Original Article

A nationwide survey of fatigue in cancer patients in Taiwan: an unmet need

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Abstract

Background: Cancer-related fatigue (CRF) is an emerging clinical issue, although its prevalence and impact on quality of life (QOL) in cancer patients in Taiwan remain unclear. The present nationwide cross-sectional study was conducted to provide a thorough overview of the prevalence, related factors and impact of CRF in Taiwan.

Methods: In this multi-center survey, data were collected using the International Classification of Diseases 10th Revision (ICD-10) Fatigue evaluation, Brief Fatigue Inventory–Taiwan (BFI-T), the Chinese version of the Symptom Distressed Scale and a fatigue experience survey. Logistic regression was used to determine the correlations between fatigue characteristics and the factors studied.

Results: A total of 1207 cancer patients were recruited from 23 hospitals in Taiwan. Fatigue was the most distressing symptom in Taiwanese cancer patients. The distress score was higher if CRF was diagnosed using ICD-10 compared with BFI-T. Rest and nutritional supplementation were the most common non-pharmacological treatments; blood transfusion was the most common pharmacological treatment. There were 45% of patients reported not receiving a timely intervention for fatigue.

Conclusions: Fatigue is the most bothersome symptom reported by Taiwanese cancer patients. Caregivers should be aware of the impact of CRF on QOL in cancer patients, constantly measure the severity of fatigue and provide appropriate interventions.

Key words: cancer, fatigue, prevalence

Introduction

Fatigue is a common symptom consisting of tiredness, lack of energy, weakness and inability to concentrate. It can be either treatment- or disease-related symptom and is an independent and strong predictor of decreased patient satisfaction and lower scores for all aspects of quality of life (QoL) (1). The National Comprehensive Cancer Network (NCCN) defines 'Cancer-related fatigue (CRF) as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with normal functioning' (2).

Causes of CRF include underlying cancer status, side effects from treatments and psychological problems. CRF is also a common and severe side effect of immunotherapy (3). Estimates of the prevalence of CRF vary widely in advanced cancer patients, from 51 to 89% (4,5), and the pathophysiological mechanisms underlying its development are still not clear. Consequently, the true prevalence of CRF and effective interventions for it has not been established; unsurprisingly, health care providers are generally not familiar with the diagnosis, evaluation or treatment of CRF. The importance of CRF has increased, not only because most cancer-related or treatment-related symptoms are now controllable by current medications, but also because CRF negatively impacts QoL and treatment outcomes.

In practice, CRF is often underestimated. The results of an electronic survey distributed via professional associations and oncology societies pointed to a need for additional resources and further education in CRF management for a range of health disciplines in oncology (6). A prevalence survey of CRF in 265 cancer patients in Taiwan identified 228 (86%) patients with at least 2 weeks of fatigue in the past month, and further diagnosed CRF in 132 (49.8%) patients using International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) criteria (7). To determine the nationwide prevalence of CRF in Taiwan and characterize CRF more fully, we conducted this nationwide survey in patients of different cancer types, stages, treatments and backgrounds. The aim of this survey of a cross-sectional sample of oncology inpatients and outpatients throughout Taiwan was to elucidate the epidemiology of CRF and its impact in Taiwan, and to survey the fatigue experience in order to enhance physicians' understanding of CRF and improve cancer care in the future.

Patients and methods

Eligibility

We recruited patients who gave consent to participate in this study and met all the following eligibility criteria. The inclusion criteria were aged 20 years and older, a diagnosis of cancer, and ability to communicate verbally and to fill out questionnaires. Patients who could not complete questionnaires due to cognitive impairment were excluded.

Procedures

Ethical approvals were obtained from the Institution Review Boards of all participating hospitals and all patients provided written informed consent to participate. Data were collected through face-to-face interview by experienced researchers using a set of questionnaire. During the study, the ICD-10 fatigue criteria, Brief Fatigue Inventory–Taiwan Form (BFI-T) (8), the Chinese version of the Functional Assessment of Cancer Therapy-General QoL questionnaire (FACT-G7) (9) and a cancer symptom survey were used to evaluate patients' fatigue and QoL. Demographic information and disease-related information were collected from medical records for comparative analysis.

In the interview, we also used the self-completed 'Fatigue Experience Survey' to determine the most-used interventions. This tool was developed for this study based on the previous research and clinical expert opinion (10,11). The 18 items were divided into three subcategories: non-pharmacologic interventions (e.g. nutrition, rest, exercise, energy conservation and activity management [ECAM], relaxation), pharmacologic interventions (e.g. blood transfusion, steroids, hematopoietics, hormones, sleep medications and sedatives, methylphenidate) and other alternative treatments (e.g. Chinese medicine, herbal medications).

Statistical analysis

Descriptive statistics (frequency distribution, percentage, means, standard deviations) were used to summarize demographic and disease characteristics, fatigue level, symptom distress and fatigue experience. The *t*-test or one-way ANOVA was used to compare the differences between the inpatient and outpatient groups. Logistic regression analyses were used to explore and compare the factors significantly related with fatigue (Yes or No), based on the results from the ICD-10 fatigue criteria and the BFI-T. All analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY) and $P < 0.05$ was considered to represent statistical significance.

Results

Patient characteristics

The patients' demographic and clinical characteristics are summarized in Table 1. A total of 1207 cancer patients, consisting of 574 (47.6%) inpatients and 633 (52.4%) outpatients, were enrolled from 23 hospitals in Taiwan, and 70% of the included patients were not working at the time of enrollment. Patients with all stages of cancer were included, but the majority of them had stages 3 and 4 disease. Nevertheless, 246 cancer patients were disease free at the time of enrollment, and most of these were outpatients. Breast cancer (*n* = 201, 16.7%), head and neck cancer (*n* = 175, 14.5%) and colorectal cancer (*n* = 140, 11.6%) were the most common cancers in the present study.

Fatigue was the most distressing symptom for cancer patients

Initially, we surveyed cancer-related symptoms and ranked them from the least to most distressing. We found that cancer patients in Taiwan, regardless of whether they were outpatients or inpatients, ranked fatigue as the most distressing symptom (Table 2).

Incidence of CRF based on the ICD-10 and BFI-T

The ICD-10 and BFI-T were used to diagnose fatigue at the time of interview. The number of patients diagnosed as having fatigue differed widely between tools. The prevalence of fatigue was 23.4% when evaluated using the ICD-10 and 71.9% when evaluated using the BFI-T (Table 3).

Table 1. Patient characteristics

	Overall (*n* = 1207)		Inpatients (*n* = 574)		Outpatients (*n* = 633)		*P* value
	n	%	n	%	n	%	
Age, years (mean ± SD)	57.12 ± 12.45	—	57.80 ± 12.55	—	56.36 ± 12.30	—	0.043
Gender							0.058
Male	630	52.2	316	55.1	314	49.6	
Female	577	47.8	258	44.9	319	50.4	
Occupational status							0.553
No work	845	70.0	410	71.4	435	68.7	
Part-time work	67	5.6	29	5.1	38	6.0	
Full-time work	295	24.4	135	23.5	160	25.3	
Stage at evaluation							0.002
I	78	6.5	26	4.5	52	8.2	
II	148	12.3	60	10.5	88	13.9	
III	225	18.6	97	16.9	128	20.2	
IV	483	40.0	257	44.8	226	35.7	
Other	273	22.6	134	23.3	139	22.0	
ECOG							<0.001
0	354	29.3	93	16.2	261	41.2	
1	616	51.0	301	52.4	315	49.8	
2	165	13.7	114	19.9	51	8.1	
3	59	4.9	54	9.4	5	0.8	
4	13	1.1	12	2.1	1	0.1	
Disease status							<0.001
Disease free	246	20.4	37	6.4	209	33.0	
Stable	498	41.3	237	41.3	261	41.2	
Partial response	122	10.1	56	9.8	66	10.4	
Progressive disease	178	14.7	130	22.6	48	7.6	
Unclear	163	13.5	114	19.9	49	7.7	
Accepted treatment within 1 week							<0.001
Yes	643	53.3	339	59.1	304	48	
No	564	46.7	235	40.9	329	52	
Cancer type							
Breast cancer	201	16.7	66	11.5	135	21.3	
Head and neck cancer	175	14.5	77	13.4	98	15.5	
Colorectal cancer	140	11.6	81	14.1	59	9.3	
Lymphoma	101	8.4	49	8.5	52	8.2	
Lung cancer	97	8.0	38	6.6	59	9.3	
Hematologic malignancy	94	7.8	38	6.6	56	8.8	
Gastric cancer	72	6.0	30	5.2	42	6.6	
Liver cancer	60	5.0	35	6.1	25	3.9	
Esophageal cancer	52	4.3	44	7.7	8	1.3	
Gallbladder cancer	28	2.3	15	2.6	13	2.1	
Pancreatic cancer	27	2.0	20	3.5	7	1.1	
Bladder cancer	19	1.6	7	1.2	12	1.9	
Prostate cancer	12	1.0	5	0.9	7	1.1	
Cervical cancer	10	0.8	5	0.9	5	0.8	
Other	119	9.9	64	11.1	55	8.7	

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Intensity of CRF and it negative impact

The average intensity of general fatigue during the past 24 hours was moderate for the overall patients (M = 3.47; SD = 2.52) and for inpatients (M = 3.97; SD = 2.51), but its level was mild for outpatients (M = 2.96; SD = 2.44). Moreover, the worst fatigue intensity during the past 24 hours was 5.14 for inpatients, indicating that inpatients experienced moderate fatigue during the day. Since many patients were diagnosed as having fatigue, we were able to evaluate the impact of CRF on daily activities using the BFI-T. We found that CRF

did interfere with patients' daily life, especially 'enjoyment of life'. However, inpatients were bothered more by CRF than outpatients (Table 4).

Factors associated with reported fatigue in ICD-10 and BFI-T

We further identified and compared factors related to fatigue based on the assessment by ICD-10 and BFI-T. Experiencing fatigue

Table 2. Rank of symptoms according to distress scores in cancer patients in Taiwan

Rank	Overall (N = 1207)			Inpatients (n = 574)			Outpatients (n = 633)		
	Item	Mean	SD	Item	Mean	SD	Item	Mean	SD
1	Fatigue	3.00	2.86	Fatigue	3.57	2.99	Fatigue	2.48	2.63
2	Insomnia	2.52	2.93	Pain	2.94	3.07	Insomnia	2.16	2.79
3	Pain	2.36	2.81	Insomnia	2.92	3.03	Pain	1.84	2.44
4	Anorexia	1.95	2.81	Anorexia	2.59	3.08	Anorexia	1.38	2.39
5	Depression	1.65	2.44	Depression	2.15	2.71	Depression	1.20	2.08

SD, standard deviation.

Table 3. Occurrence rate of cancer-related fatigue based on ICD-10 and BFI-T criteria

Variable	Overall (n = 1207)		Inpatients (n = 574)		Outpatients (n = 633)	
	n	%	*n*	%	*n*	%
ICD-10 fatigue						
Yes	282	23.4	183	31.9	99	15.6
No	925	76.6	391	68.1	534	84.4
BFI-T fatigue						
Yes	868	71.9	459	80.0	409	64.6
No	339	28.1	115	20.0	224	35.4

BFI-T, Brief Fatigue Inventory–Taiwan; ICD-10, International Classification of Diseases 10th Revision.

Table 4. Fatigue intensity and its interference reported by BFI-T

	Overall (n = 1207)		Inpatients (n = 574)		Outpatients (n = 633)	
	Mean	SD	Mean	SD	Mean	SD
General fatigue during the past 24 hours	3.47	2.52	3.97	2.51	2.96	2.44
Worst fatigue during the past 24 hours	4.60	3.06	5.14	2.96	4.06	3.08
Interference of fatigue	2.40	2.45	3.01	2.59	1.81	2.16
General activity	2.54	2.86	3.24	3.05	1.85	2.47
Mood	2.50	2.71	3.04	2.79	1.97	2.52
Walking ability	2.34	2.84	2.97	3.07	1.71	2.43
Normal work[a]	2.58	3.17	3.24	3.46	1.93	2.70
Relations with other people	1.80	2.52	2.20	2.72	1.40	2.23
Enjoyment of life	2.67	3.09	3.35	3.26	1.99	2.75

SD, Standard deviation.
[a]Includes both work outside the home and daily chores.

(Yes or No) was assessed by both tools and logistic regression was used to examined the related factors (demographic, disease characteristics, fatigue management and communication experience). Based on the assessment using ICD-10 criteria, current stage (III and IV), and poor functional status as indicated by Eastern Cooperative Oncology Group (ECOG) score, liver cancer, having tried to manage their fatigue by themselves, and having actively reported that they suffered from fatigue were associated with a significant higher probability of being diagnosed as having CRF within the past month. As assessed by BFI-T, female, cancer stage > II, ECOG score > 3, progressive disease, having tried to manage their fatigue

by themselves, and having actively reported that they suffered from fatigue were associated with a significantly higher probability of being diagnosed as having CRF within the past 7 days (Table 5).

Fatigue experience related to communication and fatigue management

The fatigue experience survey asked about the patient's experience in communicating fatigue to health care providers and managing fatigue using non-pharmacological and pharmacological treatments (Table 6). Cancer patients who were aware of fatigue

Table 5. Logistic regression analysis of the factors associated with reported fatigue in the ICD-10 and BFI-T (*N* = 1207)

Variable	Reported fatigue in ICD-10			Reported fatigue in BFI-T		
	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Age, years	0.997	(0.984–1.010)	0.661	0.989	(0.978–1.001)	0.070
Gender (female = 1; male = 0)	1.185	(0.824–1.704)	0.361	1.419	(1.009–1.995)	**0.044**
Stage (stage I = 0)						
Stage II	1.674	(0.811–3.452)	0.163	0.555	(0.308–0.999)	**0.049**
Stage III	2.079	(1.068–4.049)	**0.031**	0.985	(0.564–1.718)	0.956
Stage IV	1.969	(1.065–3.639)	**0.031**	0.611	(0.362–1.033)	0.066
ECOG (ECOG 0 = 0)						
ECOG 1	3.370	(2.013–5.641)	<**0.001**	1.884	(1.365–2.600)	<**0.001**
ECOG 2	11.344	(6.235–20.641)	<**0.001**	4.779	(2.552–8.948)	<**0.001**
ECOG 3	17.138	(7.757–37.865)	<**0.001**	7.842	(2.228–27.595)	**0.001**
ECOG 4	34.353	(7.753–152.215)	<**0.001**	3.391	(0.668–17.209)	0.141
Disease status (disease free = 0)						
Stable	1.324	(0.749–2.340)	0.334	2.105	(1.408–3.149)	<**0.001**
Progressive disease	1.541	(0.780–3.045)	0.214	4.197	(2.188–8.048)	<**0.001**
Partial response	1.494	(0.756–2.952)	0.248	2.412	(1.321–4.406)	**0.004**
Unclear	1.378	(0.702–2.704)	0.352	2.303	(1.362–3.896)	**0.002**
Accepted treatment within 1 week (Yes = 1; No = 0)	1.025	(0.745–1.412)	0.878	1.621	(1.200–2.188)	**0.002**
Cancer type (breast cancer = 0)						
Head and neck cancer	0.979	(0.527–1.819)	0.947	0.956	(0.523–1.748)	0.884
Colorectal cancer	0.623	(0.328–1.183)	0.148	0.679	(0.376–1.226)	0.199
Lymphoma	0.792	(0.311–2.014)	0.624	0.796	(0.376–1.686)	0.551
Lung cancer	1.160	(0.591–2.277)	0.665	0.904	(0.469–1.743)	0.763
Hematologic malignancy	0.654	(0.237–1.807)	0.413	1.262	(0.578–2.758)	0.559
Gastric cancer	0.535	(0.248–1.156)	0.112	0.904	(0.430–1.897)	0.789
Liver cancer	2.551	(1.005–6.477)	**0.049**	0.536	(0.217–1.323)	0.176
Esophageal cancer	0.865	(0.371–2.015)	0.736	1.357	(0.500–3.683)	0.548
Others	1.013	(0.580–1.772)	0.963	0.678	(0.399–1.151)	0.150
Medical personal provide treatment to improve fatigue (Yes = 1; No = 0)	1.144	(0.804–1.628)	0.454	0.974	(0.694–1.368)	0.880
Patients tried to improve fatigue (Yes = 1; No = 0)	2.198	(1.294–3.735)	**0.004**	2.968	(2.035–4.328)	<**0.001**
Patients actively mentioned fatigue (Yes =1; No = 0)	1.488	(1.040–2.130)	**0.030**	1.690	(1.210–2.361)	**0.002**
Place (inpatients =1; outpatients = 0)	1.406	(0.997–1.982)	0.052	1.264	(0.913–1.751)	0.158
Intercept	0.013		<**0.001**	0.419		0.084

BFI-T, Brief Fatigue Inventory–Taiwan; ECOG, Eastern Cooperative Oncology Group; ICD-10, International Classification of Diseases 10th Revision; OR, Odd Ratio; 95% CI, 95% Confidence Interval.

ICD-10 Omnibus test for model: X^2: 261.924, *P* < 0.001; BFI-T Omnibus test for model: X^2: 247.934, *P* < 0.001; Using bold emphasis is for meaning that it is statistics significance.

employed several strategies to overcome their CRF. Nutritional supplements (52.0%) and rest (51.6%) were the most common non-pharmacological treatments, but exercise (47.3%) was also used, when possible, to overcome the feeling of fatigue. From the self-reported survey, few pharmacological treatments were used. Because anemia might be the most common abnormality detectable by blood tests and the most straightforward reason for fatigue, blood transfusion was the most common pharmacological treatment. Some physicians treated fatigue by prescribing steroids or other hormonal treatments (such as thyroid hormone), but they rarely prescribed herbal medications. Among 1207 patients, 83.5% had tried to manage their fatigue by themselves and 56.2% had actively reported that they suffered from fatigue. In 54.8% of patients, health care providers had provided some intervention to help them manage fatigue, but 45% of patients reported not receiving a timely intervention for fatigue.

Discussion

Among the many symptoms for cancer patients of all stages, pain has long ranked as the most distressing. Recent improvements in medical and non-medical management for cancer pain have resulted in patients becoming more satisfied with their pain control (12). In our current survey, fatigue was the most distressing symptom reported by both inpatient and outpatient cancer patients in Taiwan, a result not reported before. Among cancer-related symptoms, 'fatigue' has been inadequately discussed and undertreated. Barsevick et al. pointed out three major obstacles to progress: (i) lack of agreement about measurement, (ii) inadequate understanding of the underlying biology and (iii) problems with conducting clinical trials of CRF interventions (13).

About 60–90% of patients with advanced cancer identify fatigue as their most debilitating symptom, while only 37% of physicians believe this to be the case (14). CRF may be caused by a variety

Table 6. Results of the Fatigue Experience Survey

Intervention	*n* (%)
Non-pharmacological treatments	
1. Nutrition	628 (52.0)
2. Rest	623 (51.6)
3. Exercise	571 (47.3)
4. ECAM	555 (46.0)
5. Relaxation	437 (36.2)
Pharmacological treatments	
1. Blood transfusion	139 (11.5)
2. Steroids	75 (6.2)
3. Hematopoietics	51 (4.2)
4. Hormone	17 (1.4)
5. Sleep & sedative drugs	16 (1.3)
6. Methylphenidate	4 (0.3)
Other	
1. Chinese herbal medicine	91 (7.5)
2. Drug extract from plant	28 (2.3)
3. Other[a]	34 (2.8)
Communication related to fatigue management	
1. Medical personal provided intervention to manage fatigue	661 (54.8)
2. Patients ever tried to manage fatigue	1008 (83.5)
3. Patients actively reported suffering from fatigue	678 (56.2)

ECAM, Energy Conservation and Activity Management.
[a]Other included distract attention (*n* = 17), *Ganoderma lucidum* and *Antrodia cinnamomea* (*n* = 7), coffee (*n* = 2), family support (*n* = 2) and other (*n* = 6).

of factors, including chemotherapy- or radiotherapy-induced anemia or leukopenia, comorbidities, bad sleep quality, malnutrition, concomitant medications and postoperative sequelae [15]. Due to a lack of agreement about measurement and the overabundance of causes for fatigue in cancer patients, CRF is difficult to study. Even so, CRF has been recognized as 'the most important untreated symptom in cancer today' [16]. Furthermore, medical providers may not be able to clarify the underlying causes of fatigue, so that patients are at risk of receiving multiple treatments for symptoms, including pharmaceutic and/or non-pharmaceutic treatments. The treatment chosen, however, may not align with the cause of fatigue. In addition, the lack of CRF awareness may lead patients and medical providers to ignore its negative impact on QoL and treatment compliance, or to misinterpret CRF as a sign of tumor progression. Finally, the lack of a simple and convenient tool to diagnose CRF and evaluate its severity makes CRF difficult to treat.

In our current study, we compared the diagnosed rate of CRF using the ICD-10 and the BFI-T. The ICD-10 criteria for the diagnosis of CRF were more difficult to meet and more time-consuming to administer. The ICD-10 questionnaire took 30 minutes to complete, whereas the BFI-T took only 10 minutes. Although fewer cancer patients were diagnosed as having CRF by the ICD-10 than by the BFI-T, they complained of more symptom distress (Tables 3 and 4). BFI-T can therefore be considered a rapid screening tool, especially in outpatient settings, and the ICD-10 can be used for a definite diagnosis of CRF when further interventions will be performed.

For both tools, we found that ECOG—advanced disease stage—having tried to manage their fatigue by themselves and having actively reported suffering from fatigue were associated with a significantly higher probability of being diagnosed with CRF. Undoubtedly, patients who tried to manage their fatigue and those who actively reported their fatigue should be counted as having CRF, and health care providers might more easily identify these patients than others. Also, inpatients in general tend to have more complications or co-morbidities than outpatients, and thus have a higher likelihood of having fatigue. On the other hand, health care providers must also monitor patients who did not seek help for fatigue but are at risk of CRF. In our study, we found that only 54.8% of medical providers had provided interventions to manage fatigue. Early diagnosis and intervention are important, because they may lead to not only better QoL but also better therapeutic compliance and outcomes.

Once CRF is diagnosed, interventions should depend on the underlying causes and severity of fatigue. In the present study, the majority of cancer patients received non-pharmacologic treatments such as nutrition and rest. Although malnutrition or/and cachexia from an underlying malignancy, especially in terminal cases, are common causes of CRF, nutritional support alone might not be enough to ameliorate CRF [17]. Patients need a well-designed nutritional plan, which can reduce inflammation. In cancer survivors, fruit, vegetables, whole grain and omega-3 fatty acid-rich foods have been reported to reduce the severity of fatigue [18].

NCCN guidelines strongly recommend exercise or maintaining optimal levels of activity for patients with CRF [2]. Exercise can ameliorate CRF in cancer patients, thereby improving health-related QoL [19]. A recent meta-analysis of 113 studies also found that exercise and psychological interventions are significantly better than other pharmaceutical options at reducing CRF during and after the cancer treatment [20]. Exercise should be encouraged in patients who can tolerate it. Personalized programs should be based on cancer type, current stage, performance status, treatments and concomitant illnesses. Training intensity should be increased step-by-step.

For patients with CRF, especially those with severe CRF, ECAM can increase energy preservation and reduce unnecessary energy waste. In a randomized study, an ECAM intervention modestly but significantly decreased fatigue over time compared with nutrition alone [21]. Performing ECAM is labor intensive; requires experienced staff to implement the three stages of the program known as 'representation', 'coping' and 'appraisal' over more than 3-week period [22]; and needs dynamic follow-up and reevaluation to ensure its success. It is not a routine practice at Taiwan. Some patients experience depression, which can be a major barrier to seeking treatment and is usually associated with poor sleep quality and poor adherence to suggested treatments [23]. Cognitive-behavior therapy performed in a group setting has been shown to relieve anxiety, depression and CRF [24–26]; therefore, psychiatrists or counselling psychologists should be important members of the cancer care team.

There are few choices for pharmacological treatment of CRF. A meta-analysis of 27 randomized controlled trials of pharmacologic treatment for CRF found that erythropoietin improved anemia and fatigue in cancer patients undergoing chemotherapy, but progestational steroids and paroxetine did not improved [27]. Unfortunately, erythropoietin may stimulate tumor growth, which limits its clinical application. Methylphenidate, a sympathomimetic psychostimulant, was shown to be more effective than placebo in improving CRF [27]. A meta-analysis of data from 1582 participants in 10 trials also concluded that methylphenidate could improve CRF [28]. Overall, the literature supports the moderate effectiveness of methylphenidate in reducing CRF [29]. The dosage of methylphenidate needs to be titrated gradually and side effects such as anxiety, dizziness, insomnia

and abdominal pain should be taken into account (30). Since inflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor may be responsible for CRF (31), it is reasonable to treat CRF with corticosteroids. Two randomized controlled trials support the effectiveness of dexamethasone and methylprednisolone in providing short-term relief of CRF (32,33). Because of the long-term toxicities of steroids, their use is limited to terminally ill patients, especially those with anorexia or pain from bone or brain metastasis. Recently, herbal medicines such as ginseng have become a treatment option for CRF (34,35), but the complexity of their composition has made application more problematic and large randomized controlled studies are still lacking.

A double-blind, randomized placebo-controlled study showed that PG2, a partially purified polysaccharide extracted from *Astragalus membranaceus*, is an effective and safe treatment for relieving CRF in advanced cancer patients. Patients with advanced cancer and moderate-to-severe CRF were randomized in a double-blind manner to receive either PG2 or normal saline (NS) for 4 weeks; thereafter, they received open-label treatment with PG2 for the next 4 weeks. Fatigue improved more after the administration of PG2 than after NS. No major or irreversible toxicities were observed (36). Astragalus polysaccharide also improved the QoL of advanced non-small-cell lung cancer and head and neck cancer patients receiving chemotherapy and radiotherapy (37). A previous study showed that PG2 has the potential to ameliorate the deterioration in QoL associated with concurrent chemoradiotherapy (CCRT) among patients with advanced pharyngeal or laryngeal head and neck squamous cell carcinoma (38). We recently completed a large randomized controlled trial of PG2 for improving fatigue in advanced cancer patients receiving standard palliative care. We found that fatigue scores improved by at least 10% in >65% of subjects after one treatment cycle compared with scores at baseline. Patients with higher Karnofsky Performance Status responded better to PG2 (39).

To our knowledge, this study is the first nationwide survey of CRF in patients with different kinds of cancer in Taiwan. The major limitation of study is that it was a cross-section study without follow-up data to determine the effects of interventions.

In conclusion, fatigue is the most bothersome symptom in cancer patients in Taiwan. To improve patients' QoL and treatment compliance, caregivers should be alert to the impact of CRF and evaluate the severity of fatigue in their patients. Rapid evaluation and diagnosis of CRF, including clarification of the underlying causes and effective treatments (both non-pharmacological and pharmacological), are urgently needed. ECAM is the mainstay, and treatment plans should be dependent on the pathogenesis of CRF, disease status, co-morbidities, performance status, availability of drugs and treatment compliance. Psychosocial therapy and physical activities, especially exercise, can also relieve CRF.

Future studies should address the motivational factors affecting adherence and the barriers to implementation of exercise and psychosocial interventions to reduce the CRF. Although non-pharmacological treatments are more popular, pharmacological treatment is more convenient. Well-designed clinical trials with minimal heterogeneity would clarify the effectiveness of various CRF interventions. Result from this study can be used to improve awareness and act as a baseline for future comparison after interventions.

Conflict of interest statement

None declared.

Authors' contributions

Drafted this article: K.M.R. Data analysis and project design: T.J.C., C.H.L., W.H.K., M.Y.L., W.T.H. and K.H.Y. Conception and study design: C.S.C. and S.C.S. Corrections of paper: R.K.H. The manuscript has been read and approved for submission by all authors. All authors have contributed to preparing the manuscript, and no person or persons other than the authors listed have contributed significantly to its preparation.

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