Prognostic potential and mechanism of SORT1 and its co-expressed genes in hepatocellular carcinoma based on integrative analysis of multiple database

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Abstract
Abnormal SORT1 expression has been reported in various cancers. However, the expression and function of SORT1 in hepatocellular carcinoma (HCC) remain to be explored. This study aims to explore the expression and function of SORT1 and to identify its co-expressed genes in HCC. Various gene expression databases were applied in our analysis. We found SORT1 was up-regulated in HCC tumor tissues and high SORT1 expression level was associated with worse overall survival (OS). Co-expressed genes with SORT1 and its potential regulators were explored using LinkedOmics. Functional network analysis of co-expressed genes by Metascape revealed that they participated in aberrant lipid metabolism, AMPK signaling pathway, and PPAR signaling pathway which were all strongly linked to the pathogenesis of HCC. In addition, co-expression genes were analyzed by Cytoscape to identify their hub genes, which included CYB5A, CYP2C9, CYP3A5, CYP4A11, and POR. The mRNA expression level of CYP2C9, CYP3A5, and CYP4A11 were down-regulated in HCC tumor tissues via GEPIA. High hub genes expression level was associated with better OS and progression free survival (PFS) in HCC. The correlations between SORT1 and hub genes with cancer immune infiltrates were investigated by TIMER. Notably, SORT1 and hub genes expression was positively correlated with infiltrating levels of different immune cells. Our findings suggested that high SORT1 expression level predicted dismal prognosis in HCC and its possible mechanism was immune-related.

KEYWORDS
co-expressed genes, HCC, prognosis, SORT1

1 | INTRODUCTION
Liver cancer has become one of the major contributors to the world’s cancer burden and its incidence continues to climb up in many countries. In 2018, the estimated number of global new cases of liver cancer was 841 080 (4.7% of total cancer cases), while the number of deaths was 781 631(8.2% of total cancer cases). Hepatocellular carcinoma (HCC) is the main type of liver cancer accounting for ~75% of the total.2 Main risk factors of HCC include chronic infection of hepatitis B or hepatitis C virus, aflatoxin exposure, heavy drinking, obesity,
smoking, and type 2 diabetes. Obesity and type 2 diabetes are usually associated with abnormal lipid metabolism which is emerging as a new pathway to explain the mechanism of HCC. In highly proliferating tumor cells, enhanced adipogenesis provides building blocks, signaling molecules, and bioactive mediators to ensure growth, proliferation, and persistence. The progression of HCC is associated with complex metabolic reprogramming and immunosuppression driven by tumor associated macrophages (TAMs) and mediated by biologically active lipid mediators. Existing targeted drugs show unsatisfactory efficacy because of complex clinical and biological behaviors of HCC and increasing drug resistance. In addition, lack of effective prognostic biomarkers that are specific for tumor subtype and stage remains an obstacle in the current understanding of HCC. Thus, it is necessary to discover novel biomarkers and drug targets to predict the prognosis of HCC and to develop novel-targeted therapy.

SORT1 encodes a member of the vacuolar protein-sorting 10 (VPS10)-related sortilin family of proteins which were initially identified in searching for new lipoprotein receptors that resemble the low-density lipoprotein receptor (LDLR). Sortilin is a 95 kDa protein receptor acting as part of the ectodomain of VPS10P. It plays an important role in trafficking different proteins to cell surface or subcellular compartments such as lysosomes and endosomes. Several genome-wide association studies (GWAS) found the encoding locus of SORT1 at 1p13.3 was related to plasma levels of cholesterol and risk of myocardial infarction in humans indicating the potential role of SORT1 in systemic cholesterol homeostasis. In recent years, the increasing number of researches indicated abnormal lipid metabolism was strongly linked to the pathogenesis of HCC. However, the relationship between SORT1 and HCC remained unexplored and further analysis via bioinformatics is required.

This research aims to investigate the prognostic potential and mechanism of SORT1 and its co-expressed genes in HCC. Results showed that high SORT1 expression level was associated with inferior outcome and its possible mechanism included metabolic pathways and immune response in HCC patients. These findings shed light on risk stratification of HCC and targeted therapy development.

2 | MATERIALS AND METHODS

2.1 | HCCDB database

HCCDB is a public HCC gene expression analysis platform which contains up to about 4000 clinical samples from TCGA and GEO database. It provides a comprehensive resolution of gene expression patterns in HCC patients. We analyzed the mRNA expression level of SORT1 via this platform.

2.2 | Oncomine database

Oncomine (https://www.oncomine.org/resource/login.html) is a useful database and data-mining platform. Currently, Oncomine contains 715 gene expression datasets comprising 86,733 samples that can be integrated to discover novel biomarkers for diagnosis and treatment of different diseases. In this study, SORT1 gene was selected as our research object and its mRNA expression level was analyzed in HCC and normal liver tissue.

2.3 | UALCAN database

UALCAN (http://ualcan.path.uab.edu) provides comprehensive analysis of cancer OMICS data and additional information about selected genes by linking to various databases such as TCGA. Using UALCAN we analyzed the expression level of SORT1 between HCC and normal liver tissues, and between sub-groups classified by stage, grade, and other clinical characteristics.

2.4 | GEPIA database

The Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/) was used for co-expression genes expression and survival analysis based on TCGA and the GTEx projects.

2.5 | LinkedOmics database

The LinkedOmics database (http://www.linkedomics.org/login.php) is a free-access database which can be used to analyze the relationship between target genes and their co-expression genes. With this tool, SORT1 co-expression genes were exported and visualized.

2.6 | c-BioPortal database

The cBio Cancer Genomics Portal (http://cbioportal.org) is mainly used to explore cancer genomics. Various genomic alterations of SORT1 and hub genes in HCC were analyzed using this tool.

2.7 | Kaplan–Meier plotter database

The Kaplan–Meier plotter (http://kmplot.com/analysis/) assesses the effects of more than 50,000 genes on survival from GEO and TCGA databases. Here, this tool was used to explore the effects of SORT1 and hub genes on survival in HCC.

2.8 | TIMER database

TIMER is a free platform for systematic exploration of immune infiltrates from TCGA database (https://cistrome.shinyapps.io/timer/). Here, we analyzed the relationship of SORT1 and hub genes with tumor-infiltrating immune cells.
2.9 | Metascape database

Metascape (http://metascape.org/) is an online gene annotation tool that can be applied for enrichment analysis. In this study, to explore the function of co-expressed genes, biological process (BP), and KEGG pathway enrichment analysis were performed using Metascape. In addition, enrichment-bubble diagram was plotted on http://www.bioinformatics.com.cn.

2.10 | PPI network construction and module analysis

Search Tool for the Retrieval of Interacting Genes (STRING; http://string-db.org; version 11.5) was used to predict protein interaction (PPI) network. SORT1 associated PPI network was constructed and displayed via Cytoscape (version 3.8.2) plug-in APP Molecular Complex Detection (MCODE). The critical genes in top one module were shown in this study.

2.11 | Statistical analysis

The $p < .05$ was defined as statistically significant between groups with different expression level of SORT1 with t-test. Overall survival (OS) and progression-free survival (PFS) of HCC patients were explored using Kaplan–Meier curves. Significance in survival time difference by log-rank test was defined as $p < .05$.

3 | RESULTS

3.1 | Elevated mRNA expression level of SORT1 in HCC

SORT1 transcription levels were evaluated via HCCDB database. By analyzing 11 HCC cohorts, we showed that HCC tumor tissues expressed higher levels of SORT1 than adjacent normal tissues (Figure 1A). Analysis based on Oncomine database also suggested elevated SORT1 expression in HCC tumor tissues (Figure 1B–E). Sub-group analysis based on multiple clinical and pathological characteristics in UALCAN database showed consistently increased mRNA expression level of SORT1. SORT1 expression level was elevated in HCC patients compared with normal individuals in different subgroups classified by ethnicity, pathological grading, age, disease stages, and gender (Figure 2).

Kaplan–Meier survival plots were applied to evaluate the relationship between the mRNA expression level of SORT1 and survival in HCC. We divided HCC patients into two cohorts based on the median value of SORT1 expression level. Results showed that patients with high SORT1 expression level had significantly shorter OS (log-rank test).
test, \( p = .039 \), no statistical significance was found in PFS (Figure 3A,B).

### 3.2 SORT1 co-expression network construction, enrichment pathway analysis, PPI network construction, and module analysis in HCC

To explore the molecular mechanism of SORT1 in HCC, we used Linke-dOmics tool to analyze SORT1 co-expression networks. Exactly 2022 genes were shown to be positively related with SORT1, while 842 genes were shown to be significantly negatively related (FDR < 0.05) (Figure 4A). The top 50 genes, both positively and negatively, were shown in heat maps, respectively (Figure 4B). SORT1 expression was positively related with the expression of CELSR2 (positive rank #1, \( r = .428, p = 6.15E^{-10} \)), PSRC1 (positive rank #2, \( r = .401, p = 9.98E^{-9} \)), and MYBPHL (positive rank #3, \( r = .361, p = 8.19E^{-12} \)), and so on. SORT1 expression was found to be negatively related with the expression of DHRS4 (negative rank #1, \( r = -.308, p = 1.36E^{-09} \)), CRYM (negative rank #2, \( r = -.300, p = 3.92E^{-09} \)), and HAAO (\( r = -.287, p = 1.80E^{-08} \)), and so on. After ruling out genes that could not be found in GEPIA, 23/47 genes in the top 50 positively correlated genes have a high possibility of being high-risk genes in HCC. However, only 6/45 genes in top 50 negatively correlated genes have high possibility of being low-risk genes (Figure 4C). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis of top 50 positive and negative co-expression genes of SORT1 annotated by Metascape displayed that these genes were involved in monocarboxylic acid metabolic process, cellular carbohydrate metabolic process, regulation of transforming growth factor beta receptor signaling pathway, and so on (Figure 5A–C). Among them, biological process (BP) analysis indicated oxidation–reduction process, long-chain fatty acid metabolic process, WNT signaling pathway, and planar cell polarity pathway were mainly involved (Figure 5D). KEGG analysis revealed metabolic pathways, peroxisome insulin resistance and AMPK signaling pathway were mainly involved (Figure 5E). PPI network was constructed via STRING, then the network was analyzed via cyto-Hubba and MCODE in Cytoscape software. The most significant module figured out from the PPI network contained 5 hub genes including Cytochrome B5 Type A (CYB5A), Cytochrome P450 Family 2 Subfamily C Member 9 (CYP2C9), Cytochrome P450 Family 3 Subfamily A Member 5 (CYP3A5), Cytochrome P450 Family 4 Subfamily A Member 11 (CYP4A11), and Cytochrome P450 Oxidoreductase (POR) (Figure 5F,G).

### 3.3 Expression and prognostic value of five hub genes in HCC and their correlation with SORT1

We evaluated the transcription levels of CYB5A, CYP2C9, CYP3A5, CYP4A11, and POR via GEPIA database (Figure 6A–E). Results
revealed that CYP2C9, CYP3A5, and CYP4A11 expression level was lower in HCC tissues than in adjacent normal liver tissues (Figure 6B–D). Then we divided HCC patients into two groups based on the median value of hub gene expression level. Results showed that high expression levels of all five hub genes was significantly associated with longer OS and PFS ($p < .05$) in HCC (Figure 7A–J).

We then analyzed the correlation of SORT1 with five hub genes via TIMER. Results displayed that SORT1 was negatively related with all these hub genes, including CYB5A ($\text{cor} = -0.163, p = 1.68e-03$), CYP2C9 ($\text{cor} = -0.188, p = 2.85e-04$), CYP3A5 ($\text{cor} = -0.206, p = 6.46e-05$), POR ($\text{cor} = -0.178, p = 5.75e-04$), and CYP4A11 ($\text{cor} = -0.206, p = 6.84e-05$; Figure 8).

We used cBioPortal to explore the classification and prevalence of SORT1 and five hub genes’ genomic alterations in HCC. Seven types of genomic alterations were identified including gene mutation, amplification, deletion, structural variant, and mRNA high. SORT1 was altered in 16 of 348 (5%) HCC patients which includes missense mutation, gene amplification, and mRNA high phenotype. CYP3A5 was altered in 25 of 348 patients (7%), POR was 31 of 348 (9%), CYB5A was 18 of 348(5%), CYP4A11 was 16 of 348 (5%), and CYP2C9 was 17 of 348 (5%) (Figure 9).

### 3.4 Association of SORT1 and hub genes with immune infiltration level in HCC

We used TIMER to explore the relationship between SORT1 and hub genes with immune infiltration level in HCC. Results showed that
SORT1 expression was positively correlated with infiltrating levels of B cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (Figure 10A). CYP3A5, CYB5A, CYP2C9, CYP4A11, and POR expression was negatively correlated with infiltrating levels of different immune cells (Figure 10B–F).

Copy number variation (CNV) of chromosome or specific genes is a marker for tumor mutational burden and is related to infiltration level of immune cells into tumor. Here, we evaluated the correlation of the CNV of SORT1 and hub genes with immune cell infiltration levels in HCC with TIMER. Results showed that SORT1 CNV had no significant correlations (Figure 11A) while CYB5A and CYP3A5 CNVs were significantly associated with infiltrating levels of CD4+ T cells and neutrophils (Figure 11B,D). CYP2C9 CNV was related with infiltrating levels of CD8+ cells, macrophages, neutrophils, and dendritic cells (Figure 11B,C). CYP4A11 CNV was related with infiltrating levels of CD8+ cells, CD4+ cells, and neutrophils (Figure 11E) while POR CNV was related with infiltrating levels of neutrophils (Figure 11F).

4 | DISCUSSION

SORT1-encoded sortilin protein is an element of VPS10P involved in cellular protein transport and plays important role in lipid metabolism pathways. In this study, we used various bioinformatic tools to gain more insights into the function of SORT1 and its regulatory network in HCC.

High expression level of SORT1 has been shown to be strongly linked to the progression or prognosis of various cancers.22 By analyzing transcriptome from more than 3563 HCC clinical samples, we confirmed that SORT1 mRNA level was significantly increased in HCC tumor tissues. Further sub-group analysis by UALCAN database revealed the up-regulation of SORT1 can be observed regardless of disease stage, tumor pathological grade, gender, race, or age. High expression level of SORT1 was significantly related with inferior survival in HCC cohorts. Our results suggest that SORT1 up-regulation is common in HCC and predicts worse clinical outcome. Further clinical studies are needed to validate its potential of being a diagnostic and prognostic biomarker.
The pathogenesis of HCC is complex and involves various signaling pathways. Investigation of carcinogenic mechanisms of SORT1 began from 2014 which revealed lower expression of SORT1 resulted in increased apoptosis and significant inhibition of proliferation in ovarian carcinoma cells. In addition, the elevated expression of SORT1 was found to predict worse prognosis in B acute lymphoblastic leukemia. 

Researches which directly linked SORT1 and HCC were scarce and to clarify the signaling events accompanying abnormal SORT1 expression, we explored its co-expression network. Our results showed that SORT1 co-expression genes participate in monocarboxylic acid metabolic process, cellular carbohydrate metabolic process, and regulation of transforming growth factor beta receptor signaling pathway. Among them, the results of biological process (BP) showed that they were significantly enriched in oxidation–reduction process, long-chain fatty acid metabolic process, WNT signaling pathway, and planar cell polarity pathway. KEGG analysis showed that metabolic pathways, PPAR signaling pathway, and AMPK signaling pathway were significantly enriched. These pathways are strongly linked to the pathogenesis of HCC in previous studies. Abnormal SORT1 expression probably influences various signaling pathways and biochemistry metabolism processes in HCC via its co-expression network. To conclude, our findings indicate a complex regulatory network of SORT1 in HCC, more in vitro and in vivo experiments are needed to validate the above pathways and the regulatory mechanism of SORT1 and its co-expressed genes.

We also found a strong negative correlation between SORT1 and its hub genes including CYB5A, CYP2C9, CYP3A5, CYP4A11, and POR. Analysis of transcriptome from GEPIA database confirmed that the mRNA expression levels of CYP2C9, CYP3A5, and CYP4A11 were significantly higher in adjacent normal tissues than HCC tissues, which were consistent with previous studies. Moreover, high
expression of CYB5A, CYP2C9, CYP3A5, CYP4A11, and POR predicted better survival in HCC by Kaplan–Meier survival analysis. We hypothesized that SORT1 might down-regulate the expression of the above hub genes via various signaling pathways to promote the development of HCC. Further mechanism studies are still needed to validate this hypothesis.
Recently, tumor microenvironment research has progressed rapidly with deeper understanding of how immune cells work in cancer development and progression. Nataliya et al. found the tumor infiltration levels of B cells, CD4$^+$ cells, CD8$^+$ T cells, and M1 macrophages were usually increased in HCC, resting NK cells, neutrophils, and resting mast cells were decreased compared with healthy people. Cyndia’s research discovered a new peptide–drug conjugates could target SORT1-mediated vasculogenic mimicry in the tumor microenvironment.

**FIGURE 7** Hub gene expression is related to survival in HCC cohort. (A–E) Kaplan–Meier plotter of OS. (F–J) Kaplan–Meier plotter of PFS.

**FIGURE 8** The correlation of SORT1 with five hub genes (TIMER).
FIGURE 9  SORT1 and hub genes’ genomic alterations in HCC (cBioPortal). Different types of genomic alterations were displayed in different colors.

FIGURE 10  SORT1 and hub genes expression levels are related to immune cell infiltration level in HCC. (A–F) Correlation of SORT1 and five hub genes’ expression levels with immune cell infiltration levels, respectively.
microenvironment of triple negative breast cancer and ovarian carcinoma. Our study showed elevated SORT1 expression in HCC and tumor-infiltrating B cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells were positively correlated with SORT1 expression level, which was partly consistent with Nataliya’s research. In spite of some research indicating that tumor-infiltrating immune cells and immune-associated molecules would influence the prognosis of HCC patients, there was lack of evidence to support the application of tumor-infiltrating immune cells as biomarkers to guide treatment in HCC. Our results suggested that the expression levels of SORT1 and its hub genes as biomarkers were related with immune cell infiltration in HCC. Our finding relied on analysis of big data from online databases and further classification of immune cells based on their function was needed. For instance, M1 macrophages exert anti-tumor effects, while M2 macrophages show pro-tumor function. Nevertheless, our research only provides a preliminary theory and these findings need to be further confirmed.

Our study has some limitations that should be addressed. First, our conclusions are based on bioinformatic methods and lack solid in vivo and ex vivo experiments to validate. Therefore, further basic experiments and clinical trials are needed to confirm the working mechanism of SORT1 in HCC. Second, our study only analyzed impact of the gene expression level and CNV of SORT1 and its associated hub genes on immune cell infiltration in rough classification, without paying attention to specific cell subtypes. Further classification of immune cells based on their function needs to be further explored.

Last but not least, in public databases, studies about SORT1 in HCC are scarce and more clinical samples should be collected for SORT1-associated research.

5 CONCLUSION

With the assistance of databases analysis, we found increased SORT1 expression level in HCC regardless of disease stage, tumor pathological grade, gender, race, or age and predicted worse survival. Enrichment pathway analysis of SORT1 co-expression genes suggested that aberrant lipid metabolism, AMPK signaling pathway, PPAR signaling pathway, regulation of transforming growth factor beta receptor signaling pathway, WNT signaling pathway, and planar cell polarity pathway were strongly linked to the pathogenesis of HCC. For mechanism study, SORT1 expression was positively related to infiltrating levels of B cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells. Both gene expression levels and CNV of its hub genes including CYB5A, CYP2C9, CYP3A5, CYP4A11, and POR had significant correlations with infiltrating levels of immune cells. In conclusion, SORT1 might work as a potential immune-related prognostic marker for HCC which requires to be validated in further experiments and clinical trials.

AUTHOR CONTRIBUTIONS

Minjie Lin, Mengying Zhu, Xiling Fu, and Jiabao Chang contributed to the design, analysis, and interpretation of data; drafting of the
manuscript; and critical revision of the manuscript. Tingqiu Ge and Naifying Lu contributed to the statistical analysis. Minjie Lin, Mengying Zhu, Xiling Fu, and Jiabao Chang contributed to the methodology. Xiling Fu and Jiabao Chang contributed to the project administration. Minjie Lin and Mengying Zhu wrote the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST
The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT
All raw and processed data are freely available from GEO (https://www.ncbi.nlm.nih.gov/geo/), and TGCA database (https://portal.gdc.cancer.gov/).

ETHICS STATEMENT
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees, and with the Helsinki.

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