Survival rate of patients with combined hepatocellular cholangiocarcinoma receiving medical cannabis treatment: A retrospective, cohort comparative study [version 1; peer review: awaiting peer review]

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Abstract

Background: Cholangiocarcinoma (CCA) incidence in Northeastern Thailand is very high and a major cause of mortality. CCA patients typically have a poor prognosis and short-term survival rate due to late-stage diagnosis. Thailand is the first Southeast Asian country to approve medicinal cannabis treatment, especially for palliative care with advanced cancer patients.

Methods: A retrospective cohort comparative study of survival rates among 491 newly diagnosed advanced CCA patients was carried out between September 1, 2019, and June 30, 2021. A total of 404 patients were in the standard palliative care pain management treatment group (ST), and 87 were in the medicinal cannabis treatment group (CT). Patients with CCA were recruited from four tertiary hospitals and two secondary hospitals in five provinces of Northeast Thailand. The cumulative survival rates were calculated by the Kaplan-Meier method, and independent prognostic factors were investigated using Cox regression.

Results: For ST patients, there was a total follow-up time of 790 person-months, with a mortality rate of 48.35/100 person-months. For CT patients the total follow-up time was 476 person-months, with mortality rate of 10.9/100 person-months. The median survival time after registration at a palliative clinic was 0.83 months (95% CI: 0.71–0.95) for ST and 5.66 months (95% CI: 1.94–9.38) for CT. Multivariate analysis showed that CT treatment protocol was
associated with a significantly better survival (P value <0.001; median time of CT, 5.66 months (95% CI: 1.94–9.38); median time of ST, 0.83 months (95% CI: 0.71–0.95). Therefore, CT had a reduced probability of dying from the disease (HR adj., 0.28 (95% CI: 0.20–0.37)

Conclusions: The medical cannabis increased overall survival rates among CCA patients.

Keywords
Survival rate, medicinal cannabis, combined hepatocellular cholangiocarcinoma, cHCC-CC, palliative care, Northeastern Thailand
Introduction

Combined hepatocellular cholangiocarcinoma (cHCC-CC) is a rare, but severely aggressive primary liver cancer manifesting characteristics of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). The incidence rate is approximately 0.59 per 1,000,000 populations worldwide but it is highly prevalent in Thailand. The highest reported CC incidence internationally is in northeastern Thailand, 118.5 per 100,000, in Khon Kaen Province, which is over 100 times higher than the global rate.

CC is generally asymptomatic in early stages and is usually diagnosed late when the disease has already metastasized. Late-stage diagnosis limits the effective therapeutic options and has an aggressive disease course and very poor prognosis, resulting in lower survival rates. Previous studies have shown the median post-diagnosis survival of CC patients to be about 9 months (95% CI: 7–11), with 1-, 3-, and 5-year survival rates at 43.4, 21.5, and 17.1%, respectively. Mean overall survival rate at 1-, 3-, and 5-year was 66.6, 41.5, and 32.7% for patients with transitional chHCC-CC, with median survival time from diagnosis 4.3 months (95% CI: 3.3–5.1), and after supportive treatment was 4 months. Survival time was increased among CC patients receiving surgery (an average of 29.38 months), best supportive treatment was 5.12 months and 13.38 months for chemotherapy patients.

At present, medical cannabis products are in use in many countries. Cannabis as a palliative treatment for patients with cancer appears to be well-tolerated, effective and a safe pain-relief option with significant improvement in quality of life shown after 6 months of treatment. In patients with cancer, cannabinoids have mainly been used as part of palliative care to alleviate pain, relieve nausea and stimulate appetite. Thailand legalized medical cannabis in February 2019, becoming the first country in Southeast Asia to regulate medical treatment. Currently, there are two treatment options for palliative cancer patients in Thailand; the standard current treatment and the new cannabis treatment. However, to the best of our knowledge, no studies on the survival rate of patients treated with medicinal cannabis from the patients’ perspective have been carried out to date. The present study aims to compare survival rates in palliative cHCC-CC patients who were treated with standard treatment (ST) or cannabis treatment (CT) palliative care protocols.

Methods

Ethical approval
This study was reviewed and approved by the Mahasarakham University Human Research Ethics Committee (Reference No. 204/2563; approved on July 24, 2020), and Roi-Et Regional Hospital (Reference RE004/2563; approved on August 26, 2020), Buriram Regional Hospital Ethics Committee for Human Research, based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines (Reference No. GCP0066/2563; approved on February 4, 2020). Because of its retrospective manner, informed consent was waived by the Roi-Et Regional Hospital and Buriram Regional Hospital.

Data were collected from August 30, 2020, to June 30, 2021, which collected event data on 491 cases from September 1, 2019, to June 30, 2021.

Study design
A retrospective cohort study was conducted with 491 cHCC-CC patients (404 received ST and 87 received CT), who were diagnosed at least by ultrasonography and treated by supportive treatment at a palliative care and/or cannabis care clinic between September 1, 2019, and June 30, 2021. Data were extracted from the four tertiary hospitals, and two secondary hospitals serving five provinces of northeastern Thailand (Roi-Et Regional Hospital, Buriram Regional Hospital, Surin Provincial Hospital, Sawang Dandin Crown Prince Hospital, Panna Nikhom Hospital and Pana Hospital).

Data collection
The independent variables were age at registration (palliative clinic and/or cannabis clinic), sex, cancer treatment and period of diagnosis to registration. The dependent variable was the survival time of patients with cHCC-CC. In order to calculate survival time, the starting point was identified as the date of registration, and the follow-up period ended when a patient passed away or on completion of the study. Censored data were used for those still alive at the end of the study (June 30, 2021) or lost to follow-up. Death status on the cause of treatment was confirmed by linkage with the death certificates from the national statistics database and by a telephone call to the patient or public health officer in community health centers.

Statistical methods
Statistical analysis was performed with Stata (RRID:SCR_012763) version 15 (free alternative, Rstudio). Descriptive statistics were used to present baseline characteristics and clinical subject data. Frequency and percentages were constructed to describe categorical data and expressed as the means deviation (in SD) or medians with ranges to describe continuous data. The Kaplan-Meier method was used for observing survival duration with 95% confidence intervals (95% CI). Then between-group comparisons were evaluated using a log-rank test. The test for associations between the diverse covariates and survival rate was performed using the Cox proportional hazard regression model. The results were
Table 1. Baseline characteristics of included patients (n=491). ST, standard palliative care pain management treatment group; CT, medicinal cannabis treatment group.

| Variable                          | Patient treatment group | Median time, month (95% CI) | Person-time, month | Incidence rate/100 person/month | HRadj. 95% CI | P-value |
|-----------------------------------|-------------------------|-----------------------------|--------------------|---------------------------------|---------------|---------|
| Overall survival rate             |                         |                             |                    |                                 |               |         |
| ST (n=404, %)                     | 0.83 (0.71–0.95)        | ST (n=404, %)               | 5.66 (1.94–9.38)   |                                 |               | <0.001  |
| Age, years, mean (SD)             | 66.60 (11.67)           | CT (n=87, %)                | 66.64 (9.82)       |                                 |               | <0.001  |
| <60                               | 105 (25.99)             | 24 (27.59)                  | 0.83 (0.60–1.00)   | 5.67 (2.87–15.00)               | 170           | 0.59    |
| 60–69                             | 121 (29.95)             | 28 (32.18)                  | 0.93 (0.73–1.04)   | 3.27 (2.0–12.00)                | 244           | 0.47    |
| ≥70                               | 178 (44.06)             | 35 (40.23)                  | 0.83 (0.67–1.27)   | 6.00 (2.33–10.03)               | 375           | 0.44    |
| Sex                               |                         |                             |                    |                                 |               |         |
| Male                              | 242 (59.99)             | 54 (62.07)                  | 0.73 (0.67–0.93)   | 6.00 (3.07–10.03)               | 427           | 0.53    |
| Female                            | 162 (40.01)             | 33 (37.93)                  | 0.97 (0.83–1.20)   | 3.50 (1.77–9.50)                | 362           | 0.42    |
| Cancer treatment                  |                         |                             |                    |                                 |               |         |
| Surgery                           | 28 (6.93)               | 4 (4.59)                    | 1.33 (0.30–2.50)   | 2.00 (1.83–10.00)               | 106           | 0.20    |
| Chemotherapy                      | 140 (34.65)             | 18 (20.70)                  | 0.93 (0.73–1.0)    | 9.50 (5.17–15.00)               | 209           | 0.65    |
| Combine                           | 149 (36.88)             | 22 (25.29)                  | 0.83 (0.67–1.27)   | 7.00 (1.67–15.00)               | 311           | 0.45    |
| Palliative care                   | 87 (21.54)              | 43 (49.42)                  | 0.73 (0.5–0.93)    | 3.07 (2.17–8.33)                | 162           | 0.51    |
| Treatment protocol                |                         |                             |                    |                                 |               |         |
| ST                                | 404                     | 87                          | 0.83 (0.71–0.95)   |                                 | 1             | <0.001  |
| CT (82.3)                         | (17.7)                  |                             | 5.66 (1.94–9.38)   |                                 | 0.28          | (0.20–0.37) |
| Period advanced diagnosis to register |                       |                             |                    |                                 |               |         |
| Mean (SD)                         | 6.12 (2.55)             | 5.46 (2.94)                 |                    |                                 |               |         |
| <3 months                         | 60 (85.14)              | 40 (45.98)                  | 0.93 (0.67–2.00)   | 3.17 (2.17–9.00)                | 115           | 0.54    |
| 3–6 months                        | 204 (49.50)             | 22 (25.28)                  | 0.83 (0.67–0.97)   | 8.17 (2.87–15.00)               | 406           | 0.46    |
| 6–9 months                        | 94 (27.23)              | 8 (9.20)                    | 1.07 (0.67–1.67)   | 5.00 (0.73–8.00)                | 210           | 0.41    |
| >9 months                         | 46 (39.11)              | 17 (19.54)                  | 0.67 (0.44–1.77)   | 5.17 (200–9.00)                 | 59            | 0.72    |
| Status at the end of study        |                         |                             |                    |                                 |               |         |
| Passed away                       | 382 (94.60)             | 52 (59.80)                  |                    |                                 |               |         |
Results
Table 1 shows the characteristics of the study participants. There were 491 patients (296 male subjects and 195 female subjects) with chHCC-CC; there were 404 in the ST group (242 male subjects and 162 female subjects) and 87 in the CT group (54 male participants and 33 female participants). The mean age of those in the ST group was 66.60 years old, and the mean age of the CT group was 65.64 years old. Most patients (43.38%) were 70 years of age. More than 71.53% in the ST received cancer chemotherapy and combinations, and 49.42% of the CT group also received palliative care. Mean point of diagnosis with advanced chHCC-CC to registration was 6.12 months for ST, and 5.46 months for CT. Most patients (38.49%) were registered at the palliative and/or cannabis care clinic, and 94.60% (ST) and 59.80% (CT) had passed away by the end of the study. The total follow-up time for ST patients was 790 person-months, with a mortality rate of 48.35/100 person-months. For the CT group follow-up was 476 person-months, with a mortality rate of 10.9/100 person-months for CT.

The survival rate data after registration at either the palliative or cannabis care clinic. The cumulative 3, 6, 9 and 12 months survival rates were 28.80% (95% CI: 24.72–32.99), 20.00% (95% CI: 16.35–23.92), 16.50% (95% CI: 12.86–20.55) and 15.75% (95% CI: 12.04–19.92) for ST, 60.48% (95% CI: 49.35–69.91), 48.63% (95% CI: 36.78–57.70), 35.73% (95% CI: 23.83–47.74) and 29.98% (95% CI: 18.15–42.73) for CT, respectively. The median duration of survival was 0.83 months (95% CI: 0.71–0.95) for ST and 5.66 months (95% CI: 1.94–9.38) for CT. None of the demographic factors were significantly associated with survival time for either ST or CT. Comparing ST with CT, there was a statistically significant difference in age, sex, cancer treatment and period diagnosis with advanced chHCC-CC to register factors (p-value<0.05). There were factors found that affected the survival of patients receiving palliative care for liver and bile duct cancer. The most significant treatment factor found was between those patients who received standard therapy and those who received medical cannabis. Those on standard therapy were 3.57% more at risk of death than those on cannabis.

Multivariate analysis showed that CT treatment protocol was associated with improved patient survival, which was statistically significant (P value <0.001, the median time of CT, 5.66 months (95% CI: 1.94–9.38) and ST, 0.83 months (95% CI: 0.71–0.95), HRadj, 0.28 (95% CI: 0.20–0.37).

Discussion
The impact of two types of treatment that affect the survival of chHCC-CC patients who either had supportive treatment at palliative clinic or a cannabis clinic. CT was the most effective treatment, with an overall survival time of 5.66 months, while overall survival time was 0.83 months for ST. Meanwhile, the overall survival times are consistent with other findings for after supportive treatment where survival time was only 4.3 months post-diagnosis. Patients diagnosed at an advanced stage were twice as likely to pass away (HR: 1.8, 95% CI: 1.1–2.9). By contrast, patients with advanced cancer using cannabis showed a significantly decreased overall survival compared to non-users.

In the univariate analysis, cancer treatment and period of diagnosis with advanced chHCC-CC to registration were associated with survival rate. It was found that the ST registered patients survived less than three months after being diagnosed with advanced-stage chHCC-CC. The reason for this might be that some patients had been consulting and were being cared for by an oncologist or other doctor rather than those patients who were registered for and receiving supportive treatment at a Palliative Clinic. Furthermore, most patients had been treated with a combination of surgery and chemotherapy, before being admitted to a Palliative Clinic. Although the registered patients at the Cannabis Clinic were >70 years old, they had no cancer treatment, only supportive treatment at the Cannabis Clinic. At the community hospitals where CT/MRI/biopsy/US have shown advanced organ metastases others who received treatment at a Cannabis clinic without waiting for a consultation with an oncologist were able to receive chemotherapy along with cannabis. This study has several limitations. A number of patients in the CT group dropped out before completion of the study. As a consequence, most patients suffering from advanced cancers and receiving heavy oncological treatments were older adults.

Patients with CCA have poor prognosis and short-term survival at the time of diagnosis. Registration and decision-making at the standard and/or cannabis clinic in each hospital differs across physicians, patients, families, stages of disease, organ metastasis, methods of treatment, and severity of symptoms. To the best of our knowledge, this is the first study that has compared survival rate and quality of life of CHCA/CCA patients who received either ST or CT across tertiary and secondary hospitals and across five provinces. Medical cannabis used in this study were standardized cannabis preparations made by the Thailand Food and Drug Administration. The side effects, safety, benefits and harms of the cannabis produced have been reviewed and are considered appropriate patient treatment. Prescribing doctors are trained, registered prescribers of medical cannabis.
Author contributions
N.P., contributed to Conceptualization, Data Curation, Formal Analysis, Resources, Methodology, Investigation, Writing – Original Draft. P.P., and A.W., contributed to Methodology, Investigation, Resources, Validation, Formal Analysis, Visualization. N.T., contributed to Conceptualization, Investigation, Supervision, Visualization, Writing – Review & Editing. M.A., contributed to Investigation, Visualization, Writing – Review & Editing. R.W., contributed to Conceptualization, Project Administration, Methodology, Investigation, Writing – Review & Editing, Funding Acquisition, and Supervision.

Data availability
Underlying data
Figshare: Data_survival_cannabis. https://doi.org/10.6084/m9.figshare.20486913.16
Figshare: F1000_survival_table1_narisara_ranee. https://doi.org/10.6084/m9.figshare.20486913.16

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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