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ORIGINAL ARTICLE

Retrospective Study

High cellular prion protein expression in cholangiocarcinoma: A marker for early postoperative recurrence and unfavorable prognosis

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Abstract

BACKGROUND

The cellular prion protein (PrP^C), traditionally associated with neurodegenerative disorders, plays an important role in cancer progression and metastasis by inhibiting apoptosis.

AIM

To investigate the influence of PrP^C expression in cholangiocarcinoma (CCA) on patient outcomes following surgical resection.

METHODS

Patients who underwent curative surgical resection for either intrahepatic or hilar

CCA were enrolled in this retrospective study. Based on the immunohistochemical staining results of the surgical specimens, patients were categorized into two groups: The low PrP^C group (negative or 1+) and the high PrP^C group (2+ or 3+). Survival analyses, including overall survival and recurrence-free survival, were conducted using the Kaplan-Meier method and compared using the log-rank test.

RESULTS

In total, seventy-six patients diagnosed with CCA (39 with intrahepatic and 37 with hilar CCA) underwent curative hepatectomy from January 2011 to November 2021. Among these patients, 38 (50%) demonstrated high PrP^C expression, whereas the remaining 38 (50%) showed low expression of PrP^C. During a median follow-up period of 31.2 months (range: 1 to 137 months), the high PrP^C group had a significantly shorter median overall survival than the low PrP^C group (40.4 months *vs* 137.9 months, respectively; $P = 0.041$). Moreover, the high PrP^C group had a significantly shorter median recurrence-free survival than the low PrP^C group (13.3 months *vs* 23.8 months, respectively; $P = 0.026$).

CONCLUSION

PrP^C expression is significantly associated with early recurrence and decreased survival period in CCA patients following surgical resection. Thus, PrP^C may be used as a prognostic factor in treatment planning.

Key Words: Cholangiocarcinoma; Cellular prion protein; Liver neoplasms; Prognosis; Recurrence; Survival

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Core Tip: High cellular prion protein (PrP^C) expression is significantly associated with early recurrence and decreased survival period in cholangiocarcinoma patients following surgical resection. PrPC expression serves as an independent prognostic factor for overall survival and recurrence-free survival. These findings suggest that PrPC could be a valuable prognostic biomarker following curative surgery.

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INTRODUCTION

Cholangiocarcinoma (CCA) arises from the epithelial cells lining the bile duct and ranks as the second most common primary liver cancer, following hepatocellular carcinoma[1]. CCA is anatomically classified into three subtypes: Intrahepatic, hilar, and distal CCA[2,3]. The global incidence of CCA is increasing, especially intrahepatic CCA, which is growing more rapidly than extrahepatic CCA[4-6]. Surgical resection remains the only curative treatment for CCA; however, only 35% of patients are considered suitable for curative resection at the time of diagnosis[7,8]. CCA has a dismal prognosis, with a five-year survival rate of less than 20%[6,9]. Even with standard chemotherapy (gemcitabine plus cisplatin), the median survival period for patients with advanced, unresectable CCA does not exceed 12 months[10]. Molecular genetic profiling of tumors and targeted therapies are emerging as important areas of research[11,12]. Despite these ongoing research efforts, the development of personalized chemotherapeutic agents is urgently needed, and the identification of novel prognostic biomarkers plays a critical role in next-generation CCA treatment.

The prion protein is a cell surface glycoprotein predominantly expressed in the central and peripheral nervous systems [13]. Prion proteins have two isoforms: The cellular prion protein (PrP^C) and the scrapie prion protein (PrP^{SC})[14]. Misfolding of PrP^C into PrP^{SC} can lead to fatal neurodegenerative disorders[15]. PrP^C plays an important role in the nervous and immune systems, influencing cell proliferation, differentiation, survival, and programmed cell death[16,17]. PrP^C is emerging as a potential target for chemotherapy, given its implicated involvement in tumor growth, metastasis, resistance to chemotherapy-induced cell death, and overall cancer progression across different cancer types[18,19]. However, the role of PrP^C expression in CCA remains unknown. In this study, we aim to investigate two questions: (1) The expression of PrP^C in CCA; and (2) The effects of PrP^C on long-term prognosis such as recurrence and survival following surgical resection.

MATERIALS AND METHODS

Study population

This retrospective study enrolled patients who underwent curative surgical resection for intrahepatic and hilar CCA at Hallym University Sacred Heart Hospital (Anyang, Republic of Korea) between January 2011 and November 2021. The inclusion criteria were as follows: (1) Adults aged 18 years or older; (2) Those who underwent radical resection for CCA; and (3) Histologically confirmed adenocarcinoma in surgical specimens. Exclusion criteria were as follows: (1) A history of being diagnosed with cancer other than primary CCA; (2) The presence of malignant ascites, peritoneal metastasis, or distant metastasis at diagnosis; (3) Prior neoadjuvant chemotherapy or chemoradiation therapy; (4) Uncontrolled infections, diabetes mellitus, hypertension, ischemic heart disease, or myocardial infarction within the last 6 months; and (5) Neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease.

After surgery, patients were monitored every three months for the first year and then every six months thereafter. Postoperative tumor recurrence evaluation included imaging tests, such as computed tomography or magnetic resonance imaging, and blood tests, including serum carbohydrate antigen 19-9 (CA19-9). If tumor recurrence was detected, appropriate treatment was administered. Data on demographics, radiologic and pathologic characteristics (tumor size, location, number of metastatic lymph nodes, resection margin, differentiation), blood tests (CA19-9 and carcinoembryonic antigen), along with survival and recurrence information, were retrospectively collected from electronic medical records. Tumor stages were assessed according to the American Joint Committee on Cancer staging system, eighth edition[20].

Immunohistochemical staining of surgical specimens using tissue microarrays

Tissue microarrays (TMAs) utilized a 2 mm tissue core from the designated region, which was subsequently re-embedded. Each sample was meticulously arranged in duplicate to minimize tissue loss. These TMA blocks were subsequently sliced into 4 μm thick sections, which were used for immunohistochemical staining. Prior to staining, TMA sections underwent deparaffinization with xylene and hydration through a graded ethanol series. Following established protocols, they were treated with a peroxidase-blocking solution (Dako, Copenhagen, Denmark) for 10 minutes to inhibit endogenous peroxidase activity. After blocking with a protein solution (Dako) for 60 minutes at room temperature, the sections were incubated with a diluted rabbit polyclonal antibody against PrP^C (8H4; Sigma-Aldrich, St. Louis, MO, United States). Detection was carried out following the primary antibody incubation, using the Dako EnVision Detection System kit (Dako), in accordance with the manufacturer's guidelines.

Evaluation of immunostainings

The TMA slides were analyzed to determine the proportion of tumor cells with positive PrP^C staining in their nuclei. An expert pancreaticobiliary pathologist (Cho YA) without any knowledge of the patients' personal or clinical data evaluated the PrP^C stainings. Immunoreactivity was assessed based on the histochemical scoring (H-score) system. The H-score was calculated by a semi-quantitative assessment of both the intensity of staining (graded as: 0, no evidence of staining; 1+, weak staining; 2+, moderate staining; or 3+, strong staining, using adjacent normal mucosa as the median) and the percentage of positive cells. Expression levels of each component were classified into low PrP^C or high PrP^C groups based on the median value of the H-score (Figure 1).

Endpoints

Overall survival (OS) and recurrence-free survival (RFS) were compared between the two groups. OS was calculated from the date of surgery to either the date of death or the last follow-up. RFS was defined as the time from the date of surgery to recurrence or death from any cause.

Statistical analysis

Continuous variables are presented as means ± SD, whereas categorical variables are presented as frequencies and proportions. Categorical data were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Continuous data were analyzed using Student's *t*-test. Survival analyses for both RFS and OS were conducted using Kaplan-Meier curves, and differences in survival were tested using the log-rank test. Multivariate analyses for recurrence and survival were conducted using the Cox proportional hazards regression model. Variables with a P value < 0.1 in univariate analysis were included in the multivariate Cox regression model. To ensure the stability of the model, the ratio of events to independent variables was maintained at a minimum of 10 events per variable. Statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Chicago, IL, United States) and R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

Table 1 summarizes the demographic and clinical characteristics of the patients. The study included seventy-six patients who underwent surgical resection for CCA. Among these patients, 38 (50%) demonstrated high PrP^C expression, whereas the other 38 (50%) showed low expression of PrP^C. The median age was 66.7 years, with most patients being men (64.5%). Nearly half of the study population had intrahepatic CCA (48.7%), whereas all other patients had hilar CCA (51.3%). All patients underwent curative-intent hepatectomy. The median tumor size was 4.7 ± 2.8 cm, and 44.7% of patients had

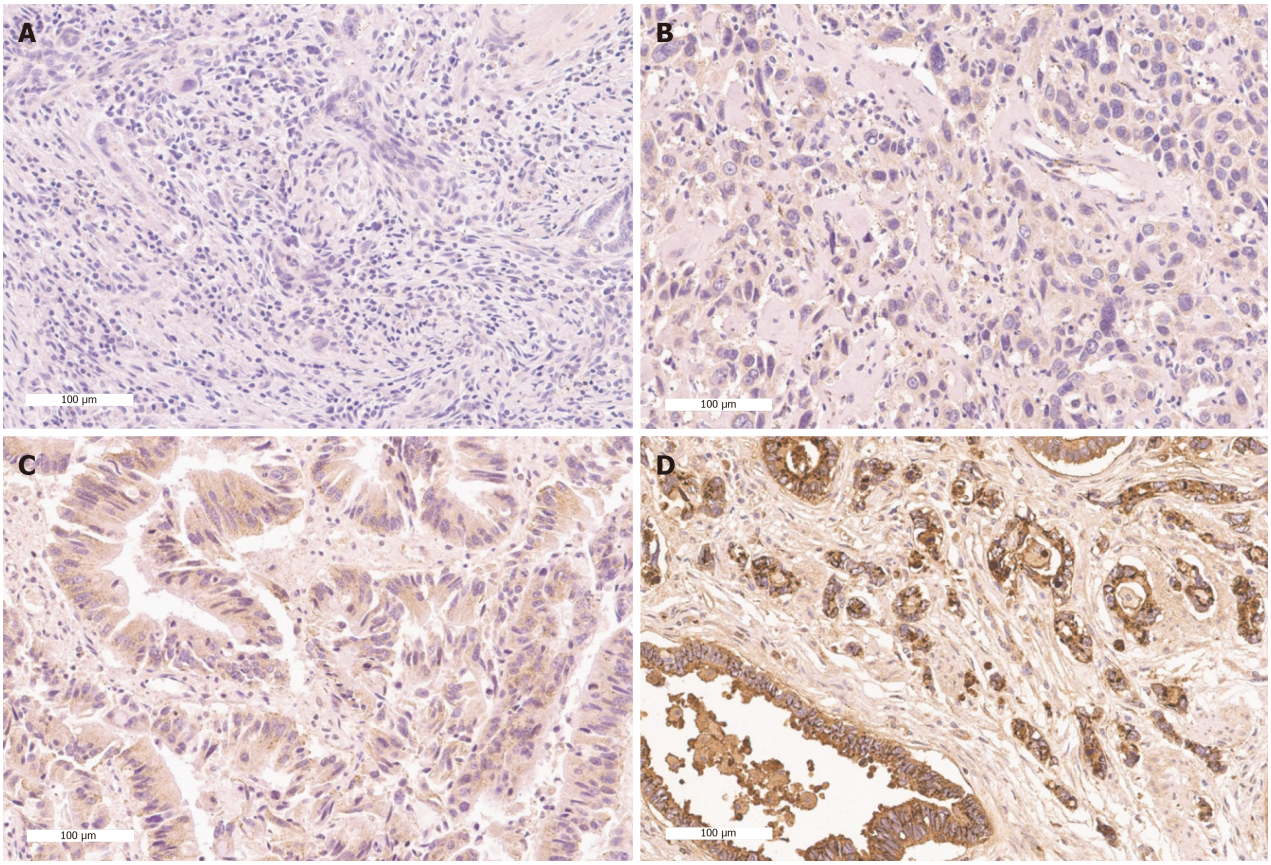

Figure 1 Representative figures of prion protein expression by immunohistochemical staining. A: No staining (0); B: Weak staining (1+); C: Moderate staining (2+); D: Strong staining (3+).

lymph node involvement. According to the American Joint Committee on Cancer 8th edition staging system, 11 (14.5%), 17 (22.4%), and 48 (63.2%) patients were classified as stages I, II, and III, respectively. Margin-negative (R0) resection was achieved in 63.2% of patients, whereas 35.5% had R1 resection. Most tumors were either well-differentiated (26.3%) or moderately differentiated (65.8%). The mean concentrations of CA19-9 and carcinoembryonic antigen were 957.8 ± 2237.2 U/mL and 8.1 ± 21.0 ng/dL, respectively. Baseline characteristics showed no significant differences between the low and high PrP^{C} groups.

OS and RFS

During the median follow-up period of 31.2 months (ranging from 1 to 137 months), 20 patients (26.3%) were alive without recurrence. The high PrP^{C} group exhibited a shorter median OS of 40.4 months [95% confidence interval (CI): 11.2-59.1] compared to the low PrP^{C} group with a median OS of 137.9 months (95%CI: 72.8-147.1; log-rank test, P = 0.041; Table 2, Figure 2A). Furthermore, the high PrP^{C} group had a shorter median RFS of 13.3 months compared to the low PrP^{C} group with a median RFS of 23.8 months (P = 0.026; Table 2, Figure 2B).

Univariate and multivariate analyses of OS and RFS

Table 3 presents the results of the univariate and multivariate analyses on the prognostic factors influencing OS. The univariate analysis identified tumor size ≥ 5 cm [hazard ratio (HR) = 2.609; 95%CI: 1.218-5.591; P = 0.014], lymph node metastasis (HR = 2.222; 95%CI: 1.039-4.753; P = 0.040), and high PrP^{C} expression (HR = 2.187; 95%CI: 1.015-4.709; P = 0.046) as independent prognostic factors. In the multivariate analysis, tumor size ≥ 5 cm [adjusted HR (aHR) = 2.448; 95%CI: 1.130-5.306; P = 0.023], lymph node metastasis (aHR = 2.633; 95%CI: 1.168-5.936; P = 0.020), and high PrP^{C} expression (aHR = 2.877; 95%CI: 1.260-6.572; P = 0.012) remained independent prognostic factors for OS. Table 4 details the results of univariate and multivariate analyses affecting RFS. The univariate analysis revealed that high PrP^{C} expression (HR = 1.985; 95%CI: 1.071-3.679; P = 0.029) was the only significant prognostic factor.

DISCUSSION

To the best of our knowledge, this is the first study investigating the expression of PrP^{C} in CCA. We found that patients with high intratumoral PrP^{C} expression had significantly shorter OS and RFS compared to those with low intratumoral PrP^{C} expression. Multivariate analysis identified PrP^{C} expression as an independent prognostic factor, similar to established factors such as tumor size and lymph node metastasis. These findings suggest that PrP^{C} expression may serve

Table 1 Patient and tumor characteristics of the study, *n* (%)

Characteristics	Category	Subgroup (based on immunostaining)		Total (*n* = 76)	*P* value
		Low PrP^C (*n* = 38)	High PrP^C (*n* = 38)		
Age (years), mean ± SD		66.7 ± 9.5	66.8 ± 9.8	66.7 ± 9.6	0.953
Male		22 (57.9)	27 (71.1)	49 (64.5)	0.338
BMI (kg/m^2), mean ± SD		24.4 ± 2.9	23.4 ± 2.7	23.9 ± 2.8	0.139
Location	Hilar CCA	22 (57.9)	15 (39.5)	37 (48.7)	0.169
	Intrahepatic CCA	16 (42.1)	23 (60.5)	39 (51.3)	
Tumor size (cm), mean ± SD		4.1 ± 1.9	5.3 ± 3.5	4.7 ± 2.8	0.056
Positive LN		17 (44.7)	17 (44.7)	34 (44.7)	1.000
TNM stage	I	6 (15.8)	5 (13.2)	11 (14.5)	0.890
	II	9 (23.7)	8 (21.1)	17 (22.4)	
	III	23 (60.5)	25 (65.8)	48 (63.2)	
Resection margin	R0	27 (71.1)	21 (55.3)	48 (63.2)	0.262
	R1	11 (28.9)	16 (42.1)	27 (35.5)	
	R2	0 (0.0)	1 (2.6)	1 (1.3)	
Differentiation	WD	8 (21.1)	12 (31.6)	20 (26.3)	0.177
	MD	25 (65.8)	25 (65.8)	50 (65.8)	
	PD	5 (13.2)	1 (2.6)	6 (7.9)	
Laboratory tests	CEA (ng/dL)	5.6 ± 4.4	11.1 ± 31.0	8.1 ± 21.0	0.406
	CA19-9 (U/mL)	813.7 ± 2038.1	1115.9 ± 2461.6	957.8 ± 2237.2	0.591

PrP^C: Cellular prion protein; BMI: Body mass index; LN: Lymph node; TNM: Tumor-node-metastasis; CCA: Cholangiocarcinoma; R0: No cancer cells seen microscopically at the primary tumor site; R1: Cancer cells present microscopically at the primary tumor site; R2: Macroscopic residual tumor at primary cancer site or regional lymph nodes; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; WD: Well-differentiated; MD: Moderately differentiated; PD: Poorly differentiated.

Table 2 Median overall survival and recurrence-free survival according to cellular prion protein expression

Characteristics	Low PrP^C (*n* = 38)	High PrP^C (*n* = 38)	*P* value
Median OS (95%CI), months	137.9 (72.8-147.1)	40.4 (11.2-59.1)	0.041
3-year survival rate (%)	28 (73.7)	27 (71.1)	-
5-year survival rate (%)	27 (71.1)	21 (55.3)	-
Median RFS (95%CI), months	23.8 (15.6-133.6)	13.3 (7.3-31.6)	0.026
3-year recurrence-free rate (%)	20 (52.6)	18 (47.4)	-
5-year recurrence-free rate (%)	19 (50.0)	16 (42.1)	-

PrP^C: Cellular prion protein; OS: Overall survival; CI: Confidence interval; RFS: Recurrence-free survival.

as a postoperative prognostic biomarker of CCA, akin to pancreatic cancer or hepatocellular carcinoma[21,22].

PrP^C is a glycosylphosphatidylinositol-anchored cell surface protein that consists of 208 amino acids[19]. The structure of PrP^C includes a flexible coil in the N-terminal domain and a globular C-terminal domain containing three α-helices and two β-sheets[23]. PrP^C is found not only in the nucleus but also in the mitochondria and Golgi complex[24-26]. Expression of PrP^C begins during embryogenesis and reaches its highest level in adulthood[27,28]. Prion disease is an untreatable, fatal, transmissible neurodegenerative disorder caused by the accumulation of misfolded PrP^{SC} in the brain[29]. Transmissible spongiform encephalopathies caused by PrP^{SC} include sporadic Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, fatal familial insomnia, Gerstmann-Straussler-Scheinker Syndrome, and Kuru[30-32]. PrP^{SC} also plays a substantial role in other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease by interacting with amyloid-β and α-synuclein[33,34].

Table 3 Univariate and multivariate Cox regression analyses of clinical and radiological parameters affecting overall survival in patients with resected cholangiocarcinoma

Subgroup	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Age ≥ 65 years	0.764 (0.357-1.635)	0.488	-	-
Male	1.496 (0.658-3.400)	0.336	-	-
Tumor size ≥ 5 cm	2.609 (1.218-5.591)	0.014	2.448 (1.130-5.306)	0.023
LN metastasis	2.222 (1.039-4.753)	0.040	2.633 (1.168-5.936)	0.020
Resection margin	2.036 (0.954-4.349)	0.066	-	-
MD tumor (WD as a reference)	1.321 (0.552-3.158)	0.532	-	-
PD tumor (WD as a reference)	1.073 (0.222-5.180)	0.930	-	-
CA19-9 ≥ 37 U/mL	2.248 (0.954-5.296)	0.064	-	-
High PrP^{C}	2.187 (1.015-4.709)	0.046	2.877 (1.260-6.572)	0.012

HR: Hazard ratio; CI: Confidence interval; aHR: Adjusted hazard ratio; LN: Lymph node; MD: Moderately differentiated; WD: Well-differentiated; PD: Poorly differentiated; CA19-9: Carbohydrate antigen 19-9; PrP^{C}: Cellular prion protein.

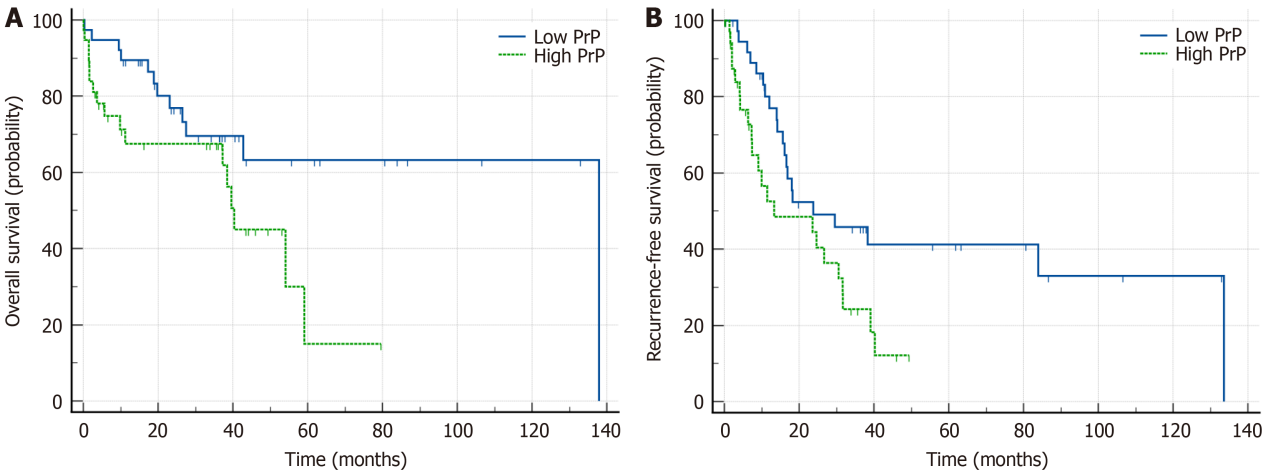

Figure 2 Kaplan Meier survival curves according to prion protein expression. A: Overall survival; B: Recurrence free survival.

PrP^{C} is not only expressed in the central nervous system but also in non-neuronal tissues such as the heart, lungs, lymphocytes, and gastrointestinal tract[28,35,36]. Interestingly, PrP^{C} is involved in several physiological processes, including stress protection, cellular differentiation, mitochondrial homeostasis, circadian rhythm, myelin homeostasis, and immune modulation[27,37]. In addition, PrP^{C} inhibits apoptosis and supports tumor progression by enhancing cancer cell proliferation and metastasis[37-44]. Therefore, PrP^{C} is involved in the development of human cancers including hepatocellular carcinoma[21], pancreatic cancer[45,46], gastric cancer[47], colorectal cancer[48], melanoma[49], and glioblastoma[50] beyond prion disease. PrP^{C} has also been identified in exosomes secreted by cancer cells[51], and such exosomes can promote tumor metastasis by increasing the permeability of endothelial cells and the secretion of angiogenic factors[52]. Recent studies suggest that PrP^{C} contributes to cancer development through various pathways that regulate tumor growth, differentiation, migration, and invasion[53-57]. Cancer tissue exhibits greater genetic instability and increased expression of the *PRNP* gene[44]. Using The Cancer Genome Atlas database, genome-wide association studies analyzing data from 10967 patients with cancer revealed 48 mutations, with eight somatic mutations (G131V, D167N, V180I, D202N, V203I, R208C, R208H, and E211Q) identified as pathogenic[44,58]. Somatic mutations in the *PRNP* gene have been found in various cancers, including lung adenocarcinoma, colorectal adenocarcinoma, endometrial cancer, head and neck squamous cell carcinoma, and melanoma[44]. Overexpression of PrP^{C} is associated with malignant phenotypes of cancer stem cells in various solid tumors[46,59,60]. In contrast, the suppression of PrP^{C} expression impairs proliferation and migration, thereby reducing invasiveness[61-63].

Hypoxia, a common condition in tumor microenvironments due to rapid cell growth outpacing the development of new blood vessels, has a close relationship with PrP^{C}. Under hypoxic conditions, cells often increase survival pathways to adapt to stress, and PrP^{C} has been observed to interact with hypoxia-inducible factor 1-alpha (HIF-1α), a key transcription factor that manages the cellular response to low oxygen levels[64,65]. Since HIF-1α regulates the expression of genes

Table 4 Univariate and multivariate Cox regression analyses of clinical and radiological parameters affecting recurrence-free survival in patients with resected cholangiocarcinoma

Subgroup	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	aHR (95%CI)	*P* value
Age ≥ 65 years	0.968 (0.510-1.840)	0.921	-	-
Male	1.163 (0.617-2.193)	0.641	-	-
Tumor size ≥ 5 cm	1.605 (0.816-3.157)	0.170	-	-
LN metastasis	1.484 (0.803-2.746)	0.208	-	-
Resection margin	1.070 (0.563-2.034)	0.837	-	-
MD tumor (WD as a reference)	1.385 (0.686-2.796)	0.363	-	-
PD tumor (WD as a reference)	0.290 (0.037-2.247)	0.236	-	-
CA19-9 ≥ 37 U/mL	1.355 (0.724-2.534)	0.342	-	-
High PrP^{C}	1.985 (1.071-3.679)	0.029	1.985 (1.071-3.679)	0.029

HR: Hazard ratio; CI: Confidence interval; aHR: Adjusted hazard ratio; LN: Lymph node; MD: Moderately differentiated; WD: Well-differentiated; PD: Poorly differentiated; CA19-9: Carbohydrate antigen 19-9; PrP^{C}: Cellular prion protein.

involved in angiogenesis, metabolism, and cell survival, PrP^{C} may indirectly help cancer cells adapt to hypoxic conditions, thus promoting tumor proliferation[66-68]. Growing evidence links increased PrP^{C} expression to the invasiveness of various cancers. HIF-1α plays a pivotal role in cancer progression as its overexpression is implicated in numerous pathways related to angiogenesis, cell proliferation, maintenance of cancer stem cells, promotion of genetic instability, and development of treatment resistance, among others[52,69,70].

High levels of PrP^{C} expression are associated with increased resistance to various types of drugs in glioblastoma, gastric cancer, breast cancer, and colorectal cancer[71-74]. Conversely, the inhibition or knockdown of PrP^{C} induces sensitivity to chemotherapy[35]. In colorectal cancer cells, PrP^{C} is involved in 5-fluorouracil resistance by activating the phosphatidylinositol 3-kinase/protein kinase B signaling pathway and increasing cell survival and proliferation through the expression of cell cycle-related proteins[75]. PrP^{C} can promote multi-drug resistance by upregulating the multidrug resistance p-glycoprotein and inhibiting apoptosis in gastric cancer and breast cancer cells[63,76]. PrP^{C} levels are significantly increased in colorectal cancer cells resistant to 5-fluorouracil and oxaliplatin[75,77]. Increased PrP^{C} expression is also linked with the radiotherapy resistance of tumors. Ionizing radiation can increase the expression of PrP^{C} by activating the ATM-TAK1-PrP^{C} pathway, thereby increasing radiotherapy resistance in glioblastoma, breast cancer, and colon cancer[78]. Taken together, PrP^{C} can regulate several signaling pathways that contribute to cancer resistance. Developing monoclonal antibodies against PrP^{C} and PrP^{C}-specific T cells could be a promising novel approach for creating new compounds for immunotherapy[79].

This study has some potential limitations that should be considered when interpreting the results. First, this is a small-scale study conducted at a single institution, focusing only on intrahepatic and hilar CCA. Therefore, a large-scale study is needed to understand the expression of PrP^{C} in bile duct cancer, including extrahepatic CCA. Second, as this is a retrospective study using existing data, it cannot control for variables that may have been inconsistently or inaccurately recorded, which could lead to selection bias. Third, research on the pathophysiological mechanisms of PrP^{C} in CCA is lacking. Further research is needed to confirm the functional role of PrP^{C} in CCA. Despite these limitations, this study has several strengths. This is the first study, to our knowledge, that explores PrP^{C} expression in patients with surgically removed CCA, offering new insights into the biology of its aggressiveness. Increasing evidence suggests that PrP^{C} is a promising target for cancer treatment, indicating the need for continued research in this field.

CONCLUSION

This study shows that CCA patients with high PrP^{C} expression have shorter postoperative OS and RFS than those with low PrP^{C} expression. The study results suggest that the level of PrP^{C} expression in CCA may serve as a significant prognostic marker following curative surgery.

FOOTNOTES

Author contributions: Shin DW and Cho YA contributed equally to this manuscript as co-first authors. Shin DW and Kim SE contributed to the conceptualization and methodology, and writing-review and editing of this manuscript; Choe JY participated in the data collection; Cho YA took part in the construction of tissue microarray of this study, interpretation of the data and contributed to writing

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