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Original Article

Association of preoperative frailty and postoperative delirium in older cancer patients undergoing elective abdominal surgery: A prospective observational study in Taiwan

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ABSTRACT

Background: Postoperative delirium (POD) is a common surgical complication in elderly patients. As frailty is a relatively novel concept, its clinical significance for POD has seldom been examined. This study aimed to investigate the association between frailty and POD in aged cancer patients undergoing elective abdominal surgery in Taiwan.

Methods: We prospectively enrolled 345 consecutive patients aged ≥65 years with newly diagnosed cancer who underwent elective abdominal surgery between 2016 and 2018. Frailty assessment was performed using the Comprehensive Geriatric Assessment (CGA). POD was assessed daily using the Confusion Assessment Method from postoperative day 1 until discharge. Patients were allocated into fit and frail groups.

Results: POD occurred in 19 (5.5%) of 345 patients. POD incidence was 1.6%, 3.1%, 4.8%, 11.5%, and 10.0% in patients with 0, 1, 2, 3, and 4+ frail conditions, respectively, which presented a positive linear correlation among patients with an increased number of frail conditions and POD incidence. Based on CGA, 159 (46.1%) and 186 (53.9%) patients were allocated to fit and frail groups, respectively. POD incidence was 2.5% and 8.1% for the fit and frail groups, respectively. Frailty status was an independent risk factor for POD occurrence in multivariate analysis.

Conclusion: Our study identified frailty as an independent risk factor for POD in aged Taiwanese cancer patients undergoing elective abdominal surgery. Given the high

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prevalence of frailty among older cancer patients, preoperative assessment is important to identify high risk of POD and to improve the quality of postoperative care.

At a glance commentary

Scientific background on the subject

Frailty assessment in geriatric cancer patients is a relatively novel concept in Taiwan and the clinical significance of postoperative delirium (POD) in older Taiwanese adult cancer patients has seldom been examined.

What this study adds to the field

This study showed that frailty is a common phenomenon in older Taiwanese cancer patients who undergo elective abdominal surgery. Frailty is an independent factor in prediction of POD, with a 2.8-fold increase in the risk of POD occurrence compared with that in fit patients.

Postoperative delirium (POD) is defined as an acute and fluctuating alteration in the mental state of the patient following surgery [1]. POD is a common postoperative complication, with an incidence of 4%–41% in the general population [2]. Since aging and POD share common predisposing factors, including comorbidity, pre-existing cognitive impairment, functional decline, and previous alcohol use disorder, the incidence of POD increases with aging, up to 8%–54% in the older population [3]. POD is a negative predictor of adverse surgical outcomes, including prolonged length of stay, postoperative intensive care unit stay, readmission rate, institutional discharge, and mortality [4].

With an increase in the aging population and the incidence of cancer, an increasing number of cancer patients are diagnosed at an older age and are considered for surgical intervention [5]. Older patients with cancer are more susceptible to POD for two important reasons. First, cancer itself might directly impede a patient's physical and psychological performance [6]. Second, surgery involves the removal of vital organs, which may further reduce the patient's functional reserve [7]. Insults from organ-specific surgery are more prominent in patients with gastrointestinal cancer [6,8]. As adverse surgical outcomes associated with POD might compromise the survival benefit of surgery, early identification of older cancer patients who may be vulnerable to POD is an urgent issue to be addressed before abdominal surgery.

Frailty is defined as a decrease in the physical reserve due to the accumulation of functional decline [9]. Frailty is an important predictor of medical outcomes in the older general population [10] and has been widely used to predict postoperative complications in geriatric patients [11]. Since the core dimensions of frailty, including physical performance, cognition, and comorbidity, are the predisposing factors for POD, the frailty status had been used as a tool to predict POD in older

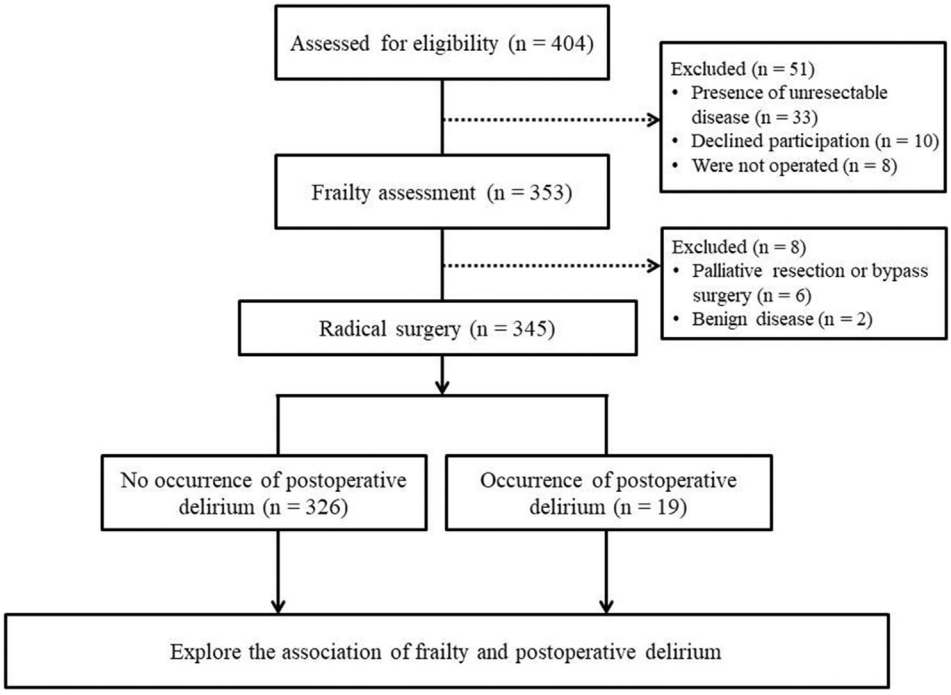

Fig. 1 Study flowchart.

Table 1 Pretreatment frailty outcomes by Comprehensive Geriatric Assessment[17] (n = 345).

Frail condition	Measures	Number of items	Score range	Cutoff value	n (%)
Nutrition	MNA-SF	6	0–14	≤11	182 (52.8)
Comorbidity	[a]CCI	17	0–33	≥2	130 (37.7)
Functional status	ADL or IADL				95 (27.5)
	Barthel Index (ADL)	10	0–100	<100	70 (20.3)
	Lawton Scale (IADL)	8	0–8	≤7	60 (17.4)
Polypharmacy	Number of medications	1	0–∞	≥5	83 (24.1)
Mood	GDS-4	4	0–4	≥2	50 (14.5)
Cognition	Mini-Mental State Examination	11	0–30	≤23	50 (14.5)
Social support	Living alone	1	0–1	1	37 (10.7)
Falls	Number of falls within the last six months	1	0–∞	≥2	21 (6.1)

Abbreviations: ADL: activities of daily living; IADL: instrumental activities of daily living; MNA-SF: Mini Nutritional Assessment Short Form; CCI.
[a] Modified CCI that excluded scores for patient age and cancer diagnosis was used in this study.

patients after cancer surgery in the Western population [12,13]. However, frailty assessment in geriatric cancer patients is a relatively novel concept in Taiwan and the clinical significance of POD in older Taiwanese adult cancer patients has seldom been examined. This study aimed to investigate the association between frailty and POD in geriatric cancer patients undergoing elective abdominal surgery in Taiwan.

Methods

Patient selection

This prospective observational study was conducted between September 2016 and November 2018 at a medical center in Taiwan. The inclusion criteria were age of ≥65 years, pathological or radiographic diagnosis of gastrointestinal malignancies, and curative-intent surgery for cancer treatment. Patients who had evidence of dementia, consciousness disturbance, other concurrent active malignancies, and received palliative resection or non-elective surgery were excluded. A total of 345 consecutive patients were enrolled in the study. All patients provided written informed consent prior to inclusion in the study. The study protocol was approved by the institutional review board (no. 201600916B0) and had been conducted in compliance with the Helsinki Declaration (1996). The flowchart of the study is shown in Fig. 1.

Surgical treatment and data collection

All patients underwent curative-intent surgery as the primary treatment for cancer. The feasibility and methodology of the operation for each patient were determined by a tumor board discussion before operation.

Patients' demographic and clinical data, including age, sex, marital status, educational level, smoking history, drinking history, cancer type, tumor stage, Eastern Cooperative Oncology Group (ECOG) performance status, and American Society of Anesthesiology (ASA) score, were collected within the week prior to surgery. Operative information including the operative method (open or laparoscopy), operative time, and amount of blood loss during the operation were recorded by a well-trained research assistant immediately after operation.

Frailty assessment

Patient frailty was assessed using Comprehensive Geriatric Assessment (CGA) within the week before cancer surgery. The eight-condition CGA questionnaires, including functional status, nutrition, comorbidity, falls, mood, cognition, polypharmacy, and family support, were used in this study. The questionnaires were completely patient-reported, and a trained research assistant assisted the patients who needed help in completing the questionnaires. Patients exhibiting impairments in 0–1 and ≥2 conditions were classified as fit and frail in this study, respectively [14,15]. The detailed CGA tool and cutoff standard for each frail condition used in this study have been validated in older Taiwanese patients diagnosed with cancer (Table 1) [14,15]. Primary care surgeons were blinded to the frailty assessment results to avoid bias in the surgeon's decision regarding the operative method and resection extent in this study.

Delirium assessment

Delirium was assessed using the Confusion Assessment Method based on a brief daily cognitive screening and interview to rate four core delirium symptoms [16]. The four core delirium symptoms included acute onset and fluctuating mental status, inattention, altered level of consciousness, and disorganized thinking. The Confusion Assessment Method was used daily from postoperative day 1 until the patient was discharged by trained physicians based on the information collected from the patient interviews and reported by family members or nurses.

Interesting outcomes

The primary outcome measure was the association between pretreatment frailty and the occurrence of POD. Moreover, the risk factors for POD in older Taiwanese patients diagnosed with cancer were investigated.

Statistical analysis

Basic patient and tumor characteristics are summarized as n (%) for categorical variables and as medians with ranges for continuous variables. The differences in clinical characteristics

Table 2 Patient's characteristics (n = 345).

Variable	Overall, n = 345	Fit, n = 159	Frail, n = 186	*p*
Age, median (range)	73 (65–99)	71 (65–90)	76 (65–99)	<0.001
Sex, n (%)				0.016
Male	206 (59.7)	106 (66.7)	100 (53.8)	
Female	139 (40.3)	53 (33.3)	86 (46.2)	
Marriage, n (%)				0.002
Married	255 (73.9)	133 (83.6)	122 (65.6)	
Others	90 (26.1)	26 (16.4)	64 (34.4)	
Education, n (%)				0.15
Less than high school	191 (55.4)	96 (60.4)	95 (51.1)	
High school or more	154 (44.6)	63 (39.6)	91 (48.9)	
Smoking, n (%)				0.12
No	213 (61.7)	91 (57.2)	122 (65.6)	
Yes	132 (38.3)	68 (42.8)	64 (34.4)	
Drinking, n (%)				0.18
No	220 (63.8)	95 (59.7)	125 (67.2)	
Yes	125 (36.2)	64 (40.3)	61 (32.8)	
Eastern Cooperative Oncology Group performance, n (%)				<0.001
0	234 (67.8)	137 (86.2)	97 (52.2)	
1	90 (26.1)	21 (13.2)	69 (37.1)	
2	19 (5.5)	1 (0.6)	18 (9.7)	
3	2 (0.6)	0	2 (1.1)	
American Society of Anesthesiologists score, n (%)				0.22
1	1 (0.3)	1 (0.6)	0	
2	19 (5.5)	12 (7.5)	7 (3.8)	
3	324 (93.9)	146 (91.8)	178 (95.7)	
4	1 (0.3)	0	1 (0.5)	
Cancer type, n (%)				0.054
Colorectal	179 (51.9)	95 (59.7)	84 (45.2)	
Stomach	81 (23.5)	30 (18.9)	51 (27.4)	
Liver	50 (14.5)	19 (11.9)	31 (6.7)	
Pancreas or extrahepatic biliary tract	35 (10.1)	15 (9.4)	20 (10.8)	
Tumor stage by 7th AJCC, n (%)				0.20
1	107 (31.0)	58 (36.5)	49 (26.3)	
2	105 (30.4)	42 (26.4)	63 (33.9)	
3	96 (27.8)	43 (27.0)	53 (28.5)	
4	37 (10.7)	16 (10.1)	21 (11.3)	
Tumor grade, n (%)				0.23
Well-differentiated	70 (20.3)	31 (19.5)	39 (21.0)	
Moderate differentiated	188 (54.5)	94 (59.1)	94 (50.5)	
Poor or undifferentiated	87 (25.2)	34 (21.4)	53 (28.5)	
Operative type, n (%)				0.007
Open surgery	175 (50.7)	68 (42.8)	107 (57.5)	
Laparoscopy	170 (49.3)	91 (57.2)	79 (42.5)	
Operative time, minutes, median (range)	276 (78–776)	270 (107–703)	280 (78–776)	0.25
Intraoperative blood loss, ml, median (range)	50 (10–3300)	50 (10–3300)	50 (10–1500)	0.93

Abbreviations: AJCC: American Joint Committee on Cancer.

between the fit and frail groups were compared using the chi-square test or Fisher's exact test. To test the linear trend of the incidence of POD and number of impaired frail conditions (*p* for trend) was examined using the Cochran–Armitage test [17]. Univariate and multivariate logistic regression analyses were performed to estimate the odds ratio (OR) and 95% confidence interval (CI) for variables associated with POD occurrence. Youden index analysis was performed to derive the optimal cutoff value in the logistic regression analysis for multinomial categorical variables and continuous variables. All variables in the univariate analysis with *p*-values <0.05 were further analyzed using multivariate analysis. Statistical analyses were conducted using SPSS 23.0 (IBM, New York, US). All statistical assessments were two-sided, and a *p*-value <0.05 was considered statistically significant.

Results

Patient and tumor characteristics

The demographic characteristics of 345 patients are presented in Table 2. The median age was 73 years (range, 65–99), and 59.7% were men. The most common primary cancer sites were the colorectum (51.9%), stomach (23.5%), liver (14.5%), and pancreatico-biliary (10.1%). The distribution of stages I, II, III, and IV was 31.0%, 30.4%, 27.8%, and 10.7% among the patients, respectively. All patients received general anesthesia for surgery; 50.7% of the patients underwent an open surgical procedure, and the remaining 49.3% underwent laparoscopic surgery.

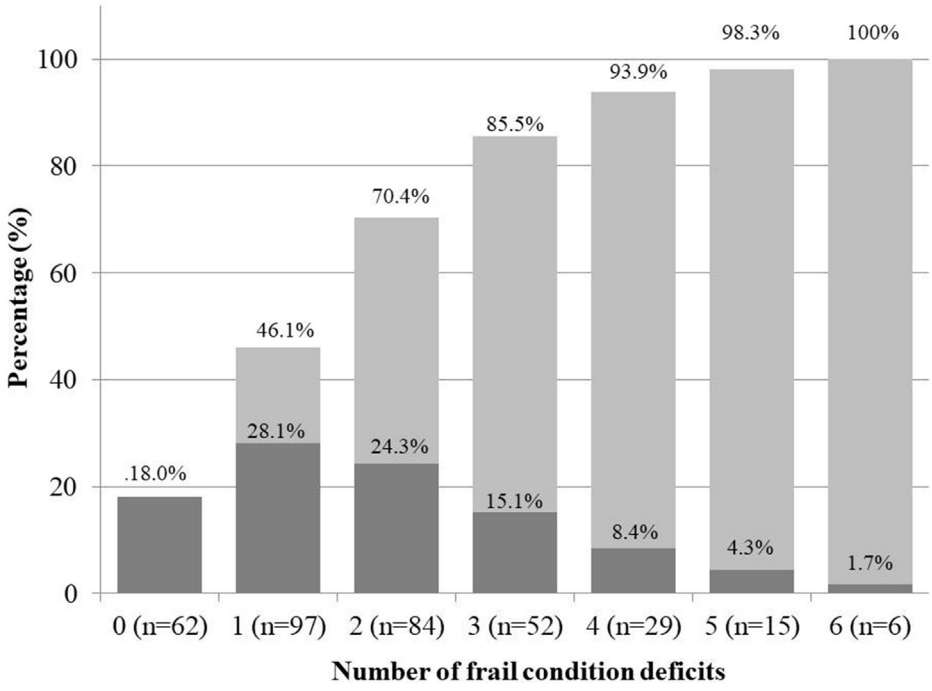

Fig. 2 Distribution of the number of frail condition deficits. The light-gray color indicated the cumulative percentage of the number of frail condition deficits.

No significant difference between the fit and frail groups was observed regarding education level, smoking, drinking, ASA score, cancer type, tumor stage, tumor grade, operative time, and intraoperative blood loss amount. Frail patients were older, constituted of more females, with only a few being married, had poorer ECOG performance, and were more likely to undergo open surgery than fit patients.

Frailty assessment results

Regarding the details of frail condition deficits in the patients (Table 1), malnutrition (52.8%), comorbidity (37.7%), and functional status decline (27.5%) were the three most common deficit frail conditions, whereas the least common deficit frail conditions were mood (14.5%), cognition (14.5%), social support (10.7%), and falls (6.1%). The proportion of frail deficits is shown in Fig. 2. The median number of frail condition deficits was 2 (range 0–6). Sixty-two (18.0%) patients had no deficits in any frail condition, whereas six (1.7%) had deficits in six frail conditions. Accordingly, 159 (46.1%) and 186 (53.9%) patients were allocated to the fit and frail groups based on the CGA, respectively.

Association of frailty and postoperative delirium

POD occurred in 19 of 345 (5.5%) patients. The distribution of POD incidence and number of frail condition deficits are presented in Fig. 3. POD incidence was 1.6%, 3.1%, 4.8%, 11.5%, and 10.0% in patients presenting with 0, 1, 2, 3, and 4+ frail conditions, respectively. Patients with an increased number of frail conditions were positively linearly associated with higher POD incidence (p for trend = 0.003).

Based on the CGA, the incidence of POD was 2.5% and 8.1% for the fit and frail groups, respectively. The results of univariate and multivariate analyses of clinical variables for predicting POD occurrence are shown in Table 3. In univariate analysis, age of ≥73 years, non-colorectal cancer, open surgery, operative time of ≥428 min, intraoperative blood loss of ≥175 ml, and the frailty status were associated with significantly higher risks of POD. Only age of ≥73 years (adjusted OR 2.94; 95% CI, 1.02–9.74; $p = 0.045$), operative time of ≥428 min (adjusted OR 3.78; 95% CI, 1.04–8.67; $p = 0.034$), and frailty status (adjusted OR, 2.87; 95% CI, 1.05–8.91; $p = 0.028$) remained independent predictors for POD occurrence in multivariate analysis.

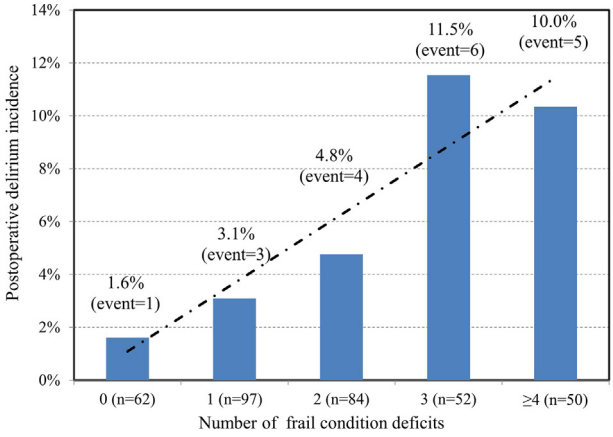

Fig. 3 Incidence of postoperative delirium according to the number of frail condition deficits.

Table 3 Univariate and multivariate analysis of the clinical variables involved in the occurrence of postoperative delirium.

Variable	Category	POD number/total number (%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Age	65–72	5/179 (2.8)	1 (reference)		1			
	≥73	14/166 (8.4)	3.21	1.13–9.11	0.029	2.94	1.02–9.74	0.045
Sex	Male	15/206 (7.3)	1					
	Female	4/139 (2.9)	0.38	0.12–1.16	0.09			
Marriage	Married	15/255 (5.9)	1					
	Others	4/90 (4.4)	0.74	0.24–2.30	0.61			
Education	Less than high school	9/191 (4.7)	1					
	High school or more	10/154 (6.5)	1.38	0.68–5.77	0.18			
Smoking	No	11/213 (5.2)	1					
	Yes	8/132 (6.1)	1.19	0.46–3.01	0.72			
Drinking	No	9/220 (4.1)	1					
	Yes	10/125 (8.0)	2.04	0.81–5.16	0.13			
BMI, kg/m^2	<20.5	1/55 (1.8)	1					
	≥20.5	18/290 (6.2)	3.57	0.47–27.3	0.22			
ECOG performance	0–1	16/324 (4.9)	1					
	2–3	3/21 (14.3)	3.21	0.86–12.0	0.08			
ASA score	1–2	1/20 (5.0)	1					
	3–4	18/325 (5.5)	1.11	0.14–8.80	0.92			
Cancer type	Colorectum	4/179 (2.2)	1			1		
	Stomach	4/50 (8.0)	4.14	1.18–14.6	0.027	1.44	0.34–621	0.62
	Liver	7/81 (8.6)	3.8	0.92–15.8	0.07	1.22	0.13–5.15	0.83
	Pancreas or extra-hepatic biliary tract	4/35 (11.4)	5.65	1.34–23.8	0.018	1.02	0.16–6.54	0.98
Tumor stage	1	2/107 (1.9)	1					
	2–4	17/238 (7.1)	4.04	0.92–17.8	0.07			
Tumor grade	Well-differentiated	3/70 (4.3)	1					
	Moderately differentiated	9/188 (4.8)	1.12	0.30–4.27	0.87			
	Poorly differentiated	7/87 (8.0)	1.95	0.49–7.85	0.35			
Operative method	Open	17/175 (9.7)	1			1		
	Laparoscopy	2/170 (1.2)	0.11	0.03–0.49	0.004	0.31	0.09–1.04	0.06
Operative time, minutes	<428	12/298 (4.0)	1			1		
	≥428	7/47 (14.9)	4.17	1.55–11.2	0.005	3.78	1.04–8.67	0.034
Intraoperative blood loss, ml	<175	9/258 (3.5)	1			1		
	≥175	10/87 (11.5)	3.59	1.41–9.16	0.007	1.73	0.50–5.93	0.39
Frailty	Fit	4/159 (2.5)	1			1		
	Frail	15/186 (8.1)	3.40	1.10–10.5	0.033	2.87	1.05–8.91	0.028

Abbreviations: OR: odds ratio; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; CCI: Charlson comorbidity index; ASA: American Society of Anesthesiologists.

Discussion

This study prospectively explored the association between pretreatment frailty and the risk of POD in older Taiwanese cancer patients undergoing elective abdominal surgery. Our results showed that the population of older patients diagnosed with cancer, who presented with an increased number of frail condition deficits, was significantly associated with POD occurrence. A recent study reported that frail patients were 2.7 times more likely to experience POD than robust patients among the older population that underwent noncardiac surgery [18]. Similarly, our study showed that frailty, along with older age and prolonged operative time, was an independent risk factor for POD, with a 2.8-fold increase in the risk of POD occurrence compared with that in fit patients.

A systemic review reported 43% median prevalence (range, 7%–68%) of frailty in geriatric cancer patients [13]. Frailty was prevalent in 54% of patients upon receiving surgery in this study. The results are similar to those of our previous report: 58% of the geriatric cancer patients had frailty upon receiving chemotherapy [14]. Furthermore, 47% of the non-geriatric Taiwanese patients with esophageal cancer were allocated to the frail group based on the same assessment criteria upon receiving concurrent chemoradiotherapy [19]. As such, higher prevalence of frailty and a significant association between frailty and the occurrence of POD in Taiwanese cancer patients indicates the importance of routine frailty assessment in predicting treatment outcomes in oncogeriatric patients before the initiation of anti-tumor treatment.

Frailty is the accumulation of functional deficits that decrease physical reserves in response to stressors [9]. Cancer and anti-tumor treatments are serious physical stressors for frail patients. Therefore, patients with frail cancer are more vulnerable to adverse outcomes after anti-tumor treatment [12–15]. However, one meta-analysis [16] based on five studies reported a discordance regarding the effect of frailty on POD in older patients diagnosed with cancer [11,20–23]. Two of these five studies reported a significant association between frailty and POD [11,20], whereas the association between frailty and POD was not significant (unadjusted OR 2.52, 95% CI 0.83–7.61, $p = 0.10$) in the pooled estimate [16]. Unfortunately, all five of these studies were limited by small patient numbers (n = 44–211), low incidence of POD in the participants (2.3%–5.1%), and only using the univariate analysis to evaluate the association between frailty and POD [11,20–23]. In contrast to the insignificant association between frailty and POD in the meta-analysis, our study showed that frailty was significantly associated with POD in geriatric cancer patients. With the recruitment of a relatively large number of patients, our study enabled us to explore the association between frailty and POD in the multivariate analysis to adjust for other potential confounding variables.

In addition to frailty, older age and prolonged operative time were independent risk factors for POD. Although these three factors are well-known predictors of POD as reported in previous studies [11,20,21,24,25], frailty was the only modifiable factor in the patient. Physicians should focus on geriatric interventions to correct patients' frailty before elective surgery. Several studies have shown that interventional strategies are effective in reducing POD by improving frailty in elderly patients. Chen et al. reported that the Hospital Elder Life Program, which includes three important interventions, early mobilization, nutritional assistance, and orienting communication, is effective in reducing frailty and the incidence of POD in the older population undergoing abdominal surgery [26]. Deeken et al. reported a multifaceted multidisciplinary intervention, including tailoring the need for patients' motor, meal, mood, and sensory stimulation significantly reduced the occurrence and duration of POD in older patients undergoing elective surgery [27]. All core domains of these interventional strategies are aimed at reducing frailty in older patients [26,27]. Although the Hospital Elder Life Program and other geriatric interventions are not routine clinical practices in Taiwan, we believe our results might assist clinicians in using frailty assessment to identify patients with high risk of POD and implement appropriate interventions for the vulnerable Taiwanese geriatric cancer population in the future.

Malnutrition was the most prevalent frailty condition in this study, which was mainly caused by direct tumor impediment of the gastrointestinal tract, specifically characterized by the cancer specificity of our patient cohort. Although the prevalence of falls and poor social support was relatively low in our cohort, patients with poor mobility and lack of social support were also prone to POD after surgery [28,29]. The frailty assessment presented accumulative deficits of multidisciplinary physical fitness, including decreased physical activity [30], malnutrition [9], comorbidity [9], depressive mood [30], cognition deficit [28], and poor social support [29], all of which are common factors associated with POD. Our results support the utility of frailty as a comprehensive assessment tool for identifying cancer patients who are vulnerable to the occurrence of POD.

In this study, impairment of ≥ 2 domains was defined as frailty [14,15,19], whereas some studies quantified frailty in the index by counting the number of deficits and dividing by the total number of domain measurements [31,32]. In addition, the cutoff level using ADL < 100, CCI ≥ 2, and living alone was adopted as the definition of frailty deficit in each domain based on our previous validated studies [14,15,19]. The concept of frailty in relation to treatment outcome in cancer patients is still in its infancy in Taiwan, so there is no consensus on the aspects of geriatric domain impairment to assess frailty in local cancer patients. Further studies are needed to explore the optimal frailty assessment tools suitable for the Taiwanese cancer population.

There are some limitations in our study that need to be addressed. First, the low incidence of POD (5.5%) may limit the statistical power to detect an association between frailty and POD in our study. Second, frail patients were prone to develop POD owing to older age and poor ECOG performance; however, the impact of frailty on POD remained significantly different after adjustment for other potential confounders in multivariate analysis. Third, the frailty assessment results were blinded to the primary care physician, and no geriatric intervention was implemented in frail patients in our study. This study provides a proof-of-concept pilot study to explore the association between frailty and POD in Taiwanese patients with oncogeriatric disease. Further studies are needed to evaluate the appropriate strategy for early identification and intervention in case of frailty to overcome the occurrence of

POD in older Taiwanese patients diagnosed with cancer before elective abdominal surgery.

In conclusion, frailty is a common phenomenon in older Taiwanese cancer patients who undergo elective abdominal surgery. This study showed a positive correlation between an increased number of frail conditions and the risk of POD. Our study identified frailty as an independent risk factor for POD in Taiwanese geriatric patients with cancer. Preoperative frailty assessment can assist physicians in identifying high risk of POD in patients, emphasizing geriatric intervention for frailty improvement and improving the quality of postoperative care for geriatric cancer patients in Taiwan.

Ethics approval and consent to participate

This study was approved by the institutional review board of Chang Gung Memorial Hospital in August 2017 (ethic code: 1608080002) and has been conducted in compliance with the Helsinki Declaration (1996).

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Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

Authors declare no conflicts of interest for this article.

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