Observational Study

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# BZW1 is a prognostic and immunological biomarker in pancreatic adenocarcinoma

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**Abstract**

Pancreatic adenocarcinoma is the most common malignant tumor of the digestive system and is called the "king of cancer" because it has been labeled with high malignancy, rapid progression, poor survival, and poor prognosis. Previously, it was reported that the basic leucine zipper and W2 domains 1 (BZW1) is involved in the progression of many tumors. However, its research in digestive system tumors such as pancreatic cancer is rarely studied. To explore potential biomarkers related to survival and prognosis of pancreatic cancer and provide a new targeted therapy for it. We first analyzed the mRNA and protein expression of BZW1 in pancreatic cancer. We then explored the correlation of BZW1 with survival prognosis and immune infiltration in pancreatic cancer patients. Finally, we explored BZW1-related gene enrichment analysis, including protein-protein interaction networks, gene ontology functional enrichment analysis, and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis. The mRNA and protein expression of the BZW1 gene in pancreatic cancer tissues were higher than those in adjacent normal tissues, and pancreatic cancer patients with high BZW1 expression had a poor prognosis. In addition, the expression of BZW1 was positively or negatively correlated with different immune cells of pancreatic cancer, such as CD4 + T lymphocytes, CD8 + T lymphocytes, B cells, macrophages, neutrophils, etc. Correlation enrichment analysis showed that we obtained 50 available experimentally determined BZW1-binding proteins and 100 targeted genes related to BZW1, and the intersection genes were eukaryotic translation termination factor 1 and Guanine nucleotide binding protein, alpha inhibiting activity polypeptide 3. Moreover, there was a positive correlation between BZW1 and eukaryotic translation termination factor 1 and Guanine nucleotide binding protein, alpha inhibiting activity polypeptide 3 genes in pancreatic cancer. Gene ontology enrichment analysis showed BZW1 was mainly related to biological processes such as "mRNA processing," "RNA splicing," "regulation of translational initiation," and "activation of innate immune response." The results of Kyoto Encyclopedia of Genes and Genomes pathway analysis further indicated that BZW1 may be involved in pancreatic carcinogenesis through the "spliceosome" and "ribosome." The BZW1 gene may be a potential immunotherapy target and a promising prognostic marker for pancreatic cancer.

**Abbreviations:** bZIP = basic leucine zipper, BZW1 = the basic leucine zipper and W2 domains 1, DAVID = database for annotation, visualization and integrated discovery, ETF1 = eukaryotic translation termination factor 1, GEPIA = Gene Expression Profiling Interactive Analysis, GNAI3 = Guanine nucleotide binding protein, alpha inhibiting activity polypeptide 3, GO = gene ontology, HPA = Human Protein Atlas, KEGG = Kyoto Encyclopedia of Genes and Genomes, PAAD = pancreatic adenocarcinoma, TME = tumor microenvironment.

**Keywords:** biomarkers, BZW1, immune infiltration, PAAD, survival prognosis

## 1. Introduction

Cancer remains the biggest threat to humanity today. The latest cancer statistics show that more than 1918,000 cancer cases will be diagnosed in the United States in 2022.[1] Pancreatic cancer is a highly malignant digestive system tumor with a very low 5-year survival rate.[2–4] In addition to conventional treatments such as surgery, radiotherapy, and chemotherapy, it is of great clinical significance to study new tumor immunity and prognostic markers.[5–7] For instance, Ma[8] found that high expression of the protein-coding gene EVA1B affects colorectal cancer-related immunity and prognosis. Zhu[9] has studied that the expression

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*The datasets generated during and/or analyzed during the current study are publicly available.*

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of TUBA1C is positively correlated with B cells, CD8 T + cells, and CD4 infiltration through some public databases, and that patients with low-grade gliomas with high TUBA1C expression have a poor prognosis. It is reported that BTN3A2 is related to the progression of many tumors, including breast cancer, pancreatic ductal carcinoma, gastric cancer, lung adenocarcinoma, etc, and highly expressed BTN3A2 is positively correlated with the survival prognosis and immune infiltration of lung adenocarcinoma.[10]

The basic leucine zipper and W2 domains 1 (BZW1) is a member of the basic leucine zipper (bZIP) superfamily of transcription factors. The BZW1 gene encodes a 45 kDa protein containing an N-terminal bZIP domain for protein interactions and a C-terminal nucleotide (ATP or GTP) binding domain.[11] Human BZW1 can activate histone H4 gene transcription and act as a co-regulator of other transcription factors to control the cell cycle.[12–14] Immunotherapy and targeted therapy are still important means of current tumor treatment.[15–17] Exploring new tumor markers can solve many difficult clinical problems. Previous studies claims that BZW1 acts as a novel proliferation regulator to promote the growth of mucoepidermoid cancer cells.[11] However, the role of BZW1 in pancreatic cancer has not been elucidated. We used bioinformatics methods to explore the relationship between survival prognosis and immune infiltration of BZW1 in pancreatic cancer through multiple treatment databases, and studied its possible mechanism of action in pancreatic adenocarcinoma (PAAD), providing a new theoretical basis for the treatment of pancreatic cancer.

## 2. Materials and methods

### 2.1. Materials

The following are databases and tools: Human Protein Atlas (HPA) database (https://www.proteinatlas.org/), TIMER 2.0 database (http://timer.comp-genomics.org/), University of ALabama at Birmingham CANcer data analysis Portal database (http://ualcan.path.uab.edu/), Gene Expression Profiling Interactive Analysis (GEPIA)2 database (http://gepia2.cancer-pku.cn), TIMER database (http://timer.cistrome.org/), CTD Platform My Venn Tools (https://bioinfogp.cnb.csic.es/tools/venny/), STRING database (www.string-db.org/), database for annotation, visualization and integrated discovery (DAVID) d-atabase (http://david.ncifcrf.gov/tools.jsp), Gene Ontology Chord Plot Tool (www.bioinformatics.com.cn/). Cytoscape 3.9.0 software.

### 2.2. Gene expression analysis

Based on the HPA database, we obtained the expression levels of the BZW1 gene in different tumors. We used the "Gene_DE" section of "Exploration" in the TIMER2.0 database to investigate the differential expression of BZW1 between different tumors and adjacent normal tissues. Finally, the TCGA Gene Analysis section in the University of ALabama at Birmingham CANcer data analysis Portal database was used to explore the expression of BZW1gene in PAAD and other digestive system tumors based on individual cancer stages.

### 2.3. Protein expression analysis

We explored the expression level of BZW1 protein in different digestive system tumors and adjacent normal tissues using the HPA database. The antibody HPA053272 was used for PAAD.

### 2.4. Survival prognostic analysis

The GEPIA2 database was used to analyze the effect of BZW1 mRNA expression on pancreatic cancer patients.

### 2.5. Immune infiltration analysis

We studied the correlation between the expression of BZW1 and the level of immune infiltration in PAAD through the TIMER database, including B Cells, CD8 + T Cells, CD4 + T Cells, macrophages, and neutrophils.

### 2.6. BZW1-related gene enrichment analysis

We first performed protein-protein interaction network functional enrichment analysis to obtain BZW1-binding proteins by using the STRING database. We entered the BZW1 protein in the "Protein by name" query and selected the species as "Homo sapiens." Then, we set the following main parameters: minimum interaction score required ["Low confidence (0.150)"], meaning of network edge ("evidence"), maximum number of interactors to display ("no more than 50 interactors" in the first shell), and active interaction sources ("experiments"). Finally, available experimentally determined BZW1-binding proteins were obtained. We use Cytoscape 3.9.0 software to visualize the results, and the degree value is proportional to the shade of gene color.

We input BZW1 into the "similar gene detection" module of the GEPIA2 database to obtain the top 100 targeted genes related to BZW1, and then intersected the 50 genes obtained by PPI with these 100 related genes by Venn. The "Gene_Corr" section of "Exploration" is used to analyze the correlation between BZW1 and the intersection genes through the TIMER2.0 database, and finally use the TIMER database to draw the expression scatter diagram between BZW1 and the intersection genes in PAAD.

The DAVID database was used for gene ontology (GO) gene enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. We uploaded the gene list to DAVID, set the selected identifier ("OFFICIAL_GENE_SYMBOL") and species ("Homo sapiens"), and obtained data for functional annotation plots, then visualized the results using the Gene Ontology Chord Plot Tool.

### 2.7. Statistical analysis

The 2 groups of expression data were compared between the tumor group and the normal group. The survival analysis of tumor patients was performed by COX regression analysis. Immunological analysis was performed by Spearman correlation analysis. $P < .05$ was statistically significant.

## 3. Results

### 3.1. Expression levels of BZW1 gene in different tumors

We obtained the expression levels of the BZW1 gene in different tumors. The results showed that BZW1 was expressed in most tumors (Fig. 1). We then further analyzed the differential expression of the BZW1 gene between different tumors and adjacent normal tissues. The results showed that the expression of the BZW1 gene in pancreatic cancer tissues was significantly higher than that in adjacent normal tissues (Fig. 2). In the end, we explored the expression of BZW1 gene in PAAD and other digestive system tumors based on individual cancer stages (Fig. 3).

### 3.2. Expression level of BZW1 protein in different digestive system tumors

We used the HPA database to analyze the expression of BZW1 protein in different digestive system tumors, and the results showed that BZW1 protein was negative in normal pancreatic tissue but moderately or highly expressed in pancreatic cancer tissue (Fig. 4).

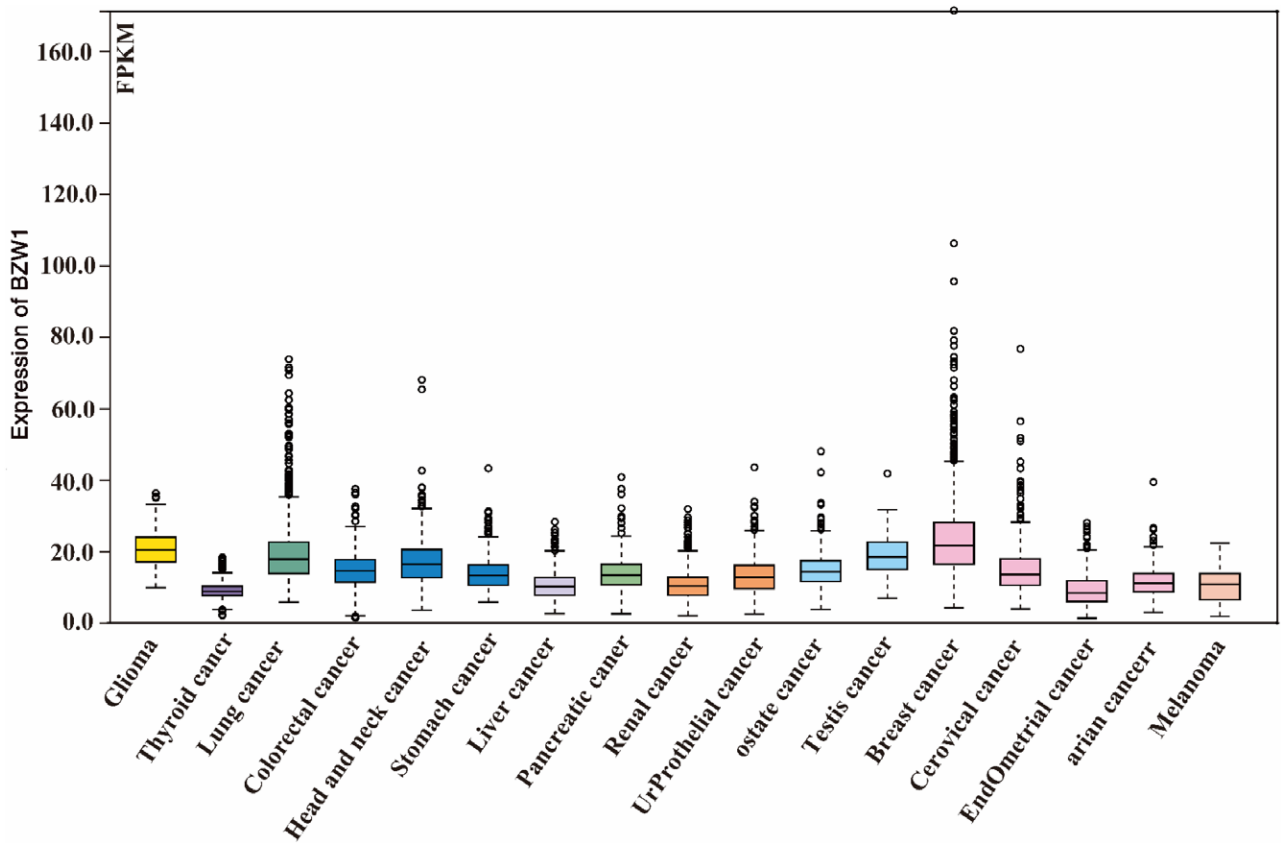


**Figure 1.** Expression levels of BZW1 gene in different tumors based on the HPA database. BZW1 = the basic leucine zipper and W2 domains 1, HPA = Human Protein Atlas.

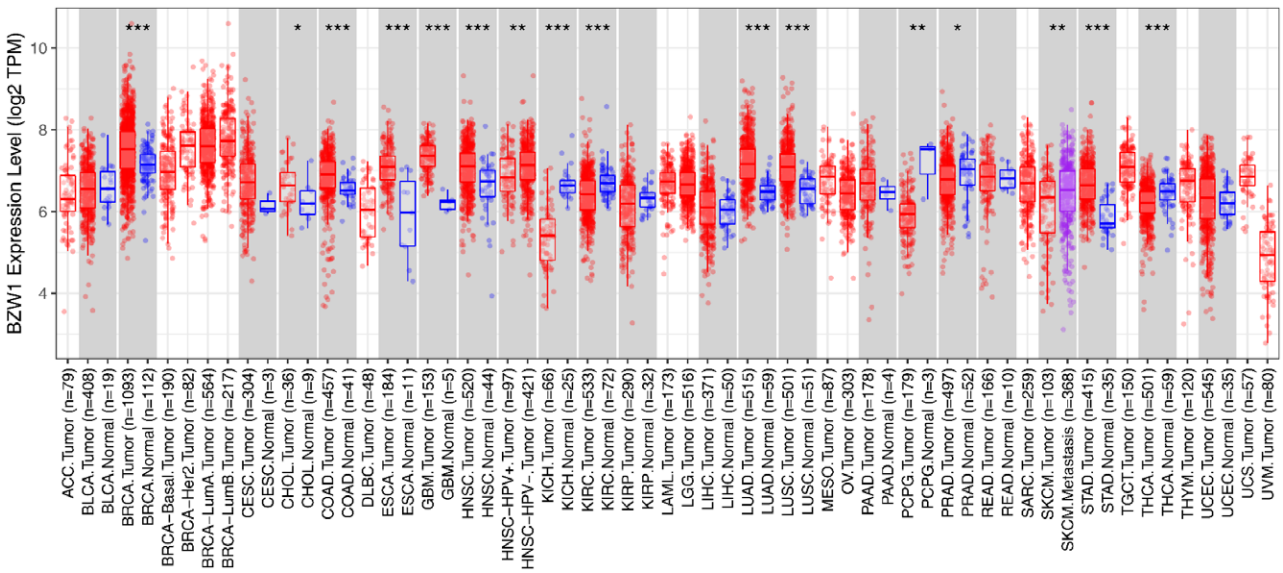


**Figure 2.** Expression of BZW1 gene between different tumors and adjacent normal tissues in the TIMER2.0 database. BZW1 = the basic leucine zipper and W2 domains 1.

### *3.3. Survival and prognostic value of BZW1 in pancreatic cancer*

We analyzed the GEPIA2 database. The results further showed the prognostic value of BZW1 in PAAD. The results showed that the prognosis of pancreatic cancer patients with high BZW1 expression was worse than that of pancreatic cancer patients with low BZW1 expression ($P = .0031$), and the prognosis was the same in patients with liver cancer. Patients with esophageal cancer and gastric cancer had no effect on the prognosis of patients (Fig. 5).

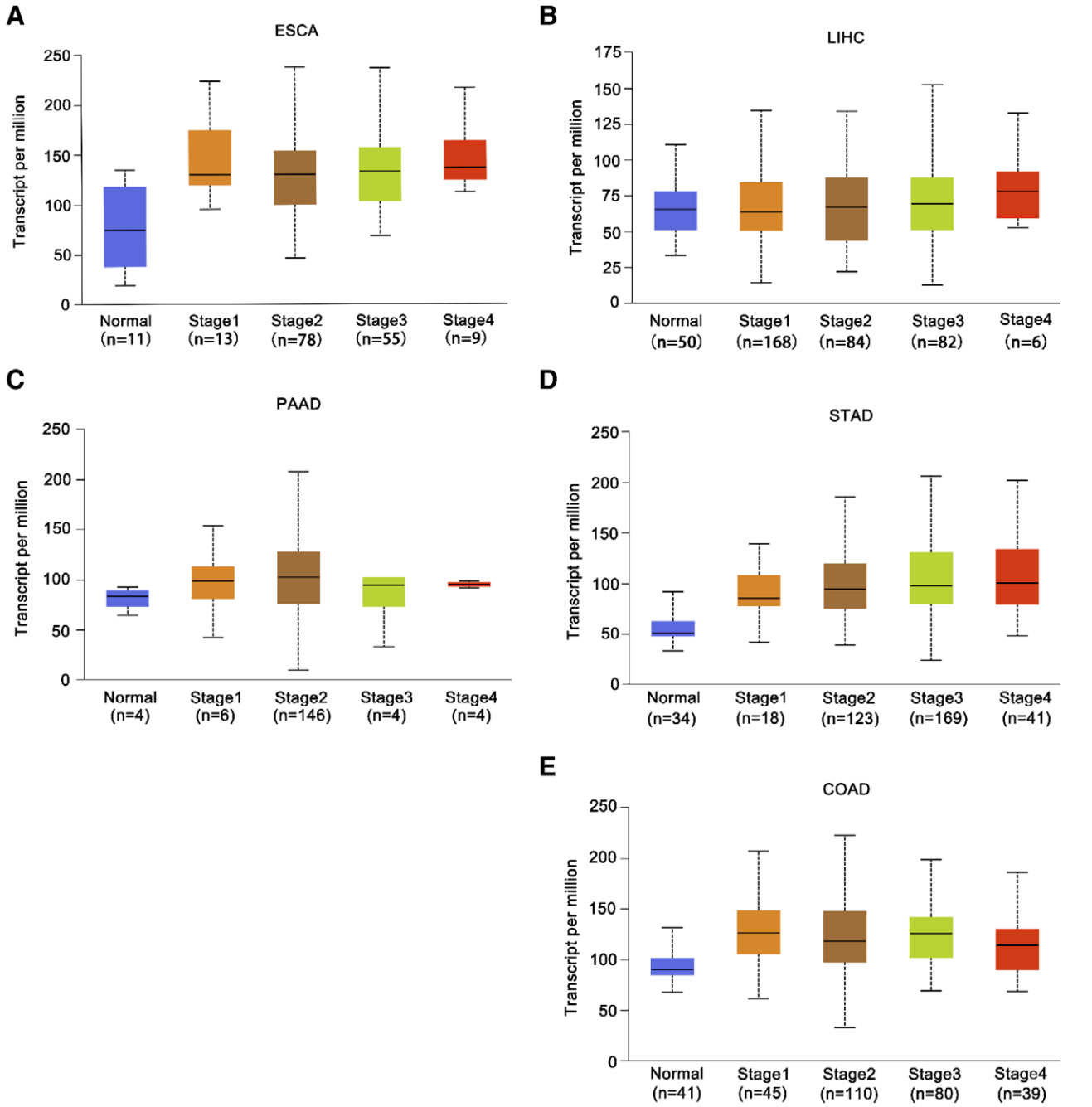


**Figure 3.** Expression of BZW1 gene in PAAD and other digestive system tumors based on individual cancer stages. BZW1 = the basic leucine zipper and W2 domains 1, PAAD = pancreatic adenocarcinoma.

### *3.4. Correlation between the expression of BZW1 and the level of immune infiltration in pancreatic carcinoma*

In order to visualize the correlation of BZW1 expression with immune infiltration level in PAAD, we analyzed the TIMER database and the results showed that the expression of BZW1 was positively or negatively correlated with different immune cells of PAAD, such as B Cells ($P$ = 6.46e-04), CD8 + T Cells ($P$ = 5.47e-14), CD4 + T Cells ($P$ = 2.75e-03), macrophages ($P$ = 3.01e-08), and neutrophils ($P$ = 6.07e-06) (Fig. 6).

### *3.5. BZW1-related gene enrichment analysis*

To further investigate the molecular mechanism of BZW1 in PAAD, 50 experimentally determined BZW1-binding proteins were obtained through STRING database, and the results were visualized using Cytoscape 3.9.0 (Fig. 7A). Then we obtain the top 100 targeted genes related to BZW1, and then use Venn to intersect the 50 genes obtained by PPI with the top 100 related genes, yielding 2 intersecting genes, eukaryotic translation termination factor 1 (ETF1) and Guanine nucleotide binding protein, alpha inhibiting activity polypeptide 3 (GNAI3) (Fig. 7B). Then we analyzed the correlation of BZW1 with the intersection genes ETF1 and GNAI3 in different cancer types by using the TIMER2.0 database, and the results showed that the expression of ETF1 and GNAI3 in most cancer types was positively correlated with BZW1 (Fig. 7C). In pancreatic cancer, the corresponding scatterplot revealed a positive correlation between BZW1 and ETF1 ($P$ = 9.73e-25) and GNAI3 ($P$ = 8.11e-27) (Fig. 7D).

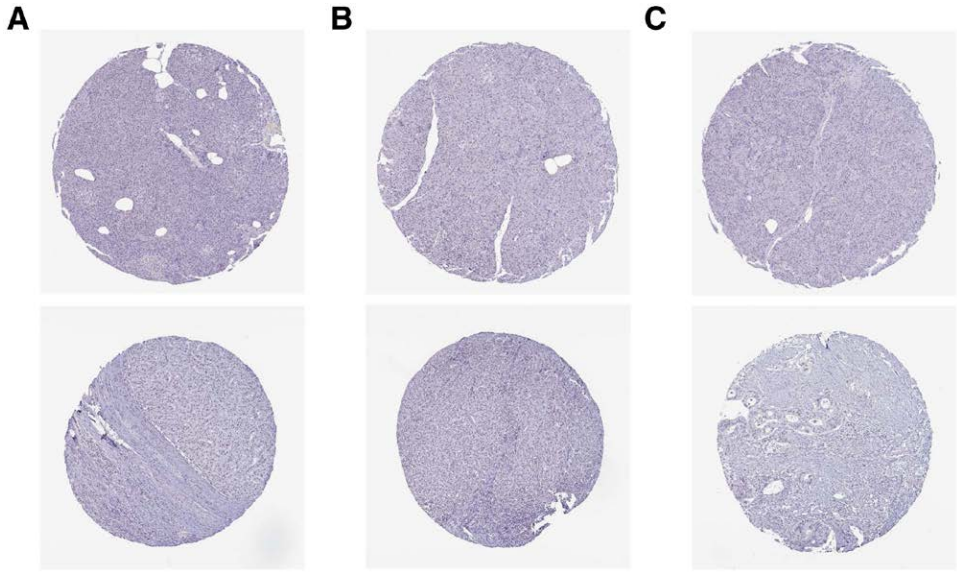


**Figure 4.** Expression of BZW1 protein in HPA datasets. BZW1 = the basic leucine zipper and W2 domains 1, HPA = Human Protein Atlas.

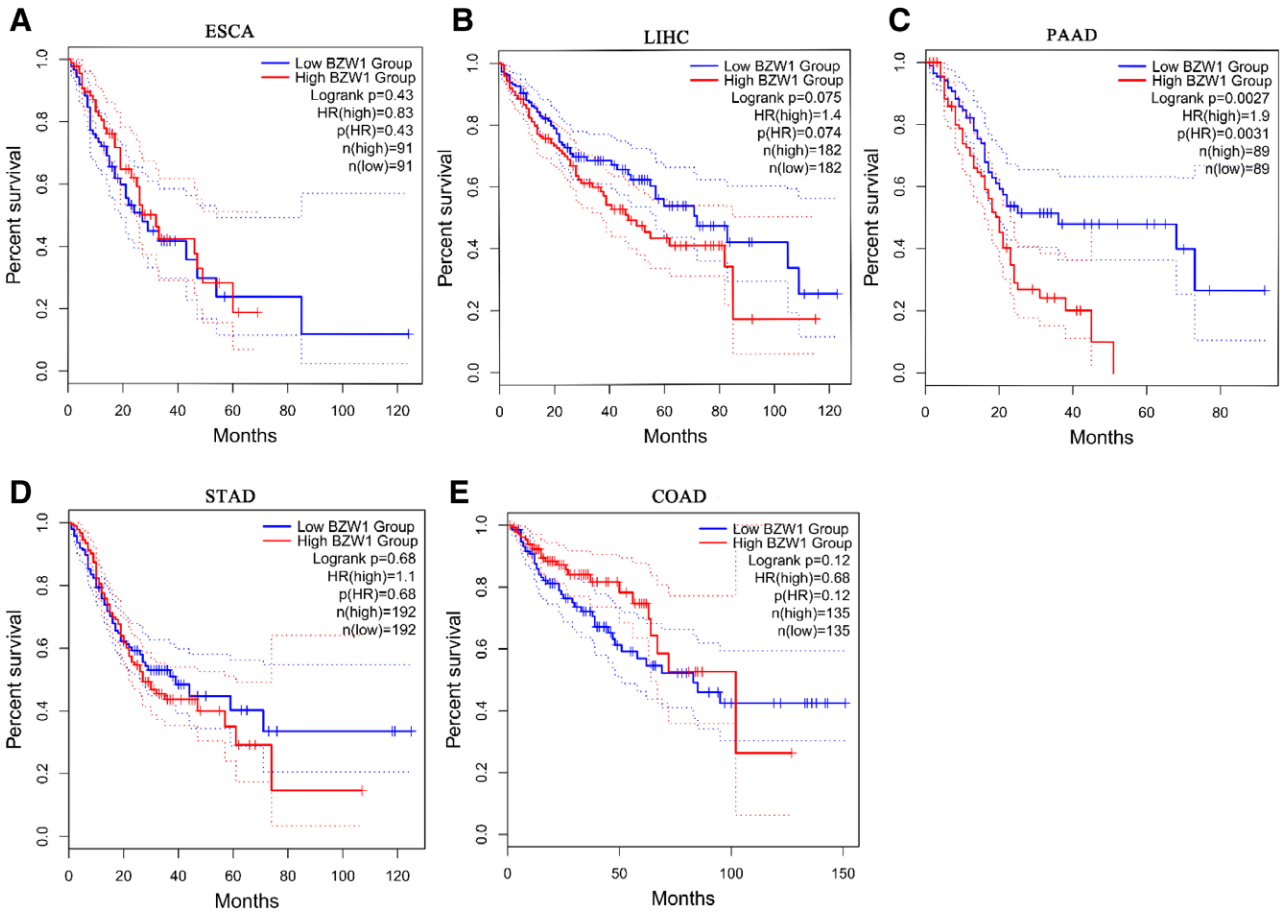


**Figure 5.** Relationship Between BZW1 Gene Expression and Survival and Prognosis of PAAD. BZW1 = the basic leucine zipper and W2 domains 1, PAAD = pancreatic adenocarcinoma.

In addition, we used the DAVID database for GO enrichment analysis and KEGG pathway enrichment analysis. In addition, we used the DAVID database for GO enrichment analysis and KEGG pathway enrichment analysis. These genes were primarily associated with biological processes such as "mRNA processing," "RNA splicing," "regulation of translational initiation," and "activation of innate immune response" (Fig. 7E). KEGG pathway analysis revealed that BZW1 may be involved in pancreatic carcinogenesis via the "spliceosome" and "ribosome" (Fig. 7F).

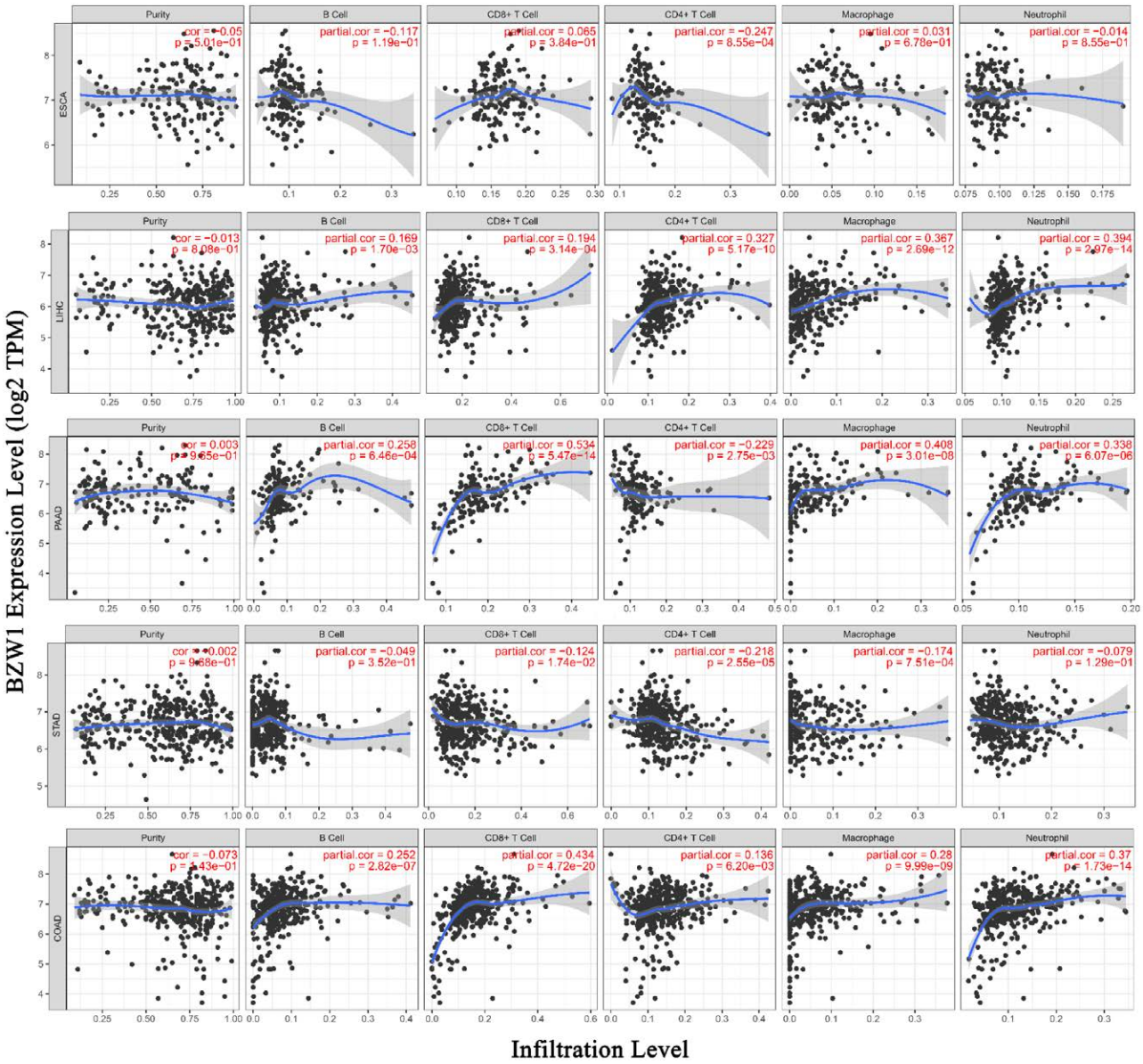


**Figure 6.** Correlation Between the Expression of BZW1 and the Level of Immune Infiltration in Pancreatic Carcinoma. BZW1 = the basic leucine zipper and W2 domains 1.

## 4. Discussion

Pancreatic cancer is a highly aggressive malignant tumor; it ranks seventh in the global malignant tumor mortality rate, and it is on a rapid upward trend.[18] Due to the lack of obvious symptoms and signs in the early stages,[19] it is often diagnosed in the middle and late stages, thus lacking opportunities for surgery, which is a very difficult problem for patients and clinicians. At the same time, pancreatic cancer shows broad tolerance to chemoradiotherapy and insensitivity to immunotherapy, resulting in poor therapeutic effect and poor prognosis.[20–22] It is of great significance for us to explore new biomarkers for early diagnosis of pancreatic cancer.[23]

Prognostic biomarkers are used to detect disease recurrence or progression in patients with a related disease or medical condition, whether these markers are observed by visual inspection of the viscera or, more recently, by histopathological or genomic characterization.[24,25] For example, EIF4G1 mRNA levels were significantly elevated in breast cancer tissues compared to normal breast samples; BRCA patients with increased EIF4G1 expression had shorter overall survival in all cohorts; and patients with high expression of EIF4G1 responded better to immunotherapy; thus, EIF4G1 may be a valid predictor of the efficacy of immunotherapy in BRCA patients.[26] The study by Bhattacharyya et al describes in detail the biomarker-guided adaptive phase III clinical trials, where first we need to identify significant genes among a large number of evaluated differential genes by high-throughput screening methods; second, estimate the gene-treatment interaction effect; and lastly, utilize an unknown-gene adaptive signature design to assess the level of significance in selecting differentially expressed genes by Bonferroni adjustment and false discovery rate.[27]

BZW1, a member of the bZIP transcription factor superfamily, is involved in the progression of multiple tumors. Shi et al[28] found that highly expressed BZW1 can significantly promote the proliferation of prostate cancer cells by regulating the TGF-β1/Smad pathway. Another study[29] showed that BZW1 and BZW2 are expressed in a variety of cancer types, but BZW1 has a more significant clinicopathological value, and its high expression has poor prognosis in lung adenocarcinoma, and its down-regulation can inhibit lung adenocarcinoma metastasis. BZW1

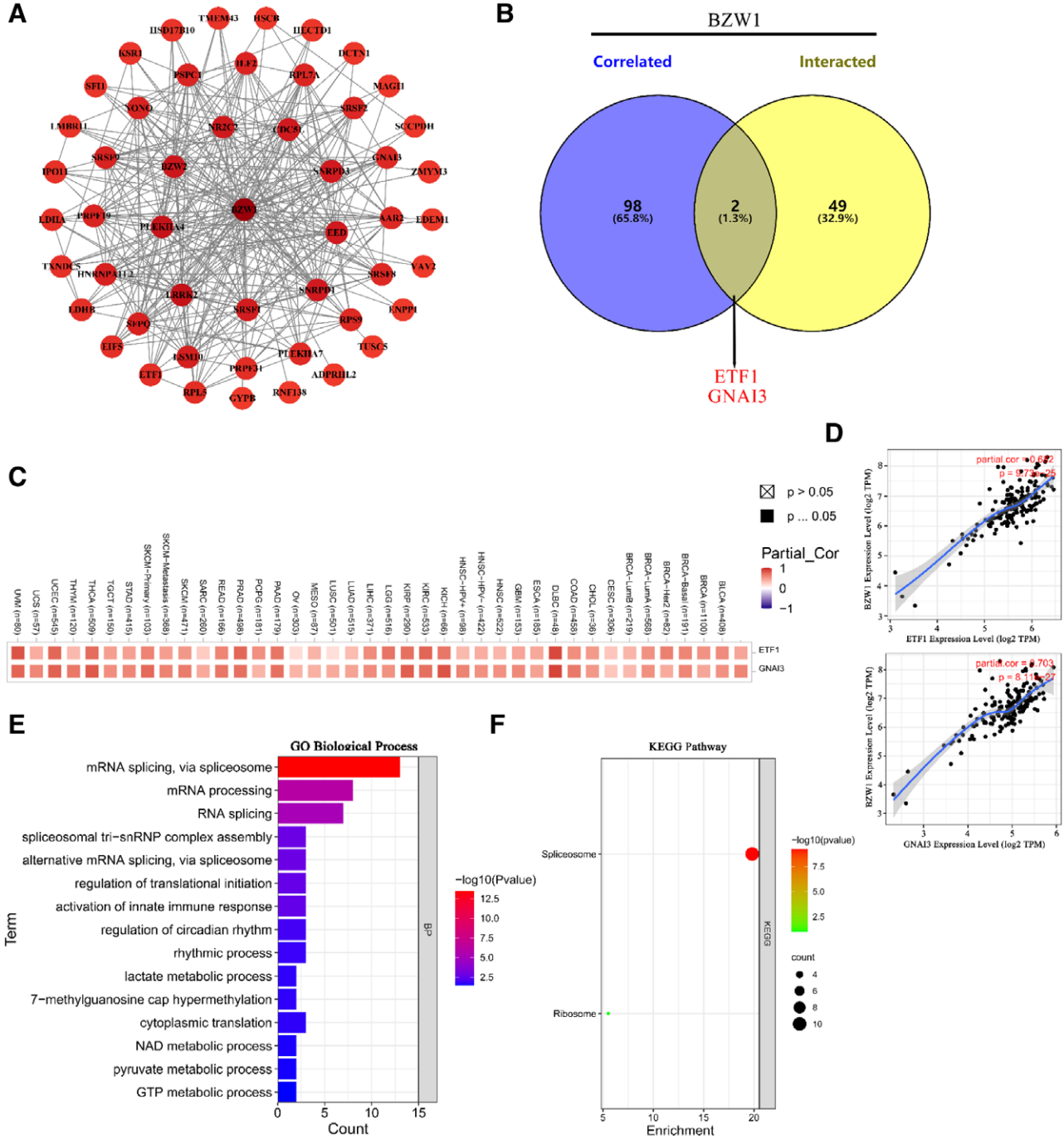


**Figure 7.** BZW1-related gene enrichment analysis. (A) 50 experimentally determined BZW1-binding proteins. (B) 2 intersecting genes. (C) the correlation of BZW1 with the intersection genes ETF1 and GNAI3. (D) the correlation of BZW1 with the intersection genes ETF1, GNAI3 in pancreatic cancer. (E) biological processes of GO enrichment analysis. (F) KEGG pathway analysis. BZW1 = the basic leucine zipper and W2 domains 1, ETF1 = eukaryotic translation termination factor 1, GNAI3 = Guanine nucleotide binding protein, alpha inhibiting activity polypeptide 3, GO = gene ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes.

has also been shown to be associated with the progression of acute myeloid leukemia,[30] ovarian cancer,[31,32] and glioma.[33] It has also been shown that BZW1 is strongly associated with the development of non-tumor diseases such as sarcoidosis.[34] In patients with PAAD, Ge et al demonstrated that BZW1 was a predictor of their poor prognosis and that BZW1 expression was positively correlated with T cell-mediated immune response to tumor cells, which may promote tumor microenvironment (TME) tumor growth in PAAD.[35] Notably, a recent study showed that BZW1 promotes the survival and proliferation of pancreatic ductal adenocarcinoma cells by increasing glycolysis under metabolic stress, and high expression of BZW1 has poor prognosis.[36]

In our study, we found that BZW1 is highly expressed in the vast majority of tumors, which is consistent with previous findings.[28,29,31–33] The expression of BZW1 in pancreatic cancer was significantly higher than that in normal tissues, and BZW1 protein was negative in normal pancreatic tissue but moderately or highly expressed in pancreatic cancer tissue. We also performed a survival prognostic analysis and an immune infiltration analysis, and the survival prognostic results showed that patients with high expression of BZW1 had a poor

prognosis, which was consistent with the latest findings.[36] One of the hallmarks of most malignancies is the infiltration of immune cells, including B cells, CD8 + T cells, CD4 + T cells, macrophages, and neutrophils. The level of immune infiltration in the TME is closely related to the occurrence, progression, or metastasis of cancer.[37] Infiltration of neutrophils has been reported to be associated with distant metastasis and poor prognosis in pancreatic cancer.[38,39] Macrophages are an important regulator of tumor progression and immunotherapy.[40–42] Multiple studies have shown that macrophages are closely related to the metastasis and poor prognosis of pancreatic cancer.[43–46] We used the TIMER database to study the correlation between the expression of BZW1 and the level of immune infiltration in PAAD. The results showed that the expression of BZW1 was positively correlated with CD8 + T Cells, macrophages, and neutrophils.

Furthermore, in order to explore the mechanism of action of BZW1 in pancreatic cancer, we analyzed the intersection of genes associated with BZW1 protein. The results showed that the expression of ETF1 and GNAI3 in most cancer types was positively correlated with BZW1. ETF1 has been reported to be associated with the progression of various malignancies.[47–49] GNAI3 belongs to the α subunit of the heterotrimeric G protein complex.[50] Studies have shown that GNAI3 affects the development of pancreatic cancer by affecting the immune cell components in the TME and is also related to the prognosis of pancreatic cancer.[51] GO enrichment analysis showed BZW1 was mainly related to biological processes such as "mRNA processing," "RNA splicing," "regulation of translational initiation," and "activation of innate immune response." The results of KEGG pathway analysis further indicated that BZW1 may be involved in pancreatic carcinogenesis through the "Spliceosome," and "Ribosome."

## 5. Conclusion

In conclusion, our data suggest that BZW1 is expressed in most tumors, is highly expressed in pancreatic cancer tissues, and high expression of BZW1 is associated with poor prognosis and immune infiltration. These results may provide new ideas for the diagnosis and treatment of pancreatic cancer. We speculated that the BZW1 gene may be a potential immunotherapy target and a promising prognostic marker for pancreatic cancer. In addition, we will conduct further experiments to verify our research.

## Author contributions

**Data curation:** An Luo.
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**Funding acquisition:** Jia Hu.
**Software:** An Luo.
**Supervision:** Ke Hu.
**Visualization:** Henglang Xu.
**Writing – original draft:** An Luo.
**Writing – review & editing:** Nan Qiao, Ke Hu, Henglang Xu, Mingjun Xie, Yiping Jiang, Jia Hu.

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