RESEARCH ARTICLE

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High Prevalence of Cannabinoid Receptor 1 Expression in Thai Patients with Cholangiocarcinoma and Its Prognostic Implications

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Abstract

Objective: Cholangiocarcinoma (CCA) is highly prevalent in Thailand and remains associated with poor outcomes. Emerging evidence suggests that dysregulation of the endocannabinoid system may be involved in CCA pathogenesis and prognosis. This study aimed to evaluate the prevalence of cannabinoid receptor 1 (*CB1*) expression and its association with clinicopathological features and survival outcomes in Thai patients with CCA. **Methods:** We retrospectively reviewed patients with histologically confirmed CCA treated at a tertiary cancer center in Thailand between January 2014 and December 2018. *CB1* expression in tumor tissues was assessed by immunohistochemistry and semi-quantitatively scored according to staining intensity and extent. **Results:** Tumor specimens from 51 patients (median age 59 years; 41% female) were analyzed. Most patients had intrahepatic CCA (80%), and 47% presented with advanced-stage disease (stages III–IV). High *CB1* expression was observed in 46 of 51 cases (90%). Patients with high *CB1* expression more frequently had advanced-stage disease. During a median follow-up of 27.8 months, 34 patients died. The median overall survival (OS) was 18.5 months (95% CI, 6.1–36.5). There was no statistically significant difference in OS between patients with high and low *CB1* expression (median OS 18.5 vs. 23.0 months, respectively; p = 0.68). **Conclusion:** High *CB1* expression is highly prevalent in Thai patients with CCA. While no significant associations with clinicopathological features or survival were found in this small cohort, the widespread overexpression of *CB1* supports its potential biological and therapeutic relevance in CCA and warrants further investigation in larger studies.

Keywords: Cannabinoid receptor 1, Cholangiocarcinoma, Prognosis, Thailand

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Introduction

Cholangiocarcinoma (CCA), an aggressive cancer originating from bile duct epithelial cells, is one of the most common cancers among the population of Thailand. The unique epidemiology of CCA in Thailand is strongly linked to chronic infection with liver fluke Ophisthorchis viverini (OV), which induces chronic inflammation and fbrosis of bile duct, leading to the carcinogenesis process [1, 2].

Most patients are diagnosed at an advanced stage, which carries a dismal prognosis. While the ABC-02 trial established cisplatin and gemcitabine as the standard of care [3], the recent treatment landscape has recently shifted. The phase 3 TOPAZ-1 trial demonstrated that adding durvalumab to chemotherapy significantly improves overall survival, however median survival improvements are measured in months [4]. There remains an urgent and unmet need for novel therapeutic strategies.

The endocannabinoid system (ECS) is a critical signaling network involved in the maintenance of physiological homeostasis. Cannabinoid receptor 1 (*CB1*) is widely distributed throughout the central nervous system, where it modulates neurotransmitter release. Increasing evidence indicates that the ECS also plays an important role in cancer-related processes, including the regulation of cell proliferation, apoptosis, and angiogenesis, thereby highlighting its potential as a therapeutic target in oncology [5-7]. Upregulation of *CB1* receptors occurs in numerous cancers such as Hodgkin lymphoma, non-Hodgkin lymphoma, and hepatocellular carcinoma [8-10]. Further, the expression of *CB1* correlates with the prognosis of different cancers. For example, *CB1* expression is associated with shorter survival of patients with colorectal cancer, breast cancer, or thyroid cancer [11, 12]. In contrast, high expression of *CB1* is associated with longer disease-free survival among patients with hepatocellular carcinoma [13-15].

Evidence indicates that cannabinoids may serve as potential antitumor agents through their proapoptotic and

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cytotoxic effects mediated by various signal transduction pathways [16].

Although preclinical studies have shown promising antitumor effects of cannabinoids, clinical data remain limited [17-20] . Notably, a recent retrospective cohort study from Thailand suggested that medicinal cannabis use as part of palliative care may be associated with prolonged survival in patients with advanced cholangiocarcinoma [21].

The limited data on *CB1* expression in patients with CCA prompted us to determine the expression levels of *CB1* in CCA and their correlation with the clinical and pathological features, aiming to validate *CB1* as a valuable therapeutic target.

Materials and Methods

Patients and sample collection

Tissue samples and clinical data were obtained from 51 patients with CCA who underwent liver surgery or biopsy at Chulabhorn Hospital, a tertiary cancer center, Bangkok, Thailand, between January 2014 and December 2018. Patients were excluded from the study if they were diagnosed with other cancers, except squamous cell carcinoma of the skin. A pathologist (TS) confirmed that all samples were CCAs. Patients' clinical characteristics were collected, including age at diagnosis, sex, performance status, tumor-node-metastasis (TNM) classification, pathological grade, subtype classification, treatment protocol, cannabinoid use, and survival outcome. The stages of tumors of the perihilar, distal, and intrahepatic bile ducts were evaluated according to the TNM classification (8th edition) [22]. Overall survival (OS) was calculated as the date of pathological diagnosis to death for any reason or to the most recent follow-up. The cut-off date of analysis was December 31, 2020. The Human Research and Ethics Committee of Chulabhorn Research Institute approved the study, which adhered to its guidelines (Certificate No. 011/2563).

Immunohistochemistry

Formalin-fixed paraffin-embedded tissue sections (3-μm thick) were deparaffinized and stained according to a standard immunohistochemistry method employing a primary anti-*CB1* antibody (Cayman Chemical, Ann Arbor, MI) and a Ventana Benchmark XT fully-automated slide system. Sections were incubated for 1 h at 37 °C with the primary antibody (diluted 1:150). Neuronal cells in brain tissue sections, known to express *CB1*, were used as the positive control, whereas periductal fibroblasts surrounding normal bile ducts served as the negative control.

The immunoreactivity of *CB1* in CCA cells was quantitatively evaluated according to the intensity and area of staining as follows: 0 = no staining, 1 =weak – moderate, and 2 = strong. Areas of staining <33%, 33-66%, and >66% were scored as 1, 2, and 3, respectively. The final score was calculated as the product of the staining intensity and the size of the stained area [23]. A cutoff score of 6 (maximum staining intensity and extent) was chosen a priori to define a "high expression" group with the most unambiguous and uniform positivity, in order to maximize the contrast with the remaining tumors, which were classified as "low expression".

Statistical analysis

Statistical analysis was performed using STATA/SE v.12 software (StataCorp LP, College Station, TX, United States). Continuous data are expressed as the median +/- range as appropriate. Categorical data are presented as the frequency (percentage). The Kaplan–Meier method and the log-rank test were used for survival analysis, and $p < 0.05$ indicates a significant difference. Due to the small sample size and numerical imbalance between groups, comparisons with clinicopathological features are presented as descriptive, hypothesis-generating observations rather than definitive statistical tests.

Results

Patients' characteristics

The study included 51 patients (21 women and 30 men, ages ranging from 42 and 77 years, median 59 years) (Table 1). Patients were classified as TNM stages I–II (35%) and III–IV (47%), 80% were diagnosed with the intrahepatic type, and 20% of tumors were classified as well-differentiated. Twenty-eight patients underwent surgery (55%). Cannabinoid use was not consistently documented.

Expression of CB1 and the clinical characteristics of patients with CCA

CB1 expression was detected in all tumor specimens, in which 48 (94%) tissue samples were collected from the primary site (Figure 1). Forty-six patients expressed high levels of *CB1* (score = 6). In addition, four patients

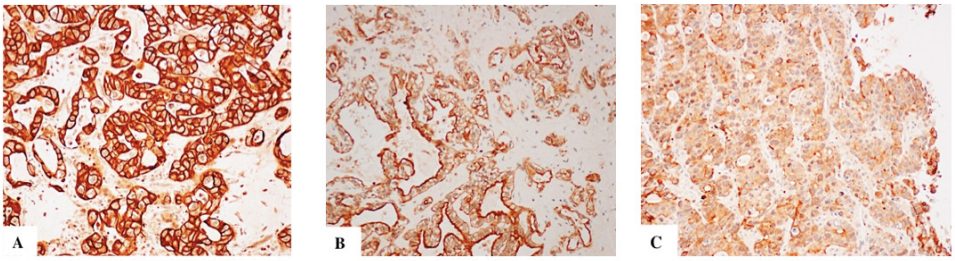

Figure 1. Immunohistochemical Analysis of *CB1* Expression in Cholangiocarcinoma Tissue. (A) Strong staining of CB1 and involved area >66% (total score = 6). (B) Strong staining of CB1 and involved area ranging from 33% to 66% (total score = 4). (C) Weak to moderate staining of CB1 receptor and involved area >66% (total score = 3). Magnification = 200×.

Table 1. Patients' baseline Characteristics

Characteristic	N = 51 (%)
Sex	
Male	30 (59)
Female	21 (41)
Median age, years (range)	59 (42–77)
ECOG performance status	
0–2	48 (94)
3–4	3 (6)
Site of histological analysis	
Primary	48 (94)
Metastatic	3 (6)
Cholangiocarcinoma subtype	
Intrahepatic CCA	41 (80)
Hilar CCA	5 (10)
Extrahepatic CCA	5 (10)
Stage	
I–II	18 (35)
III–IV	24 (47)
Unknown	9 (18)
Tumor grade	
Well-differentiated	10 (20)
Moderately differentiated	18 (36)
Poorly differentiated	2 (4)
Unknown	21 (41)
Surgery	28 (55)

ECOG, Eastern Cooperative Oncology Group; CCA, Cholangiocarcinoma

had a total score of 4, and one patient had a total score of 3, reflecting low levels of expression (Table 2). As a descriptive observation, more patients with high *CB1* expression were seen at advanced stages; however, this did not reach statistical significance and was not definitively concluded due to the limited power resulting from group imbalance (Table 3).

Table 2. Cannabinoid Receptor 1 Expression

Area (score)\	<33% (1)	33%– 66% (2)	>66% (3)
Staining Intensity (score)			
Undetectable (0)	0	0	0
Weak–Moderate (1)	0	0	1
Strong (2)	0	4	46

Specimens acquired from 51 patients were subjected to immunohistochemistry. The scores were determined as described in Materials and Methods.

Table 3. Relationship between *CB1* Expression and Clinicopathological Variables of Patients with Cholangiocarcinoma

Variable	Expression of *CB1*		p-value
	Low *CB1* N = 5	High *CB1* N = 46	
Age			0.66
≥60 years	3	22	
<60 years	2	24	
Sex			0.37
Men	4	26	
Women	1	20	
ECOG performance status			1
0-2	5	42	
3-4	-	3	
Unknown	-	1	
Stage			0.31
I–II	3	15	
III–IV	1	23	
Unknown	1	8	
Histology grade			0.06
Well-differentiated	1	9	
Moderately–Poorly differentiated	4	16	
Unknown	-	21	
Tumor type			0.25
Intrahepatic	3	38	
Hilar-Extrahepatic	2	8	

N, number of patients; ECOG, Eastern Cooperative Oncology Group

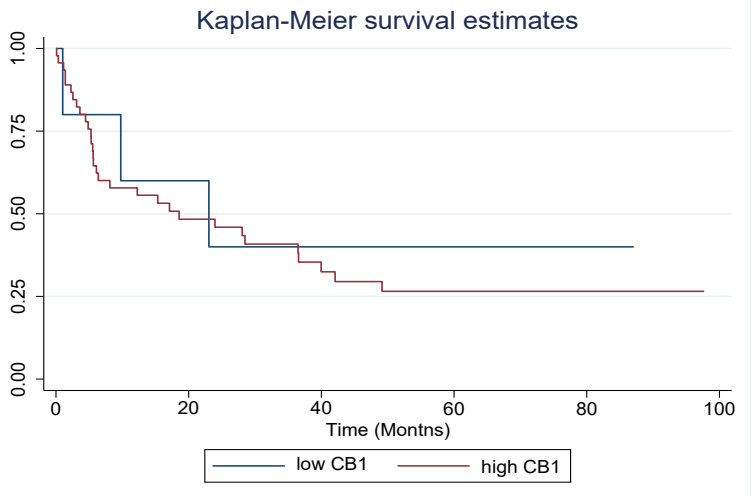

Figure 2. Kaplan–Meier Analysis of Overall Survival (OS) Associated with *CB1* Expression. The OS values of patients with high and low expression of *CB1* were 18 months and 23 months, respectively (p = 0.68).

The relationship between CB1 expression and survival

During follow-up (median 27.8 months), 34 patients died. The median overall survival of all patients was 18.5 months (95% CI, 6.1–36.5). Overall survival was not significantly different among patients with high or low *CB1* expression (median OS 18.5 vs 23.0 months, respectively, p = 0.68) (Figure 2).

Discussion

CCA is a biologically complex malignancy characterized by marked heterogeneity in its genetic and molecular landscape. Current classification systems are primarily based on anatomical location or pathological features. In Thailand, CCA is strongly associated with chronic infection by the liver fluke and exhibits distinct clinical characteristics and genomic alterations. Notably, these tumors are predominantly driven by epigenetic dysregulation induced by chronic parasitic inflammation rather than by classical oncogenic mutations [24].

Among genes reported to be aberrantly methylated in CCA, cannabinoid receptor–interacting protein 1 (CNRIP1) demonstrates one of the highest methylation frequencies, reaching up to 82% [25]. CNRIP1 functions as a putative tumor suppressor in CCA, and its downregulation through DNA hypermethylation has been shown to increase *CB1* expression. This epigenetic alteration promotes intrahepatic cholangiocarcinoma pathogenesis via suppression of parkin-dependent ubiquitination of pyruvate kinase M1 [26]. This mechanism may partly explain the high *CB1* expression observed in our cohort. To our knowledge, this study is the first to demonstrate such a high prevalence of high-level *CB1* expression (90%) in CCA tissues.

Another notable finding of this study was the presence of *CB1* expression in adjacent non-neoplastic cholangiocytes. Although normal biliary epithelium typically exhibits minimal *CB1* expression [20], this upregulation is consistent with previous reports demonstrating *CB1* induction in ductular proliferating cells under chronic inflammatory conditions [27]. Our findings likely reflect a field effect resulting from chronic OV infection. The parasite-derived growth factor granulin, called Ov-GRN-1 is secreted into bile and disseminated throughout the biliary tree [28], potentially inducing *CB1* upregulation in both malignant and neighboring non-malignant epithelial cells. This widespread induction underscores the systemic influence of parasite-derived growth factors on the biliary microenvironment and supports their role in CCA carcinogenesis.

Downregulation of CNRIP1 has previously been associated with poor prognosis in CCA [26], which is concordant with our observations. In our cohort, patients with high *CB1* expression tended to present with more advanced disease compared with those with low *CB1* expression, although these differences did not reach statistical significance. Similar associations between elevated *CB1* expression and aggressive tumor behavior have been reported in other malignancies. In prostate cancer, for example, high *CB1* expression in tumor tissue significantly correlates with higher Gleason scores and the presence of metastatic disease at diagnosis [29]. Likewise, high-grade gliomas and invasive ovarian cancers exhibit higher *CB1* expression compared with lower-grade tumors [12, 30].

From a mechanistic perspective, *CB1* receptors are coupled to multiple intracellular signaling cascades, including inhibition of cyclic adenosine monophosphate (cAMP) signaling and activation of the extracellular signal–regulated kinase (ERK) pathway. Both pathways play key roles in regulating cell proliferation and survival. Enhanced ERK activation in *CB1*-expressing tumors may therefore contribute to cancer progression and tumor growth [29].

In the present study, patients with CCA and high *CB1* expression demonstrated a trend toward shorter overall survival compared with those with low *CB1* expression (median overall survival, 18 months vs. 23 months), although this difference did not reach statistical significance (p = 0.68). Nevertheless, this trend is consistent with prior studies reporting a significant association between high *CB1* expression and poor prognosis [29, 31]. Similar observations have been reported in thyroid, breast, colorectal, and pancreatic cancers [15, 16, 23]. In contrast, overexpression of *CB1* has been associated with improved prognosis in hepatocellular carcinoma [13], underscoring the context-dependent and cancer-specific roles of cannabinoid receptors.

The discrepant prognostic implications of *CB1* expression across tumor types may be attributable to methodological differences, including variations in immunohistochemical staining protocols, antibody selection, scoring systems, and thresholds defining high versus low expression. Additionally, the relatively small and unbalanced number of patients with low *CB1* expression in our cohort may have limited the statistical power to detect significant survival differences.

The overexpression of *CB1* has emerged as a potentially attractive therapeutic target in cancer; however, the complexity of *CB1*-mediated signaling necessitates cautious interpretation. While dysregulated endogenous cannabinoid signaling may promote tumor progression, accumulating evidence suggests that exogenous cannabinoids particularly phytocannabinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD) may exert antitumor effects.

Recent studies have demonstrated that CBD induces autophagy and cancer cell death in CCA cell lines through modulation of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway [32, 33]. Similarly, THC has been shown to inhibit cell proliferation, migration, and invasion, while inducing apoptosis in CCA cell lines and mouse xenograft models [34]. In addition, THC suppresses tumor cell survival by inhibiting actin polymerization [20]. Collectively, these findings support the biological relevance of *CB1* signaling in CCA and highlight its potential therapeutic implications.

Establishing an association between high *CB1* expression and responsiveness to cannabinoid-based therapies represents an intriguing and clinically relevant possibility. Previous studies suggest that *CB1* expression

levels may influence the efficacy of cannabinoids in inducing apoptosis in cancer cells [35]. However, cannabinoid use was not documented among patients in the present study, precluding direct assessment of the potential therapeutic benefit of cannabinoids in this cohort.

Several limitations of this study should be acknowledged. First, the most significant limitation of this study is the small sample size and the extreme numerical imbalance between the *CB1* expression groups (46 vs. 5). Consequently, the study is underpowered to detect any meaningful differences in clinicopathological features or survival, and the negative survival finding should be interpreted with extreme caution. The primary value of this study lies in describing the high prevalence of *CB1* expression, not in its comparative analyses. Second, the retrospective design and single-center setting may limit the generalizability of the findings. Finally, epigenetic regulatory mechanisms, such as hypermethylation of the CNRIP1 gene, were not evaluated in tumor specimens, limiting insight into mechanisms underlying altered *CB1* expression. Future studies on this cohort should investigate the molecular underpinnings of the observed high *CB1* expression, including analysis of CNRIP1 promoter methylation and correlation with markers of chronic inflammation, to validate the proposed mechanistic link in a Thai population.

In conclusion, in this cohort of Thai CCA patients, high *CB1* expression was observed in 90% of tumors, representing a near-ubiquitous feature. This finding supports the biological relevance of the endocannabinoid system in CCA and suggests that *CB1* could be a viable therapeutic target. Larger studies are needed to definitively assess its relationship with disease stage and prognosis.

Author Contribution Statement

Conceptualization, C.A. and T.U.; methodology, T.U..; software, C.A.; validation, C.A., T.S. and T.U.; formal analysis, C.A., T.S. and T.U.; investigation, C.A., T.S. and T.U.; resources, C.A.; data curation, C.A., T.S. and T.U..; writing—original draft preparation, C.A.; writing-review and editing, T.U.; visualization, T.S. and T.U..; supervision, T.U.; project administration, C.A.; funding acquisition, T.U. All authors have read and agreed to the published version of the manuscript.

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General

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Ethical Declaration

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Human Research and Ethics Committee of Chulabhorn Research Institute (protocol code 011/2563).

Data Availability Statement

The data presented in this study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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