RESEARCH ARTICLE

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Survival after Surgery among Cholangiocarcinoma Patients Comparing between Mucin Producing and Non-Mucin Producing

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Abstract

Background: Mucin-producing cholangiocarcinoma (MPCC) was rare biliary tract malignancy. Studies regarding this type of cholangiocarcinoma (CCA) were limited, particularly the survival outcome. We aim to evaluate the survival rate, median survival time after surgery among CCA patients and to determine the association between MPCC and survival. Objective: To evaluate survival rate, median survival time after surgery among cholangiocarcinoma patients and to determine the association between mucin-producing cholangiocarcinoma and survival. **Methods:** CCA patients who underwent surgery between 2013 and 2020 from the Cholangiocarcinoma Screening and Care Program (CASCAP), Northeast Thailand were included in the study. The MPCC was based on pathological findings after surgery. The survival of CCA patients was verified through medical records and civil registration. Survival rates and median survival time since the date of CCA surgery and its 95% confidence intervals (CI) were estimated. Multiple cox regression was performed to evaluate factors associated with survival which were quantified by adjusted hazard ratios (AHR) and their 95% CI. **Results:** Of 1,249 CCA patients which constituted 24,593 person-months, 687 died at the completion of the study. The overall incidence rate was 2.79 per 100 patients per month, the median survival time was 21.77 months (95% CI: 19.87 - 23.84), and the 5-year survival rate was 28.29% (95% CI: 24.99 - 31.67). From these patients, 210 (16.81%) were MPCC, the incidence rate was 1.81 per 100 patients per month, median survival time was 41.21 months (95% CI: 26.16 - 81.97), and 5-year survival rate was 44.69% (95% CI: 32.47 - 56.16). MPCC were 35% less likely to died compared with non-MPCC (AHR = 0.65; 95% CI: 0.50 - 0.84). **Conclusions:** Our study revealed that CCA patients with MPCC had longer survival times and higher survival rates than those without MPCC. This classification will lead to appropriate treatment guidelines for CCA patients.

Keywords: Cholangiocarcinoma- Mucin-producing- survival- CASCAP- Thailand

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Introduction

Cholangiocarcinoma (CCA) is a biliary tract malignancy that occurs with high incidence in the northeastern part of Thailand, while in other countries it is usually a rare cancer [1]. CCA is characterized by its highly aggressive and heterogeneous nature, evident at both intertumoral and intratumoral levels, leading to a challenging prognosis [2]. CCA is frequently associated with a grim prognosis, largely attributable to the prevalent diagnosis at advanced stages. The potential for improved survival outcomes lies in the early detection of CCA through screening initiatives. Unfortunately, a significant portion of patients are diagnosed at later stages, impeding the effectiveness of available interventions. Previous study shows the 5-year survival rate for CCA patients stands at approximately 30% [3], underscoring the formidable challenges associated with managing this aggressive cancer.

The situation is particularly daunting in Northeastern Thailand, where the 5-year survival rate dips even further to 20.6% [4]. Furthermore, a recent analysis utilizing data

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from a CCA screening program in northeastern Thailand revealed a median survival time of 17.8 months for patients undergoing surgery, with a corresponding 5-year survival rate of 24.6% [5]. This regional disparity highlights the complex interplay of factors influencing CCA outcomes and underscores the critical need for strategies to enhance early detection and access to effective treatments.

According to the histological classification by the World Health Organization (WHO), adenocarcinoma is the predominant histologic type in CCA, constituting over 95% of identified histological variants [6]. Mucin-producing cholangiocarcinoma (MPCC) is a distinctive characteristic and is precisely defined as a malignant neoplasm in which extracellular mucinous components contribute to a minimum of 50% of the total tumor volume [7]. There is a potential association between MPCC and the carcinogenic processes originating from biliary tree stem, contributing to the pathogenesis of CCA [8, 9]. The prevalence of MPCC exhibits variability across different studies. A study conducted in Japan reported a prevalence of 4.7% [10], whereas a study in Taiwan identified a higher prevalence of 12.9% [11]. Notably, in the context of intrahepatic CCA, MPCC was found to be exceptionally rare, with a prevalence of 0.4% [12], characterizing it as an uncommon histological subtype.

The profile of MPCC is marked by accelerated growth, extensive metastases, and an overall dismal prognosis, frequently manifesting at advanced stages [13] especially in the northeastern region of Thailand [14, 15]. Nevertheless, conflicting findings propose that mucinous CCA might exhibit less advancement compared to its conventional counterpart [11]. Given the rarity of this disease and the existing controversies surrounding its outcomes, no study to date has provided comprehensive insights into MPCC with a sufficiently large sample size. The objective of this study is to assess the survival rate and median survival time following surgery among patients with MPCC within the spectrum of CCA. Additionally, the investigation aims to elucidate any potential associations between MPCC and overall survival in this cohort.

Materials and Methods

Design overview

All patients diagnosed with CCA were enrolled participants in the Cholangiocarcinoma Screening and Care Program (CASCAP) in Northeast Thailand [16], and they underwent surgical procedures between 2013 and 2020. The data relied on histological diagnoses. MPCC was pathologically confirmed through the presentation of large extracellular mucus lakes containing floating carcinoma cells, constituting more than 50% of the neoplasm, and only cases meeting this criterion were included in the study. CCA patients whose pathological results did not confirm CCA were excluded from the analysis.

Primary outcome and study factors

The primary outcome for this study was the duration, measured in months, from the date of surgery for CCA (start date) to the date of death or the last follow-up (end date), confirmed through medical records and civil registration, with a total follow-up period of five years. The factors of interest included the diagnosis of MPCC, categorized into two groups (non-MPCC and MPCC). Additionally, various covariates were considered, such as gender, age at enrollment (in years), educational levels, main occupation, *O. viverrini* infection, history of PZQ treatment, smoking history, alcohol consumption history, and the stage of CCA.

Statistical analysis

The demographics of CCA patients were characterized by categorical data, encompassing variables such as MPCC diagnosis, gender, age groups at enrollment, educational levels, occupation, *O. viverrini* infection, PZQ treatment, smoking history, alcohol consumption history, and the stage of CCA. Descriptive statistics, including frequency numbers and percentages, were employed to portray these characteristics for the overall cohort and were further stratified by non-MPCC and MPCC groups. Continuous data, such as age in years, were summarized using mean and standard deviation (SD), along with the minimum and maximum range.

The incidence rate of CCA mortality per 100 person-months following surgery for CCA was calculated using Poisson distribution assumptions. In this calculation, the numerator represents the number of deaths attributed to CCA, while the denominator comprises the cumulative survival times of all patients included in the study. The study reports this rate along with its corresponding 95% confidence interval (CI). Survival rates and median survival times from the date of surgery until death due to CCA, along with their respective 95% CIs, were estimated using Kaplan-Meier methods. The association between MPCC and CCA survival, without considering other factors, was assessed through simple Cox regression analysis, presenting crude hazard ratios (CHR) and their 95% CI. Subsequently, the association between MPCC and CCA survival, adjusted for other factors, was presented using adjusted hazard ratios (AHR) and their 95% CI, determined through multiple Cox regression analysis. All statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant. The analyses were conducted using STATA version 18 (Stata, College Station, TX).

Results

Characteristics of study participants

Participants included in the CASCAP who underwent surgery between 2013 and 2020 were filtered based on confirmed histological evidence of CCA. The study comprised 1,249 cases of CCA, with a mean age of 61.65 (SD = 8.67) years. Approximately two-thirds of the participants were male (63.25%), the majority were engaged in farming occupations (68.21%), and slightly over half were diagnosed at a late stage of CCA (58.66%). Among all CCA patients, 210 cases (16.81%) were identified as MPCC. Within the MPCC subgroup, more than half were male (58.57%), with a mean age of 63.57 (SD = 7.97) years, and over half were classified at an early

Table 1. Baseline Demographic and Clinical Characteristics of Patients with Cholangiocarcinoma

Characteristics	Overall		Non-MPCC		MPCC	
	Number	%	Number	%	Number	%
Gender						
Female	459	36.75	372	35.8	87	41.43
Male	790	63.25	667	64.2	123	58.57
Age at enrollment (years)						
<50	107	8.57	100	9.62	7	3.33
50-60	413	33.07	354	34.07	59	28.1
>60	729	58.37	585	56.3	144	68.57
Mean (Standard deviation)	61.65 (8.67)		61.26 (8.76)		63.57 (7.97)	
Educational levels						
Secondary and lower	1,145	91.67	958	92.2	187	89.05
Certificate and higher	104	8.33	81	7.8	23	10.95
Occupation						
Farmer	852	68.21	722	69.49	130	61.9
Non-Farmer	397	31.79	317	30.51	80	38.1
O. viverrini infection						
No	948	75.9	793	76.32	155	73.81
Yes	301	24.1	246	23.68	55	26.19
Praziquantel treatment						
None	765	61.25	637	61.31	128	60.95
Yes	484	38.75	402	38.69	82	39.05
Smoking history						
No	626	50.12	523	50.34	103	49.05
Yes	623	49.88	516	49.66	107	50.95
Alcohol consumption history						
No	401	32.11	337	32.44	64	30.48
Yes	848	67.89	702	67.56	146	69.52
Stage of CCA						
Early	470	41.34	363	38.87	107	52.71
Late	667	58.66	571	61.13	96	47.29

CCA, Cholangiocarcinoma; MPCC, Mucin-producing cholangiocarcinoma; Min, Minimum number; Max, Maximum number

stage of CCA (52.71%) (Table 1).

Survival analysis

A total of 1,249 CCA patients which constituted 24,593 person-months, 687 were died at the completion of the study. The overall incidence rate of CCA mortality was 2.79 per 100 patients per month, the median survival time was 21.77 months (95% CI: 19.87 - 23.84), and the 5-year survival rate was 28.29% (95% CI: 24.99 - 31.67) (Table 2, Figure 1A, and Table 3). The incidence rate of MPCC mortality was 1.81 per 100 patients per month, the median survival time was 41.21 months (95% CI: 28.16 - 81.97), and the 5-year survival rate was 44.69% (95% CI: 32.47 - 56.16) (Figure 1B and Table 3). The median survival time for early-stage CCA was 64.92 months (95% CI: 46.85 - 78.13) (Figure 1C). In terms of CCA stage, the median time for MPCC at stage I was 64.92 (95% CI: 45.34 - 85.44) (Figure 1D).

The bivariate analysis, following a simple cox regression, revealed a statistically significant association between MPCC and CCA survival (CHR = 0.55; 95% CI: 0.43 - 0.70) when comparing the MPCC group to the

Table 2. Incidence Rate and Median Survival Time among Cholangiocarcinoma Patients Stratified by non-MPCC and MPCC

Cholangiocarcinoma	Number of CCA	Person-months	IR per 100	95% CI	Median time	95% CI
Overall	1,249	24,593	2.79	2.59 - 3.01	21.77	19.87 - 23.84
Mucinous types						
Non-MPCC	1,039	20,554	2.99	2.76 - 3.23	19.77	17.21 - 21.97
MPCC	210	4,040	1.81	1.44 - 2.27	41.21	28.16 - 81.97

CI, Confidence interval; IR, Incidence rate; MPCC, Mucin-producing cholangiocarcinoma

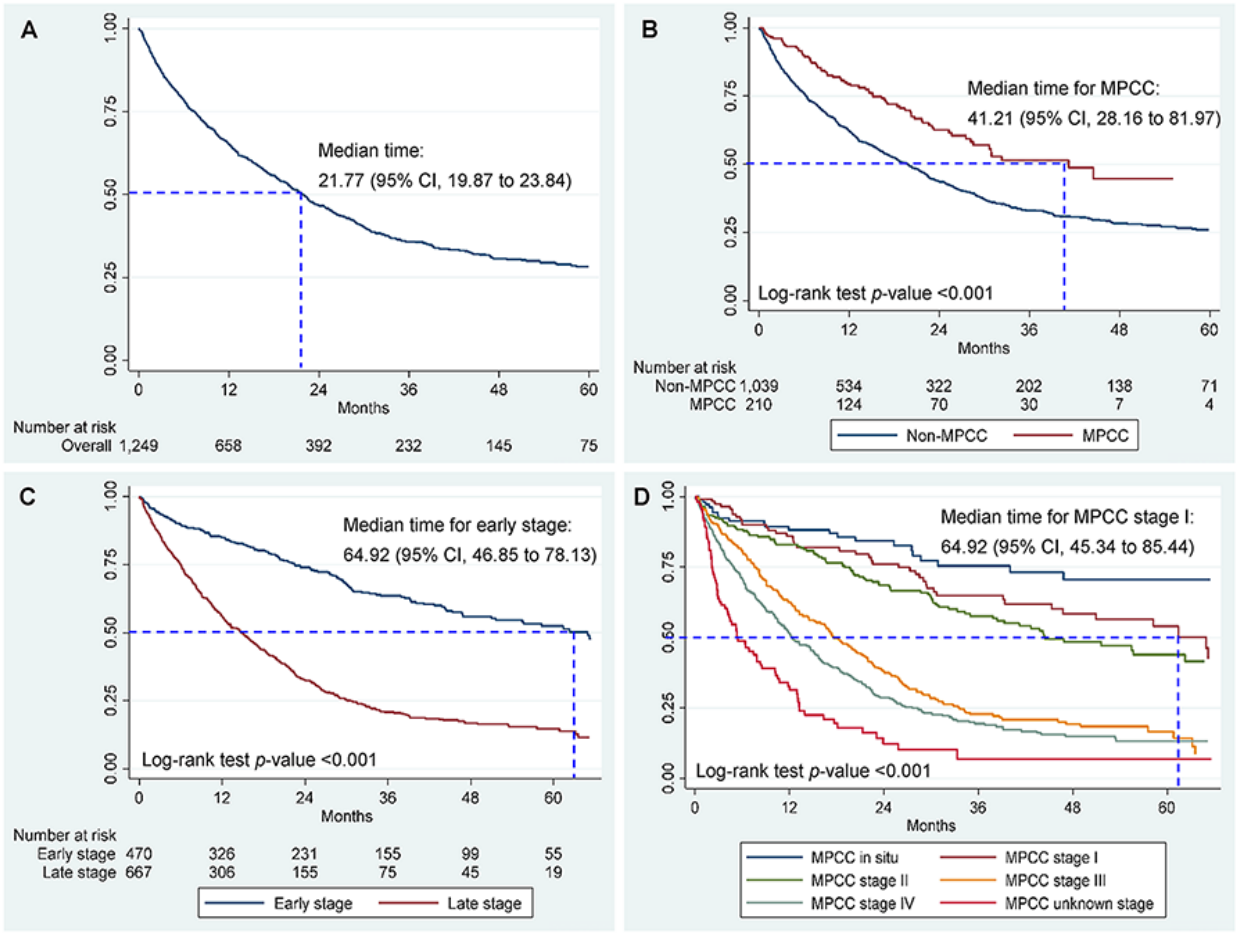

Figure 1. Kaplan-Meier Survival Estimates of Cholangiocarcinoma (CCA) (A: Overall survival, B: According to mucin-producing cholangiocarcinoma (MPCC) and Non MPCC, C: According to stage of CCA, and D: According to MPCC and stage of CCA). CI: Confidence interval

non-MPCC group (Table 4). Subsequent multivariable analyses, which controlled for related factors such as gender, age at enrollment, education levels, occupation, *O. viverrini* infection, PZQ treatment, history of smoking, history of alcohol consumption, and stage of CCA, were conducted using multiple cox regression models. These analyses also demonstrated a significant association between MPCC and CCA survival. Specifically, individuals in the MPCC group were 35% less likely to die compared to those in the non-MPCC group (AHR = 0.65; 95% CI: 0.50 - 0.84).

Discussion

Mucin-producing cholangiocarcinoma (MPCC) represents a rare histological subtype within the spectrum of cholangiocarcinoma (CCA) [12]. Our study endeavors to assess the survival rate and median survival time following surgery among CCA patients, with a particular focus on elucidating the association between MPCC and overall survival. The study encompasses a total of 1,249 CCA patients from northeast Thailand. Our findings revealed a predominant occurrence of male patients, and the population exhibited an older age profile, aligning with previous studies that reported an average age exceeding

Table 3. One-Year, Three-Year, and Five-Year Survival Rates of Cholangiocarcinoma Categorized by Mucinous Types

Factors	Survival rate (95% CI)				
	1-year	2-year	3-year	4-year	5-year
Overall	65.1	46.73	35.82	30.71	28.29
	(62.19 - 67.85)	(43.59 - 49.80)	(32.65 - 38.99)	(27.52 - 33.96)	(24.99 - 31.67)
Mucinous types					
Non-MPCC	62.16	43.65	33.04	28.26	25.92
	(58.91 - 65.22)	(40.27 - 46.97)	(29.74 - 36.38)	(25.01 - 31.59)	(22.62 - 29.34)
MPCC	79.4	62.5	51.46	44.69	44.69
	(72.75 - 84.60)	(54.25 - 69.69)	(41.91 - 60.19)	(32.47 - 56.16)	(32.47 - 56.16)

CI, Confidence interval; MPCC, Mucin-producing cholangiocarcinoma

Table 4. Association between Mucinous Types and Survival of Patients with Cholangiocarcinoma

Mucinous types	HR (95% CI)	p-value
Unadjusted		<0.001
Non-MPCC	1	
MPCC	0.55 (0.43 - 0.70)	
Adjusted for gender, age, education, occupation, *O. viverrini* infection, PZQ treatment, smoking, alcohol consumption, and stage of CCA		0.001
Non-MPCC	1	
MPCC	0.65 (0.50 - 0.84)	

CCA, Cholangiocarcinoma; CI, Confidence interval; HR, Hazard ratios; MPCC, Mucin-producing cholangiocarcinoma; PZQ, Praziquantel

50 years and a male predominance [7, 17]. Interestingly, our study did not establish any significant associations between demographic factors and CCA, representing a deviation from the findings of earlier investigations. In our study, patients with CCA predominantly presented at late stages, outnumbering those at early stages. This aligns with the characteristic asymptomatic nature of early-stage CCA. Notably, MPCC patients displayed a different pattern, presenting more frequently at early stages compared to late stages. Surgical intervention with curative intent, a key modality for achieving favorable survival outcomes, was emphasized, particularly given its potential efficacy in the context of both CCA and MPCC [18].

Our findings reveal that the prevalence of MPCC in this cohort was 16.81% (210 out of 1,249), surpassing the figures reported in previous studies by Laohawetwanit et al, where the prevalence was a mere 0.5% in intrahepatic CCA, and Sumiyoshi et al, who reported on a notably smaller patient population [7, 13]. This phenomenon can likely be attributed to the inclusion of a substantial number of CCA patients, encompassing all morphological types in our study. The prognostic outlook for MPCC following treatment has generally been characterized by poor outcomes in the existing literature. However, our study yielded contrasting results, revealing a 5-year survival rate among MPCC patients that surpassed that of non-MPCC patients. This discrepancy challenges previous studies that reported lower survival outcomes for MPCC, aligning with observations seen in mucinous carcinoma affecting other organs [19]. This intriguing discovery warrants further exploration to elucidate the etiological factors contributing to this phenomenon. One potential factor under consideration is the influence of peribiliary glands, which are implicated in the development of both mucinous and papillary neoplasms. Previous evidence has suggested that patients with MPCC and those exhibiting a combination of papillary and MPCC characteristics demonstrate a more favorable 5-year survival outcome compared to non-MPCC patients [20, 11, 21]. All relevant factors, including gender, age at enrollment, education levels, occupation, *O. viverrini* infection, praziquantel (PZQ) treatment, smoking, alcohol consumption, and the stage of CCA were comprehensively examined for associations and subjected to analysis and adjustment in a multiple Cox regression model. The results consistently supported the notion that MPCC exhibits a superior survival outcome compared to non-MPCC patients [20].

The robustness of our study lies in its utilization of a substantial sample size, encompassing individuals residing in a region with one of the highest incidences of CCA globally. Consequently, our study serves as a highly representative snapshot of the population in this area, providing insights that are contextually relevant and reflective of the broader epidemiological landscape.

Our study is subject to several significant limitations. Firstly, reliance on self-reported data gathered through interviews without supplementary evidence from confirmatory investigations, such as a history of PZQ treatment, *O. viverrini* infection, smoking, and alcohol consumption, introduces a potential source of bias. Moreover, the absence of detailed information regarding the performance status before the initiation of surgery may exert an influence on the study outcomes. Additionally, it is crucial to recognize that our study participants belonged to a cohort with an elevated risk for CCA, inherently increasing the likelihood of developing this form of cancer within the studied group.

In conclusion, our study contributes valuable insights into the long-term survival outcomes of a substantial cohort of MPCC patients, providing evidence that mucinous variants exhibit improved outcomes, particularly in early stages. Following the implementation of the Cholangiocarcinoma Screening and Care Program (CASCAP) in the northeastern part of Thailand, there has been a noteworthy increase in the identification of early-stage CCA cases, resulting in a concomitant enhancement in survival rates. The classification of MPCC patients offers a foundation for formulating tailored treatment guidelines for individuals diagnosed with CCA. Consequently, there is a compelling rationale for the expansion of CCA screening programs into high-incidence areas to optimize outcomes and enhance the overall well-being of the population.

Author Contribution Statement

This study was conducted by HM and under supervision of KT, BT, and AT. Data was received from CASCAP program to construct the study cohort. Data cleaning was performed by KT, HM performed data analysis under supervision of KT and BT. Manuscript was drafted by HM and revised by KT, AT, and MK. All authors have read and approved this manuscript before submission.

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Approval

This paper is a part of the dissertation submitted in fulfillment of the requirements for the degree of Epidemiology and Biostatistics Program, Faculty of Public Health, Khon Kaen University, Thailand.

Ethics considerations

The Khon Kaen University Ethics Committee for Human Research approved the research protocol, reference number HE651112 which requested the data from Cholangiocarcinoma Screening and Care Program (CASCAP). The CASCAP data collection was conducted according to the principles of Good Clinical Practice, the Declaration of Helsinki, and national laws and regulations about clinical studies. It was approved by the Khon Kaen University Ethics Committee for Human Research under the reference number HE551404. All subjects gave written, informed consent to participate in the study and for their anonymized data to be used for statistical analysis and dissemination.

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 interest

The authors declare that they have no competing interests.

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