

RESEARCH ARTICLE

Editorial Process: Submission:11/24/2022 Acceptance:04/14/2023

Factors Associated with the Quality of Life among Family Caregivers of Cholangiocarcinoma Survivors in Northeastern Thailand

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Abstract

Background: Cholangiocarcinoma (CCA) is a common and usually lethal liver cancer especially in Southeast Asia. Family caregivers (FCs) and their quality of life (QOL) is important for the care process to operate effectively. However, there are only few research articles about the QOL of CCA FCs. The goal of this study was to assess the QOL and its associated factors among CCA FCs. **Material and Methods:** This cross-sectional study was undertaken with 231 CCA FCs who were the primary FCs for CCA patients in a tertiary hospital in Northeastern Thailand. The QOL was measured using the Thai version of the World Health Organization's Quality of Life Questionnaire. Multivariate regression models were developed to investigate the predictors of the QOL, including the demographic characteristics, symptoms, anxiety and depression, and support care need. **Results:** The CCA caregivers had moderate to high QOL for all of four domains: the mean score was 27.03 (SD=2.81) for physical, 23.13 (SD=2.81) for psychological, 11.32 (SD=1.08) for social relationships, and 28.08 (SD=2.81) for environment. Multivariable analysis shows that, symptoms, support care need, age and education level were significant predictors of FCs's QOL. Moreover, the QOL was lower in younger FCs ($p<0.001$). **Conclusion:** Symptoms, support care needs, age, and education level were associated with QOL among FCs for CCA patients. A holistic strategy that includes caregiver training, psychosocial therapies, and proper support may help these FCs for a better QOL.

Keywords: Cholangiocarcinoma- caregivers- quality of life- symptoms- support care need

Asian Pac J Cancer Prev, 24 (4), 1249-1255

Introduction

Cholangiocarcinoma (CCA) is a global public health issue since it is the leading cause of mortality. According to the World Health Organization's (WHO) International Agency for Research on Cancer [IARC] report from 2020, there were 905,677 new CCA cases globally with 830,180 of them dying (Sung et al., 2021). However, the number of cancer patients surviving has increased as a result of advancements in; cancer screening and treatment modalities with a wider range of contributing CCA survival factors (Miller et al., 2019).

In general, CCA survivors had at least one or more common symptom such as a feeling of tiredness, pain, and psychological distress, and these symptoms may reduce their quality of life (QOL) as well as the QOL of their family caregivers (FCs) (Wen et al., 2018). Therefore, these FCs experienced high levels of psychological and

physical stress along with other conflicts while caring for cancer patients, resulting in their poor QOL (Lim et al., 2021). FCs have a significant impact on how well a patient manages his or her illness, and they are frequently the patient's primary source of social and emotional support (Fumaneeshoat and Ingviya, 2020). Similarly FCs desired to know more about the condition and its progression in order to better manage their lives and make decisions (Hashemi et al., 2018), and they also needed additional instruction about what to do after the patient death (Cui et al., 2014). In addition, FCs' unpleasant experiences can affect not only their personal QOL, but also their ability to provide care (Abdullah et al., 2019). Therefore, to improve the QOL for both patients and their carers. The patient's treatment modalities, including; surgery, chemotherapy, and radiotherapy, should be communicated to them depending on the progression of the cancer and of the consequences of that communication. As the

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cancer metastasized, most FCs are asked to take on more responsibilities, such as longer periods of home care and more frequent hospital visits, putting them under more stress and compromising their QOL (Kilic and Oz, 2019).

Even though prior studies have reported many factors influence FCs' QOL including those that affect both patients and FCs, such as; their patient's underlying diseases, the cancer progression, the number of hours they spend caring for them each day, their age, income, educational level, and their personal relationships that may suffer because of their responsibilities. (TIAN et al., 2012; Aun and Mohd, 2016; Ndikuno et al., 2016; Yu et al., 2017; Fumaneeshoat and Ingviya, 2020). Nevertheless, these studies included patients with various type of cancers, this approach has the advantage of a larger sample size, but it may obscure potential differences in individuals who care for cancer patients of various types (Turkoglu and Kilic, 2012; Kong and Guan, 2019; Abbasi et al., 2020). There is a scarcity of information in the literature about FC's cancer specific QOL, and the few current studies have targeted on liver cancers (Hansen et al., 2021).

In Thailand, only a few studies have been conducted concerning FCs of cancer patients (Meecharoen et al., 2013; Fumaneeshoat and Ingviya, 2020). However, no research has specifically examined CCA patients and their FCs' QOL and workloads, as well as associated factors. Therefore, the aim of this study was to assess the QOL and its associated factors among FCs. of CCA patients.

Materials and Methods

Study design and sample

In this cross-sectional study, 231 primary CCA FCs from a public tertiary care university with a teaching facility were enrolled. Only one family member was recruited for each CCA patient. Questionnaires were administered in February 2021 to April 2021. The inclusion criteria were a family member of a CCA survivor who assumes primary responsibility for the patient's care and devotes the most amount of time to it, 18 years of age or older, ability to speak and understand Thai language, full literacy (reading and writing in Thai and attending the hospital,

Permission to collect the data was obtained from the head of each hospital unit, and all participants provided their informed consent. The ethics committees of Khon Kaen University (HE631628) approved the study protocol.

Instrument

The first part of the questionnaire consisted of FCs'; demographic data including gender, age, marital status, income, educational level, number of family members, and relationship status with the CCA survivor.

The Thai version of the World Health Organization's Quality of Life Questionnaire (WHOQOL-BREF-THAI), a questionnaire which contains 26 items including 2 items, concern QOL and general health and 24 items that deal with degrees of satisfaction, which were; physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (3 items) are covered in this section (8 items). Each item

is graded on a scale of 1 to 5 on a 5-point Likert scale. The domain score was calculated using the mean score of items within each domain and translated into 4-10 and 0-100 scores according to the questionnaire rules. Higher scores indicated a higher standard of living (Gholami et al., 2013). The WHO has officially recognized the WHOQOL-BREF-dependability, and this tool has a Cronbach's alpha coefficient of 0.841 and a content validity score of 0.652.

The Memorial Symptom Assessment Scale Short Form (MSAS-SF), a 32-items questionnaire with a 5-point Likert scale, is aimed to measure the frequency, severity, and discomfort associated with 32 different multidimensional symptoms that patients experience. The MSAS-SF has been used to diagnose a wide spectrum of conditions and can be utilized in both clinical and research contexts (Menezes et al., 2017).

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) is commonly used to examine anxiety and depression symptoms. In Thailand. It has 14 questions which seven questions are for assessing anxiety symptoms (all odd numbers) and seven questions for measuring depression symptoms (all even numbers). Each response has a score on a Likert scale ranging from 0 to 3. The anxiety and depressive episode scores are divided into parts ranging from 0 to 21, with the following categories: Three scales are used to determine the score range: non-anxiety and depression are defined as 0-7 points. 8-10.

The Supportive Care Needs Survey for Partners and Caregivers (SCNS-P&C) was created to measure the multi-dimensional supportive care needs of FCs at various of the illness of those receiving the care (Girgis et al., 2011). The SCNS-P&C items were translated from English to Thai in our study. The 45 items in this tool are divided into four categories: communication and relationships (10 items), health care and information (16 items), social and work (11 items), and psychological (8 items). A five-point rating scale is used for all the products (1-no need: not applicable; 2-no need: satisfied; 3- low need; 4-moderate need; 5-high need). The overall score is calculated by adding all the need items together, with higher scores indicating more unmet requirements.

Statistical analysis

Study outcome

The mean scores of each domain of the WHOQOL-BREF, including physical, psychological, social relationship, and environmental, were treated as dependent variables.

Descriptive statistics were used, with continuous variables being described using means and standard deviation (SD) and categorical variables being represented using numbers and percentages. Pearson's correlation coefficient was used for investigating the relationships among demographic factors, MSAS-SF, HADS, the SCNS-P&C, and WHOQOL-BREF domains. The differences between demographic characteristics and WHOQOL-BREF domains were explored using an independent t-test and one way ANOVA (followed by a Bonferini test) as appropriate to determine which specific factors that affect FCs' QOL.

The four QOL domains were included as dependent

variables in multivariate linear regression models, with the factors that demonstrated a significant correlation ($p < 0.05$) with QOL. All independent variables were coded or translated into categorical measurements before being put into the regression models. We used an enter method, with statistical significance defined as a p value less than 0.05.

The tolerance and variance inflation factor (VIF) were used to check for multicollinearity in all models. A multicollinearity problem is indicated by a tolerance of less than 0.1 and/or a VIF of more than 5, however none of the variables demonstrated severe multicollinearity.

Results

Family caregiver Characteristics

Most FCs were female (69.7%) with a mean age of 46.11 years ($SD = 11.47$). The majorities of FCs were son/daughter (56.7%) or spoused (41.1%), married (70.5%), under academic study (73.2%), and the household income was low compared with the local average, more than two third (74.4%) earning less than 15,000 thb. The FCs had a prominent level of emotional distress, with 50.2% having severe anxiety. In contrast, for depression, only 4 FCs (1.7%) reported having severe depression (Table 1).

Quality of life of family caregivers

Most FCs of CCA survivors had a moderate to high level QOL scores in both a total QOL and all four domains. For the total QOL scores, two third of FCs (70.1%) reported having a high QOL including Physical Health (71.9%), Psychological (70.1%), and Social Relationships (57.5%). Conversely, for the Environment domain, the majority of FCs (71.9%) expressed that they had a moderate level of QOL (Table 2).

Symptom of family caregivers

The top 5 symptoms are presented in Table 3, and the mean total score of symptoms was 7.76 ($SD = 5.38$). Sleep problem was the highest symptom occurrences among FCs with a mean score of 1.23 ($SD = 0.48$), followed by tiredness with a mean score of 0.95 ($SD = 0.30$) and depression with a mean score of 0.38 ($SD = 0.77$) (Table 3).

Descriptive Statistics and Correlations among Study Variables

The means, SDs, and intercorrelations across multiple variables are shown in Table 3. The mean anxiety score was 11 ± 3.23 , with 116 FCs (50.2%) exceeding the scale cut-off for severe anxiety. WHOQOL-BREF domains

Table 1. Demographic Characteristics of Family Caregivers (n=231)

Baseline characteristics	Number	Percent
Gender		
Male	70	30.3
Female	161	69.7
Age		
Mean (\pm SD)	46.11(\pm 11.47)	
Median (min: max)	45(19:74)	
Education level		
Primary	73	31.6
Secondary	96	41.6
Bachelor or higher	62	26.8
Household income		
Less than 5000	53	22.9
5,000-9,999	53	22.9
10,000-14,999	66	28.6
15,000-19,999	33	14.3
$\geq 20,000$	26	11.3
Marital status		
Single	45	19.5
Married	186	70.5
Relationship status		
Partner	95	41.1
Son/Daughter	136	58.9
Family member		
Less than 5	96	41.6
≥ 5	135	58.4
Anxiety		
Normal	12	5.2
Doubtful case	103	44.6
Case	116	50.2
Mean anxiety score (\pm SD)	11.02 (\pm 3.23)	
Depression		
Normal	193	83.5
Doubtful case	34	14.8
Case	4	1.7
Mean depression score (\pm SD)	8.03 (\pm 2.96)	
MSAS-SF score (\pm SD)	7.76 (\pm 5.38)	
SCNS-P&C score (\pm SD)	154.63 (\pm 20.36)	

showed significantly negative correlations ($p < 0.05$) among the MSAS-SF, Social Relationships QOL,

Table 2. Distribution of Family Caregiver's Quality of Life Scores

WHOQOL-BREF Domains	Mean (\pm SD)	Average score (1-5)	Number (%)		
			Low	Medium	High
Physical Health	27.03(\pm 2.81)	3.87	0 (0.0)	65 (28.1)	166 (71.9)
Psychological	23.13(\pm 2.81)	3.86	6 (2.6)	63 (27.3)	162 (70.1)
Social Relationships	11.32(\pm 1.08)	3.77	8 (3.5)	90 (39.0)	133 (57.5)
Environment	28.08(\pm 2.81)	3.51	0 (0.0)	166 (71.9)	65 (28.1)
Total	97.13(\pm 9.28)	3.74	0 (0.0)	69 (29.9)	162 (70.1)

Table 3. Distribution of Family Caregiver's Symptoms

Symptom	Mean	SD
Sleep problem	1.23	0.48
Fatigue	0.95	0.3
Depression	0.38	0.77
Weight lost	0.3	0.67
Pain	0.16	0.42
Total	7.76	5.38

Environment QOL, and SCNS-P&C.

The QOL and its associated factors among FCs for CCA survivors

Physical Health domain

According to the standardized regression coefficient in Table 5, the factors that are significantly associated with Physical Health domain of FCS were age 40-49 years (B = 1.57; p < 0.05), academic level (B = 2.95; p < 0.001), income 5,000-9,999 baht per month (B = 1.32; p < 0.05) and marital status (B = 0.98; p < 0.05), respectively. On the other hand, both the SCNS-P&C

Table 4. Means Standard Deviations, and Correlation among Study Variables (n=231)

Variables	1	2	3	4	5	6	7	8
1. Anxiety	1							
2. Depression	0.33*	1						
3. MSAS-SF	0.01	-0.06	1					
4. SCNS-P&C	0.11	0.01	0.18*	1				
5. Physical Health QOL	-0.07	0.04	-0.32*	-0.12	1			
6. Psychological QOL	-0.04	-0.08	-0.36*	-0.03	0.83*	1		
7. Social Relationships QOL	-0.02	0.09	-0.33*	-0.20*	0.58*	0.51*	1	
8. Environment QOL	0.05	-0.03	-0.21*	-0.21*	0.64*	0.53*	0.62*	1
Mean	11	8.03	7.76	154.63	27.03	23.13	11.32	28.08
SD	3.23	2.96	5.38	20.36	2.81	2.81	1.08	2.81

*p-value<0.05

Table 5. Results of Multiple Linear Regressions, Including Factors Related WHOQOL-BREF Domain of CCA Caregivers.

Variables	Physical Health		Psychological		Social Relationships		Environment	
	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p
Age								
Less than 40	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
40-49	1.57 (0.50)	0.002	1.79 (0.46)	<0.001	0.61 (0.20)	0.002	0.72 (0.45)	0.11
50-59	0.48 (0.51)	0.341	1.70 (0.46)	<0.001	0.03 (0.20)	0.883	0.36 (0.45)	0.432
≥ 60	-0.38 (0.71)	0.594	1.23 (0.65)	0.064	0.91 (0.28)	0.001	0.76 (0.64)	0.234
Education level								
Primary	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Secondary	2.02 (0.56)	<0.001	3.50 (0.52)	<0.001	0.51 (0.22)	0.021	2.62 (0.50)	<0.001
Bachelor/ higher	2.95 (0.68)	<0.001	3.99 (0.62)	<0.001	0.87 (0.27)	0.001	1.33 (0.60)	0.028
Income								
< 5,000	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
5,000-9,999	1.32 (0.51)	0.01	0.07 (0.47)	0.875	0.59 (0.20)	0.004	1.48 (0.45)	0.001
10,000-14,999	-0.53 (0.57)	0.348	-0.84 (0.52)	0.105	0.21 (0.22)	0.339	-0.49 (0.51)	0.33
15,000-19,999	0.11 (0.65)	0.866	-0.12 (0.60)	0.841	0.38 (0.26)	0.146	2.83 (0.58)	0.001
≥ 20,000	0.67 (0.73)	0.363	0.30 (0.67)	0.651	0.74 (0.29)	0.011	4.52 (0.65)	0.001
Marital status								
Single	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Married	0.98 (0.47)	0.037	0.53 (0.43)	0.219	-0.43 (1.18)	0.019	0.12 (0.42)	0.771
SCNS-P&C	-0.03 (0.31)	<0.001	-0.02 (0.01)	0.008	-0.01 (0.01)	<0.001	-0.02 (0.01)	0.008
MSAS-SF	-0.11 (0.03)	<0.001	-0.02 (0.29)	<0.001	-0.07 (0.01)	<0.001	-0.10 (0.02)	0.001
Model characteristic	R ² =32.3% p<0.001		R ² =44.5% p<0.001		R ² =29.7% p<0.001		R ² =46.1% p<0.001	

subscales and MSAS-SF were marginally negatively correlated with the Physical Health domain ($B=-0.01$ and -0.07 ; $p < 0.001$). Furthermore, when the SCNS-P&C and MSAS-SF subscales were added to the model, there was a considerable improvement in the model ($R^2 \text{ adj}=32.3\%$; $p < 0.001$).

Psychological Domain

For the Psychological domain, age 40-49 years and age 50-59 years ($B=1.79$, $B=1.79$; $p < 0.001$), secondary and Bachelor/ higher education level were significantly related to this domain ($B=3.50$, and $B=3.99$; $p < 0.001$). In contrast, both the MSAS-SF and SCNS-P&C subscales were marginally negatively correlated with Psychological ($B=-0.02$, and $B=-0.02$; $p < 0.001$). When the SCNS-P&C and MSAS-SF subscales were added to the model, there was a reasonable enhancement in the model ($R^2 \text{ adj} = 44.5\%$; $p < 0.001$).

Social Relationships Domain

Age less than 40 years and age more than 60 years ($B = 0.61$ and $B=0.91$; $p < 0.05$), secondary and Bachelor/ higher education level ($B = 0.51$, and $B=0.87$; $p < 0.05$), and income 5,000-9,999 and more than 20,000 baht ($B=0.59$ and 0.74 ; $p < 0.05$) were all significantly positively associated with the Social Relationships Domain of the FCS. Marital status ($B = -0.43$, $p=0.019$), the SCNS-P&C subscales ($B=-0.01$, $p < 0.001$), and MSAS-SF ($B=-0.07$, $p < 0.001$), on the other hand, were significantly negatively linked with this domain. In the Social Relationships model, there was a considerable improvement ($R^2 \text{ adj} = 29.7\%$, $p < 0.001$).

Environment Domain

Secondary and bachelor/ higher education levels ($B = 2.62$ and 1.33 ; $p < 0.001$ and $p = 0.028$), income 5,000-9,999, 15,000-19,999 baht, and more than 20,000 baht ($B = 1.48$, 2.83 , and 4.52 , $p= 0.001$), and income 5,000-9,999, 15,000-19,999 baht ($B=1.48$, 2.83 , and 4.52 , $p=0.001$). Furthermore, the Environment domain was slightly negative linked with the SCNS-P&C subscales and MSAS-SF ($B = -0.02$ and -0.01 ; $p = 0.008$ and $p=0.001$). When the SCNS-P&C subscales and MSAS-SF were included to the model, the Social Relationships model improved significantly ($R^2 \text{ adj} = 46.1\%$; $p < 0.001$). (Table 5)

Discussion

The relationship between FCs and their patients is widely acknowledged to have a significant impact on FCs' quality of life. FCs' poor QOL demands special attention, especially in a culture that emphasizes family contribution, but little dependence on social/professional care (Fadhilla et al., 2019). As a result, the goal of this study was to determine the CCA FCs' QOL. In Thailand, family members play an important part on patient care in the hospitals. They do a variety of tasks that would normally be performed by nurses in Asian countries. This result shows that the level of QOL of FCs was Middle to High because of the superior quality of the health care team

for CCA patients and their FCs. This result supports the results recorded by Abdullah et al. (Abdullah et al., 2019)

In the present study, our findings illustrated that the level of QOL of FCs was middle to high as a result of a good quality of health care team for CCA patients and their FCs. As a consequence of this hospital care which delivered unique treatments directly to CCA patients may have contributed indirectly to the higher QOL in that study. This result is supported by Abdullah et al (Abdullah et al., 2019). However, FCs' QOL in a research of leukemia patients was lower than ours because they were all at an advanced stage, whereas our cancer patients were in various stages. In comparison to prior studies, FCs in our study reported higher burden domain QOL scores (Yu et al., 2017).

In our study, all WHOQOL domains including physical health, psychological, social relationships and environment were negatively correlated with SCNS-P&C and MSAS-SF scores due to the experience of long-term stressors because of long-term care of cancer patients that impact on FCs' physical symptom occurrences and their unmet needs. Moreover, this study shows that the CCA FCs have high levels of unmet needs which impact on all domain of their QOL. When considering with other developing countries, where FCs are typically the primary source of assistance for cancer patients, this conclusion is unsurprising (Almutairi et al., 2017). As the need for information related to cancer and their process of cares were the most prioritized unmet need of FCs. In other studies, the most essential demand of informal caregivers of cancer patients has been identified as information. The key needs of FCs in a study conducted by Sajadian et al. (Hydari and Mokhtari Hesari, 2015) were acquiring knowledge about breast cancer, self-care, and patient care. Likewise, Cui et al. (Cui et al., 2014) found that the most common unmet needs, among 649 family caregivers in Shanghai hospitals, were a knowledge about the disease and its treatment, as well as assistance from healthcare professionals.

Most FCs were affected by stress related to unmet need deficit as evidenced by each of the variables examined. Over 75% of FCs experienced sleep difficulties, fatigue, pain, and depression, which is consistent with prior research findings (Lee et al., 2015; Valero-Cantero et al., 2021). These findings underscore our study's unique contribution, as little previous research has been done on the impact of advanced cancer symptoms on carers' QOL. We show that a higher overall severity of symptoms in advanced cancer patients is linked to a lower QOL for the caregiver. Only one previous study has looked into this relationship; in this case, the patient's distress was directly linked to the caregiver's symptom impairment (Otto et al., 2019). Financial assistance may be helpful to alleviate the financial strain of FCs. In connection to their physical, psychological, and environmental functioning, this study discovered that patient insurance coverage was a predictor of higher QOL of FCs. Tian and colleagues (TIAN et al., 2012) conducted a study on support and found a positive correlation between household income and the QOL of FCs. Because medical treatments for CCA patients are expensive, it places financial stress on patient families.

Even though many care responsibilities are delegated to FCs or hired care workers, due to nursing shortages, these costs are not covered by social health insurance programs. Families in financial distress are not only limited in their treatment options, but they are also less likely to recruit paid caregivers to help relieve the load of caregiving (Son et al., 2012).

The stress, that married FCs face, has a significant influence on their QOL, particularly for married women who leave their jobs to care for aging parents (Aun and Mohd, 2016). According to our research. Our findings were in line with those in Taiwan and Turkey, which found substantial links between caregiver burden and QOL (Turkoglu and Kilic, 2012).

The multivariable regression models demonstrated a positive relationship between age and FCs' QOL, implying that older FCs have a higher QOL. This is in direct contrast to the findings of a recent study on cancer patients, which found that younger FCs had a higher QOL than older FCs, resulting in a higher QOL for their patients (Shahi et al., 2014). Kim et al. (Kim et al., 2009) discovered that when patients and FCs grew older, they were better able to adapt to new settings and develop the knowledge and abilities needed to manage their critical illnesses. Several studies reported that older carers had a lower QOL compared to younger FCs (Rivera-Navarro et al., 2009; Alptekin et al., 2010). This can be explained by the fact that older carers may have had more experience of adapting to change and overcoming challenges in their life. Also, older caregivers reported better psychosocial adjustment than younger caregivers. Older caregivers may have understood the changes in their lives more than those who were younger (Kim et al., 2012).

As stated in the literature, various degrees of schooling had different influences on QOL in the tested sample. Participants with lower educational levels were found to have poorer physical and social effects, with statistically significant disparities. Many studies found that low levels of education are associated with poorer QOL outcomes, acting as a risk factor for psychosocial diseases such as depression and a growing dissatisfaction with health care services (Calvo et al., 2011; Ndikuno et al., 2016).

However, some of the conditions that cause patients and FCs to become associated may be beyond the competence or area of responsibility of physicians and nurses. As a result, multidisciplinary care teams and other systems that provide support and palliative services become more important, and they can play a vital role in reducing the burden of care for FCs and improving their QOL by implementing the right strategies and interventions.

This study has some limitations. As a cross-sectional survey, it is not possible to make a causal inference about the associations between the investigated factors and the QOL of FCs. The participants were recruited from one hospital in Thailand, and therefore the findings, of this study, should be cautiously accepted. However, the findings on the factors associated with the QOL of FCs are unlikely to be seriously influenced by the sample selection bias.

The research highlights on the QOL of FCs for CCA

survivors. The majority FCs' QOL is moderate to high, which is determined by both patient and FCs features. Symptoms, support care needs, age, and education level were associated with QOL among FCs for CCA patients. A holistic strategy that includes caregiver training, psychosocial therapies, and proper support may help these FCs for a better QOL

Author Contribution Statement

MS., MS., UP, and YW. envisioned the research idea. US. and MT. analyzed, interpreted the data, and helped to draft the manuscript. That was also discussed with MS, YW and US. who supervised the research project. ST, NC. who collected data and literature reviewed. All authors revised the manuscript critically and approved the final version to be published.

Acknowledgements

The authors would like to thank the caregivers who participated in this study, and Mr. Peter Barney for assistance for the English -language presentation of this manuscripts.

Funding

This research is funded by the Young Research Development Project of Khon Kaen University Year 2021.

Ethical Approval

This research was approved by the research ethics committee of Khon Kaen University, Thailand (HE631628). The informed written consent was obtained from each of the study participants of this study. Besides, every participant was assured about the confidentiality of his personal information.

Availability of the data

Due to ethical restrictions, the datasets are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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