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Distinct Prognostic Values of Alcohol Dehydrogenase Family Members for Non-Small Cell Lung Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACE 1 Peng Wang
ABC 1 Linbo Zhang
DF 1 Chunxia Huang
DF 1 Ping Huang
AEFG 2 Jianquan Zhang

1 Department of Health Management and Division of Physical Examination, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, P.R. China
2 Department of Respiratory Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, P.R. China

Corresponding Author: Jianquan Zhang, e-mail: jqzhang2002@126.com
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Background: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related death worldwide. The relationships of alcohol dehydrogenase (ADH) enzymes, encoded by the genes *ADH1* (*1A*), *ADH1B* (*ADH2*), *ADH1C* (*ADH3*), *ADH4*, *ADH5*, *ADH6*, and *ADH7*, with NSCLC have not been studied. The aim of this study was to explore the associations between NSCLC prognosis and the expression patterns of ADH family members.

Material/Methods: The online resource Metabolic gEne RApid Visualizer was used to assess the expression patterns of *ADH* family members in normal and primary lung tumor tissues. The GeneMANIA plugin of Cytoscape software and STRING website were used to evaluate the relationships of the 7 ADH family members at the gene and protein levels. Gene ontology enrichment analysis and KEGG pathway analysis were performed using DAVID. The online website Kaplan-Meier Plotter was used to construct survival curves between NSCLC and ADH isoforms.

Results: The prognosis of patients with high expression levels of the *ADH1B*, *ADH1C*, *ADH4*, and *ADH5* genes was better than those with low expression in adenocarcinoma and all (containing adenocarcinoma and squamous cell cancer) histological types (all $P<0.05$). Low expression of *ADH7* was associated with a better prognosis in patients with both the adenocarcinoma and squamous cell cancer histological types ($P=9e-05$). Moreover, expression of ADH family members was associated with smoking status, clinical stage, and chemotherapy status.

Conclusions: *ADH1B*, *ADH1C*, *ADH4*, *ADH5*, and *ADH7* appear to be useful biomarkers for the prognosis of NSCLC patients.

MeSH Keywords: Alcohol Dehydrogenase • Biological Markers • Carcinoma, Non-Small-Cell Lung • Multigene Family • Prognosis

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Background

Lung cancer, which is a main cause of cancer-related mortality worldwide [1,2], is classified into 3 major histologic subtypes: adenocarcinoma, squamous carcinoma, and non-small cell lung cancer (NSCLC), with the latter being the major histological subtype. In 2012, there were 1 800 000 new lung cancer cases, which accounted for 13% of the total number of cancer diagnoses [3]. As compared with other high-onset cancers, the 5-year survival rate of lung cancer remains as low as 15% [4]. The conventional treatment for lung cancer is whole-body chemotherapy with cisplatin, but the efficacy of such regimens is limited [5]. Although several biomarkers have been reported with lung cancer prognosis, including ELF3 [6], miRNA-135 [7], miRNA-34 [8], the survival status of lung cancer patients are still not satisfactory. Thus, further studies focusing on the mechanisms of initiation and progression, and the identification of prognostic molecular markers are of crucial significance.

The members of the alcoholic dehydrogenase (ADH) family include 7 enzymes, ADH1–7. In humans, these 7 *ADH* enzyme-encoding genes (*ADH7*, *ADH1C*, *ADH1B*, *ADH1A*, *ADH6*, *ADH4*, and *ADH5*) are clustered within a small region of chromosome 4 (4q21–24) in a head-to-tail array that is approximately 370 kb in length [9,10]. The transformation of ethanol into its carcinogenic metabolite, acetaldehyde, is especially important for the elimination of *ADH1* in the liver [10]. A significant association was found between gastric cancer risk and a common 3'-untranslated region flanking a single-nucleotide polymorphism near rs1230025 of *ADH1A* [11]. The most important function-associated polymorphism in *ADH* is considered to be *ADH1B* Arg48His (rs1229984) [12]. Rs17033 of *ADH1B* is related to the risk of gastric cancer and smoking may further affect the role of rs671 [11]. Positive responses of *ADH1B**3 and alcohol dependence have been found in African and Native American populations [13,14]. The interactions between *ADH1B* + 3170A> G and *ADH1C* + 13044A> G are related to environmental factors as well as lifestyle factors, such as drinking and smoking [15]. The *ADH1B* + 3170A> G and *ADH1C* + 13044A> G single-nucleotide polymorphisms are associated with an increased risk of head and neck squamous cell carcinoma (SCC), and can be used as biomarkers for high-risk South Korean populations [16]. The latest evidence suggests that the cancer risk in Africans and Asians may be caused by the polymorphism *ADH1C* Ile350Val (rs698) [17]. Candidate gene studies have reported that at least 4 functional *ADH* gene variants significantly affect the risk of alcohol dependence, namely rs1229984 (*ADH2* * 2; Arg48His), rs2066702 (*ADH2* * 3; Arg370Cys), rs1693482 (*ADH3* * 2; Arg272Gln), and rs698 (*ADH3* * 2; Ile350Va) [18]. The ADH1 and ADH4 enzymes may play roles in the development of retinol endocrine function in the mouse embryo [19]. Studies have shown that the human *ADH5* gene can give rise to different carboxyl terminal proteins dependent on the transcriptional materials that produce variable splicing patterns [20]. As compared with other mammals, the deduced amino acid sequences of the gene products of *ADH5* and *ADH6* demonstrate a deficiency of ADH enzymatic activity [21]. Recent studies have found that early (pre-absorbed or first) alcohol metabolism changes are associated with the *ADH7* mutation [22].

Members of the ADH gene family have been associated with various diseases, including alcoholism and cancers, but such relationships in NSCLC remain unclear. Therefore, the aim of this study was to evaluate the potential prognostic values of ADH family members for NSCLC to provide new clues for individualized treatments and better prognostic indicators for NSCLC patients.

Material and Methods

Data collection

In total, 1926 patient samples were classified according to the median and overall survival rates. Clinical data, including sex, smoking history, histology, AJCC stage, grade, success of surgery, radiotherapy, and applied chemotherapy for all NSCLC patients, were collected from 3 datasets: the Cancer Biomedical Informatics Grid (*http://cabig.cancer.gov/*, microarray samples are published in the caArray project), the Gene Expression Omnibus (*www.ncbi.nlm.nih.gov/geo/*), and the Cancer Genome Atlas (*http://cancergenome.nih.gov*).

Expression analysis of ADH family members

The online resource Metabolic gEne RApid Visualizer (*http://merav.wi.mit.edu/*; accessed on January 14, 2018) was used to identify *ADH* family genes. Five ADH family members were entered into the site to analyze the level of expression between them, but only 3 could be analyzed, as the other 2 were not identified [23].

Interaction and enrichment analysis of ADH family members

The GeneMAMIA plugin of Cytoscape software was used to analyze the relationship between the 5 genes [24,25] Moreover, the STRING online resource was used to analyze the biological interactions at the protein level of ADH family members [26]. Pearson correlation analysis of ADH family members was performed using R version 3.4.2 (*https://www.r-project.org/*). Finally, enrichment analysis was performed with the Database for Annotation, Visualization, and Integrated Discovery website (DAVID, version 6.7), which includes the Gene Ontology

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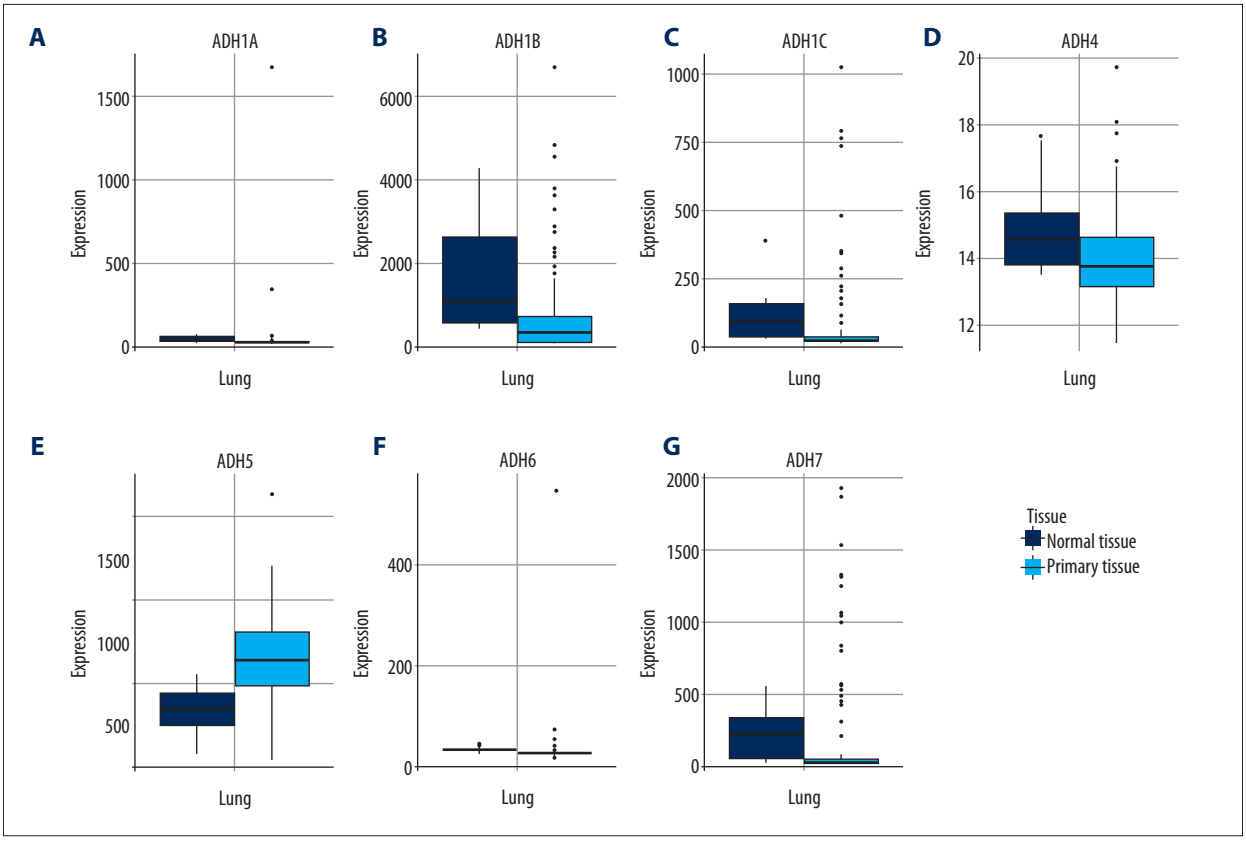

Figure 1. Expression levels of ADH family members in normal and primary lung tumor tissues. (**A**) Expression levels of *ADH1A* in normal and primary lung tumor tissues; (**B**) Expression levels of *ADH1B* in normal and primary lung tumor tissues; (**C**) Expression levels of *ADH1C* in normal and primary lung tumor tissues; (**D**) Expression levels of *ADH4* in normal and primary lung tumor tissues; (**E**) Expression levels of *ADH5* in normal and primary lung tumor tissues; (**F**) Expression levels of *ADH6* in normal and primary lung tumor tissues; (**G**) Expression levels of *ADH7* in normal and primary lung tumor tissues.

(GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways [27,28].

Survival analysis of ADH family members

A database was created using the Kaplan–Meier Plotter (*http://kmplot.com/analysis/*) to determine the correlation between ADH family members at the mRNA level and prognosis of overall survival of NSCLC patients [29]. At present, the website contains data of breast cancer, lung cancer, ovarian cancer, gastric cancer, and hepatocellular carcinoma (HCC).

Results

Collection of patient data

In this study, Kaplan-Meier Plotter was used to analyze the medical records of 1926 lung cancer patients, so approval by the Ethics Committee was not needed because this study did not involve human participants or animals.

Expression analysis of ADH family members in normal and primary lung tumor tissues

The expression levels of the ADH family members in normal and primary lung tumor tissues varied, with only slight expression of *ADH1A* and *ADH6* in both normal and primary lung tumor tissues, and *ADH1C* and *ADH7* in lung primary tumor tissues. Other than *ADH5*, expression of other members was relatively high in normal lung tissues (Figure 1).

Interaction analysis of ADH family members at the gene and protein levels

Pearson correlation analysis was conducted using expression data of ADH family members collected from the OncoLnc website (*www.oncolnc.org/*). In lung adenocarcinoma, *ADH1A* was significantly associated with *ADH1B*, *ADH1C*, and *ADH6* (r=0.62, $P<0.001$; r=0.12, $P<0.01$; r=0.14, $P<0.01$, respectively), while ADH1C was significantly associated with *ADH5* and *ADH6* (r=0.12, $P<0.01$; r=0.14, $P<0.01$, respectively), and *ADH5* was significantly associated with *ADH6* (r=0.21, $P<0.001$, Figure 2A).

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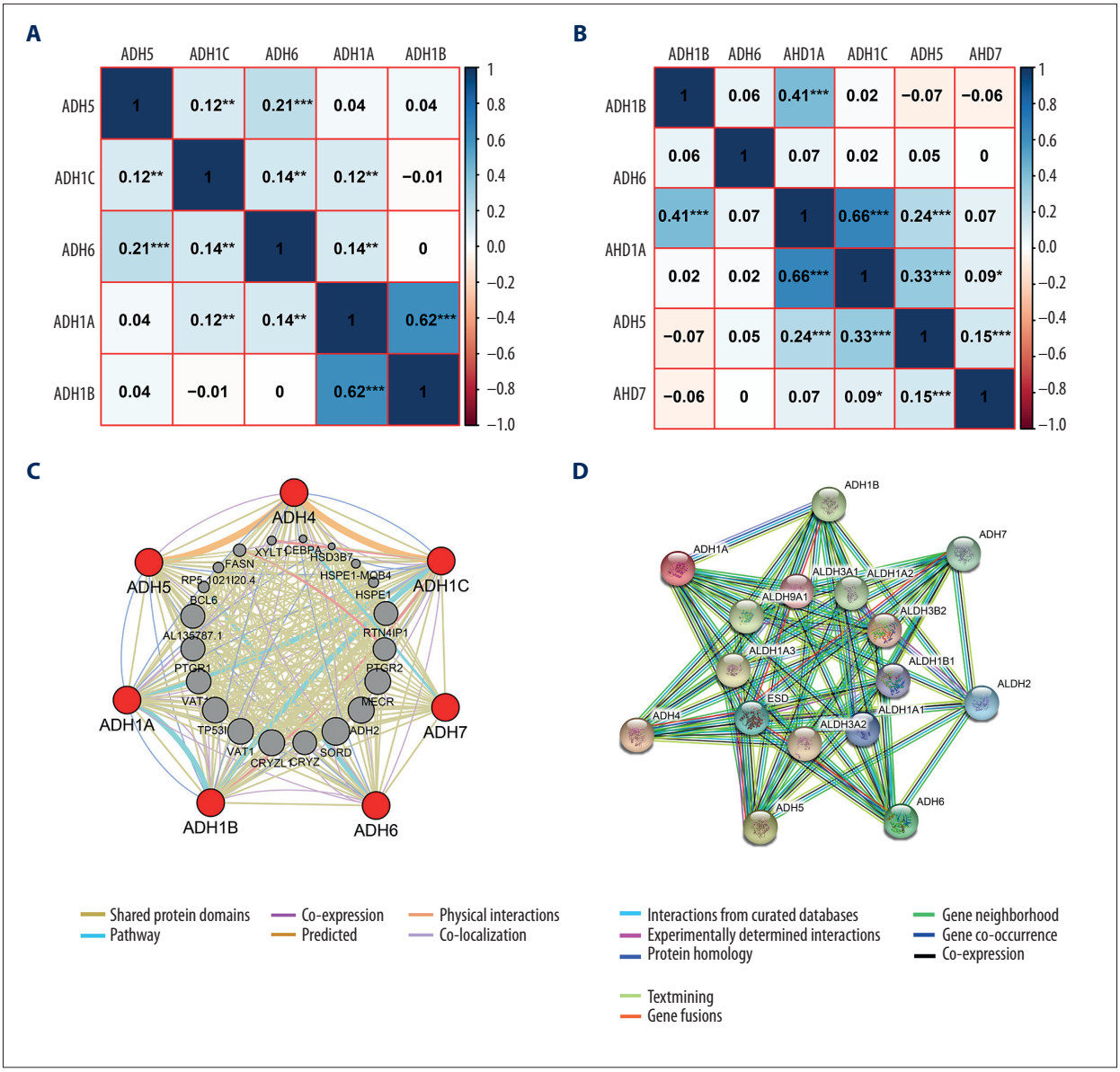

Figure 2. Interaction analysis of ADH family members. (**A**) Pearson correlation of ADH family members in lung adenocarcinoma; (**B**) Pearson correlation of ADH family members in lung SCC; (**C**) Gene-gene interaction network among ADH family members; (**D**) Protein-protein interaction network among ADH family members.

In lung SCC, *ADH1A* was significantly associated with *ADH1B*, *ADH1C*, and *ADH5* (r=0.41, *P*<0.001; r=0.66, *P*<0.001; r=0.24, *P*<0.001, respectively), and *ADH1C* was significantly associated with *ADH5* and *ADH7* (r=0.33, *p*<0.001; r=0.09, *P*<0.05, respectively). Detailed results are presented in Figure 2B.

GeneMANIA was used to conduct correlation analysis of ADH family members at the gene level, which revealed relationships in pathways, shared protein domains, co-localization, and co-expression between *ADH1A* and *ADH1B*, as well as *ADH1A* and *ADH1C* (*ADH3*). There were relationships between *ADH1C* (*ADH3*) and *ADH4* in co-expression, prediction, and shred protein domains. There were also relationships between *ADH4* and *ADH6* in co-localization, shared protein domains, and co-expression. There were shared protein domains between *ADH4* and *ADH7*. In addition, there were relationships in co-expression and shared protein domains, and predicted relationships between *ADH4* and *ADH5*. *ADH1A* and *ADH7* had shared protein domains. *ADH1A* and *ADH5* also shared protein domains and co-localization. Detailed results are presented in Figure 2C.

STRING analysis was conducted to identify interactions of ADH gene family members at the protein expression level. ADH1C

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Table 1. Correlation analysis between ADH family members and smoking status.

Isoenzymes	Smoking status	Cases	HR	95% CI	*p* Value
ADH1A/ADH1	Yes	820	1.19	0.97–1.47	0.095
	No	205	1.24	0.71–2.16	0.449
ADH1B/ADH2	Yes	820	0.77	0.62–0.94	**0.012**
	No	205	0.33	0.18–0.61	**0.0002**
ADH1C/ADH3	Yes	820	0.72	0.58–0.88	**0.017**
	No	205	0.84	0.38–1.88	0.672
ADH4	Yes	300	0.57	0.37–0.87	**0.009**
	No	141	0.84	0.38–1.88	0.672
ADH5	Yes	820	0.83	0.67–1.02	0.075
	No	205	0.36	0.2–0.66	**0.0005**
ADH6	Yes	820	1.26	1.03–1.55	**0.027**
	No	205	1.89	1.07–3.33	**0.026**
ADH7	Yes	820	1.44	1.17–1.78	**5e-04**
	No	205	1.72	0.98–3.04	0.057

ADH – alcohol dehydrogenase; ADH1A – alcohol dehydrogenase 1A; ADH1B – alcohol dehydrogenase 1B; ADH1C – alcohol dehydrogenase 1C; ADH2 – alcohol dehydrogenase 2; ADH3 – alcohol dehydrogenase 3; ADH4 – alcohol dehydrogenase 4; ADH5 – alcohol dehydrogenase 5; ADH6 – alcohol dehydrogenase 6; ADH7 – alcohol dehydrogenase 7.

was not recognized by STRING. ADH1A was shown to interact with ADH1B, ADH4, and ADH6 in regards to gene co-occurrence, text-mining, co-expression, and protein homology. ADH4 was found to interact with ADH6 and ADH7 in regards to gene co-occurrence, text-mining, co-expression, and protein homology. Detailed results are presented in Figure 2D.

Enrichment analysis of GO terms and KEGG pathways

Correlations among the 3 factors of smoking, clinical staging, and chemotherapy were also assessed among ADH gene family members. The results showed that smoking status was significantly associated with *ADH1C* (*ADH3*), *ADH4*, and *ADH7* (*P*=0.017, 0.009, and 5E-04, respectively). Non-smoking status was significantly associated with *ADH5* (*P*=0.0005), while *ADH1B* (*ADH2*) and ADH6 were significantly associated with both smoking and non-smoking status (*P*=0.012, 0.0002, 0.027, and 0.026, respectively). *ADH1A* (*ADH1*) was not significantly associated with smoking or non-smoking status (*P*=0.095 and 0.449, respectively, Table 1).

Correlation analysis of ADH family members with clinical stage showed that various clinical stages were significantly associated with *ADH1A*, *ADH1B*, *ADH1C*, *ADH2*, *ADH3*, *ADH4*, *ADH5*, and *AHD7* (*P* = 0.043, 1.1E-11, 8.7E-09, 0.039, 2.7E-12, 0.0017, 1.8E-06, and 0.003, respectively), but not *ADH6* (*P*=0.55, 0.2009, and 0.476, respectively, Table 2).

Correlation analysis of ADH family members with chemotherapy status showed that *ADH1C* (*ADH3*) was significantly associated with non-chemotherapy status, while *ADH6* was significantly associated with chemotherapy status (*P*=0.007, 0.004). Others members were not significantly associated with chemotherapy status (all *p*>0.05, Table 3).

GO analysis with the terms of biological process, cellular component, and molecular function and KEGG pathways enrichment analysis were performed using DAVID. The top 5 results of the enrichment analysis were ethanol metabolic process, monohydric alcohol metabolic process, ethanol oxidation, alcohol dehydrogenase (NAD) activity, alcohol dehydrogenase activity, and zinc-dependent (Table 4). The enriched KEGG pathways included fatty acid metabolism, tyrosine metabolism, retinol metabolism, metabolism of xenobiotics by cytochrome P450, glycolysis/gluconeogenesis, and drug metabolism (Table 5).

Survival curve analysis of ADH family members using Kaplan-Meier Plotter

First, the prognostic value of ADH family members were assessed using the Kaplan–Meier Plotter online website. The Affymetrix ID of *ADH1A* was 207820. There was no statistically significant difference in the adenocarcinoma and SCC types (*P*=0.78, HR=1.02, 95% confidence interval [CI]=0.90–1.16); *P*=0.24, HR=0.87, 95% CI=0.69–1.10; *P*=0.88, HR=1.02, 95%

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Table 2. Correlation analysis between ADH family members of clinical stage of NSCLC.

Isoenzymes	Clinical stage	Cases	HR	95% CI	*P* value
ADH1A/ADH1	I	577	0.82	0.62–1.08	0.163
	II	244	1.46	1.01–2.11	**0.043**
	III	70	0.61	0.36–1.06	0.077
ADH1B/ADH2	I	577	0.38	0.28–0.51	**1.1E-11**
	II	244	0.93	0.64–1.34	0.691
	III	70	1.32	0.77–2.27	0.318
ADH1C/ADH3	I	577	0.45	0.34–0.59	**8.7E-09**
	II	244	0.68	0.47–0.98	**0.039**
	III	70	1.35	0.77–2.35	0.295
ADH4	I	449	0.29	0.2–0.42	**2.7e-12**
	II	161	0.48	0.33–0.77	**0.0017**
	III	44	0.81	0.4–1.64	0.553
ADH5	I	577	0.52	0.39–0.68	**1.8e-06**
	II	244	0.83	0.57–1.19	0.305
	III	70	0.72	0.41–1.24	0.230
ADH6	I	577	1.08	0.83–1.42	0.55
	II	244	1.27	0.83–1.83	0.2009
	III	70	0.82	0.48–1.41	0.476
ADH7	I	577	1.5	1.14–1.96	**0.003**
	II	244	1.14	0.79–1.64	0.489
	III	70	1.37	0.79–2.35	0.257

ADH – alcohol dehydrogenase; ADH1A – alcohol dehydrogenase 1A; ADH1B – alcohol dehydrogenase 1B; ADH1C – alcohol dehydrogenase 1C; ADH2 – alcohol dehydrogenase 2; ADH3 – alcohol dehydrogenase 3; ADH4 – alcohol dehydrogenase 4; ADH5 – alcohol dehydrogenase 5; ADH6 – alcohol dehydrogenase 6; ADH7 – alcohol dehydrogenase 7; NSCLC – non-small cell lung cancer; HR – hazard ratio; 95%CI – 95% confidence interval.

CI=0.80–1.30, Figure 3). The Affymetrix ID of *ADH1B* was 209612. There were statistically significant differences in both adenocarcinoma and all (adenocarcinoma and SCC) histological types, (*P*=5.4e-11, HR=0.65, 95% CI=0.58–0.74; *P*=5.4e-10, HR=0.47, 95% CI=0.37–0.60), but no significant difference in SCC (*P*=0.91, HR=0.99, 95% CI=0.78–1.25, Figure 4).

The Affymetrix ID of *ADH1C* (*ADH3*) was 206262. There was a significant difference in adenocarcinoma and all (adenocarcinoma and SCC) histological types (*P*=3.3e-09, HR=0.68, 95% CI=0.60–0.77; *P*=9.5e-10, HR=0.48, 95% CI=0.38–0.61, respectively), but no significant difference in SCC (*P*=0.31, HR=0.89, 95% CI=0.70–1.12, Figure 5). The Affymetrix ID of *ADH4* is 223781. There were significant differences in both tissue types and adenocarcinoma (*P*=8.1e-07, HR=0.65, 95% CI=0.55–0.77; *P*=7.2e-07, HR=0.53, 95% CI=0.41–0.68, respectively), but no significant difference in SCC (*P*=0.83, HR=1.04, 95% CI=0.76–1.41, Figure 6).

The Affymetrix ID of *ADH5* was 208847. There were significant differences in both tissue types and adenocarcinoma (*P*=0.037, HR=0.87, 95% CI=0.77–0.99; *P*=1.3e-08, HR=0.50, 95% CI=0.40–0.64), as well as SCC (*P*=0.53, HR=1.08, 95% CI=0.85–1.37, Figure 7). The Affymetrix ID of *ADH6* was 207544. There was no significant difference in any category (*P*=0.82, HR=0.99, 95% CI=0.87–1.12; *P*=0.46, HR=0.92, 95% CI=0.72–1.16; *P*=0.93, HR=1.01, 95% CI=0.8–1.28), respectively, Figure 8). The Affymetrix ID of *ADH7* was 210505. There were significant differences in both tissue types (*P*=9e-05, HR=1.29, 95% CI=1.13–1.46), but no significant difference between

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Table 3. Correlation analysis between ADH family members and chemotherapy outcomes of NSCLC.

Isoenzymes	Smoking status	Cases	HR	95% CI	*p* Value
ADH1A/ADH1	Yes	176	1.09	0.72–1.64	0.682
	No	310	0.93	0.67–1.31	0.685
ADH1B/ADH2	Yes	176	1.23	0.82–1.85	0.31
	No	310	0.72	0.52–1.01	0.056
ADH1C/ADH3	Yes	176	1.04	0.69–1.55	0.861
	No	310	0.63	0.45–0.88	**0.007**
ADH4	Yes	34	0.42	0.12–1.39	0.140
	No	21	1.66	0.3–9.19	0.555
ADH5	Yes	176	1.11	0.73–1.66	0.632
	No	310	0.94	0.67–1.31	0.708
ADH6	Yes	176	0.55	0.36–0.82	**0.004**
	No	310	0.99	0.71–1.39	0.972
ADH7	Yes	176	1.26	0.84–1.90	0.271
	No	310	1.18	0.84–1.65	0.342

ADH – alcohol dehydrogenase; ADH1A – alcohol dehydrogenase 1A; ADH1B – alcohol dehydrogenase 1B; ADH1C – alcohol dehydrogenase 1C; ADH2 – alcohol dehydrogenase 2; ADH3 – alcohol dehydrogenase 3; ADH4 – alcohol dehydrogenase 4; ADH5 – alcohol dehydrogenase 5; ADH6 – alcohol dehydrogenase 6; ADH7 – alcohol dehydrogenase 7; NSCLC – non-small cell lung cancer; HR – hazard ratio; 95%CI – 95% confidence interval.

adenocarcinoma and SCC (*P*=0.8, HR=1.03, 95% CI=0.82–1.30; *P*=0.75, HR=0.96, 95% CI=0.76–1.22, Figure 9).

Discussion

The aim of this study was to assess the associations between *ADH* gene family members and NSCLC prognosis. The study results showed that the expression levels of *ADH1B*, *ADH1C*, *ADH4*, and *ADH5* were associated with the prognosis of NSCLC and both the adenocarcinoma and SCC histological types, but not with the SCC histological type. High expression of *ADH1B*, *ADH1C*, *ADH4*, and *ADH5* at the gene level, as opposed to low expression, was associated with a better prognosis. Low expression of *ADH7* was associated with a better prognosis among patients with both the adenocarcinoma and SCC histological types. Moreover, expression of *ADH* family members was associated with smoking status, clinical stage, and chemotherapy status.

ADH catalyzes the conversion between ethanol and aldehydes and ketones. Members of the ADH family have been extensively researched. ADH catalyzes the conversion of ethanol into acetaldehyde, a very active and toxic substance [30]. In the metabolic process of insects, from the larval to the adult stage, various kinds of alcohol produced by microbial fermentation are converted into the corresponding aldehydes and ketones (in homogeneous dimer form) [31]. A recent study reported that ADH family members have potential values in pancreatic adenocarcinoma patients' prognosis [32]. Levels of AHD1A, ADH1B encoding enzymes in the omega oxidation pathway are associated with hexadecanedioate levels, which can regulate the effect of alcohol of blood pressure [33]. Animal studies using pyrazole have shown that ADH is a specific inhibitor and the key enzyme in the metabolism of ethanol [34]. ADH1A, ADH1B, and ADH1C, which are encoded by genes located on chromosome 4q23, are responsible for most of the metabolism of ethanol in the liver [35]. A recent study indicated that a genetic variant of *ADH1B*, rs1229984, is a risk factor for esophageal cancer [11]. A meta-analysis of 35 case-control studies found that a single-nucleotide polymorphism of *ADH1C* (rs698) can increase the risk of cancer in African and Asian populations [36]. *ADH1* and *ADH4* are retinol dehydrogenases involved in the process of retinol oxidation, which is necessary for the synthesis of retinoic acid from retinoic acid [19].

As compared with other promoters, the *ADH2* gene product promotes the translation of various molecules. When the biomass concentration is appropriately increased, *ADH2* expression is relatively high, which optimizes bioethanol fermentation. However, the 573-bp *ADH2* promoter is suppressed by hundreds of times in the presence of glucose [37,38]. *ADH2*

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Table 4. Enrichment analysis of gene ontology of ADH family members.

Category	Term	Count	%	*P* value	FDR
GOTERM_BP_FAT	GO: 0006067~ethanol metabolic process	5	100	3.58E-15	3.34E-12
GOTERM_BP_FAT	GO: 0034308~monohydric alcohol metabolic process	5	100	3.58E-15	3.34E-12
GOTERM_BP_FAT	GO: 0006069~ethanol oxidation	5	100	3.58E-15	3.34E-12
GOTERM_MF_FAT	GO: 0004022~alcohol dehydrogenase (NAD) activity	5	100	2.96E-14	2.73E-11
GOTERM_MF_FAT	GO: 0004024~alcohol dehydrogenase activity, zinc-dependent	4	80	4.39E-11	4.06E-08
GOTERM_BP_FAT	GO: 0055114~oxidation reduction	5	100	4.93E-06	0.00463976
GOTERM_BP_FAT	GO: 0001523~retinoid metabolic process	3	60	1.66E-05	0.01556916
GOTERM_BP_FAT	GO: 0016101~diterpenoid metabolic process	3	60	1.66E-05	0.01556916
GOTERM_BP_FAT	GO: 0006721~terpenoid metabolic process	3	60	1.96E-05	0.01845758
GOTERM_BP_FAT	GO: 0006720~isoprenoid metabolic process	3	60	6.18E-05	0.05808355
GOTERM_BP_FAT	GO: 0019748~secondary metabolic process	3	60	2.01E-04	0.18840753
GOTERM_MF_FAT	GO: 0035276~ethanol binding	2	40	6.16E-04	0.56876933
GOTERM_MF_FAT	GO: 0008270~zinc ion binding	5	100	0.001002	0.92332089
GOTERM_MF_FAT	GO: 0046914~transition metal ion binding	5	100	0.002114	1.93934293
GOTERM_MF_FAT	GO: 0004745~retinol dehydrogenase activity	2	40	0.003078	2.81253478
GOTERM_MF_FAT	GO: 0019841~retinol binding	2	40	0.003692	3.36573224
GOTERM_MF_FAT	GO: 0005501~retinoid binding	2	40	0.006455	5.8174382
GOTERM_MF_FAT	GO: 0008289~lipid binding	3	60	0.006866	6.17736413
GOTERM_MF_FAT	GO: 0019840~isoprenoid binding	2	40	0.007068	6.35398528
GOTERM_MF_FAT	GO: 0016620~oxidoreductase activity, acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor	2	40	0.007068	6.35398528
GOTERM_MF_FAT	GO: 0043178~alcohol binding	2	40	0.007681	6.88755783
GOTERM_BP_FAT	GO: 0006081~cellular aldehyde metabolic process	2	40	0.008254	7.49884376
GOTERM_MF_FAT	GO: 0046872~metal ion binding	5	100	0.010329	9.162224
GOTERM_MF_FAT	GO: 0043169~cation binding	5	100	0.010724	9.49713106
GOTERM_MF_FAT	GO: 0043167~ion binding	5	100	0.011375	10.0467972
GOTERM_MF_FAT	GO: 0051287~NAD or NADH binding	2	40	0.014404	12.5650629
GOTERM_BP_FAT	GO: 0010033~response to organic substance	3	60	0.015839	13.9415732
GOTERM_BP_FAT	GO: 0045471~response to ethanol	2	40	0.018792	16.339828
GOTERM_MF_FAT	GO: 0019842~vitamin binding	2	40	0.039459	31.1056241
GOTERM_MF_FAT	GO: 0050662~coenzyme binding	2	40	0.054616	40.5359414
GOTERM_MF_FAT	GO: 0009055~electron carrier activity	2	40	0.066378	47.0415213
GOTERM_MF_FAT	GO: 0048037~cofactor binding	2	40	0.074545	51.1777008

ADH – alcohol dehydrogenase; FDR – false discovery rate.

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Table 5. Enrichment analysis of KEGG pathways of ADH family members.

Term	Count	%	P value	FDR	Genes
hsa00071: Fatty acid metabolism	5	100	3.28E-09	1.69E-06	ADH4, ADH1C, ADH5, ADH6, ADH1B, ADH7, ADH1A
hsa00350: Tyrosine metabolism	5	100	4.88E-09	2.52E-06	ADH4, ADH1C, ADH5, ADH6, ADH1B, ADH7, ADH1A
hsa00830: Retinol metabolism	5	100	1.14E-08	5.86E-06	ADH4, ADH1C, ADH5, ADH6, ADH1B, ADH7, ADH1A
hsa00980: Metabolism of xenobiotics by cytochrome P450	5	100	1.75E-08	9.03E-06	ADH4, ADH1C, ADH5, ADH6, ADH1B, ADH7, ADH1A
hsa00010: Glycolysis/ Gluconeogenesis	5	100	1.75E-08	9.03E-06	ADH4, ADH1C, ADH5, ADH6, ADH1B, ADH7, ADH1A
hsa00982: Drug metabolism	5	100	2.00E-08	1.03E-05	ADH4, ADH1C, ADH5, ADH6, ADH1B, ADH7, ADH1A

ADH – alcohol dehydrogenase; ADH1A – alcohol dehydrogenase 1A; ADH1B – alcohol dehydrogenase 1B; ADH1C – alcohol dehydrogenase 1C; ADH2 – alcohol dehydrogenase 2; ADH3 – alcohol dehydrogenase 3; ADH4 – alcohol dehydrogenase 4; ADH5 – alcohol dehydrogenase 5; ADH6 – alcohol dehydrogenase 6; ADH7 – alcohol dehydrogenase 7; FDR – false discovery rate.

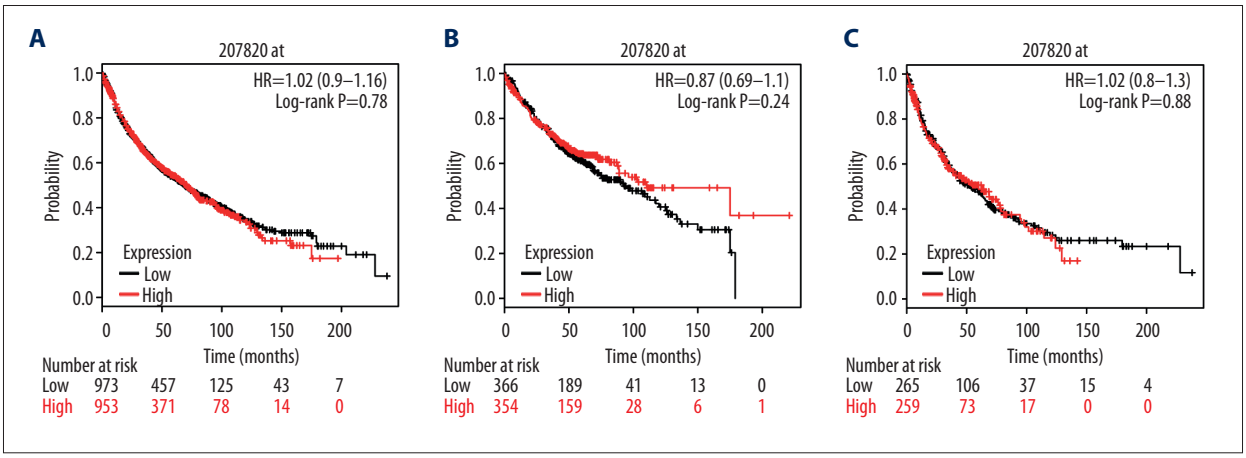

Figure 3. Survival analysis of *ADH1A* (207820_at) in NSCLC. (**A**) Survival analysis of *ADH1A* in both adenocarcinoma and squamous cell cancer; (**B**) Survival analysis of *ADH1A* in adenocarcinoma; (**C**) Survival analysis of *ADH1A* in squamous cell cancer.

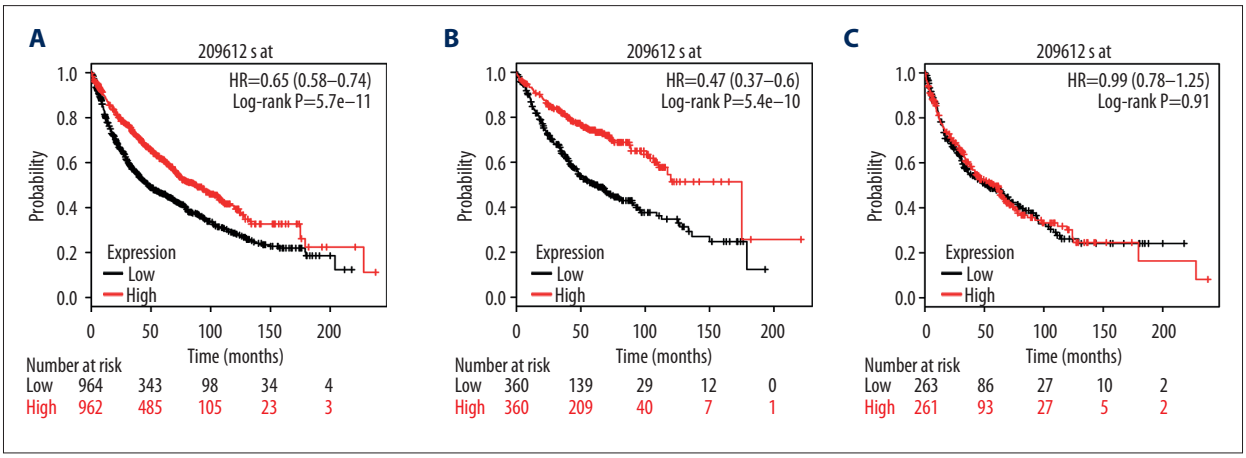

Figure 4. Survival analysis of *ADH1B* (209612_at) in NSCLC. (**A**) Survival analysis of *ADH1B* in both adenocarcinoma and squamous cell cancer; (**B**) Survival analysis of *ADH1B* in adenocarcinoma; (**C**) Survival analysis of *ADH1B* in squamous cell cancer.

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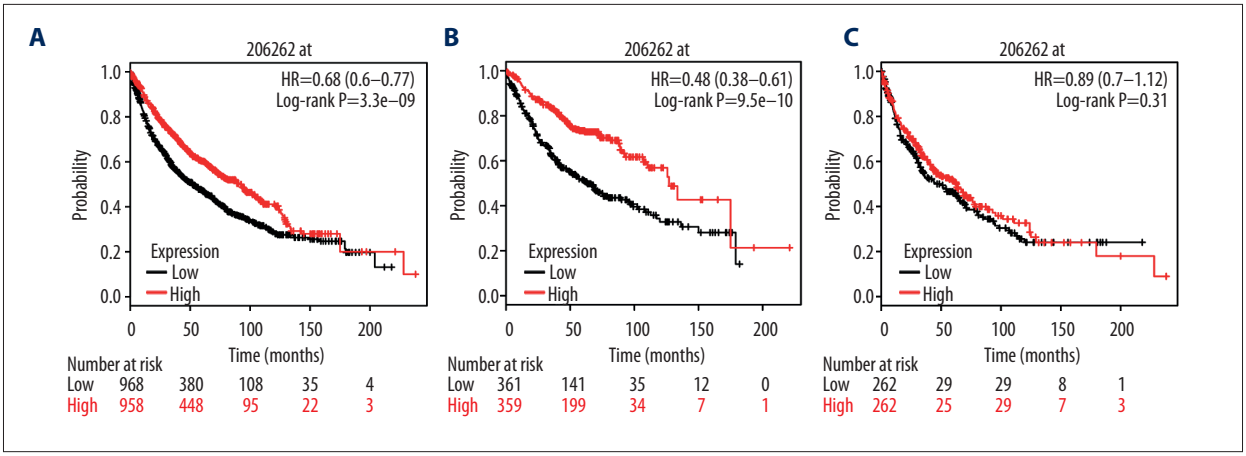

Figure 5. Survival analysis of *ADH1C* (206262_at) in NSCLC. (**A**) Survival analysis of *ADH1C* in both adenocarcinoma and squamous cell cancer; (**B**) Survival analysis of *ADH1C* in adenocarcinoma; (**C**) Survival analysis of *ADH1C* in squamous cell cancer.

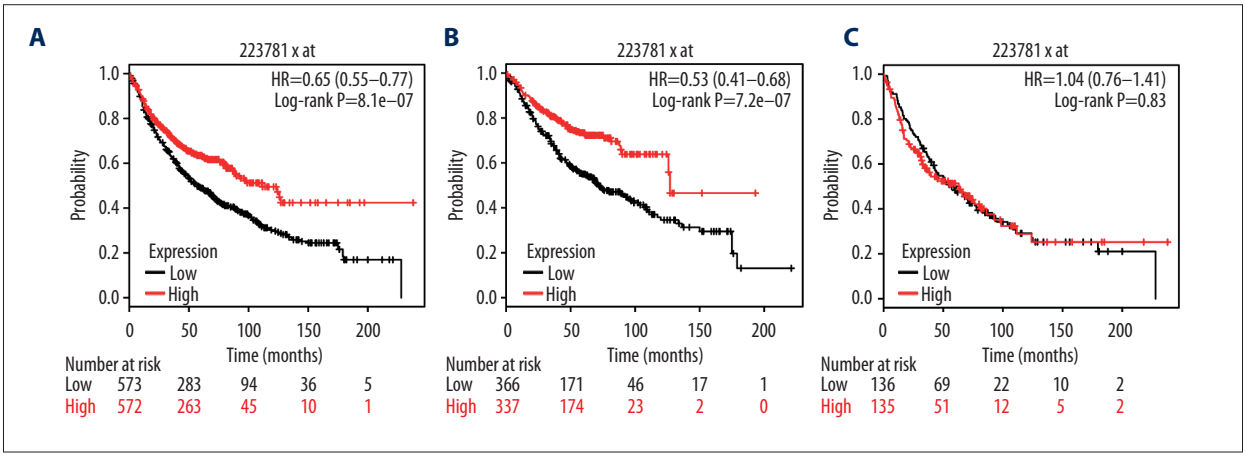

Figure 6. Survival analysis of *ADH4* (223781_at) in NSCLC. (**A**) Survival analysis of *ADH4* in both adenocarcinoma and squamous cell cancer; (**B**) Survival analysis of *ADH4* in adenocarcinoma; (**C**) Survival analysis of *ADH4* in squamous cell cancer.

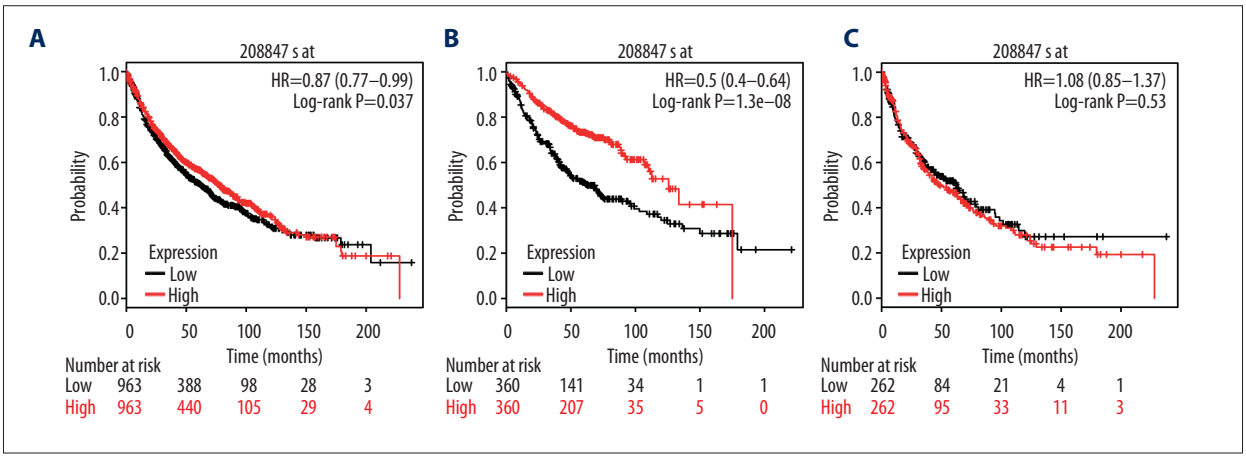

Figure 7. Survival analysis of *ADH5* (208847_at) in NSCLC. (**A**) Survival analysis of *ADH5* in both adenocarcinoma and squamous cell cancer; (**B**) Survival analysis of *ADH5* in adenocarcinoma; (**C**) Survival analysis of *ADH5* in squamous cell cancer.

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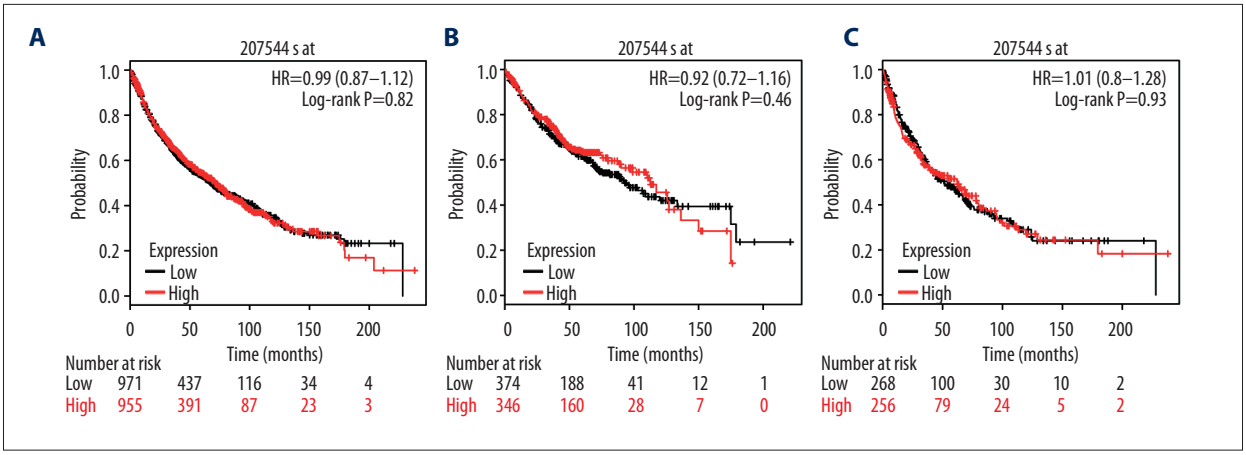

Figure 8. Survival analysis of *ADH6* (207544_at) in NSCLC. (**A**) Survival analysis of *ADH6* in both adenocarcinoma and squamous cell cancer; (**B**) Survival analysis of *ADH6* in adenocarcinoma; (**C**) Survival analysis of *ADH6* in squamous cell cancer.

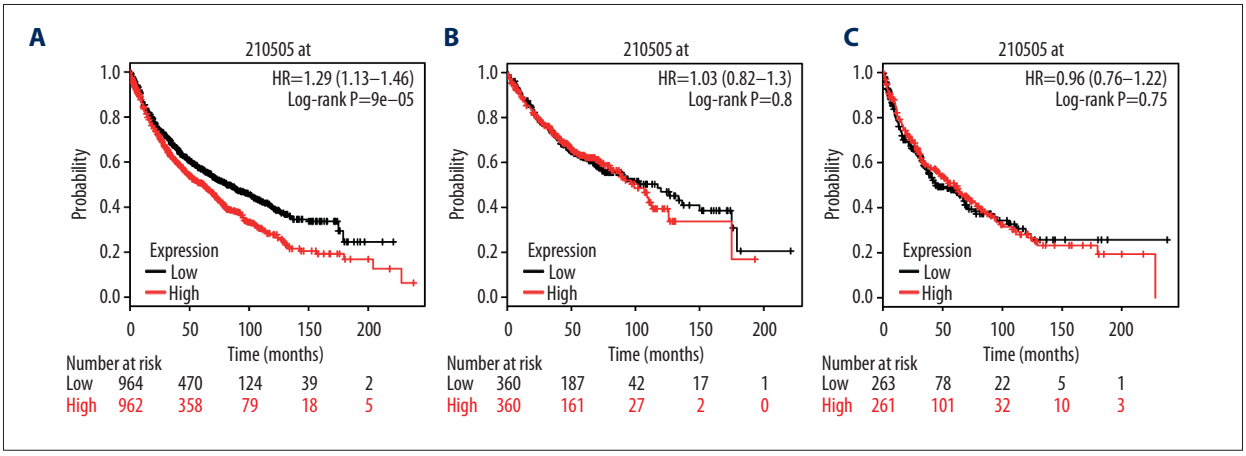

Figure 9. Survival analysis of *ADH7* (210505_at) in NSCLC. (**A**) Survival analysis of *ADH7* in both adenocarcinoma and squamous cell cancer; (**B**) Survival analysis of *ADH7* in adenocarcinoma; (**C**) Survival analysis of *ADH7* in squamous cell cancer.

gene expression can be activated by the yeast regulatory protein ADR1 and, therefore, inhibition of ADH2 expression should control the synthesis of the ADR1 protein [39]. In addition, *ADH2* complement can be used to determine the function of the gene in *Saccharomyces cerevisiae* As2.4 [40]. *ADH1* and *ADH2* are mainly expressed in the liver and gastric mucosa, where both are involved in the metabolism of oral alcohol, that is, the conversion of ethanol into the carcinogenic metabolite acetaldehyde, especially in the elimination stage [41–43]. In the esophageal muscle tissue, 2 single-nucleotide polymorphisms (rs1126671 and rs1800759) were associated with lower *ADH4* expression levels in fibroblasts [44]. The *ADH4* gene encodes the π subunit in humans and can metabolize many substances, including ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid peroxidation products [45]. The *ADH5* gene encodes the χ subunit, which participates in the metabolism of alcohols and aldehydes [46]. According to a literature review, an *ADH7* variant is associated with Parkinson's disease [47]. Another study reported that the modulating effect of *ADH7* is dependent on the gene sequence and the extracellular environment [48].

ADH may be involved in the metabolic pathway of several neurotransmitters involved in the neurobiology of neuropsychiatric diseases, in addition to catalyzing the oxidation of retinol and ethanol. Studies have shown that the common ADH mutation carries risks associated with schizophrenia in African-Americans and European Americans [49]. *ADH1* expression plays an important role in the transformation of extracellular matrix in the etiology of uterine fibroids. Although no significant difference was found in the activity of *ADH1*, the number of tumors was negatively correlated with the expression level of *ADH1* [50]. According to the literature, *ADH1B* mRNA levels were reduced (>10-fold) in 65% of lung cancer cDNA samples, which was associated with the onset and progression of human lung cancer [51]. Also, the *ADH1C* SspI polymorphism could play a significant role in the etiology of oral cancer and genetic polymorphisms of ethanol-metabolizing enzymes may

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affect individual susceptibility to oral cancer [52]. Chip data show that *ADH4* mRNA and protein expression levels were significantly reduced in HCC and there was a significant correlation with survival rate, indicating that *ADH4* is a potential prognostic marker for HCC patients [53]. Another study provided abundant evidence that the rs3805322 polymorphism of the *ADH4* gene may be related to an increased risk of SCC in 2 populations of Han Chinese [54]. Also, the *ADH1A-ADH1B-ADH7* cluster single-nucleotide polymorphisms conferred susceptibility to esophageal SCC in 2 case-control sets [55].

Many studies have focused on the associations between ADH family members and various diseases, including alcoholism, Parkinson's disease, schizophrenia, and HCC, among others. In addition, the roles of some ADH family members in lung cancer have also been explored. The results of the present study found that, with the exception of *ADH5*, the expression levels of other SDH family members were relatively high in normal lung tissues. The expression levels of *ADH1B*, *ADH1C*, *ADH4*, and *ADH5* were associated with the prognosis of NSCLC patients with adenocarcinoma and both the adenocarcinoma and SCC histological types. In fact, the prognosis of patients with high expression levels of *ADH1B*, *ADH1C*, *ADH4*, and *ADH5* was better than that of those with low expression levels. Low expression of *ADH7* was associated with a better prognosis among patients with the adenocarcinoma and SCC histological types. Moreover, expression of ADH family members was associated with smoking status, clinical stage, and chemotherapy status. Therefore, our findings indicate that *ADH1B* (*ADH2*), *ADH1C* (*ADH3*), *ADH4*, *ADH5*, and *ADH7* may be suitable as potential markers for the prognosis of NSCLC. Furthermore, we hypothesized that *ADH1B* (*ADH2*), *ADH1C* (*ADH3*), and *ADH4* may function as tumor-suppressors, and that *ADH5* and *ADH7* may play oncogenic roles in NSCLC tumorigenesis. Smoking status, clinical stage, and chemotherapy may influence the expression of ADH family members.

There were some limitations to this study that should to be addressed. First, the study cohort was relatively small; thus, larger studies are needed to verify these findings. In addition, further studies of multiple centers with patients of various races are needed. To address these issues, we are planning well-designed functional verification studies, including *in vitro* and *in vivo* models, in the near future. As other potential shortcomings, *ADH1B (ADH2)*, *ADH1C* (*ADH3*), *ADH4*, *ADH5*, and *ADH7* were all associated with the prognosis of NSCLC and smoking may influence the expression of genes and the clinical stage of disease. Thus, *ADH1B*, *ADH1C* (*ADH3*), *ADH2*, *ADH4*, *ADH5*, and *ADH7* are potential prognostic biomarkers for NSCLC.

Conclusions

In conclusion, the aim of this study was to explore the associations between NSCLC prognosis and the expression patterns of ADH family members. Our study found that *ADH1B (ADH2)*, *ADH1C* (*ADH3*), *ADH4*, *ADH5*, and *ADH7* were all associated with the prognosis of NSCLC and smoking may influence the expression of genes and the clinical stage of disease. Thus, *ADH1B (ADH2)*, *ADH1C* (*ADH3*), *ADH4*, *ADH5*, and *ADH7* are potential prognostic biomarkers for NSCLC.

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Conflicts of interest

None.

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