Hepatocellular carcinoma (HCC) is one of the most frequent malignancies and the fourth-leading cancer-related death worldwide. Most patients with HCC are diagnosed at a late stage in which curable therapies are limited. Thus, identifying biomarkers for early diagnosis and prognosis of HCC is essential for improving the treatment effectiveness in patients with HCC. In this paper, the SLC10A1 expression levels in the cells and the tissues and their correlation with HCC were analyzed using bioinformatics tools. Clinical information data and gene expression profiles were retrieved from the Gene Expression Omnibus and The Cancer Genome Atlas. Chi-square tests, log-rank tests, and Kaplan-Meier curves were performed using R packages. In all statistical analyses, a p-value of less than 0.05 was considered significant. We found that SLC10A1 primarily expresses in the liver, especially on the plasma membrane. The expression levels of SLC10A1 in tumors were consistently lower than that in normal tissue. Down-regulation of SLC10A1 was correlated with a poor survival outcome (p = 4.50e-05) and recurrence-free survival (p = 8.0e-04) in patients with HCC. In addition, multivariate analysis indicated that the expression of SLC10A1 was an independent predictor for survival outcome (p = 2.17e-05) and recurrence-free survival (p = 1.63e-04). We concluded that SLC10A1 is a potential biomarker for the early diagnosis and prognosis of HCC in the era of personalized medicine.
SLC10A1 gene was inactivated in human or mouse liver cells, the hepatitis B virus infection was significantly reduced [24]. The expression of NTCP is reduced in patients with cirrhosis [25] and is increased in patients with nonalcoholic fatty liver or early stage of liver transplantation [26]. SLC10A1 has been extensively studied, but its role in HCC remains unclear. To learn more about the relationship between SLC10A1 and HCC, we analyzed the gene expression, and distribution of SLC10A1 in cells, and the correlation with survival and recurrence in HCC patients.

2. Methods

2.1. Subcellular localization and expression of SLC10A1 among normal and cancer tissues

Subcellular localization of SLC10A1 was predicted and visualized by using the COMPARTMENTS, a subcellular localization database (http://compartments.jensenlab.org) [27]. The gene type from Homo sapiens was selected for further steps.

To investigate the gene expression levels of SLC10A1 across human tissues, RNA-sequencing analyses were conducted via the GTEx consortium (http://www.gtexportal.org) [28]. All data were browsed and searched by gene symbol.

mRNA expression levels of SLC10A1 across all cancers and paired normal tissues were analyzed by GEPIA [29]. In the Single Gene Analysis tab, the gene symbol was used to search for interesting information.

2.2. The protein expression of SLC10A1 by immunohistochemistry

Protein expression levels of SLC10A1 were identified using the Tissue Atlas and the Pathology Atlas from Human Protein Atlas database (https://www.proteinatlas.org/) [30]. The protein expression data from 44 normal human tissue types and 17 different forms of human cancer is derived from antibody-based protein profiling using immunohistochemistry. Gene symbol was used to search for information from the database. The IHC staining of normal liver tissues from tissue atlas and HCC tissues from pathology atlas were collected and analyzed.

2.3. Protein-protein interaction analysis

Protein-protein interactions were conducted using the Search Tool for Retrieval of Interacting Genes/Proteins (STRING) database (http://www.string-db.org/) [31]. Search for a single protein by name was performed in the Homo sapiens database. Protein networks were linked based on the following six criteria: experimental evidence and existing databases, neighborhood, gene fusion, co-occurrence, and co-expression.

2.4. Patients and gene expression profiles

Gene expression profiles and clinical information of HCC patients were downloaded from TCGA (https://www.cbioportal.org/) and the National Center for Biotechnology Information Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/). The robust multi-array method (RMA) was used to adjust the raw data to the median via Cluster 3.0. The dataset GSE14520 [32] has been selected as the main data for the construction of our experiment. 242 patients with available clinical information were used for this study. The probe set identifiers have been transferred to gene symbols. Patients were classified into low or high expression groups. Patients with SLC10A1 expression level higher than the median were in the high expression group, and patients with SLC10A1 expression level less or equal to than median were in the low expression group. These groups were used for further study.

2.5. SLC10A1 expression and its correlation with clinical information

607 patients were selected from GSE14520 [32] and TCGA [33] datasets to observe the mRNA expression levels of SLC10A1 between normal and tumor tissues. The Kaplan-Meier method was used to compare the survival of two patient groups based on mRNA expression. Chi-square and log-rank tests were used to assess survival risk and recurrence time. Cox univariate and multivariate proportional regression analyzes were performed to evaluate independent prognostic factors associated with survival and recurrence time.

2.6. Statistical methods

The Kaplan-Meier curves, a two-sample t-test, Chi-squared tests, and log-rank tests were performed using the R language environment (www.r-project.org). The Wilcoxon signed-rank test was used to compare two groups of clustered data, and the Kruskal-Wallis test was applied to examine more than two independent clustered data and displayed by a boxplot. In the tests, a p-value less than 0.05 was considered statistically significant.

3. Results

3.1. SLC10A1 subcellular localization and expression among normal and cancer tissues

According to COMPARTMENTS, a subcellular localization database considering multiple information sources regarding different cell types, the SLC10A1 protein product was identified with the highest confidence (confidence level 5) in the plasma membrane. Low confidence (confidence level 2) was in the extracellular, mitochondrion, peroxisome nucleus, endoplasmic reticulum, endosome, and cytosol. And the lowest confidence (confidence level 1) was in the cytoskeleton, lysosome, and Golgi apparatus (Figure 1).

According to the GTEx database, the expression of SLC10A1 was very high in the liver (median transcripts per million (TPM) is 94.29), low in whole blood (median TPM is 0.10), and very low or no expression in other tissues (Figure 2A). In tissue from HCC patients, the median expression of SLC10A1 was 33.82 (TPM). This expression level was lower than that in normal tissues (69.57 TPM) (Figure 2B). SLC10A1 is mainly expressed in the liver. It shows very low or no expression of other tissues (Figure 2C). In both females and males, protein expression of SLC10A1 through immunohistochemistry differed between HCC tissues and normal liver tissues (Figure 3). The expression level of SLC10A1 was higher in normal liver tissues than in hepatocellular carcinoma tissue. SLC10A1 has only one variant that was ENSG00000100652.4 primarily expressing in the liver (Figure 4).

3.2. Protein-protein interaction analysis

To study the relationship of SLC10A1 with other proteins, we performed a molecular network by introducing SLC10A1 into the STRING database. SLC10A1 was closely related to other proteins, such as ABCC11, and ALB (Figure 5).

3.3. SLC10A1 expression and its correlation with clinical information

To investigate the association between the SLC10A1 expression level and clinicopathological characteristics, including gender, age at diagnosis, and BCLC stage, we performed Chi-square (x2) test. As shown in Table 1, Gender and age were not significantly correlated with SLC10A1 expression. BCLC stage, survival and recurrence were significantly associated with SLC10A1 expression (BCLC, p = 1.61e-03; OS, p = 9.72e-04; RFS, p = 2.74e-02). To compare the prognostic value of SLC10A1 with other prognostic variables, such as age and gender, we performed univariate and multivariate Cox regression analysis by using the GSE14520 dataset (Table 2). In univariate analysis, age was not significant in both OS and RFS but gender was significant with RFS (HR 2.40; 95% CI 1.20–4.5; p = 0.01). In multivariate analysis, age was not
Figure 2. Gene expression for SLC10A1. (A) Gene expression for SLC10A1 (ENSG00000100652.4) among different tissues. (B) The median expression of tumor and normal samples in the body map. (C) The gene expression profile of SLC10A1 across all tumor tissue and paired normal tissues. (LIHC, liver hepatocellular carcinoma; ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangio carcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRK, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma).
significant for both OS and RFS but gender was significant with RFS (HR 2.63; 95% CI 1.38–5.03; \(p = 3.36 \times 10^{-3}\)).

GSE14520 (\(n = 242\)) and TCGA (\(n = 365\)) were used to analyze the association between SLC10A1 expression and survival and recurrence outcomes. Patients in GSE14520 dataset were classified into high expression group (\(n = 121\)) and low expression group (\(n = 121\)). The Kaplan-Meier method was performed and showed that SLC10A1 expression level was significantly associated with survival outcome in patients with HCC (\(p = 2.61 \times 10^{-5}\); Figure 6A). Patients with low SLC10A1 expression had a shorter survival time than patients with high SLC10A1 expression.

We further analyzed the association of SLC10A1 with recurrence in the GSE14520 dataset. We found that patients with a low expression level of SLC10A1 had a higher recurrence rate than patients with a high expression level of SLC10A1 (\(p = 6.75 \times 10^{-4}\); Figure 6C).

4. Discussion

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, and the number of HCC-related death per year has increased worldwide [1, 34]. Many major risk factors for hepatocellular carcinoma have been identified, such as chronic cirrhosis, viral hepatitis, nonalcoholic fatty liver, alcohol use, genetic disease, and exposure to hepatotoxicity (aflatoxin) [35]. The diagnosis of patients with HCC remains challenging, especially in the early stages of the disease. If the patient is diagnosed early and correctly with HCC, the 5-year survival rate is >70% [34]. However, there are no single biomarkers with high specificity and sensitivity for the accurate detection of HCC, especially in the early stages of HCC to increase survival for the patients [27].

In this study, we found that the SLC10A1 encodes only for NTCP, and it has only one variant. Furthermore, NTCP was expressed specifically in the liver with primary function in bile salt metabolism to transport extracellular bile salts into hepatocytes. It accounts for greater than 80% of the hepatic uptake [36, 37]. NTCP was recently shown to serve as an entry receptor for hepatitis B and D viruses [21]. Increased or decreased SLC10A1 expression level is associated with cirrhosis or fatty liver [25, 26], which is one of the risk factors for HCC. The median expression level of SLC10A1 in HCC tissues was significantly lower than its level in normal liver tissues. The significance of SLC10A1 was further confirmed by analysis of immunohistochemistry from the protein atlas database. The expression levels of SLC10A1 were significantly higher in normal liver tissues and significantly lower in tumor tissues from both male and female. This finding suggests that SLC10A1 expression levels may be used as a biomarker for assessing the risk of HCC development.

Univariate Cox analysis suggests that SLC10A1 can predict patients’ survival and disease recurrence. It predicts better after adjustment with other clinical variables such as age, and sex in multivariate Cox analysis. This suggests that SLC10A1 is an independent biomarker for survival and recurrence outcomes of patients with HCC. The better performance of SLC10A1 in multivariate analysis suggests that it may be more useful for the detection of HCC in clinical practice.

Long-term survival has been achieved in HCC patients after hepatic resection of HCC. But, it significantly reduces since the development of recurrence with the rate of 70% at 5 years after resection of HCC [34, 38].
Therefore, biomarkers useful for the prediction of tumor recurrence still need to be investigated. We show that \textit{SLC10A1} expression levels were correlated with survival and recurrence outcome. HCC patients with low expression of \textit{SLC10A1} were associated with significantly lower survival and recurrence rate than HCC patients with high expression of \textit{SLC10A1}. This finding suggests that the upregulation of \textit{SLC10A1} can serve as a biomarker for predicting recurrence in early-stage HCC.

\textit{SLC10A1} interacts with other proteins, such as NR1H4, ABCB11, and CYP7A1. It is primarily known for its involvement in the bile salt reabsorption transport pathway, through NTCP. Expression of NTCP is regulated by many transcription factors, such as farnesoid X receptor (FXR or NR1H4), small heterodimer partner (SHP or NR0B2), bile salt export pump (BSEP or ABCB11), and cholesterol 7α-hydroxylase (CYP7A1) [37]. FXR does not interact directly with the NTCP promoter but it induces the expression of other factors that indirectly suppress NTCP expression. An analysis based on the TCGA dataset indicated that NR1H4 was downregulated in liver cancer. This

\textbf{Figure 4.} Exon expression of \textit{SLC10A1} (ENSG00000100652.4).

\textbf{Figure 5.} \textit{SLC10A1} protein interactive network.
suggests that NR1H4 may play an important role in tumorigenesis [39]. If bile acid levels increase, FXR activates the expression of SHP and then SHP inhibits transcription of NTCP [40]. NR0B2 involved in regulatory processes in HCC, which acts as a tumor suppressor through inhibition of cell growth and activation of apoptosis in this tumor entity [41]. The activation of FXR reduces the expression level of CYP7A1, an important enzyme involved in bile acid biosynthesis [17, 37]. CYP7A1 is the rate-limiting enzyme in the classic pathway of bile acid synthesis. Overexpression of an exogenous CYP7A1 gene impaired liver regeneration after 70% partial hepatectomy. This was accompanied by increased hepatocyte apoptosis and liver injury [42]. FXR upregulates the bile salt export pump (BSEP) to prevent the intracellular accumulation of cytotoxic bile salts [43]. BSEP has a vital role in maintaining bile acid homeostasis. A lack of BSEP leads to severe

**Table 1.** Clinicopathological features of SLC10A1 in two expression group of GSE14520 data set.

| Variables | Total | SLC10A1 expression |  | p-value |
|-----------|-------|---------------------|---|---------|
|           |       | Low                 | High |         |
| Number of patients | 242   | 121 (50.0%)         | 121 (50.0%) |         |
| Gender    |       |                      |     |         |
| Female    | 31    | 18 (14.9%)          | 13 (10.7%) | 0.19    |
| Male      | 211   | 103 (85.1%)         | 108 (89.3%) |         |
| Age       |       |                      |     |         |
| ≥50       | 117   | 53 (43.8%)          | 64 (52.9%) | 0.44    |
| <50       | 125   | 68 (56.2%)          | 57 (47.1%) |         |
| BCLC      |       |                      |     | 1.61e-03|
| 0         | 20    | 12 (60.9%)          | 8 (46.1%) |         |
| A         | 152   | 61 (50.4%)          | 91 (75.2%) |         |
| B         | 24    | 16 (66.7%)          | 8 (64.1%) |         |
| C         | 29    | 21 (74.1%)          | 8 (64.1%) |         |
| NA        | 17    | 11 (64.7%)          | 6 (35.3%) |         |
| OS        |       |                      |     | 9.72e-04|
| 0         | 146   | 60 (41.6%)          | 86 (79.1%) |         |
| 1         | 96    | 61 (58.4%)          | 35 (20.9%) |         |
| RFS       |       |                      |     | 2.74e-02|
| 0         | 106   | 44 (41.5%)          | 62 (58.5%) |         |
| 1         | 136   | 77 (56.3%)          | 59 (43.7%) |         |

BCLC, Barcelona Clinic Liver Cancer; OS, overall survival; RFS, recurrence free survival; p -values were obtained from the χ² -test.

**Table 2.** Univariate and multivariate Cox proportional hazard regression analyses of clinical variables in the GSE14520 dataset.

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
|          | HR         | 95% CI       | p Value | HR         | 95% CI       | p Value |
| OS       | Gender     | 1.90 | 0.62–1.40 | 0.69 | 2.09 | 1.01–4.32 | 0.04 |
|          | Age        | 0.92 | 0.90–3.80 | 0.903 | 1.07 | 0.71–1.60 | 0.76 |
|          | Expression | 2.40 | 1.60–3.60 | 4.50e-05 | 2.49 | 1.63–3.79 | 2.17e-05 |
| RFS      | Gender     | 2.40 | 1.20–4.50 | 0.01 | 2.63 | 1.38–5.03 | 3.36e-03 |
|          | Age        | 1.10 | 0.77–1.50 | 0.66 | 1.25 | 0.89–1.77 | 0.19 |
|          | Expression | 1.80 | 1.30–2.50 | 8.0e-04 | 1.94 | 1.37–2.74 | 1.63e-04 |

OS, overall survival; RSF, recurrence-free survival; HR, hazard ratio; CI, Confidence Interval; p -values were obtained from the χ² -test.

**Figure 6.** Kaplan Meier plots of SLC10A1 expression with survival and recurrence. (A) SLC10A1 expression with the survival of the GSE14520 dataset. (B) SLC10A1 expression with the survival of the TCGA dataset. (C) SLC10A1 expression with the recurrence of the GSE14520 dataset.
cholestasis and hepatocellular carcinoma [44]. Thus, SLC10A1 interacts with proteins, which are major risk factors of HCC.

This study showed the correlation between SLC10A1 expression and hepatocellular carcinoma. SLC10A1 is expressed mainly in liver cells. The mRNA expression of SLC10A1 in hepatocellular carcinoma tissue was lower than its expression in normal tissue. SLC10A1 is an independent biological indicator that can be used in the diagnosis and prognosis of HCC. Low expression of SLC10A1 was related to worse prognosis and recurrence in patients with HCC. We conclude that SLC10A1 is a potential biomarker for the early diagnosis and prognosis of hepatocellular carcinoma.

Declarations

Author contribution statement

Quynh Hoa Tran: Conceived and designed the experiments; Wrote the paper.

Van Gio Nguyen: Analyzed and interpreted the data; Wrote the paper.

Cong Manh Tran: Analyzed and interpreted the data.

Minh Nam Nguyen: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Funding statement

This research is funded by Vietnam National University Ho Chi Minh City (VNU-HCM) under grant number C2021-44-02 to Minh Nam Nguyen.

Quynh Hoa Tran was supported by Ho Chi Minh City University of Food Industry, HCM City, Vietnam (145/H-DCT).

Data availability statement

Data included in article supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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