Article

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Long Noncoding RNA AP000695.2 as a Novel Prognostic Biomarker for Gastric Cancer

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Background: Long non-coding RNA (lncRNA) AP000695.2 (ENSG00000248538) expresses abnormally in various malignancies, what shows its role as oncogene. However, it has not been extensively studied in gastric cancer. The aim of the current study was to explore the clinical value of AP000695.2 to prognose gastric cancer.
Methods: The cancer genome atlas (TCGA) and the gene expression profiling interactive analysis (GEPIA) online tool were used to analyze AP000695.2 expression pattern, diagnostic and prognostic role in gastric cancer. Kaplan–Meier and Cox regression analyses were used to assess survival in patients with gastric cancer. Receiver operating curve (ROC) analysis was used to assess AP000695.2 diagnostic capacity. Nomograms were created to predict overall survival (OS) and progression free survival (PFS).
Results: LncRNA AP000695.2 was abnormally upregulated in 19 types of malignancy, including gastric cancer. Survival analysis indicated that high expression of AP000695.2 was associated with poor survival of gastric cancer. Multivariate Cox regression analysis verified the independent prognostic value of AP000695.2 to predict OS (HR (hazard ratio): 1.104, 95% CI (confidence interval): 1.035–1.178, $p = 0.003$) and PFS (HR: 1.170, 95% CI: 1.090–1.256, $p < 0.001$). ROC analysis indicated a favorable AP000695.2 diagnostic capacity (area under the curve (AUC) = 0.890). Nomograms were also constructed for OS and PFS based on AP000695.2 expression-related risk score. Additionally, AP000695.2 was found to be positively associated with tumor-infiltrating immune cells, including classically activated (M1) macrophages, neutrophils, alternatively activated (M2) macrophages, and natural killer (NK) cells.
Conclusions: It was observed that AP000695.2 can be used as a novel biomarker to diagnose or predict survival of gastric patient.

Keywords: lncRNA; AP000695.2; gastric cancer; prognostic marker; diagnostic marker

Introduction

Gastric cancer incidence and mortality is high, with about 26,560 estimated new cases and 11,180 estimated deaths in USA, during 2021 [1]. Although great advances in screening and treating gastric cancer have occurred, gastric adenocarcinoma prognosis is still dismal [2]. This may be due to the lack of an effective diagnostic measure for gastric cancer at an early stage [3]. Thus, it is crucial to identify novel biomarkers that are able to diagnose and predict gastric cancer.

Tumor biomarkers have been extensively studied due to their ability to diagnose or predict malignancies with excellent specificity and sensitivity [4]. Recent evidence revealed that lncRNA (long non-coding RNA) are involved in the progression and occurrence of multiple human carcinomas, including gastric cancer [5–7]. Moreover, accumulating reports have shown that lncRNA can serve as promising diagnostic or prognostic biomarkers in multiple malignancies [8], such as colorectal cancer [9], pancreatic cancer [10], gastric cancer [11], and cervical cancer [12]. Hence, it is crucial to evaluate the potential of lncRNA to diagnose and prognose gastric cancer.

A recent study found that lncRNA AP000695.2 was an optimal diagnostic and prognostic biomarker for head and neck squamous cell carcinoma [13]. Moreover, lncRNA AP000695.2 was able to act as a novel prognostic biomarker in lung adenocarcinoma [14]. Further cytological experiments showed that AP000695.2 could promote lung cancer cells growth, migration, and invasion. In this study, AP000695.2 prognostic and diagnostic role was

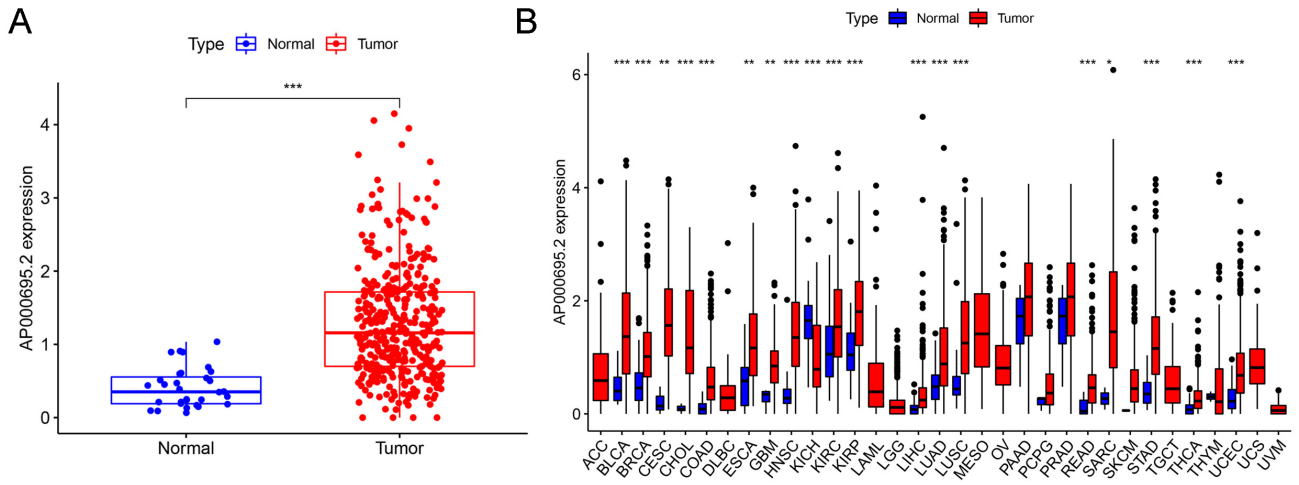

Fig. 1. AP000695.2 expression levels in gastric cancer and other types of cancers. (A) AP000695.2 expression in gastric cancer (n = 375) is higher than that in normal tissue (n = 32). (B) AP000695.2 expression differences between different types of tumor tissues and normal tissues. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

evaluated in gastric cancer. Additionally, the association between tumor-infiltrating immune cells and AP000695.2 expression was assessed.

Materials and Methods

Data Extraction

RNA sequencing data and associated gastric cancer samples clinical information was extracted from TCGA (the cancer genome atlas) database (https://portal.gdc.cancer.gov/). Samples basic clinical information available in the TCGA is listed in **Supplementary Table 1**. First, fragment per kilobyte per million (FPKM) format of RNA sequencing data was converted into transcripts per million reads (TPM). Then, RNA sequencing data were compared based on its clinicopathological information.

Correlation between AP000695.2 and Gastric Cancer

AP000695.2 expression pattern in colon cancer was assessed. In addition, AP000695.2 expression level in different types of cancer from the TCGA extracted data was evaluated. ROC (receiver operating curve) analysis was used to compare AP000695.2 expression between gastric tumor and normal tissues, to assess AP000695.2 diagnostic potential in gastric cancer. Data on gastric cancer tissues (number: 375) and normal tissues (number: 32) were extracted from TCGA. R package (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria) "pROC" was used to analyze the data. Data visualization was performed with "ggplot2".

Kaplan–Meier and Cox regression analyses were conducted to assess the potential of AP000695.2 to predict survival in gastric cancer patients. Nomograms were developed to forecast OS (overall survival) and PFS (progression free survival) with a follow-up of 1-, 3- and 5-years using the R package "rms" and "survival". An estimation of the consistency between the observed outcomes and the predictions based on the nomogram was performed by plotting calibration curves. All statistical analyses were conducted using R (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria). *p* values less than 0.05 were considered statistically significant.

The Identification of DEGs and Pathway Analysis

Pearson correlation coefficients >0.5 and *p* values below 0.001 were considered as AP000695.2 related differentially expressed genes (DEGs). To assess the potential biological function and signaling pathway affected by AP000695.2, co-expressed genes Kyoto encyclopedia of genes and genomes (KEGG), and enrichment and gene ontology (GO) analyses were performed using the R package "cluster Profiler". GO analysis consisted of three parts, including cell composition (CC), molecular function (MF), and biological processes (BP).

Association with Tumor-Infiltrating Immune Cells

To determine whether AP000695.2 expression was correlated with immune cell characteristics, CIBERSORT (cell-type identification by estimating relative subsets of RNA transcripts) method was used to evaluate the immune infiltration statues among gastric cancer samples. Spearman correlation analysis was performed to evaluate the association between AP000695.2 and immune infiltrated cells. A lollipop diagram was used to illustrate correlation coefficients. This analysis was performed using the R package "ggplot2".

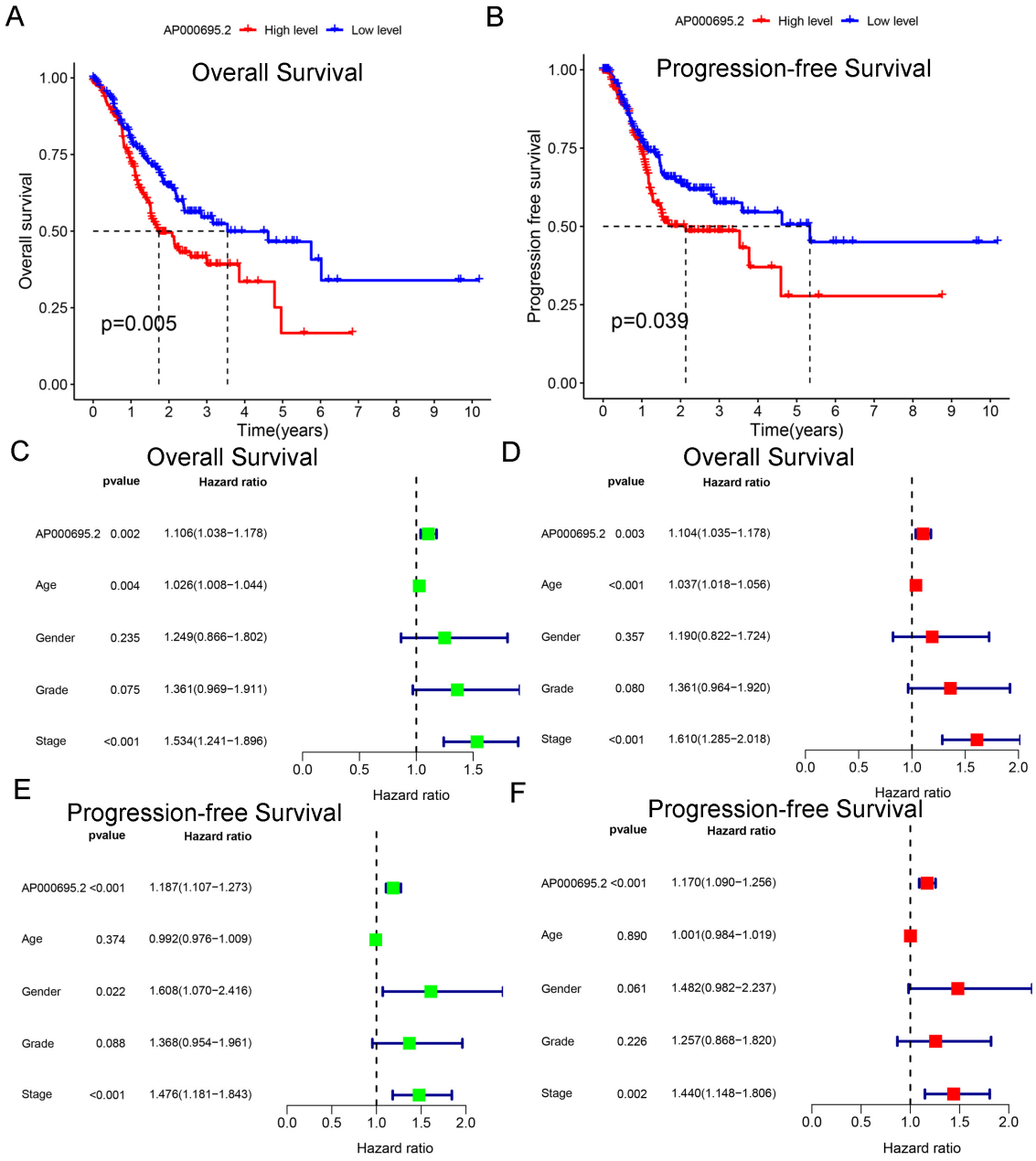

Fig. 2. AP000695.2 expression prognostic value in gastric cancer patients. (A) The relationship between AP000695.2 expression and OS by Kaplan–Meier (n = 371). (B) The relationship between AP000695.2 expression and PFS by Kaplan–Meier (n = 372). (C) Univariate Cox regression analysis of AP000695.2 expression with OS. (D) Multivariate Cox regression analysis of AP000695.2 expression with OS. (E) Univariate Cox regression analysis of AP000695.2 expression with PFS. (F) Multivariate Cox regression analysis of AP000695.2 expression with PFS.

Results

AP000695.2 Expression Profiles in Pan-Cancer Datasets

TCGA data analysis indicated that gastric tumor tissues had higher AP000695.2 expression compared to normal tissues ($p < 0.001$, Fig. 1A). Moreover, AP000695.2 expression was further verified with the GEPIA (gene expression profiling interactive analysis) database, 408 tumor samples and 211 normal samples were included. As shown in **Supplementary Fig. 1**, gastric tumor tissues expressed higher levels of AP000695.2 compared to normal control tissues. In addition, it was surprising to observe that AP000695.2 was upregulated in 19 of the 33 cancer types, such as breast invasive carcinoma (BRCA), bladder urothelial carcinoma (BLCA), and head and neck squamous cell carcinoma (HNSC) (Fig. 1B).

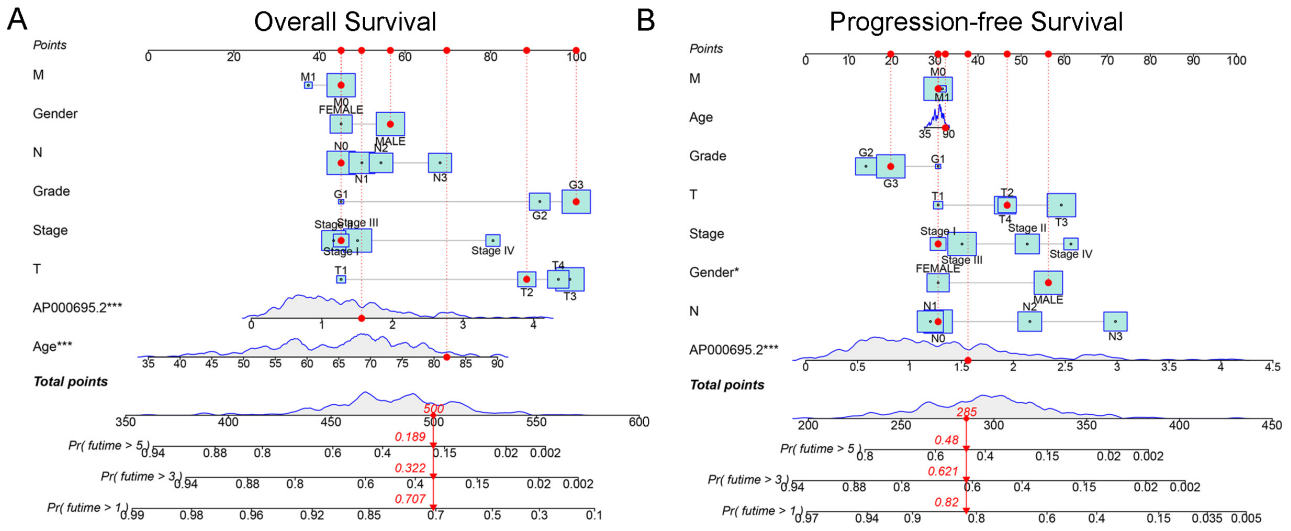

Fig. 3. Nomograms predicting survival probability. (A) Nomograms created to predict OS. (B) Nomograms created to predict PFS. $^{*}p < 0.05$, $^{***}p < 0.001$

AP000695.2 Diagnostic and Prognostic Role in Gastric Cancer

ROC curve analysis showed AP000695.2 had a high area under the curve to prognose gastric cancer diagnosis (AUC (area under the curve)) of 0.890, 95% confidence interval [CI]: 0.839–0.932) (**Supplementary Fig. 2**).

Gastric cancer patients with high AP000695.2 expression had shorter OS (p = 0.005) and PFS (p = 0.039) (Fig. 2A,B). The 5-year OS rate was 46.7% in the high-expression group versus 17.4% in the low-expression group. The 5-year PFS rate was 49.4% in the high-expression group versus 27.4% in the low-expression group. Univariate Cox regression analysis indicated that AP000695.2 expression, age and gastric cancer stage were significantly associated with OS (Fig. 2C). Multivariate analysis showed that AP000695.2 expression (hazard ratio [HR]: 1.104, 95% CI: 1.035–1.178, p = 0.003) and stage (HR: 1.61, 95% CI: 1.285–2.018, $p < 0.001$) were independent risk factors (Fig. 2D). Additionally, AP000695.2 expression, gender and stage were associated with PFS (Fig. 2E). Meanwhile, AP000695.2 expression (HR: 1.170, 95% CI: 1.090–1.256, $p < 0.001$) and gastric cancer stage (HR: 1.440, 95% CI: 1.148–1.806, p = 0.002) remained independent risk factors (Fig. 2F).

Subsequently, prognostic nomograms were created with several variables as prognostic factors, including age, gender, pathological stage, histologic grade and AP000695.2 expression. For each gastric cancer patient, total points were calculated based on their clinicopathologic characteristics included in the point scale in the nomogram. Thus, a model to predict 1-, 3-, and 5-year survival probability was created. For example, as shown in, the clinicopathological features of randomly selected patients resulted in a total point score of 500, leading to 1-, 3-, and 5-year OS of 70.7%, 32.2% and 18.9%, respectively (Fig. 3A). Meanwhile, a total point score of 285 led to 1-, 3-, and 5-year PFS of 82.0%, 62.1% and 48.0%, respectively (Fig. 3B). A higher score was generally associated with a worse prognosis in gastric cancer patients. Moreover, a plot of the calibration curves revealed that there was good consistency between the predicted survival probability and the observed survival probability (**Supplementary Fig. 3**).

AP000695.2-Associated DEGs Functional Annotation in Gastric Cancer

We used a Pearson correlation coefficient of >0.4 and $p < 0.001$ to screen for AP000695.2 coexpressed genes. As a result, a heatmap of the top 57 DEGs which were positively correlated with AP000695.2 expression was created (Fig. 4).

According to GO analysis, genes associated with the BP term were significantly enriched in wound healing, external encapsulating structure organization, extracellular structure organization, and extracellular matrix organization. In case of the CC term, most of the genes were found in the focal adhesion, collagen-containing extracellular matrix, and cell-substrate. And genes related to extracellular matrix constituent, integrin binding and endopeptidase activity were enriched in the MF term (Fig. 5A). PI3K (phosphoinositide 3-kinase)-Akt (protein kinase B) signaling pathway, focal adhesion, human papillomavirus infection, and ECM (extracellular matrix)-receptor interaction were the top pathways based on KEGG analysis (Fig. 5B).

Estimation of Tumor-Infiltrating Immune Cells

Since lncRNAs may initially be associated to immune-related genes, the association between AP000695.2 expression and tumor immune microenvironment was evaluated.

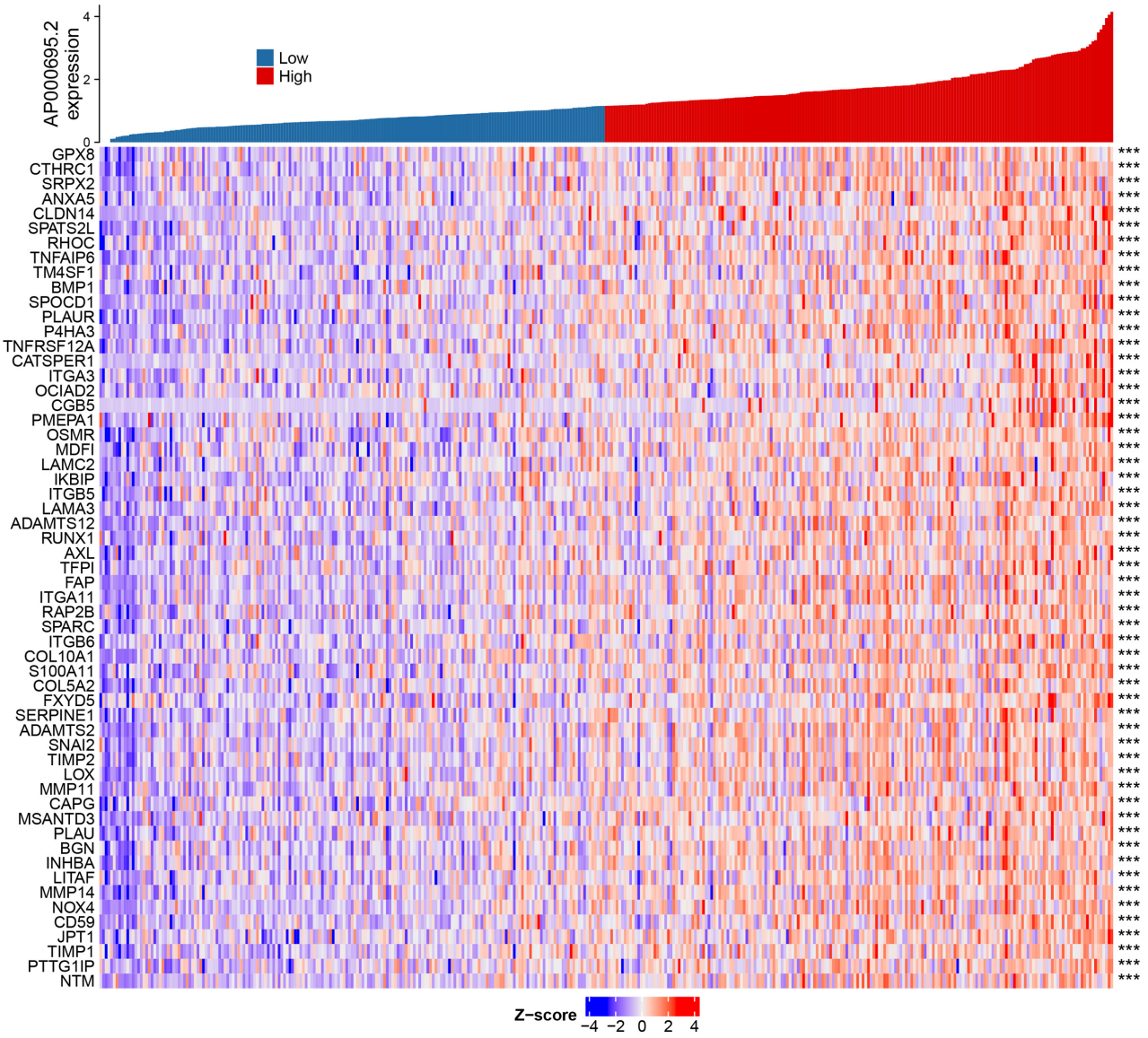

Fig. 4. Heatmap of the top 57 DEGs which were positively correlated with AP000695.2 expression in gastric cancer. $^{***}p < 0.001$.

AP000695.2 expression level was associated to tumor-infiltrating immune cells; Positively with macrophages M1, neutrophils, macrophages M2, and NK cells resting, and negatively with B cells memory, T cells regulatory (Tregs), T cells follicular helper, and CD8 (cluster of differentiation). Fig. 6 shows spearman correlation analysis results derived from the associations assessment between AP000695.2 and tumor cells microenvironment.

Discussion

Gastric cancer is one of the leading cause of death worldwide, with about 70% gastric cancer patients diagnosed in developing countries [15]. Even though anti-HER2-targeted therapy and immune checkpoint inhibitors have made big advances in gastric cancer treatment, patient's prognosis is still unsatisfied. Hence, exploring the underlying molecular mechanisms and identifying new prognostic biomarkers to early diagnose gastric cancer is important.

Researchers have found that lncRNAs play a crucial role in cancer pathogenesis and progression [16]. There are some pivotal lncRNAs that have been identified as promising diagnostic and prognostic biomarkers, such as HOX transcript antisense intergenic RNA (*HOTAIR*) [17], small nucleolar RNA host gene 1 (*SNHG1*) [18], and antisense non-coding RNA at the INK4 locus (*ANRIL*) [19]. Moreover, lncRNAs prognostic value have been well studied in gastric cancer [20,21].

Here, TCGA was used to analyze AP000695.2 expression profiles in 33 cancer types. As a result, AP000695.2 is found to be abnormally overexpressed in 19 different types of malignancy, especially in gastric cancer, which highlight its oncogenic roles in human malignancies. ROC

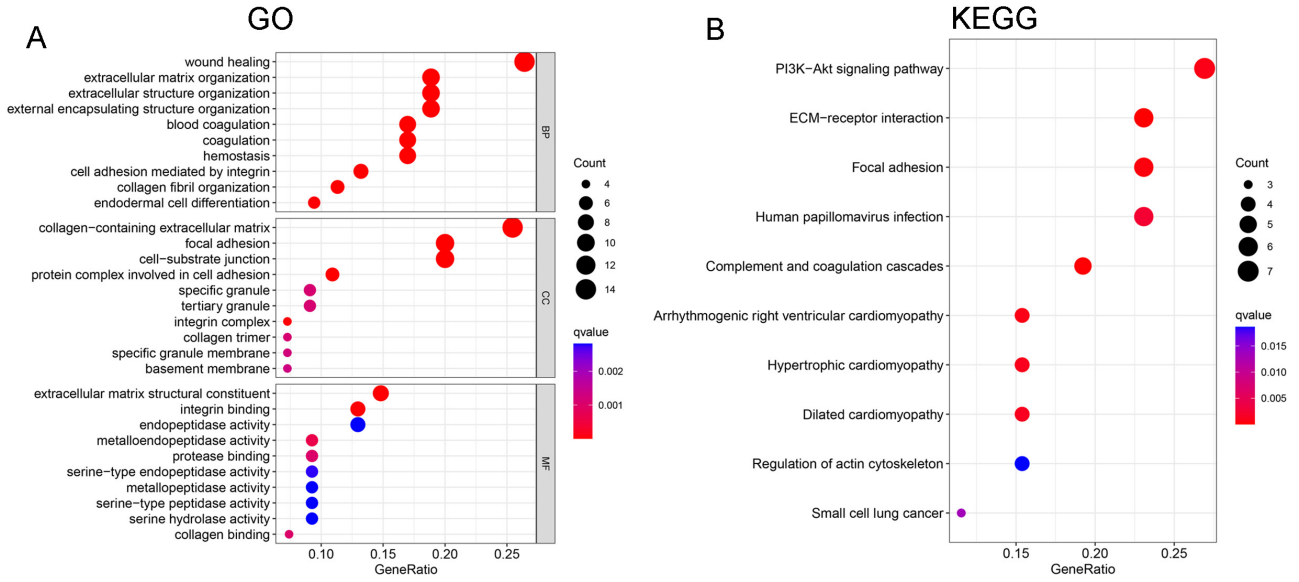

Fig. 5. AP000695.2-associated DEGs pathway analysis in gastric cancer. (A) DEGs GO pathway analysis. (B) DEGs KEGG pathway analysis.

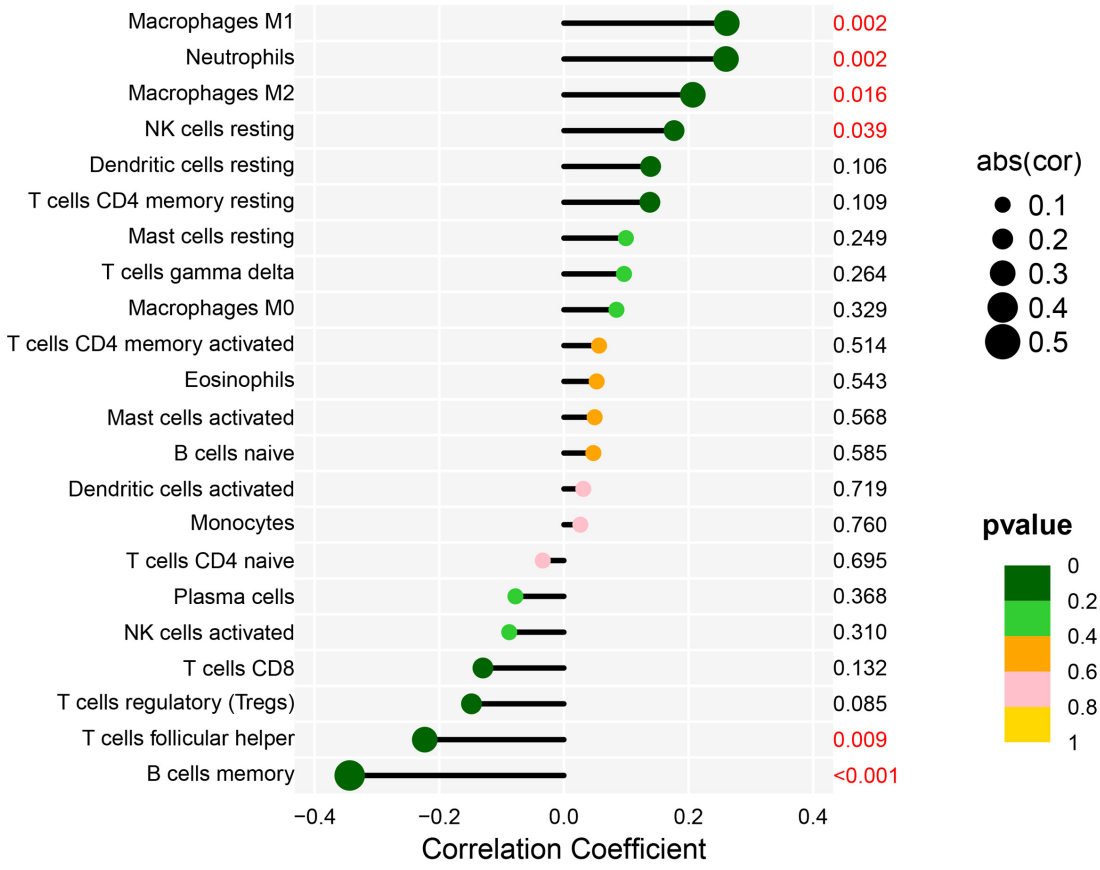

Fig. 6. Lollipop diagram showing the associations between AP000695.2 expression and tumor immune microenvironment.

curve could be used to evaluate the diagnostic potential by calculating the AUC value [22]. This study showed that AP000695.2 expression had a good capacity to diagnose gastric cancer, with an acceptable AUC close to 0.9, indicating that AP000695.2 is a promising diagnostic biomarker in gastric cancer. Survival analysis indicated that patients who

had higher AP000695.2 expression had poor OS and PFS, revealing AP000695.2 prognostic value in gastric cancer. Moreover, multivariate Cox regression analysis further determined that AP000695.2 expression was an independent predictor of gastric cancer outcomes. Additionally, prognostic nomograms were able to effectively predict 1-, 3-, and 5-year survival probability of OS and PFS. These results, taken together, suggest that AP000695.2 is a reliable prognostic and diagnostic biomarker in gastric cancer.

Analysis of co-expressed genes exhibited that LINC01614 was closely related to the collagenassociated process. Previous reports have shown that collagen constitutes a major component of the tumor microenvironment, involved in the process of tumor fibrosis [23]. Moreover, PI3K-Akt signaling, a cancer-related pathway, was observed in the KEGG analysis [24]. Recent evidence indicated that anti-checkpoint blockade response can be affected by tumor-infiltrating immune cells. For instance, KEYNOTE-001 showed that patients with more CD8+ T cell infiltration responded better to pembrolizumab compared to those with less CD8+ T cell infiltration [25]. Moreover, some studies reported that lncRNA could influence tumor-infiltrating immune cells infiltration level [26,27]. Result of a currently acknowledged method, CIBERSORT [28], indicated that AP000695.2 was positively associated with tumor-infiltrating immune cells including macrophages M1, neutrophils, macrophages M2, and NK cells. This finding may provide new insights for new immunotherapy strategies of gastric cancer.

Some limitations need to be acknowledged. Since AP000695.2 was well studied in other type of cancer, it detracts from the novelty of the article.

Conclusions

Our study revealed that AP000695.2 could serve as a novel biomarker to diagnose and predict survival in gastric patient. Additionally, AP000695.2 expression was associated with various tumorinfiltrating immune cells, which may provide new insights for new immunotherapy strategies.

Availability of Data and Materials

The data generated and/or analysed during the current study are available in the TCGA database (https://portal.gdc.cancer.gov/).

Author Contributions

YC, XY and HX—designed the research study; YC, XY, SF, JC and WL—analyzed the data; YC, XY, JC and HX—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202335174.4.

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