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SLC2A14 In Hepatoblastoma Clinical Significance And Potential Roles In Ferroptosis

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KEYWORDS

Hepatoblastoma, SLC2A14, Ferroptosis, GLUT Family, Pediatric Oncology, Tumor Metabolism

ABSTRACT

The study aimed to investigate the role of SLC2A14 in hepatoblastoma (HB), a prevalent pediatric liver tumor.Through RNA-seq analysis of public and in-house datasets,we found SLC2A14 upregulated in HB and linked to ferroptosis.Our analysis revealed SLC2A14s potential as a diagnostic marker and its association with tumor metabolism,suggesting it may be a therapeutic target.The study concludes that SLC2A14s role in HB should be further explored for clinical applications.

1. Introduction

Hepatoblastoma (HB) is the most common liver malignant tumor in children, accounting for 80% of liver malignancies together with hepatocellular carcinoma in children [1]. In the recent decades, the survival time and survival quality had been increased significantly thanks to the technological progress of surgery and new chemoradiotherapy [2]. However, an effective treatment must be based on effective diagnosis. The early detection of HB also mainly depends on the expression level of alpha fetoprotein (AFP) except imaging examination [3]. Nevertheless, the expression of AFP often increases physiologically in a period of time after birth, which decreased the accuracy of AFP in detecting HB [4]. Therefore, we hoped to find a new target and applied it to diagnosis and treatment of HB.

Solute carrier family 2 member 14 (SLC2A14, also known as GLUT14) is a member of glucose transporter (GLUT) family, located on 12p13.31 and was first reported to be related to hexose transport [5]. In the previous study, researchers had reported the clinical significance of SLC2A14 in a variety of malignant tumors. Chai et al. reported expression of SLC2A14 was upregulated in patients with thyroid papillary carcinoma, and had a significant positive correlation with the mortality [6]. Through analyzing the expression levels of GLUT family members, Januchowski et al. thought downregulated SLC2A14 was related to chemoresistance of ovarian cancer cells [7]. In a research managed by Valli et al., the researchers pointed out upregulated SLC2A14 was able to promote ingestion of glucose in hypoxic conditions, so then regulating the metabolic process of tumor cells, which could provide a new target to targeted therapy

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[8]. Sharpe et al. indicated that glioblastoma cells could metabolize galactose by upregulated expression of SLC2A14 and other key enzymes, and replaced low concentration glucose as a new energy source [9]. Through years of researches in various cancers, the researchers had further understood the mechanisms of SLC2A14 in glucose metabolism of tumor cells. Interestingly, some researchers had put forward new ideas. Li et al. reported overexpressed SLC2A14 and its family members would influence the activity of GPX4, and reduced Malt-PEG-Abz@RSL3 Into tumor cells, then induced iron accumulated in tumor cells and ferroptosis [10].

As a newly discovered process of apoptosis in recent years, ferroptosis was increasingly reported in cancer. Lee et al. found upregulated ELOVL5 and FADS1 could reduce the resistance of gastric cancer cells to iron accumulation, which promoted ferroptosis occurred [11]. Liang et al. also reported that ruscogenin was able to increased the concentration of ferrous ions in pancreatic cancer cells and caused excessive iron accumulation and ferroptosi [12]. To date, researchers have invested a lot of energy in exploring the application of ferroptosis as a result of recent studies had shown that the effect of inducing ferroptosis in tumor cells that have become resistant to traditional therapy is superior [13]. Wang et al. thought the occurrence of ferroptosis might be related to anti tumor immunity mediated by CD8+ T cells, it was conducive to the application of ferroptosis in the treatment of malignant tumors by blocking checkpoint of this pathway [14]. Lee et al. found ferroptosis induced by AMPK had a high correlation with acetyl CoA carboxylase phosphorylation and polyunsaturated fatty acid biosynthesis, which indicated that there is a coupling between ferroptosis and energy emergency signal mediated by AMPK [15]. Unfortunately, how ferroptosis influences HB had never been reported, rhe relationship between ferroptosis and SLC2A14 in HB is unknown.

Therefore, we herein first used RNA-seq and mRNA-seq to explore the expression level and clinical significance of SLC2A14 in HB, and we also predicted the potential signal pathway of differentially expressed SLC2A14 regulating HB. Moreover, the presented study discussed the relationship between SLC2A14 and ferroptosis in HB.

2. Method

2.1. Expression Level and Discrimination Potential of SLC2A14 in HB

In the present study, the authors first searching datasets from public databases including Gene Expression Omnibus (GEO), Sequence Read Archive (SRA) and ArrayExpress with “Hepatoblastoma” as keyword. The included series should meet the following conditions: (1) The series must be containing mRNA-seq or RNA-seq data; (2) The data should contain normal and HB tissues or body fluid groups; (3) Presence of SLC2A14 expression data. Finally, a total of 311 samples from 7 series were included. Then, we performed $\log_2(x+1)$ conversion for above data in order to make the results more objective. Moreover, 3 pairs of samples from the First Affiliated Hospital of Guangxi Medical University was also included for analyzing.

Next, we estimated standard mean difference (SMD) of 7 studies and in-house data with Stata 14.0. The studies would be considered to be heterogeneous and applied a random-effect model if $P < 0.05$ or $I2 > 50\%$, otherwise a fixed-effects model would be adopted. Moreover, diagnostic test was applied to assess the discrimination potential of SLC2A14 in HB. IBM SPSS Statistics v23.0 and Graphpad Prism 8.0 were preformed to plot Receiver operating characteristic (ROC) curves. Additionally, in order to objectively evaluate the potential of SLC2A14 in the diagnosis of HB, a summary receiver operating characteristic (sROC) was plotted. The area under the curve (AUC) of sROC represents the diagnostic value of SLC2A14. In order to explore the relationship between SLC2A14 and patients with difference clinical parameters, we collected and analyzed the expression levels of SLC2A14 in patients with difference clinical parameters.

2.2. The Identified of SLC2A14 DCEGs

2.2.1. Identification of SLC2A14 Co-Expressed Genes in HB

Co-expressed genes (CEGs) means genes had similar expressed tendency with SLC2A14, aiming to find out those genes had close relationships with SLC2A14 and probably influence SLC2A14 in HB. Genes expression data from the above studies was extracted and evaluated Pearson’s coefficient between SLC2A14 and other genes. Those genes were considered as CEGs when $|r| > 0.3$ and $P < 0.05$, and

CEGs of SLC2A14 would be chosen for subsequent research if they appeared more than 5 times in 8 series.

2.2.2. Identification of SLC2A14 Differential Expressed Genes in HB

We estimated SMD of all genes from the above series. If lower 95%CI > 0 and SMD > 0, the gene would be considered to upregulate in HB. In the same light, If higher 95%CI < 0 and SMD < 0, the gene would be considered to downregulate in HB. Genes would be chosen as differential expressed genes (DEGs) for follow-up research if they appeared more than 5 times in 8 series.

The screened CEGs and DEGs of were intersected and identified as SLC2A14 DCEGs.

2.3. Functional Enrichment Analysis of SLC2A14 DCEGs

In order to further explore the mechanisms of overexpressed SLC2A14 regulated development of HB, the screened upregulated and downregulated DCEGs were entered into Database for Annotation, Visualization, and Integrated Discovery (DAVID) v6.8. separately. Gene ontology (GO) analysis was chosen to explore their potential pathways. Then, Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed to explore the potential signaling pathways of SLC2A14 DCEGs. When $P < 0.05$, the GO terms and KEGG signaling pathways were identified. In addition, we constructed PPI networks with Search Tool for the Retrieval of Interacting Genes (STRING), and screened hubgenes of SLC2A14 by applying Cytoscape v3.8.2. Moreover, Bgee is a database included gene expression data in various animal, was also used to explore expression levels of hubgenes.

2.4. The Exploring of Relationship Between SLC2A14 and Ferroptosis in HB

We found SLC2A14 was reported that had a correlation with ferroptosis, so we determined to explore the relationship between SLC2A14 and ferroptosis in HB. GSE104462 was a study containing with HepG2 cell line, researchers divided 6 samples into 2 groups and treated with DMSO and erastin. By comparing expression level of SLC2A14 in DMSO group with erastin group, we revealed the different expression of SLC2A14 in ferroptosis. Moreover, we herein extracted expression data of ferroptosis-related genes from the above series and evaluated Pearson's coefficient between SLC2A14 and ferroptosis-related genes. A heatmap was plotted to show the results.

2.5. Immune Infiltration of SLC2A14

To discuss the immune infiltration of SLC2A14 in varieties of adults' tumors, TISIDB was also performed to analyze the correlation between SLC2A14 and immune-related genes in various of tumors in present study.

Different from adult's tumors, a simple analytical tool for analyzing the immune infiltration of SLC2A14 in HB had never been seen. To explore the Immune infiltration of SLC2A14 in HB, we extracted immune-related genes from the above series and calculated Pearson's coefficient between immune-related genes and SLC2A14. A heatmap was plotted to show our results.

2.6. Clinical Significnce of SLC2A14 in Common Adults' and Children's Tumors

we were trying to reveal the expression levels of SLC2A14 in adults' and children's pan-cancer, so we download and analyzed data from public databases. The Cancer Genome Atlas (TCGA) was managed by National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI), is a database which collected more than 10 thousands patients with 39 types of cancers. Therapeutically Applicable Research To Generate Effective Treatments (TARGET) was an available database containing data of children's cancer, which included 7 types of cancer common in children. We downloaded mRNA-seq series from the above database and analyzed SLC2A14 expression levels.

3. Results

3.1. Expression Level and Discrimination Potential of SLC2A14 in HB

In the present study, we collected 7 public series from databases, combining with sequencing data from our hospital, we revealed the expression level and discrimination potential of SLC2A14 in HB for the first time. 8 pairs of scatter plots and ROC curves were showed on Fig.1. To observe the expression of SLC2A14 in all HB series comprehensively, a SMD was estimated (Fig.2 A). Due to $I2 = 86.1\%$ and $P < 0.001$, a random-effect model was chosen, and the

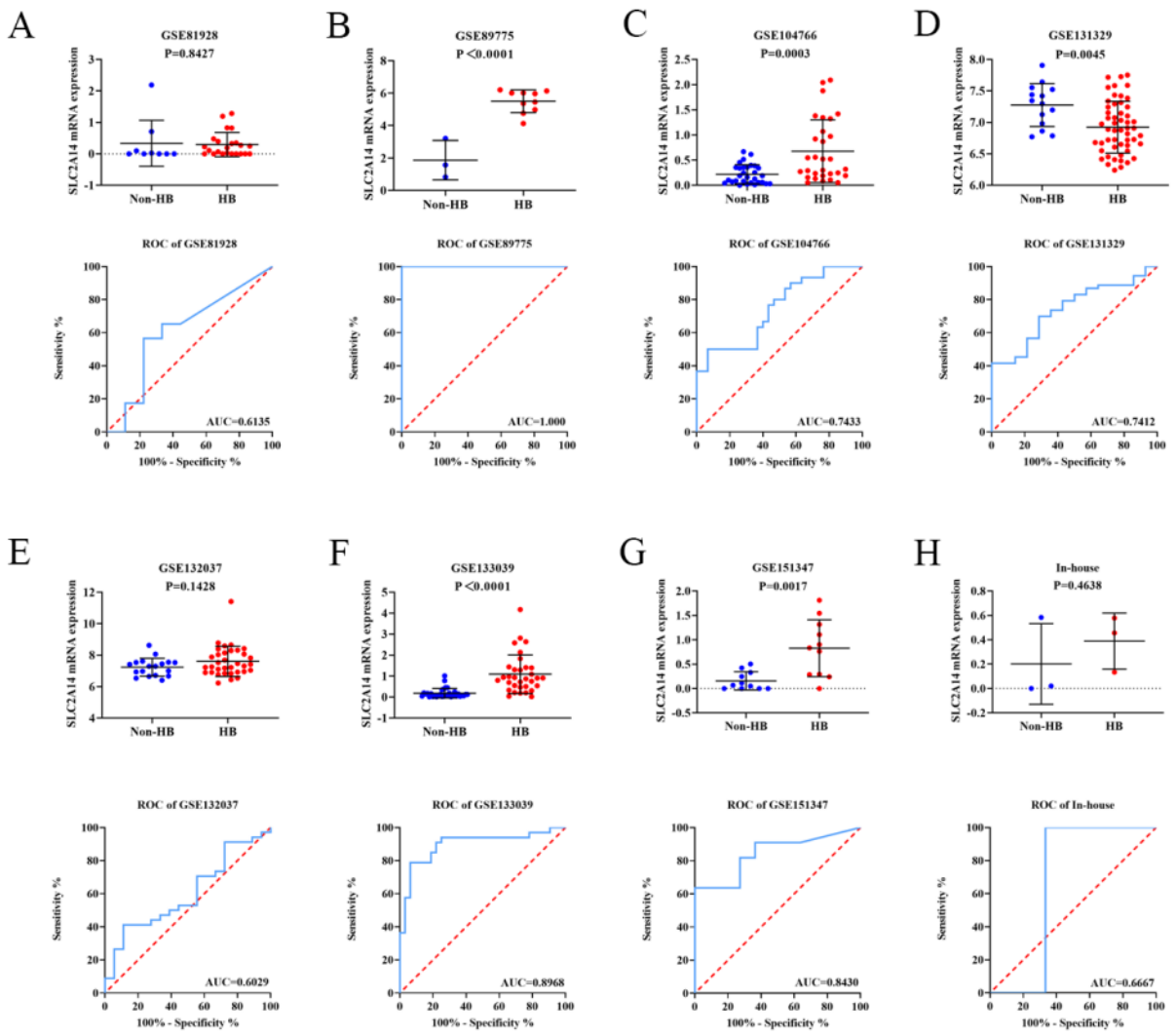

Figure 1

Illustrates the Receiver Operating Characteristic (ROC) curves for the expression levels of SLC2A14 in Hepatoblastoma (HB) samples compared to non-HB samples across various datasets.The scatter plot illustrates the differences in SLC2A14 mRNA expression levels between HB samples and non-HBnormal or control-samples.. With the x-axis showing the false positive rate and the y-axis showing the true positive rate. The Area Under the Curve (AUC) values are provided, indicating the diagnostic potential of SLC2A14.

result showed that SLC2A14 expression was upregulated in HB (SMD = 0.80, and 95%CI = 0.07 to 1.53). Heterogeneity analysis did not provide heterogeneity for us (Fig.2 B). And no publication bias was observed in funnel plots (Fig.2 C-E). Moreover, a sROC curve was plotted and showed the discrimination potential of SLC2A14 in HB intuitively. With a 0.91 (95%CI = 0.88 to 0.93) AUC value, we thought SLC2A14 had a high discrimination potential in HB (Fig.2 F). Additionally, our results got a high credibility because a high positive diagnostic likelihood ratio (DLR) and low negative DLR (Fig.2 G).

To make SLC2A14 more conducive to clinical diagnosis and treatment, we tried to explore whether SLC2A14 expressed differently in patients with different clinical parameters. We collected clinical information of patients and extracted expression data of SLC2A14. Then violin plots were showed on Fig.3.

3.2. Functional Enrichment Analysis of SLC2A14 DCEGs

Upregulated and downregulated DCEGs were entered into DAVID and predicted potential GO pathway, bubble plots were used to show our results (Fig.4 A,B). Then, upregulated and downregulated DCEGs were entered into STRING to construct PPI network and show the connectedness among them (Fig.4 A,B). In addition, all of the DCEGs were en-

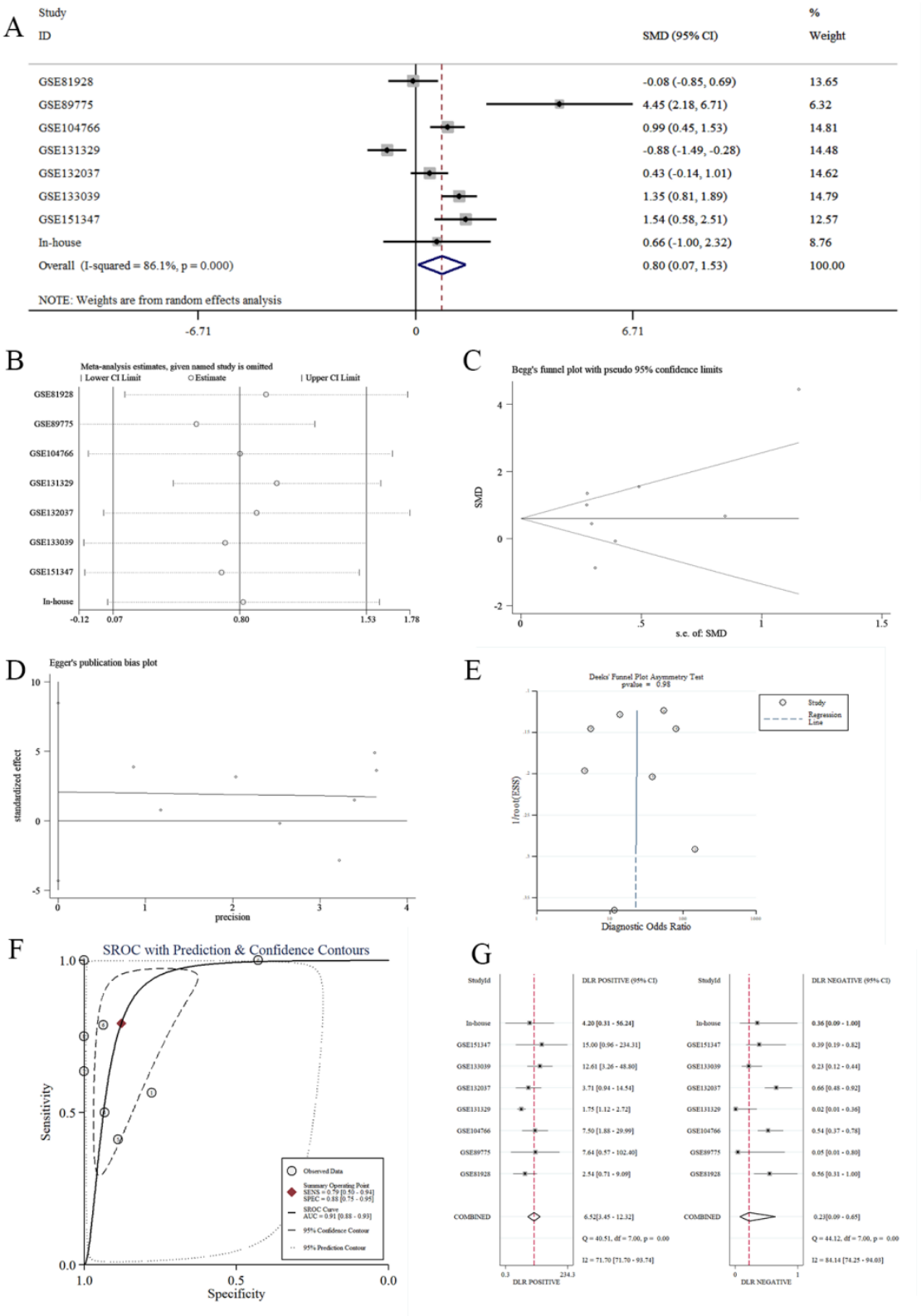

Figure 2

(A) The standardized mean differences (SMD) and their 95% confidence intervals for each study, showing the differences in SLC2A14 mRNA expression levels between HB and non-HB samples.(B) Meta-analysis estimates after omitting each study, showing the impact on the overall estimate.(C) A forest plot displaying the effect size estimates and confidence intervals for each study.(D)A forest plot displaying the effect size estimates and confidence intervals for each study.(E) Precision of studies and diagnostic odds ratios.(F) SROC curve with prediction and confidence contours.(G) The pooled effect size and its confidence interval, showing the overall diagnostic performance of SLC2A14 as a biomarker.

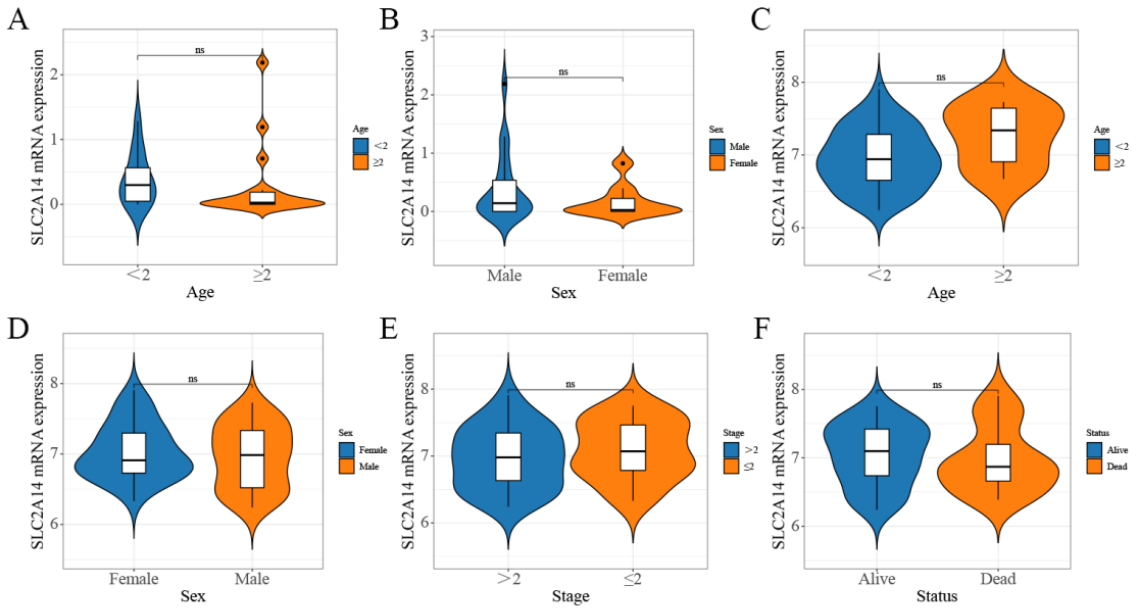

Figure 3

Illustrates the impact of SLC2A14 mRNA expression levels on patient characteristics such as gender,age,tumor staging,and survival status across various subgroups.

tered into DAVID and performed a KEGG enrichment analysis, PPI network also been structured (Fig.5 A,B).

After identified H2AFZ, C3, POLR2A, CDK7, CENPK, CCNA2, BUB1B, MAPRE1, CCNB1 and DSN1 as hubgenes of SLC2A14, we determined to further explore these potential hubgenes (Fig.5 C). We herein discussed expression level of hubgenes in liver, and the results indicated that the above hubgenes had high expression scores in liver (Fig.6 A,B). Then, as the most probably be target gene, the expression H2AFZ was considered had correlations with SLC2A14 (Fig.6 C-J).

3.3. The Relationship Between SLC2A14 and Ferroptosis in HB

In the previous study, SLC2A14 was reported had a correlation with ferroptosis, we wondered if SLC2A14 also regulated development of HB through regulating ferroptosis. First, we downloaded GSE104462, a study including 2 group treated with DMSO and erastin. After screened out DEGs from GSE104462, we surprised to find SLC2A14 was on the list, which indicated that SLC2A14 was downregulated after treated with ferroptosis inducer (Fig.7 A). Thus, we extracted expression data of SLC2A14 from GSE104462 and analyzed its expression level (Fig.7 B).

3.4. Immune Infiltration of SLC2A14 in HB

We herein wanted to further explore clinical significance of SLC2A14 in various types of cancer. Correlation analysis between SLC2A14 and immune cells in various of cancers also be performed. Through TISIDB, the results indicated SLC2A14 was related to a various kinds of immune-related cells in adults' cancers (Fig.8 B-E). However, data of children's cancers were different from adults' cancers, we need to extracted expression data of immune-related genes. The correlated heatmap was showed on Fig.2 B.

3.5. Clinical Significnce of SLC2A14 in Common Adults' and Children's Tumors

Based on TCGA database, the expression of SLC2A14 in common adults' tumors were extracted and assessed, the results show that SLC2A14 was differential expressed in multiple types of tumors. The scatter and box plot displayed the results intuitively (Fig.8 A). Showing only the expression levels of SLC2A14 in adults' tumors were still not convincing, so we collected and analyzed data from TARGET. The results were showed on Fig.9 A. Unfortunately, due to lacking of healthy samples, we were not able to show whether the expression of SLC2A14 in tumors is different from that in normal tissues.

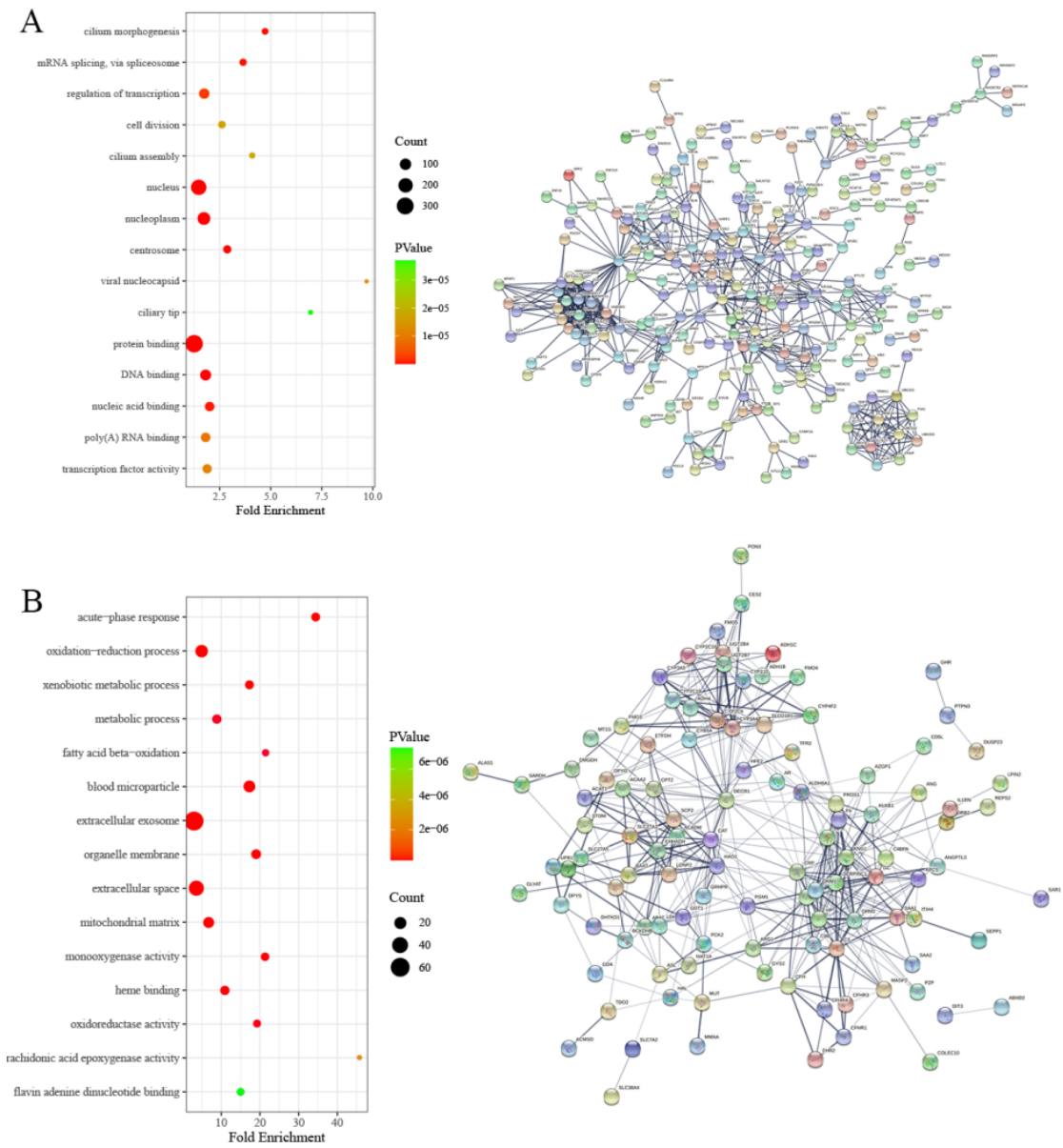

Figure 4

(A) Illustrates the biological processes and functions associated with SLC2A14, such as cilium morphogenesis, mRNA splicing, transcription regulation, and cell division, along with their statistical significance.(B) Depicts functions related to metabolic processes, including oxidation-reduction reactions, xenobiotic metabolism, and fatty acid beta-oxidation, along with their enrichment levels.

4. Discussion

The present study explored the clinical significance and potential molecular mechanisms of SLC2A14 in development of HB. Our results showed overexpressed SLC2A14 had a potential to be a signal of existed HB. We herein provided some highlights. We collected 7 series from public databases to show mRNA expression level of SLC2A14 in HB. Moreover, SLC2A14 expression levels of tissues from HB patients in our hospital were also included into SMD. Then, the relationship between SLC2A14 and immune-related genes was revealed. We also discussed the relationship between SLC2A14 and ferroptosis in HB. In our study, metabolic pathway was considered to play an important role in development of HB regulated by SLC2A14 DCEGs.

As mentioned earlier, SLC2A14 was originally reported to be associated with hexose transport [16]. Some study also found differential expressed SLC2A14 could influence glucose metabolism of tumor cells, including thyroid papillary carcinoma, ovarian cancer and glioblastoma [6,17,18]. To date, there are

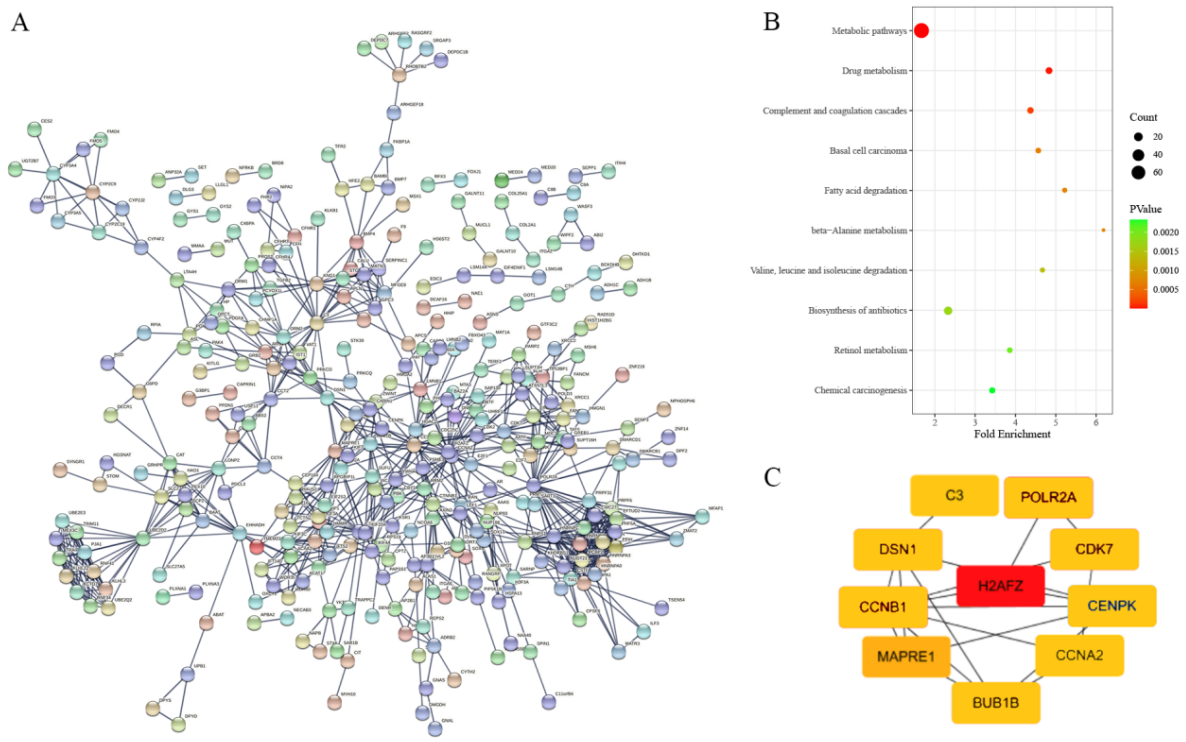

Figure 5

showcases the KEGG pathway enrichment analysis of SLC2A14 DCEGs. (A) Highlights the metabolic pathways associated with SLC2A14 DCEGs, showing the enrichment of these genes in metabolic processes.(B) Displays the enrichment of the complement and coagulation cascade pathways, which may be related to the functions of SLC2A14 DCEGs.(C) Shows other pathways related to SLC2A14 DCEGs, including their roles in various biological processes.

some researches on SLC2A14 in various diseases. In a study included 597 Alzheimer's disease (AD) patients and 605 healthy people, Wang et al. indicated that gene polymorphism of SLC2A14 was probably an important factor causing AD, and this factor was associated with clinical parameters such as ages and sexes [19]. Bitar et al. also reported differential expressed SLC2A14 might influence morbidity of AD [20]. Nag et al. identified the overlapping sites of SLC2A14 were able to regulate intraocular pressure, which could be a target to treat glaucoma, but the researchers thought SLC2A14 expression had no correlation with hypertension [21]. By observing 454 Turner syndrome patients, Prakash et al. thought the lacking of SLC2A14 influenced expression of cardiac development-related genes [22]. In the above study, we found some researches had reported the relationship between the function of SLC2A14 and clinical parameters. In the present study, we showed SLC2A14 expression was upregulated in HB (SMD=0.80, 95%CI=0.07, 1.53), and we indicated that SLC2A14 had a high discrimination potential between HB patients and healthy people (AUC=0.91, 95%CI=0.88, 0.93). Though all of the results showed the expression of SLC2A14 was not related to clinical parameters, these results were instrumental in clinical application of SLC2A14. Additionally, we thought the more accurate results should be obtained in a larger sample sizes.

In summary, after revealing the expression level and discrimination potential of SLC2A14 in HB, to explore the molecular mechanisms of SLC2A14 in regulating HB development, we obtained DCEGs of SLC2A14 by intersecting CEGs and DEGs. Through GO annotation and KEGG pathway enrichment analysis, we found SLC2A14 DCEGs significantly enriched in metabolic pathway, which indicated the correlations between the above genes and material metabolisms had potential research value. In the previous study, intracellular metabolism has been widely reported to be related to the development, metastasis and apoptosis of HB. Wang et al. thought downregulated SLC10A1 could improve viability of HB cells by promoting intracellular metabolism, when SLC10A1 expression was induced by drugs, cell cycle arrest

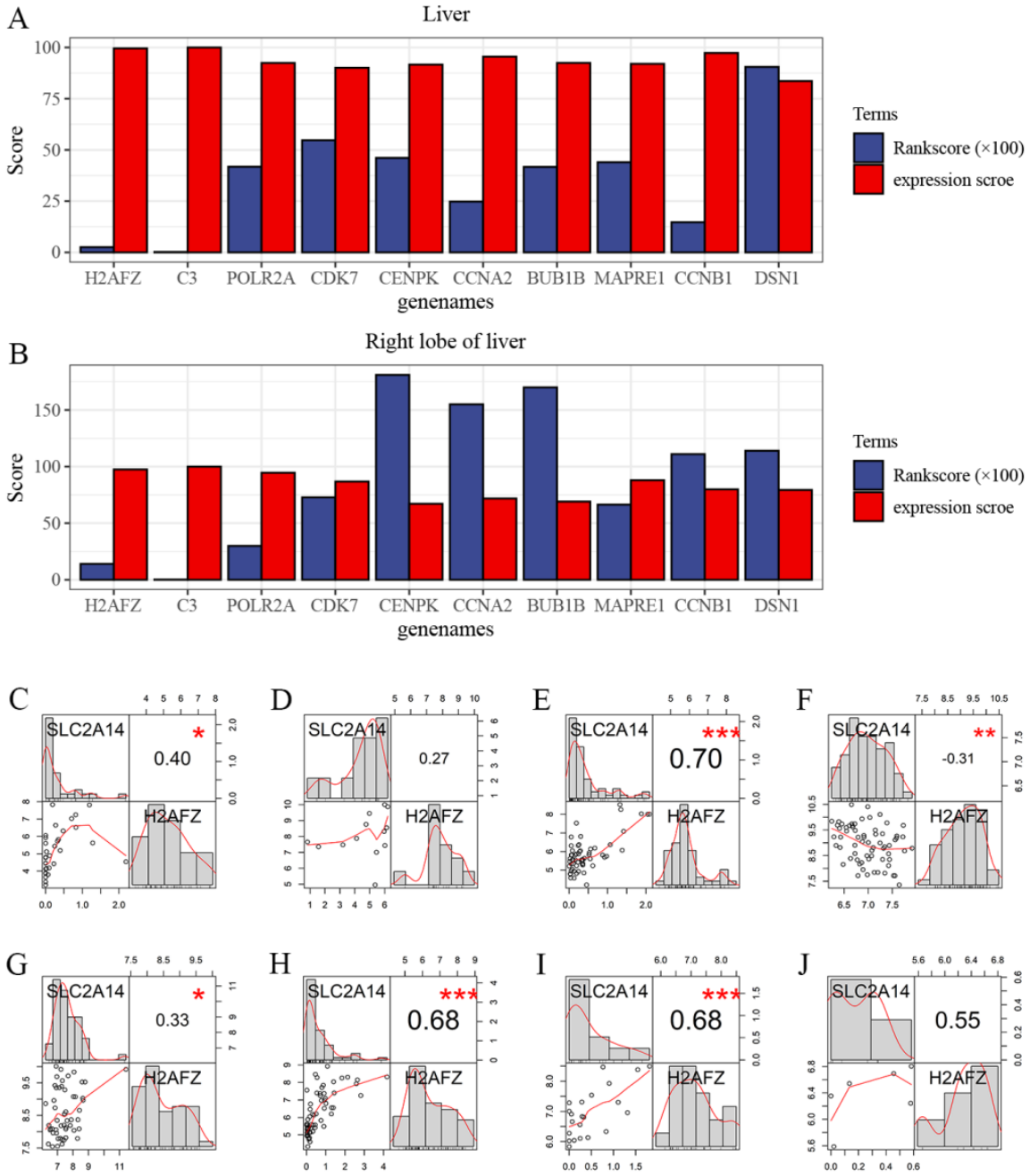

Figure 6

(A) Displays the expression scores and rankscores of specific genes in the liver, highlighting their expression levels within this tissue.(B) Focuses on the expression scores and rankscores of the same genes in the right lobe of the liver, providing region-specific gene expression information.

(C-J)Demonstrates the correlation between SLC2A14 and other genes in hepatoblastoma, with asterisks indicating statistical significance.

and apoptosis would occurred in HB cells [23]. Crippa et al. found HB cells were sensitive to silenced hexokinase-1 through researching glycolytic potential, this study indirectly indicated SLC2A14 hexose transport capacity might affect the glucose metabolism of HB, which coincided with our results [24]. Moreover, in a research managed by Wang et al. researchers found differential expressed Myc would influence metabolic reprogramming and promote growth of tumors [25]. Unfortunately, as for the relationship between SLC2A14 and metabolic pathway in HB, remains to be clarified by the followed research.

We analyzed the PPI network through Cytoscape v3.8.2 and found H2AFZ might be the hubgene of

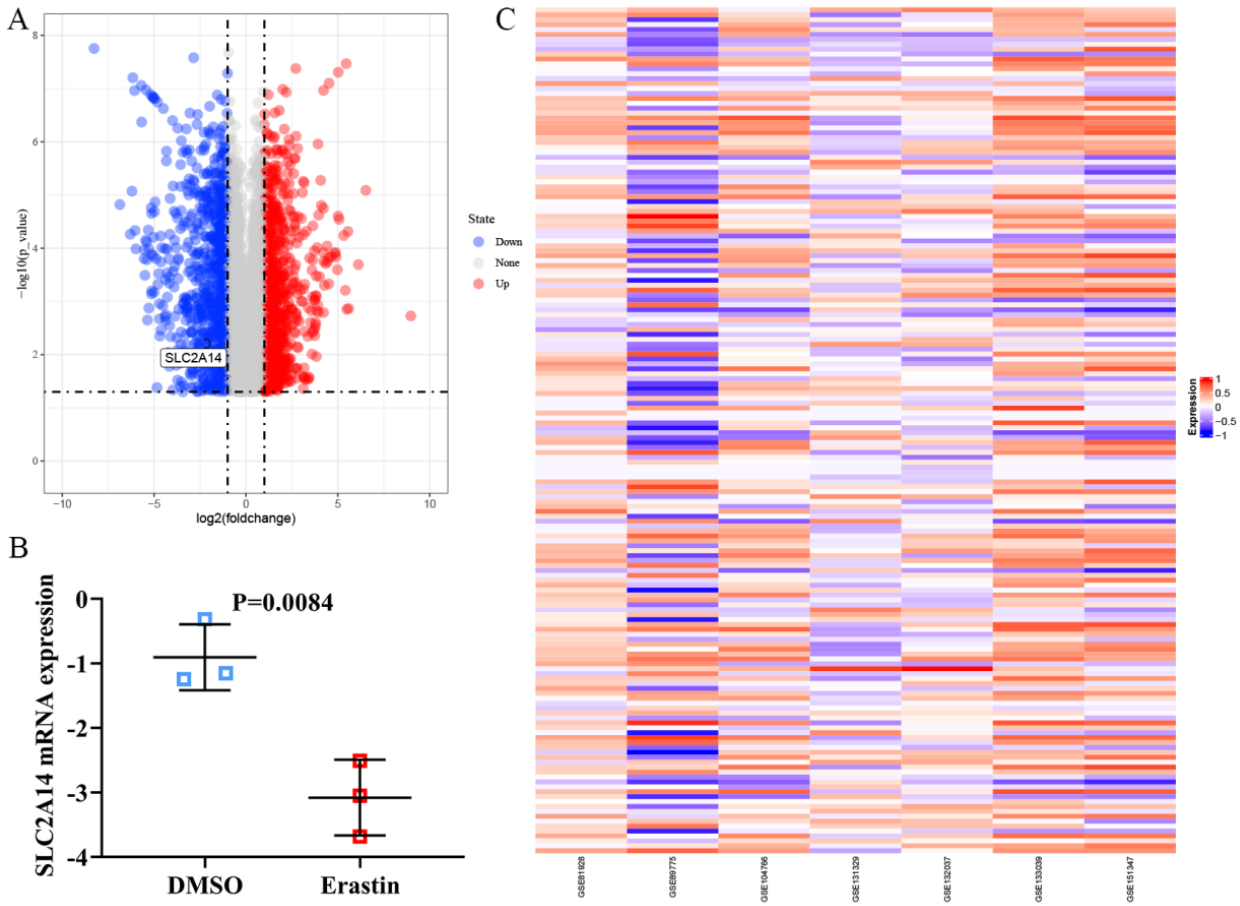

Figure 7

(A)Compares the SLC2A14 mRNA expression levels between samples treated with DMSO and erastin. (B)Presents log2(fold change) values for SLC2A14 across different datasets.(C)Depicts the regulation state of SLC2A14 based on -log10(p_value), indicating upregulation, no change, or downregulation.

SLC2A14 DCEGs. Though there is no researches about H2AFZ in HB, clinical significance of H2AFZ in various malignant tumors had been reported. Qi et al. reported H2AFZ was upregulated in breast tumor, and could be considered as individual adverse prognostic factor [26]. Tang et al. indicated H2AFZ was significantly upregulated in many series of hepatocellular carcinoma, overexpressed H2AFZ regulated the proliferation of hepatocellular carcinoma cells and was related to the poor prognosis of patients [27]. Baptista et al. also indicated nicotinamide would inhibited expression of H2AFZ in prostate cancer, and reduced interaction between sirtuin 1 and H2AFZ, which could also influence proliferation of tumor cells [28]. In the present research, we explore expression levels of H2AFZ and other potential hubgenes in normal liver tissues, and discussed the correlation between H2AFZ and SLC2A14. We indicated potential clinical significance of H2AFZ in HB.

Interestingly, in the process of searching literature, we found SLC2A14 was reported to affect iron metabolism in tumor cells and to regulate ferroptosis of tumor cells [29]. As one of the metabolic types, iron metabolism was also considered to be a part of our research. In a research of Lippmann et al., the researchers reported the effects of different reactive oxygen species modulators and ferroptosis inducers on human HB cells, they thought the activity of HB cells was significantly inhibited by combining use of ferroptosis inducers, the results indicated ferroptosis was expected to be used in the targeted therapy of HB [30]. Up to now, only seldom researches about ferroptosis in HB, but there are many researches reported function of ferroptosis in various of cancers. In many cancers, including gastric cancer, ovarian cancer and lung cancer, the occurrence of ferroptosis was considered to be associated with metabolism of reactive oxygen species and iron, and might be arranged by various of differential expressed mole-

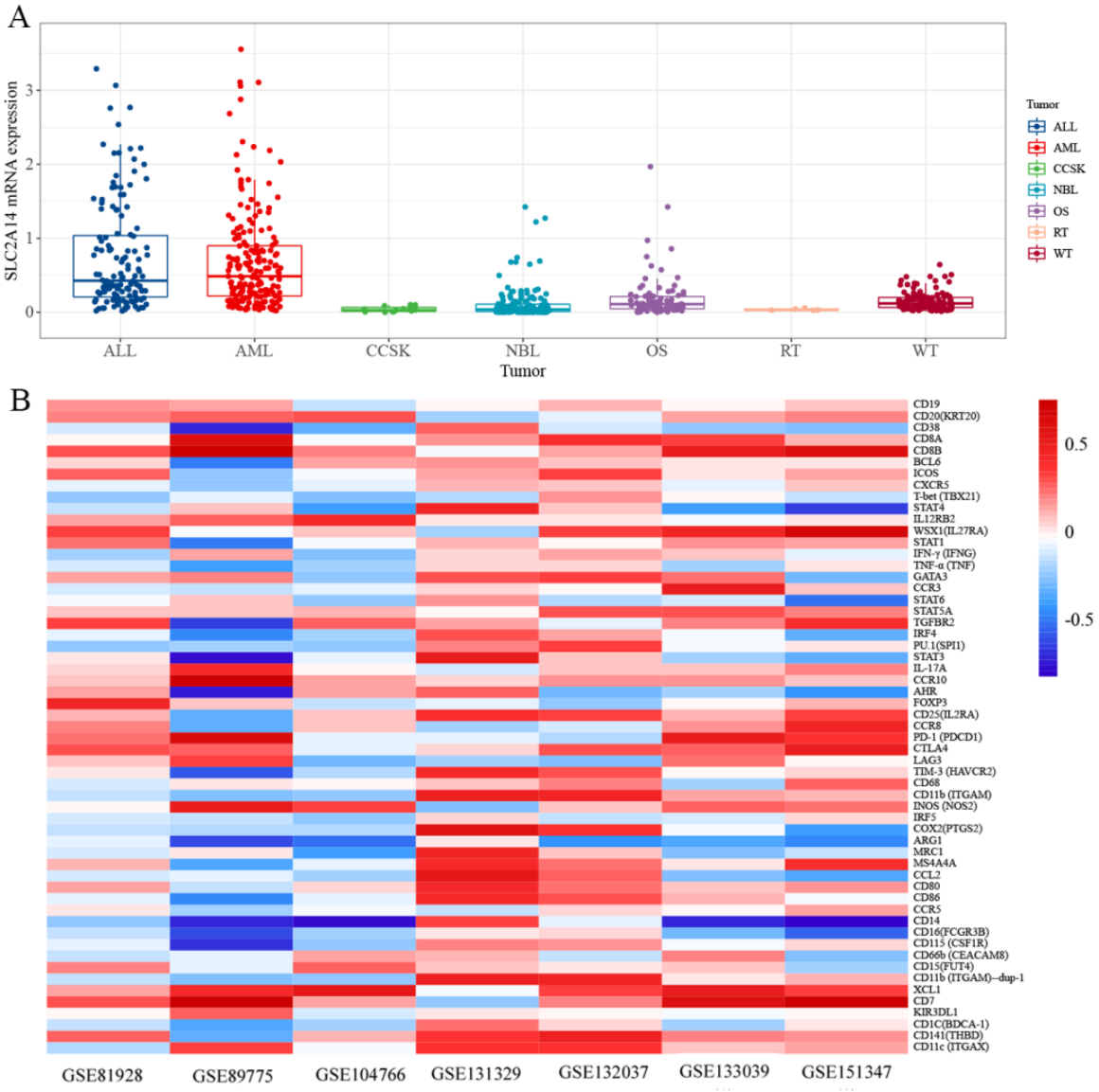

Figure 8

(A)Displays SLC2A14 mRNA expression across different tumor types including ALL, AML, CCSK, NBL, and OS, compared to normal controls (RT and WT).(B)Shows the expression levels of various immune markers such as CD19, CD20, CD38, CD8A, and others, in relation to SLC2A14 mRNA expression.

cules[31–33]. The present study analyzed changes in expression levels of SLC2A14 after being treated with ferroptosis inducer, and the analysis results illuminated downregulated SLC2A14 promoted the development of ferroptosis, then regulated apoptosis of HB cells. Additionally, we also found SLC2A14 expression was related to expression levels of many ferroptosis-related genes.

Some limitations should be pointed out in the present study. The showed results were all collected from HB and paracancerous tissues, we could not simply assume that our results applies to body fluids, so a further research should be managed in the future. In addition, these samples could not necessarily represent the objective situation, larger sample sizes researches are essential.

In conclusion, based on mRNA-seq and sequencing data, we thought SLC2A14 was upregulated in HB, and indicated overexpressed SLC2A14 was associated with occurred of ferroptosis for the first time. Differential expressed SLC2A14 and its DCEGs might regulate ferroptosis by taking part in metabolic pathway, which should be verified in vitro and in vivo.

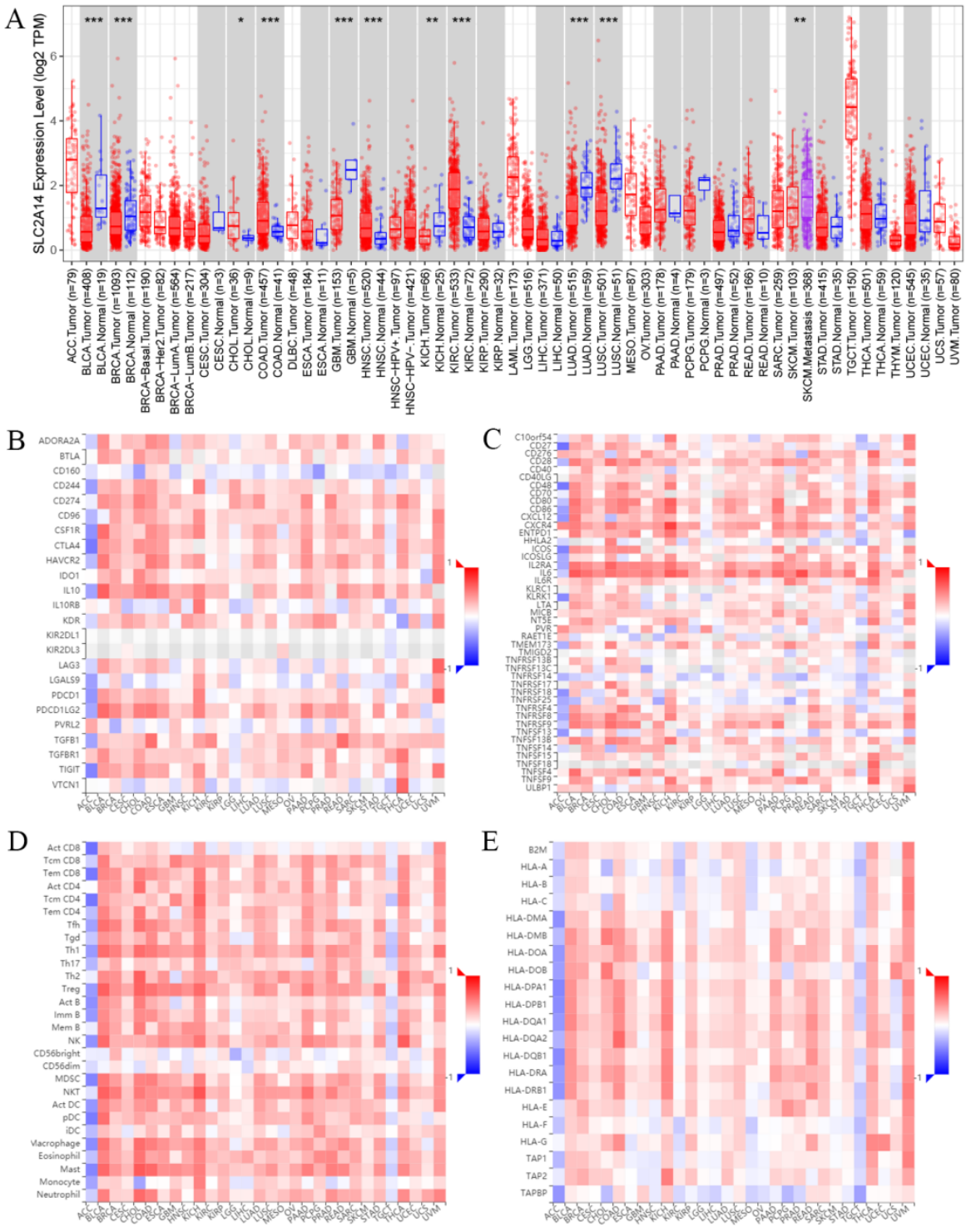

Figure 9

(A)The distribution of SLC2A14 gene expression levels (in log2 TPM) in different tumor types is shown. In the figure, red represents the tumor samples, blue represents the normal samples, each point represents a sample, and the boxplot shows the distribution range of the data.(B)The heat map demonstrates the correlation between different tumor types (rows) and multiple immune-related genes (columns).(C)Presents data on SLC2A14 expression levels (log2 TPM) in a variety of tumor types, comparing tumor samples to normal tissues.(D)Highlights specific immune checkpoint molecules and their potential relationship with SLC2A14 in the tumor microenvironment. (E)Provides an overview of SLC2A14 expression in various cancer types.

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