ORIGINAL

Impact of L-type amino acid transporter 1 on intrahepatic cholangiocarcinoma

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Abstract : Background : Amino acid transporters, such as L-type amino acid transporter 1 (LAT1), have an effect on tumor growth, metastasis, and survival of various solid tumors. However, the role of LAT1 in patients with intrahepatic cholangiocarcinoma (IHCC) remains unknown. Methods : Forty-six patients who had undergone initial hepatic resection for IHCC at Tokushima University Hospital were enrolled in this study. Immunohistochemical analysis of LAT1 and phosphorylated Akt (p-AKT) was performed using resected specimens. Clinicopathological factors, including prognosis, were analyzed between LAT1-high and LAT1-low groups. Results : The LAT1-high group showed a higher proportion of periductal infiltrating type and higher carcinoembryonic antigen/carbohydrate antigen 19-9 levels compared with the LAT1-low group. Multivariate analysis revealed that LAT1-high expression was an independent prognostic factor for disease-free survival. Furthermore, the proportion of p-AKT positivity was higher in the LAT1-high group than in the LAT1-low group. Conclusions : LAT1 expression was associated with poor prognosis of IHCC and higher p-Akt expression. J. Med. Invest. 70 : 160-165, February, 2023

Keywords **:** *L-type amino acid transporter 1, intrahepatic cholangiocarcinoma, phosphorylated Akt*

INTRODUCTION

Intrahepatic cholangiocarcinoma (IHCC) is a primary liver cancer with incidence only second to hepatocellular carcinoma (HCC) (1), which arises from the epithelial cells of the intrahepatic bile ducts (2). Despite its rarity, it tends to be advanced or even lethal when diagnosed owing to the difficulty in the detection and treatment of the disease (3).

L-type amino acid transporter 1 (LAT1) is a system L-amino acid transporter that transport large neutral amino acids, such as leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine, and histidine. System L-amino acid transporters transport large branched and aromatic neutral amino acids in almost all cell types independent of Na^+ (4). LAT1 provides cancer cells with the essential amino acids required for protein synthesis and growth stimulation (5) LAT1 has been reported to be related to cancer stem cell activity in lung cancer (6), and its expression correlates with high-grade prostate cancer (7). However, the role of LAT1 in IHCC remains to be elucidated.

Multiple kinase signaling pathways, including the PI3K/Akt pathway, are predominately activated in IHCC tissues and cell lines (8). Moreover, it was reported that the PI3K/Akt pathway is upregulated during cholangiocarcinogenesis (9). Akt is a serine/threonine protein kinase that plays a central role after phosphorylation in regulating diverse biological functions, including cell metabolism, protein synthesis, cell survival, apoptosis inhibition, and cell cycle progression (10).

Overexpressed LAT1 on lymphoma cells reflects cancer dependence on increased nutrient uptake for Akt activation and malignancy (11). Therefore, we hypothesized that high expression of LAT1 is associated with poor prognosis in IHCC and that p-Akt activation is the mechanism of its malignant potential.

In this study, we assessed the relationship between LAT1 expression and the clinicopathological factors of IHCC, including prognosis, via immunohistochemical analysis and investigated its mechanism with respect to p-Akt expression.

MATERIALS AND METHODS

Patients

Forty-six patients with histologically confirmed IHCC who underwent surgical resection at Tokushima University Hospital between January 1994 and December 2017 were enrolled in this study. We included only patients who (a) had no history of treatment prior to surgery, (b) had no extrahepatic metastasis, and (c) had pathologically proven IHCC. Pathological and morphological parameters and the Japanese Tumor–Node–Metastasis stage were determined according to the Liver Cancer Study Group of Japan (12). Median follow up period was 2.0 years (0.4-11.2), and total number of non-censored event was 33. This study was approved by the Institutional Review Board of our institute (No. 4144).

Immunohistochemical analysis and evaluation

Immunohistochemical analysis was performed according to the protocol used in our department, which has been previously reported by Ishikawa *et al*. (13). The following antibodies were used : a rabbit monoclonal antibody to LAT1 (1:1000 dilution, 4A2 : provided by J-Pharma Co., Ltd, Kanagawa, Japan) and

List of Abbreviation :
IHCC : ntrahepatic cholangiocarcinoma
HCC : hepatocellular carcinoma
LAT1 : L-type amino acid transporter 1
CEA : carcinoembryonic antigen
CA19-9 : carbohydrate antigen 19-9

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a rabbit polyclonal antibody to phosphor-Akt (1:100 dilution, ab81283 ; Abcam, Tokyo, Japan). The LAT1 expression scores were assessed depending on the extent of obvious staining in the cell membrane or cytoplasm as follows : 0, <5% of the tumor area stained ; 1, 5%–10% stained ; 2, 11%–25% stained ; 3, 26%–50% stained ; and 4, ≥51% stained. Tumors in which the stained tumor cells were scored >1 were considered to show high expression (14). Regarding p-Akt staining, when >10% of the tumor cells were stained in the cytoplasm and/or nucleus, the samples were considered positive (15). Representative images of expression of LAT1 and p-Akt are shown in Figure 1. In assessing immunohistochemical staining, five random fields per section were evaluated at x400 magnification, and approximately 1000 cancer cells were counted.

Statistical analysis

For each high and low LAT1 group, summary statistics of clinicopathologic factors (mean and standard deviation for continuous variables and number and percentage of cases per category (%) for discrete variables) were calculated, and the Mann-Whitney U test or chi-squared test was performed to compare between groups. Cancer-specific survival and disease-free survival curves were obtained using the Kaplan–Meier method, and differences were compared using the log-rank test. Multivariate analysis was conducted using the Cox proportional hazard regression model. Factors for multivariate analysis were selected as follows : 1) confounder with LAT1 and also 2) previously reported as prognostic factor (16-20). For all statistical analyses, $p < 0.05$ was considered significant. All statistical analyses were performed using a statistical software (JMP 8.0.1., SAS Campus Drive, Cary, NC, USA).

RESULTS

Based on immunohistochemical analysis, 46 patients were divided into the LAT1-low group (n = 21) and LAT1-high group (n = 25). Table 1 summarizes the clinicopathological factors of patients in both groups. The LAT1-high group showed a significantly higher proportion of periductal infiltrating type, higher carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels compared with the LAT1-low group ($p < 0.05$ for both). The LAT1-high group also had a higher rate of hilar type ($p = 0.07$) than the LAT1-low group, although this difference was not significant. However, the groups did not significantly differ in terms of age, sex, viral infection status, and other tumor factors, including tumor size, stage, vessel invasion and adjuvant chemotherapy. Adjuvant chemotherapy was performed in 16 cases (S-1 : 2 cases, Tegafur/Uracil : 2 cases, CDDP : 1 case, gemcitabine/5-FU/CDDP : 11 cases). Regarding treatment after recurrence in 38 cases, chemotherapy was performed in 14 cases (CDDP : 1 case, S-1 : 2 cases, gemcitabine/S-1 : 1 case, gemcitabine/5-FU/CDDP : 10 cases), resection was performed in 9 cases, and no treatment was performed in 15 cases. The cancer-specific and disease-free survival rates were lower in the LAT1-high group than in the LAT1-low group, indicating a worse prognosis for patients in the LAT1-high group (both $p < 0.05$, Log-rank test, Figures 2 and 3). In the multivariate analysis, confounding factors with LAT1 in this study and also previously reported as prognostic factors were selected in addition to LAT1 high expression ; periductal infiltration, high CEA/CA19-9. Result of multivariate analysis for cancer-specific survival was shown in Table 2. Hazard ratio (HR) of LAT1 high expression was 2.16 (95%CI : 0.98-4.74, $p = 0.06$).

Result of multivariate analysis for disease-free survival was shown in Table 3. HR of LAT1 high expression was 2.79 (95%CI : 1.32-5.91, $p < 0.01$).

Furthermore, the LAT1-high group showed a significantly higher proportion of p-Akt positivity compared with the LAT1-low group (68.0% and 23.8% for LAT1-high and -low group, respectively, $p < 0.01$ Figure 4).

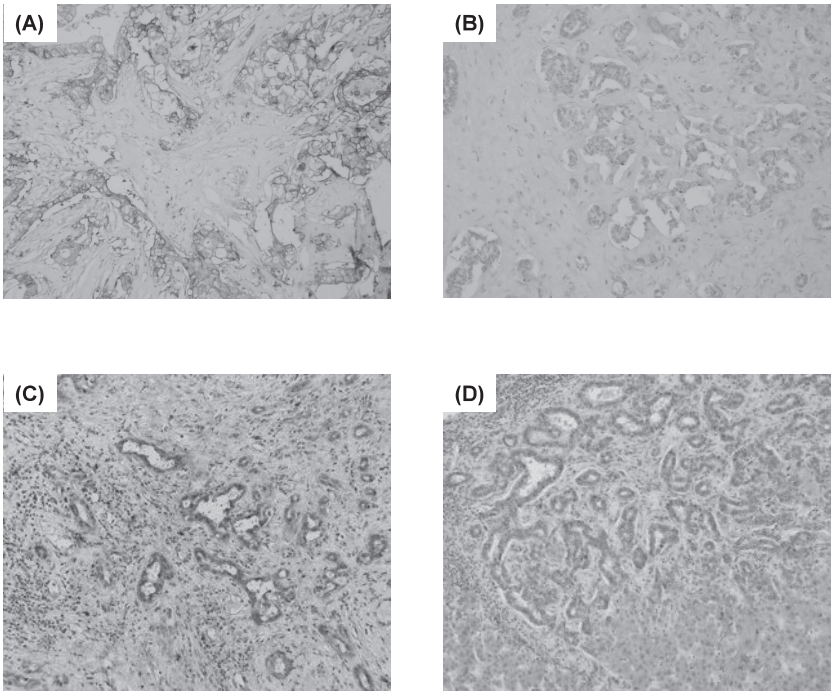

Fig 1. Representative images of immunohistochemical analysis
(A) LAT1 high (B) LAT1 low (C) p-Akt positive (D) p-Akt negative (magnification ×400).

Table 1. Patients' characteristics in the LAT1-low and LAT1-high groups

Variable	Low (n=21)	High (n=25)	*P*-value
Age (years)	70.5±7.2	68.6±10.1	0.60
Sex : Male	16 (76.2%)	14 (56.0%)	0.15
Female	5 (23.8%)	11 (44.0%)	
Tumor size : < 3 cm	4 (19.0%)	8 (32.0%)	0.31
≥ 3 cm	17 (91.0%)	17 (68.0%)	
Location : Peripheral	17 (91.0%)	14 (56.0%)	0.07
Hilar	4 (19.0%)	11 (44.0%)	
Tumor type : MF	11 (52.4%)	6 (24.0%)	0.046
MF + PI	10 (47.6%)	19 (76.0%)	
LN metastasis : No	16 (76.2%)	17 (68.0%)	0.54
Yes	5 (23.8%)	8 (32.0%)	
Stage : I, II	7 (33.3%)	6 (24.0%)	0.48
III, IV	14 (66.7%)	19 (76.0%)	
Differentiation : Tub	14 (66.7%)	15 (60.0%)	0.64
Others	7 (33.3%)	10 (40.0%)	
Vp : No	14 (66.7%)	13 (52.0%)	0.31
Yes	7 (33.3%)	12 (48.0%)	
Vv : No	18 (85.7%)	21 (84.0%)	0.87
Yes	3 (14.3%)	4 (16.0%)	
CEA : <10 ng/ml	20 (95.2%)	16 (64.0%)	<0.01
≥10 ng/ml	1 (4.8%)	9 (36.0%)	
CA19-9 : <100 U/ml	14 (66.7%)	9 (36.0%)	0.04
≥100 U/ml	7 (33.3%)	16 (64.0%)	
HBV : No	17 (91.0%)	22 (88.0%)	0.51
Yes	4 (19.0%)	3 (12.0%)	
HCV : No	19 (90.5%)	21 (84.0%)	0.51
Yes	2 (9.5%)	4 (16.0%)	
Operation : Hr0, 1	8 (38.1%)	4 (16.0%)	0.09
HR2, 3	13 (61.9%)	21 (84.0%)	
Adjuvant chemotherapy : No	14 (66.7%)	16 (64.0%)	0.85
Yes	7 (33.3%)	9 (36.0%)	

MF : mass forming, PI : periductal infiltrating, LN : lymph node, vp : portal vein invasion, vv : hepatic vein invasion, CEA : carcinoembryonic antigen, CA19-9 : carbohydrate antigen 19-9, HBV : Hepatitis B virus, HCV : Hepatitis C virus, H0 : partial hepatectomy, Hr1: segmentectomy, Hr2 : bi-segmentectomy, Hr3 : tri-segmentectomy
Continuous variable (age) was expressed as mean ± standard deviation.

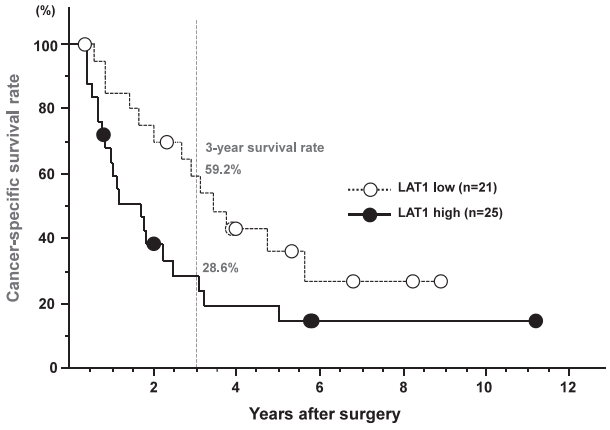

Fig 2. Cancer-specific survival rate in the LAT1-low and LAT1-high groups
The LAT1-high group showed poor survival compared with the LAT1-low group.

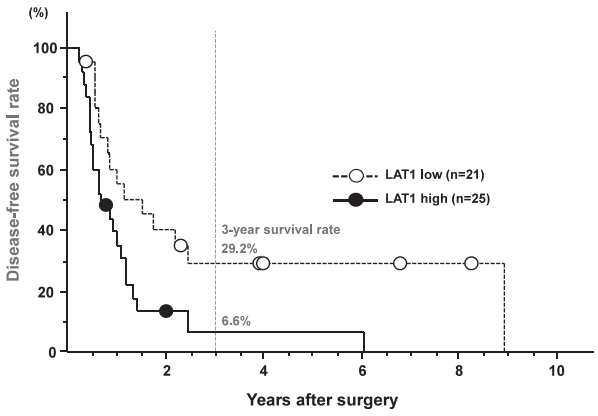

Fig 3. Disease-free survival rate in the LAT1-low and LAT1-high groups
The LAT1-high group showed poor survival compared with the LAT1-low group.

DISCUSSION

The present study evaluated the clinical significance of LAT1 expression in IHCC. Relationship was observed between LAT1-high expression and periductal infiltrating type, and higher CEA/CA19-9 levels. IHCC in the hilar location showed a tendency of the periductal infiltrating type, similar to pancreatic cancer in molecular marker and pathological morphology (21). Periductal infiltrating type and high CEA/CA19-9 levels were also reported as prognostic factors in IHCC (16-20). Thus, LAT1-high expression seemed to be related to the aggressive malignant phenotype of IHCC. It has been shown that increased LAT1 expression is involved in cancer cell proliferation and progression, resulting in a poor prognosis for various cancers. LAT1 expression was highly correlated with the Gleason score in prostate cancer (22) and resulted in progression to the T stage in bladder cancer (23). Herein, there was no significant difference in the stage. However, a malignant potential seemed to exist

Table 2. Multivariate analysis for cancer-specific survival

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Tumor type (MF+PI [Ref : MF])	1.81 (0.86-3.82)	0.11	1.71 (0.76-3.85)	0.19
CEA (≥10 [Ref : < 10 ng/ml])	1.05 (0.46-2.44)	0.90	0.67 (0.27-1.71)	0.41
CA19-9 (≥ 100 [Ref : < 100 U/m])	1.88 (0.93-3.80)	0.07	1.39 (0.64-2.98)	0.40
LAT1 (High [Ref : Low])	2.07 (1.02-4.21)	0.04	2.16 (0.98-4.74)	0.06

Table 3. Multivariate analysis for disease-free survival

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Tumor type (MF+PI [Ref : MF])	1.27 (0.64-2.50)	0.49	1.51 (0.71-3.23)	0.28
CEA (≥ 10 [Ref : < 10 ng/ml])	1.06 (0.48-2.34)	0.88	0.68 (0.29-1.61)	0.38
CA19-9 (≥ 100 [Ref : < 100 U/m])	1.16 (0.60-2.21)	0.66	0.89 (0.44-1.78)	0.74
LAT1 (High [Ref : Low])	2.37 (1.20-4.70)	0.01	2.79 (1.32-5.91)	<0.01

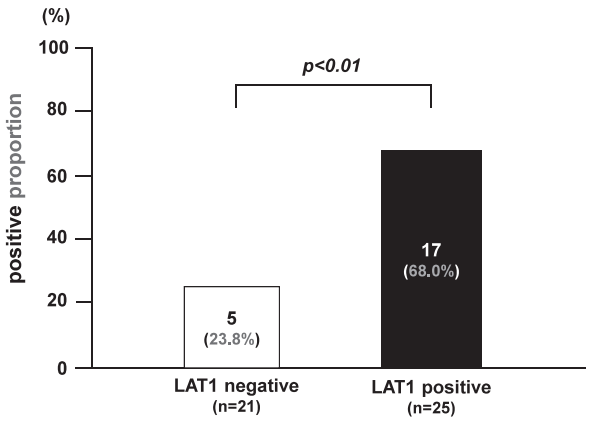

Fig 4. p-Akt positivity proportion in the LAT1-low and LAT1-high groups
The LAT1-high group showed a significantly higher p-Akt positivity proportion compared with the LAT1-low group.

in the LAT1-high group. Furthermore, LAT1 expression was associated with worse cancer-specific survival and disease-free survival in patients with IHCC. LAT1 expression has been considered a significant factor indicating a poor outcome in various human cancers (24-27).

LAT1 is an amino acid transporter that transports neutral amino acids, most of which are essential amino acids. The findings suggest that LAT1 can supply essential amino acids to tumor cells to support tumor cell proliferation and growth. Among the amino acids, leucine has been reported to promote myofibroblast differentiation via the Akt signaling pathway (28). Considering that the Akt signaling pathway is a signaling pathway correlated with cell survival, apoptosis inhibition, and cell cycle progression (10), we focused on Akt signaling. In non-small cell lung cancer, LAT1 inhibition led to the suppression of the cancer stemness gene through decreased Akt activation (6). It was also reported that increased LAT1 expression in bladder cancer could potentially trigger Akt/mTOR signaling and further contribute to bladder cancer progression and treatment resistance (23). In this study, the LAT1-high group showed a significantly higher rate of p-Akt positivity. Therefore, LAT1 expression seemed to enhance the malignant potential of IHCC via Akt signaling. Yanagisawa *et al*. (29) reported that overexpression of LAT1 in bile duct adenocarcinoma, including 15 IHCC cases, predicts poor prognosis. Furthermore, Yothaisong *et al*. (30) reported that inhibition of LAT1 activity was related with apoptosis induction in cholangiocarcinoma cells using in *vitro and in vivo* experiment. To the best of our knowledge, this is first report that LAT1 expression was related with worse prognosis via Akt signaling using resected IHCC specimen.

Kaira *et al*. (31) reported that LAT1 inhibition could enhance chemosensitivity such as 5-FU and gemcitabine. In this study, adjuvant chemotherapy was performed in 16 cases, and chemotherapy was performed in 14 cases after recurrence. However, Gemcitabine/5-FU treatment showed no difference in cancer-specific and disease-free survival compared with other treatment.

This study has several limitations. First, we only investigated LAT1 and p-Akt expression in resected specimens. Recently, JPH203, a LAT1 inhibitor, has been reported to show anticancer effects in various tumors (4). We plan on performing an *in vivo* study using a cholangiocarcinoma cell line with JPH203. Second, this was a single-center study wherein all patients were enrolled from only one hospital and the number of cases was small. Thus, prospective studies with larger patient populations are warranted in the future.

CONCLUSIONS

In conclusion, LAT1 expression was associated with poor prognosis of IHCC and higher p-Akt expression.

DECLARATIONS

Ethics approval and consent for participate statement : This study was approved by the Institutional Review Board of Tokushima University Hospital (No. 4144). Informed consent was waivered and information disclosure statement was upload in homepage of our hospital for opt-out.

Consent for publication : We understand that the text and any pictures published in the article will be freely available on the internet and may be seen by the general public. The pictures and text may also appear on other websites or in print, may be translated into other languages or used for commercial purposes.

Availability of data and materials : The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests : We state the potential conflicts of interest with regard to our study as follows : Mitsuo Shimada declares receiving unrestricted research grant from TAIHO PHARMACEUTICAL CO., LTD. Japan. All other authors report no conflict of interest.

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Author's contributions : B. S and S. Y contributed to data collection, and participated in writing the manuscript. Y. M, T. I, Y. S, H. T, S. O and M. S designed the study and checked the manuscript. S. Y and C. T evaluated the pathological findings.

CONFLICT OF INTEREST

The authors have no financial support to disclose.

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