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Prognostic and Immunological Role of CNIH1 in Cervical Cancer: A Pan-Cancer Analysis

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Abstract

Objective: Cervical cancer remains one of the most common malignancies among women. Improving prognosis, particularly for patients with metastatic or recurrent disease, is of great clinical importance. Cornichon Homolog 1 (CNIH1), a member of the AMPA receptor auxiliary protein family, plays a role in immune response and signal transduction, although its precise mechanisms remain unclear. Its function in cancer prognosis and immune regulation has rarely been reported.

Methods: Pan-cancer and cervical cancer datasets were obtained from the UCSC XENA and GITEX databases. Prognostic value was evaluated using Cox regression and Kaplan-Meier analyses. The relationship between CNIH1 expression and immune cell infiltration was analyzed using TIMER and CIBERSORT algorithms.

Results: CNIH1 was found to be highly expressed in multiple tumor types. Kaplan-Meier analysis showed a significant association between high CNIH1 expression and poor Overall Survival (OS) in several cancers, including cervical cancer. ROC curves demonstrated a strong diagnostic performance of CNIH1 in cervical and other cancers. Immune correlation analyses revealed a relationship between CNIH1 expression and various tumor-infiltrating immune cells.

Conclusion: This study is the first to report the pan-cancer and cervical cancer-specific roles of CNIH1, highlighting its potential as both a diagnostic biomarker and a prognostic indicator in cervical cancer.

Keywords: Cervical cancer; CNIH1; Diagnostic biomarker; Prognosis; Immune infiltration.

Introduction

Cancer poses a serious threat to global public health, with both its incidence and mortality rates continuing to rise annually [1]. Among the most common and lethal cancers worldwide are lung, pancreatic, and liver cancers [1]. Although significant advancements have been made in cancer diagnosis and treatment, the five-year Overall Survival (OS) rate for many malignancies remains unsatisfactory [2]. Additionally, the global economic burden of cancer continues to grow [3]. Therefore, there is an urgent need for novel diagnostic and therapeutic strategies. Increasing attention has been paid to the identification and application of cancer biomarkers, which has driven research efforts to explore new molecular targets [4-6].

Cervical cancer is currently the fourth most common malignancy among women worldwide [1], with approximately 500,000 new cases diagnosed annually-accounting for nearly

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5% of all female cancers. Over 80% of these cases occur in developing countries, and more than 260,000 women die from cervical cancer each year in low- and middle-income countries [7]. In China alone, there are an estimated 131,500 new cases and approximately 53,000 cervical cancer-related deaths annually, accounting for 18.4% of all female cancer deaths [8]. Cervical carcinoma in situ is most commonly diagnosed in women aged 30-35 years, while invasive cervical cancer frequently occurs in those aged 45–55 years. Although surgical treatment combined with radiotherapy and chemotherapy can improve patient outcomes, a substantial proportion of patients still experience recurrence or metastasis, leading to poor prognosis. As a major malignancy threatening women's health and survival globally, cervical cancer urgently requires the identification of reliable biomarkers for comprehensive prognostic evaluation. Cornichon Homolog 1 (CNIH1), a member of the cornichon protein family and an auxiliary subunit of AMPA receptors, is involved in immune response and signal transduction, though its specific mechanisms remain poorly defined. To date, the role of CNIH1 in pan-cancer analysis and cervical cancer has not been thoroughly investigated. In this study, we examined CNIH1 expression across multiple tumor types by comparing cancerous and adjacent normal tissues, as well as tumor versus non-tumor tissues, using data from The Cancer Genome Atlas (TCGA). We further evaluated its diagnostic and prognostic value in pan-cancer settings. Specifically, we focused on assessing the prognostic significance of CNIH1 in cervical cancer and explored its association with immune cell infiltration. Together, these analyses offer new insights into the potential roles of CNIH1 in cancer progression and tumor immunity.

Materials and methods

Gene expression data analysis: RNA-seq data and corresponding clinical information from 15,776 samples across 33 tumor types and normal tissues were obtained from the Cancer Genome Atlas (TCGA) via the UCSC XENA platform, as well as the Genotype-Tissue Expression (GITEX) database.

(https://xenabrowser.net/datapages/). RNA-seq data (FPKM format) and clinical data for cervical cancer were also downloaded from TCGA. The data were converted to TPM format and subsequently log2-transformed for analysis. All statistical analyses were performed using R software (v3.6.3), and data visualization was carried out using the ggplot2 package. The Wilcoxon rank-sum test was used for comparisons between two groups, and p-values < 0.05 were considered statistically significant.

Construction of Protein-Protein Interaction (PPI) network: Fifty CNIH1-binding proteins were identified using the STRING database.

(https://string-db.org/). The resulting interaction data were visualized using Cystoscope software (version 3.7.2) to construct the Protein-Protein Interaction (PPI) network.

GO and KEGG enrichment analysis: Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed on the 50 CNIH1-interacting proteins using the cluster Profiler package in R. Data visualization was conducted using the ggplot2 package. Gene Set Enrichment Analysis (GSEA) was also used to explore the biological functions of CNIH1 in cervical cancer.

Diagnostic value analysis: Receiver Operating Characteristic (ROC) curve analysis was used to assess the diagnostic value of CNIH1 across multiple cancer types. The Area Under the Curve (AUC) was used to evaluate diagnostic accuracy: an AUC of 0.5-0.7 indicated low accuracy, 0.7-0.9 indicated moderate accuracy, and AUC > 0.9 indicated high accuracy.

Survival and prognostic Analysis: Kaplan-Meier survival analysis was used to evaluate the association between CNIH1 expression and Overall Survival (OS). Visualization and statistical analysis were performed using the servicer and survival packages in R.

Immune infiltration analysis: The potential correlation between CNIH1 expression and immune cell infiltration was assessed using the TIMER database (https://cistrome.shinyapps.io/timer/) [9], which applies a deconvolution-based statistical approach [10], to estimate immune cell abundance from gene expression data. The association between CNIH1 expression and the infiltration levels of CD4+ T cells, dendritic cells, B cells, CD8+ T cells, neutrophils, and macrophages was evaluated. TIMER also provides estimates of tumor purity in relation to gene expression [11], Additionally, the CIBERSORT algorithm (http://cibersort.stanford.edu/) [12], was used to evaluate immune responses involving 24 types of immune cells and their association with CNIH1 expression in cervical cancer.

Statistical analysis

Univariate and multivariate Cox proportional hazards models were used to estimate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) to assess the relationships between clinical-pathological features and overall survival. Logistic regression analysis was employed to examine the correlation between CNIH1 expression and clinical characteristics. A p-value < 0.05 was considered statistically significant.

Results

Differential expression of CNIH1 between tumor and normal or adjacent tissues across multiple cancers: To explore the expression pattern of CNIH1 across various cancers, we analyzed its expression levels between tumor and normal tissues, as well as between tumor and adjacent non-tumorous tissues. Our results revealed no significant differences in CNIH1 expression between tumor and normal tissues in Adrenocortical Carcinoma (ACC), Bladder Urothelial Carcinoma (BLCA), Cholangiocarcinoma (CHOL), Chromophobe Renal Cell Carcinoma (KICH), Papillary Renal Cell Carcinoma (KIRP), Pheochromocytoma and Paraganglioma (PCPG), Uterine Corpus Endometrial Carcinoma (UCEC), and Uterine Carcinosarcoma (UCS) (Figure 1A). In contrast, CNIH1 expression was significantly different ($p<0.05$) in most other cancer types when comparing tumor to normal tissues.

Further analysis of CNIH1 expression in tumor versus adjacent non-tumor tissues revealed significant differences in many cancers, except for cervical squamous cell Carcinoma and Endocervical Adenocarcinoma (CESC), bladder urothelial carcinoma, cholangiocarcinoma, Colon Adenocarcinoma (COAD), Clear Cell Renal Cell Carcinoma (KIRC), Pancreatic Adenocarcinoma (PAAD), Pheochromocytoma And Paraganglioma, Rectal Adenocarcinoma (READ), Thyroid Carcinoma (THCA), and endometrial carcinoma ($p<0.05$, Figure 1B).

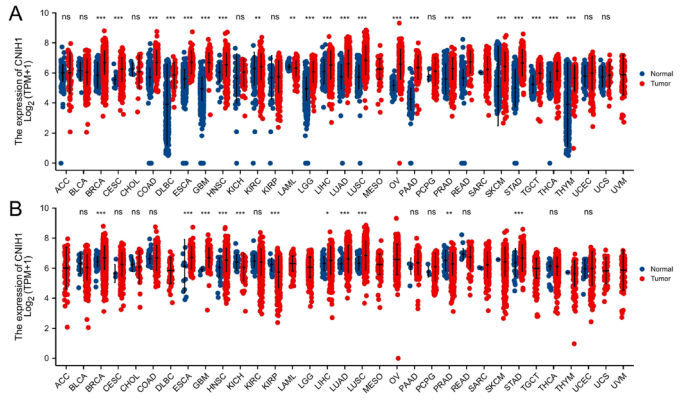


Figure 1: Differential Expression of CNIH1 Across Multiple Cancer Types. **(A)** CNIH1 expression between tumor and normal tissues in various cancer types. **(B)** CNIH1 expression between tumor and adjacent non-tumorous tissues.
*P<0.05; **P<0.01; ***P< 0.001

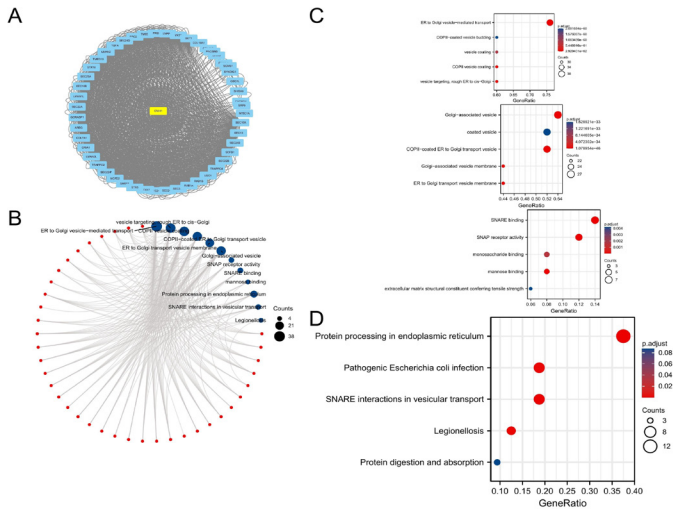


Figure 2: Protein-Protein interaction network and functional enrichment analysis of CNIH1. **(A)** CNIH1 interaction network with 50 binding proteins visualized by Cystoscope. **(B)** Circular plot showing functional categories and signaling pathways associated with CNIH1. **(C)** GO enrichment analysis, including BP, CC, and MF terms. **(D)** KEGG pathway enrichment analysis.

Construction of the CNIH1 Protein-Protein Interaction (PPI) network and functional enrichment analysis (GO/KEGG): To explore the functional landscape of CNIH1 at the protein level, we identified 50 potential CNIH1-interacting proteins using the STRING database and visualized the resulting interaction network using Cystoscope software (Figure 2A).GO enrichment analysis of these interacting proteins revealed the following: Biological Processes (BP): Enriched terms included ER-to-Golgi vesicle-mediated transport, COPII-coated vesicle budding, vesicle coating, COPII vesicle coating, and vesicle targeting from rough ER to the cis-Golgi. Cellular Components (CC): Interacting proteins were mainly localized to Golgi-associated vesicles, coated vesicles, COPII-coated ER-to-Golgi transport vesicles, Golgi-associated vesicle membranes, and ER-to-Golgi vesicle membranes. Molecular Functions (MF): Enriched molecular functions included SNARE complex binding, SNAP receptor activity, monosaccharide binding, mannose binding, and extracellular matrix structural constituents conferring tensile strength (Figure 2B and 2C).KEGG pathway enrichment analysis indicated significant involvement in protein processing in the endoplasmic reticulum, pathogenic Escherichia coli infection, SNARE interactions in vesicular transport, Legionellosis, and protein digestion and absorption (Figure 2D).

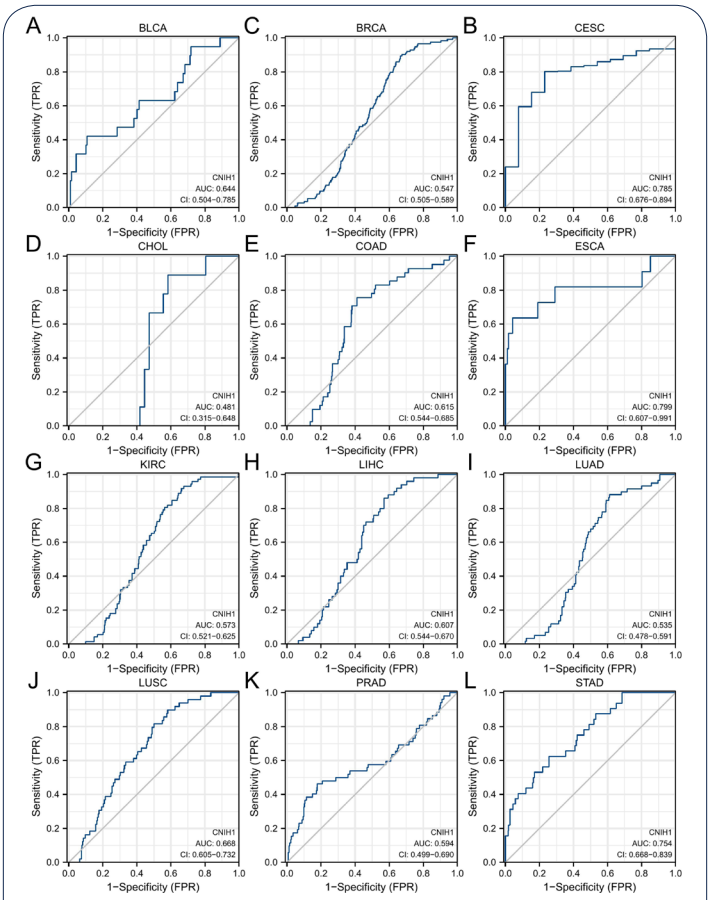


Figure 3: ROC curve analysis of CNIH1 across different cancer types. **(A)** BLCA (AUC = 0.644, 95% CI: 0.504-0.785), **(B)** BRCA (AUC = 0.547, 95% CI: 0.505-0.589), **(C)** CESC (AUC = 0.785, 95% CI: 0.676-0.894), **(D)** CHOL (AUC = 0.481, 95% CI: 0.315-0.648), **(E)** COAD (AUC = 0.615, 95% CI: 0.544-0.685), **(F)** ESCA (AUC = 0.799, 95% CI: 0.607-0.991), **(G)** KIRC (AUC = 0.573, 95% CI: 0.521-0.625), **(H)** LIHC (AUC = 0.607, 95% CI: 0.544-0.670), **(I)** LUAD (AUC = 0.535, 95% CI: 0.478-0.591), **(J)** LUSC (AUC = 0.668, 95% CI: 0.605-0.732), **(K)** PAAD (AUC = 0.594, 95% CI: 0.499-0.690), **(L)** STAD (AUC = 0.754, 95% CI: 0.668-0.839).

ROC curve analysis of CNIH1 in various tumor types: After identifying the differential expression of CNIH1 and its involvement in diverse biological functions and pathways, we further evaluated its diagnostic value across multiple cancers using Receiver Operating Characteristic (ROC) curve analysis.CNIH1 showed varying levels of diagnostic performance in 12 cancer types, including Bladder Urothelial Carcinoma (BLCA), Invasive Breast Carcinoma (BRCA), Cervical Squamous Cell Carcinoma And Endocervical Adenocarcinoma (CESC), Cholangiocarcinoma (CHOL), Colon Adenocarcinoma (COAD), Esophageal Carcinoma (ESCA), Kidney Clear Cell Carcinoma (KIRC), Liver Hepatocellular Carcinoma (LIHC), Lung Adenocarcinoma (LUAD), Lung Squamous Cell Carcinoma (LUSC), Pancreatic Adenocarcinoma (PAAD), and Stomach Adenocarcinoma (STAD).As shown in (Figure 3), CNIH1 demonstrated good diagnostic efficacy in Cervical Cancer (CESC), Esophageal Cancer (ESCA), and gastric cancer (STAD), with area

under the curve (AUC) values ranging from 0.7 to 1.0. In other tumor types, however, CNIH1 displayed limited diagnostic performance (Figure 3A - 3L).

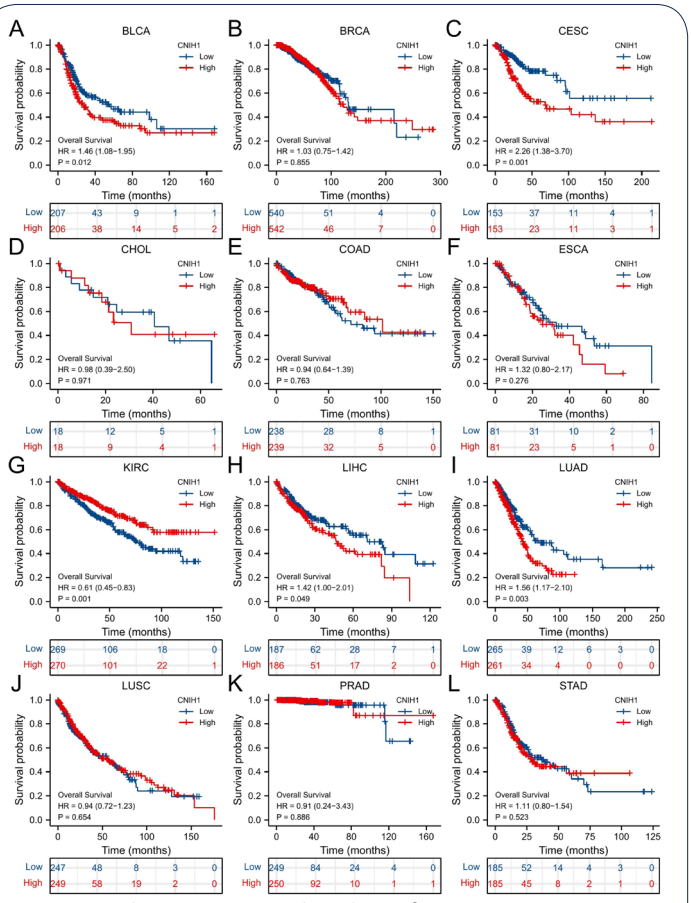


Figure 4: Kaplan-Meier Survival Analysis of CNIH1 Expression in Various Cancers.
(A) BLCA, **(B)** BRCA, **(C)** CESC, **(D)** CHOL, **(E)** COAD, **(F)** ESCA, **(G)** KIRC, **(H)** LIHC, **(I)** LUAD, **(J)** LUSC, **(K)** PAAD, **(L)** STAD.

Prognostic analysis of CNIH1 expression across multiple cancer types: Having established CNIH1's diagnostic potential in various cancers, we further investigated its prognostic value by analyzing Overall Survival (OS) across 12 cancer types: Bladder Urothelial Carcinoma (BLCA), invasive Breast Carcinoma (BRCA), Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (CESC), Cholangiocarcinoma (CHOL), Colon Adenocarcinoma (COAD), Esophageal Carcinoma (ESCA), Kidney Clear Cell Carcinoma (KIRC), Liver Hepatocellular Carcinoma (LIHC), Lung Adenocarcinoma (LUAD), Lung Squamous Cell Carcinoma (LUSC), Pancreatic Adenocarcinoma (PAAD), And Stomach Adenocarcinoma (STAD).

As shown in (Figure 4), high CNIH1 expression was significantly associated with poorer OS in BLCA, CESC, KIRC, LIHC, and LUAD. Specifically: In BLCA, high CNIH1 expression correlated with worse OS (Hazard Ratio [HR] = 1.46, 95% confidence interval [CI]: 1.08-1.95, p=0.012). In CESC, patients with high CNIH1 expression exhibited significantly worse OS (HR= =2.26, 95% CI: 1.38-3.70, p=0.001). In KIRC, lower CNIH1 expression was associated with worse prognosis (HR=0.61, 95% CI: 0.45-0.83, p=0.001), suggesting a potentially protective role. In LIHC, high CNIH1 expression also indicated poorer OS (HR=1.42, 95% CI: 1.00-2.01, p=0.049). In LUAD, high expression of CNIH1 was significantly associated with decreased OS (HR=1.56, 95% CI: 1.17-2.10, p=0.003).

Survival outcomes and variable analysis of CNIH1 expression in cervical cancer: Given the high expression level, diagnostic potential, and prognostic relevance of CNIH1 in cervical cancer, we further examined its association with survival outcomes and clinicopathological variables in CESC (cervical squamous cell carcinoma and endocervical adenocarcinoma). As shown in (Figure 5A), CNIH1 expression was significantly higher in cervical cancer tissues compared to normal tissues (p<0.001).Univariate Cox regression analysis revealed that T stage (HR=3.863, p<0.001), N stage (HR=2.844, p=0.002), M stage (HR=3.555, p=0.023), clinical stage (HR=2.369, p<0.001), and CNIH1 expression (HR=2.008, p=0.005) were significantly associated with Overall Survival (OS) (Table 1). Multivariate Cox regression further identified CNIH1 expression as an independent prognostic factor (HR=9.242, 95% CI: 1.440-59.322, p=0.019), as shown in (Figure 5B). Patient survival status and CNIH1 expression distribution are depicted in (Figure 5C), illustrating that high CNIH1 expression correlates with increased mortality.

Time-dependent ROC curve analysis demonstrated the prognostic capability of CNIH1, with AUC values of 0.634, 0.649, and 0.626 for 1-, 3-, and 5-year survival predictions, respectively (Figure 5D).

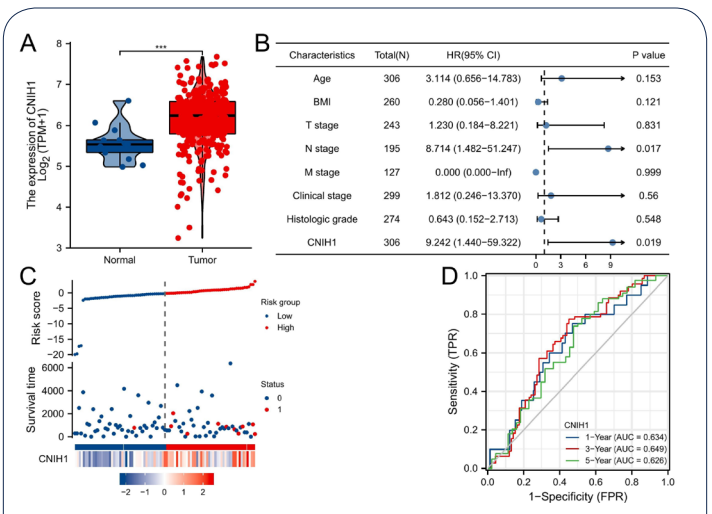


Figure 5: Prognostic significance of CNIH1 in cervical cancer.
(A) CNIH1 expression in normal vs. tumor tissues. **(B)** Multivariate Cox regression analysis including CNIH1 and clinicopathological variables. **(C)** Distribution of CNIH1 expression and patient survival status. **(D)** Time-dependent ROC curves for 1-, 3-, and 5-year overall survival prediction.

Table 1: Univariate and multivariate cox regression analysis of clinicopathological features associated with overall survival in cervical cancer.

Characteristics	Total(N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (>50 vs. <=50)	306	1.289 (0.810-2.050)	0.284	3.114 (0.656-14.783)	0.153
BMI (>25 vs. <=25)	260	0.600 (0.348-1.034)	0.066	0.280 (0.056-1.401)	0.121
T stage (T3&T4 vs. T1&T2)	243	3.863 (2.072-7.201)	**<0.001**	1.230 (0.184-8.221)	0.831
N stage (N1 vs. N0)	195	2.844 (1.446-5.593)	**0.002**	8.714 (1.482-51.247)	**0.017**
M stage (M1 vs. M0)	127	3.555 (1.187-10.641)	**0.023**	0.000 (0.000-Inf)	0.999
Clinical stage (Stage III& Stage IV vs.Stage I& Stage II)	299	2.369 (1.457-3.854)	**<0.001**	1.812 (0.246-13.370)	0.560
Histologic grade (G3&G4 vs. G1&G2)	274	0.866 (0.514-1.459)	0.589	0.643 (0.152-2.713)	0.548
CNIH1 (High vs. Low)	306	2.008 (1.235-3.265)	**0.005**	9.242 (1.440-59.322)	**0.019**

Association between CNIH1 expression and clinicopathological characteristics in cervical cancer: We next examined the relationship between CNIH1 expression and various clinicopathological features in cervical cancer patients. As shown in (Figure 6A & 6B), elevated CNIH1 expression was not significantly associated with clinical stage or histological grade. To further explore potential clinical relevance, univariate logistic regression was conducted to assess the association between CNIH1 expression and prognostic variables. The analysis revealed no significant correlation between CNIH1 expression and TNM stage, clinical stage, or histologic grade. However, significant associations were observed between CNIH1 expression and both patient age (p=0.035) and BMI (p=0.016), suggesting that elevated CNIH1 may be more common in older patients and those with lower BMI. These findings imply that high CNIH1 expression is not indicative of more aggressive clinicopathological characteristics in terms of staging or grading, but may reflect differences related to patient age and body composition (Table 2).

Table 2: Logistic regression analysis of the association between CNIH1 expression and clinicopathological characteristics in cervical cancer.

Characteristics	Total(N)	Odds Ratio (OR)	P value
Age (>50 vs. <=50)	306	0.607 (0.380-0.964)	**0.035**
BMI (>25 vs. <=25)	260	0.536 (0.321-0.889)	**0.016**
T stage (T2 vs. T1)	212	0.674 (0.377-1.195)	0.180
T stage (T3 vs. T1)	161	0.750 (0.289-1.884)	0.542
T stage (T4 vs. T1)	150	1.500 (0.411-6.082)	0.543
T stage (T3&T4 vs. T1&T2)	243	1.070 (0.499-2.284)	0.860
N stage (N1 vs. N0)	195	0.605 (0.323-1.117)	0.112
M stage (M1 vs. M0)	127	1.286 (0.368-4.685)	0.692
Clinical stage (Stage II vs. Stage I)	231	0.858 (0.487-1.510)	0.596
Clinical stage (Stage III vs. Stage I)	208	0.680 (0.348-1.311)	0.251
Clinical stage (Stage IV vs. Stage I)	184	1.060 (0.433-2.645)	0.898
Clinical stage (Stage III & Stage IV vs. Stage I & Stage II)	299	0.822 (0.477-1.413)	0.479
Histologic grade (G2 vs. G1)	154	1.846 (0.699-5.228)	0.225
Histologic grade (G3 vs. G1)	138	1.686 (0.633-4.806)	0.306
Histologic grade (G3&G4 vs. G1&G2)	274	1.000 (0.620-1.613)	1.000

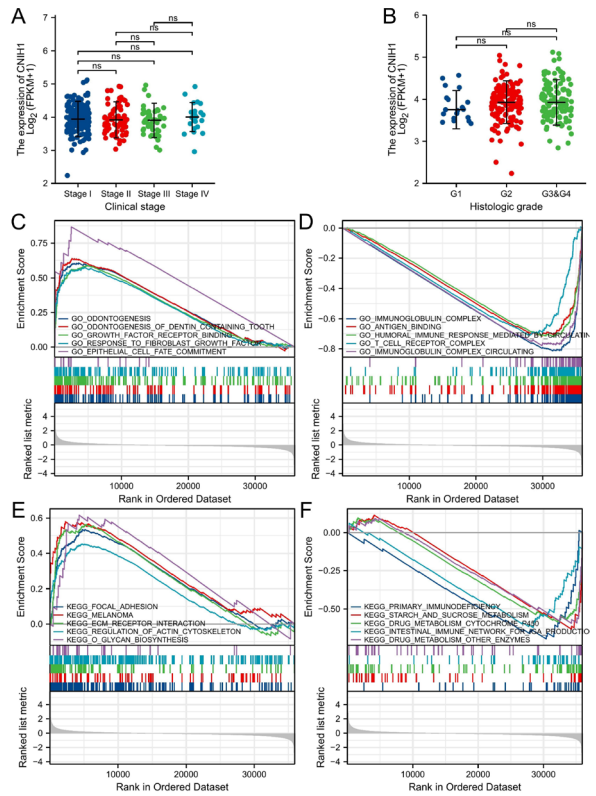


Figure 6: (A) Relationship between CNIH1 expression and clinical stage in cervical cancer. **(B)** Relationship between CNIH1 expression and histologic grade. **(C,D)** GO enrichment analysis (top 5 positive and negative correlated terms). **(E,F)** KEGG enrichment analysis (top 5 positive and negative correlated pathways).

Gene Set Enrichment Analysis (GSEA) of CNIH1 in cervical cancer: To investigate the potential biological functions and signaling pathways associated with CNIH1 in cervical cancer, we performed Gene Set Enrichment Analysis (GSEA) based on its expression levels. GO enrichment analysis revealed five biological categories that were positively correlated with CNIH1 expression, including: Odontogenesis of dentin-containing tooth Growth factor receptor binding Response to fibroblast growth factor Epithelial cell fate commitment (Table 3). In contrast, the five most negatively correlated GO terms included: Immunoglobulin complex Antigen binding Humoral immune response mediated by circulating immunoglobulin T cell receptor complex Circulating immunoglobulin complex.

As shown in Figure 6C, one of the most significant functions positively associated with CNIH1 was growth factor receptor binding, suggesting potential involvement in tumor progression and differentiation. KEGG pathway analysis identified five pathways positively associated with high CNIH1 expression: Focal adhesion, Melanoma, ECM-receptor interaction, Regulation of actin cytoskeleton, O-glycan bi synthesis, Conversely, five negatively associated KEGG pathways were: Primary immunodeficiency, Starch and sucrose metabolism, Drug metabolism by cytochrome e P450,Intestinal immune network for IgA production, Other drug-metabolizing e enzymes, These findings (Figure 6E) suggest that CNIH1 may play important roles in extracellular matrix organization and cytoskeletal regulation in cervical cancer, while its downregulation is associated with impaired immune function and metabolism.

Table 3: GO and KEGG pathways positively and negatively correlated with CNIH1 expression.

	ID	NES	P value	q value
Positive	GO_ODONTOGENESIS GO_ODONTOGENESIS_OF_DENTIN_CONTAINING	2.475544961	0.003012048	0.05637483
	_TOOTH	2.450763509	0.002873563	0.05637483
	GO_GROWTH_FACTOR_RECEPTOR_BINDING GO_RESPONSE_TO_FIBROBLAST_GROWTH_FACT	2.422555507	0.003058104	0.05637483
	OR	2.370767309	0.00308642	0.05637483
	GO_EPITHELIAL_CELL_FATE_COMMITMENT	2.349627543	0.002544529	0.05637483
	KEGG_FOCAL_ADHESION	2.319934584	0.003472222	0.02093469
	KEGG_MELANOMA	2.150542333	0.002906977	0.020596672
	KEGG_ECM_RECEPTOR_INTERACTION	2.143915391	0.003039514	0.020596672
	KEGG_REGULATION_OF_ACTIN_CYTOSKELETON	1.984861996	0.003610108	0.02093469
	KEGG_O_GLYCAN_BIOSYNTHESIS	1.917559736	0.005263158	0.023490564
Negative	GO_IMMUNOGLOBULIN_COMPLEX	3.140430385	0.001472754	-0.05637483
	GO_ANTIGEN_BINDING	2.772506556	0.001485884	0.05637483
	GO_HUMORAL_IMMUNE_RESPONSE_MEDIATED	2.760601583	0.001464129	0.05637483
	BY_CIRCULATING_IMMUNOGLOBULIN GO_T_CELL_RECEPTOR_COMPLEX	2.638763623	0.001508296	0.05637483
	GO_IMMUNOGLOBULIN_COMPLEX_CIRCULATING	2.628818326	0.001533742	0.05637483
	KEGG_PRIMARY_IMMUNODEFICIENCY	2.067166917	0.001610306	0.020596672
	KEGG_STARCH_AND_SUCROSE_METABOLISM	2.054231068	0.001552795	0.020596672
	KEGG_DRUG_METABOLISM_CYTOCHROME_P450	1.999292516	0.001519757	0.020596672
	KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IG	1.96667087	0.001577287	0.020596672
	A_PRODUCTION-KEGG_DRUG_METABOLISM_ OTHER_ENZYMES	1.921070702	0.0015625	0.020596672

Relationship between CNIH1 expression and tumor-infiltrating immune cells: We investigated the association between CNIH1 expression and immune infiltration levels in cervical cancer. As shown in Figure 7A, CNIH1 expression was significantly correlated with B cells (P=0.0008) and CD4⁺ T cells (P=0.012), suggesting that CNIH1 plays a pivotal role in modulating immune infiltration in cervical cancer. To further explore the tumor immune microenvironment, we stratified patients based on CNIH1 expression levels and examined the differences using the CIBERSORT algorithm to quantify 24 immune cell subtypes (Figure 7B). Our analysis revealed that the infiltration levels of B cells, T cells, cytotoxic cells, dendritic cells, T helper type 2 cells (Th2), regulatory T cells (Tregs), CD8⁺ T cell–associated dendritic cells, follicular helper T cells (Tfh), T helper type 1 cells (Th1), CD56⁺ natural killer (NK) cells, and T helper type 17 cells (Th17) were influenced by CNIH1 expression. Among these, B cells, T cells, cytotoxic cells, dendritic cells, Th2 cells, and Tregs exhibited pronounced expression differences between the high and low CNIH1 expression groups (P<0.001). Moderate expression differences were observed in CD8⁺ T cell–associated dendritic cells, Tfh cells, and Th1 cells (P<0.01). Expression differences in NK CD56⁺ cells and Th17 cells were comparatively less marked (P<0.05). Finally, we assessed the correlations among all 24 immune cell subtypes. The interrelationships among tumor-infiltrating immune cell subsets ranged from weak to moderate, as depicted in Figure 7C.

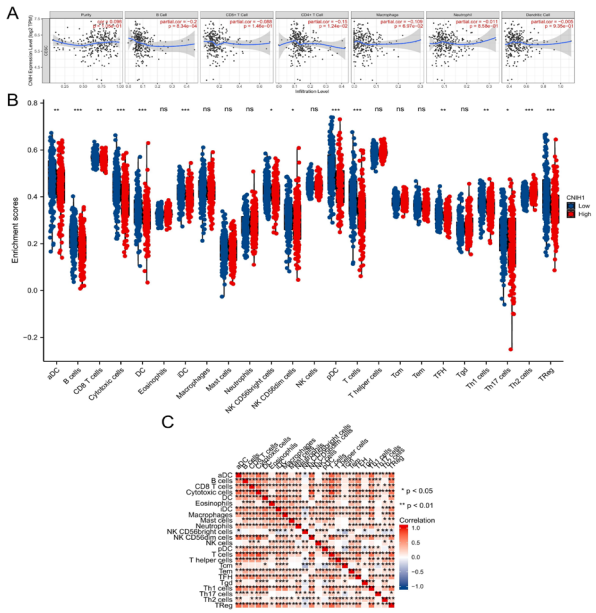


Figure 7: Immune infiltration analysis related to CNIH1 expression in cervical cancer. **(A)** Correlation between CNIH1 expression and immune infiltration levels. **(B)** Differential abundance of 24 immune cell subtypes between high and low CNIH1 expression groups. **(C)** Intercellular correlation among the 24 tumor-infiltrating immune cell subtypes.

Discussion

Cervical cancer ranks as the fourth most commonly diagnosed malignancy and the fourth leading cause of cancer-related mortality among women [13]. Despite significant advances in prevention, screening, and treatment strategies, the overall outcomes for cervical cancer have not markedly improved [14,15]. Particularly, patients with metastatic or recurrent cervical cancer face a poor prognosis, with a 5-year Overall Survival (OS) rate of only 17% [16]. Consequently, identifying reliable biomarkers for the prediction and prognosis of cervical cancer is of great clinical importance. In this study, we explored the pan-cancer expression profile of CNIH1 and its association with clinical outcomes. Our results revealed that CNIH1 expression varies across different cancer types and significantly impacts patient prognosis. Notably, CNIH1 expression was markedly different between tumor and normal tissues in most cancer types, except for adrenocortical carcinoma, bladder urothelial carcinoma, cholangiocarcinoma, chromophobe renal cell carcinoma, papillary renal cell carcinoma, pheochromocytoma and paraganglioma, endometrial carcinoma, and uterine sarcoma, where expression differences were not significant. These findings suggest that CNIH1 may exert distinct functions depending on the cancer type. Both Cox regression and Kaplan-Meier analyses indicated that high CNIH1 expression is significantly correlated with poorer OS in bladder urothelial carcinoma, cervical squamous cell carcinoma and adenocarcinoma, clear cell renal cell carcinoma, hepatocellular carcinoma, and lung adenocarcinoma. Functionally, CNIH1 is involved in the selective transport and maturation of TGF-α family proteins. Currently, there is limited literature on the relationship between CNIH1 and cancer. However, it is noteworthy that Castro et al. [17] identified CNIH1 localization to the cis-Golgi apparatus in HeLa cells using immunofluorescence and electron microscopy. CNIH1 co-localized with calnexin and GM130, markers of the Golgi apparatus, and partially with SEC23, a component of the COPII vesicle coat located at ER exit sites. Additionally, CNIH1 was co-immunoprecipitated with GM130 and GRASP55, which interacts with TGF-α, both of which reside in the Golgi apparatus. These findings suggest that CNIH1 functions as a recycling protein between the endoplasmic reticulum and the Golgi apparatus. While previous studies have demonstrated the relationship between CNIH1 and HeLa cells, our findings further confirm its elevated expression in HeLa cells. Nevertheless, the exact mechanisms by which CNIH1 contributes to cervical cancer progression remain to be elucidated. Consistent with our previous analyses, we observed a significant correlation between CNIH1 expression and cervical cancer prognosis. Cox regression analysis using external datasets identified CNIH1 as an independent prognostic factor, and Receiver Operating Characteristic (ROC) curve analysis confirmed its strong predictive value. Clinically, these findings may guide prognostic assessment and patient follow-up in cervical cancer. However, the precise mechanisms by which aberrant CNIH1 expression promotes cervical cancer remain unclear. Protein-Protein Interaction (PPI) network analysis indicated potential involvement of CNIH1 in ER-to-Golgi vesicle transport, COPII-coated vesicle budding, and COPII-mediated cargo trafficking-processes consistent with previous studies by Castro et al. Collectively, our results suggest that dysregulated CNIH1 expression may play an indispensable role in intracellular transport within cervical cancer cells. While this study provides new insights into the potential role of CNIH1 in cancer progression and prognosis, further investigation is warranted. As our research is based on bioinformatics analysis and publicly available datasets, certain limitations exist. First, variations in data quality and methodology may influence analytical outcomes. Second, our findings have not been experimentally validated in laboratory or clinical settings. Additional in vitro and in vivo studies are needed to corroborate CNIH1 expression patterns and functional relevance.

Conclusion

CNIH1 exhibits differential expression across various malignancies and is implicated in tumor progression, particularly in cervical squamous cell carcinoma and adenocarcinoma. Aberrant expression of CNIH1 is closely associated with immune cell infiltration in cervical cancer. Therefore, CNIH1 may serve as a promising diagnostic and prognostic biomarker for cervical cancer.

Declarations

Consent for publication: Not applicable.

Data sharing statement: The datasets generated and/or analyzed during the current study are available in the TCGA database (https://portal.gdc.cancer.gov/).

Declaration of competing interest: The authors declare that they have no competing interests.

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