

# UBE2R2-AS1, as a prognostic marker of gastric cancer, promotes the malignant phenotype of gastric cancer cells

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**Summary.** Background and Objectives. This study aimed to unveil the potential of UBE2R2-AS1 dysregulation in gastric cancer. In addition, its biological function was assessed.

**Materials and Methods.** UBE2R2-AS1 expression was predicted in the ENCORI database. Paired gastric cancer and noncancerous tissues were collected. UBE2R2-AS1 expression was confirmed using RT-qPCR in our patient set. The association of UBE2R2-AS1 with the clinical data of patients was analyzed. Evaluation of the prognostic value of UBE2R2-AS1 was via Kaplan-Meier and Univariate/Multivariate Cox analyses. The effect of UBE2R2-AS1 on the cancer cell malignant phenotype was investigated.

**Results.** Gastric cancer tissues and cells significantly overexpressed UBE2R2-AS1. UBE2R2-AS1 was significantly more abundant in unfavorable clinical pathology, including advanced TNM stage and lymph node metastasis. High expression of UBE2R2-AS1 predicted a poor prognosis with a hazard ratio (HR) of 3.041 and 2.805 after Univariate and Multivariate Cox analysis, respectively. UBE2R2-AS1 can act as a sponge for miR-302b-5p to promote cell proliferation, migration, and invasion of gastric cancer.

**Conclusion.** The expression of UBE2R2-AS1 allowed the prognostic stratification of gastric cancer patients. UBE2R2-AS1 may accelerate the progression of gastric cancer via miR-302b-5p.

**Key words:** Gastric cancer, UBE2R2-AS1, Progression, Prognosis

## Introduction

With over one million new cases in 2020, gastric cancer was responsible for 7.7% of new deaths worldwide and is ranked the fourth most lethal cancer type (Sung et al., 2021). Notably, dietary factors such as nitrites and salted foods, and, in particular, *Helicobacter pylori* infection are known dominant causes of gastric cancer (Machlowska et al., 2020). Despite improved food preservation and decreased *Helicobacter pylori* infection in young Chinese people, people with chronic infection since early childhood are at high risk of gastric cancer (de Martel et al., 2020). Gastric adenocarcinoma accounts for the vast majority of gastric malignancies, around 95% (Balakrishnan et al., 2017). Currently, the prognosis of gastric cancer is mainly dependent on the tumor diagnostic stage and classification (intestinal or diffuse type), with only 28.3% of newly discovered gastric cancer patients surviving more than five years after diagnosis (Marqués-Lespier et al., 2016). This makes the discovery and confirmation of prognostic markers very important.

With the development and application of microarray techniques and bioinformatics, a large number of protein-coding and non-protein-coding molecules, such as long noncoding RNAs (lncRNAs), have been screened for their potential prognosis of specific diseases, including gastric cancer (Mirzaei et al., 2018; To et al., 2018). lncRNAs, despite not having the ability to encode genes, can alter gene expression post-transcriptionally by sponging microRNAs (miRNA) as competing endogenous RNAs (ceRNAs), thus influencing messenger RNA (mRNA) translation (Ali Syeda et al., 2020). Many studies have documented the association between lncRNA dysregulation and the diagnosis, prognosis, and pathogenesis of cancer, including gastric cancer (Jafari and Abediankenari, 2017; García-Sancha et al., 2019; Zou et al., 2019). The

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lncRNA UBE2R2-AS1 is involved in the cancer progression of glioma, hepatocellular carcinoma, and prostate cancer (Xu et al., 2019; Wu et al., 2020; Wang et al., 2022). UBE2R2-AS1 has been identified as a prognostic marker of non-small cell lung and prostate cancer (Liu et al., 2022; Wang et al., 2022). Nevertheless, current knowledge is still lacking on the specific clinical significance and effect of UBE2R2-AS1 dysregulation on gastric cancer.

In this article, we determined the expression of UBE2R2-AS1 and estimated its prognostic value, as well as its potential role in gastric cancer progression.

## Materials and methods

### *Patients and collection of gastric tissues*

This retrospective analysis enrolled 125 patients diagnosed with gastric cancer and treated with gastric resection at the 2nd Affiliated Hospital of Fujian Medical University from January 2013 to December 2015. Patient characteristics were collected and listed in Table 1. The cutoff between young and old is now considered to be 60 years (Wauters et al., 2021), being the value employed for comparisons between groups. All human samples were obtained with written informed consent from patients. The ethics committee of the 2nd Affiliated Hospital of Fujian Medical University approved the research use of these tissues.

### *RNA interference and plasmid construction*

The siRNA against UBE2R2-AS1 (si-UBE2R2-AS1) and negative control against UBE2R2-AS1 (si-NC) were synthesized by Genechem (Shanghai, China), as well as the miR-302b-5p inhibitor (anti-miR) and the corresponding negative control (anti-NC). Recombinant vectors pmirGLO wt-UBE2R2-AS1 and pmirGLO mut-UBE2R2-AS1 from site-directed mutagenesis were constructed by TSINGKE Biological (Beijing, China).

### *Gastric cell line culture and transfection*

Four gastric cancer cell lines, AGS, SNU-16, NCI-N87, and KATO-III, and one immortalized normal gastric epithelial cell line, GES-1, were purchased from China's National Collection of Authenticated Cell Cultures. These cells were grown in RPMI 1640 medium (Sigma-Aldrich, USA) and maintained in a humidified atmosphere containing 5% CO<sub>2</sub> (v/v) at 37°C. Transfection was mediated with Lipofectamine 3000 transfection reagent (Invitrogen, USA) according to the manufacturer's application notes. The transfection efficiency was monitored via quantitative real-time polymerase chain reaction (qRT-PCR).

### *Total RNA isolation and qRT-PCR*

For UBE2R2-AS1 analysis, total RNA was isolated

with TRIzol<sup>®</sup> reagent (Thermo Fisher Scientific, USA) from cells or tissues, and reversely transcribed to cDNA using the SuperScript III Reverse Transcriptase kit (Thermo Fisher Scientific, USA). For the miR-302b-5p expression assay, total RNA was extracted with TRIzol<sup>®</sup> reagent and reversely transcribed to cDNA with the miScript Reverse Transcription Kit (Qiagen, Germany). qRT-PCR detection with SYBR Green qPCR system (Roche, Germany) was performed on a LightCycler 480 II (Roche Diagnostics, Switzerland). Data were normalized to the expression of the housekeeping *GAPDH* gene for UBE2R2-AS1 and *U6* for miR-302b-5p using the method of 2<sup>-ΔΔCt</sup>.

### *Proliferation assayed by Cell Counting Kit-8 (CCK-8)*

AGS and NCI-N87 cells were seeded into 96-well plates at 2×10<sup>3</sup> per well and incubated at 37°C with 5% CO<sub>2</sub>. At the detection time points every 24 hours over 72 hours, CCK-8 solution was added to each well and the plates were incubated for a further 2 hours. The absorbance at each time point was read using a Spectra Max M2e (Molecular Devices, USA).

### *Migration and invasion assay via Transwell chambers*

For migration assays, Transwell chambers (Corning, USA), 8 μM PET Transwell inserts, without Matrigel-coating were used. For invasion assays, Matrigel Invasion Chambers coated with Matrigel (BD Biosciences) were used. Two×10<sup>4</sup> starved AGS and NCI-N87 cells were seeded in the upper inserts containing serum-free RPMI 1640 medium, whereas the lower inserts were filled with RPMI 1640 medium with 10% FBS. Cells were incubated for 24 hours. Non-migrated or non-invasive cells on the upper side of the inserts were cleaned with a cotton swab and the cells that passed through the porous membrane were fixed and stained with crystal violet. The cells were counted in five random fields.

### *Dual-luciferase reporter assay*

The luciferase reporter assay was performed to clarify the binding between UBE2R2-AS1 and miR-302b-5p. Cells were co-transfected with wt-UBE2R2-AS1 or mut-UBE2R2-AS1 and anti-miR or anti-NC. After transfection for 48h, luciferase activity was measured. The results were calculated by normalizing firefly luciferase activity with Renilla luciferase activity.

### *Statistical analysis*

The student's t-test was utilized to assess differences between two groups. Comparisons between multiple groups were made using a two-way analysis of variance (ANOVA). Pearson's Chi-square test was used to analyze the relationship between UBE2R2-AS1 expression and the clinicopathological parameters of the patients. Survival analysis was depicted by Kaplan-

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Meier curves using the log-rank test. The prognostic value of parameters in gastric cancer was evaluated by Univariate and Multivariate Cox regression analyses. Values of  $P < 0.5$  were statistically significant.

### Results

#### UBE2R2-AS1 was overexpressed in gastric cancer tissues and cells

After retrieval in the ENCORI database, stomach adenocarcinoma (STAD) tissues presented higher UBE2R2-AS1 levels compared with normal tissues (Fig. 1A). A total of 125 patients with gastric cancer were confirmed with UBE2R2-AS1 expression using the qRT-PCR assay. The result revealed that UBE2R2-AS1 was upregulated in gastric cancer tissues when compared with adjacent noncancerous tissue ( $P < 0.001$ , Fig. 1B). To further confirm this, we also examined UBE2R2-AS1 expression in four gastric cancer cell lines and one normal gastric epithelial cell line. As shown in Figure 1C, UBE2R2-AS1 was more highly expressed in cancerous cells than in normal gastric cells ( $P < 0.001$ ).

#### Correlation of UBE2R2-AS1 expression with clinicopathological features of gastric cancer patients

Two groups, high and low UBE2R2-AS1 expression, were formed according to the median value of UBE2R2-AS1 expression in our patient set. Then, the relationship between UBE2R2-AS1 expression and clinical parameters was analyzed. Correlations between high UBE2R2-AS1 expression and advanced TNM stage ( $P = 0.004$ ) or lymph node metastasis ( $P = 0.009$ ) were observed (Table 1).

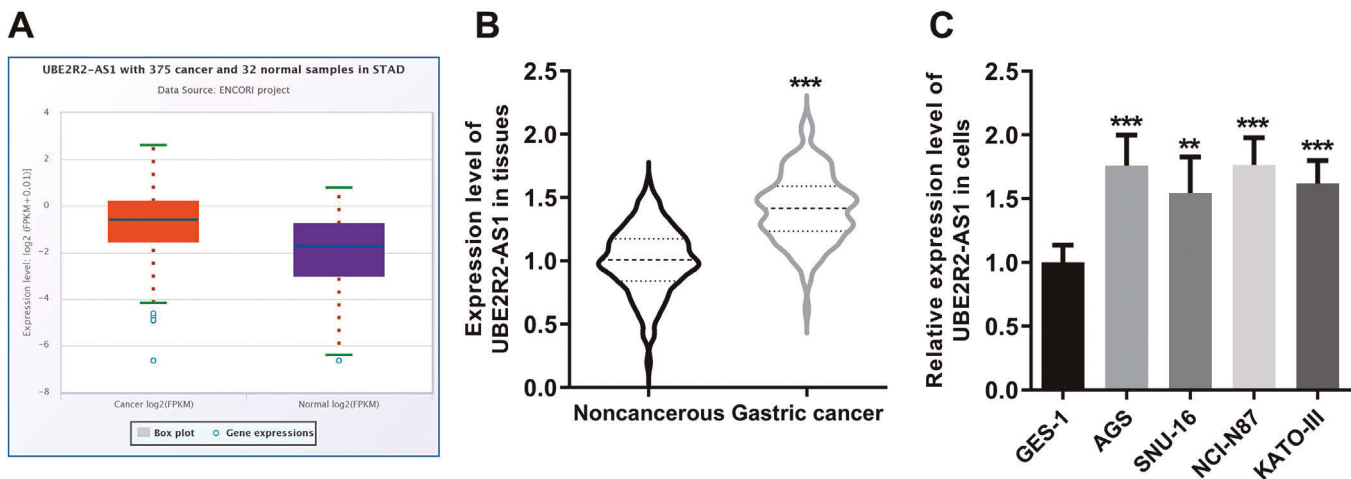
#### High expression of UBE2R2-AS1 predicted poor five-year survival for gastric cancer patients

Next, to confirm the clinical significance of UBE2R2-AS1 in the prognosis of gastric cancer patients, the clinical survival information of the patients was

**Table 1.** Association between UBE2R2-AS1 expression level and pathologic characteristics in patients with gastric adenocarcinoma.

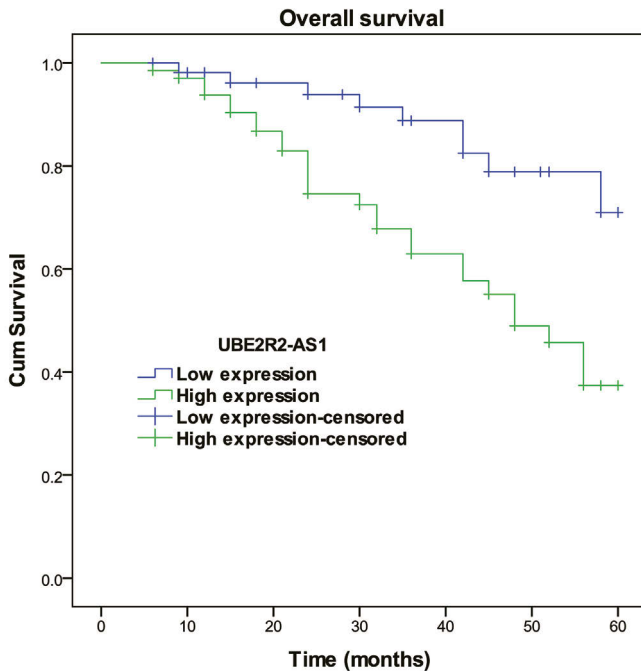
Parameters		UBE2R2-AS1 expression			P-value
		Total 125	High 57	Low 68	
Gender	Male	72	30	42	0.303
	Female	53	27	26	
Age (years)	<60	62	25	37	0.240
	≥60	63	32	31	
Tumor size (mm)	<50	67	36	31	0.050
	≥50	58	21	37	
Tumor location	Upper and GEJ junction	50	25	25	0.420
	Middle and lower	75	32	43	
Lauren classification	Intestinal	58	29	29	0.358
	Diffuse	67	28	39	
Invasion depth	T1/T2	76	39	37	0.110
	T3/T4	49	18	31	
TNM stage	I-II	68	39	29	0.004**
	III-IV	57	18	39	
Lymph node metastasis	N0	79	43	36	0.009**
	N1/N2/N3	46	14	32	
Helicobacter pylori	Negative	87	49	38	0.514
	Positive	38	19	19	

\*\* $P < 0.001$ . GEJ, gastro-esophageal junction; TNM, tumor-nodes-metastasis.



**Fig. 1.** Expression levels of UBE2R2-AS1 in gastric cancer and noncancerous tissues. **A.** UBE2R2-AS1 expression in stomach adenocarcinoma (STAD) tissues was analyzed by ENCORI. **B.** Comparison of UBE2R2-AS1 expression levels in gastric cancer and noncancerous tissues in 125 matched specimens. The expression level of UBE2R2-AS1 was higher in cancerous tissues than in noncancerous tissues. **C.** Comparison of UBE2R2-AS1 expression levels in gastric cancer cell lines (AGS, SNU-16, NCI-N87, and KATO-III) and a normal gastric epithelial cell line (GES-1). The expression levels of UBE2R2-AS1 were significantly higher in gastric cancer cells than in normal cells. \*\*\* $P < 0.001$ .

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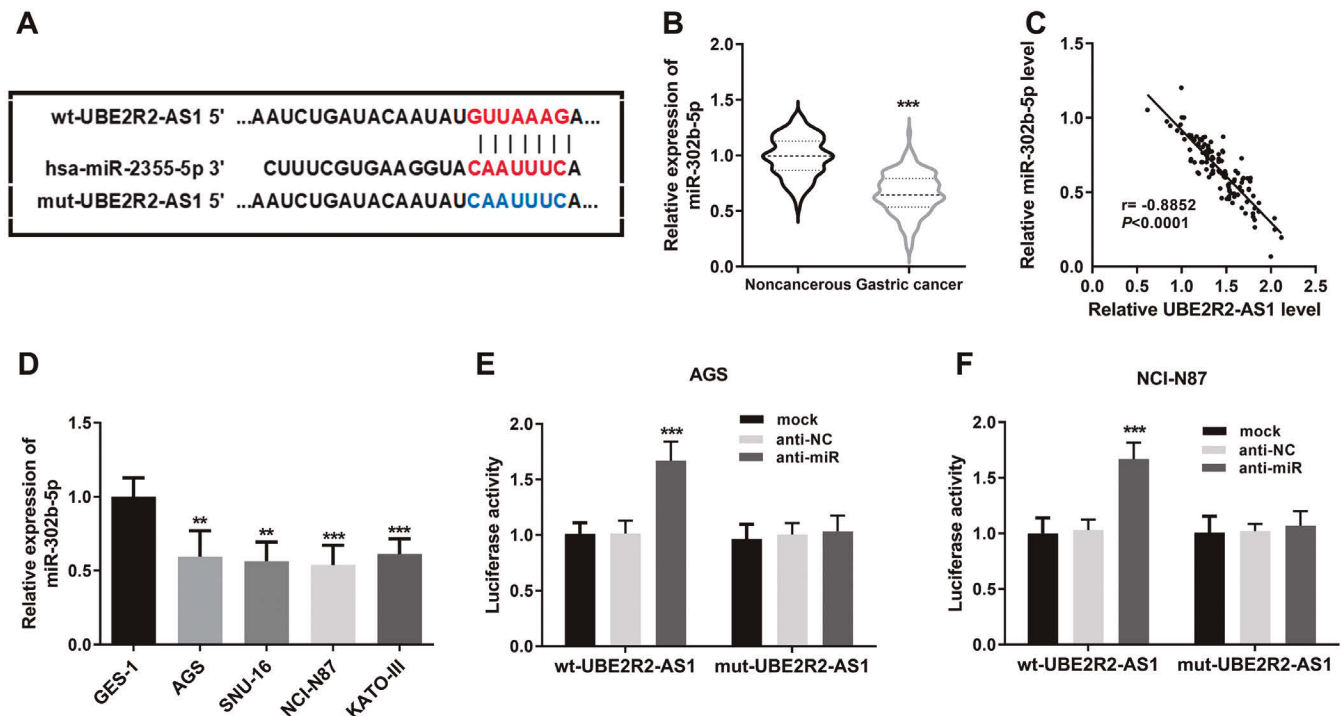


**Fig. 2.** Kaplan-Meier overall survival curves of patients with gastric cancer based on UBE2R2-AS1 expression levels. Patients from the higher expression group had significantly lower overall survival than those in the low-level group (Log-rank test,  $P=0.002$ ).

analyzed by Kaplan-Meier estimation. As shown, patients with high expression of UBE2R2-AS1 were associated with poor overall survival (Log-rank  $P=0.002$ , Fig. 2). Furthermore, UBE2R2-AS1 expression was an independent factor for predicting five-year overall survival in gastric cancer patients by univariate (HR=3.041, 95%CI: 1.428-6.475,  $P=0.004$ ; Table 2) and multivariate Cox regression analysis (HR=2.805, 95%CI: 0.951-5.133,  $P=0.008$ ; Table 2). These data indicate that UBE2R2-AS1 is a potential biomarker for predicting the prognosis of gastric cancer patients.

## UBE2R2-AS1 can sponge miR-302b-5p

By prediction in starBase 3.0, miR-302b-5p shares complementary binding sites with UBE2R2-AS1 (position 81-88) (Fig. 3A). MiR-302b-5p was downregulated in both gastric cancer tissues and cells ( $P<0.01$ , Fig. 3B,C), with a negative correlation between the expression of UBE2R2-AS1 and miR-302b-5p ( $r=-0.8852$ ,  $P<0.001$ , Fig. 3D). To verify their targeting relationship, the dual-luciferase reporter assay was conducted with AGS cells co-transfected with wt- or mut-UBE2R2-AS1 luciferase reporter plasmid, and anti-NC or anti-miR. As demonstrated in Figure 3E, luciferase activity was significantly reduced when AGS



**Fig. 3.** MiR-302b-5p was the target of UBE2R2-AS1. **A.** UBE2R2-AS1 contained a set of binding sites for miR-302b-5p. **B.** The expression level of miR-302b-5p was lower in gastric cancer tissues than in noncancerous tissues. **C.** The expression level of miR-302b-5p was lower in gastric cancer cells than in normal cells. **D.** The expression of UBE2R2-AS1 and miR-302b-5p was inversely correlated. **E, F.** The dual-luciferase reporter assay revealed the interaction between miR-302b-5p and UBE2R2-AS1. \*\* $P<0.01$ , \*\*\* $P<0.001$ .

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cells were co-transfected with anti-miR and wt-UBE2R2-AS1, while no change was observed in cells co-transfected with anti-miR and mut-UBE2R2-AS1. Accordingly, UBE2R2-AS1 can sponge miR-302b-5p in AGS cells.

### UBE2R2-AS1 promotes gastric cell proliferation, migration, and invasion via miR-302b-5p

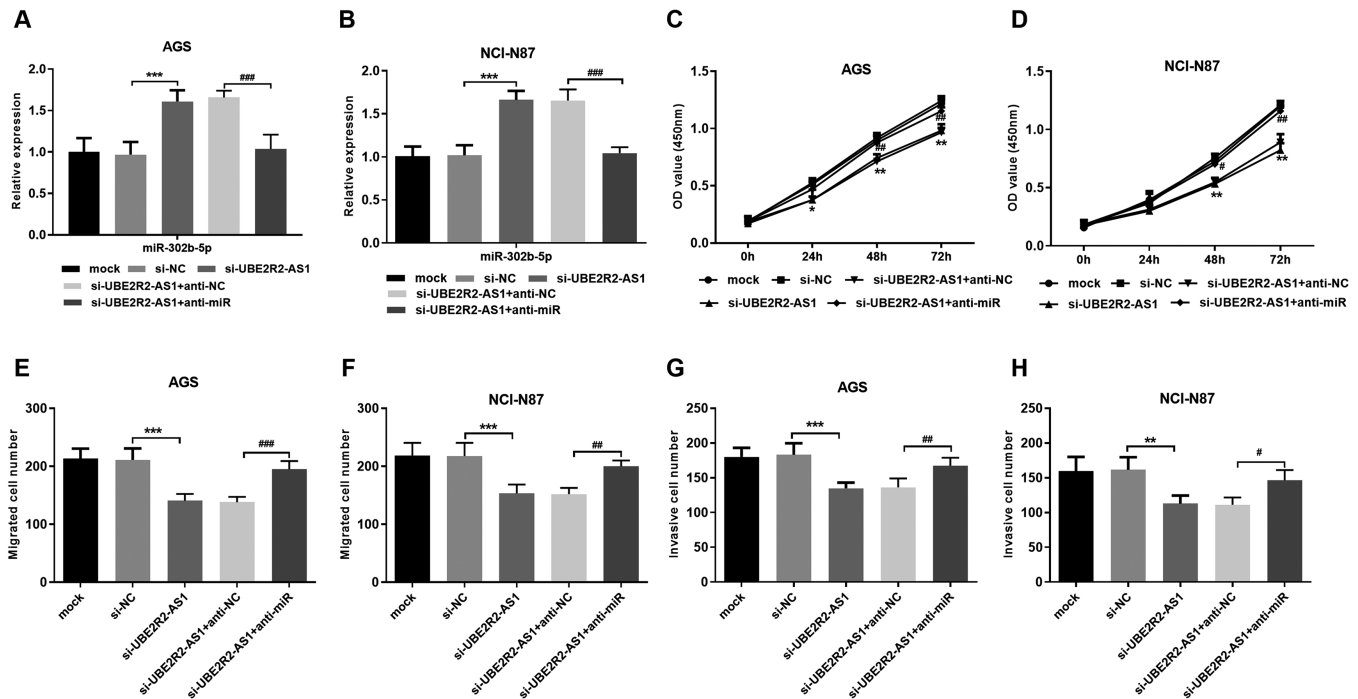
Subsequently, the role of UBE2R2-AS1 in the cellular function of gastric cancer cells was investigated. RT-qPCR data indicated that the expression levels of

UBE2R2-AS1 and TOP1MT mRNA were significantly altered in AGS and NCI-N87 cells after transfection ( $P < 0.001$ , Fig. 4A,B). Cell proliferation, migration, and invasion abilities were subsequently examined. As indicated in Figure 4C-H, the proliferation, invasion, and migration of AGS and NCI-N87 cells were significantly suppressed by a UBE2R2-AS1 inhibitor (anti-miR) compared with the anti-NC group ( $P < 0.05$ ). Nevertheless, TOP1MT inhibition reversed most of the inhibitory effects of UBE2R2-AS1 on the proliferation, migration, and invasion of AGS and NCI-N87 cells. These findings imply that UBE2R2-AS1 inhibits the

**Table 2.** Univariate and multivariate analyses of clinical characteristics associated with overall survival of gastric cancer patients.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
UBE2R2-AS1	3.041	1.428-6.475	0.004**	2.805	0.951-5.133	0.008**
Gender	1.649	0.824-3.299	0.157			
Age	1.262	0.642-2.482	0.500			
Tumor size	1.649	0.849-3.200	0.139			
Tumor location	2.536	1.109-5.799	0.027*	2.210	0.951-5.133	0.065
Lauren classification	2.546	1.197-5.417	0.015*	2.469	1.155-5.279	0.020*
Invasion depth	1.545	0.803-2.970	0.192			
TNM stage	2.378	1.213-4.663	0.012*	1.783	0.922-3.449	0.044
Lymph node metastasis	2.319	1.203-4.472	0.012*	2.805	1.305-6.031	0.086
Helicobacter pylori	1.351	0.650-2.810	0.421			

\* $P < 0.05$ , \*\* $P < 0.01$ . TNM, tumor-nodes-metastasis; HR, hazard ratio.



**Fig. 4.** Downregulation of UBE2R2-AS1 suppressed AGS and NCI-N87 cell proliferation, migration, and invasion by regulating miR-302b-5p. **A, B.** qRT-PCR was utilized to detect the transfection efficiency of UBE2R2-AS1 siRNA (si-UBE2R2-AS1) and miR-302b-5p inhibitor in AGS and NCI-N87 cells. **C, D.** Cell proliferation was assayed by the CCK-8 method. **E, F.** A Transwell assay was used to detect cell migration. **G, H.** A modified Transwell assay was utilized to assess cell invasion. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  (si-UBE2R2-AS1 vs. si-NC); # $P < 0.05$ , ## $P < 0.01$ , ### $P < 0.001$  (si-UBE2R2-AS1 + anti-miR vs. si-UBE2R2-AS1 + anti-NC).

cell's proliferative, migratory, and invasive ability, at least partially, by targeting TOP1MT.

## Discussion

Abnormal expression of lncRNAs has been observed in various cancers (Gu et al., 2015; Wang et al., 2018; Ghafouri-Fard and Taheri, 2020). Previous studies demonstrated that the dysregulated expression level of lncRNAs is usually associated with cancer/tumor prognosis, including gastric cancer (Yuan et al., 2020). Many factors may affect the prognosis of cancer patients, however, research developments in lncRNA's potential role in patient prognosis could lead to the use of lncRNAs as a new approach for medical treatment in the future (Sexton et al., 2020). From this perspective, the discovery of lncRNAs involved in the prognosis of gastric cancer patients will help develop therapeutic targets in the future. In this study, the expression of UBE2R2-AS1 was found to be upregulated in gastric cancer tissues and cell lines. Furthermore, this upregulation was associated with unfavorable clinical features, such as high TNM stage and positive lymph node metastasis. In addition, gastric cancer patients with high UBE2R2-AS1 expression exhibited a shorter overall survival; therefore, it could act as a potent prognosis predictor of gastric cancer. This was in line with the results of Jin et al., who reported that UBE2R2-AS1 was a member of prognosis-related lncRNAs in stomach adenocarcinoma (Jin et al., 2023).

Clarification of the mechanism of lncRNAs is essential to elucidate their physiological role in cancer (Salilew-Wondim et al., 2020). Dysfunction of lncRNAs sponges downstream miRNAs and thus disturbs the expression of miRNA-targeting genes, which is implicated in the pathogenesis of cancer (Tan et al., 2021). To explore the function that UBE2R2-AS1 may perform in gastric cancer, its putative target miRNA was deduced to be miR-302b-5p by bioinformatics. The negative correlation between their expression and luciferase activity changes verifies that miR-302b-5p was the miRNA target of UBE2R2-AS1. Notably, downregulation of miR-302b-5p was reported in gastric cancer patients (Khalili et al., 2012). The expression of miR-302b-5p was inversely correlated with poor overall survival in stage IV gastric cancer patients (Tang et al., 2018).

Dysregulation of lncRNAs in cancer inevitably changes the miRNA profile, which in turn influences the function of lncRNA via a feedback loop (Hu et al., 2016). In this study, the regulated role of UBE2R2-AS1 in gastric cancer cells was detected from aspects of cell proliferation, migration, and invasion. The CCK-8 and Transwell assays revealed that the inhibition of UBE2R2-AS1 can repress the proliferation, migration, and invasion of gastric cancer cells, which, from a side view, shows that UBE2R2-AS1 may promote gastric cancer. However, the suppression of cellular function caused by UBE2R2-AS1 downregulation can be

eliminated by inhibition of miR-302b-5p. Likewise, knockdown of miR-302b-5p was reported to actuate gastric cancer cell migration and invasion via the CDK2/ERK signaling pathway (Liu et al., 2016). These results indicate that UBE2R2-AS1 may accelerate gastric cancer cell proliferation, migration, and invasion by regulating miR-302b-5p.

To summarize, this study demonstrated that the upregulation of UBE2R2-AS1 is a promising biomarker of poor gastric cancer prognosis. Inhibition of UBE2R2-AS1 can suppress the proliferation, migration, and invasion of gastric cancer cells by mediating miR-302b-5p. Together, these findings provide important evidence for the further development of prognosis factors and future molecular targeted therapy for gastric cancer.

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*Competing interests.* The authors declare that they have no competing interests.

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