Brief Communication  
Pancreatic ductal adenocarcinoma with a high expression of alcohol dehydrogenase 1B is associated with less aggressive features and a favorable prognosis

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Abstract: Alcohol dehydrogenase (ADH) oxidizes alcohol into acetaldehyde (AA), which is a known carcinogen. Aldehyde dehydrogenase (ALDH) oxidizes AA into acetate. Therefore, pancreatic cancer that expresses a high level of ADH1B that generates more AA is expected to be associated with aggressive cancer. On the other hand, given that the differentiated cells that retain their cellular functions typically exhibit lower proliferation rates, it remains unclear whether pancreatic adenocarcinoma (PDAC) with high \textit{ADH1B} gene expression is linked to aggressive features in patients. The Cancer Genome Atlas (\(n = 145\)) was used to obtain data of PDAC patients and GSE62452 cohort (\(n = 69\)) was used as a validation cohort. PDAC with high \textit{ADH1B} expression was associated with less cancer cell proliferation as evidenced by lower \textit{MKI67} expression and lower histological grade; with a higher fraction of stromal cells consistent with less proliferative cancer. PDAC with high \textit{ADH1B} expression also had lower homologous recombination deficiency and mutation rates, lower \textit{KRAS} and \textit{TP53} mutation rates. \textit{ADH1B} expression correlated with \textit{ALDH2} expression in PDAC, but not with DNA repair genes. High \textit{ADH1B} expression PDAC was associated with high infiltration of anti-cancerous CD8\textsuperscript{+} T cells and pro-cancerous M2 macrophages but with lower levels of Th1 T cells, with a higher cytolytic activity. PDAC patients with a high \textit{ADH1B} expression had better disease-specific survival (DSS) and overall survival (OS) and \textit{ADH1B} was an independent prognostic biomarker for both DSS (HR = 0.89, 95% CI = 0.80-0.99, \(P = 0.045\)) and OS (HR = 0.90, 95% CI = 0.82-0.99, \(P = 0.044\)) in multivariate analysis. In conclusion, PDAC with high \textit{ADH1B} expression had less cell proliferation and malignant features, along with higher immune cell infiltration, and had a better prognosis.

Keywords: Pancreatic ductal adenocarcinoma, ADH1B, gene expression, signaling, prognosis, alcohol metabolism

Introduction

Unlike the other cancer types, the overall prognosis for pancreatic ductal adenocarcinoma (PDAC) remains challenging, making it one of the deadliest cancers [1]. The incidence of PDAC is increasing by 0.5% to 1.0% every year, and it is projected to become the second-leading cause of cancer-related mortality by 2030 [1, 2]. Numerous epidemiological studies have shown that alcohol consumption is linked with the onset of gastrointestinal and pancreatic cancers [3, 4]. Excess consumption of alcohol is known to lead to the development of chronic pancreatitis, which is strongly associated with pancreatic cancer [3]. Although hepatocytes in the liver are the major cells that metabolize alcohol, pancreatic cells are also known to oxidize alcohol [5].

There are two enzymes that significantly contribute to alcohol metabolism within cells [6].
Alcohol dehydrogenase (ADH) is primarily responsible for converting alcohol into acetaldehyde (AA), which is subsequently oxidized into acetate by aldehyde dehydrogenase (ALDH) [7]. Among all different classes of ADH isoenzymes, class I is the dominant isoenzyme responsible for alcohol metabolism [6]. Furthermore, class 1B (ADH1B) is involved in the major alcohol metabolic pathway and increases the risk of developing alcohol dependence [8]. It has been shown that AA rather than alcohol itself is the most likely cause of alcohol-associated cancer development [9]. In agreement, a number of studies have shown that AA has a direct carcinogenic and mutagenic effect [6]. Since AA affects multiple DNA repair and synthesis sites, the extent of AA exposure to cells or tissues following alcohol ingestion may have a significant effect on cancer development [6]. ADH and ALDH were found in both normal pancreatic cells and pancreatic cancer cells [10-12]. In line with this hypothesis, it is theoretically postulated that pancreatic cancer expressing high levels of ADH1B, which potentially generates more AA, could be associated with aggressive cancer development. Conversely, given that differentiated cancer cells that maintain their original cellular functions exhibit lower proliferation rates, pancreatic cancer cells that highly express ADH1B may demonstrate less aggressiveness and be linked to better survival. To date, the clinical significance of the expression of ADH1B gene in pancreatic cancer remains uncertain.

As previously reported, our group has been engaged in silico translational research, utilizing bioinformatics analysis of transcriptomic profiles to unravel the clinical significance of gene expression [13-17]. Analyzing the transcriptome of a bulk tumor enables the simultaneous examination of multiple cellular markers, cell functions, and cancer cell interaction with their tumor microenvironment (TME). Interpreting analyses of single gene expression becomes challenging due to the intricate relationships among various cells in the TME. To date, we have utilized different algorithms that have been developed to overcome this challenge. Gene set enrichment analysis (GSEA) was utilized to estimate the activation pathways of several components in the TME including cancer cells and stromal cells [18]. Additionally, employing the xCell algorithm, the proportions of 64 immune and stromal cell types in the TME were estimated based on the transcriptome of a bulk tumor [19].

In this study, The Cancer Genome Atlas (TCGA) [20] and United States (US) National Institutes of Health’s Gene Expression Omnibus (GEO) is used to evaluate the clinical significance of ADH1B in PDAC [21].

**Methods**

**Clinical data acquisition for PDAC patients**

Using the Genomic Data Commons Data Portal (GDC), we downloaded the clinical data and transcriptomic profiling of pancreatic cancer patients (n = 176) from the TCGA pancreatic cancer cohort (TCGA-PAAD) [20]. Among 176 pancreatic cancer patients, 82.4% of the samples were identified as PDAC patients (n = 145) [22]. cBioportal was used to download the mutation data [23]. The cohort published by Hussain et al. (GSE62452; n = 69) [21] was used as a validation cohort. Normalized genomic and clinical data are provided by the US National Institutes of Health’s GEO. All analyses were based on log2-transformed gene expression data. The study did not require an Institutional Review Board (IRB) waiver since TCGA and GEO datasets are publicly available and de-identified.

**Cell composition of the tumor microenvironment (TME)**

As previously described, we utilized the xCell algorithm to correlate the expressions of ADH1B with the infiltration of stromal cells and immune cells within the tumor microenvironment (TME) [13, 24-26]. Thorsson et al. evaluated the TCGA cohort, providing additional scores such as homologous recombination defects (HRD), intratumor heterogeneity, silent mutations, non-silent mutations, indel neoantigens, and single-nucleotide variant (SNV) neoantigens [27]. As mentioned earlier, the determination of the cytolytic activity score (CYT) entailed evaluating the gene expression levels of granzyme A and perforin [28].

**Gene set enrichment analysis (GSEA)**

A gene set enrichment analysis (GSEA) with Molecular Signatures Database Hallmark col-
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lecion (http://www.gsea-msigdb.org) [29] and Gene Ontology Biological Process (GOBP) gene sets [30, 31] was performed to compare tumors with low and high expression of ADH1B. Following the recommendations from the Broad Institute, gene sets with a false discovery rate (FDR) < 0.25 were defined as statistically significant enrichment for GSEA.

Statistical analysis

R software (version 4.1.0, www.r-project.org) was used for all statistical analyses. The groups were compared via Fisher's exact test, Mann-Whitney U test, and Kruskal-Wallis test. Inter-quartile ranges were displayed using Turkey's boxplots. The association between ADH1B and survival outcomes (overall survival (OS) and disease-specific survival (DSS)) were examined using a Cox-proportional hazards regression model and showed using the Kaplan-Meier survival curve. Statistical significance was set at $P < 0.05$ for all analyses.

Results

ADH1B expression in PDAC was associated with lower cancer cell proliferation

AA generated by ADH1B is known to be carcinogenic, while differentiated cancer cells retain their original functions and are less aggressive. Therefore, we conducted an investigation into the clinical relevance of ADH1B gene expression in patients with pancreatic cancer. PDAC patients from TCGA-PAAD were analyzed as the testing cohort, while GSE62452 was used as the validation cohort. Supplementary Figure 1 displays histograms illustrating the ADH1B expression levels in two cohorts: The Cancer Genome Atlas (TCGA; $n = 145$) and GSE62452 ($n = 69$). The distribution of these expression levels exhibits a roughly bell-shaped pattern. In each cohort, the high ADH1B group was defined as the top 25th percentile, while the remaining samples were categorized as the low ADH1B group (indicated by the green lines in Supplementary Figure 1). High ADH1B expression was consistently associated with significantly lower MKI67 expression, a molecular parameter of cancer cell proliferation, in both the TCGA and GSE62452 cohorts (Figure 1A; $P = 0.025$ and $P < 0.001$, respectively). Histological grade, which determines cancer cell proliferation by morphology, demonstrated a significant inverse correlation with ADH1B expression in the GSE62452 cohort. While a similar trend was noticed in the TCGA cohort, it did not attain statistical significance (Figure 1B; $P = 0.006$ and $P = 0.205$, respectively). These observations indicate that PDAC cases exhibiting elevated ADH1B levels are linked to diminished cell proliferation, as supported by both histological and molecular analyses.

High ADH1B PDAC was associated with lower homologous recombination deficiency (HRD), silent and non-silent mutation rate, and single nucleotide variation (SNV) neoantigens, as well as lower mutation rates of KRAS and TP53

Mutation-driven genomic instability is a known mechanism of carcinogenesis and aggressiveness of tumors. Incorporating the pre-calculated scores by Thorsson et al. [25, 32, 33], our analysis revealed a significant association between high ADH1B expression in PDAC and lower rates of HRD, silent and non-silent mutation rates, as well as SNV neoantigens within the TCGA cohort (Figure 1C). Frequently mutated in pancreatic cancer, KRAS, TP53, SMAD4, and CDKN2A are well-established genes linked with an inferior prognosis in the disease [1]; thus, the relationship between their mutation rates and expression of ADH1B was of interest. Our findings demonstrated a significant association between high ADH1B expression and lower mutation rates of KRAS and TP53 in PDAC (Figure 1D). However, no significant associations were observed with CDKN2A or SMAD4. These results suggest that PDAC cases with elevated ADH1B expression exhibit reduced mutation rates and genomic instability, aligning with their less proliferative nature.

High ADH1B PDAC was significantly associated with higher stromal cell fraction

It has been repeatedly shown that highly proliferative cancers are associated with lesser infiltration of stromal cells in the TME [24, 34, 35]. Therefore, we examined the correlation between ADH1B expression and the infiltration of stromal cells, including adipocytes, fibroblasts, microvascular endothelial cells (mvECs), lymphatic endothelial cells (lyECs), and pericytes, within the TME of both the TCGA and GSE62452 cohorts. This analysis was conducted using the xCell algorithm. We found that PDAC with high ADH1B expression was associated with signifi-
Figure 1. Association of ADH1B expression with clinical parameters of cancer cell proliferation, as well as homologous recombination deficiencies, intratumor genomic heterogeneity, mutation rates, neoantigens and gene mutation by low vs. high ADH1B expression. A. Boxplots of Ki67 gene (MKI67) expression by low and high ADH1B PDAC. Median and inter-quartile level values are visualized using Tukey-type boxplots, and we used the analysis of variance (ANOVA) test to calculate the p-values. B. Boxplots of ADH1B expression by pathological grade. C. The relationship between ADH1B and homologous recombination defects (HRD), intratumor heterogeneity, mutation rates, and neoantigens in the TCGA pancreatic cancer cohort. D. Bar plots depicting the mutation rates of KRAS, TP53, CDK2A, and SMAD4 in the ADH1B low and ADH1B high groups.
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Figure 2. Association of ADH1B expression with alcohol metabolic process, correlation between ADH1B expression and ALDH2 expression within PDAC, as well as association between ADH1B expression and DNA repair gene pathway. A. Enrichment plots of the representative Gene Ontology Biological Process (GOBP) ‘Alcohol Metabolic Process’ by low vs. high ADH1B expression. B. Correlation plot of ADH1B and ALDH2 in both cohorts. C. Box plots of DNA repair pathway by low vs. high ADH1B expression.

Significantly higher infiltration of adipocytes, fibroblasts, and ly endothelial cells consistently in both cohorts (Supplementary Figure 2). However, the association between PDAC with high ADH1B expression and infiltration of mv endothelial cells and pericytes, both of which are components of mature blood vessels, was significant in one of the cohorts but was not validated by another. Based on these data, PDAC with high ADH1B expression was associated with higher infiltration of stromal cells in the TME, except for mature blood vessel cells. This association is consistent with lower cancer cell proliferation. High ADH1B expression correlated with ALDH2 expression, but not with the DNA repair gene set in PDAC

As an initial part of alcohol metabolism, ADH produces AA, which is a known carcinogen that disrupts the DNA repair mechanism. Hence, we were interested in examining the relationship between ADH1B expression and alcohol metabolism, ALDH2 expression, as well as the level of DNA repair in patients with PDAC. High ADH1B expression in PDAC was found to enrich the alcohol metabolism-related gene set in the TCGA cohort. However, this enrichment was not validated in the GSE62452 cohort (Figure 2A). Interestingly, we found a significant correlation between the expression of ADH1B and ALDH2, the main enzyme that breaks down AA, consistently in both PDAC cohorts (Figure 2B). In addition, a significant association was observed between high ADH1B expression and lower DNA repair scores in the GSE62452 cohort. However, this association was not validated in the TCGA cohort (Figure 2C). Our findings suggest that while AA is known to damage DNA and contribute to cancer development, ADH1B expression correlates with the expression of ALDH2 which further metabolize AA in patients.
with PDAC. However, the correlation between \textit{ADH1B} expression and alcohol metabolism or DNA repair deficiency is not consistent. In summary, these findings contradict our hypothesis that \textit{ADH1B} gene expression alone would exacerbate cancer biology through alcohol metabolism.

High \textit{ADH1B} PDAC had a higher cytolytic activity (CYT) score and exhibited higher infiltration of anti-cancerous CD8 T cells and pro-cancerous M2 macrophages in PDAC with high \textit{ADH1B} expression consistently (Figure 3A, all \( P < 0.001 \)). Significant infiltration of CD4 memory T cells, dendritic cells, and B cells was observed in the TCGA cohort; however, these findings were not validated in the GSE62452 cohort (Figure 3A, \( P < 0.001 \) in TCGA only). In contrast, the infiltration of T helper type 1 (Th1) cells consistently exhibited lower levels in both the TCGA and GSE62452 cohorts (Figure 3A, all \( P < 0.001 \)). Additionally, T helper type 2 (Th2) cells displayed a decrease in infiltration in only one of the cohorts (Figure 3B, all \( P < 0.001 \)). Our findings indicate that PDAC with elevated \textit{ADH1B} expression did not exhibit enrichment in any of the immune-related genes measured by each Hallmark set of Gene Set Variation Analysis (GSVA), including interferon (IFN)-\( \alpha \), IFN-\( \gamma \) response, and inflammatory response (Figure 3C). Nevertheless, a noteworthy increase was observed in the CYT score among PDAC cases exhibiting higher \textit{ADH1B} expression, suggesting an enhanced immune cell-mediated destruction within the TME (Figure 3D). Based on these results, immune cell infiltration and overall immune response were correlated with \textit{ADH1B} expression.

High \textit{ADH1B} PDAC patients were associated with better overall survival (OS)

As \textit{ADH1B} expression was linked to reduced cancer cell proliferation and enhanced immune response, we were intrigued to explore the correlation between \textit{ADH1B} expression and OS in patients with PDAC. In the GSE62452 cohort, we found that PDAC patients with high levels of \textit{ADH1B} were associated with significantly better OS in TCGA, which was validated (Figure 4; \( P = 0.03 \) and \( P < 0.006 \), respectively).

\textit{ADH1B} expression was an independent prognostic biomarker of PDAC

\textit{ADH1B} expression was evaluated as a prognostic biomarker. As anticipated, the univariate analysis of overall survival (OS) within the TCGA cohort revealed a significant hazard ratio (HR) associated with \textit{ADH1B} expression (Table 1). \textit{ADH1B} expression in PDAC patients was associated with improved DSS (HR = 0.89, 95\% confidence interval [CI] = 0.80-0.99, \( P = 0.045 \)) and OS (HR = 0.90, 95\% confidence interval [CI] = 0.82-0.99, \( P = 0.044 \)) in multivariate cox-regression model analysis. Based on these results, \textit{ADH1B} expression can be considered an independent prognostic biomarker for PDAC.

Discussion

In this study, high expression of \textit{ADH1B} in PDAC was associated with decreased aggressiveness of the tumor and was identified as a biomarker for prognosis. PDACs with high \textit{ADH1B} expression had lower cancer cell proliferation, lower HRD, silent and non-silent mutation rates, SNV neoantigen, as well as lower KRAS and TP53 mutation rates. High \textit{ADH1B} expression in PDAC was significantly associated with a higher fraction of stromal cell infiltrations. \textit{ADH1B} expression in PDAC consistently correlated with \textit{ALDH2} expression that metabolizes AA and is not consistently associated with the DNA repair pathway, which implies that \textit{ADH1B} expression is not strongly associated with alcohol metabolism-related carcinogenesis. PDAC with high \textit{ADH1B} expression was associated with infiltrations of CD8 T cells and M2 macrophages but with less Th1 T cells, and with higher CYT score. PDAC patients with a high \textit{ADH1B} expression had better OS and DSS. \textit{ADH1B} gene expression was identified as an independent prognostic biomarker for PDAC patients as evidenced in the multivariate analysis.

Alcohol and the resulting toxic metabolites are known to cause significant organ injury [37]. Multiple mechanisms have been proposed for alcohol-induced damage to the exocrine pan-
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Figure 3. Immune cell fractions in the PDAC tumor immune microenvironment by ADH1B expression. Boxplots were generated to compare immune cell fractions in the TCGA and GSE62452 cohorts based on low versus high ADH1B expression. (A) Represents the anti-cancerous immune cells, including CD8$^+$ T cells, CD4$^+$ memory T cells, T helper type 1 (Th1) cells, M1 macrophages, and dendritic cells (DC). (B) Showcases the pro-cancerous immune cells, such as T helper type 2 (Th2) cells, regulatory T (Treg) cells, and M2 macrophages. (C) Displays enrichment plots of representative Hallmark immune response gene sets, including interferon (IFN)-α response, inflammatory response, and IFN-γ response. The normalized enrichment score (NES) and false discovery rate (FDR) are provided. Finally, (D) demonstrates the cytolytic activity (CYT) score based on low versus high ADH1B expression.
Table 1. ADH1B expression and clinicopathological factors

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<th>TCGA (DSS)</th>
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<th>TCGA (OS)</th>
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<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td>Univariate</td>
<td>Multivariate</td>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
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<tr>
<td>Age</td>
<td>1.01 (0.99-1.04)</td>
<td>0.418</td>
<td>1.02 (0.99-1.04)</td>
<td>0.126</td>
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<tr>
<td>Gender (Male vs. Female)</td>
<td>0.77 (0.47-1.25)</td>
<td>0.282</td>
<td>0.82 (0.53-1.26)</td>
<td>0.361</td>
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<td>Race (Caucasian vs. other)</td>
<td>1.82 (0.83-4.01)</td>
<td>0.137</td>
<td>1.45 (0.76-2.75)</td>
<td>0.260</td>
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<td>Primary site (Head vs. Body/Tail)</td>
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<td>0.871</td>
<td>1.06 (0.56-2.00)</td>
<td>0.869</td>
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<td>Grade (G3/4 vs. G1/2)</td>
<td>1.44 (0.86-2.41)</td>
<td>0.165</td>
<td>1.38 (0.87-2.18)</td>
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<td>pT (pT3/4 vs. pT1/2)</td>
<td>1.54 (0.66-3.58)</td>
<td>0.318</td>
<td>1.17 (0.58-2.34)</td>
<td>0.668</td>
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<td>pN (N+ vs. N-)</td>
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<td>1.94 (0.45-8.36)</td>
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<td>pM (M+ vs. M-)</td>
<td>1.92 (1.14-3.22)</td>
<td>0.014*</td>
<td>1.90 (1.13-3.19)</td>
<td>0.015*</td>
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<td>Resection (R1/2 vs. R0)</td>
<td>0.89 (0.81-0.99)</td>
<td>0.027*</td>
<td>0.89 (0.80-0.99)</td>
<td>0.045*</td>
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<td>ADH1B</td>
<td>1.01 (0.99-1.04)</td>
<td>0.418</td>
<td>1.02 (0.99-1.04)</td>
<td>0.126</td>
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CI, confidence interval; DSS, disease-specific survival; OS, overall survival; HR, hazard rate. *P < 0.05.

Figure 4. Association of ADH1B with survival in the TCGA and GSE62452 cohorts. The Kaplan-Meier survival plots illustrate a comparison between tumors demonstrating high (red lines) and low (blue lines) ADH1B expression, accompanied by the log-rank test. The provided p-values correspond to overall survival (OS).

creas [38], where alcohol is metabolized primarily by the acinar cells [39]. Alcohol metabolism involves both oxidative and nonoxidative pathways [40]. The oxidative pathway involves
ADH is a key enzyme involved in alcohol metabolism and detoxification. It generates AA, which plays a crucial role in cancer development. ADH activity is higher in cancer cells than in normal cells, indicating altered metabolic characteristics in cancer cells. This altered metabolism can lead to changes in the activities of alcohol metabolism enzymes and an increase in the generation of AA.

In pancreatic cancer, ADH is considered a possible prognostic biomarker. However, its role in pancreatic cancer is still unclear. A recent study suggests that higher ADH expression is associated with better survival, possibly due to the detoxification of AA, a known carcinogenic compound.

### Conclusion

PDAC with high ADH1B expression was associated with lower cell proliferation, higher immune response, and a better prognosis. Our study suggests ADH1B is a possible prognostic biomarker for PDAC patients, and further prospective studies are needed to establish its role in PDAC and other cancers.
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Disclosure of conflict of interest

None.

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**Supplementary Figure 1.** Histograms of TCGA and GSE62452 cohorts by ADH1B expression. Histograms of TCGA and GSE62452 cohorts by ADH1B expression. The vertical green lines divide the ADH1B expression into low and high; high ADH1B groups were defined as top 25th percentile and the rest were defined as low ADH1B groups.

**Supplementary Figure 2.** The relationship between ADH1B and stromal cells in the tumor microenvironment (TME). Boxplots comparing the fraction of stromal cells (adipocytes, fibroblasts, microvascular (mv) endothelial cells, lymphatic (ly) endothelial cells, and pericytes) between low and high ADH1B expression groups in both the TCGA and GSE62452 cohorts.