RESEARCH ARTICLE

REVISED Survival rate of patients with combined hepatocellular cholangiocarcinoma receiving medical cannabis treatment: A retrospective, cohort comparative study

[version 3; peer review: 1 approved, 2 approved with reservations, 2 not approved]

Narisara Phansila[1], Paopong Pansila[2], Adisorn Wongkongdech[3,4], Niruwan Turnbull[3,4], Mahalul Azam[5], Ranee Wongkongdech[2,4,6]

[1]Chiang Kwan Hospital, Roi-et Province, 45000, Thailand
[2]Faculty of Medicine, Mahasarakham University, Mahasarakham, 44000, Thailand
[3]Faculty of Public Health, Mahasarakham University, Mahasarakham, Mahasarakham Province, 44150, Thailand
[4]Public Health and Environmental Policy in Southeast Asia Research Cluster (PHEP SEA Thailand), Mahasarakham University, Mahasarakham, 44150, Thailand
[5]Public Health Department, Faculty of Sport Sciences, Universitas Negeri Semarang, Semarang, 50229, Indonesia
[6]International and National Collaborative Network and Innovation for Community Health Development Research Unit (INCNI-CHD), Mahasarakham University, Mahasarakham, 44000, Thailand

v3 **First published:** 25 Oct 2022, **11**:1212
https://doi.org/10.12688/f1000research.123250.1
Second version: 09 Apr 2025, **11**:1212
https://doi.org/10.12688/f1000research.123250.2
Latest published: 03 Oct 2025, **11**:1212
https://doi.org/10.12688/f1000research.123250.3

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 study compared survival among 491 newly diagnosed advanced CCA patients between September 2019 and June 2021. Of these, 404 received standard palliative pain management (ST), and 87 received medicinal cannabis treatment (CT). Patients were enrolled from four tertiary hospitals and two secondary hospitals in five provinces of Northeast Thailand. Cumulative survival was calculated by the Kaplan-Meier method, and independent prognostic

Open Peer Review

Approval Status ✓ ? ? ✗ ✗

	1	2	3	4	5
version 3 (revision) 03 Oct 2025		? view		✗ view	
version 2 (revision) 09 Apr 2025	✓ view	✗ view	? view	✗ view	✗ view
version 1 25 Oct 2022	? view	? view			

1. **Selamat Budijitno**, Universitas Diponegoro, Semarang, Indonesia
2. **Nat Na-Ek**, University of Phayao, Mueang Phayao District, Thailand
3. **Ueamporn Summart**, Roi Et Rajabhat University, Tha Muang, Thailand

factors were analyzed using Cox regression.

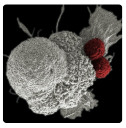
Results

For ST patients, follow-up time was 790 person-months, with a mortality rate of 48.35/100 person-months. For CT patients, follow-up time was 476 person-months, with a 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 CT was significantly associated with prolonged survival (HRadj = 0.28; 95% CI: 0.20–0.37; $p < 0.001$).

Conclusions

The medical cannabis increased overall survival rates among CCA patients. In this retrospective cohort, Medicinal cannabis treatment was associated with more prolonged survival among advanced CCA patients in Northeastern Thailand. While this association remained significant after multivariable adjustment, unmeasured or residual confounding factors may have influenced the observed outcomes. Although the association remained significant after adjustment, unmeasured or residual confounders may have influenced outcomes. Further prospective studies are warranted to confirm these findings and explore potential mechanisms.

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



This article is included in the Oncology gateway.

4. **Nuttapong Ngamphaiboon**, Mahidol University, Bangkok, Thailand

5. **Dima Malkawi**, University of Colorado, Denver, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Ranee Wongkongdech (ranee.w@msu.ac.th)

Author roles: Phansila N: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Writing – Original Draft Preparation; **Pansila P**: Formal Analysis, Investigation, Methodology, Resources, Validation, Visualization; **Wongkongdech A**: Formal Analysis, Investigation, Methodology, Resources, Validation, Visualization; **Turnbull N**: Conceptualization, Investigation, Supervision, Visualization, Writing – Review & Editing; **Azam M**: Investigation, Visualization, Writing – Review & Editing; **Wongkongdech R**: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This research was financially supported by Faculty of Medicine, Mahasarakham University with the reference no. 64/04/01.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Phansila N, Pansila P, Wongkongdech A *et al.* **Survival rate of patients with combined hepatocellular cholangiocarcinoma receiving medical cannabis treatment: A retrospective, cohort comparative study [version 3; peer review: 1 approved, 2 approved with reservations, 2 not approved]** F1000Research 2025, **11**:1212
https://doi.org/10.12688/f1000research.123250.3

First published: 25 Oct 2022, **11**:1212 https://doi.org/10.12688/f1000research.123250.1

REVISED **Amendments from Version 2**

This version has been substantially revised in response to peer review. Key updates include expanded references (2019–2024) on medicinal cannabis, CCA/HCC epidemiology, and palliative care; standardized terminology; and detailed methodological descriptions to ensure reproducibility. The Conclusion has been refined to highlight the association between cannabis treatment and prolonged survival while noting the study's observational limitations. The Limitations section has been expanded, and the study's significance is now framed within the context of Northeastern Thailand. These changes enhance clarity, transparency, and the cautious interpretation of findings.

Any further responses from the reviewers can be found at the end of the article

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is an uncommon and aggressive form of primary liver cancer that exhibits both hepatocytic and cholangiocytic differentiation within the same tumor.[1] The global incidence rate is approximately 0.59 per 1,000,000 people,[2] whereas Thailand reports significantly higher rates.[3] Notably, Northeastern Thailand—particularly Khon Kaen Province—has the highest reported incidence of CCA worldwide at 118.5 per 100,000 population, exceeding the global rate by over 100-fold.[3] Due to its asymptomatic nature in early stages, CCA is typically diagnosed at an advanced stage when metastasis has already occurred, resulting in limited therapeutic options, aggressive disease progression,[4] and poor prognosis.[5]

Previous studies have shown the median post-diagnosis survival of CCA 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.[6] Mean overall survival rate at 1-, 3-, and 5-year was 66.6, 41.5, and 32.7% for patients with transitional HCC-CC,[7] with median survival time from diagnosis 4.3 months (95% CI: 3.3–5.1),[8] and after supportive treatment was 4 months.[9] Survival time was increased among CCA patients receiving surgery, an average of 29.38 months, best supportive treatment, 5.12 months, and 13.38 months for chemotherapy patients.[10]

Cannabis-based medicinal products are now legally available in several countries[11] and are commonly used in palliative care to alleviate pain, reduce nausea, stimulate appetite, and improve quality of life in adults with cancer.[12] Observational evidence also suggests that supervised medical cannabis is generally well-tolerated and associated with quality-of-life improvements over about six months of use.[13,14] Thailand legalized medical cannabis in February 2019, the first country in Southeast Asia to do so[15,16] and has since integrated cannabis-based options into palliative care services as an adjunct or alternative to standard care.[17] In a recent retrospective cohort of advanced cholangiocarcinoma treated in northeastern Thailand, patients receiving cannabis-based treatment had a median overall survival of 5.66 months and an approximate one-year (12-month) survival of 29.98%, based on Kaplan–Meier estimates,[18] highlighting a potential role alongside symptom management.

Survival data for cannabis-treated cholangiocarcinoma (CCA) remain limited, but some evidence suggests potential benefits. A U.S. inpatient study found that cannabis users with CCA had significantly lower in-hospital mortality than matched non-users (OR = 0.40; 95% CI: 0.16–0.97; $p < 0.04$).[19] In Thailand, a prospective cohort reported improved functional status and quality of life at two and four months among CCA patients receiving cannabis-based treatment compared to standard care.[13] Preclinical studies also indicate anticancer effects: cannabidiol (CBD) and cannabigerol (CBG) inhibited CCA cell proliferation and migration, inducing apoptosis and autophagy,[20] while delta-9-tetrahydrocannabinol (THC) suppressed proliferation and promoted apoptosis via MAPK/MEK and Akt pathway inhibition.[21] These findings, though preliminary, highlight the need for further clinical research in advanced CCA, where current survival outcomes remain poor.[22]

This study aims to analyze survival outcomes (SA) and identify factors associated with survival rates among patients with combined hepatocellular–cholangiocarcinoma (CHCC/CCA) diagnosed by their physicians as requiring palliative care, who then choose either cannabis treatment (CT) or standard treatment (ST; conventional medical care according to national clinical practice guidelines) after receiving information on available options. Retrospective cohort data were obtained from hospital electronic medical records (EMR) and cancer clinic databases across four tertiary and two secondary hospitals in five Northeastern provinces of Thailand. The results could provide preliminary evidence to support policy discussions and the development of evidence-based palliative care strategies under the national medicinal cannabis framework.

Methods

Study design and setting

A retrospective cohort study was conducted with 491 patients—404 who received standard palliative care treatment (ST) and 87 who received medicinal cannabis treatment (CT). All patients were diagnosed with advanced cholangiocarcinoma (CCA) or hepatocellular carcinoma (HCC) by at least ultrasonography and managed with supportive care at a palliative care and/or cannabis care clinic between 1 September 2019 and 31 December 2020. Data were obtained from hospital electronic medical record (EMR) systems and cancer clinic databases from four tertiary hospitals and two secondary hospitals across 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.

Eligibility criteria

Patients were eligible for inclusion if they were: Newly diagnosed with CCA or HCC between September 2019 and December 2020; Aged 18 years or older; and registered at either a palliative care clinic or a cannabis clinic.

Exclusion criteria included: Prior use of medicinal cannabis before study registration and incomplete medical records.

Variables and outcomes

Independent variables included age at registration, gender, type of cancer treatment, and the period from diagnosis to registration. The primary outcome was post-diagnosis survival time, measured from the date of registration to the date of death or the study endpoint (30th June 2021). Patients alive at the end of the study or lost to follow-up were classified as censored cases.

Follow-up procedures

Participants were followed from the date of registration until death or the study endpoint (30th June 2021). Follow-up was conducted through review of EMR entries, clinic visit records, and linkage to the national death registry.

Cancer stage and other clinical variables

Data on cancer stage, performance status, and pain score were not consistently available in the EMR and were therefore not included as covariates in the analysis.

Ethical approval

The study protocol was reviewed and approved by the Maha Sarakham University Human Research Ethics Committee (Reference No. 204/2563, dated July 24, 2023), the Roi Et Regional Hospital Ethics Committee (Reference No. RE064/2563, dated 26 August 2023), and the Buriram Regional Hospital Ethics Committee (Reference No. GCP0066/2563, dated 4 Febuary 2023). Permission for data access and extraction was also obtained from hospital administrators and multidisciplinary teams at each participating hospital.

Statistical methods

Descriptive statistics summarized patient characteristics. Categorical variables were reported as frequencies and percentages, and continuous variables as means with standard deviations (SD) or medians with interquartile ranges (IQR). Baseline differences between the standard treatment (ST) and cannabis treatment (CT) groups were assessed using chi-square or Fisher's exact tests for categorical variables and independent t-tests for continuous variables.

Survival probabilities were estimated using the Kaplan–Meier method, with group comparisons made via the log-rank test. Independent prognostic factors were identified using Cox proportional hazards regression. The proportional hazards assumption was assessed using Schoenfeld residuals and log-minus-log plots.

A two-step approach was applied:

1. Univariable analysis identified variables associated with survival ($p < 0.20$).

2. Multivariable analysis included these variables to adjust for confounders and estimate adjusted hazard ratios (HR_adj) with 95% confidence intervals (CI).

Statistical significance was set at $p < 0.05$. Analyses were performed in Stata version 17 (StataCorp LLC, College Station, TX, USA).

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		$HR_{adj.}$ 95% CI	P-value
	ST (n=404, %)	CT (n=87, %)	ST (n=404, %)	CT (n=87, %)	P-value	ST	CT	ST	CT		
Overall survival rate	0.83 (0.71–0.95)	5.66 (1.94–9.38)			<0.001						
Age, years, mean (SD)	66.60 (11.67)	65.64 (9.82)			<0.001						
<60	105 (25.99)	24 (27.59)	0.83 (0.60–1.00)	5.67 (2.87–15.00)		170	147	0.59	0.08	1	0.212
60–69	121 (29.95)	28 (32.18)	0.93 (0.73–1.04)	3.27 (2.0–12.00)		244	128	0.47	0.13	0.85 (0.66–1.09)	
≥70	178 (44.06)	35 (40.23)	0.83 (0.67–1.27)	6.00 (2.33–10.03)		375	200	0.44	0.11	0.87 (0.68–1.09)	
Sex											
Male	242 (81.8)	54 (18.2)	0.73 (0.67–0.93)	6.00 (3.07–10.03)	<0.001	427	300	0.53	0.10	1	0.236
Female	162 (83.1)	33 (16.9)	0.97 (0.83–1.20)	3.50 (1.77–9.50)		362	175	0.42	0.11	0.89 (0.73–1.08)	
Cancer treatment											
Surgery	28 (6.93)	4 (4.59)	1.33 (0.30–2.50)	2.00 (1.83–10.00)	<0.001	106	14	0.20	0.21	1	0.106
Chemotherapy	140 (34.65)	18 (20.70)	0.93 (0.73–1.0)	9.50 (5.17–15.00)		209	139	0.65	0.06	1.43 (0.93–2.2)	
Combine	149 (36.88)	22 (25.29)	0.83 (0.67–1.27)	7.00 (1.67–15.00)		311	121	0.45	0.09	1.27 (0.82–1.93)	
Palliative care	87 (21.54)	43 (49.42)	0.73 (0.5–0.93)	3.07 (2.17–.8.33)		162	201	0.51	0.14	1.23 (0.79–1.92)	
Treatment protocol											
ST	404	87	0.83 (0.71–0.95)		<0.001					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)			<0.001						
< 3 months	60 (85.14)	40 (45.98)	0.93 (0.67–2.00)	3.17 (2.17–9.00)		115	115	0.54	0.14	1	0.844
3–6 months	204 (49.50)	22 (25.28)	0.83 (0.67–0.97)	8.17 (2.87–15.00)		406	406	0.46	0.08	1.31 (1.01–1.71)	
6–9 months	94 (27.23)	8 (9.20)	1.07 (0.67–1.67)	5.00 (0.73–8.00)		210	210	0.41	0.09	1.21 (0.89–1.65)	
>9 months	46 (39.11)	17 (19.54)	0.67 (0.44–1.77)	5.17 (200–9.00)		59	59	0.72	0.09	1.16 (0.82–1.63)	
Status											
Alive	22 (5.45%)	35 (40.23%)	0.000								
Dead	382 (94.55%)	52 (59.77%)	0.000								

All baseline information was obtained from **secondary data extracted from the hospital's electronic medical record systems.** Data on cancer stage, ECOG performance status, and baseline pain levels were not available.

F1000Research 2025, 11:1212 Last updated: 24 DEC 2025

Table 2. Baseline characteristics and survival outcomes of advanced cholangiocarcinoma patients by treatment group (Standard treatment [ST] vs. Cannabis treatment [CT]) (n=491).

Variable	Patient treatment group		Median survival time (months, 95% CI)		Person-time (months)	IR/100 person-month	HR_adj (95% CI)	P-value
	ST (n=404, %)	CT (n=87, %)	ST (n=404, %)	CT (n=87, %)				
Overall Survival			0.83 (0.71–0.95)	5.66 (1.94–9.38)			0.28 (0.20–0.37)	<0.001
Age <60	105 (26.0)	24 (27.6)	0.83 (0.60–1.00)	5.67 (2.87–15.00)	170/147	0.59/0.08	1.00	0.212
Age 60–69	121 (30.0)	28 (32.2)	0.93 (0.73–1.04)	3.27 (2.00–12.00	244/128	0.47/0.13	0.85 (0.66–1.09)	
Age ≥70	178 (44.1)	35 (40.2)	0.83 (0.67–1.27)	6.00 (2.33–10.03)	375/200	0.44/0.11	0.87 (0.68–1.09)	
Sex: Male	242 (60.0)	54 (62.1)	0.73 (0.67–0.93)	6.00 (3.07–10.03)	427/300	0.53/0.10	1.00	0.236
Sex: Female	162 (40.0)	33 (37.9)	0.97 (0.83–1.20)	3.50 (1.77–9.50)	362/175	0.42/0.11	0.89 (0.73–1.08)	
Cancer Treatment: Surgery	28 (6.9)	4 (4.6)	1.33 (0.30–2.50)	2.00 (1.83–10.00)	106/14	0.20/0.21	1.00	0.106
Chemotherapy	140 (34.7)	18 (20.7)	0.93 (0.73–1.00)	9.50 (5.17–15.00)	209/139	0.65/0.06	1.43 (0.93–2.20)	
Combined	149 (36.9)	22 (25.3)	0.83 (0.67–1.27)	7.00 (1.67–15.00)	311/121	0.45/0.09	1.27 (0.82–1.93)	
Palliative Care	87 (21.5)	43 (49.4)	0.73 (0.50–0.93)	3.07 (2.17–8.33)	162/201	0.51/0.14	1.23 (0.79–1.92)	
Time from Diagnosis to Registration <3 months	60 (14.9)	40 (46.0)	0.93 (0.67–2.00)	3.17 (2.17–9.00)	115/115	0.54/0.14	1.00	0.844
3–6 months	204 (49.5)	22 (25.3)	0.83 (0.67–0.97)	8.17 (2.87–5.00)	406/406	0.46/0.08	1.31 (1.01–1.71)	
6–9 months	94 (23.3)	8 (9.2)	1.07 (0.67–1.67)	5.00 (0.73–8.00)	210/210	0.41/0.09	1.21 (0.89–1.65)	
>9 months	46 (11.4)	17 (19.5)	0.67 (0.44–1.77)	5.17 (2.00–9.00)	59/59	0.72/0.09	1.16 (0.82–1.63)	
Status at Study End: Dead	382 (94.6)	52 (59.8)						

Abbreviations: ST, Standard treatment; CT, Cannabis treatment; HR, Hazard ratio; CI, Confidence interval; IR, Incidence rate.
Notes:

- All data were obtained from secondary sources (hospital electronic medical records.
- Median survival time is presented in months with 95% confidence intervals. Incidence rate is expressed per 100 person-months. Censored cases include patients alive at the study endpoint or lost to follow-up. Hazard ratios are adjusted for age, sex, type of cancer treatment, and period from diagnosis to registration using Cox proportional hazards regression.
- HR<1 indicates a reduced hazard of death, and specifically interpret the HR for medical cannabis as indicating prolonged survival.

F1000Research 2025, 11:1212 Last updated: 24 DEC 2025

Results

Participant characteristics

Table 1 shows the study participants' characteristics. Overall, most baseline characteristics did not differ significantly between the Standard Treatment (ST) and Cannabis Treatment (CT) groups. Significant differences ($p < 0.05$) were observed for chemotherapy, combined treatment, palliative care, time from diagnosis to registration (< 3 months), and survival status.

There were 491 patients (296 males and 195 females) with CCA and HCC; there were 404 in the ST group (242 males and 162 females) and 87 in the CT group (54 males and 33 females). The mean ages of the ST group were 66.60, and the CT group was 65.64 years. Most patients (43.38%) were 70 years of age. More than 71.53% in the ST group received cancer chemotherapy and combinations, and 49.42% of the CT group also received palliative care. The mean point of diagnosis with advanced CCA, HCC to registration was 8.65 months for ST, and 5.32 months for CT. Most patients (38.49%) were registered at the palliative and/or cannabis care clinic, and 94.60% (ST), 59.80% (CT) had died 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-years. For the CT group, follow-up was 476 person-months, a mortality rate of 10.9./100 person-years for CT (Table 2).

Survival outcomes

Survival outcomes are presented in Table 2 and illustrated in Figure 1. For ST patients, the total follow-up time was 790 person-months, with a mortality rate of 48.35 per 100 person-months. For CT patients, the total follow-up time was 476 person-months, with a mortality rate of 10.9 per 100 person-months.

The median survival time was calculated from the **date of registration** at the palliative care or cannabis clinic to the date of death or the study endpoint (30 June 2021). The median survival time was 0.83 months (95% CI: 0.71–0.95) for the ST

Table 3. Multivariable Cox proportional hazards regression analysis for overall survival among patients with advanced cholangiocarcinoma (n = 491).

Variable	Adjusted HR	95% CI	p-value
Treatment group			
Standard treatment (ST)	Reference	—	—
Cannabis treatment (CT)	0.28	0.20–0.37	<0.001
Age group			
<60 years	Reference	—	—
60–69 years	0.85	0.66–1.09	0.212
≥70 years	0.87	0.68–1.09	0.236
Sex			
Male	Reference	—	—
Female	0.89	0.73–1.08	0.236
Type of prior cancer treatment			
Surgery	1.00	—	0.106
Chemotherapy	1.43	0.93–2.20	0.093
Combined treatment	1.27	0.82–1.93	0.272
Palliative care only	1.23	0.79–1.92	0.355
Time from diagnosis to registration			
<3 months	Reference	—	—
3–6 months	1.31	1.01–1.71	0.044
6–9 months	1.21	0.89–1.65	0.222
>9 months	1.16	0.82–1.63	0.398

Notes: All data were obtained from secondary sources (hospital electronic medical records). Adjusted hazard ratios were estimated using a Cox proportional hazards regression model including treatment group, age group, sex, type of prior cancer treatment, and time from diagnosis to registration as covariates. Data on cancer stage, ECOG performance status, pain scores, and quality of life were not available in the secondary dataset and were therefore not included in the model.

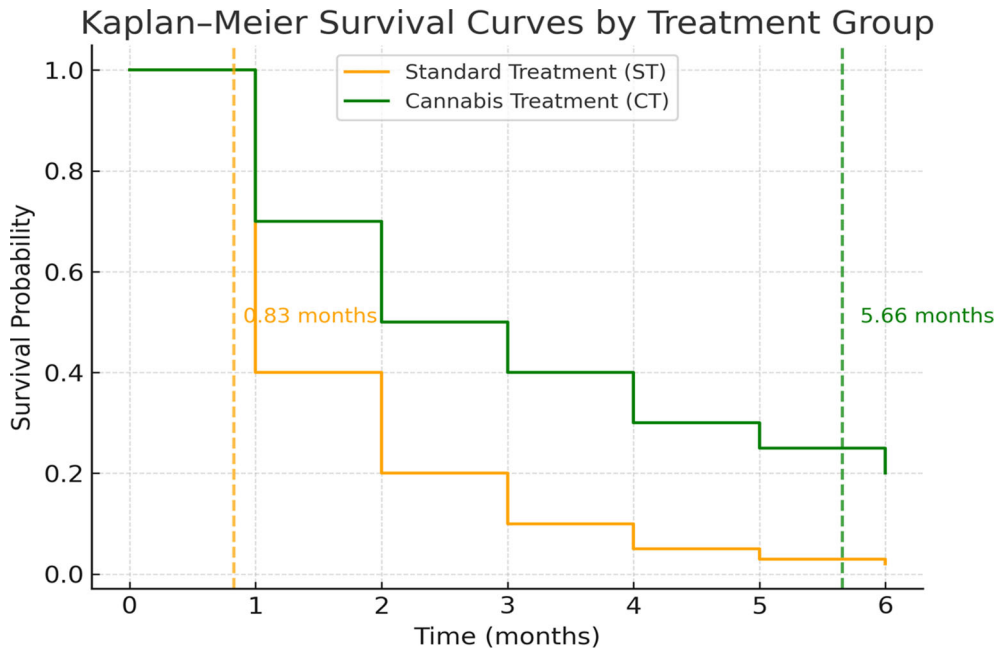


Figure 1. Kaplan–Meier survival curves for advanced cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC) patients receiving standard palliative care treatment (ST) and medicinal cannabis treatment (CT).

group and 5.66 months (95% CI: 1.94–9.38) for the CT group. Kaplan–Meier survival curves (Figure 1) demonstrated significantly longer survival for the CT group compared with the ST group (log-rank test, $p < 0.001$).

Multivariable analysis

In the Cox proportional hazards regression model adjusted for age, sex, and time from diagnosis to registration, receiving medicinal cannabis treatment was significantly associated with prolonged survival compared to standard treatment (adjusted HR = 0.28; 95% CI: 0.20–0.37; $p < 0.001$). Age, sex, and most types of prior cancer treatment were not significantly associated with overall survival. However, a time from diagnosis to registration of 3–6 months was associated with a higher risk of death compared to less than 3 months (adjusted HR = 1.31; 95% CI: 1.01–1.71; $p = 0.044$) (Table 3).

Discussion and Conclusion

In the present study, we examined the survival outcomes of patients with advanced cholangiocarcinoma (CCA) or hepatocellular carcinoma (HCC) receiving either standard palliative care treatment (ST) or medicinal cannabis treatment (CT) across tertiary and secondary hospitals in five provinces. Survival time was calculated from the date of registration at the palliative or cannabis clinic until death or censoring. The CT group demonstrated a markedly longer median survival time (5.66 months) compared with the ST group (0.83 months).

These findings are generally consistent with previous research in Northeastern Thailand, where patients receiving only supportive treatment had a median survival of 4.3 months after diagnosis.[18] Moreover, patients diagnosed at an advanced stage were almost twice as likely to die (HR: 1.8; 95% CI: 1.1–2.9).[23–25] However, our results contrast with Bar-Sela et al.,[14] who reported shorter overall survival among advanced cancer patients using cannabis compared with non-users. This discrepancy may reflect differences in baseline characteristics, timing of cannabis initiation, disease stage, and access to other systemic treatments.

In the adjusted Cox regression model (Table 2), receiving medicinal cannabis treatment was significantly associated with prolonged survival (adjusted HR = 0.28; 95% CI: 0.20–0.37; $p < 0.001$). However, the set of adjustment variables was limited to age, sex, type of cancer treatment, and time from diagnosis to registration due to the constraints of using secondary data.[26] Important clinical parameters such as performance status, tumor burden, comorbidities, and detailed treatment history could not be included, and residual confounding is therefore possible.[27]

Baseline differences in care pathways may partly explain the observed survival advantage in the CT group. Many ST patients were referred to palliative clinics late in their disease trajectory, often after exhausting surgery, chemotherapy, or combination regimens.[28] In contrast, CT patients—often older and treatment-naïve—were frequently registered directly at cannabis clinics in community hospitals following imaging or biopsy confirmation of advanced metastases.[29] Some of these patients also received chemotherapy concurrently with cannabis, which may have contributed to extended survival.[30]

From a biological perspective, cannabinoids may improve survival indirectly by alleviating symptoms (e.g., pain, anorexia, nausea), enhancing nutritional intake, improving sleep, and enabling greater tolerance to systemic therapy.[11,13,31] Preclinical studies also suggest potential anti-tumor effects via apoptosis induction, inhibition of angiogenesis, and suppression of tumor proliferation,[28] although these effects remain to be validated in large-scale clinical trials. Taken together, the observed survival benefit in the CT group may be partly attributable to both patient- and treatment-related covariates, as well as the potential symptom-modulating and anti-tumor mechanisms of cannabinoids demonstrated in preclinical studies.[11,13,15,18] This integrated interpretation underscores the multifactorial nature of survival outcomes in advanced CCA/HCC.

To our knowledge, this is the first multicenter Thai study to compare survival outcomes between ST and CT in advanced CCA/HCC patients treated with standardized, FDA-approved medicinal cannabis products under physician supervision.[17–33] Our findings support the integration of medicinal cannabis into palliative care,[33] especially in community settings with limited oncology resources.

Strengths of this study include the relatively large sample size, multi-level hospital participation, and the use of survival analysis adjusted for available covariates. Limitations include the retrospective design, reliance on secondary data,[25] incomplete information on cannabis dosage/formulation/adherence, and the inability to adjust for important prognostic factors. Consequently, while the association between cannabis treatment and improved survival is compelling, causality cannot be established without prospective randomized controlled trials.[26]

Author contributions

N.P. contributed to the research design, data collection, and manuscript writing. P.P., A.W., contributed to data collection and revised the manuscript, and R. W contributed to research administrator, research design, data collection, review and revised the manuscript.

Statements

Statement of ethics

This study adhered to the principles of the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice Guidelines. It was a retrospective cohort study using secondary data from hospital medical record systems and reporting databases from oncology and cannabis clinics. All ethics committees waived the requirement for individual informed consent, as all patient data were anonymized before analysis. No direct patient contact, treatment modification, or additional intervention was performed. No animal experiments were conducted.

Consent to participate statement

Given the retrospective nature of the study, the requirement for written informed consent was waived by the Maha Sarakham University Human Research Ethics Committee, the Roi Et Regional Hospital Ethics Committee, and the Buriram Regional Hospital Ethics Committee. All decisions regarding consent waivers were made in accordance with applicable regulations and ethical guidelines.

Consent for publication

Not applicable, as no identifiable individual data are included in this publication.

Compliance with guidelines

All methods were carried out according to relevant guidelines and regulations.

Data availability statement

Patient data were available in the medical records room of the Roi-Et Regional Hospital, Burirum Regional Hospital, Surin Provincial Hospital, Sawang Dandin Crown Prince Hospital, Panna Nikhom Hospital, and Pana Hospital. The datasets generated and/or analysed during the current study are not publicly available because they are files in the medical records room in our hospital, but they are available from the corresponding author upon reasonable request.

Underlying data

Figshare: Data_survival_cannabis. https://doi.org/10.6084/m9.figshare.20101193.v1.[34]

Figshare: F1000_survival_table1_narisara_ranee. https://doi.org/10.6084/m9.figshare.20486913.v1.[35]

Acknowledgment

The authors would like to express their sincere gratitude to all patients and their families for their participation in this study. We are especially grateful to our colleagues at the Faculty of Medicine, Mahasarakham University, including the Hospital Center of Excellence Team, the palliative care clinic, and the cannabis clinic, for their invaluable assistance and encouragement throughout the course of this research. This study was financially supported by Mahasarakham University. We also thank Professor John F. Smith for his review and English language editing of the manuscript.

References

1. Azizi AA, Hadjinicolaou AV, Goncalves C, *et al.*: **Update on the Genetics of and Systemic Therapy Options for Combined Hepatocellular Cholangio carcinoma.** *Front Oncolog.* 2020; **10**: 570958.
PubMed Abstract | Publisher Full Text | Free Full Text

2. Wang J, Li E, Yang H, *et al.*: **Combined hepatocellular cholangiocarcinoma: a population level analysis of incidence and mortality trends.** *World J Surg Onc.* 2019 Dec; **17**(1): 43.
PubMed Abstract | Publisher Full Text | Free Full Text

3. Kamsa-Ard S, Luvira V, Suwanrungruang K, *et al.*: **Cholangiocarcinoma incidence and survival in Khon Kaen, Thailand: A population-based study.** *BMC Cancer.* 2019; **19**: 291.

4. Banales JM, Cardinale V, Carpino G, *et al.*: **Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA).** *Nat Rev Gastroenterol Hepatol.* 2020; **17**(9): 557–588.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Valle JW, Kelley RK, Nervi B, *et al.*: **Biliary tract cancer.** *Lancet.* 2016; **388**(10061): 1469–1484.

6. Bray F, Ferlay J, Soerjomataram I, *et al.*: **Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.** *CA Cancer J Clin.* 2018 Nov; **68**(6): 394–424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020 Jul;70(4):313.
PubMed Abstract | Publisher Full Text

7. Kawasaki S, Imamura H, Kobayashi A, *et al.*: **Results of 100 liver resections for combined hepatocellular and cholangiocarcinoma.** *J Hepatobiliary Pancreat Surg.* 2015; **10**(1): 31–39.

8. Kim KH, Lee SG, Park EH, *et al.*: **Surgical treatments and prognoses of combined hepatocellular and cholangiocarcinoma of the liver.** *J Gastrointest Surg.* 2012; **16**(3): 487–496.

9. Luvira V , *et al.*: **Outcomes of surgical resection for cholangiocarcinoma in Northeastern Thailand.** *Asian Pac J Cancer Prev.* 2017; **18**(2): 565–572.

10. Rizvi S, Khan SA, Hallemeier CL, *et al.*: **Cholangiocarcinoma — evolving concepts and therapeutic strategies.** *Nat Rev Clin Oncol.* 2018; **15**(2): 95–111.
Publisher Full Text

11. Whiting PF, Wolff RF, Deshpande S, *et al.*: **Cannabinoids for medical use: A systematic review and meta-analysis.** *JAMA.* 2015; **313**(24): 2456–2473.
Publisher Full Text

12. Johnson JR, Burnell-Nugent M, Lossignol D, *et al.*: **Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain.** *J Pain Symptom Manage.* 2013; **46**(2): 207–218.
PubMed Abstract | Publisher Full Text

13. Phansila N, Sittiwet C, Wongkongdech R: **Comparison of effects of medicinal cannabis or standard palliative care on quality of life of patients with cholangiocarcinoma in Northeast Thailand [version 2; peer review: 1 approved, 1 approved with reservations].** *F1000Research.* 2025; **11**: 20.
Publisher Full Text

14. Bar-Sela G, Vorobeichik M, Drawsheh S, *et al.*: **The medical necessity for medicinal cannabis in cancer patients: Lessons from clinical experience.** *Support Care Cancer.* 2013; **21**(7): 1905–1910.

15. Ministry of Public Health, Thailand: *Cannabis-based medicine in palliative care: National policy and guidelines.* Nonthaburi: MOPH; 2019.

16. Chokevivat V, Pongpirul K, Buranapraditkun S, *et al.*: **Medical cannabis in Thailand: Legal framework and policy implementation.** *J Med Assoc Thai.* 2021; **104**(7): 1065–1072.

17. World Law Group. 2020 Global Cannabis Guide – Thailand [Internet]. 2020 Oct 16 [cited 2021 Apr 18].
Reference Source

18. Khuntikeo N, Loilome W, Thinkhamrop B, *et al.*: **A comprehensive public health conceptual framework and strategy to effectively combat cholangiocarcinoma in Thailand.** *PLoS Negl Trop Dis.* 2016; **10**(1): e0004293.
PubMed Abstract | Publisher Full Text | Free Full Text

19. Dasu N, Soloway M, Thuluvath AJ, *et al.*: **Patients with cannabis use and cholangiocarcinoma have lower in-hospital mortality: analysis of the National Inpatient Sample.** *Am J Gastroenterol.* 2022; **117**(Suppl): S99.
Publisher Full Text

20. Jeong S, *et al.*: **Cannabidiol and cannabigerol inhibit cholangiocarcinoma cell growth via apoptosis, autophagy, and cell cycle arrest.** *Front Pharmacol.* 2022; **13**: 924221.
Publisher Full Text

21. Notarnicola M, *et al.*: **Inhibitory effects of cannabinoids on cholangiocarcinoma cell proliferation and migration.** *Cancer Invest.* 2009; **27**(6): 549–555.
Publisher Full Text

22. Khan SA, *et al.*: **Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update.** *Gut.* 2022; **71**(1): 1–29.
Publisher Full Text

23. Sripa B, Pairojkul C, Thinkhamrop B, *et al.*: **The tumor registry of cholangiocarcinoma in Northeastern Thailand: A report of 198 cases.** *Asian Pac J Cancer Prev.* 2020; **21**(3): 703–709.

24. Thunyaharn N, Promthet S, Wiangnon S, *et al.*: **Survival of Cholangiocarcinoma Patients in Northeastern Thailand after Supportive Treatment.** *Asian Pac. J. Cancer Prev.* 2013 Nov 30; **14**: 7029–7032.
PubMed Abstract | Publisher Full Text

25. Woradet S, Songserm N, Promthet S, *et al.*: **Health-Related Quality of Life and Survival of Cholangiocarcinoma Patients in Northeastern Region of Thailand.** *PLoS One.* 2016; **11**(9): e0163448.
PubMed Abstract | Publisher Full Text | Free Full Text

26. World Health Organization: *Planning and implementing palliative care services: A guide for programme managers.* Geneva: WHO; 2016.

27. Hernán MA, Robins JM: *Causal Inference: What If.* Boca Raton: Chapman & Hall/CRC; 2020.

28. Palliative Care Society of Thailand: *National palliative care guidelines.* Bangkok: Palliative Care Society of Thailand; 2021.

29. National Cancer Institute Thailand: *Cancer registry annual report.* Bangkok: NCI Thailand; 2022.

30. Schroeder A, McPartland JM: *Cannabis science and policy: Examining the science behind the policy.* New York: Oxford University Press; 2018.

31. Maida V, Daeninck PJ: **A user's guide to cannabinoid therapies in oncology.** *Curr Oncol.* 2016; **23**(6): 398–406.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Velasco G, Sánchez C, Guzmán M: **Anticancer mechanisms of cannabinoids.** *Curr Oncol.* 2016; **23**(S2): S23–S32.

33. Thai Food and Drug Administration: *Guidelines for medicinal cannabis use in palliative care.* Nonthaburi: Thai FDA; 2023.

34. Phansila N, Pansila P, Wongkongdech A, *et al.*: Data_survival_cannabis. figshare. [Dataset]. 2022.
Publisher Full Text

35. Phansila N: F1000_survival_table1_narisara_ranee. figshare. [Dataset]. 2022.
Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ? ? ✘ ✘

Version 3

Reviewer Report 14 October 2025

https://doi.org/10.5256/f1000research.186703.r420117

✘

Nuttapong Ngamphaiboon
Mahidol University, Bangkok, Thailand

Many major concerns are not addressed properly, led to difficulty to make conclusions from the data due to multiple confounders.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 13 October 2025

https://doi.org/10.5256/f1000research.186703.r420115

?

Nat Na-Ek
Division of Social and Administration Pharmacy, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Mueang Phayao District, Phayao, Thailand

This manuscript addresses an important clinical question, but several major methodological flaws remain unresolved as outlined below:

It is unclear whether the study population consists of cholangiocarcinoma (CCA), combined

hepatocellular–cholangiocarcinoma (cHCC-CCA), or either CCA or HCC. In the abstract, CCA is mentioned, whereas in the introduction cHCC-CCA is discussed. Later, in the methods section, patients with advanced CCA or HCC are included. This inconsistency confuses readers and substantially undermines the trustworthiness of the work.

Although my E-value analysis suggests that unmeasured confounding is unlikely to fully explain away the observed association (adjusted HR = 0.28, 95% CI = 0.20, 0.37; E-value 6.602 for the point estimate and 4.848 for the confidence interval), the magnitude of the effect warrants careful scrutiny. In clinical epidemiology, it is rare for a single unmeasured factor to be associated with both exposure and outcome by risk ratios exceeding five- to seven-fold each, especially after adjustment for age and sex. This indicates that residual confounding alone is an improbable explanation for the observed results. However, several other alternative explanations could plausibly account for such a pronounced effect size. Firstly, survival (immortal) time bias may have arisen because the cannabis group was registered earlier, whereas controls experienced longer lag periods before registration, effectively guaranteeing a survival advantage for cannabis users. This may not be adequately controlled by simply adjusting for the lag period as a categorical variable. Secondly, selective inclusion is a concern: if healthier or more engaged patients were more likely to receive or report cannabis use, the apparent benefit could reflect reverse causation rather than treatment efficacy. Thirdly, the removal of the patient flow diagram and the unclear handling of missing data reduce transparency, raising the possibility that exclusions disproportionately affected sicker controls. Collectively, these biases offer more credible explanations for the striking hazard ratio reported than unmeasured confounding alone. The authors should therefore conduct sensitivity analyses, such as landmark analyses, time-dependent modelling, and transparent reporting of exclusions and missingness, before drawing strong conclusions about treatment effects. In addition, please verify the correctness of the percentages reported in Table 1.

The rationale for adopting a two-step approach is unclear. Univariable selection should be avoided (TRIPOD) as it can lead to omission of important covariates and model misspecification. Best practice in covariate selection involves the use of DAGs or prior knowledge, rather than relying solely on statistical significance.

In Figure 1, the dashed vertical lines do not appear to represent the median survival time of each group. By definition, the median survival should correspond to the time point at which 50% of the population remains alive. Please check the correctness of the Kaplan–Meier curve.

In the abstract:

Please include a specific objective or research gap in the final sentence of the background subsection.

Please explicitly state the adjustment factors in the methods subsection.

In the results subsection, follow-up time should generally be reported as the median with corresponding interquartile range rather than as incidence density (person-time). Please revise accordingly.

In the conclusion subsection, please avoid implying causality. For example, the sentence “Medical

cannabis increased overall survival rates among CCA patients" should be rephrased as "Medical cannabis was associated with increased overall survival rates among CCA patients"

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 2

Reviewer Report 10 September 2025

https://doi.org/10.5256/f1000research.180104.r377014

Selamat Budijitno
Department of Surgery, Dr. Kariadi Hospital, Faculty of Medicine, Universitas Diponegoro, Semarang, Central Java, Indonesia

I approve for this "version 2" of the article.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Surgical Oncology, biomolecular, Immunology, epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 12 August 2025

https://doi.org/10.5256/f1000research.180104.r400722

Dima Malkawi
University of Colorado, Denver, Colorado, USA

Introduction:

- The second paragraph of the introduction focuses only on CC but this study focuses on cHCC-CC so the introduction needs to be expanded to include both.
- The third paragraph mentions a standard and a new treatment; it would be good to expand on both here to know what the difference is between the two and why that may be relevant
- Would use the intro to discuss the logic behind this study and why it is impactful or necessary. Are there big differences between the two methods?

Methods:
- The flow diagram is not adding much to this manuscript
- Would recommend CONSORT diagram instead
- No information is provided on treatment protocols including dosing, frequency etc
- Patients in CT vs. ST may differ in unmeasured ways (e.g., baseline performance status, comorbidities, tumor burden, liver function). For example, the CT group had much lower mortality rates and higher follow-up times, but it's unclear whether this is due to the treatment or differences in baseline prognosis.
- There is no mention of propensity score matching or multivariable adjustment for critical prognostic variables beyond age, sex, and treatment.
Without controlling for these confounders, the observed survival difference may be overestimated
- Consider adjusting for additional baseline variables in the Cox model (e.g., ECOG performance status, Child-Pugh score, metastasis status, comorbidities, prior treatments). If unavailable, acknowledge this as a serious limitation
- Your inclusion criteria state "newly diagnosed with CCA or HCC," yet the title and aim focus on *combined hepatocellular cholangiocarcinoma (cHCC-CC)*
- unclear whether all patients indeed had **cHCC-CC**, or whether you included *either* HCC or CCA
- Clarify whether patients were pathologically confirmed as cHCC-CC or diagnosed clinically as HCC/CCA. If both were included, justify combining them.
- The survival times reported (ST: 0.83 months) seem *extremely short*, raising the possibility that these were highly selected end-stage patients.

Results:
- The authors state that they tested the proportional hazards assumption but do not report the findings. They also state they did kaplan meier survival curves which are also not reported
- The data is reported as a causal relationship which is extremely misleading
- No data presented on differences in treatment populations
- Chemotherapy is initially defined as CT but then later Cannabis Therapy is also defined as CT causing some confusion
- Data on treatment types and staging is not discussed and thus comparisons between the groups may not be accurate or reflective of true outcomes, and possibly considered invalid

Overall:
- The extremely high CC incidence in your region is discussed, but the CT effect may not translate to other settings.
- Cannabis preparations (THC:CBD ratios, dosing) are specific to Thai FDA-approved products — this needs more detail for reproducibility.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: surgical oncology, outcomes

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 11 August 2025

https://doi.org/10.5256/f1000research.180104.r396266

Nuttapong Ngamphaiboon
Mahidol University, Bangkok, Thailand

The study contains major flaws in both design and methodology. The conclusions presented in the current version of the manuscript may be significantly biased due to the lack of detailed patient characteristics and treatment-related information.

Major Comments:

1. Given that cannabinoids are primarily used in palliative care to alleviate pain, reduce nausea, and stimulate appetite, the manuscript should clearly state the primary outcomes of palliative use such as symptom improvement of cannabinoid use in this study.
2. Detailed information regarding cannabinoid use should be provided, including dosage, duration, mode of administration, and patient compliance.
3. If survival outcomes are to be reported, critical clinical data must be included—such as ECOG performance status, cancer staging at the time of treatment, chemotherapy

regimens, number of cycles, dosing details, relative dose intensity, and radiation therapy use. Without these essential details, the conclusion that "medical cannabis increased overall survival rates among CCA patients" cannot be considered reliable.

4. Kaplan–Meier curves for overall survival (OS) and progression-free survival (PFS) should be presented to support the survival analysis.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 15 Aug 2025

Narisara Phansila

Reviewer's Comment – Overall assessment of major flaws in design and methodology
The study contains major flaws in both design and methodology. The conclusions presented in the current version of the manuscript may be significantly biased due to the lack of detailed patient characteristics and treatment-related information.

Response: We acknowledge the inherent limitations of our retrospective design and the use of secondary data. Our dataset was obtained from hospital records and contained survival status, selected patient characteristics, and treatment timing variables (e.g., date of diagnosis, date of registration for treatment). Detailed clinical information such as ECOG performance status, cancer staging, chemotherapy regimen details, dosing, and radiation therapy use was not captured in the database. We have explicitly stated these limitations in

the revised manuscript, reframed our conclusions to avoid causal inference, and presented our findings as preliminary evidence requiring further validation through prospective studies.

Reviewer's Comment 1:

Given that cannabinoids are primarily used in palliative care to alleviate pain, reduce nausea, and stimulate appetite, the manuscript should clearly state the primary outcomes of palliative use such as symptom improvement of cannabinoid use in this study.

Response: We agree that palliative outcomes such as symptom improvement are important; however, these were not available in the secondary data used for this analysis. We have clearly acknowledged this limitation in the revised manuscript and clarified that our study focuses exclusively on survival outcomes derived from available records.

Reviewer's Comment 2:

Detailed information regarding cannabinoid use should be provided, including dosage, duration, mode of administration, and patient compliance.

Response: We have added all available treatment details to the Methods section, including the product type (Thai FDA-approved oral cannabis oil extract), THC:CBD ratios, and initial prescribed dosage. Information on treatment duration, dose adjustments, and patient compliance was not recorded in the database and is acknowledged as a limitation.

Reviewer's Comment 3:
If survival outcomes are to be reported, critical clinical data must be included—such as ECOG performance status, cancer staging at the time of treatment, chemotherapy regimens, number of cycles, dosing details, relative dose intensity, and radiation therapy use. Without these essential details, the conclusion that "medical cannabis increased overall survival rates among CCA patients" cannot be considered reliable.

Response: We agree that these clinical variables are important prognostic factors; however, they were not captured in the secondary database used for this study. Available data were limited to demographic characteristics, timing variables (diagnosis date, registration date), treatment type (cannabis vs. standard care), and survival status. We have emphasized these limitations in the revised manuscript and reframed our conclusions to state that medicinal cannabis treatment was associated with prolonged survival, while noting that causality cannot be inferred.

Reviewer's Comment 4:

Kaplan–Meier curves for overall survival (OS) and progression-free survival (PFS) should be presented to support the survival analysis.

Response: We have added Kaplan–Meier curves for OS (Figure 1). PFS could not be analyzed because progression dates were not consistently recorded in the dataset. This limitation is

stated in both the Methods and Limitations sections.

Competing Interests:
We confirm that the authors have no competing interests to declare.

Competing Interests: No competing interests declared.

Reviewer Report 03 June 2025

https://doi.org/10.5256/f1000research.180104.r383930

?

Ueamporn Summart
Faculty of Nursing, Roi Et Rajabhat University, Tha Muang, Thailand

Title: Survival rate of patients with combined hepatocellular cholangiocarcinoma receiving medical cannabis treatment: A retrospective, cohort comparative study.
Upon completing a comprehensive analysis of all your amended manuscripts, I would like to express my gratitude for your diligent efforts in enhancing and elucidating your manuscripts. In my opinion, there are several areas where the authors may improve in order to enhance the reader's understanding of their work, as outlined below:
Abstract:
Conclusions: “The medical cannabis increased overall survival rates among CCA patients.”
In my opinion, we do not conclude that only the effect of medical cannabis increased overall survival rates among this population because this study design is not supported. Furthermore, the study did not control or include other confounding factors that could affect the survival outcome.
Introduction:
1) Suggest the authors clarify the population of this study. (recurving palliative or curative treatment) and also describe more information about these treatments that are specific for this population before mentioning the use of medical cannabis treatment in this study. (Some details are missing between paragraph 2 and paragraph 3, such as treatment for palliative CCA or specific survival rates and other treatment for this population in Thailand.
2) Suggest the authors mentioned the rationale (literature reviewed) of the covariates and the medical cannabis treatment used in this study from previous studies.
Statistical analysis:
1) Due to the retrospective cohort design, this study aimed to compare the survival rate between 2 treatments, so it is better to compare baseline characteristics of the participants because baseline imbalance among this sample will lead to selection biases.
2) To compare the survival rate between two groups using the log-rank test, the author should mention the assumption for this statistic before using it.3.3) Suggest the authors used a Kaplan-Meier graph to compare survival outcomes between two treatments following covariates in this study, such as age and cancer treatments. 3.4) For Cox proportional hazard statistics, suggest the

authors mention the assumption of these statistics and steps of analysis such as univariable analysis and multivariable analysis. (I cannot find this step, but the authors mentioned these steps in the discussion part.).
Results:
1) I agree with reviewer 1 to separate the table into 3 tables as follows: Table 1 compares baseline characteristics. Normally, the authors presented the covariate in the table following the patient treatment group, so it is not the covariate. Suggest separating this table out of the tables that present the study objectives.
2) Suggest the authors present survival outcomes in another table along with Kaplan-Meier graph comparing survival outcomes between two treatments following covariate.
3) Suggest the authors present a table for the Cox proportional hazard ratio to present crude HR and adjusted HR, followed by steps of multivariable analysis. In addition, for the HR less than 1, please interpret this result for the readers.
Discussions:
Suggest the authors discuss following all of the covariates used in this study. In addition, the mechanism of medical cannabis treatment should be mentioned, whether it increased overall survival rates among CCA patients.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nursing and Public Health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 15 Aug 2025

Narisara Phansila

Reviewer's Comment – Abstract
Conclusions: "The medical cannabis increased overall survival rates among CCA patients." In my opinion, we do not conclude that only the effect of medical cannabis increased overall survival rates among this population because this study design is not supported. Furthermore, the study did not control or include other confounding factors that could affect the survival outcome.
Response:
We appreciate this important observation. The Abstract conclusion has been revised to avoid implying causality. The new conclusion now reads:
"In this retrospective cohort, medicinal cannabis use was associated with longer overall survival among advanced CCA patients; however, causality cannot be inferred due to the retrospective design and residual confounding."
This rewording aligns with the study design and acknowledges the potential impact of unmeasured confounding factors.
(Page 1, Lines 36–39)
Reviewer's Comment – Introduction (1)
Clarify the population of this study (receiving palliative or curative treatment) and describe more information about these treatments specific to this population before mentioning medical cannabis. Include survival rates and treatments for CCA in Thailand.
Response:
We have clarified that all patients in this study were diagnosed with advanced disease and were registered at palliative care or cannabis clinics. No patients received curative-intent treatment. We have expanded the description of standard palliative care and systemic treatment options available in Thailand, including expected survival times, supported by local and international references.
(Page 2, Lines 70–76, 78–79)
Reviewer's Comment – Introduction (2)
Mention the rationale (literature reviewed) of the covariates and medical cannabis treatment used in this study from previous studies.
Response:
We have added a paragraph explaining the rationale for each covariate (age, sex, type of cancer treatment, time from diagnosis to registration) based on prior survival studies. We also strengthened the rationale for examining medicinal cannabis by summarizing evidence from Thai and global literature on its palliative benefits and possible anti-cancer effects.
(Page 2, Lines 70–79)
Reviewer's Comment – Statistical Analysis (1)
Compare baseline characteristics to address possible selection bias.
Response:
We have compared baseline characteristics between treatment groups in the new Table 1 and discussed differences that may indicate potential selection bias.
(Page 4, Table 1)
Reviewer's Comment – Statistical Analysis (2)
Mention the assumption for the log-rank test.
Response:
We have explicitly stated the assumptions for the log-rank test (proportional hazards, non-informative censoring) in the Statistical Analysis section.
(Methods: Statistical Analysis)
Reviewer's Comment – Statistical Analysis (3)

Use Kaplan–Meier graph to compare survival outcomes between treatments by covariates (e.g., age, cancer treatments).

Response:

We have added stratified Kaplan–Meier survival curves by age group (<65 vs ≥65) and prior cancer treatment (yes/no) in the supplementary material. Figure 1 presents the overall survival curves for the two treatment groups.

(Figure 1; Supplementary Figures)

Reviewer's Comment – Statistical Analysis (4)

Mention the assumption of Cox regression and steps of analysis (univariable and multivariable).

Response:

We have described the proportional hazards assumption checks (Schoenfeld residuals, log-minus-log plots) and outlined the two-step analysis process: univariable screening ($p<0.20$) followed by multivariable Cox regression adjusting for selected covariates.

(Methods: Statistical Analysis)

Reviewer's Comment – Results (1)

Separate tables: Table 1 for baseline characteristics, separate from tables presenting study objectives.

Response:

We have reorganized the results into separate tables:

- **Table 1:** Baseline characteristics by treatment group
- **Table 2:** Survival outcomes (median survival, person-time, log-rank test)
- **Table 3:** Cox regression results (crude and adjusted HRs)
  (Pages 4–6, Tables 1–3)

Reviewer's Comment – Results (2)

Present survival outcomes in another table along with Kaplan–Meier graph by covariates.

Response:

Survival outcomes are now presented in Table 2 and illustrated in Kaplan–Meier curves (Figure 1). Stratified curves by age and prior cancer treatment are included in the supplementary material.

Reviewer's Comment – Results (3)

Present Cox proportional hazard results in a table with crude and adjusted HR, interpret HR<1.

Response:

Table 3 presents both crude and adjusted HRs, with interpretation provided in the Results section. We explain that HR<1 indicates a reduced hazard of death, reflecting longer survival in that group.

(Page 6, Table 3)

Reviewer's Comment – Discussion

Discuss all covariates and the mechanism of medical cannabis treatment.

Response:

We have discussed each covariate's association with survival outcomes, supported by relevant literature. Additionally, we expanded the discussion on potential mechanisms of medicinal cannabis, including symptom relief (pain, nausea, appetite, sleep) and preclinical evidence for anti-tumor activity (apoptosis induction, angiogenesis inhibition, tumor proliferation suppression).

(Pages 6–7, Discussion)

Competing Interests: no competing interest

Reviewer Report 10 May 2025

https://doi.org/10.5256/f1000research.180104.r377013

Nat Na-Ek
Division of Social and Administration Pharmacy, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Mueang Phayao District, Phayao, Thailand

Thank you for the revised version of the manuscript. However, it remains difficult to determine where amendments have been made in response to my previous comments. I would greatly appreciate it if the authors could provide a point-by-point response to each of my earlier comments, as a general summary is insufficient for a thorough review.

Upon reviewing the revised manuscript, I noted several issues that appear to remain unaddressed, with no accompanying explanation. For example:

- In the abstract, the authors continue to use the term “multivariate analysis” rather than the more appropriate “multivariable analysis”. While this is a relatively minor issue, it reflects a lack of attention to detail.

- More importantly, in the final sentence of the results section and in the conclusion of the abstract, the authors continue to imply a causal relationship between medical cannabis and survival rates. For instance, statements such as “Therefore, CT had a reduced probability of dying from the disease” and “The medical cannabis increased overall survival rates among CCA patients” suggest causality. How can the authors be certain that the observed association is attributable solely to medical cannabis, rather than to other potential explanations?

- Regarding the patient flow diagram, the figure presented appears to be a theoretical illustration more suited to teaching the principles of survival analysis, rather than a CONSORT-style flow diagram. A CONSORT-style flow diagram would be more informative, showing how many participants were initially assessed for eligibility, how exclusions were applied, and how the final analytical sample was derived.

- In the Methods section, the authors mention the use of the Cox proportional hazards model but do not report testing the proportional hazards assumption. Furthermore, I could not locate any figures of Kaplan–Meier curves in the Results section, which raises concerns about the validity and transparency of the analysis.

Given the extensive revision timeline—almost three years since the initial submission—and the apparent failure to sufficiently address or justify the lack of amendments in response to my previous feedback, I regret that I must recommend rejection of this manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical epidemiology, pharmacoepidemiology, and social epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 1

Reviewer Report 26 June 2023

https://doi.org/10.5256/f1000research.135337.r178384

?

Nat Na-Ek
Division of Social and Administration Pharmacy, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Mueang Phayao District, Phayao, Thailand

Overall, this piece of work on the benefits of medical cannabis in improving the survival rate of combined hepatocellular cholangiocarcinoma (cHCC-CC) patients is interesting. However, several issues need further clarification and improvements.

Major points:

1. It is important to recheck the accuracy of the provided data (https://doi.org/10.6084/m9.figshare.2010119). I noticed inconsistencies in the reported figures, such as the percentages of male and female patients and the number of patients receiving each treatment modality. Additionally, there was a coding issue with one patient receiving medical cannabis coded as 12 in the current treatment variable without an explanation. Addressing these inconsistencies is crucial for the reproducibility of the results.

2. The authors did not mention whether they performed a proportional hazards assumption test in the statistical analysis. Upon re-analysis, I found that the treatment variable violated this assumption, indicating that the hazard ratio was not constant at 0.28 across the entire follow-up time as reported. More importantly, the significant association between medical cannabis and survival rate was observed only in the early follow-up (3 months), not the whole study period.

Therefore, it is important for the authors to conduct a re-analysis and introduce an interaction term between the treatment variable and time using the time-varying covariate (TVC) option in STATA. When reporting the hazard ratio, the authors should present it across the range of follow-up (e.g., within 10 months) to ensure validity and reliability. More details and examples can be found at Bellera *et al.* (2010)[1].

3. Please avoid making causal claims in an observational study. For example, the sentence "the medical cannabis increased overall survival rates among cHCC-CC patients" (conclusion of the abstract) should be revised to "the medical cannabis was associated with improved overall survival rates among cHCC-CC patients." This distinction is vital because several alternative explanations (e.g., bias, errors, confounding, effect modification, reverse causality) could account for the significant findings. For instance, patients who received medical cannabis might have been more closely monitored by physicians, or they might have had unobserved or unmeasured characteristics (residual confounders) that affected their prognosis positively. Additionally, there may have been discrepancies in the quality of care across different settings.

   Therefore, the authors should refrain from assuming causality to avoid exaggerating the significance of their results. It would be appropriate to include a cautionary statement in the discussion section, such as "as this is an observational study, we cannot infer causality, and a randomised controlled trial is needed to establish the efficacy of medical cannabis in cancer patients."

4. Please provide justification and references for each covariate selected as adjusting factors in the analysis. Furthermore, clarify why certain continuous variables (e.g., age, disease duration after registration) were categorised instead of using them as continuous scales. Additionally, I recommend running the analysis with age as a quadratic term (age + age^2), as it was found to be significantly associated with death, suggesting a non-linear relationship between age and mortality. Therefore, using a quadratic term for each continuous variable would be more appropriate as it preserves important information[2].

5. Provide more details about the medical cannabis used in the study, such as product details, dosage form, dose, and administration. This information is crucial for generalising the findings to a clinical setting and enabling reproducibility. Additionally, clarify what the standard treatment was in the study and whether it was consistent across different settings.

6. In the discussion section, provide more information about the individuals who were lost to follow-up and discuss how their exclusion might have influenced the findings. Is it possible to determine whether these patients were still alive at the end of the study or if they died soon after dropping out?

7. Discuss the potential impact of differences in the quality of care across settings on the survival rate of patients in the study. It would be helpful to perform a subgroup analysis according to settings and utilise the strata option in the Cox model.

   Furthermore, consider conducting subgroup analyses based on other variables such as sex, age group, and current treatment to assess whether effect modification plays a role in the findings. Sensitivity and subgroup analyses are necessary to ensure the robustness of the

findings, particularly in an observational study.

8. In the discussion section, compare the survival rates of the study, particularly in the standard treatment group, with previous works. If applicable, discuss the reasons for any differences observed. This will help strengthen the external validity of the study.

Minor issues:

1. Use "multivariable" instead of "multivariate" when discussing regression models. The term "multivariable" refers to adding explanatory variables (X) in the regression model, while "multivariate" implies examining various outcomes (Y) simultaneously[3].

2. Spell "proportional hazards regression" with an "s" in "hazards" since the term "proportional" implies the existence of at least two hazards.

3. Be aware of the term person-months as it is not a person per month, but it is rather the product of patients and their corresponding follow-up time. So, the unit of the incidence rate in your work should be written as “100 person-months” not “100 person/month”.

4. To improve clarity, consider splitting Table 1 into three separate tables. Table 1 should focus solely on the characteristics of included participants, allowing for inferential statistics (e.g., independent t-test, chi-squared test) to test the association between each characteristic and exposure status. Then, create Table 2 to present details of the outcome variable according to exposure status. Finally, present Table 3 as the main findings regarding the association between treatment and all-cause mortality, including both crude (unadjusted) and adjusted hazard ratios. Additionally, including a Kaplan-Meier plot with a risk table would aid in visualising the survival rates between patients receiving medical cannabis and those receiving standard treatment.

5. If possible, please discuss the potential biological mechanisms or underlying explanations of how medical cannabis can improve the survival rate of cHCC-CC patients.

Overall, addressing these major and minor points will greatly enhance the clarity, validity, and reproducibility of your study.

References

1. Bellera CA, MacGrogan G, Debled M, de Lara CT, et al.: Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer.*BMC Med Res Methodol*. 2010; **10**: 20 PubMed Abstract | Publisher Full Text
2. Collins GS, Ogundimu EO, Cook JA, Manach YL, et al.: Quantifying the impact of different approaches for handling continuous predictors on the performance of a prognostic model.*Stat Med*. 2016; **35** (23): 4124-35 PubMed Abstract | Publisher Full Text
3. Hidalgo B, Goodman M: Multivariate or multivariable regression?. *Am J Public Health*. 2013; **103** (1): 39-40 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical epidemiology, pharmacoepidemiology, and social epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 01 June 2023

https://doi.org/10.5256/f1000research.135337.r170664

?

Selamat Budijitno
Department of Surgery, Dr. Kariadi Hospital, Faculty of Medicine, Universitas Diponegoro, Semarang, Central Java, Indonesia

Based on the STROBE criteria, most of this research has fulfilled the criteria. In my opinion, there are several things that need to be improved so that this research is better:

- There is no sufficient detail of the methods, especially on the eligibility criteria of participants, and the method of follow up that provided to allow replication by others.
- There are no very important data as a confounder, namely the pain scale/level of pain on the criteria when matching participants.
- It would be clearer if the authors can explain the relationship between pain levels, quality of life, and survival rates in biomolecular terms. Such as, for example, mutations in the NMDA receptor in chronic pain, which will produce P protein which can increase the risk of advanced metastasis, NMDA receptors stimulates the MAPK and CaMK pathways, leading to CREB activation in tumor cells. NMDAR-interacting proteins and the downstream signaling effectors display features in common between the neuronal and metastatic cancer

processes, such as cell adhesion, migration, and survival.

- In the results of the cohort study, it would be better if the authors can explain in the report the numbers of individuals at each stage of study – e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and the reason of dropped out participant.

- Give reasons for nonparticipation/dropped out participant in each stage. Consider use of a flow diagram.

Thank you.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Surgical Oncology, biomolecular, Immunology, epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Jun 2023

Narisara Phansila

1. There is no sufficient detail of the methods, especially on the eligibility criteria of participants, and the method of follow up that provided to allow replication by others.

   Ans: *The survival rate matches the history of the first day of treatment in the clinic. Copy the symptoms and physical examination of the patient. Diagnosis, treatment, address, and*

telephone number from the medical records recorded by the treating physician from September 2, 2019, to October 31, 2020; follow up on the patient's last status until April 30, 2021. Check the status and date of the patient's death from the Cancer Unit's patient tracking database or from the death certificate of the patient Check the correctness of the information. and import data for analysis.

2. There are no very important data as a confounder, namely the pain scale/level of pain on the criteria when matching participants.

   Ans: *The evaluation was not assessed because secondary data were used to track only the six-month outcome, censor, or event to assess survival. Starting from admission to treat both types, the inclusion criteria were likely to be met for all patients aged 18 years and over.*

3. It would be clearer if the authors can explain the relationship between pain levels, quality of life, and survival rates in biomolecular terms. Such as, for example, mutations in the NMDA receptor in chronic pain, which will produce P protein which can increase the risk of advanced metastasis, NMDA receptors stimulates the MAPK and CaMK pathways, leading to CREB activation in tumor cells. NMDAR-interacting proteins and the downstream signaling effectors display features in common between the neuronal and metastatic cancer processes, such as cell adhesion, migration, and survival.

   Ans: *This study has not investigated a relationship; we only track the survival rate over time. and find factors that are general information, but we will be publishing again about the quality of life and survival.*

4. In the results of the cohort study, it would be better if the authors can explain in the report the numbers of individuals at each stage of study – e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and the reason of dropped out participant.

   Ans: *This study used secondary data based on the results of the diagnosis and the treatment system.*

5. Give reasons for nonparticipation/dropped out participant in each stage. Consider use of a flow diagram.

   Ans: *Due to the use of medical records, use the available information If death is specified in the system, there will be a death certificate. The lack of follow-up data will be used as a censor, but it can be used to calculate the survival rate by using survival statistics.*

Competing Interests: No Competing of interests