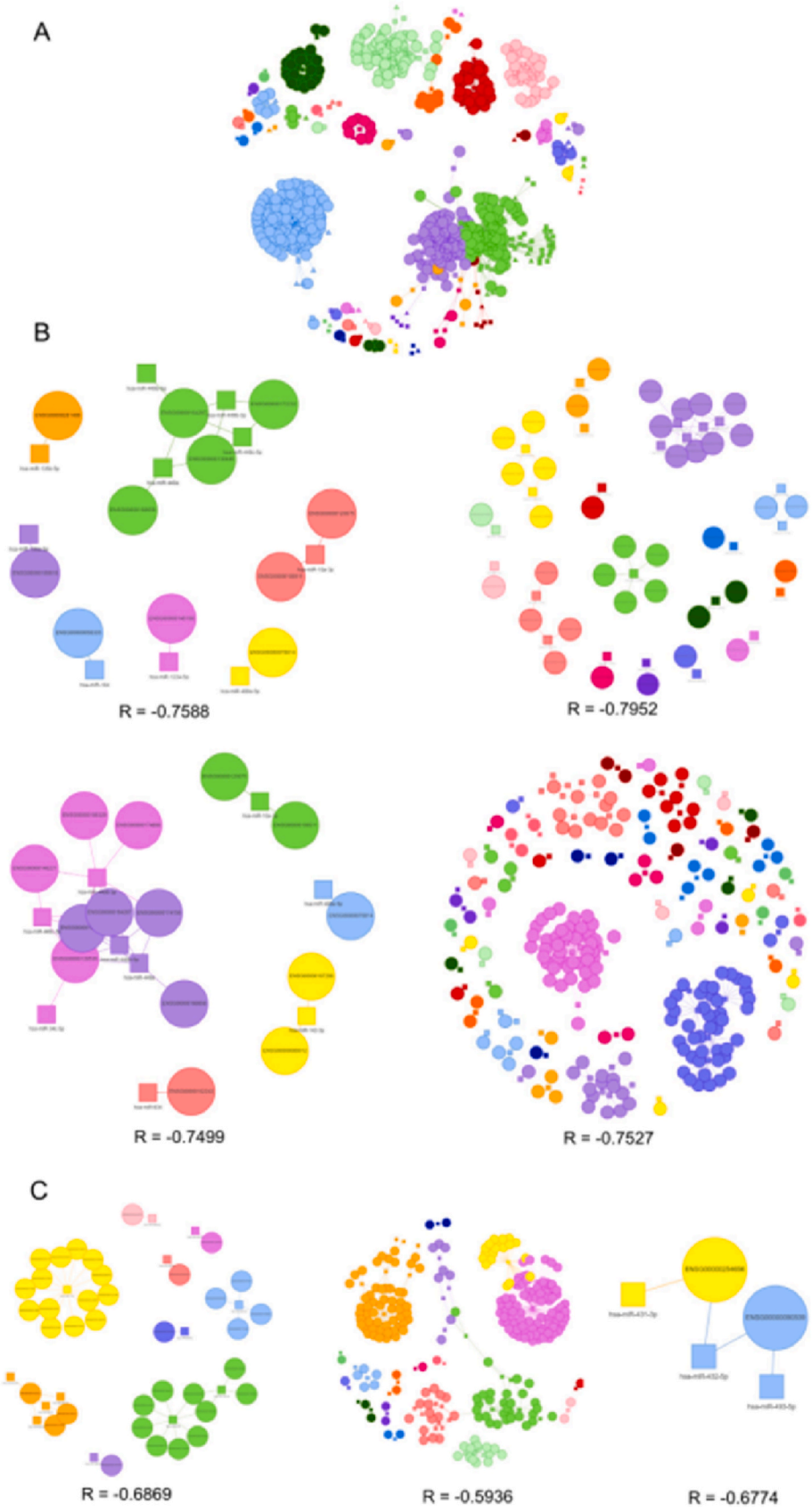

**Fig. 6.** Kaplan-Meier (KM) and forest plot exemplifying downregulated miRNAs in TCGA-UCEC and TCGA-OV
(A) KM-plot and forest plot of has-mir-497-5p in TCGA-UCEC. (B) KM-plot and forest-plot of has-mir-128-3p in TCGA-OV. (C) KM-plot and forest plot of has-mir-30a-5p in TCGA-BRCA.

were upregulated in stages III and IV, consistent with existing literature [47,48]. Similarly, in TCGA-BRCA, we observed a regulatory pattern consistent with that reported in previous literature [49]. In particular, has-miR-497-5p, hsa-miR-224-3p/5p, hsa-miR-130a-3p, hsa--miR-126-5p/3p, hsa-miR-140-3p, hsa-miR-206, and hsa-miR-335-5p/3p were downregulated in tumor tissues compared to normal tissues (Table 7). In contrast, hsa-miR-200c-5p/3p, hsa-miR-141-5p/3p, hsa-miR-210-3p, and hsa-miR-30a-5p were upregulated in tumor tissues (Table 7).

### *3.11.2. Survival analysis of differentially regulated miRNAs in TCGA-UCEC, TCGA-OV, and TCGA-BRCA*

Survival analysis of the differentially regulated miRNAs in TCGA-UCEC, TCGA-OV, and TCGA-BRCA revealed significant associations with patient prognosis [37,38].

In TCGA-UCEC, the upregulated miRNAs (has-mir-497-5p/3p, hsa-miR-23b-3p/5p, hsa-miR-125b-5p, hsa-miR-199a-3p, hsa-miR-221-3p, and hsa-miR-424-5p) correlated with poor survival at higher tumor stages. Fig. 6A highlights the median survival of approximately 4 years for stage IV patients, and the hazard ratio of advanced stages (III and IV)




*(caption on next page)*

**Fig. 7. Co-expression network of miRNA-mRNA-lncRNA in TCGA-UCEC and TCGA-OV.** (A) Co-expression network of dysregulated miRNA-mRNA-lncRNA in normal vs tumor tissue of TCGA-UCEC. (p-value <0.05, |logFC| >1, |r| > 0.545 and assortativity correlation coefficient = −0.6958). The square shape indicates miRNA, circle indicates mRNA and triangle indicates lncRNA. Each hub module of a network is colored differently by the hub ID. (B) Co-expression network of dysregulated miRNA-mRNA-lncRNA in TCGA-UCEC at each progressing clinical stage (Stage I, II, III and IV) compared against the normal tissue. The dysregulated miRNAs and genes are selected by cutoff of p-value <0.01, |logFC| > 1 and the correlation cutoff, |r| <0.75. (C) Co-expression network of dysregulated miRNA-mRNA-lncRNA in TCGA-OV at each progressing clinical stage (Stage II, III and IV) compared against each other. The dysregulated miRNAs and genes are selected by cutoff of p-value <0.05, |logFC| > 0.5 and the correlation cutoff, |r| < 0.5. In (B and C), R stands for the assortativity coefficient for network.

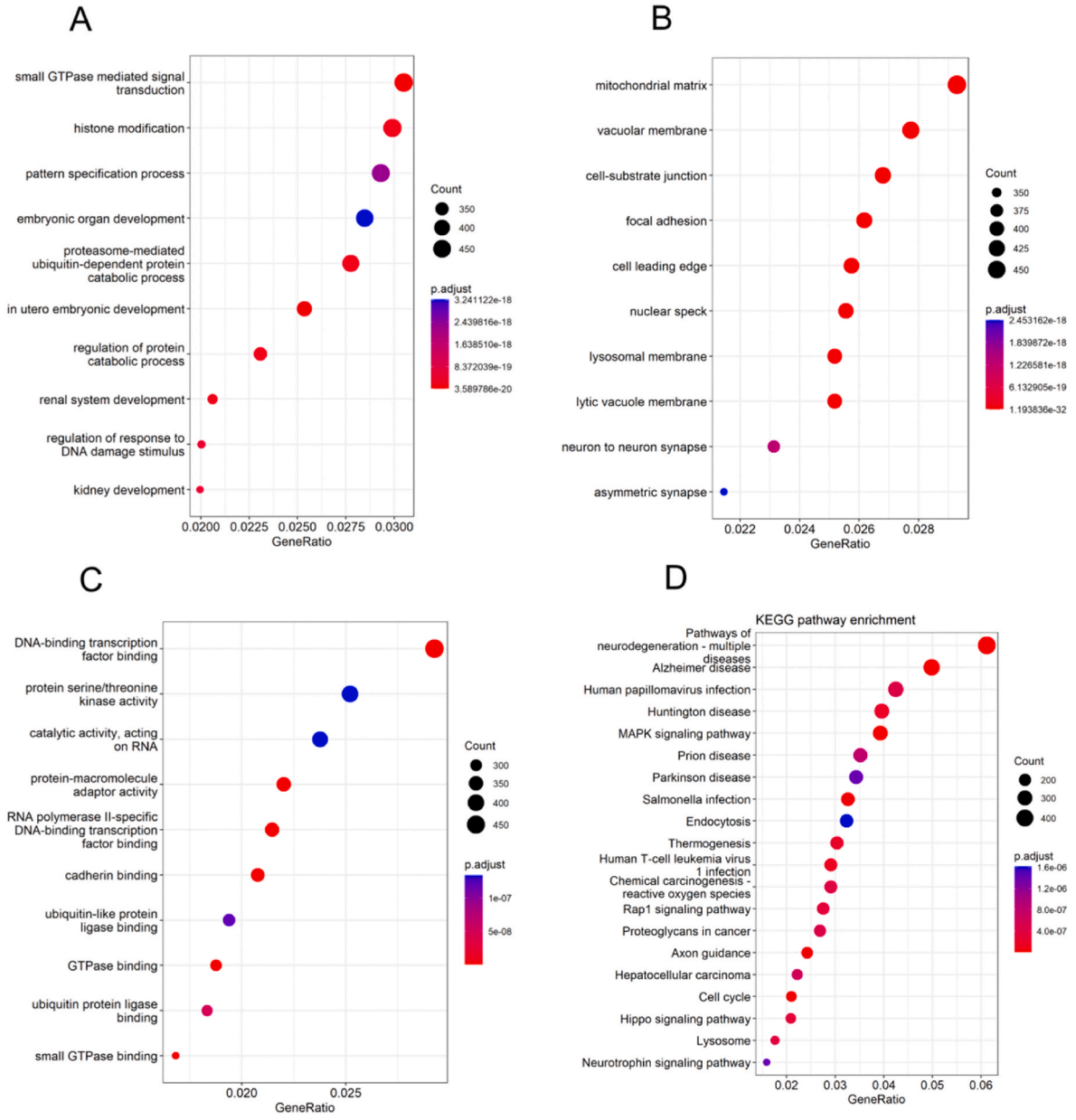



**Fig. 8. Functional enrichment based on the DEmiRNA list in TCGA-UCEC.**The dot-plot shows the top 10 enriched GO terms for DEmiRNAs in TCGA-UCEC (adj. P-value <0.01 & |logFC| >1). (A–C) feature top 10 enriched biological processes, cellular components, and molecular functions, respectively. (D) Top 20 enriched KEGG pathways.

was significantly higher (p-value <0.001) than that of early stages (I–II) in TCGA-UCEC.

In TCGA-OV, significant associations were observed between specific miRNAs (hsa-miR-19b-3p/1-5p, hsa-let-7f-5p, hsa-let-7b-3p, hsa-miR-128-3p, hsa-miR-98-5p, hsa-miR-323a-3p, and hsa-miR-323b-3p) and patient prognosis. For example, hsa-mir-128-3p expression correlated with a median survival of approximately 2.7 years. Fig. 6B shows the hazard ratios for patients with stage II (p-value <0.01), stage III (p-value <0.01), and stage IV cancers (p-value <0.001).

In TCGA-BRCA, higher expression of has-miR-30a-5p was linked to improved survival. Fig. 6C illustrates the KM-plot, demonstrating a median survival of approximately 10 years for stage IV cancer. The forest plot displayed a reduced hazard ratio (p-value <0.001) associated with lower expression of has-miR-30a-5p. Additionally, patients in clinical stages I and II showed a decreased hazard ratio (p-value <0.05). Notably, our findings are consistent with prior studies [37,38],

indicating a good level of comparability.

*3.11.3. miRNA–mRNA–lncRNA network in TCGA-UCEC and TCGA-OV*

Using a network panel, we constructed the co-expression networks of miRNAs, mRNAs, and lncRNAs in both TCGA-UCEC (Fig. 7A) and TCGA-OV (Fig. 7C). We identified hub networks and modules and analyzed the interactions between the dysregulated miRNAs and genes. Negative assortativity coefficients were observed for TCGA-UCEC and TCGA-OV, as shown in Fig. 7B and C, respectively. Thus, our analysis indicates a probable loss of regulatory control in different cancer cell populations, as suggested in previous studies [50,51].

*3.11.4. Gene set and pathway enrichment analyses*

In the gene set and pathway enrichment analyses, we utilized the target enrichment panel in the tool interface to identify the targets of DEmiRNAs in TCGA-UCEC tumor tissues compared to normal tissues. The analysis revealed the enrichment of biological processes and pathways (Fig. 8A and D) involved in tumor progression, such as the Rap1 and Hippo signaling pathways, which have been previously implicated in promoting proliferation, migration, and invasion in endometrial cancer [52,53]. The functional enrichment analysis performed using gProfiler2 corroborated these findings and also identified enrichment in other functional terms, including transcription factor (TF) targets, WikiPathways (WP), Human Phenotype (HP), Human Protein Atlas (HPA), and Reactome pathways. These results are shown in Supplementary Fig. S7 and provide additional insights into the underlying mechanisms associated with the dysregulation of miRNAs in TCGA-UCEC.

## 4. Discussion

Our study aimed to develop a web tool that enables users to explore miRNA expression profiles and their correlation with mRNA and lncRNAs in human gynecological and breast cancers. Additionally, we aimed to provide a stage-wise exploration, which can be particularly useful for examining stage-specific biomarker candidates without requiring programming skills.

ExplORRNet integrates various functions to facilitate the identification of dysregulated miRNAs, their target genes, and their potential biological functions. The differential expression analysis module enables users to identify stage-specific miRNAs, mRNAs, and lncRNAs that are significantly upregulated or downregulated in specific gynecological cancer types. This information is invaluable for understanding the molecular landscape of gynecological cancers and may facilitate the discovery of novel biomarkers for early detection and prognosis.

Furthermore, ExplORRNet incorporates functional enrichment analysis, enabling researchers to gain insights into the biological processes and molecular pathways that are influenced by dysregulated miRNAs. By identifying enriched gene ontology terms and signaling pathways, researchers can unravel the underlying mechanisms by which miRNAs affect cancer development and progression. This information may guide the design of targeted therapies or combination treatment strategies that exploit the vulnerabilities associated with aberrant miRNA expression.

The miRNA–mRNA–lncRNA interaction network analysis module of ExplORRNet provides a visual representation of the regulatory relationships among miRNAs, mRNAs, and lncRNAs, enabling users to explore the complex interplay between different RNA molecules and to identify key regulatory hubs within the network. By highlighting central miRNAs or lncRNAs and their associated target genes, researchers can prioritize candidate biomarkers or therapeutic targets for further investigation.

ExplORRNet incorporates survival analysis illustrated by Kaplan–Meier curves and forest plots, enabling researchers to stratify cancer patients and further identify miRNAs or genes associated with favorable or adverse clinical outcomes. These findings may aid the development of personalized treatment approaches and prognostic biomarkers.

Example case studies using ExplORRNet have demonstrated its efficiency in identifying and comparing potential biomarkers in gynecological cancers, highlighting the significance of c-miRNAs as non-invasive biomarkers.

Our study had certain limitations. The use of only publicly available data and criteria for selecting gynecological cancers limited the number of samples in the current study. It is worth noting that the availability of samples could be influenced by updates to public data repositories. Moreover, our analysis covered only cancer stages and not subtypes because, the lack of sufficient data hindered this possibility. From a technical perspective, network generation is slow (>1 min) on the tool interface, especially when the number of input genes is high. Finally, although fundamental studies have highlighted the importance of miRNAs in cancer tissues and cell-free samples for cancer diagnosis and prognosis [54], miRNAs are not commonly used for decision making in clinical practice. There are multiple reasons for the limited use of miRNAs in clinics, such as different levels of miRNA regulation in different cancer types, varying concentrations of cell-free miRNAs, and variability in factors originating from the clinical and demographic criteria of patients [54]. Thus, there is still a need to clinically validate the regulated miRNAs and genes to support their roles as biomarkers.

## 5. Conclusions

In conclusion, we believe that ExplORRNet is a valuable tool for clinical and basic researchers working in the field of gynecological cancer. By facilitating the identification of potential biomarkers and their correlation patterns, ExplORRNet provides a platform for the development of more precise and personalized treatment strategies. Furthermore, our tool offers cancer stage-wise information that can be of interest to oncologists for identifying stage-specific biomarker candidates without requiring advanced computational programming knowledge. Additionally, the network analysis capability of our tool enables the identification of cancer-specific drivers for cancer progression. We aim to continue updating and improving our tool to compete with the latest advancements in the field of cancer genomics, thereby enabling improved survival and outcomes for patients with gynecological and breast cancers.

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## CRediT authorship contribution statement

**Ankita Lawarde:** Conceptualization, Data curation, Formal analysis, Investigation, Software, Visualization, Methodology, Writing - original draft. **Edris Sharif Rahmani:** Software, Investigation, Writing - review & editing. **Adhiraj Nath:** Software, Writing – review & editing. **Darja Lavogina:** Conceptualization, Writing - original draft, Writing - review & editing. **Jana Jaal:** Conceptualization, Supervision, Writing - review & editing. **Andres Salumets:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Vijayachitra Modhukur:** Conceptualization, Formal analysis, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ncrna.2023.10.006.

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