Original Article

# Overexpression of Long Non-coding RNAs *MCM3AP-AS1* and *LINC00092* Predict Poor Prognosis in Patients with Gastric Adenocarcinoma

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## Abstract

**Background:** LINC00092 and MCM3AP-AS1 long non-coding RNAs (LncRNAs) play significant roles in the development and pathogenesis of many cancers. However, their expression levels and prognostic values were not evaluated in human gastric adenocarcinoma (GAC). Therefore, the present study aimed to investigate the clinico-pathological correlations of LINC00092 and MCM3AP-AS1, LncRNAs expression in GAC, and evaluate their prognostic values.

**Materials and Methods:** The expression of LINC00092 and MCM3AP-AS1 was detected in 89 GAC tissues by quantitative real-time reverse-transcription PCR (qRT-PCR).

**Results:** Our results showed that LINC00092 and MCM3AP-AS1 are overexpressed in GAC patients and positively correlated with GAC invasion and vascular, peritoneal, and lymph node metastasis ($P < 0.05$). Furthermore, the results indicated that MCM3AP-AS1 ($P = 0.0225$) and LINC00092 ($P < 0.001$) have positive correlations with GAC patients' overall survival.

**Conclusion:** Altogether, the present results indicated that LINC00092 and MCM3AP-AS1 overexpression is associated with clinico-pathological characteristic of GAC patients. In addition, both of these LncRNAs may have prognostic value for estimation of patients' overall survival.

**Keywords:** Gastric cancer, long non-coding RNA, prognosis, survival

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## Introduction

Gastric cancer (GC) has been classified as the fifth most common malignancies in worldwide.[1] Although, the global incidence of GC shows declining trends in most countries, an alarming increase incidence was observed in younger ages (<50 years old).[2] With 620,000 deaths in 2021,[3] GC considered as one of the deadliest cancers. Most of the GC patients are sub-divided into GAC, which is based on histological characteristics has two different, intestinal and diffuse GAC, types[4]

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In general, heterogenic entity of GC makes this disease to have very bad outcomes and prognosis.[5] So, recent studies have been tried to introduce potential prognostic biomarkers.[6] As one of the interesting biomarkers, long non-coding RNAs (LncRNAs) have been studied in GC patients for their prognostic values.[7] LncRNAs comprise more than 200 nucleotide in size and play key roles in tumor biology.[8] Present study aimed to evaluate MCM3AP-AS1and LINC00092 expression in

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GAC tissues and analysis correlation of their expression levels with clinico-pathological characteristics. Both of these LncRNAs are involved in glycolytic pathways.[9,10] Because of unique profile of glucose metabolism in GAC cells, the ability of proliferation, invasion and metastasis depends on such pathways.[11] Indeed, enzymatic changes of glycolytic pathways cause metabolic reprogramming to ensure GAC growth and genesis.[12]

According to the bioinformatics analyses, enrichment of signaling pathways in GC implicated that LINC00092 involved in the Wnt signaling pathway and work together with several key genessuch as TCF7L1 (Transcription Factor 7 Like 1)/EGFR (Epidermal growth factor receptor)/FZD9 (Frizzled Class Receptor 9)/SHC4 (SHC Adaptor Protein 4)/RARB (Retinoic acid receptor beta). Besides of the Wnt pathway, these genes are essential for various biological processes, such as cell survival, proliferation, tissue regeneration.[13] In ovarian cancer it has been shown that LINC00092 stabilize PFKFB2 in cancer associated fibroblasts to help progression.[14] PFKFB (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) enzyme has an important role in the proliferation and survival of cancer cells by activating Warburg effect and generation of energy through glycolysis.[15] Moreover, its expression was associated with metastasis and poor survival of xenograft animal models.[14] In contrast, its low expression in lung adenocarcinoma is poor predictive of prognosis.[16] In addition, hypomethylated LINC00092 expression has no significant survival association with bladder cancer patients.[17]

Recently it has been reported that upregulation of LncRNAMCM3AP-AS1 could promote glycolytic pathways to regulate cell proliferation in Infantile Hemangiomas.[9] Recent in vitro studies showed that MCM3AP-AS1 regulate proliferation and apoptosis of GC cell lines, MGc-803 and SGC-7901, through regulating miR-708-5p levels.[18] Indeed, knockdown of this LncRNA significantly promoted apoptosis in these cells. Moreover, MCM3AP-AS1 has been found to be higher in cisplatin-resistant GC cell lines AGS, MKN45, NCI-N87 and SNU638.[19] It has been mentioned that MCM3AP-AS1 silencing could reverse cisplatin resistance in these cells. At molecular levels, MCM3AP-AS1 up-regulates FOXC1 levels through sponging of miR-138. FOXC1 is one of the key players of resistance to cisplatin.[19] Finally, MCM3AP-AS1 expression in solid tumors such as cervical, endometrioid, and hepatocellular carcinoma, correlated with poor survival, differentiation, size, and lymph node metastasis which predicts unfavorable prognosis.[20] New meta-analysis indicates that MCM3AP-AS1 expression in solid tumors such as cervical, endometrioid, and hepatocellular carcinoma, correlated with poor survival, differentiation, size, and lymph node metastasis which predicts unfavorable prognosis.[20]

Since, to the best of our knowledge, there is no study elucidates LINC00092 and MCM3AP-AS1 levels in GAC patient, the primary objective of present study was to assess the LINC00092 and MCM3AP-AS1 expression levels and evaluate their utility as prognostic biomarkers in patients diagnosed with GAC. For the first time at the present study we aimed to assess correlation of LINC00092 and MCM3AP-AS1 expression with clinico-pathological characteristics, prognosis and survival outcomes of GAC patients. Moreover, using bioinformatics tools, we investigated correlation of LINC00092 and MCM3AP-AS1 expression with other genes that might construct a network with these LncRNAs and involved in pathogenesis of GAC. Indeed, considering the diagnostic, prognostic, and treatment role of lncRNAs in the GAC, the present study results introduce LINC00092 and MCM3AP-AS1 as two new molecular biomarkers for management of personalized therapies in patients with GAC.

# Materials and Methods

## Patients and clinical sample collection

The present study was approved by the Research Ethics Committee of Baqiyatallah University of Medical Sciences (Accession code: IR.BMSU.REC.1398.381). A total of 89 samples of GAC with adjacent normal counterpart tissues were collected from Baqiyatallah Hospital (Tehran, Iran). All of these samples were paraffin-embedded and archived in pathology section of hospital between March 2012 and February 2018. Samples of patients with radio- or chemotherapy were excluded. Pathological characteristics of each sample including tumor size, differentiation, lymph nodes metastasis and vascular invasion were recorded by pathology specialists at the time of GAC patient's recruitment. For survival analysis all patients were followed up by telephone contact at the time of performing present study.

## Gene expression analysis

Total RNA was extracted from paraffin-embedded specimens using specific RNArich FFPE Tissue Kit (Azma Elixir Pajooh, Tehran, Iran), according to the manufacturer's instruction. Then, complementary DNA (cDNAs) was constructed using PrimeScript reverse transcriptase (TaKaRa) based on kit's instruction, as previously performed.[21]

LINC00092, MCM3AP-AS1 and GAPDH primers [Table 1] have been designed using following online tools: *NCBI* (National Center for Biotechnology Information), and *Primer3 Input* to find sequences and pick best primers, respectively. Primer sequences have been aligned by *NCBI Blast* (Basic Local Alignment Search Tool). LINC00092, MCM3AP-AS1, and GAPDH (as an internal control) amplicons were extended by Real-time PCR and Real Q Plus 2x Master Mix Green, low ROXTM (Amplicon company,). The heating protocol was 95°C for 10 min as activation step followed by 45 cycling steps each include 95°C for 15 sec, 57°C for 30 sec, and 72°C for 30 sec. At the end, for plotting of melting curves PCR reactions were heated at 95◦C for 10 sec, 57°C for 5 sec and 95°C for 50 sec. The instrument that has been used for Real-time PCR was BioradCFX96 real time system. Results

**Table 1: List of primers used for amplification of LINC00092, MCM3AP-AS1, and GAPDH amplicons**

| Name | Forward | Reverse |
|---|---|---|
| MCM3AP-AS1 | CTCCTCGCATCAGATCCTC | TTCCCATACCATTGCTTCAC |
| LINC00092 | GGTTAGGCTGGTCTGGAAC | AGGGTGGTGAGAGAGAGG |
| GAPDH | TTCTTTTGCGTCGCCAGC | TCCCGTTCTCAGCCTTGAC |

of Real-time PCR were presented as the cycle threshold (Ct or Cq in instrument software). The Ct values have been extracted into the Excel software. Normalization of LINC00092and MCM3AP-AS1 Ct values in each sample were obtained by calculation of ΔCt (ΔCt = Ct [LncRNAs] – Ct [GAPDH]). Then, the $2^{-\Delta Ct}$ formula was used to calculate differences in LncRNAs expression levels between GAC tumoral tissues with adjacent non-tumoral tissues for each sample. The $2^{-\Delta\Delta Ct}$ method has been used for relative expression assessment of each LncRNAs. This relative quantification has been used forstatistical correlation analysis with demographic characteristics of included patients.

### Data collection and preprocessing

GSE184336 profile was obtained from NCBI GEO database (https://www.ncbi.nlm.nih.gov/geo) to collect RNA sequencing data. This dataset included 123 tumor samples and 167 normal samples.

### Correlation analysis

The DGCA software package, available in R version 4.2.1, was utilized to probe the correlation dynamics between the lncRNAs "LINC00092" and "MCM3AP-AS1" across tumor and normal samples. Moreover, Benjamini-Hochberg (BH) correction method has been used to adjust *P* values that accounted for multiple comparisons.

### Statistical analysis

SPSS statistics package version 24 and Graphpad prism 9.2.0 (332) have been used to perform statistical analysis. LINC00092 and MCM3AP-AS1 gene expression levels compared between the two groups of GAC tumor tissue and adjacent normal tissues using t test. The Chi-square test was applied to evaluate relationship between LINC00092 and MCM3AP-AS1 expression levels and clinic-pathologic parameters. Using the Kaplan–Meier methodand log-rank test, survival curves was plotted. Cox proportional hazards model was performed for multivariate analysis. *P* values < 0.05 corresponding tothe confidence interval of 95% was considered statistically significant.

## Results

### GAC tumoral tissues express high level of LINC00092 and MCM3AP-AS1 LncRNAs

Using quantitative real-time reverse-transcription PCR (qRT-PCR) indicated that expression of LINC00092 and MCM3AP-AS1 LncRNAs unregulated in GAC tumoral tissues in comparison with normal tissue adjacent [P < 0.001, Figure 1]. Median interquartile range (IQR) for normal tissue expression level of LINC00092 and MCM3AP-AS1 were 2.499 (1.432-4.364), and 3.861 (2.116- 5.523) and for cancerous tissue were 5.098 (3.222-7.060) and 8.228 (4.117- 8.228), (P < 0.001), respectively.

As mentioned in Figure 1, LINC00092 and MCM3AP-AS1 LncRNAs expression in poor, moderate and well differentiated tissues were upregulated in cancerous in comparison with normal adjacent tissues (P < 0.05).

Altogether, our results indicated that LINC00092 and MCM3AP-AS1 LncRNAs expression were upregulated in cancerous tissues. Moreover, the expression levels significantly differ between poor, moderate and well differentiated GAC, which may implicate their possible role in GAC biology.

### MCM3AP-AS1 and LINC00092 LncRNAs expression correlate with clinico-pathological features in GAC patients

Based on LINC00092 and MCM3AP-AS1 LncRNAs median expression level, included samples were classified into low and high expression groups. Then, clinico-pathological characteristics correlation of LINC00092 and MCM3AP-AS1 LncRNAs expression has been compared between low and high levels. Our results indicated LINC00092 and MCM3AP-AS1LncRNAsexpression are associated with some of these features [Table 2]. Both of these LncRNAs had positive correlation with invasion status of tumors (P < 0.05). MCM3AP-AS1 expression showed significant correlations with peritoneal and lymph node metastasis (P < 0.05).However, LINC00092, had positive correlations just with peritoneal and lymph node metastasis, respectively. Thus, patients with higher expression levels ofLINC00092 and MCM3AP-AS1 LncRNAs were significantly more likely to have lymph node, peritoneal metastases and invasion than those with lower expression levels. For all of these LncRNAs, no significant correlations were observed with gender and age.

Altogether, our results implicated that the expression levels of LINC00092 and MCM3AP-AS1 LncRNAsis in positive correlation with clinical characteristics such as metastasis and invasion.

### Overexpression of MCM3AP-AS1 and LINC00092 LncRNAs predict poor prognosis of GAC patients

Analysis of Kaplan–Meier method and log-rank test were employed to predict the prognostic value and overall survival of LINC00092 and MCM3AP-AS1 expression for GAC. Our results indicated that MCM3AP-AS1 (P < 0.022), and LINC00092 (P < 0.001) LncRNAs expression have significant correlation with overall survival in 89 GAC

**Table 2: Correlations between LINC00092 and MCM3AP-AS1 gene expression and clinico-pathological characteristicsin GAC patients**

| Features | *n* | MCM3AP-AS1 exp. Level# | | | LINC00092 exp. Level# | | |
|---|---|---|---|---|---|---|---|
| | | Low | High | *P* | Low | High | *P* |
| Gender | | | | | | | |
| Male | 63 | 31 | 32 | >0.05 | 29 | 33 | >0.05 |
| Female | 26 | 13 | 13 | | 14 | 12 | |
| Age | | | | | | | |
| <65 | 44 | 24 | 20 | >0.05 | 24 | 20 | >0.05 |
| ≥65 | 45 | 20 | 25 | | 19 | 26 | |
| Vascular Metastasis | | | | | | | |
| Present | 55 | 27 | 28 | >0.05 | 23 | 32 | >0.05 |
| Absent | 32 | 16 | 16 | | 20 | 12 | |
| Peritoneal Metastasis | | | | | | | |
| Present | 45 | 23 | 22 | <0.05* | 20 | 25 | <0.05* |
| Absent | 44 | 21 | 27 | | 26 | 18 | |
| Lymph node Metastasis | | | | | | | |
| N0-N1 | 38 | 17 | 21 | <0.05* | 21 | 17 | >0.05 |
| N2-N3 | 50 | 23 | 27 | | 24 | 26 | |
| Invasion | | | | | | | |
| I-II | 47 | 24 | 23 | >0.05 | 24 | 23 | <0.05* |
| III-IV | 41 | 20 | 21 | | 19 | 22 | |

*exp. Level: gene expression level, #*p* <o.o5 considered significant

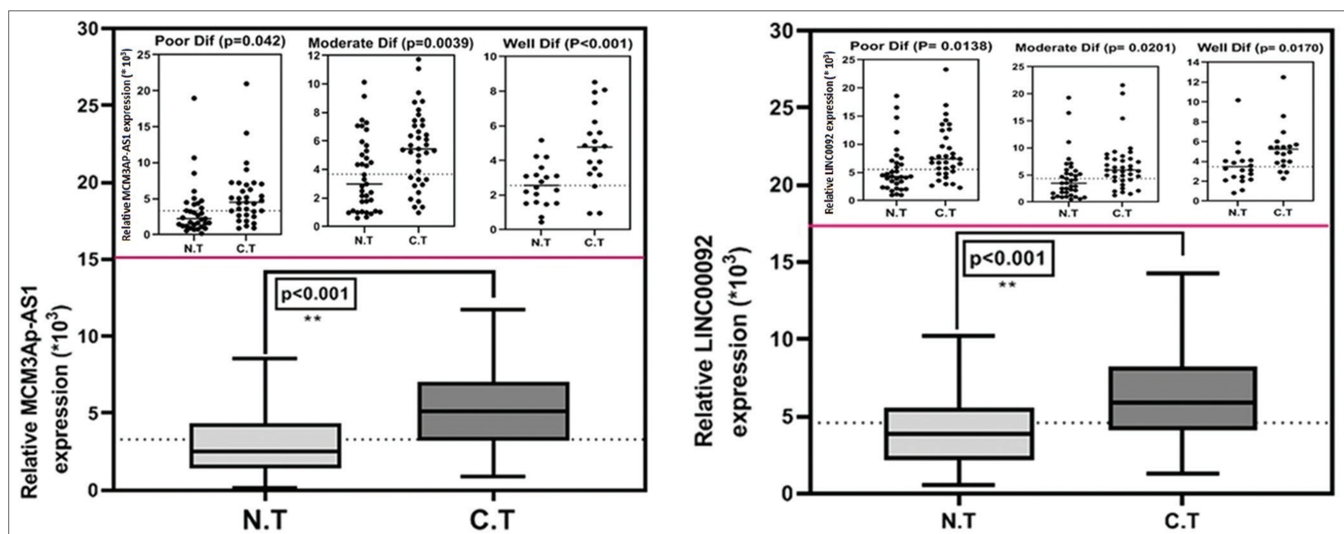


**Figure 1:** Expression of MCM3AP-AS1and LINC00092 LncRNAs are increased in GAC tissues compared with adjacent normal tissues. Gene expression levels of these LncRNAs were performed using qRT-PCR. As indicated, data distributions of each LncRNA expression level were presented for poor, moderate and well differentiated GAC. Box plots indicate median (IQR). *P* value < 0.05 was considered significant statistically. N.T and C.T represent normal and cancerous tissues, respectively

patients [Figure 2]. According to these data, patients with higher MCM3AP-AS1 and LINC00092 expression have poor prognosis for survival.

### MCM3AP-AS1 and LINC00092 LncRNAs are independent prognostic factors in GAC patients

For assessment of the dependent and independent relationship between each clinico-pathological characteristic, MCM3AP-AS1 and LINC00092 LncRNAs expression, and patient survival, Univariate and Multivariate analysis had been performed using Cox regression model. Univariate analysis indicated that lymph node, vascular, and peritoneal metastasis predict independent poor prognosis of GAC ($P < 0.05$) [Table 3]. Furthermore, MCM3AP-AS1 and LINC00092 LncRNAs may be considered as independent prognostic factors for GAC patient survival ($P < 0.05$).

Regardless lymph node metastasis, Multivariate analysis using Cox proportional hazards model implicated that

**Table 3: Univariate and multivariate Cox regression analyses of clinico-pathological parameters predicting overall survival in GAC**

| Parameter | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Gender (female vs. male) | 1.216 | 0.6361-2.449 | 0.5654 | _ | _ | _ |
| Age (<60 vs. ≥60) | 0.8889 | 0.5013-1.569 | 0.6837 | _ | _ | _ |
| Histological grade (differentiated vs. undifferentiated) | 0.9394 | 0.5284 to 1.718 | 0.8342 | _ | _ | _ |
| Tumor depth (T1–T2 vs. T3–T4) | 2.697 | 1.795-3.756 | 0.0045* | 1.980 | 1.048-3.823 | 0.0375* |
| Vascular metastasis (Absent vs. Present) | 2.628 | 1.866-3.490 | 0.0021* | 0.7766 | 0.3194-1.923 | 0.5795 |
| Peritoneal metastasis (Absent vs. Present) | 2.197 | 1.456-2.985 | 0.0368* | 0.5958 | 0.3057-1.164 | 0.1268 |
| Lymph node metastasis (N0–N1 vs. N2–N3) | 2.678 | 1.846-3.641 | 0.0073* | 1.969 | 1.5898-2.415 | 0.022* |
| MCM3AP-AS1 (low vs. high) | 2.471 | 1.6246-3.322 | 0.0002* | 1.3636 | 1.1693-2.7414 | 0.0070* |
| LINC00091 (low vs. high) | 4.419 | 2.211 to 9.368 | <0.000* | 2.473 | 1.8538-5.154 | <0.000* |

*$P$<0.05, HR: hazard ratio, 95% CI: 95% confidence interval

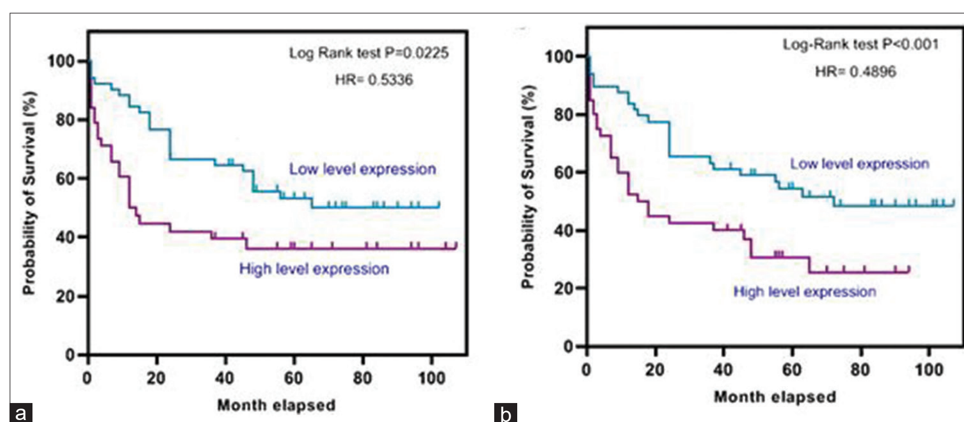


**Figure 2:** Overall survival estimation based on MCM3AP-AS1andLINC00092 LncRNAs expression level. The association between patient survival and (a) MCM3AP-AS1, (b) LINC00092, expression was evaluated by the Kaplan–Meier method and the log-rank test ($P < 0.05$). For each LncRNAs, expression median was considered as cut-off of high and low expression group. HR: Hazard ratio

MCM3AP-AS1 and LINC00092 LncRNAs overexpression were unfavorable independent predictor of overall survival. The hazard ratio of MCM3AP-AS1 and LINC00092 have been estimated 1.3636 and 2.473 with a 95% confidence interval ranging from 1.1693-2.7414 and 1.8538-5.154, respectively [Table 3].

### *Correlation dynamics*

Correlation Dynamic analysis of GSE184336 dataset indicated that 5377 genes expression correlated with MCM3AP-AS1 levels, significantly [adjusted *P* value > 0.05, see the Table S1]. Of them, 2668 showed positive (coefficients ranged between 0.16 to 0.63) and 2709 negative correlations, coefficients ranged between -0.16 to -0.57. Figure 3a showed top 10 genes that their expression showed a significant negative and positive correlation with MCM3AP-AS1 [Table S2]. As mentioned in Figure 3a, MCM3AP-AS1 displayed a negative correlation with genes "TMED7-TICAM2", "EFCAB14-AS1", "LOC101929918", "KAT6A-AS1", "KIAA1671", "MIR1281", "LOC100507346", "KIAA0754", "LOC102723786", and "HDLBP-AS1». The correlation coefficients for this set ranged between -0.46 to -0.57 [Figure 3a]. Positive correlation, as well as, were obtained for U2AF1, LUC7L, LOC102724594, HNRNPH 1, PRKRIP1, LOC100630923, ZBTB17, DPH 7, NIPIPB12, with correlation coefficients ranged between 0.53 to 0.63 [Figure 3a].

As well as, for LINC00092, 11882 genes showed significant correlations [adjusted *P* value > 0.05, see the Table S3], with 5979 genes for positive (coefficients ranged between 0.14 to 0.71) and 5903 for negative correlations, coefficients ranged between -0.14 to -0.63. As, top 10 candidate with a significant negative correlation [Table S4] was observed for genes "CCT6A", "PSMD14", "KPNB1", "KPNA2", "STIP1", "CBX3", "CDCA4", "INTS7", "CCT5", and "E2F3" that coefficients spanned a range from -0.61 to -0.63 [Figure 3b]. Positive correlation, as well as, were for GNGG7, C16orf89, MYRIP, FAM107A, AFF3, ASPA, LCN6, ADRN2, and ADHFE1 genes with coefficients spanned between 0.64 to 0.71 [Figure 3b].

## Discussion

Previous studies implicated long non-coding RNAs (lncRNAs) are involved in pathogenesis, invasion, and metastasis of gastric adenocarcinoma (GAC).[8] In this regards, the main idea of present

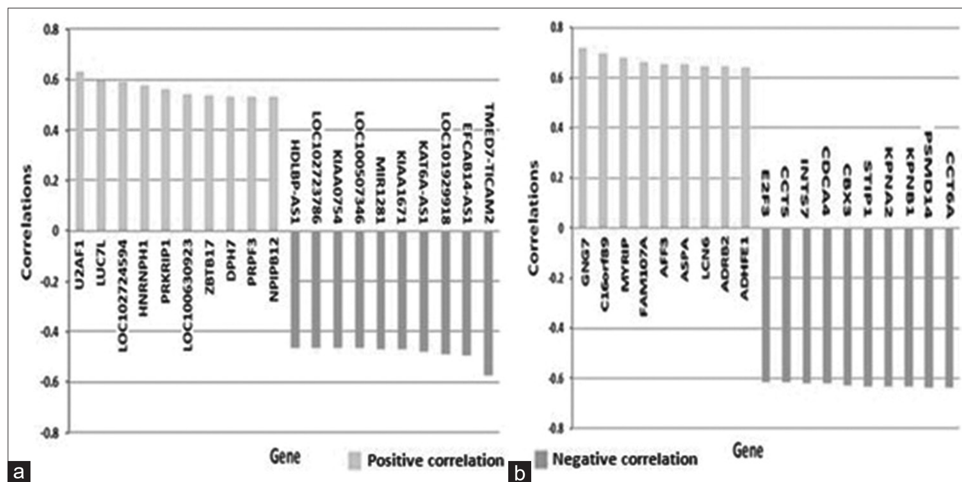


**Figure 3:** Correlation Dynamic analysis of GSE184336 dataset for top 10 genes that their expression showed a significant negative and positive correlation withMCM3AP-AS1 (a) and LINC00092 (b). *P* value for correlation was < 0.05

study was to investigate prognostic values of MCM3AP-AS1 and LINC00092 LncRNAs in GAC patients. Recent studies have been reported that MCM3APAS1 is involved in GC cell proliferation and its knockdown promotes apoptosis.[18] In addition, this LncNRA play a role in cisplatin resistance of GC cells through sponging of microRNA (miR) 138 and upregulation of FOXC1.[19] As one of the prognostic factors, FOXC1 overexpression correlated with poor survival of GAC patients.[22] Our results demonstrated that MCM3AP-AS1 is overexpressed in GAC tumoral tissues compared with normal adjacent. Also the overexpression of this LncRNA, predicts poor survival of GAC patients. Somehow, our results of MCM3AP-AS1 correlation with GAC patient clinico-pathological characteristics and survival are in companion with these studies.[18,19,22] Moreover, literature reviews indicate MCM3AP-AS1 is overexpressed in breast tumoral tissues[23] and predicts poor prognosis of cervical squamous cell carcinoma,[24] hepatocellular carcinoma,[25] and prostate cancer.[26]

The present findings indicated LINC00092 was overexpressed in GAC tumoral tissues compared with normal adjacent, significantly ($P < 0.05$). Also, in ovarian cancer cells, LINC00092 upregulated by CXCL14 factor, acts as an oncogenic LncRNA, and promotes cancer progression.[14] In addition, our results showed patients with higher expression levels of LINC00092 have poor overall survival. Parallel with these results, upregulation of this LncRNA associates with poor survival of patients with ovarian cancer.[14] However, based on data mining and bioinformatics analysis, downregulation of LINC00092 in lung adenocarcinoma was involved in tumorigenesis and metastasis.[16] In this adenocarcinoma, patients with high expression levels of LINC00092 have better prognosis and overall survival. Despite of different entity of lung and GACs, LINC00092 methylation status controls its expression levels and is in relation with patients survival.[17] Unfortunately, as one of the limitations, methylation status of LINC00092 was not determined at the present study.

Our results indicated overexpression of MCM3AP-AS1 and LINC00092 in patients with GAC. In this regards, LncRNA targeting approaches that decrease their expression levels could provide therapeutic opportunities against GAC. Antisense oligonucleotides (ASOs) or small interfering RNA (siRNAs) approaches are available to block or knockdown LncRNAs.[27] As, it was used to excise lncRNA-21A, UCA1, and AK023949,[28] CRISPR-Cas9 engineering, as well as, considered as one of the high-technic methods that can be used to reduce MCM3AP-AS1 and LINC00092 expression.

Our correlation dynamic analysis introduced top 10 genes that correlated significantly with MCM3AP-AS1 and LINC00092 expression levels. Indeed, focusing on these gene correlations can reveal some of important regulatory factors that involved in multiple biological processes of GAC pathogenicity. At least, for MCM3AP-AS1 case, positive correlated genes U2AF1 (U2 Small Nuclear RNA Auxiliary Factor 1), LUC7L (RNA-binding protein Luc7-like 1), HNRNPH 1 (Heterogeneous Nuclear Ribonucleoprotein H1), PRKRIP1 (PRKR Interacting Protein 1), ZBTB17 (Zinc finger and BTB domain-containing protein 17) appears to be related in different malignancies.

Although, presented results highlighted valuability of MCM3AP-AS1and LINC00092LncRNAs in predicting GAC patient prognosis and survival, however, larger sample sizes may be needed to confirm these results. Because of imperfect recorded data for H.pylori infection, unfortunately, we could not evaluate correlation of MCM3AP-AS1and LINC00092expression with H.pylori infectious status in patients with GAC. Moreover, *in vitro* approaches are needed to reveal underlying mechanism of proliferation and possible chemoresistance regulation by MCM3AP-AS1and LINC00092.

## Conclusion

Our study demonstrated that MCM3AP-AS1 and LINC00092

LncRNAs were overexpressed in tumoral margin of GAC compared with normal adjacent tissues. These LncRNAs have positive correlations with invasion and metastasis of GAC. According to our results, MCM3AP-AS1 and LINC00092 LncRNAs may be independent prognostic factors of overall survival in GAC patients. Considering overexpression of these LncRNAs, and correlation dynamics, the presented results could be the base of further studies to investigate regulatory mechanism, direct down-regulation approaches to suppress GAC growth. In clinic, expression levels assessment of these LncRNAs possibly could be helpful for personalized medicine and to predict GAC patient prognosis.

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### Ethics

All of the material, methods, and data reports were according to the Research Ethics Committee of Baqiyatallah University of Medical Sciencesand approved by the Accession code: IR.BMSU.REC.1398.381.

### Author contributions

MKSH, SA and MBwere involved for conception and design of the study. MKSH and MAR are contributed to data gathering and analysis. AMGKH, MA, MS, SA, MBengaged in interpretation, manuscript writingand editing.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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