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Original Article

A pan-cancer analysis of HAVCR1 with a focus on diagnostic, prognostic and immunological roles in human cancers

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Abstract: Objectives: Cancer is one of the most prominent causes of death world wide. Identification of novel cancer biomarkers woud help with cancer diagnosis and possible treatment. Methods: In this study, we comprehensively studied the diagnostic, prognostic, and therapeutic values of the hepatitis A virus cellular receptor 1 (HAVCR1) gene across multiple cancers from a pan-cancer point of view via a detailed *in silico* approach. Results: HAVCR1 expression was up-regulated in a variety of malignancies. The up-regulated HAVCR1 was closely related to the poor prognosis in patients with esophageal carcinoma (ESCA), lung adenocarcinoma (LUAD), and stomach adenocarcinoma (STAD). Moreover, DAVID analysis showed that HAVCR1, along with different other associated genes, was involved in numerous cancer-associated signaling pathways across ESCA, STAD, and LUAD. Furthermore, in these cancers, HAVCR1 was also found closely associated with some other parameters such as promoter methylation, tumor purity, level of CD8+ T immune cells, genomic alterations, and chemotherapeutic drugs. Conclusion: HAVCR1 was overexpressed in multiple tumors. However, the up-regulated HAVCR1 is a valuable diagnostic and prognostic biomarker as well as a therapeutic target in only ESCA, STAD, and LUAD patients.

Keywords: HAVCR1, pan-cancer, therapeutic, biomarker

Introduction

Cancer is still the most challenging disease that threaten human's life and living condition [1]. In 2020, a total of 19.3 million new cancer cases were registered worldwide [2]. Due to the recent increase in cancer cases around the globe, it is urgently required to get a comprehensive understanding of the molecular mechanisms underlying this disease. Such understanding will help in devising novel and accurate treatment options for cancer patients.

So far, various advanced technologies have been introduced and utilized worldwide to devise new treatment strategies and uncover novel molecular biomarkers for the diagnosis and prognosis of cancer [3]. In this regard, numerous bioinformatics-based methods have recently been used in the field of molecular biology for analyzing and explaining biological data in more detail. These methods can recognize biologically important molecular interactions and also help to obtain the associated signaling pathways relating to cancer [4].

In the current research, our focus is the hepatitis A virus cellular receptor 1 (HAVCR1) gene, which has been linked to the development of human cancers [5], but the evidence is limited. However, the oncogenic role of HAVCR1 in distinct human cancers remains to be uncovered. Therefore, further research to explore key factors behind cancer pathogenesis is of great interest and significance for patients with cancer.

The HAVCR1 gene encodes for a type I transmembrane glycoprotein [6]. Previously, dysregulation of HAVCR1 was established as a potential diagnostic and prognostic molecular biomarker of hepatitis [7], and acute kidney injury [8]. *Vila et al.* were the first to demonstrate the oncogenic role of HAVCR1 in clear cell renal cell carcinoma [5]. In addition, the latest molecular evidence has also correlated HAVCR1 dysregulation with a few other cancers, including renal cell carcinoma [9], colon cancer [10], and ovarian clear cell carcinoma [11].

In this study, we aim to determine the potential participation of HAVCR1 in multiple human cancers in a pan-cancer view point, which may be used as a novel therapeutic target and diagnostic, and prognostic biomarker to treat and prolong the survival of cancer patients. This research may provide a solid theoretical basis, directions, and a framework for expanding the mechanism-related research on HAVCR1.

Material and methods

UALCAN and TIMER analysis

UALCAN (http://ualcan.path.uab.edu/analysis.html) [12] and TIMER (https://cistrome.shinyapps.io/timer/) [13] are cancer-associated web portals, which are linked to the TCGA database. These web portals obtain multi-omics data from TCGA datasets to analyze the expression of the gene(s) of interest. In our study, we used both the web portal for the pan-cancer and clinical variable-based differential expression analysis of HAVCR1. *P*-value <0.05 = significant.

KM plotter

The Kaplan-Meier plotter (http://kmplot.com/analysis) tool makes online survival graphs based on the survival data taken from cancer patients [14]. In our study, the HAVCR1 expressions' effect on the overall survival (OS) of the distinct cancer patients was analyzed using this tool, and the cut-off value was determined by the median.

GENT2 database

GENT2 (http://gent2.appex.kr/) is a cancer transcriptomics data analysis web server [15]. We conducted GENT2 in this research for validating HAVCR1 expression. For statistics, this tool used the student t-test. *P*-value <0.05 = significant.

Human protein atlas (HPA)

HAVCR1 expression at the proteomic level in different cancerous was analyzed through HPA (http://www.proteinatlas.org/) [16]. *P*-value <0.05 = significant.

MEXPRESS

MEXPRESS (https://mexpress.be/) was developed for identifying correlation between promoter methylation and expression levels [17]. We used this platform for computing associations among expression and methylation status of HAVCR1 across different cancers. *P*-value <0.05 = significant.

cBioportal database

cBioPortal database (available at: http:/cbioportal.org) in-house multiple cancer-related genomic datasets, that are collected from 91 individual studies. These datasets include data on copy number variations (CNVs), genetic mutations, microRNA, mRNA expression, and promoter methylation [18]. This database helped us in identifying HAVCR1-associated genetic diversities across different cancers.

PPI network construction, visualization, and gene enrichment

STRING (https://string-db.org) is an online database, that in-house the experimentally proven and theoretically predicted protein-protein interaction-related information. This database assists scientist in constructing the PPI of any gene(s) of interest [19]. In the current study, a PPI network of HAVCR1-associated genes was drawn using STRING and visualized with the help of Cytoscape software [20]. In addition, pathway enrichment of HAVCR1-related genes was done using the DAVID tool [21]. During the analysis, the critical error detection rate (EDR) value for KEGG terms was kept less than 0.05.

Tumor purity, CD8+ T immune cells, and HAVCR1 expression

TIMER (https://cistrome.shinyapps.io/timer/) is an internet platform, that was developed

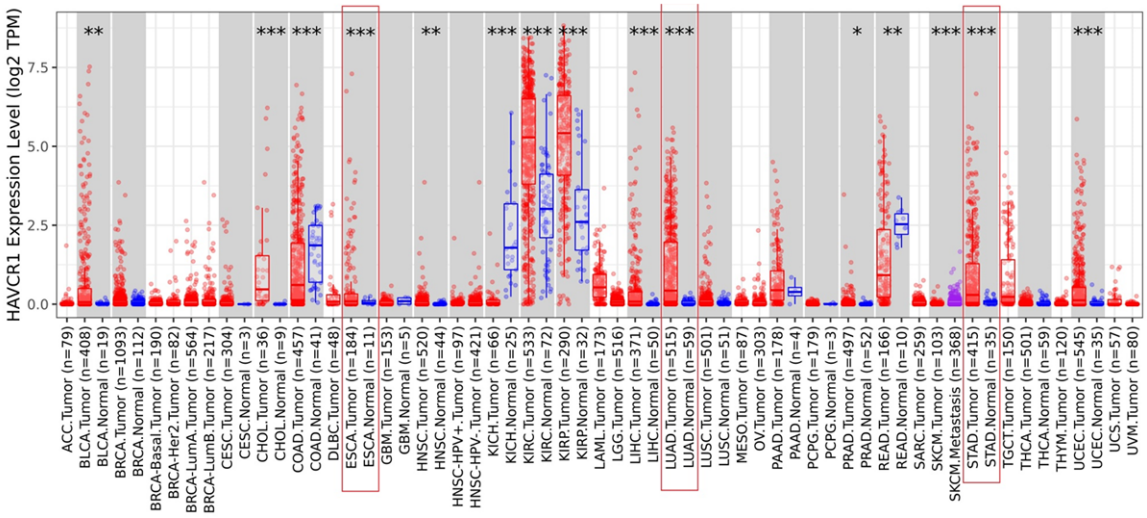

Figure 1. HAVCR1 expression profile in different types of human cancers through the TIMER database. *P*-value <0.05 = significant.

for the in-depth evaluation of associations between, tumor purity, different immune cells, and distinct cancers [13]. This platform applied a variety of algorithms to analyze immune cell's abundance from the view point of gene expression. In this research, using this database, we studied the correlations between tumor purity, CD8+ T immune cell infiltration, and HAVCR1 expression across different cancers. A *P*-value <0.05 was considered significant.

The effect of chemotherapeutic drugs on HAVCR1

Based on the Comparative Toxicogenomics Database (CTD) [22], we explored different chemotherapeutic drugs that are capable of affecting HAVCR1 expression at the mRNA level. For this purpose, HAVCR1 was searched across CTD, and relevant drugs were visualized as a gene-drug interaction network via Cytoscape software [20].

Results

The level of HAVCR1 expression in tumor and normal tissues

The level of HAVCR1 mRNA expression across twenty-four types of tumor tissues matched with normal tissues was evaluated using TCGA datasets in a pan-cancer view point using UALCAN (**Figure 1**). Results of the analysis demonstrated that with the exception of six types of the human tumors in which HAVCR1 was down-regulated, its mRNA expression was remarkably up-regulated in 18 different other types human tumor tissues relative to controls, including the tumor tissues of esophageal adenocarcinoma (ESCA), lung adenocarcinoma (LUAD), and stomach adenocarcinoma (STAD) (**Figure 1**).

Prognostic significance of HAVCR1

The relationship between HAVCR1 expression and the prognosis of cancer patients was evaluated using TCGA datasets via the KM plotter (**Figure 2**). The KM OS curves obtained showed that HAVCR1 higher expression is significantly correlated with the shorter OS in ESCA (HR=1.94, 95% CI: 0.99-3.81, P=0.049), LUAD (HR=1.52, 95% CI: 1.14-2.03, P=0.0044), and STAD (HR=1.75, 95% CI: 1.26-2.41, P=0.00064) patients (**Figure 2**). Results of this analysis have shown that HAVCR1 up-regulation is a significant risk factor for oncogensis and poor prognosis of ESCA, LUAD, and STAD patients with regard to OS.

HAVCR1 expression and pathological features

The data on HAVCR1 expression in different pathological features, i.e., cancer stage, gender, race, and nodal metastasis, was taken from TCGA datasets via UALCAN (**Figure 3**). Results of the analysis demonstrated that mRNA expression of HAVCR1 also exhibited a

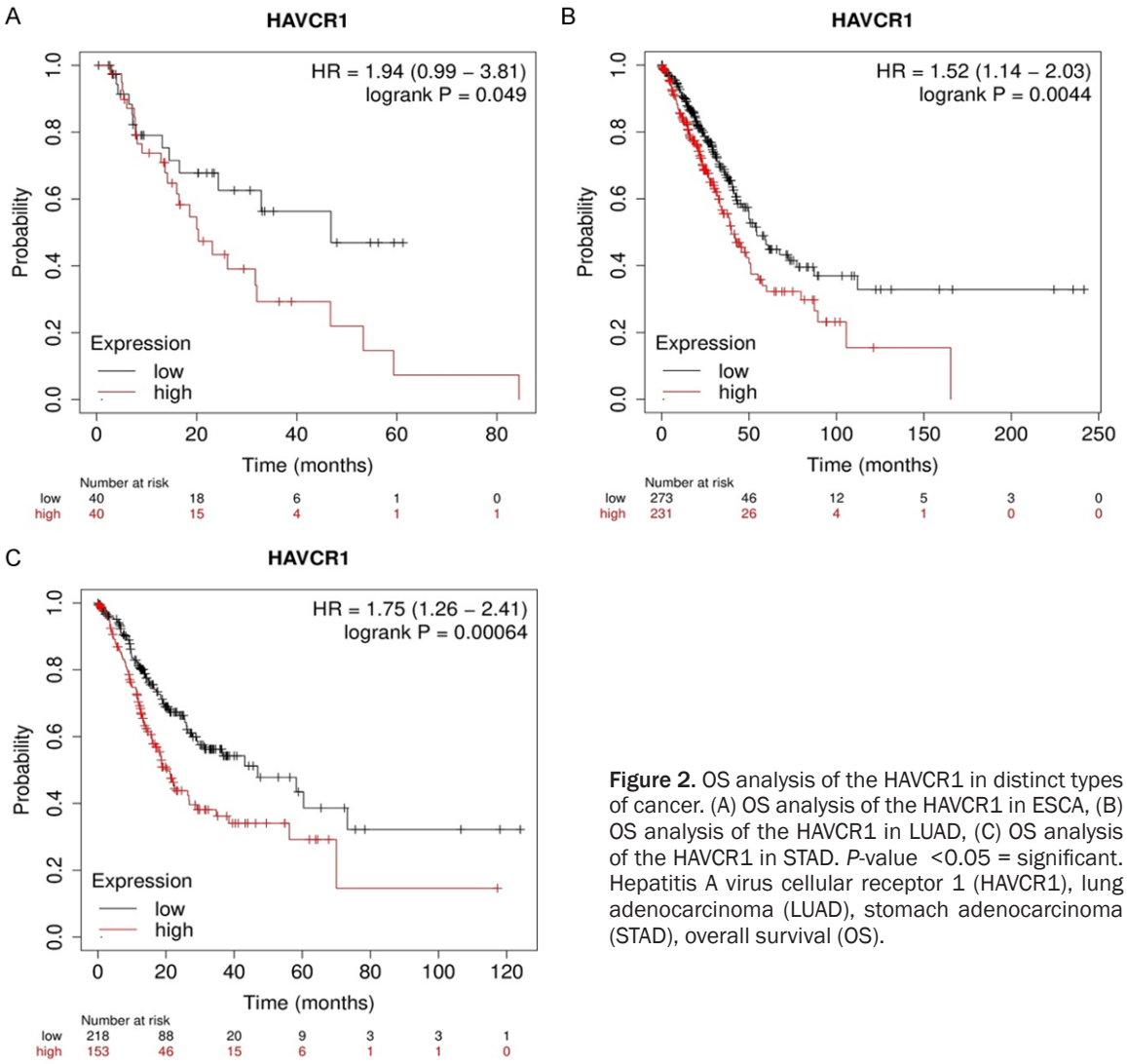

Figure 2. OS analysis of the HAVCR1 in distinct types of cancer. (A) OS analysis of the HAVCR1 in ESCA, (B) OS analysis of the HAVCR1 in LUAD, (C) OS analysis of the HAVCR1 in STAD. *P*-value <0.05 = significant. Hepatitis A virus cellular receptor 1 (HAVCR1), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD), overall survival (OS).

significantly higher level in terms of different pathological features (cancer stage, gender, race, and nodal metastasis) across ESCA, LUAD, and STAD patients as compared to normal controls (**Figure 3**). The pathological feature distribution of the analyzed ESCA, LUAD, and STAD cohorts has been given in **Tables 1**-**3**.

HAVR1 transcription expression validation analysis

We further confirmed the higher expression of HAVCR1 at the mRNA level by GENT2 analysis. In view of the analysis results, the expression of HAVCR1 mRNA across ESCA, LUAD, and STAD samples from new TCGA cohorts was also significantly higher as compared to the normal controls (**Figure 4A**). Therefore, our results further validated that HAVCR1 overexpression is a particular factor in ESCA, LUAD, and STAD pathogenesis.

HAVCR1 translation expression validation analysis

To document the expression profile of HAVCR1 at the protein level across esophageal, lung, and stomach cancers, we mined the HPA database to verify HAVCR1 expression level at the protein level. Results of the analysis revealed that HAVCR1 was overexpressed in esophageal (high staining), lung (medium staining), and stomach (medium staining) cancerous tissues relative to normal esophageal (medium staining), lung (low staining), and stomach (low staining) tissues (**Figure 4B**). In sum, based on HPA,

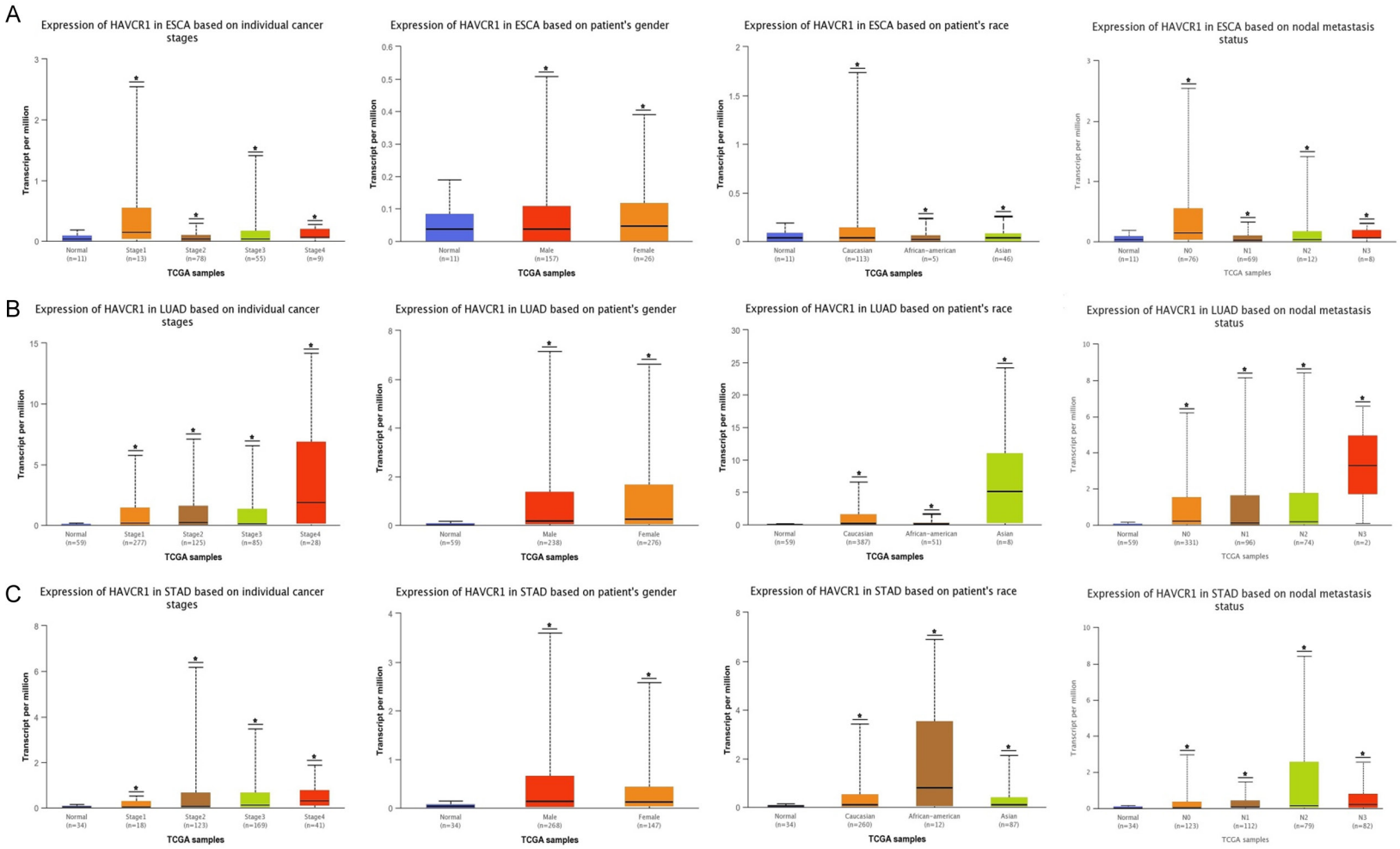

Figure 3. Expression analysis of HAVCR1 in various pathological parameters of ESCA, LUAD, and STAD. (A) HAVCR1 expression in various pathological parameters of ESCA, (B) HAVCR1 expression in various pathological parameters of LUAD, and (C) HAVCR1 expression in various pathological parameters of STAD. *P*-value <0.05 = significant.

Table 1. Pathological features of the ESCA cohort (via UALCAN)

Sr. No	Pathological features	Sample count	Total sample count of ESCA patients	Sample count of excluded ESCA patients due to missing clinical data	Total number of samples undertaken analysis
1	Cancer stage (S)		184	29	155
	S1	13			
	S2	78			
	S3	55			
	S4	09			
2	Gender			01	183
	Male	157			
	Female	26			
3	Geographical distribution			20	164
	Caucasian	113			
	African-American	05			
	Asian	46			
4	Nodal metastasis			19	165
	N0	76			
	N1	69			
	N2	12			
	N3	08			

S (Stage).

Table 2. Pathological features of the LUAD cohort (via UALCAN)

Sr. No	Pathological features	Sample count	Total sample count of LUAD patients	Sample count of excluded LUAD patients due to missing clinical data	Total number of samples undertaken analysis
1	Cancer stage		515	00	515
	S1	277			
	S2	125			
	S3	85			
	S4	28			
2	Gender			01	514
	Male	238			
	Female	276			
3	Geographical distribution			69	446
	Caucasian	387			
	African-American	51			
	Asian	08			
4	Nodal metastasis			12	502
	N0	331			
	N1	96			
	N2	74			
	N3	2			

S (Stage).

we further validated the overexpression of HAVCR1 at protein level in ESCA, LUAD, and STAD.

HAVCR1 promoter methylation status

We next try to elucidate the underlying mechanisms, that may be responsible for the higher expression of HAVCR1. In this aspect, we checked the HAVCR1 methylation level through the MEXPRESS database. In ESCA, LUAD, and STAD samples, significantly lower HAVCR1 promoter methylation levels were seen relative to controls (**Figure 5**). It is scientifically proven that an aberrant promoter methylation level, which is an epigenetic modification, can cause

Table 3. Pathological features of the STAD cohort (via UALCAN)

Sr. No	Pathological features	Sample count	Total sample count of STAD patients	Sample count of excluded LUAD patients due to missing clinical data	Total number of samples undertaken analysis
1	Cancer stage		415	64	351
	S1	18			
	S2	123			
	S3	169			
	S4	41			
2	Gender			08	407
	Male	268			
	Female	139			
3	Geographical distribution			56	359
	Caucasian	260			
	African-American	12			
	Asian	87			
4	Nodal metastasis			19	396
	N0	123			
	N1	112			
	N2	79			
	N3	82			

S (Stage).

the overexpression or silencing of gene expression [23]. In our research, the observed hypomethylation of the HAVCR1 promoter region across ESCA, LUAD, and STAD samples may possibly explain the partial reason of the HAVCR1 overexpression.

Mutational landscape of HAVCR1

The mutational landscape of HAVCR1 was obtained via cBioPortal across TCGA, ESCA, STAD, and LUAD datasets. As shown in **Figure 6**, the HAVCR1 harbors genetic alterations (deep deletion and missense mutations) in only 1.1% cases of the ESCA, 1.3% cases of the LUAD, and 2% cases of the STAD out of the total analyzed cases (**Figure 6**). Moreover, among the observed genetic alterations, missense mutations were the most common genetic alterations in ESCA, LUAD, and STAD samples. In addition to this, we also observed that most frequently noted genetic mutation in HAVCR1. i.e., P250S in ESCA, T140I in LUAD, and G111R in STAD mainly lie outside the v-set domain, which is the functional domain of this protein (**Figure 6**). Taken together, it is speculated that the low percentages of the genetic alterations in ESCA, LUAD, and STAD samples highlight that these alterations have the least participation in the expression regulation of HAVCR1, and the v-set domain of the HAVCR1 gene is a highly conserved domain in these cancer patients with respect to the occurrence of mutations.

HAVCR1 protein interaction network

We looked into the STRING database for searching a network of HAVCR1 interacting proteins. Results of the analysis revealed an enclosure of the protein network containing ten functional partners of HAVCR1 with the highest interactive confidence scores (**Figure 7A**). The KEGG terms (explored via DAVID) related to these genes were primarily involved in six diverse pathways including Bile secretion, Natural killer cell mediated cytotoxicity, Axon guidance, Measles, Endocytosis, and Cytokine-cytokine receptor interaction (**Figure 7B**; **Table 4**).

Tumor purity, CD8+ T immune level of infiltration and HAVCR1

To understand the immune microenvironment of ESCA, LUAD, and STAD, the associations between tumor purity, and the level of CD8+ T immune cell infiltration regarding HAVCR1 overexpression were explored via TIMER analysis. Results showed that tumor purity negatively

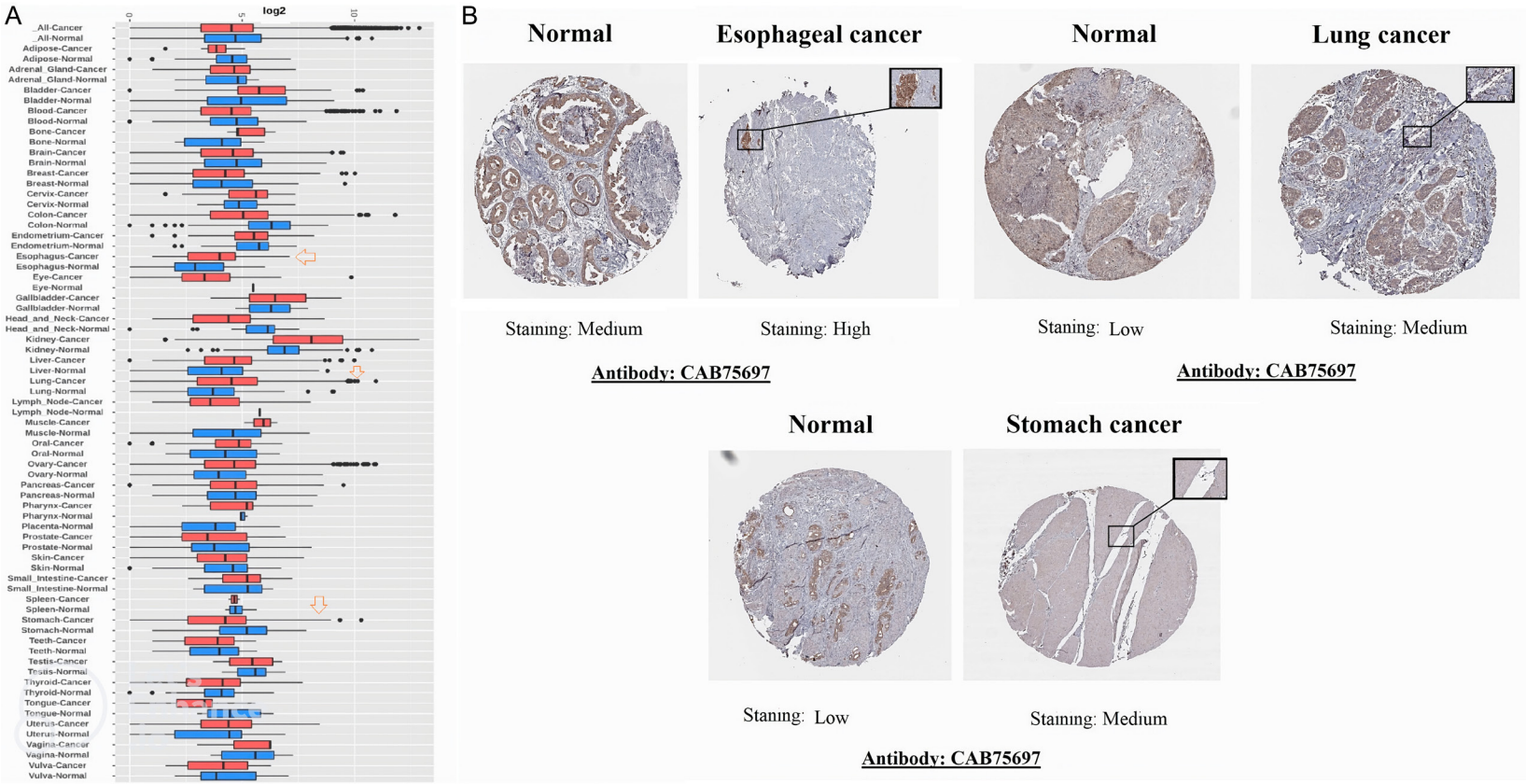

Figure 4. Transcription and translation level validation of HAVCR1 using independent ESCA, LUAD, and STAD cohorts via the GENT2 and HPA databases. (A) Transcription expression validation of HAVCR1 via GENT2, and (B) Translation level validation of HAVCR1 via HPA. *P*-value <0.05 = significant. Hepatitis A virus cellular receptor 1 (HAVCR1), esophageal carcinoma (ESCA), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD).

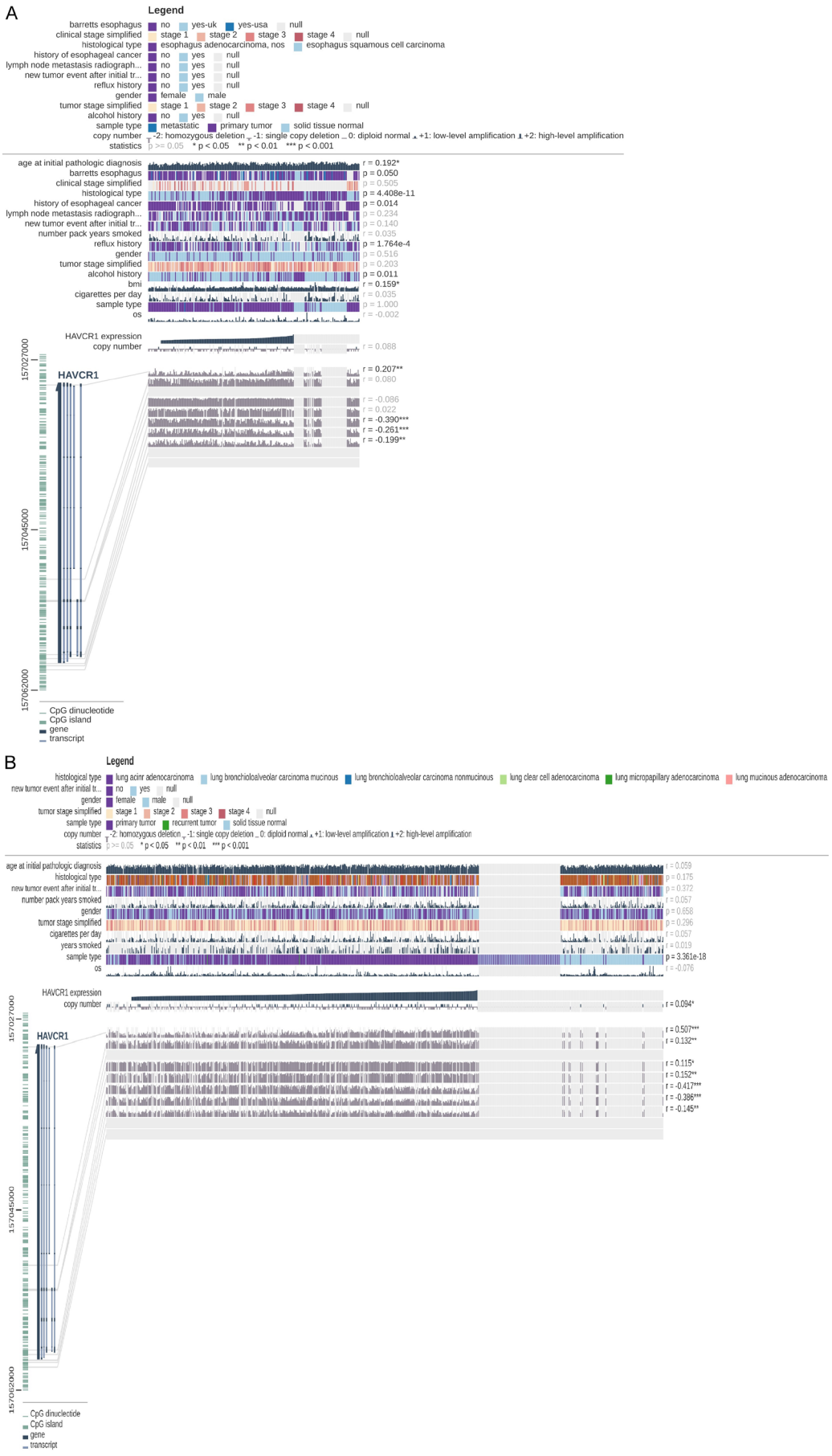
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Figure 5. A MRXPRESS-based correlation analysis between HAVCR1 expression and its promoter methylation in ESCA, LUAD, and STAD. (A) In ESCA, (B) In LUAD, and (C) In STAD. A negative sign indicates the negative correlation between HAVCR1 expression and its promoter methylation using a specific probe at a specific CpG island. Hepatitis A virus cellular receptor 1 (HAVCR1), esophageal carcinoma (ESCA), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD), stomach adenocarcinoma (STAD).

(*P*<0.05) correlated with HAVCR1 expression across LUAD (**Figure 8**), while positively (*P*<0.05) correlated across ESCA and STAD (**Figure 8**). Moreover, it was further observed that CD8+ T immune cell infiltration has a significant (*P*<0.05) positive correlation with HAVCR1 expression across ESCA, LUAD, and STAD (**Figure 8**).

The effect of chemotherapeutic drugs on HAVCR1 expression

The effect of different chemotherapeutic drugs on HAVCR1 expression was explored via the CTD database. In view of the information obtained from CTD, it was observed that the expression of HAVCR1 can be controlled through a variety of chemotherapeutic drugs. For example, ochratoxin and gentamicins can elevate the expression level of HAVCR1, while natamycin and metaformin can reduce HAVCR1 expression level (**Figure 9**).

Discussion

Genetic factors, such as accumulated genetic alterations/variations are known to contribute to the abnormal and unrestrained growth of the cells ultimately resulting in a malignant phenotype [24]. Despite the progress of treatment and prevention, cancer is still one of the major health concerns around the globe, especially in the low and middle-income countries [25]. The incidence and mortality of cancer have even risen sharply across developing countries, especially in young women [26]. So far, medical

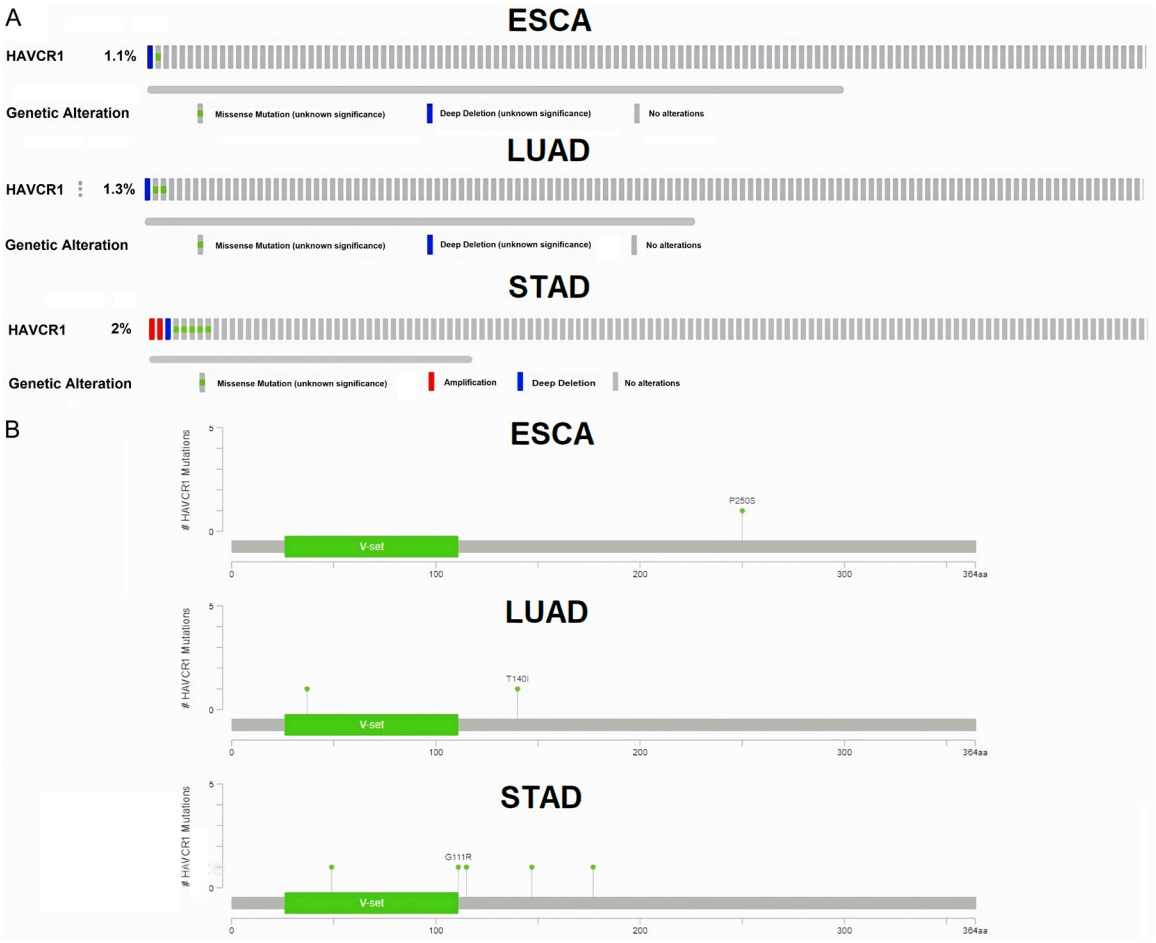

Figure 6. HAVCR1 genetic alterations and mutational hotspots status in ESCA, LUAD, and STAD. (A) Genetic alterations status of HAVCR1 in BRCA, KIRP, LIHC, and LUAD and (B) Mutational hotspots analysis of HAVCR1 in BRCA, KIRP, LIHC, and LUAD. Hepatitis A virus cellular receptor 1 (HAVCR1), esophageal carcinoma (ESCA), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD).

and scientific research approaches exploring diagnostic and prognostic biomarkers of cancer have not yet provided any reliable biomarker for cancer diagnostic and prognostic outcomes accurately. Recent studies have suggested the diagnostic and prognostic significance of HAVCR1 in human cancers, including RCC [27]. However, very little is reported in the medical literature regarding the diagnostic and prognostic values of HAVCR1 in other types of cancer. Therefore, in this study, we explored the role of the HAVCR1 gene systematically in various types of cancer in a pan-cancer point of view.

Hepatitis A virus cellular receptor 1 (HAVCR1) belongs to the T-cell immunoglobulin mucin (TIM) family of genes, which is involved in immune response regulation [28]. HAVCR1 has been confirmed to be mainly expressed in almost all human tissues. *H*owever, its functional role has yet to be completely elucidated [29]. Previous reports have highlighted the HAVCR1 overexpression in a limited number of cancers and associated it with cancer development and progression. For example, in clear cell renal carcinoma (RCC) cells, the up-regulation of HAVCR1 activates the IL-6/STAT-3/HIF-1A axis, which enhance the tumor growth through angiogenesis [9]. In addition, the elevated HAVCR1 expression in the urine specimen of the RCC patients was also highlighted as a possible novel diagnostic biomarker of RCC [27]. Similarly, HAVR-1 up-regulation may also be used as a diagnostic and prognostic biomarker of colorectal cancer for predicting early diagnosis and estimating disease-free survival [30].

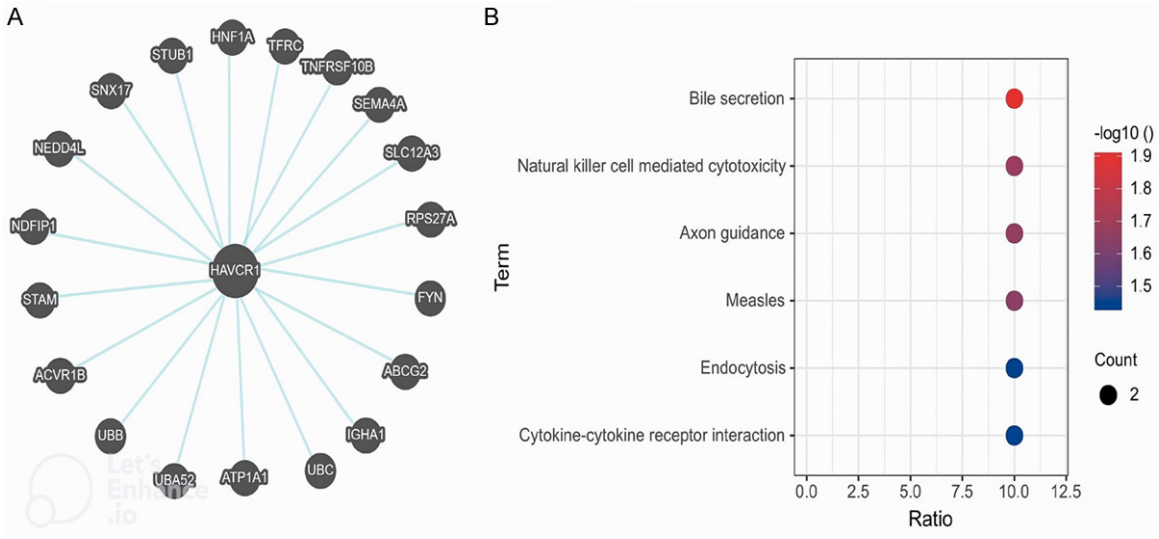

Figure 7. A PPI network and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis of the HAVCR1 enriched genes. (A) A PPI network of HAVCR1 enriched genes, (B) KEGG pathway analysis of the HAVCR1 enriched genes. Hepatitis A virus cellular receptor 1 (HAVCR1).

Table 4. Detail of Kyoto Encyclopedia of Genes and Genomes analysis of the HAVCR1 related genes

Pathway ID	Pathway Name	Gene count	*P*-value	Gene name
hsa04976	Bile secretion	2	0.01229	ATP1A1, ABCG2
hsa04650	Natural killer cell mediated cytotoxicity	2	0.02077	TNFRSF10B, FYN
hsa04360	Axon guidance	2	0.02153	SEMA4A, FYN
hsa05162	Measles	2	0.02243	TNFRSF10B, FYN
hsa04144	Endocytosis	2	0.03712	TFRC, STAM
hsa04060	Cytokine-cytokine receptor interaction	2	0.03737	TNFRSF10B, ACVR1B

Hepatitis A virus cellular receptor 1 (HAVCR1).

We revealed that HAVCR1 was up-regulated in the majority of human cancers, and its overexpression was significantly correlated with the decreased OS durations of the ESCA, LUAD, and STAD patients, which suggests the vital role of HAVCR1 in the tumorgenesis of these cancers. We further evaluated that HAVCR1 was also remarkably overexpressed in ESCA, LUAD, and STAD patients with different pathological features, including different cancer stages, gender, race, and nodal metastasis. Further analysis showed that HAVCR1 carried deep deletion, deep amplification, and missense mutation type genetic abnormalities in the little proportions (1.1%, 1.3%, and 2% samples) of the total analyzed TCGA, ESCA, LUAD, and STAD samples, respectively, showing no impact on the HAVCR1 expression. Additionally, it was also observed that the v-set domain of HAVCR1 remains the highly conserved domain in ESCA, LUAD, and STAD, and mutations in this gene could change amino acids at different positions outside the v-set domain.

Furthermore, via promoter methylation analysis, significant negative correlations were documented among the expression and promoter methylation levels of HAVCR1 across ESCA, LUAD, and STAD samples relative to controls. This situation of HAVCR1 promoter methylation in our study partially favored the role of promoter hypomethylation in up-regulating HAVCR1 expression across ESCA, LUAD, and STAD.

Till now, many studies have been conducted to analyze biomarkers in ESCA, LUAD, and STAD. For example, a study by *Yue et al.* predicted the dysregulation of Interleukin 8 (IL8) and C-X-C chemokine receptor type 7 (CXCR-7) in ESCA patients relative to normal controls, which was significantly associated with the ESCA patients' prognosis [31]. *Liu et al.* have predicted the roles of eight different lncRNAs, including

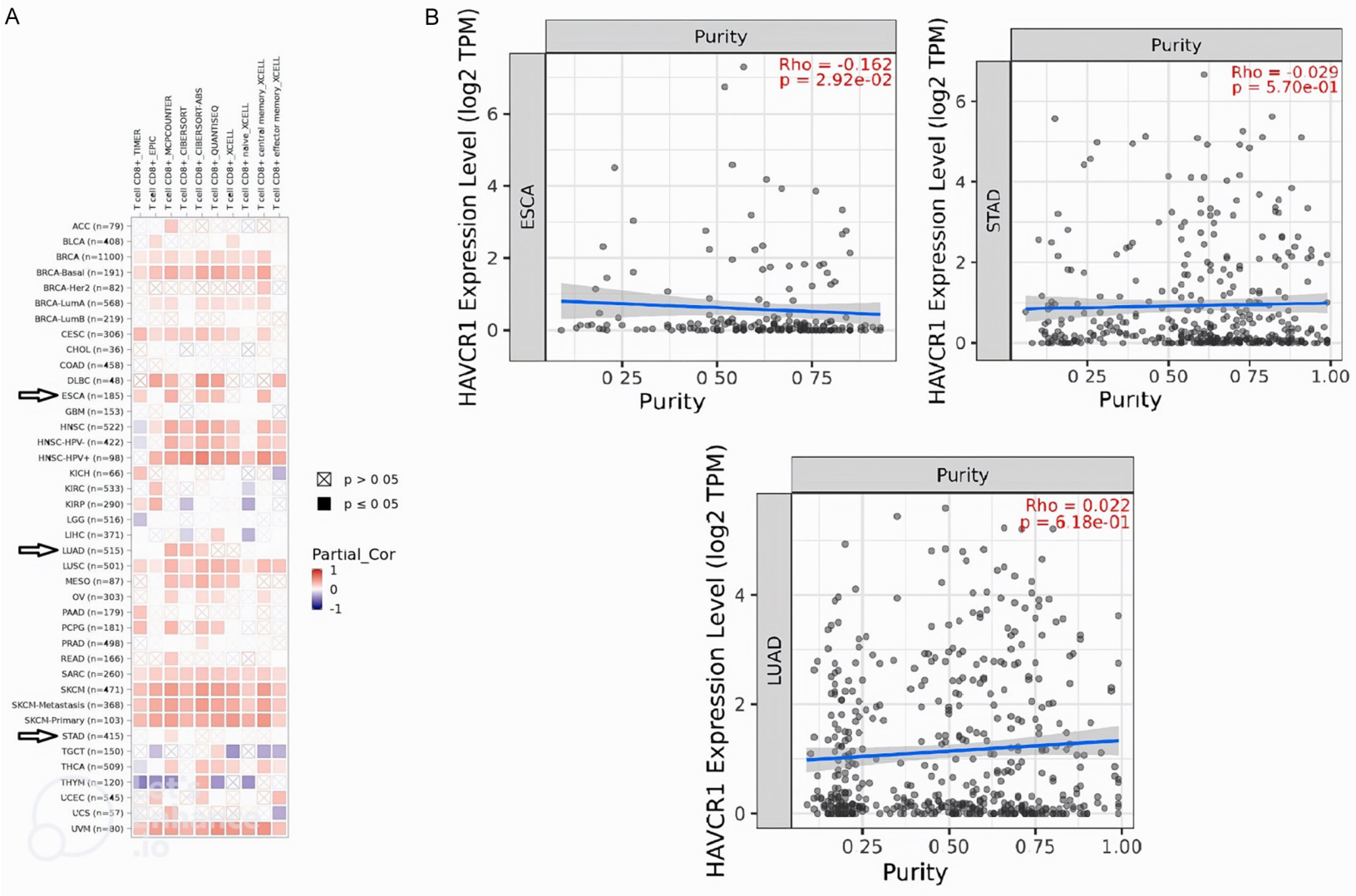

Figure 8. HAVCR1 correlation with tumor purity and CD8+ T immune cell infiltration in ESCA, LUAD, and STAD. (A) HAVCR1 correlation with CD8+ T immune cell infiltration in ESCA, LUAD, and STAD, (B) HAVCR1 correlation with tumor purity in ESCA, LUAD, and STAD. Hepatitis A virus cellular receptor 1 (HAVCR1), esophageal carcinoma (ESCA), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD).

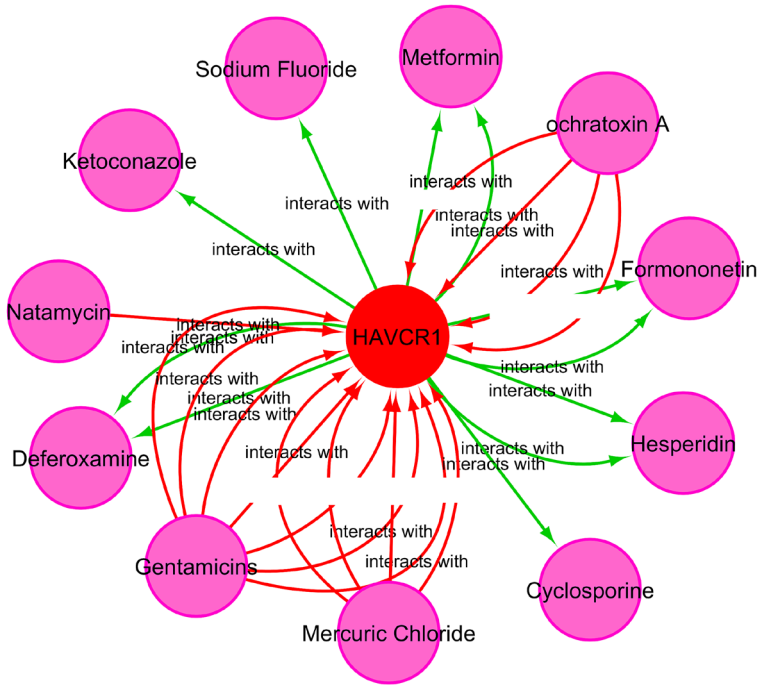

Figure 9. HAVCR1 interaction with different chemotherapeutic drugs. Red arrows: Those drugs which can potentially up-regulate the HAVCR1 expression; Green arrows: Those drugs which can potentially down-regulate the HAVCR1 expression. Count of arrows: Supported numbers of studies in the medical literature. Hepatitis A virus cellular receptor 1 (HAVCR1).

AC092803.2, WDFY3-AS2, AC016205.1, CASC8, UGDH-AS1, AC007128.1, RAP2C-AS1, and AC079949.2, in ESCA by constructing a network of lncRNA, mRNA, and miRNA [32]. Similarly, *Zeng et al.* conducted research on ESCA patients and predicted the role of five differentially expressed miRNAs (miRNA-93, miRNA-21, miRNA-196a-2, miRNA-4746, and miRNA-196a-1) in the development of ESCA [33]. A previous study by *Chen et al.* has highlighted the vital role of SBF2-AS1 (a lncRNA) in the tumorigenesis of LUAD [34]. In another study, the LINC00857 lncRNA was predicted to be associated with the tumorigenesis and poor overall survival in LUAD patients [35]. Furthermore, the HOXA11-AS lncRNA was found to be associated with cisplatin resistance in LUAD patients by dysregulating the miR-454-3p/Stat3 axis [36]. Another lncRNA, the HCP5, was also predicted to promotes metastasis of LUAD by dysregulating the miR-203/SNAI axis [37]. Currently, in STAD, a total of 9 differentially expressed genes, including H19, OPN, SPP1, CHI3L1, INHBA, KRT1, GRB7, STIP1, COL4A2, and PCOLCE [38-40], have been suggested as possible diagnostic and prognostic biomarkers.

To the best of our knowledge, none of the above-mentioned or any other biomarkers have been widely acknowledged so far in ESCA, LUAD, and STAD patients of different pathological features. However, in the present study, we revealed the significant up-regulation of HAVCR1 expression in ESCA, LUAD, and STAD patients with different pathological features (different cancer stages, genders, race, and nodal metastasis) relative to normal controls. In addition, we have also shown that HAVCR1 overexpression was significantly associated with the decreased OS of ESCA, LUAD, and STAD patients. Therefore, we suggested that HAVCR1 up-regulation is a potential reliable diagnostic and prognostic biomarker of ESCA, LUAD, and STAD.

Immunotherapy has revolutionized cancer therapy by providing alternative and additional treatment options [41]. Immunotherapy trigger the antitumor immune response against cancer cells by recognizing and binding to special immunosuppressive proteins expressing over tumor and T cells [42]. Moreover, in the tumor microenvironment, the CD8+ T immune cell play a key role in the growth of tumor cells [43]. In addition, the increased level of CD8+ T immune cells infiltration is found to be correlated with better prognosis and longer survival of the cancer patients [44]. In our study, tumor purity was negatively correlated with HAVCR1 expression across LUAD while positively correlated with HAVCR1 expression across ESCA and STAD. Moreover, CD8+ T immune cell infiltration was found to have significant positive correlations with HAVCR1 expression across ESCA, LUAD, and STAD. These important correlations may bring new ideas for the treatment of ESCA, LUAD, and STAD patients.

Moreover, the HAVCR1-associated genes' enrichment analysis revealed their involvement in three diverse signaling pathways, including Bile secretion, Natural killer cell mediated cytotoxicity, Axon guidance, Measles, Endocytosis,

and Cytokine-cytokine receptor interaction. Another important finding of this study is that we have found some potential drugs that can be a valuable weapon against fighting the ESCA, LUAD, and STAD by regulating HAVCR1 expression.

Conclusion

In this research, we comprehensively identified the diagnostic and prognostic roles of HAVCR1 across ESCA, LUAD, and STAD patients. Given that a significant proportion of the cancer samples have a higher expression of HAVCR1, we believe that further investigation on a large cohort of cancer patients is warranted for establishing the role of HAVCR1 in ESCA, LUAD, and STAD.

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Disclosure of conflict of interest

None.

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