

Identification of dysregulated long noncoding RNA and associated mechanism in gastric cancer

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Abstract

Backgrounds

Gastric cancer (GC) is one of the most malignant epithelial tumors. The incidence of GC varies worldwide, and nearly half of the cases occur in Asian countries, especially in Japan and China. GC is the 3rd leading cause of cancer-related deaths in the world, and current prognosis of advanced GC remains dismal despite improvements in diagnosis and therapy. Our current study aimed to identify significant long noncoding RNAs with the prognostic potential and preliminarily to investigate the underlying mechanisms the identified long noncoding RNAs.

Methods

We retrieved articles reporting human LncRNA microarray in GC patients and pooled eligible studies for meta-analysis. GEO2R and Qigen's IPA analysis was utilized for searching potential interacted molecules with differentially expressed LncRNA in GC. The expression of eligible LncRNA and molecules in GC were validated in public GC dataset by GEPIA website. And Kaplan Meier plots was employed to analyze the correlation between target molecules and prognosis of GC.

Results

This study identified a variety of reports to investigate the expression of lncRNAs in GC development using high-throughput lncRNA detection. Eight of them were further verified with significant expression in GC tissues by using Gene Expression Profiling Interactive Analysis (GEPIA). Next, the molecular interactions with eight lncRNAs were further identified by using Qiagen's IPA system. Simultaneously, differentially expressed genes (DEGs) of GC were also identified via the GEO2R online tool and datasets (GSE54129, GSE19826, and GSE79973). Finally, through Venn diagram analysis, our study found that IGF2BP3 and FOLR1 have strong relationship with lncRNAs H19 and PVT1 respectively in the background of stomach cancer. The expression of IGF2BP3 and FOLR1 in GC was further revealed to be correlate to a worsening prognosis for GC patients by Kaplan Meier plots. IGF2BP3 promotes the expression of H19 and PEG10, the down-regulation of which might improve the GC prognosis. FOLR1 is a crucial component of cell metabolism and DNA synthesis/repair required for cancer cell division. Currently, there is no evidence to report IGF2BP3 and FOLR1 to correlate to GC prognosis.

Conclusion

In summary, using an integrated bioinformatic approach we identified eight lncRNAs with prognostic potential in GC patients and further revealed two axes - H19-IGF2BP3 and PVT1-FOLR1 – that might interpret the underlying mechanism involving in prognosis of GC and provide new insights into the etiology and management of GC patients.

1 Backgrounds

Gastric cancer (GC) is one of the most common cancers worldwide [1, 2] and has become the 3rd leading cause of death related to cancer. GC incidence varies significantly, from the highest rate in Eastern Europe, South America and East Asia to the lowest rate in North America, and risk factors for GC—e.g. diet, lifestyle[3], and chronic *H. pylori* infection[4]—are unique for each region. Since two-thirds of newly diagnosed patients have either locally advanced or metastatic disease, as a result, the 5-year overall survival of GC patients remains 20-40% worldwide [5], and the median survival time after surgery is only 9 to 10 months [6] for patients with metastatic disease. Improved health care and screening programs in Japan have shown that over 70% of patients with early-stage of GC survive over 5 years [7], indicating a decisive role of early diagnosis and treatment for the survival of GC patients. The most common diagnostic methods - endoscopy and pathological examination - are the 'gold standard' for GC diagnosis [8]. Unfortunately, they cannot be used for screening in many countries due to the costs of the procedure and potential risk of patient's injury [9], and existing common serum markers—CEA, CA199, and CA72-4[10]—lack sensitivity and specificity essential for early cancer screening.

Long noncoding RNA (lncRNA) is a 200-nucleotide long transcript that regulates gene expression and messenger RNA (mRNA) splicing in the nucleus. Over time, a growing number of studies explored the role of lncRNA in the regulation of different physiological and pathological functions, e.g. cell differentiation and proliferation [11], carcinogenesis [12], and metastasis [13]. Several lncRNAs have been identified as oncogenes and tumor-suppressors: for example, up-regulation of HOTAIR drives proliferation, migration, and invasion of GC cell [14], H19 has oncogenic activity in GC and colon cancer [15], while CASC2 suppresses proliferation of GC cells through the MAPK signaling pathway [16]. Recent evidence indicates that lncRNAs can also modulate and be regulated by cancer immune microenvironment [17], making lncRNAs a potential biomarker and a therapeutic target that can improve the management and treatment of GC.

In this study, we did a meta-analysis of lncRNAs to assess their overall accuracy for the diagnosis of GC. Using Gene Expression Profiling Interactive Analysis (GEPIA), we compared expression patterns in GC and normal tissue and found eight lncRNAs with marked differences in expression. We also identified two genes that had different levels of expression in normal tissue and GC and could interact with these lncRNAs. Taken together, our results suggest a connection between lncRNAs and prognosis in GC patients

2 Methods

2.1 Search strategy and eligibility criteria

Publicly available databases (PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/>; and EMBASE: <https://www.embase.com>) were comprehensively searched to identify relevant English-language articles reporting microarray data for human lncRNAs in GC patients and published up to the end of 2018. The following keywords and phrases were used: (lncRNA OR long noncoding RNA) AND ((gastric cancer) OR GC OR stomach neoplasms OR (stomach AND neoplasms) OR (gastric AND cancer)). Duplicate articles

were manually removed using Reference Manager (Thomson Reuters EndNote X7, New York, NY, USA). To determine eligible studies the titles, abstracts, and full texts were evaluated independently by two investigators. Another investigator extracted data from identified papers, and the reference lists of eligible articles were reviewed to obtain associated studies. All disagreements were resolved by an independent investigator. The criteria for inclusion were: 1) studies with a confirmed diagnosis of gastric cancer; 2) studies with lncRNAs microarray analysis and reports on altered lncRNAs; 3) studies on diagnostic value of lncRNAs in tissue, serum, plasma, peripheral blood, or gastric juice (if published data were sufficient to allow meta-analysis); 4) original articles published in English with full text available. Articles that did not satisfy these criteria were excluded. General information from the eligible studies was arranged in tables, and data on lncRNAs were pooled into forest plots.

2.2 mRNA microarray data information and processing DEGs

We used NCBI-GEO, an online public microarray database, to acquire gene expression profiles for GC and normal stomach tissues from GSE54129, GSE19826 and GSE79973 datasets that had been produced using GPL570 Platform ([HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array). GPL570 contained 111 human GC tissues and 21 noncancerous tissues, 12 adjacent normal/tumor-paired gastric tissues, and 10 pairs of GC tissue and adjacent non-tumor mucosa, respectively. DEGs in tumor and normal tissues were identified with GEO2R online tools [6]. The DEGs with $|\log_2FC| < 0$ were considered to be down-regulated, while the DEGs with $|\log_2FC| > 0$ - up-regulated. Three microarrays were compared, and upregulated and downregulated genes with $|\log_2FC| > 2$ and adjusted p-value less than 0.05 in TXT format were pooled into Venn software online to identify common DEGs.

2.3 Bioinformatics analysis

Bioinformatics analysis was performed to determine relationships between altered lncRNAs and DEGs of overlapping mRNA microarrays. Briefly, lncRNAs from selected studies were uploaded into GEPIA to validate their expression in GC tissues. Then lncRNAs with altered expression were imported into Qiagen's IPA system and overlaid with a global network of interactions in gastrointestinal disease. Next, we overlaid identified DEGs and genes related to the altered lncRNAs to find potential interactions. Finally, we used GEPIA and Kaplan Meier plotter online database to validate expression levels and effects of identified genes and lncRNAs on survival time.

2.4 Statistical methods

The confidence interval (CI) of diagnostic value was calculated using meta-disc (version 1.4; Ramon Cajal Hospital, Madrid, Spain), the results were considered significant for a two-sided p-value less than 0.05. Heterogeneity was inferred by calculating inconsistency (I^2) (heterogeneity was considered substantial for I^2 values above 50%), and the results were incorporated into a random-effects model. Potential reasons for heterogeneity were analyzed by regression analysis. The sensitivity and specificity of potential biomarkers were evaluated using summary receiver operating curve (sROC) and area under the curve (AUC). In addition, LR^+ (positive likelihood ratio), LR^- (negative likelihood ratio), and DOR

(diagnostic odds ratio) were calculated. The method for differential analysis to compare molecules expression in GC tissues and normal tissues is one-way ANOVA, which was achieved by GEPIA website. The overall survival analysis related to targeted molecules in GC was generated by Kaplan Meier Plot website.

3 Results

3.1 lncRNAs expression levels altered in GC

The summary of 13 studies reporting changes in lncRNA expression in GC tumor genesis and development is presented in **Table 1**. Different types of samples were used: Zhang et al. compared lncRNA between GC and non-GC patients using tissue and plasma [18]; gastric mucosae were used in one study [19]; all other studies analyzed GC cancer tissue and adjacent healthy tissue. Among all identified studies, differences in lncRNAs expression levels were detected for at least 75 lncRNAs [18]. Because of the re-annotation of the published microarray database, two studies did not provide fold changes of dysregulated lncRNAs [18, 20, 21]. A study from Hu et al. used a 1.5-fold change for selection criteria [22], while 2 fold change was used for other studies [18, 23-30]. The median age of GC patients enrolled in the analysis was at least 57.8 years, except one study [29] that did not have detailed information. Gender distribution and histopathological information of GC patients are shown in **Table 1**.

In summary, the analysis of identified microarray data showed substantial lncRNAs alteration in GC patients. However, data reported by different research groups were extremely variable. Thus, we concentrated on the potential of lncRNAs for GC diagnosis.

3.2 Meta-analysis of differentially expressed lncRNAs in GC patients.

To further investigate the diagnostic value of lncRNAs in GC, all articles exploring lncRNAs as a novel biomarker for GC patients were collected using the search strategy indicated in the flowchart in **Fig. 1**. Twenty-three studies were included and pooled into meta-analysis.

The number of patients in each study ranged from 30 to 132, and tissue, plasma, serum, or gastric juice samples were used. Besides b-actin or GAPDH, U6 [31, 32] and 18s RNAs [33] were used as endogenous standards for diagnostic evaluation. Quantitative methods and cut-off values were also different in different studies, and both individual lncRNAs and panels [33, 34] were selected as novel diagnostic biomarkers for GC. Additionally, classic GC biomarkers (e.g. CEA and CA19-9) were compared with novel GC biomarkers [34], and the lncRNA panel showed markedly higher AUC value for discriminating GC patients from controls. Considering this evidence, we performed a meta-analysis with meta-disc software version 1.4. We pooled data from various specimens and generated forest plots shown in **Fig. 2**. The pooled sensitivity was 0.76 (95% CI: 0.74-0.77; $Q = 195.59$, $p = 0.0000$, $I^2 = 85.2\%$) and the specificity was 0.66 (95% CI: 0.64-0.68; $Q = 208.98$, $p = 0.0000$, $I^2 = 86.1\%$), which indicated a presence of substantial heterogeneity. Then a random-effects model was used to re-analyze the diagnostic threshold of pooled data. The Spearman correlation coefficient was 0.238 ($p = 0.214$, data not shown), suggesting

no evidence of a diagnostic threshold. Afterward, forest plots of DOR were generated, which revealed that substantial heterogeneity was still present. This might result from the discrepancy of the studied populations, endogenous references, or specimen types. Meta-regression analysis on the possible factors indicated that specimen type was probably the reason for heterogeneity. Thus, the results (e.g. sensitivity) extracted from identified studies could not be simply pooled and were only suitable for subgroup analyses. Filtering studies based on specimen type reduced heterogeneity, however, it was still higher than acceptable levels. On the sROC curve of plasma samples, which included 16 lncRNAs, the maximum joint sensitivity and specificity (Q value) was 0.7443, and the area under the curve was 0.8096, indicating a moderate level of overall accuracy. The combined sensitivity, specificity, LR+, LR- and DOR in plasma were 0.84 (95% CI: 0.81-0.86; I² =82.1%), 0.50 (95% CI: 0.56-0.62; I² =86.8%), 2.32 (95% CI: 1.88-2.85; I² =84.4%), 0.27 (95% CI: 0.20-0.36; I² =73.7%), and 9.53 (95% CI: 6.21-14.61; I² =68.4%), respectively (shown in Fig. S1). Thus, the results indicated that a pooled study was not appropriate. In the other 14 studies that used tissues as specimens the pooled sensitivity, specificity, LR+, LR-, and DOR were 0.69 (95% CI: 0.66-0.71; I² =68.1%), 0.72 (95% CI: 0.69-0.74; I² =76.9%), 2.50 (95% CI: 2.11-2.96; I² =63.5%), 0.44 (95% CI: 0.38-0.50; I² =52.2%), and 6.08 (95% CI: 4.65-7.96; I² =51.8%), respectively (shown in Fig. S2). The data showed a lower pooled sensitivity for tissue.

3.3 Validation of lncRNAs expression by GEPIA

Since heterogeneity was not reduced to an acceptable level through subgroup analysis, we used GEPIA[35] analysis, a web-based tool to deliver fast and customizable functionalities based on TCGA [36] and GTEx data[37], to validate the expression of those lncRNAs between primary GC tissues and normal gastric tissues. We observed increased expression of six lncRNAs (ABHD11-AS1, H19, PVT1, UCA, HOTTIP, and SUMO1), and two lncRNAs (FER1L4 and LINC00982) decreased in GC tissues compared to normal stomach tissue. The specific data related to expression of those lncRNAs recorded by dataset is shown in Fig. 3.

3.4 Identification of DEGs in GCs and investigation of correlation to modulated lncRNAs by IPA

To investigate the underlying mechanism related to lncRNAs, we extracted 3944, 629 and 1406 DEGs from GSE54129, GSE19826[38] and GSE79973[39] via GEO2R online tools, respectively. The gastric samples used for those arrays were collected during surgery. Healthy gastric mucosa (GSE54129) or adjacent normal gastric tissue (GSE19826, GSE79973) was used as control. Subsequently, Venn diagram software [40] was used to identify common DEGs in these datasets. A total of 226 common DEGs were identified, including 142 up-regulated genes ($p < 0.05$ & $\log_2FC > 2$) and 84 down-regulated genes ($p < 0.05$ & $|\log_2FC| > 2$) in the GC tissues (Fig. 4). Meanwhile, IPA analysis identified molecules that interacted with the altered lncRNAs in gastrointestinal diseases (Table 2). Then we pooled these molecules and DEGs in GC into the Venn diagram and identified two genes (IGF2BP3 and FOLR1), which probably interacted with altered lncRNAs in GC.

3.5 Validation of genes interacted with lncRNAs in GC

To investigate the potential role of these genes in GC, we further validated the expression of IGF2BP3 and FOLR1. GEPIA website [35] and Kaplan Meier plotter (<http://kmplot.com/analysis>), a website established on TCGA [36] and GTEx data [37] were used to recognise the correlation between the expression of those genes and the prognosis of GC patients. We found a dramatically increased expression of IGF2BP3 and significantly reduced expression of FOLR1 in GC patients compared to healthy controls, the altered expression of these two genes was reported to be correlated with poor overall survival time of GC patients, especially the altered expression of FOLR1 ($P < 0.01$, shown in Fig. 5).

4 Discussion

To improve the survival time of GC patients, early diagnosis and treatment have been recognised as effective methods. Thus, the exploration of useful biomarkers for early diagnosis and positive management based on the mechanism of GC development is required. To date, several available biomarkers, such as CA-199, CA72-4, and CEA, are used. However, the sensitivity and specificity of those biomarkers are limited. Since the first study of lncRNAs in GC has been reported in 1997 [41], with more research focused on the clinical value of lncRNAs in GC diagnosis. Exploration of dysregulated lncRNAs as biomarkers for GC diagnosis has several advantages: 1) lncRNAs can be detected and resist ribonuclease degradation in body fluids [42]; 2) expression of lncRNAs has temporal and tissue specificity [43]; 3) ectopic expression of lncRNAs is responsible for tumor genesis [44, 45]. Therefore, investigation of lncRNAs might produce novel diagnostic and prognostic biomarkers for GC and help us understand the molecular mechanisms of GC development and progression.

To explore the potential role of lncRNAs in GC, the present study reviewed and analyzed published studies that reported differentially expressed lncRNAs between GC and normal tissue using microarray analysis. Due to the substantial variety of reported data, for meta-analysis we retrieved articles reporting on the diagnostic value of lncRNAs (Fig.1). However, the data pooled from all studies showed marked heterogeneity (Fig. 2) that was most likely associated with specimen types as evidenced by meta-regression analysis. Although we performed a subgroup meta-analysis (Figure S1&S2) and also revealed that individual or specific lncRNA combinations could potentially serve as novel biomarkers for diagnosis of GC, the heterogeneity was still too high. Meanwhile, we found that the data from different research groups had significant differences in quality. Therefore, we validated and found eight lncRNAs with significant differences of expression in GC compared to normal tissue using GEPIA website (Fig.3). To further investigate the potential mechanism underlying the function of these lncRNAs in GC, we utilised IPA analysis to disclose molecules interacting with these lncRNAs in gastrointestinal diseases. Subsequently, bioinformatics methods was performed to identify DEGs in GC based on three datasets (GSE52149, GSE19826, and GSE79973, shown in Fig.4). Then results for lncRNAs and DEGs were pooled into the BioVenn diagram to identify two genes (IGF2BP3 and FOLR1, shown in Fig.4), which might be regulated by altered lncRNAs in GC samples. Finally, we utilised GEPIA and Kaplan Meier plotter analysis to verify that IGF2BP3 and FOLR1 both changed significantly and moreover, correlated with worse survival time in GC patients (Fig.5).

Insulin-like growth factor-2 mRNA-binding protein 3 (IGF2BP3) was revealed a significant elevation in GC patients and a marked correlation with GC prognosis. IGF2BP3, also known as IMP3, belongs to a conserved IGF2 mRNA-binding protein family. It has been first recognised in 1997, due to its high expression in pancreatic carcinoma [46]. Subsequently, IGF2BP3 has been found to be overexpressed in various tumors [47-50]. Moreover, it has been demonstrated to modulate tumor cell fate by promoting tumor growth [51], cell proliferation [2], drug-resistance [52], and invasiveness [53]. The expression of IGF2BP3 has also been shown to correlate with prognosis and metastasis of human cancer. H19, PEG10, and IGF2BP3 have been reported to promote the expression of each other and the suppression of those genes can decrease cell proliferation, anchorage-independent growth, invasion, and chemoresistance in GC [54]. Although IGF2BP3 has been confirmed to be an embryonic regulator, the research related to IGF2BP3 in human is still very limited. IGF2BP3 expressed a high level in progenitor cells, but also was observed in mature cells, e.g. placenta, lymph nodes, tonsils and testes. Moreover, IGF2BP3 transgenic mice were observed an increased biogenesis of endocrine pancreas, resulting in pancreas resemble to be embryonic tissue and intestinal cells with rearrested capacity of differentiation. Those recapitulation fetal-like phenotypes regulated by IGF2BP3 suggested a potential diagnostic role of IGF2BP3 in tumor genesis. However, currently, few evidence has been elucidated the expression and function of IGF2BP3 in the GC progression. Our study firstly put forward a higher expression of IGF2BP3 in GC tissues, and a significant correlation with prognosis of stomach cancer patients (shown in Fig.5). According to the bioinformatics data, as RNA binding protein, we also provide a putative mechanism interpreting its association with poor prognosis of GC patients.

Folate receptor 1 (FOLR1) is a membrane-bound protein with a high affinity to folate that binds and transports folate with physiological levels into cells. Folate, one of the crucial components of cell metabolism and DNA synthesis and repair, is a requirement for the rapid division of cancer cells [55]. A higher expression of FOLR1 has been found in specific epithelial-derived malignant tumors [56] and solid tumor like breast[57], lung[58] and ovarian [59]cancer, and also illustrated to positively correlate with tumor grade and stage [55]. During early carcinogenesis, FOLR1 promotes cells to increase folate uptake and DNA damage repair [60]. Overexpression of FOLR1 results in a growth advantage of tumor cells through a possible mechanism involving folate uptake[61] and translocation to nucleus by regulating the key developmental gene in cancer cells[62]. Therefore, the increased expression of FOLR1 suggested a higher activity of cancer cells and might predict a poor prognosis of cancer patients. Recently, FOLR1 has been confirmed as a potential target for immunotherapy with chimeric antigen receptor (CAR) T cell in GC [63]. In line with the previous data, the present study also found a higher expression of FOLR1 in GC patients, which was correlated with poor prognosis of GC patients. However, currently, no evidence has been focused on the implication of FOLR1 in prognostic prediction of GC and our analysis pointed out a novel insight to explore the potential of FOLR1 in the development and prognostic prediction of GC.

Nevertheless, this study has shown substantial evidence to support the potential prognostic role of IGF2BP3 and FOLR1 in progression of GC and close relationship with LncRNAs. More research is still required to investigate the mechanisms underlying these observations rather than theoretical assumption based on the fundamental of bioinformatics. In fact, the present study in fact also inspires informatics

analysis as a supplementary tool to investigate the potential mechanism of LncRNAs alteration in the progression of GC.

5 Conclusion

In conclusion, our study revealed two axes - H19-IGF2BP3 and PVT1-FOLR1 might correlate to the GC development, and IGF2BP3 and FOLR1 are further identified to be potential for diagnostic prediction in GC patients. Therefore, the present study provides novel insights for elucidating the role of IGF2BP3 and FOLR1 in stomach cancer and new potential candidates to predict the GC prognosis.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the GEO datasets.

Competing interests:

The authors declare that they have no competing interests, and all authors should confirm its accuracy.

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Author's contributions:

LS and YM analyzed and interpreted the data from eligible publications. LS analyzed the GEO datasets and identified the potential interaction between selected LncRNAs and DEGs in GC patients. ZZ and YM were major contributor in conclusion and writing the manuscript. All authors read and approved the final manuscript.

Abbreviations

| | |
|---------------------|---|
| ABHD11-AS1 | ABHD11 antisense RNA 1 |
| AUC | Area under the curve |
| CA199 | Carbohydrate antigen19-9 |
| CA72-4 | Carbohydrate antigen 72-4 |
| CAR | Chimeric antigen receptor |
| CASC2 | Cancer susceptibility candidate 2 |
| CEA | Carcino-embryonic antigen |
| CI | Confidence interval |
| DEGs | Differentially expressed genes |
| DNA | Deoxyribonucleic acid |
| DOR | Diagnostic odds ratio |
| FER1L4 | Fer-1-like protein 4 |
| FOLR1 | Folate receptor 1 |
| GAPDH | Glyceraldehyde-3-phosphate dehydrogenase |
| GC | Gastric cancer |
| GEO | Gene Expression Omnibus |
| GEPIA | Gene Expression Profiling Interactive Analysis |
| GPL | GEO platform |
| GTE _x | Genotype-Tissue Expression Project |
| H19 | H19 Imprinted Maternally Expressed Transcript |
| HOTAIR | HOX transcript antisense RNA |
| HOTTIP ₁ | HOXA transcript at the distal tip |
| I^2 | Inconsistency |
| IGF2BP3 | Insulin-like growth factor 2 mRNA binding protein 3 |
| LINC00982 | Long non-coding RNA00982 |
| lncRNA | Long noncoding RNAs |
| LR ⁻ | Negative likelihood ratio |
| LR ⁺ | Positive likelihood ratio |
| MAPK | Mitogen-activated protein kinase |

| | |
|-------|---|
| NCBI | The National Center for Biotechnology Information |
| PEG10 | Paternally expressed imprinted gene 10 |
| PVT1 | Plasmacytoma variant translocation 1 |
| RNA | Ribonucleic acid |
| sROC | Summary receiver operating curve |
| SUMO1 | Small ubiquitin-related modifier 1 |
| TCGA | The Cancer Genome Atlas |
| U6 | U6 spliceosomal RNA |
| UCA | Urothelial cancer associated 1 |

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Tables

Table1 LncRNA expression profiles included in the systematic review

| Studies | Platform of LcRNA microarray | Sources of samples (N or pairs) | The number of dysregulated LncRNA | Gastric cancer patients | | |
|------------------------|--|---------------------------------|---|-------------------------|-----------|------------------------|
| | | | | Age | Sex (M/F) | AJCC stage |
| Cao, 2013[20] | the Affymetrix GeneChip Human Exon 1.0 ST Array (re-annotation) | 22pairs, tissue | 88(p<0,01) | 59.4(34-84) | 53/27 | 4/7/54/15(I/II/III/IV) |
| Li, 2016[23] | RiboArray Custom Array1*90K+ q RT-PCR | 10/10, tissue | 1046(folds >2 & p<0,01) | 58.5(45-70) | 7/3 | 1/6/3 (II/III/IV) |
| Zhang, 2017[18] | The LncRNA Human Gene Expression Microarray V4.0 | 15/15 plasma; tissue | Plasma:77 Tissue:75(folds >2 & p<0,05) | 60.21 | 9/6 | 7/8 (II/III) |
| Hu, 2014[22] | ArrayStar lncRNA microarray | 10/10 , tissues | 1368(folds >1,5 & p<0,05) | 63(48-76) | 8/2 | NR |
| Song, 2016[24] | the Human LncRNA Expression Microarray V3.0 | 6/2, tissue | 1379(folds >2 & p<0,05) | 60.2(45-77) | 4/2 | 2/4 (II/III) |
| Lin, 2014[25] | The Human 12x135k lncRNA expression microarray | 8 pairs, tissue | 2621(folds >2 & p<0,05) | 58.75 | 6/2 | 1/3/4(I/II/III) |
| Song, 2013[26] | NimbleGen Hybridization System | 3/3, tissue | 135(folds >2) | 73(55-88) | 2/1 | NR |
| Wang, 2014[27] | the Human LncRNA Expression Microarray V2.0 | 15/15, tissue | 5139(folds >2) | 57.8(42-77) | 13/2 | 1/1/13(I/II/III) |
| Yuan, 2016[28] | Affymetrix Human Genome U133 Plus 2.0 chips | 20 pairs ,tissue | 2323(folds >2 & p<0,05) | 62(41-76) | 16/4 | 4/5/8/3(I/II/III/IV) |

| | | | | | | |
|-----------------------|---|------------------|-------------------------|-------------|-----|-------------------|
| Tian, 2017[21] | Affymetrix Human Genome U133 Plus 2.0 chips | 10 pairs ,tissue | 339(p<0,01) | 57.9 | 7/3 | 2/5/3 (II/III/IV) |
| Gu, 2015[29] | Arraystar Human LncRNA Microarray v2.0 | 6/6, tissue | 1297(folds >2 & p<0,05) | NR | NR | NR |
| Zhao, 2015[30] | Arraystar Human LncRNA Microarray v3.0 | 6/6, tissue | 3141(folds >2 & p<0,05) | 61.2(42-73) | 3/3 | 3/3(II/III) |
| Liu, 2018 [64] | Agilent human lncRNA V6 Microarray | 4/4, plasma | 267 (p<0,05) | 61(29-83) | 2/2 | NR |

AJCC: American Joint Committee on Cancer; NR: No reported, qRT-PCR: Real-time Quantitative polymerase chain reaction; M: male; F: female.

Table2 The molecules interacted with selected eight LncRNAs through IPA system.

| LncRNA | Related molecules |
|--------|--|
| H19 | CDKN3 Symbol ERK1/2 ATP7B staurosporine ABCB4 Gsk3 Map3k7 DMD CTCF lipopolysaccharide IGF2 SUZ12 carbon tetrachloride HNRNPA2B1 TERF2IP SOX9 Rb halofuginone PHB IL1 dicarbethoxydihydrocollidine DDX43 COL2A1 PDGF BB NOS2 TNF INSR tamoxifen PI3K (complex) CDC73 IGF2BP3 SOX2 APP TERC corticosterone H19 bucladesine EOMES IGF1R DICER1 Gm21596/Hmgb1 IRS1 DNMT3A IL1B beta-estradiol PGR E2F1 tetradecanoylphorbol acetate PARP1 ZBTB7A cigarette smoke ESR1 ERBB2 HNRNPU ZFP57 |
| UCA1 | Akt NUPR1 PTEN HNF1A ARID1A YAP1 TGFB1 ARL2 CEBPA CCND1 EZH2 |
| PVT1 | FOLR1 HR let-7 STAT5B NFIB LIN28A GAS2L3 |
| FER1L4 | RB1 |

ABCB4: ATP-binding cassette (ABC) subfamily B member 4; APP: Amyloid beta precursor protein; ARID1A: AT-rich interactive domain-containing protein 1A; ARL2: ADP Ribosylation Factor Like GTPase 2; ATP7B: ATPase copper transporting beta; CCND1: Cyclin D1; CDC73: Cell division cycle 73; CDKN3: Cyclin dependent kinase inhibitor 3; CEBPA: CCAAT enhancer binding protein alpha; COL2A1: Collagen type II alpha 1 chain; CTCF: CCCTC-binding factor; DDX43: DEAD-Box helicase 43; DMD: Dystrophin; DNMT3A: DNA methyltransferase; E2F1: E2F Transcription Factor 1; EOMES: Eomesodermin; ERK: extracellular signal-regulated kinase; ERBB2: Receptor tyrosine-protein kinase erbB-2; ESR1: Estrogen Receptor 1;

EZH2: Enhancer of zeste homolog 2; FOLR1: Folate receptor 1; GAS2L3: Growth arrest specific 2 like 3; HNF1A: HNF1 homeobox A; HNRNPA2B1: Heterogeneous nuclear ribonucleoprotein A2/B1; HNRNPU: Heterogeneous nuclear ribonucleoprotein U; HR: HR Lysine demethylase and nuclear receptor corepressor; IGF2: Insulin-like growth factor 2; IGF2BP3: Insulin-like growth factor 2 mRNA binding protein 3; IGF1R: Insulin-like Growth Factor 1 Receptor; IL1: Interleukin-1; INSR: Insulin receptor; IRS1: Insulin Receptor Substrate 1; LIN28A: Lin-28 homolog A; NFIB: Nuclear factor 1 B; NOS2: Nitric oxide synthase 2; NUPR1: Nuclear protein 1, transcriptional regulator; PARP1: Poly(ADP-ribose) polymerase 1; PDGF BB: Platelet-derived growth factor with two B subunits; PGR: Progesterone receptor; : Prohibitin; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN: Phosphatase and tensin homolog; RB1: The retinoblastoma protein; SOX2: SRY-Box Transcription Factor 2; SOX9: SRY-Box transcription factor 9; STAT5B: Signal transducer and activator of transcription 5B; TERF2IP: TERF2 interacting protein; TGFB1: Transforming growth factor beta 1; TNF: Tumor necrosis factor; TERC: Telomerase RNA component; YAP1: yes-associated protein 1; ZBTB7A: Zinc Finger And BTB Domain Containing 7A; ZFP57: Zinc Finger Protein57;

Figures

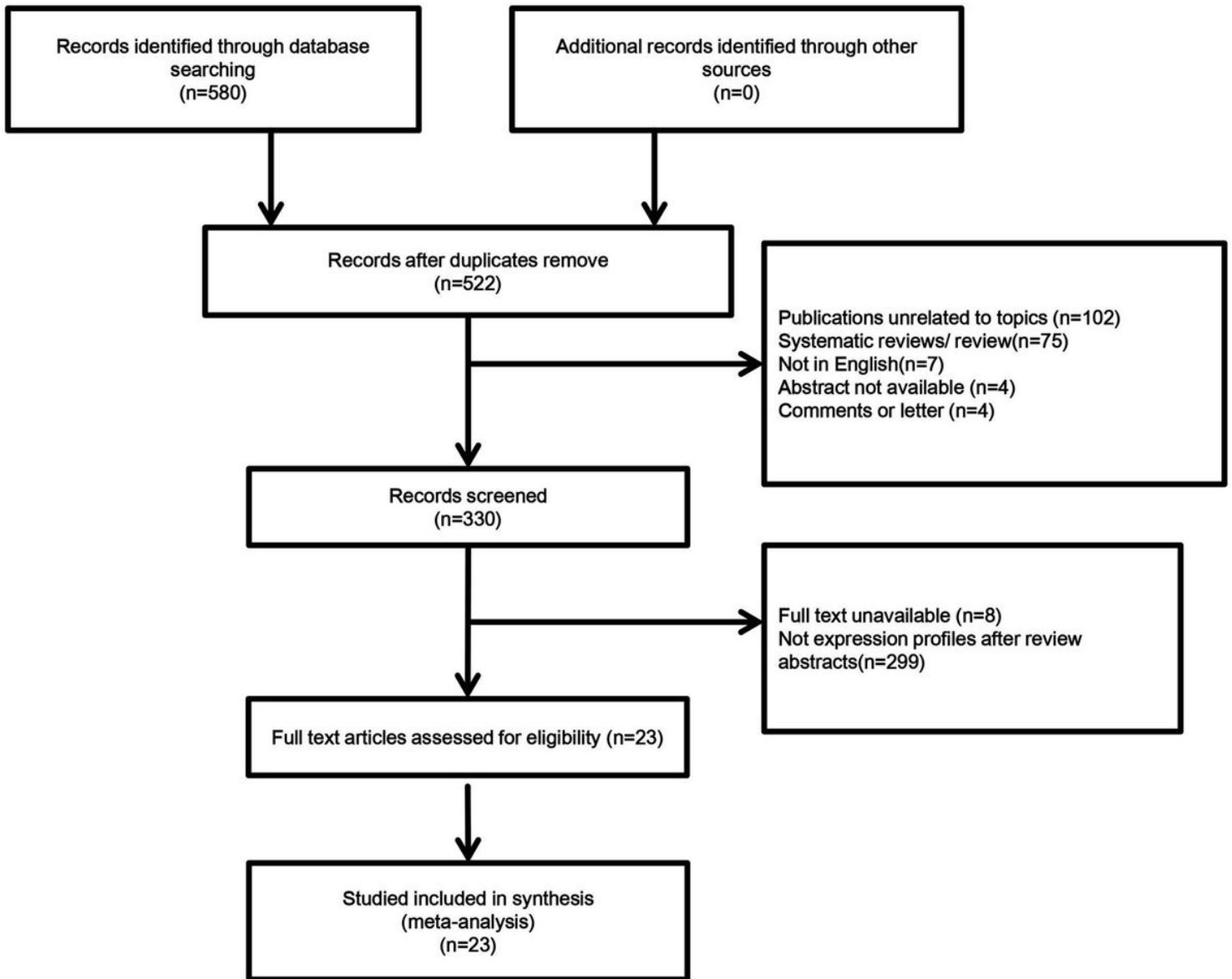


Figure 1

Flowchart showing the procedures for identifying eligible articles for inclusion. This comprehensive algorithm determined at least 23 suitable studies that used LncRNAs as biomarkers for gastric cancer diagnosis.

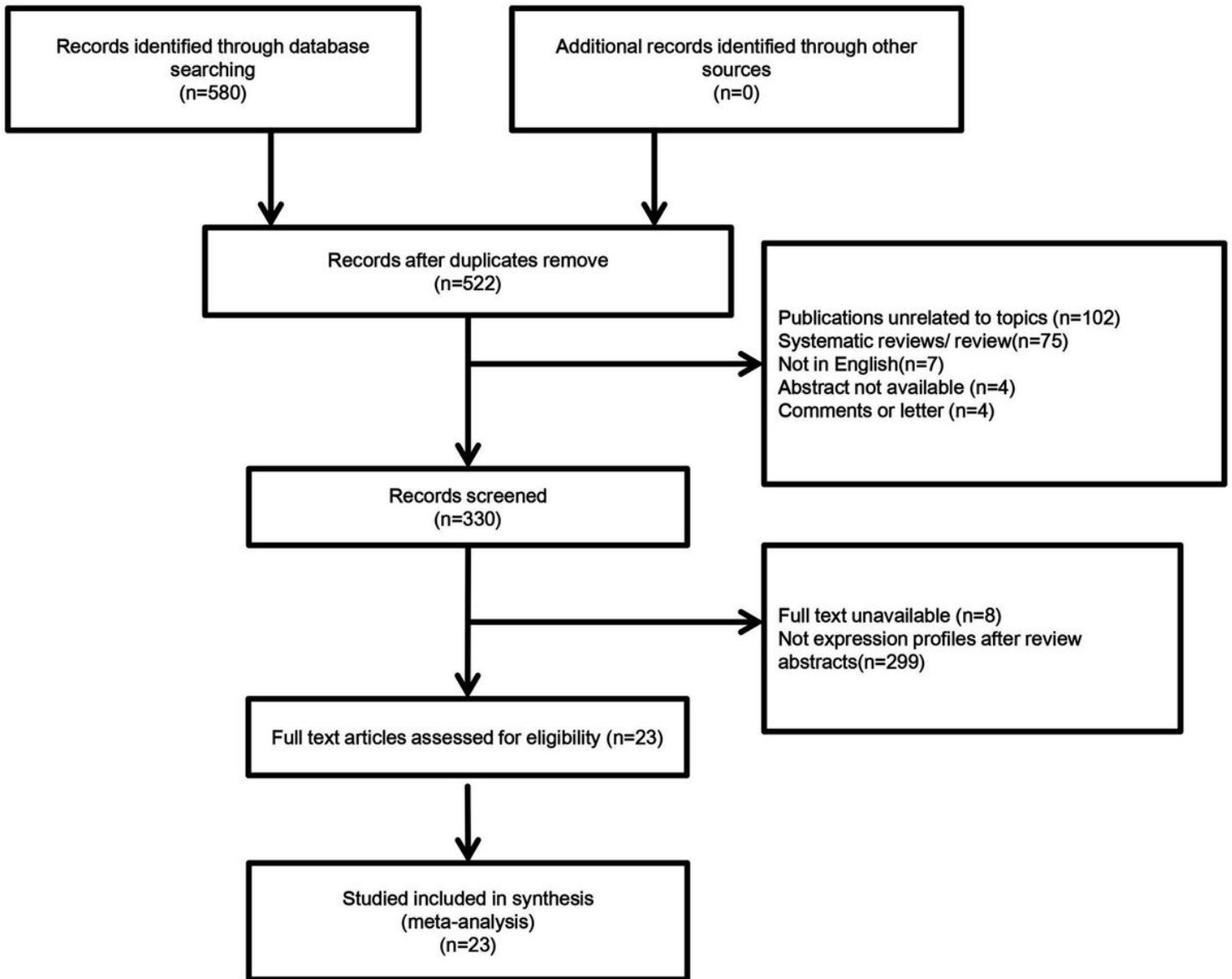


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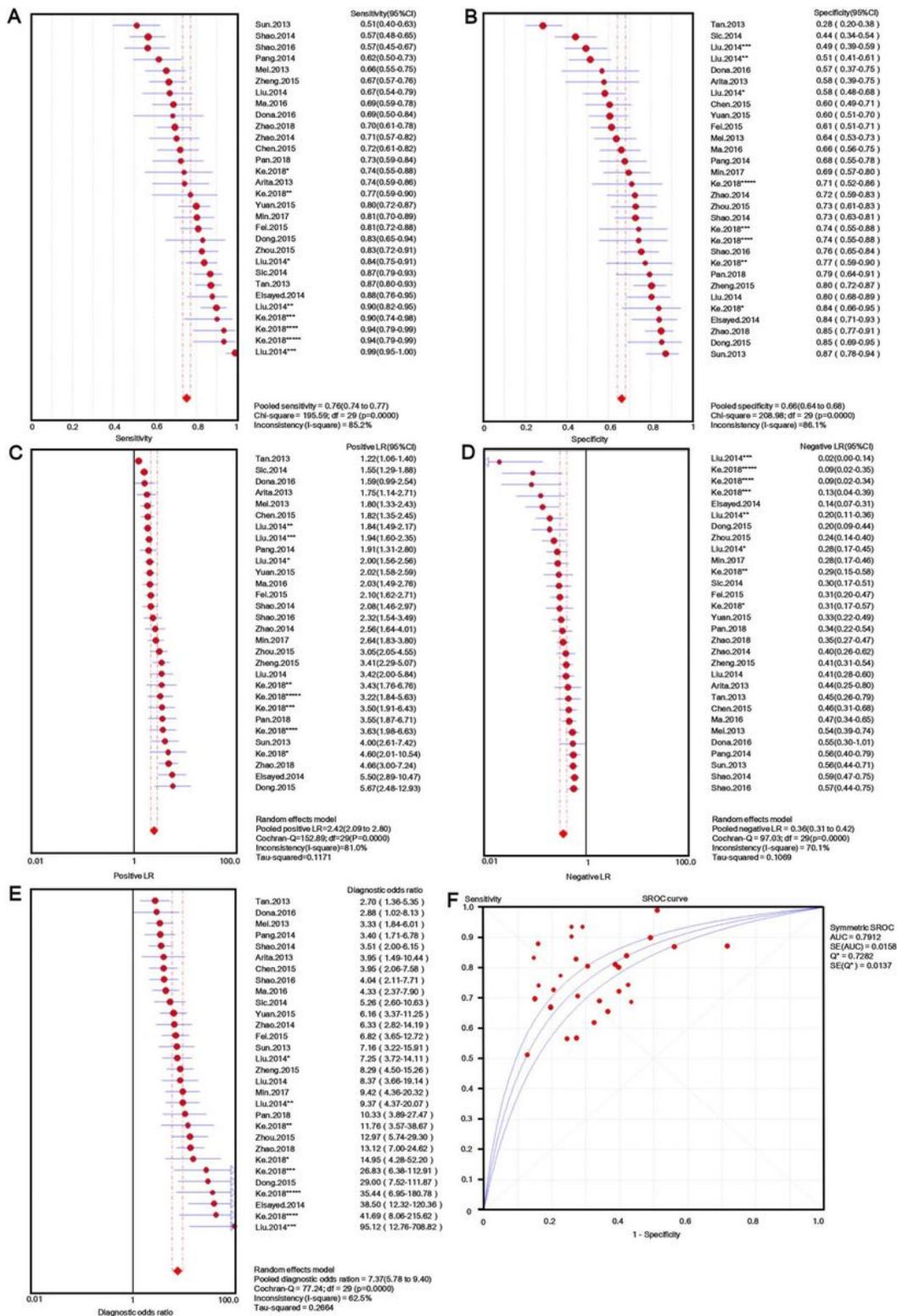


Figure 2

Forest plot of diagnostic value of each index of dysregulated LncRNAs expression in GC. A, Pooled sensitivity of dysregulated LncRNAs. B, Pooled specificity of dysregulated LncRNAs. C, Pooled positive likelihood ratio of dysregulated LncRNAs. D, Pooled negative likelihood ratio of dysregulated LncRNAs. E, Pooled diagnostic odds ratio of dysregulated LncRNAs. F, sROC of dysregulated LncRNAs.*:Selected LncRNAs reported by one publication.

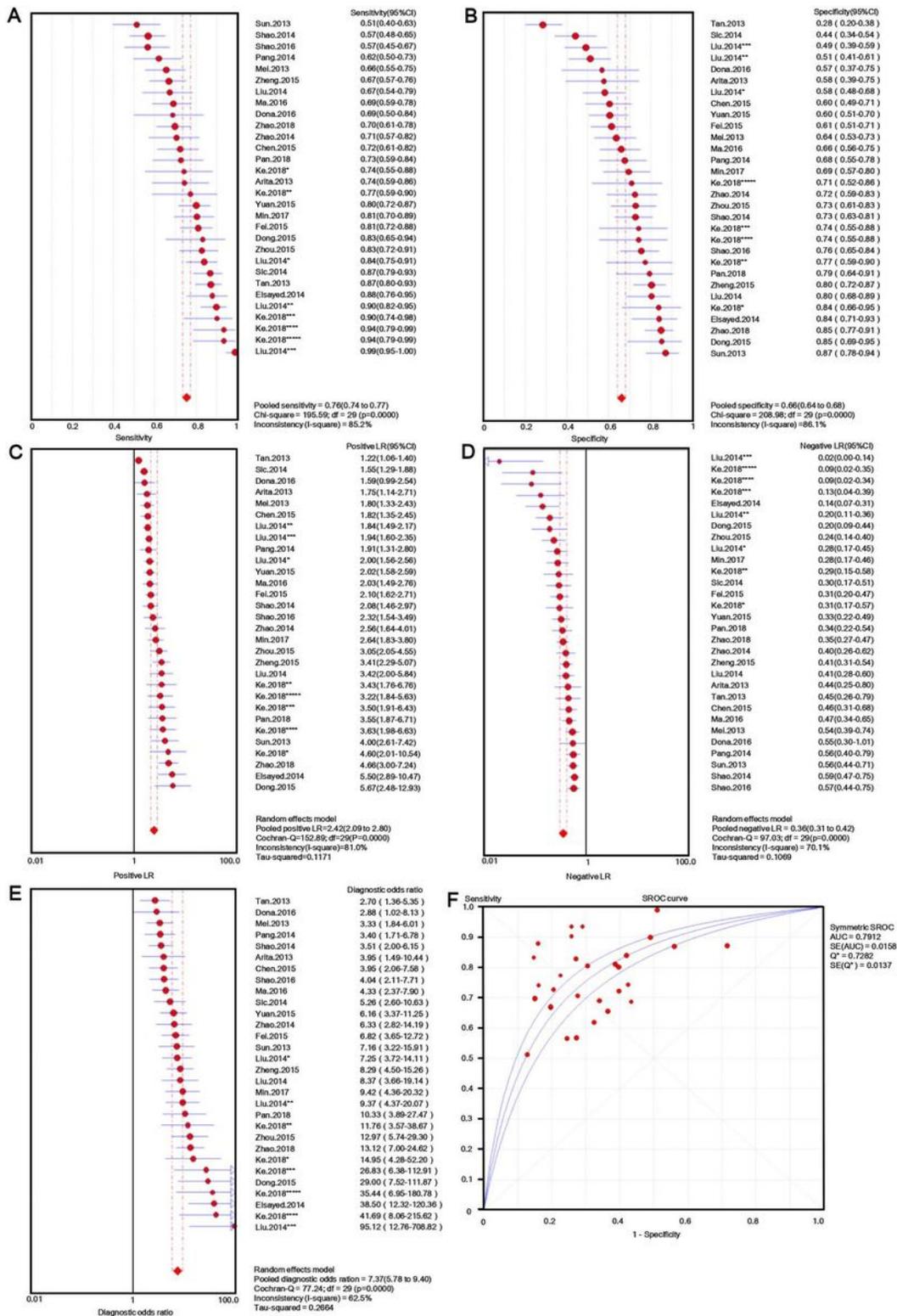


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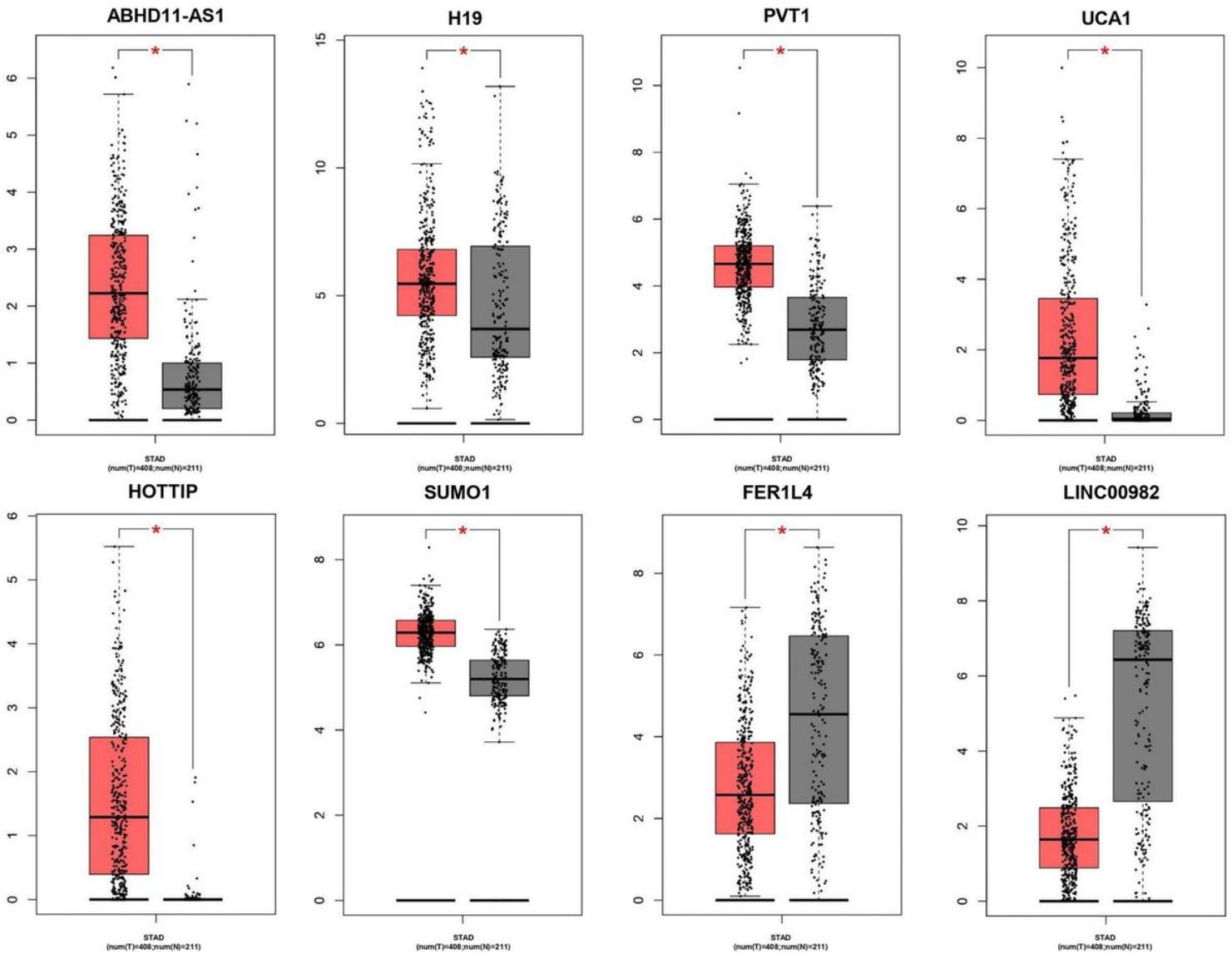


Figure 3

Eight LncRNAs with significant difference in GC specimen compared to normal specimen. To further identify the reported LncRNAs' expression levels for GC and normal people, all genes were further analysed by the GEPIA website. Eight LncRNAs were verified in significant expression levels in GC patients compared to healthy people (The method for differential analysis is one-way ANOVA, using stomach tissue and normal tissue as variable for calculating differential expression. Matched Normal data was selected the dataset from TCGA normal + GTEx normal tissue. Genes with higher $|\log_2FC|$ values and lower q values than pre-set thresholds are considered differentially expressed genes. *P < 0.01, Tumour: Red colour; Normal: Grey colour).

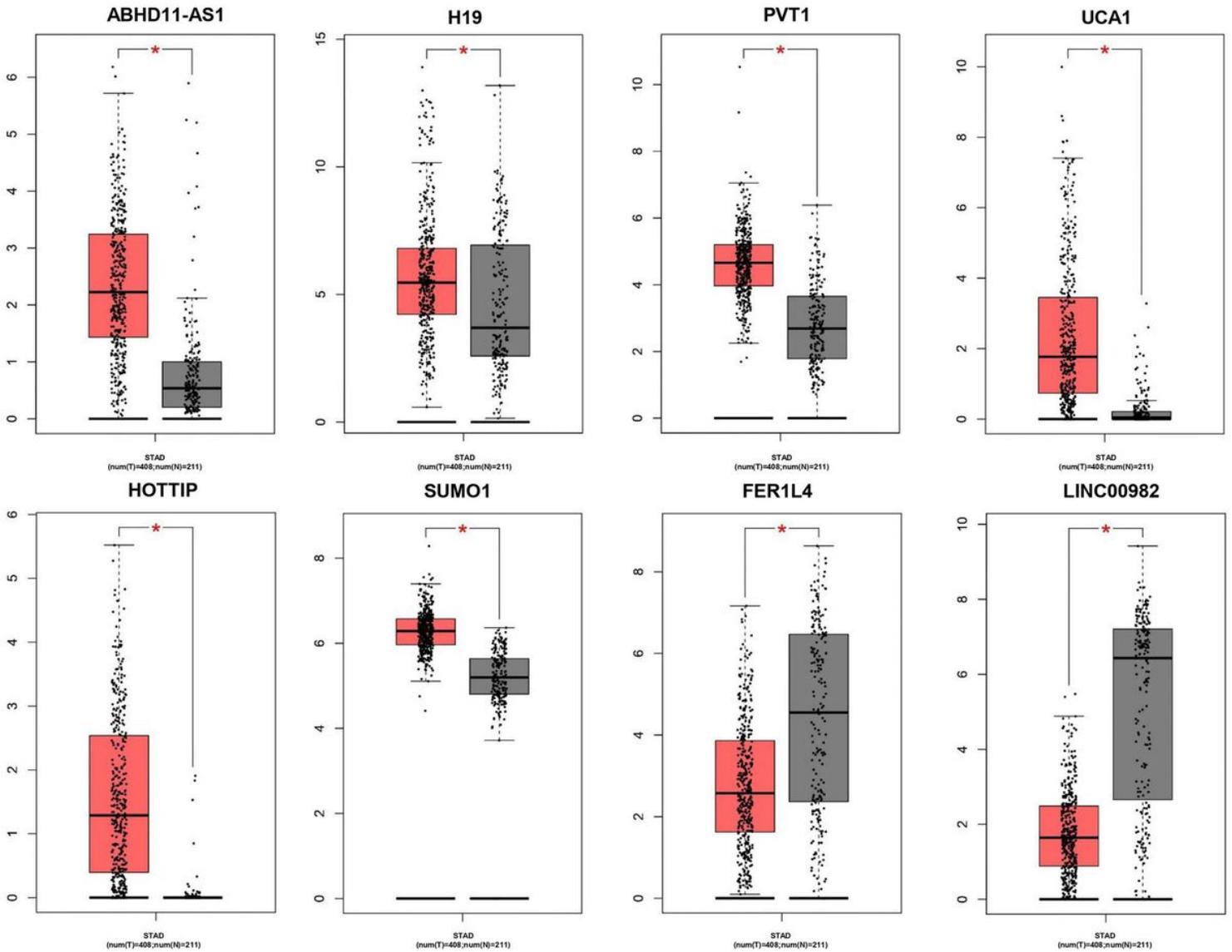


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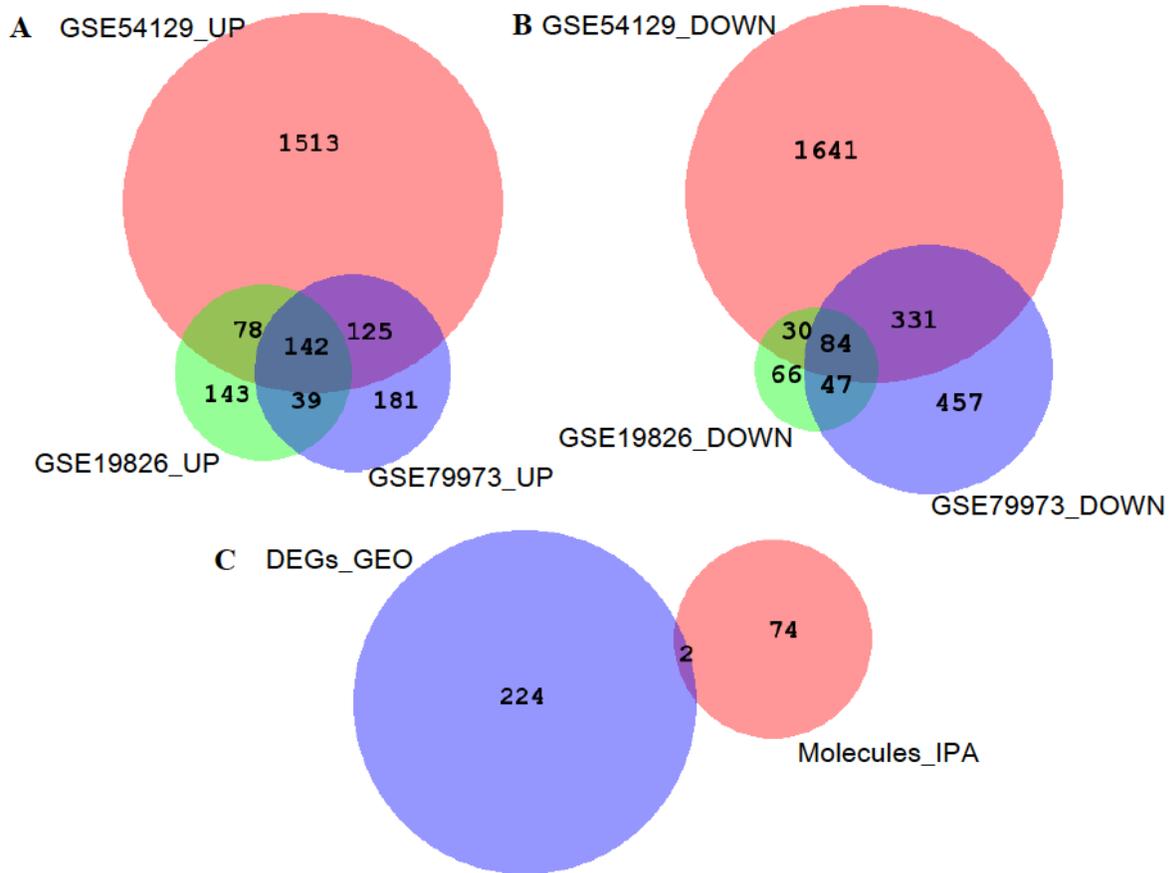


Figure 4

Relationships between DEGs and eight dysregulated LncRNAs in GC patients. A. Venn diagram demonstrating the DEGs upregulated in three datasets (GSE52149, GSE19826 and GSE 79973, $P < 0.05$, $\text{LogFC} > 2$); B. Venn diagram demonstrating the DEGs downregulated in three datasets ($P < 0.05$, $|\text{log}_2\text{FC}| > 2$); C. Venn diagram showing the molecules selected from DEGs that interacted with dysregulated LncRNAs in GC patients.



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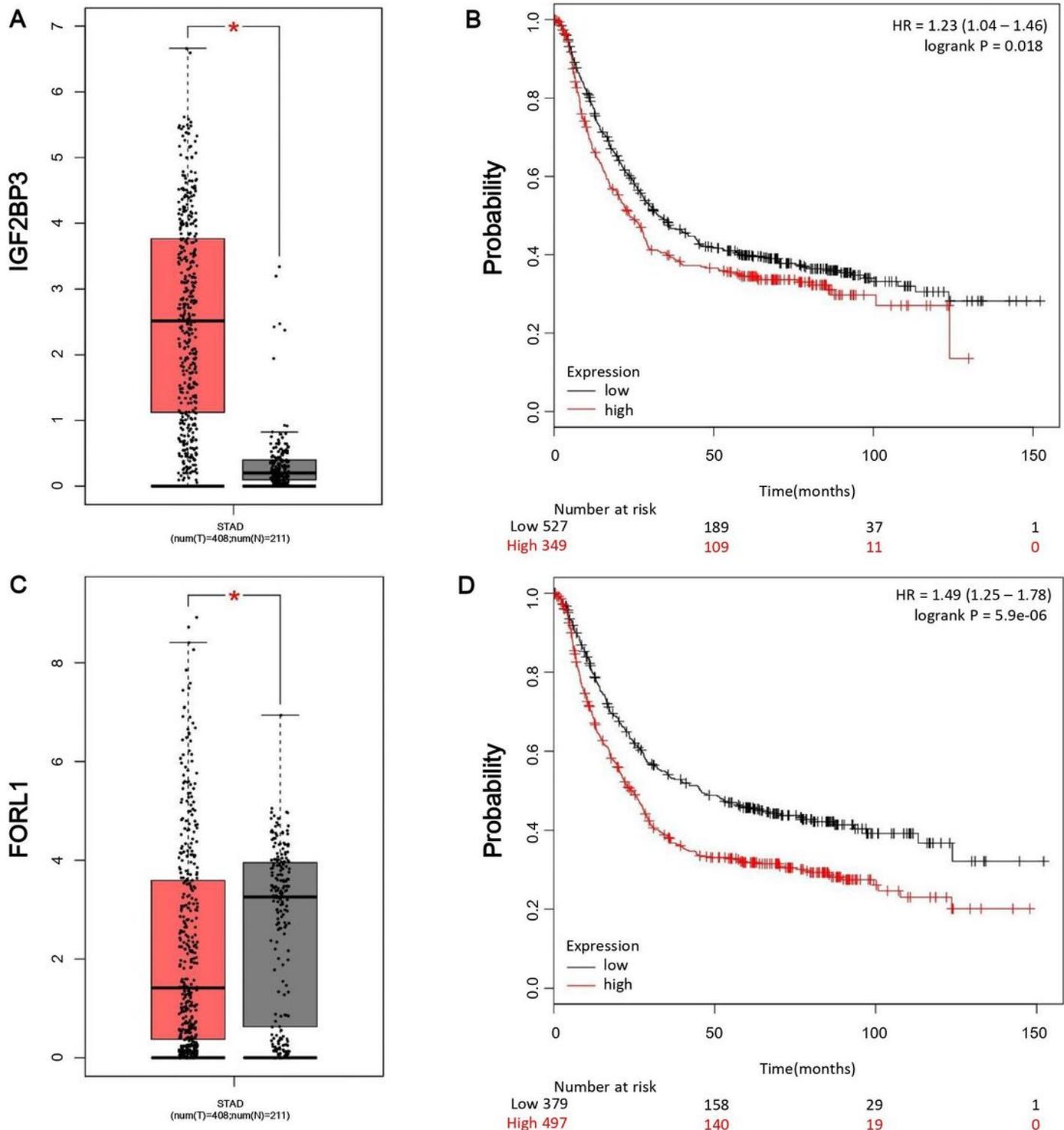


Figure 5

Expression and prognostic value of IGF2BP3 and FOLR1 in GC patients. The expression and potential role of IGF2BP3 and FOLR1 in prognosis in GC were further identified through the GEPIA website and Kaplan Meier Plotter online tools. A. Expression of IGF2BP3 in GC specimen and normal specimen. B. Prognostic relationship of IGF2BP3 in GC patients. C. Expression of FOLR1 in GC specimen and normal specimen. D. Prognostic relationship of FOLR1 in GC patients. (The method for differential analysis is one-way ANOVA,

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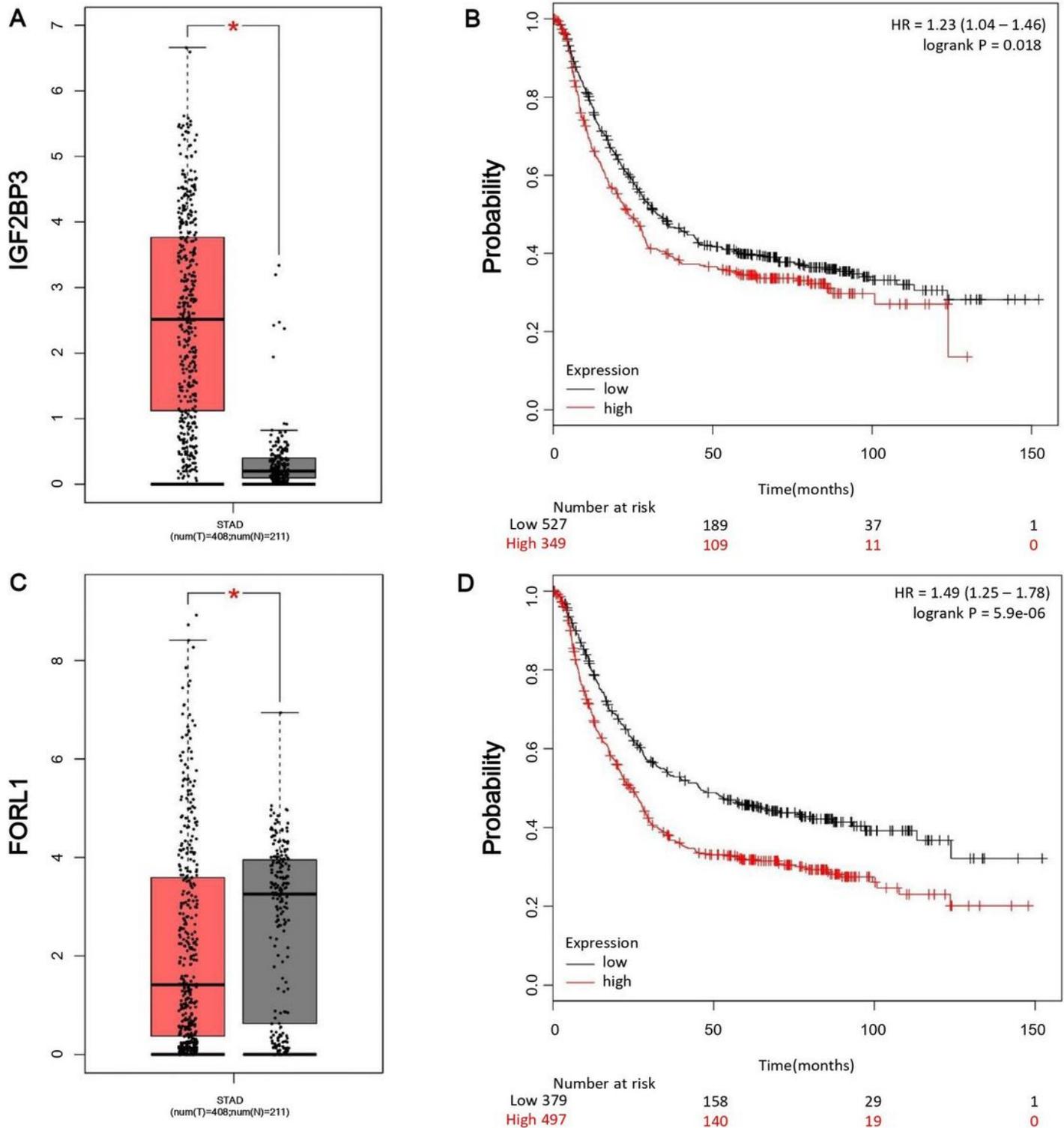


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