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Evaluating the Clinical Value of PVT1 Associated Genes in Predicting Prognosis and Guiding Treatment of Gastric Cancer Patients

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Abstract: Background: Gastric cancer (GC) is one of the most frequently occurring malignant tumors in the world with poor prognosis in digestive tract. LncRNA PVT1 is a potential oncogene, which is crucial for the occurrence and development of GC. The purpose of this study is to investigate the prognostic value of PVT1 associated genes in GC. Methods: PVT1 associated gene (PAG) expression was evaluated on cBioPortal. The gene expression data of PAGs and its corresponding clinical characteristics were extracted from The Cancer Genome Atlas (TCGA) database. Kaplan–Meier survival analysis was performed to assess the prognostic value of PAG in GC. Risk score model was built by lasso COX regression analysis and its prognostic efficacy was evaluated by the Receiver-operator Characteristic (ROC) curve. Cox regression analyses were conducted to investigate risk factors related to GC patient prognosis. Results: There were 10 postively and 5 negatively associated genes that showed a significant difference between normal and GC tissue. Based on the 8 gene signature, the GC patients could be classified into high- or low-risk subgroups with different OS ($P<0.001$). Cox regression analyses indicated that the PAG risk model score was an independent prognostic factor for OS. Further analysis showed that adding chemotherapy drugs can not prolong the survival of high-risk GC patients. For low-risk patients, chemotherapy combined with radiotherapy is recommended. Even if distant metastasis has occurred, low-risk patients are worthy of active treatment, because their prognosis is often better. Conclusion: PAGs are potential biomarkers to predict the prognosis of GC patients and may assist oncologists to formulate individualized treatment plans for this patient population.

Keywords: LncRNA PVT1, Gastric Cancer, Prognostic, Risk Model

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy and the second leading cause of cancer-related death worldwide [1]. Although chemotherapy and radiotherapy have made significant progress, the five-year overall survival (OS) rate and disease-free survival (DFS) rate of GC are still unsatisfactory. It is exceedingly important to explore the effective diagnosis, predictive prognosis and treatment of GC in order to improve the prognosis of patients with GC.

In recent years, high-throughput sequencing technology has been developed rapidly, followed by an increase in accuracy and the decrease in cost. This promotes the application of new tumor markers in predicting tumor prognosis and drug sensitivity. The Cancer Genome Atlas (TCGA) is a large collection of tumor gene sequencing data and clinical information, which can help us discover the internal mechanism of cancer occurrence and

development, ultimately allowing us to develop new diagnosis and treatment strategies [2]. Using the sequencing and clinical information of public databases, many new tumor markers, including coding genes and non-coding genes, have been discovered and used to determine the prognosis of tumors [3]. Noncoding RNAs, such as small RNAs and long noncoding RNAs (lncRNA), are abnormally expressed in a variety of malignant tumors. LncRNA refers to RNA transcripts with a length of more than 200nt, which is closely related to the biological behavior of many malignant tumors [4].

Zhu *et al.* used multivariate Cox regression model to identify 24 lncRNA that related to the prognosis of GC patients [5]. The ROC of the 24-lncRNA signature risk score combined with AJCC stage was significantly greater than AJCC stage alone. Tian *et al*. used LASSO Cox regression method to build a 12-lncRNA signature [6]. Further analysis showed that the prognostic value of this 12-lncRNA signature was independent of AJCC stage. Miao *et al*. gathered 4 lncRNAs as a single prognostic signature and suggested that the prognostic value of this 4-lncRNA signature was independent in clinical features. The risk score could largely predict the 5-year survival of GC patients, as the area under ROC curve (AUC) was 0.627 [7].

Plasmacytoma variant translocation 1 (PVT1) is a lncRNA encoded by the human PVT1 gene. The lncRNA PVT1 is located on chromosome 8q24, a location shared with the well-known oncogene c-myc [8]. Studies on the association between PVT1 and cancer have shown that PVT1 is a potential oncogene in a variety of cancer types, such as GC [9, 10] breast cancer [11], lung cancer [12] and hepatocellular carcinoma [13]. TGF-β, Wnt/β-catenin, PI3K/AKT, and mTOR pathways have been among the most dysregulated pathways in PVT1-upregulated cell [14]. Our previous study found that PVT1 can activate STAT3/VEGFA signaling pathway and promote angiogenesis in GC [10]. In addition, it was also found that PVT1 can enhance the resistance of GC cells to 5-FU by regulating BCL2 protein. Retrospective analysis showed that patients with high PVT1 expression did not benefit from 5-FU chemotherapy [9]. However, although there are many studies on the mechanism of PVT1 in GC, the application value of PVT1 in guiding clinical diagnosis and prognosis of GC is still unknown.

Gene co-expression is a type of analytic method which uses a large number of gene expression data to construct the correlation between genes. In biology, the co-expression patterns of genes in the same pathway will show the trend of co-expression [15]. Gene co-expression network is more stable than that of single gene, for the expression of single gene may be replaced or changed by other modules. Co-expression Gene can more effectively reveal the consistent differences in tumorigenesis and development [16].

In this study, the genes related to PVT1 expression were screened and named PVT1 associated gene (PAG). Based on these genes, molecular typing of GC patients was conducted and a risk score model was established. The survival time of GC patients varied greatly depending on their different risk scores ($p<0.001$). Based on the analysis of PAG risk model, multi-drug chemotherapy is unnecessary to high-risk GC patients. Moreover, radiotherapy combined with chemotherapy can significantly improve the survival rate of low-risk patients, which demonstrate chemoradiotherapy is the best treatment option for low-risk patients. These results showed that PVT1 combined with its associated genes can serve as a strong indicator when predicting the prognosis of GC patients and may help oncologists to formulate individualized treatment plans for this patient population.

2. Patients and Methods

2.1. Datasets

The available RNA-seq transcriptome data of 32 normal stomach tissue and 372 GC tissues and corresponding clinicopathological data was downloaded from the TCGA database (https://portal.gdc.cancer.gov/). Genes related to PVT1 expression in GC were analyzed and downloaded from cBioPortal (http://www.cbioportal.org). The downloaded raw data pre-procession and bioinformatics analysis were conducted using the R studio software. The clinical features of gastric cancer patients were collected in Supplementary File.

2.2. Consensus Clustering Analysis

"Consensus Clusterplus" R package was conducted to investigate the expression characteristics of PAGs in GC and cluster the patients into different groups. Then, principal component analysis (PCA) was performed to verify the PAGs expression patterns in different GC groups. The OS of GC patients in different groups was analyzed by "survival" R package. The association of expression pattern of PAGs and clinical features in different groups were showed by "pheatmap" R package. The distribution of each clinical characters was compared by Fisher test.

2.3. Prognostic Evaluation of 16 PAG in GC

To assess the predictive value of each PAGs gene, an univariate Cox regression analysis was performed based on gene expression and survival time. Lasso Cox regression was performed with 16 PAG to optimize the prognostic meaning. The equation for risk score is as follow: Risk score = $\sum_{i=n}^{n}$ Coefi $*$ Xi (where Coefi is the coefficient of each selected gene, Xi is the expression value). According to this risk scoring model, each GC patient can get a risk score. Patients with a score higher than the median were assigned to the high-risk group, whereas those with a score lower than the median score were assigned to the low-risk group. The Kaplan-Meier analysis was carried out to evaluate the predictive value of this risk scoring system. Correlation analysis was performed to investigate the correlation between subgroups stratified by the risk model and clinicopathologic features.

2.4. Independent Prognostic Ability of the PAG Risk Scoring Model

Univariate and multivariate Cox regression analyses of risk score and clinicopathological characters were performed to identify the prognostic performance of these characters,

including gender, age and stage. These are important factors affecting the survival time of patients.

2.5. Statistical Analysis

All data were sorted out, analyzed and plotted by the R (R version 4.1.0) software. As mentioned above, the corresponding R-packets were used for different analyses. A two-tailed $p<0.05$ was considered to be statistically significant.

3. Results

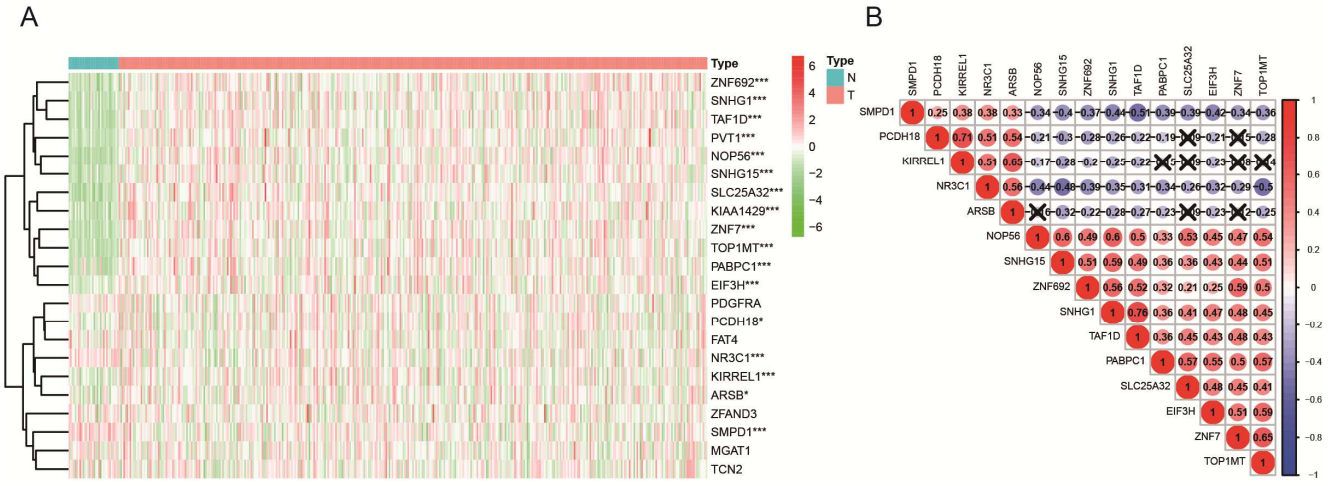
3.1. Identification of PAG in GC

In order to identify the PAG for predicting the prognosis of GC, we searched cBioPortal and selected 20 genes (including 10 positive and 10 negative related genes) which were associated with the expression of PVT1 significantly in GC according to Spearman correlation coefficient (Table 1). Compared with 32 normal and 372 cancer tissue samples within TCGA datasets, all of the 10 positive and only 5 negative related genes out of the above 20 genes showed significant differences in expression level (Figure 1A). According to the Spearman value and the significance of gene expression differences in normal and cancer tissues, we finally selected 16 genes (10 genes with the strongest correlation, 5 negative related genes and PVT1) as PAG to establish prognostic evaluation model and evaluate its reliability. In addition, the Pearson correlation analysis was performed to analyze the interaction among these genes in GC, indicating that there is a distinct correlation among ten positive related genes, but the relationship between positive and negative related genes is not consistent, particularly KIRREL1 and ARSB genes have weak correlation with multiple positive related genes (Figure 1B).

Table 1. *Ten positive and ten negative genes with the highest correlation with PVT1 expression from cBioPortal.*

Gene name	Spearman's correlation	p-Value	Gene name	Spearman's correlation	p-Value
SNHG15[#]	0.550	6.14e-34	PDGFRA	-0.404	1.38e-17
SNHG1[#]	0.517	1.56e-29	SMPD1[#]	-0.396	6.45e-17
ZNF7[#]	0.508	1.93e-28	ZFAND3	-0.392	1.30e-16
TOP1MT[#]	0.497	3.80e-27	TCN2	-0.382	9.70e-16
ZNF692[#]	0.494	1.08e-26	MGAT1	-0.375	3.23e-15
NOP56[#]	0.481	2.68e-25	FAT4	-0.367	1.50e-14
EIF3H[#]	0.477	7.83e-25	ARSB[#]	-0.365	2.05e-14
SLC25A32[#]	0.474	2.05e-24	PCDH18[#]	-0.365	2.11e-14
PABPC1[#]	0.473	2.34e-24	NR3C1[#]	-0.361	3.79e-14
TAF1D[#]	0.472	2.81e-24	KIRREL1[#]	-0.361	4.12e-14

[#] significant difference between normal and gastric cancer tissues.



*p < 0.05, **p < 0.01, ***p < 0.001.

Figure 1. *The expression pattern of 20 selected PAGs in TCGA GC cohort. (A) Heatmap visualizing the expression levels of PAGs in tumor samples and normal samples. (B) The Pearson correlation analysis of the 15 selected PVT1 associated genes in TCGA GC cohort.*

3.2. Consensus Clustering of PAG Identified Three Clusters of GC with Distinct OS

Based on the 16 genes we identified, we clustered the tumor samples into different groups by the "Consensus Cluster Plus" R package. As shown in Figure 2A-B, the value of K=3 is the most reasonable choice, which could divide the GC patients into 3 groups, called cluster 1, cluster 2 and cluster 3 respectively. Next, PCA analysis revealed that the transcriptional information among cluster 1, cluster 2 and cluster 3 subgroups were obviously different (Figure 2C).

In order to reveal whether or not there are differences in

survival time among different clusters, we compared the overall survival of three clusters. The results indicated that GC patients in cluster 3 suffered the shortest survival time, but the survival rate of GC patients in different clusters were not statistically significant (p=0.058, Figure 2D). Furthermore, heatmap showed no clinicopathological characteristics among different clusters to be significantly different (Figure 2E). The above results indicate that although PAG can clearly divide GC into different clusters, the cluster results based on PAG is not a qualified prognostic indicator.

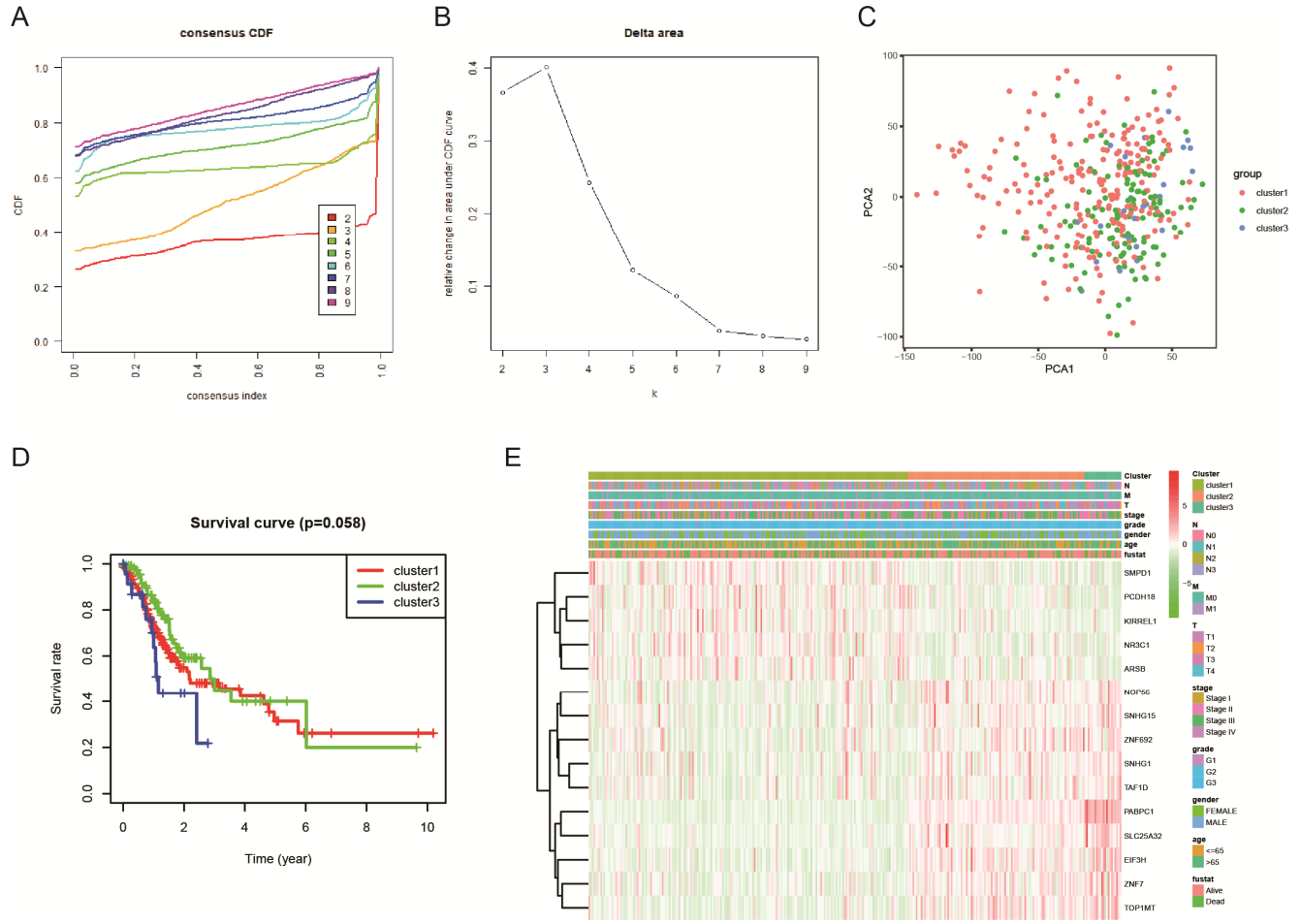


Figure 2. *Differential expression pattern and clinical outcome of TCGA GC patients in the three different clusters. (A) Consensus clustering cumulative distribution function (CDF) for k = 2-9; (B) Relative change in area under CDF curve for k =2-9;(C) Principal component analysis of the total RNA expression profile in the TCGA GC cohort; (D) The survival analysis for the three clusters by Kaplan–Meier method; (E) Heatmap and clinicopathologic features of the three clusters defined by the PAGs consensus expression.*

3.3. Construction of Risk Model with Significant Prognostic Value

Considering that the consensus cluster result based on PAGs was not satisfactory, we turned to exploring the predictive value of PAGs by establishing a risk score model. To better predict the clinical outcomes of GC, all 16 PAG were included in Lasso Cox regression analysis, consequently, 8 genes were selected and adopted to build the risk model (Figure 3A-C). Risk score=-0.023*ARSB + 0.036*NR3C1 + 0.042*PCDH18 -0.086*PVT1 + 0.022*SLC25A32 + 0.022*SMPD1 + 0.023*TAF1D - 0.091*ZNF692.

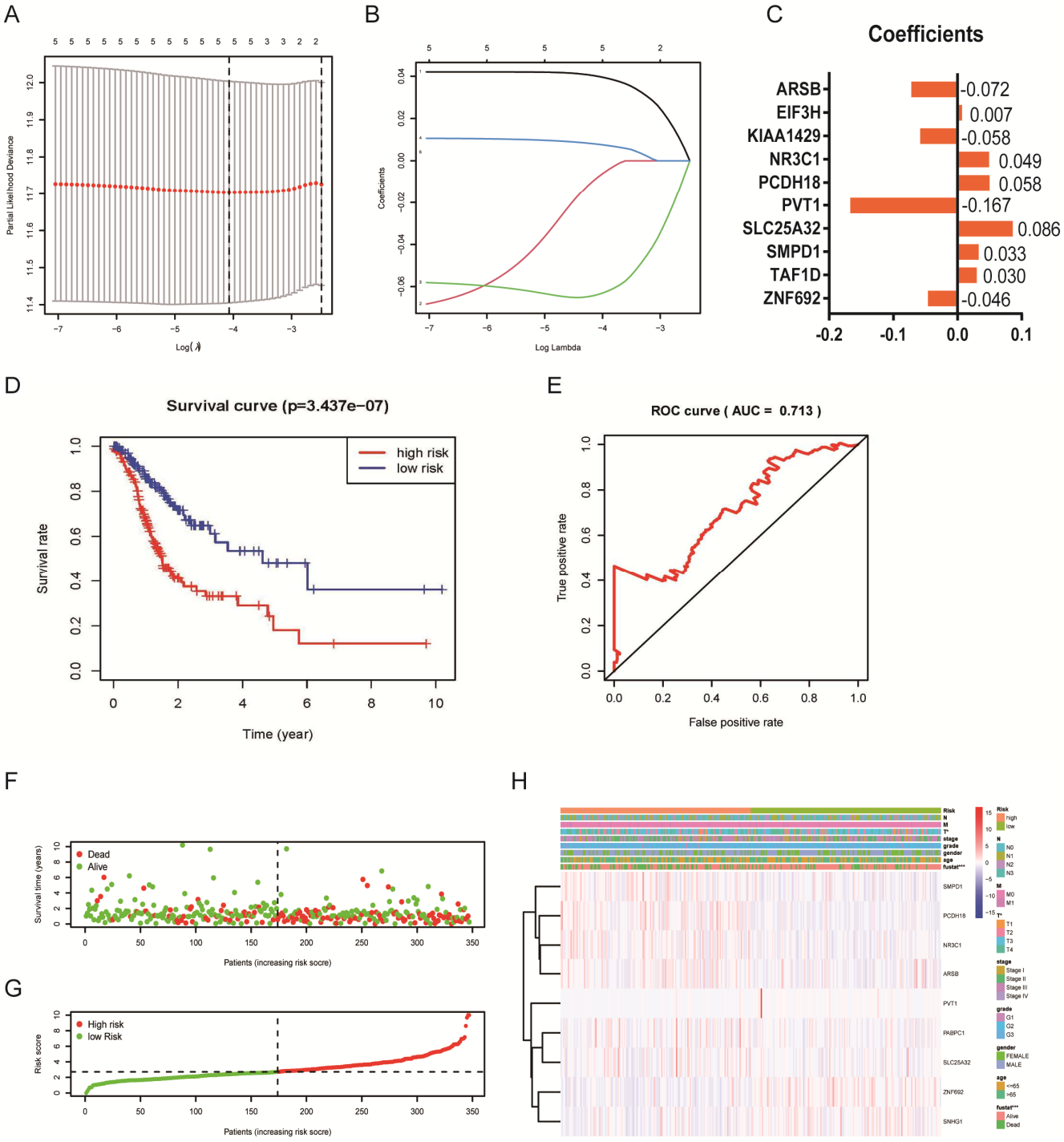
Next, we used the survival information of patients in the TCGA database to verify the effectiveness of the risk score model. Patients were placed in the high-risk group when their risk score was higher than the median risk score, and placed in the low-risk group when their risk score was lower than the median value. Then the OS between two groups was compared. Kaplan-Meier analysis illustrated that GC patients in the high-risk group suffer worse survival time than those in the low-risk group significantly (Figure 3D). The 1-, 3-, 5-year survival rates of patients with different levels of risk of GC were distinctly different (Table 2).

Table 2. *Overall survival in patients with high-risk and low-risk gastric cancer.*

Year	Low score group	High score group
1	85.5%	66.8%
2	71.6%	39.4%
3	61.2%	33.2%
4	53.5%	29.1%
5	48.2%	18.2%

Subsequently, we performed an ROC analysis to test the

reliability of the risk score model. The ROC results and prediction reliability analysis showed that the prediction model does indeed have an acceptable prediction efficiency (AUC=0.713, Figure 3E). The detailed risk score and survival information of PAG risk model were shown in Figure 3F-G. Figure 3H showed the relationship between the risk score model and the clinicopathological features. We noticed that the risk score is correlated with the T stage of GC significantly in addition to the survival time. In conclusion, this prediction model based on PAG can effectively and reliably predict the survival outcome of GC patients.



*p < 0.05, **p < 0.01, ***p < 0.001.

Figure 3. *Construction of prognostic risk signature with PAG. (A-B) The process of building lasso model with size and coefficients by multivariate Cox regression. (C) The coefficients of 8 PAG involved in lasso risk model. (D) Kaplan-Meier survival plots for high and low risk score groups in the TCGA dataset. (E) ROC curve estimating the performance of the risk score model predicting survival in the TCGA dataset. (F) The survival status and time of TCGA cohort. (G) The detailed information of the low and high score groups in the TCGA dataset. (H) Heatmap of 8 PAG involved in the lasso risk model and relationship between clinicopathological characters and risk subgroup.*

3.4. The PAG Risk Score Was an Independent Prognostic Factor in GC

Univariate and multivariate analyses were performed to evaluate whether the PAG risk score model can surve as an independent prognostic factor in GC. Univariate analysis demonstrated the age, depth of infiltration, lymph node metastasis and TNM stage, including the risk score was associated with poor prognosis significantly (Figure 4A). On this basis, all variables were analyzed again using multivariate analysis. The results showed that only the PAG risk score and age was still significantly linked to the prognosis of GC patients (Figure 4B). This data suggests that PAG risk model is a reliable prognostic indicator which can run independent of TNM stage.

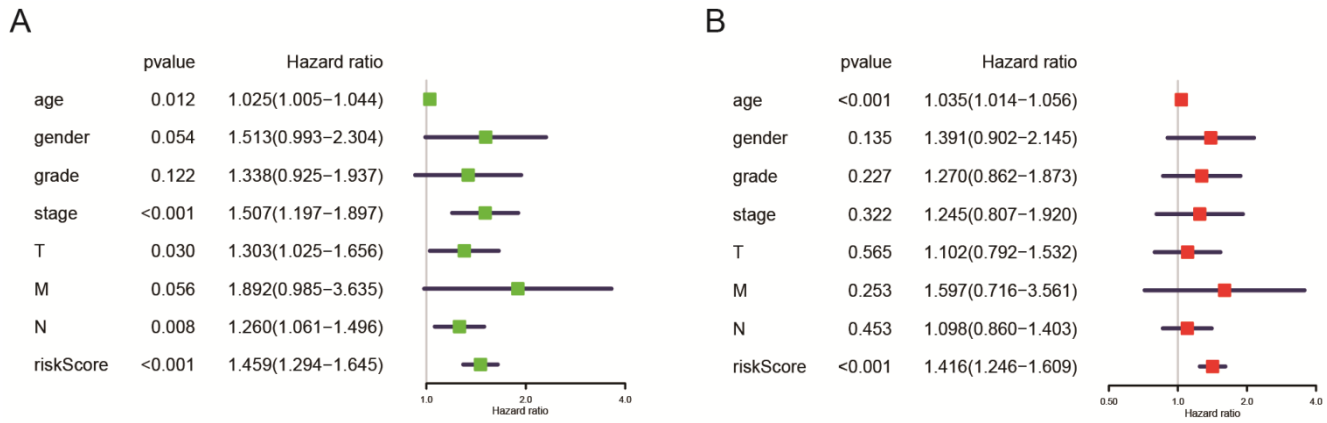


Figure 4. *Identification of the independent prognostic factors. Univariate Cox regression (A) and multivariate Cox regression (B) analysis for evaluating the prognostic role of clinicopathological characters and risk scores in GC.*

3.5. PAG Risk Model Can Guide the Treatment of GC

Next, we were concerned about the potential of PAGs risk model in guiding the clinical treatment of GC. We analyzed the curative effect of 5-FU-based chemotherapy in patients with different risk scores. As shown in Figure 5A, the low-risk group was much more sensitive to 5-FU than the high-risk group ($p<0.05$). We noted that when compared to monotherapy, 5-FU based multidrug combination therapy does not improve the survival time of high-risk patients ($p>0.05$). Low-risk patients are not only sensitive to chemotherapy, but also to radiotherapy, and those patients benefit most from concurrent chemoradiotherapy ($p<0.05$). In addition, we analyzed the survival of patients with distant metastasis. The results showed that even if distant metastasis has occurred, the survival time of low-risk patients is notably longer than that of high-risk patients (Figure 5B). The above results show that the PAG risk model is a promising indicator in assessing GC treatment efficacy.

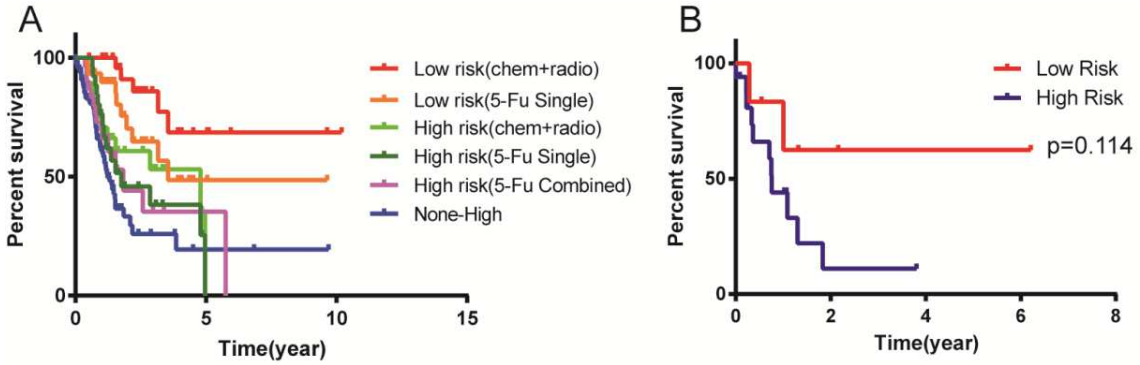


Figure 5. *PAG risk model can guide the treatment of GC. (A) Survival time of high-risk and low-risk group GC patients after different treatments. (B) Kaplan-Meier survival plots for high and low risk GC patients in M1 stage.*

4. Discussion

The establishment of prognosis prediction models based on lncRNA is in the exploratory period. Although lncRNA is involved in many processes of tumorigenesis and development, it does not encode proteins but rather plays a regulatory role [17]. Our exploration found that lncRNA with its related genes can establish a reliable molecular predictive model, and show a strong predictive effect. PVT1 is considered to be a carcinogenic lncRNA due to its high expression in various malignant tumors, and it often plays a

similar molecular mechanism in different types of tumors. Although the mechanism of PVT1 in promoting cancer has been extensively and deeply studied, the clinical value of PVT1 is still worthy of further exploration. In this study, we first screened and analyzed the role of PVT1 related genes, and revealed the important value of PVT1 related genes in predicting the prognosis of GC.

Unlike existing literature and research protocol, we screened some genes that are significantly related to PVT1 according to Spearman correlation coefficient, particularly the genes that have a negative impact on PVT1 expression, which together constitute PAG. The analysis results showed that this new method yields a good predictive value and opens up a new way to find better markers and measures for tumor diagnosis, treatment efficacy, and prognosis.

M6A modification can regulate mRNA maturation, transcription and degradation, it plays an important role in a variety of tumors, such as breast cancer, lung cancer and colorectal cancer [18]. Guan *et al.* constructed a risk score model by using the related gene of m6A [19]. However, the AUC of the risk model based on m6A was only 0.58 in the TCGA library, and Cox regression analyses showed it can not independently predict the prognosis of GC patients. In contrast, the AUC value of the risk prediction model based on PAG was 0.714. This means that our prediction model based on the PAG has a better predictive value than that of m6A model.

In clinical practice, it is often noticed that although patients have similar TNM stages, their prognosis is very different. This indicates that the TNM stage system can not fully reflect the intrinsic properties of tumors, and other indicators are still needed to reflect the malignant degree of tumor. Based on the PAG risk model, survival analysis of GC patients with different levels of risk showed that the survival time of the high-risk group was significantly shorter than that of the low-risk group. Significant differences in 1-, 3-, and 5-year survival rates among different risk groups can help doctors predict the prognosis of patients. There was no correlation between the PAG risk model and TNM staging, which indicated that the PAG risk model is independent of the existing prediction system. PAG risk model can help oncologists make a more accurate judgment on the prognosis of GC patients, to identify patients with the same TNM stage but suffer shorter survival time, so as to make up for the deficiency of the TNM staging system.

The ideal treatment strategy, especially for GC patients, is to use individualized treatment modalities that are highly heterogeneous and insensitive to chemotherapy on different patients. We were intrigued as to whether the PAG risk model can be used as a reference index to guide treatment, thus we further analyzed the response of patients in different risk levels to different treatment modalities. The results showed that the survival time for the high-risk patient group was equivocal when comparing patients who received a single drug to patients who received a multi-drug chemotherapy regimen. This indicated that the high-risk group of patients was not sensitive to chemotherapy, and that multi drug combination chemotherapy did not improve the efficacy, but may increase the cost and side effects of chemotherapy. For high-risk GC patients in PAG model, multi-drug chemotherapy is not suitable. We also observed that radiotherapy is an effective treatment modality to improve the prognosis of patients, especially for patients with low-risk GC. Chemotherapy combined with radiotherapy can significantly prolong the survival time for low-risk patients, which suggests that the addition of radiotherapy on the basis of chemotherapy may be an excellent treatment option for patients in low-risk gastric cancer.

There is a phenomenon in clinical practice that, although distant metastasis has occurred, the survival time of some late stage GC patients is much longer than expected, and for such patients, if tumor reduction surgery or more active treatment is given, patients may benefit significantly. This phenomenon may be caused by the intrinsic characteristics of the tumor, but can't be screened with by the existing prediction methods. Can PAG risk model solve this dilemma? In this paper, we selected the patients with distant metastasis (M1 stage) from TCGA data, and used PAG risk model to grade the risk and analyze the survival. The results showed that even in patients with distant metastasis, the survival time of patients with low-risk classification was much longer than that of patients with high-risk. This means that for those patients who have distant metastasis but are at low risk, it is worth giving more active and effective treatment measures.

However, our research has some limitations. We have not improved the reliability of the risk score model in other databases. Moreover, the predictive value of the risk score model in M1 patients based on the PAG risk score model is merely an analytical result derived from an existing small sample size, and the validity of this results needs to be further verified by a larger sample size.

5. Conclusion

In conclusion, PVT1 and its related co-expression genes play an important role in GC. The risk score model based on PAGs can effectively distinguish the prognosis of patients with different risks, and it is a factor that is independent of the current prognosis prediction system. The results of this study not only provide a method to predict the survival of patients with GC, but also provide guidance for the development of treatment strategies for GC.

Declaration of Interest Statement

The authors declare that they have no conflicts of interest.

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