



รายงานวิจัยฉบับสมบูรณ์

**Project Title:** Prevalence of frailty and sarcopenia in biliary tract cancer patients

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เมษายน 2561

**Contract No. MRG-5980172**

**Final Report**

**Project Title**

Prevalence of frailty and sarcopenia in biliary tract cancer patients

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**This project granted by the Thailand Research Fund**

สัญญาเลขที่ MRG-5980172

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โครงการ Prevalence of frailty and sarcopenia in biliary tract cancer patients

ผู้วิจัย

สังกัด

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สนับสนุนโดยสำนักงานคณะกรรมการการอุดมศึกษาและสำนักงานกองทุน

สนับสนุนการวิจัย

(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกอ. และ สกว. ไม่จำเป็นต้องเห็นด้วยเสมอไป)

**Frailty syndrome in biliary tract cancer patients: prevalence and associated factors**

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**Keywords:** bile duct neoplasm; biliary tract neoplasm; cholangiocarcinoma; FRAIL scale; pre-frail

## **Abstract**

Frailty is a risk factor for unfavorable outcomes, as it can lead to the inability of patients to adapt to stressors. It is a common condition in the elderly, but can also occur in younger patients with cancer. This study focused on the prevalence of frailty in biliary tract cancer (BTC) patients and its associated factors. A total of 75 BTC patients who received chemotherapy during the period between January 2016 and September 2017 were enrolled. Frailty was diagnosed using the FRAIL scale (Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight). Univariate and multivariate regression analyses were used to analyze factors associated with frailty. The prevalence rates of frailty and pre-frailty were 12% (nine cases) and 60% (45 cases), respectively. According to multivariate logistic analysis, three factors were associated with frailty, including advanced age, high body mass index (BMI), and history of liver surgery. The adjusted odds ratio (OR) of these factors were 1.12 (95%CI: 1.01, 1.24), 1.28 (95%CI: 1.01, 1.64), and 6.16 (95%CI: 1.11, 34.16), respectively. In conclusion, frailty is not uncommon in BTC patients. Advanced age, high BMI, and history of liver surgery are important risk factors for frailty.

## **Introduction**

Frailty is characterized by a loss of ability to adapt to stress as a result of diminished functional reserves [1]. This decline is a result of multisystem involvement and increases the risk of poor outcomes [2]. The prevalence of frailty is about 10% in the general population of people 65 and over and 25-40% in those aged over 85 [3-5]. The condition has become increasingly widely recognized as an important health issue in older adults and in patients with cancer.

Frailty is common in but not limited to patients of advanced age. Younger patients, especially those with cancer, can suffer from frailty as well. Both the disease and its treatments could be additional stressors that increase the risk of adverse events [6]. Frailty is one of the important issues in cancer patients who are undergoing surgery, radiation therapy, or chemotherapy [6-8]. Frail patients are more likely to develop postoperative complications, experience adverse events from chemotherapy, and have shorter progression-free and overall survival [7, 9].

Biliary tract cancer (BTC) is an aggressive tumor with poor survival outcomes [10]. Patients usually suffer from obstructive jaundice, malnutrition, and abdominal pain. The benefits of chemotherapy are modest [10]. Frailty might be under-recognized unless

actively looked for in an individual, whereas physicians might be focused on only the disease and treatment. Better knowledge of frailty in this setting will guide treatment decisions and to balance the risks and benefits of chemotherapy in cases of BTC, as well as provide appropriate support in order to reduce the incidence of avoidable adverse outcomes. This study examined the prevalence of and factors associated with frailty in BTC patients who received chemotherapy.

### **Material and methods**

This prospective study included BTC patients whom were scheduled to receive chemotherapy at the chemotherapy unit in Khon Kaen University from January 2016 to September 2017. Patients were excluded if the ECOG performance status was  $\geq 2$ , had other active medical illnesses, were unable to undergo the dual-energy X-ray absorptiometry (DXA), or had conditions that would affect the DXA results.

### **Frailty syndrome**

Frailty syndrome was defined using the FRAIL scale, which is a validated screening tool

[11] consisting of five items:

- F      Fatigue (feeling exhausted most of the time)
  
- R      Resistance (limitations climbing 1 flight of stairs)

- A Ambulation (inability to walk alone for 100 m)
- I Illness (five to 11 of these diseases: hypertension, diabetes mellitus, cancer, chronic lung disease, heart attack, congesting heart failure, angina, asthma, arthritis, stroke, kidney disease)

L Loss of weight (unintentional weight loss of 0.5% over a past year)

Patients scored one point for each item that corresponded to their condition.

Patients who scored one or two were defined as pre-frail, while those who had three or more of the five criteria were defined as frail.

### **Statistical analysis**

Baseline and clinical characteristics were analyzed using descriptive statistics. Wilcoxon rank sum and Fisher's exact tests were used to compare the number and proportion differences between frail and fit groups. Factors associated with frailty were evaluated using univariable logistic regression analysis. All clinically significant variables were included in subsequent multivariable logistic regression analyses. Factors in the final model were considered predictors for frailty if they exhibited a p-value of less than 0.05. Analytical results were presented as adjusted ORs and 95 % confidence intervals. Survival analysis was performed using the Kaplan-Meier method and log-rank test. All data

analysis was performed using STATA software (StataCorp LP, College Station, TX, USA). This study was approved by the Khon Kaen University Faculty of Medicine Ethics Committee as instituted by the Declaration of Helsinki (Number HE581333).

## **Results**

### **Prevalence of frailty and pre-frailty in biliary tract cancer patients**

A total number of 75 BTC patients were included. Although adenocarcinoma with neuroendocrine differentiation is one of the important prognostic factors [12], there was no adenocarcinoma with neuroendocrine differentiation or neuroendocrine carcinoma in this cohort. The prevalence of frailty and pre-frailty according to the FRAIL scale was 12% (nine cases) and 60% (45 cases) and prevalence of frailty syndrome increased with age (7.8%, 15%, and 50% in patients aged <65, 65-74,  $\geq$ 75 years respectively, Figure 1).

Frail patients had a mean age of 64.22 years and a mean BMI of 23.20 kg/m<sup>2</sup>; six of the patients with frailty were male. The subjects who were found not to be suffering from frailty had a mean age of 58.6 years and a mean BMI of 21.43 kg/m<sup>2</sup>. Fifty-two of these subjects were male (Table 1). In addition, a significantly higher number of subjects in the frail group had a history of liver surgery than the control group (66.67% vs 30.30%).

## **Distribution of frailty components**

In all of the FRAIL scale categories with the exception of illness, a higher percentage of frail patients met the criteria compared to non-frail patients ( $p < 0.05$ ). The odds ratio (OR) was 19.4 (95% CI 3.7, 101.7) for fatigue, 1.0 for resistance and ambulation, and 5.2 (95%CI 0.6, 44.1) for weight loss as shown in Figure 2

## **Factors associated with frailty**

After adjustment by multivariate logistic regression, the final model was comprised of four factors (Table 2). Three of these factors were associated with frailty syndrome, including advanced age, BMI, and history of liver surgery, the adjusted ORs of which were 1.12 (95%CI: 1.01, 1.24), 1.28 (95%CI: 1.01, 1.64), and 6.16 (95%CI: 1.11, 34.16), respectively.

Median survivals in frail patients who received a cisplatin-based regimen and those who received a carboplatin-based regimen were similar (12.3 months vs not reached; HR 0.83, 95%CI 0.09-7.36). Nevertheless, fit patients who received a carboplatin-based regimen exhibited a significantly shorter survival compared to those who received cisplatin-based chemotherapy (8.5 vs 14.7 months: HR 2.30, 95% CI 1.19-4.47, Figure 3).

## **Discussion**

Frailty syndrome is common in elderly patients with BTC. The prevalence of frailty in this cohort was 12%. Advanced age, high BMI, and history of liver surgery were found to be independent factors associated with frailty.

The prevalence of frailty in this study was comparable to those found in other studies that used the same phenotype model evaluate gynecological patients and older patients who underwent surgery [13, 14]. Frailty was less common in our study when compared to a systematic review that included solid tumor patients [7]. A possible explanation for this is differences in study population. Our study included patients of all ages and only included patients who were suitable for chemotherapy, implying good ECOG performance status, while other studies have included only older adults with various functional statuses.

In our study, advanced age was related to a high risk of frailty, a result that is similar to those found in several studies - both in cancer and non-cancer patients. This is because both aging and frailty are related to increased vulnerability to stressors due to a loss of homeostasis [14]. Previous studies have shown that patients who underwent liver surgery had a high risk for frailty syndrome, and vice versa. In addition frailty is

associated with risk of postoperative morbidity and poorer outcomes [9, 15]. This leads us to conclude that screening should be conducted for frailty as a preoperative risk assessment.

Obesity was the primary risk factor for frailty in our study. For each 1 mg/m<sup>2</sup> BMI increase, risk of frailty increased by 1.3 times. This result is well supported by the data that have been published on community-dwelling adults [16]. Although high-fat mass was another factor indicating frailty, it was not an independent factor after adjustments were made for other factors. These data suggest that obesity is important in frailty but not just in terms of high-fat mass. There are other factors related to or consequences of obesity that were not measured in this study, such as nutritional status, physical activity, and inflammation.

Frailty has been reported to associate with shorter survival in various malignancies [7]. In contrast to the results of other reported studies, however, we found that it was not a risk factor for poor survival outcomes in patients with BTC. The aggressiveness of the tumor, poor response to chemotherapy, and low prevalence of frailty are the potential causes of this discrepancy.

According to the pooled analysis, platinum-based chemotherapy with gemcitabine resulted in the highest response rate [17]. Cisplatin and gemcitabine chemotherapy is

currently the standard regimen in cases of advanced BTC due to its resulting in better survival when outcomes compared to gemcitabine alone [18, 19]. However, there have been no head-to-head comparisons between cisplatin-based and carboplatin-based regimens. In this study, we found that fit patients who received cisplatin-based regimen had longer survival compared to those who received carboplatin-based regimen. On the contrary, this difference between two regimens was not observed among vulnerable patients. Given that cisplatin has more side effects, we suggest cisplatin be administered only in “fit” patients.

The strength of this study was that all the patients had BTC and ECOG 0-1, reducing confounding bias due to primary tumor and performance status, which are important risk factors for frailty. There were several limitations to this study. First, patients with poor performance status or who had physical limitations were excluded. Second, some factors, such as nutritional status were not included. Third, the results of this study may not be applicable to other cancer populations.

## **Conclusion**

Frailty is prevalent among biliary tract cancer patients receiving chemotherapy. Advanced age, high BMI, and history of liver surgery were associated with frailty syndrome. Elderly patients should be carefully evaluated for frailty syndrome and performance status.

## **Acknowledgment**

The authors would like to acknowledge Mr. Dylan Southard, Research Affairs, Faculty of Medicine, Khon Kaen University, Thailand, for editing the manuscript. This project was supported by the Research Grant for New Scholar co-funded by the Office of the Higher Education Commission, TRF and Khon Kaen University (KKU) (MRG-5980172).

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**Table 1** Comparison of clinical factors between patients without and with frailty syndrome

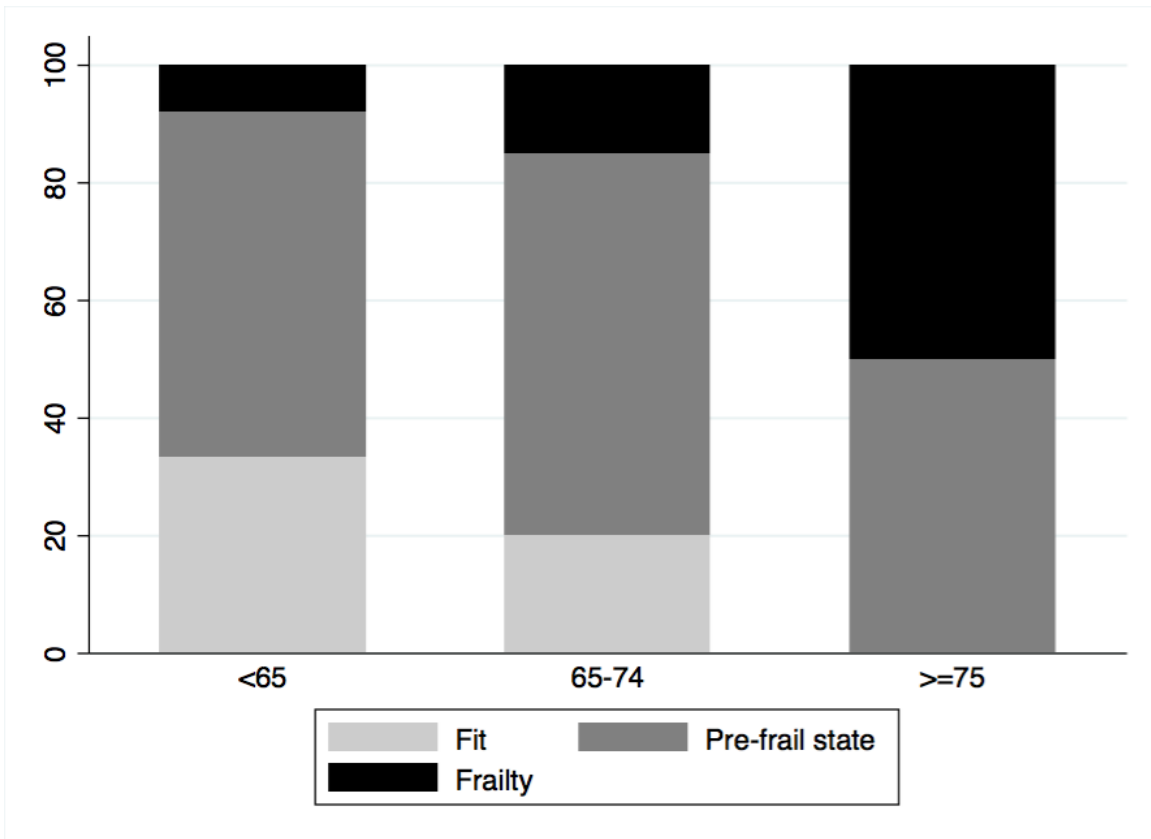
Factors	Frail (n=9)	Not frail (n=66)	p-value
Age, years	64.22 (8.42)	58.56 (8.56)	0.066
Male, n (%)	6 (66.67)	52 (78.79)	0.415
Weight, kg	59.89 (8.68)	56.38 (8.90)	0.270
Height, m	161.11 (6.01)	162.30 (6.28)	0.593
BMI, kg/m <sup>2</sup>	23.20 (4.07)	21.43 (3.37)	0.155
Muscle mass, (kg)	38.84 (6.33)	46.13 (43.60)	0.620
Fat mass, (kg)	16.43 (7.34)	12.61 (6.85)	0.124
NLR $\geq$ 3	3 (33.3)	29 (43.9)	0.546
White blood cell count, cells/mm <sup>3</sup>	8155 (3542)	8631 (3689)	0.717
Stage IV, n (%)	8 (88.89)	56 (84.85)	0.663
Liver surgery, n (%)	6 (66.67)	20 (30.30)	0.032*

**Abbreviation:** BMI, body mass index; NLR, neutrophil-lymphocyte ratio

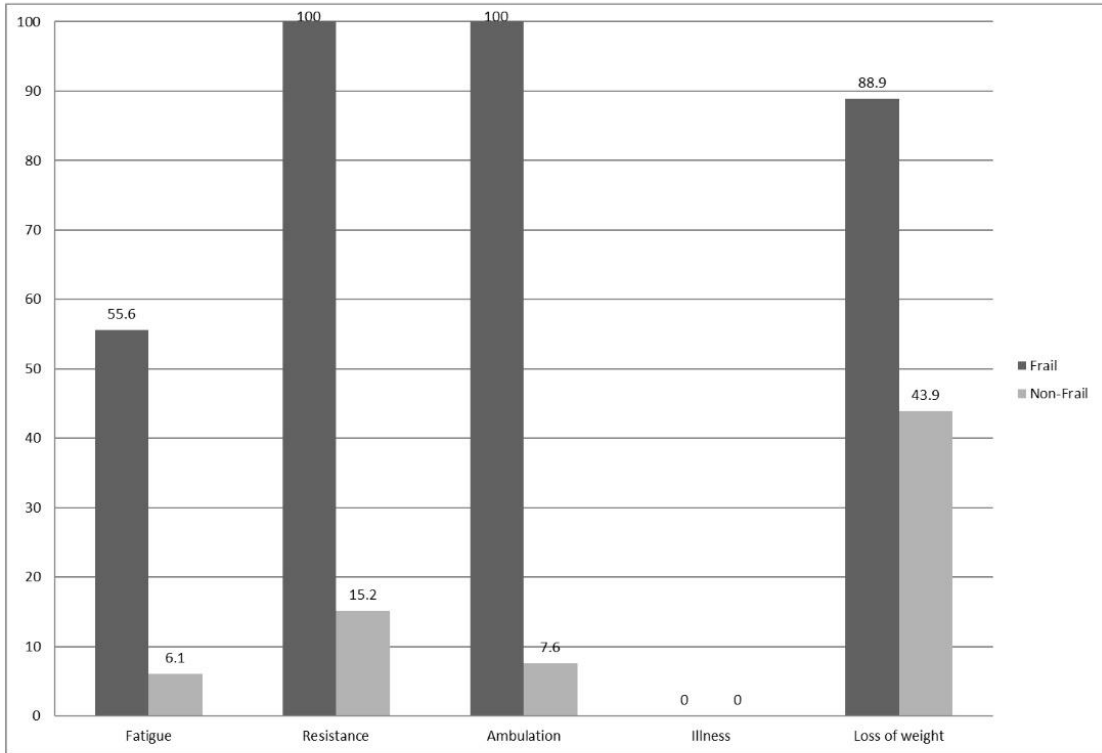
**Table 2** Univariable and multivariable logistic regression analyses of factors associated with frailty syndrome

<b>Factors</b>	<b>Crude OR (95% CI)</b>	<b>Adjusted OR (95% CI)</b>
Age	1.08 (0.99, 1.18)	1.120 (1.01, 1.24)
BMI	1.15 (0.95, 1.39)	1.285 (1.01, 1.64)
Female gender	1.86 (0.41, 8.38)	1.951 (0.33, 11.59)
Liver surgery	4.60 (1.05, 20.25)	6.160 (1.11, 34.16)

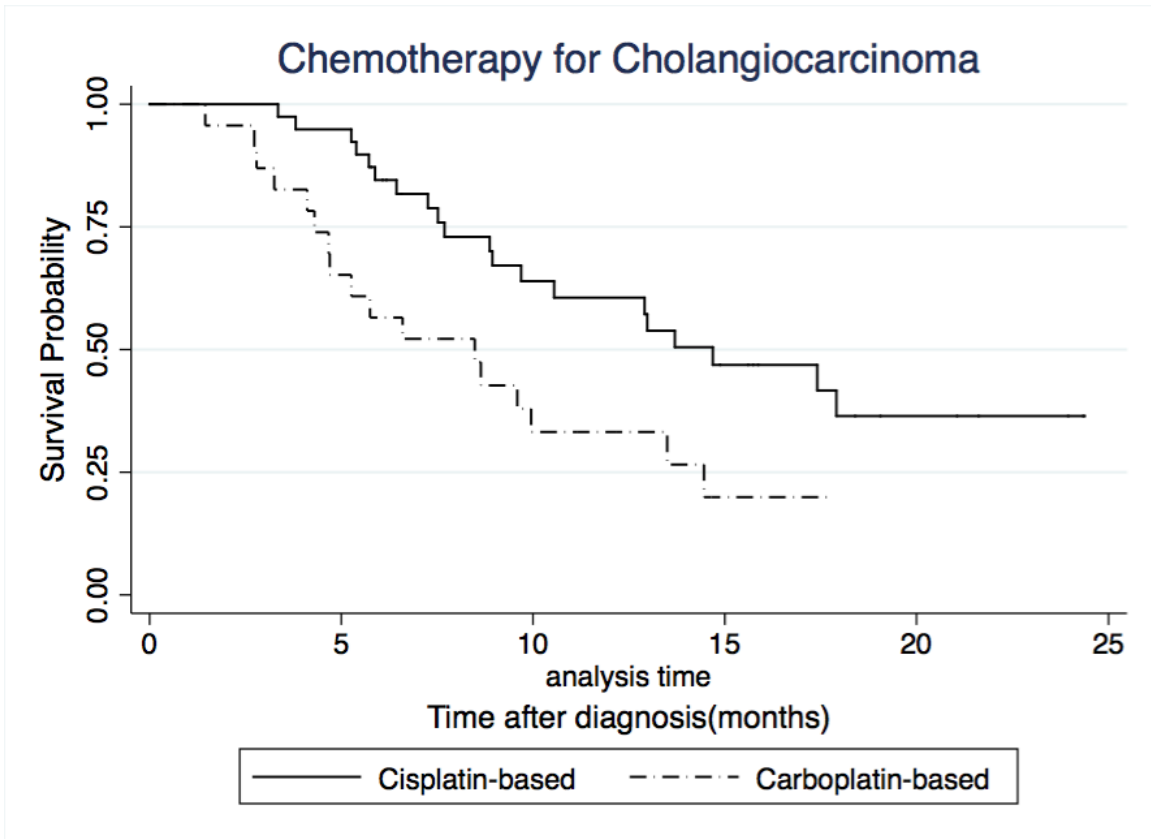
**Abbreviation:** OR, odds ratio; CI, confidence interval; BMI, body mass index



**Figure 1** Prevalence of frailty syndrome according to age group.



**Figure 2** Distribution of frailty components between frail and non-frail patients



**Figure 3** Survival curve comparing cisplatin and carboplatin-based chemotherapy in fit patients.

**Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.**

1. ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ (ระบุชื่อผู้แต่ง ชื่อเรื่อง ชื่อวารสาร ปี เล่มที่ เลขที่ และหน้า) หรือผลงานตามที่คาดไว้ในสัญญาโครงการ
    - กำลังรอตีพิมพ์ในวารสารวิชาการนานาชาติ
  2. การนำผลงานวิจัยไปใช้ประโยชน์
    - เชิงวิชาการ (มีการพัฒนาการเรียนการสอน/สร้างนักวิจัยใหม่)
    - มีการพัฒนาการเรียนการสอนผลจากงานวิจัยในการสอนระดับบัณฑิตศึกษาของแพทย์ประจำบ้านต่อยอดมะเร็งวิทยา
    - สร้างนักวิจัยใหม่

พญ.กุสุมา พิมสอน แพทย์ประจำบ้านอายุรกรรม คณะแพทยศาสตร์  
มหาวิทยาลัยขอนแก่น
  3. อื่นๆ (เช่น ผลงานตีพิมพ์ในวารสารวิชาการในประเทศ การเสนอผลงานในที่ประชุมวิชาการ หนังสือ การจดสิทธิบัตร)
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