PREVALENCE AND ASSOCIATED FACTORS OF CANCER-RELATED FATIGUE AMONG CANCER PATIENTS IN UNIVERSITY MALAYA MEDICAL CENTRE

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ABSTRACT

Prevalence and Associated Factors of Cancer-related Fatigue among Cancer Patients in University Malaya Medical Centre.

Background: Cancer-related fatigue is a distressing symptom commonly experienced by our patients diagnosed with cancer. However, there is no data on cancer-related fatigue among our local population. The objective of this study was to evaluate the prevalence of cancer-related fatigue and its association with sociodemographic factors, clinical characteristics of patients, depression, anxiety and demoralisation. Correlation between cancer-related fatigue, depression, anxiety and demoralization were also studied.

Method: A cross-sectional study was conducted using convenience sampling among one hundred and fifty patients from Oncology Clinic, University Malaya Medical Centre, Kuala Lumpur from July 2020 until December 2020. Data were collected from self-administered questionnaire consisted of sociodemographic data, clinical characteristic of patients, Fatigue Symptom Inventory (FSI), Hospital Anxiety and Depression Scale (HADS) and Demoralisation Scale. The study participants were also interviewed to assess fatigue using Proposed ICD-10 criteria for Cancer-related Fatigue (interview was conducted based on Diagnostic Interview Guide for Cancer-related Fatigue). Chi-square test, Spearman's correlation and logistic regression were used to study the relationship between cancer-related fatigue and its associated factors.

Result: The mean age of the study participants was 63.3 ± 10.29 years old. Majority of the subjects were female (*n*=102, 68.0%), of Chinese ethnicity (*n*=74, 49.3%) and married (*n*=135, 90.0%). Most of our patients were diagnosed with solid tumours (*n*=149, 99.3%), with breast cancer being the commonest (*n*=50, 33.3%). Most of the subjects were at Stage IV (*n*=68, 45.3%), having had the diagnosis of malignancy between one to five

years (n=105, 70.0%). Out of 150 study participants, 58.7% of them were diagnosed to have cancer-related fatigue. Among patients with cancer-related fatigue, 97.7% of them were reported to have clinically meaningful fatigue (p<0.001), 17.0% reported anxiety symptoms (p=0.009), 34.1% had depressive symptoms (p<0.001) and 28.4% had high demoralisation level (p=0.001). All assessment scales were significantly correlated to each other (p<0.001). ICD-10 scoring was positively correlated with Total Disruption Index of FSI (r=0.761, p<0.001) and FSI composite (r= 0.751, p<0.001). Cancer-related fatigue also correlated positively with anxiety (r= 0.454, p<0.001), depression (r=0.544, p<0.001) and demoralisation (r= 0.461, p<0.001). Stages of cancer was the significant contributing factor to cancer-related fatigue (p=0.021). No significant association was found between fatigue and sociodemographic data, other clinical characteristics of patients. In addition, stages of cancer, anxiety, depression and demoralization independently predict the presence of cancer-related fatigue in our study population.

Conclusion: 58.7% of our cancer patients have reported cancer-related fatigue. Stages of cancer was identified to be a significant contributing factor. Cancer-related fatigue was positively associated with depression, anxiety and demoralisation. Routine assessment should be done to screen for fatigue and related psychological factors in our clinical practice.

Keywords: Cancer-related Fatigue, prevalence, depression, anxiety, demoralisation

ABSTRAK

Keletihan Berkaitan dengan Kanser dan Faktor-faktor yang Berhubungan Dengannya di Kalangan Pesakit Kanser di Pusat Perubatan Universiti Malaya.

Latar Belakang: Keletihan berkaitan dengan kanser adalah salah satu gejala yang membebankan dan sering dialami oleh pesakit-pesakit kanser. Tetapi, sehingga hari ini tiada kajian mengenai keletihan berkaitan dengan kanser di kalangan pesakit kanser dijalankan di Malaysia. Tujuan kajian ini adalah untuk mengkaji tahap kekerapan keletihan berkaitan dengan kanser dan faktor-faktor lain yang berkaitan dengannya seperti faktor sociodemografi, faktor klinikal, kemurungan, kegelisahan dan dimoralisasi. Korelasi antara keletihan berkaitan dengan kanser dan kemurungan, kegelisahan, dimoralisasi juga dikaji.

Kaedah: Satu kajian keratan rentas telah dijalankan dengan menggunakan *convenience sampling* di kalangan seratus lima puluh orang pesakit kanser di Klinik Onkologi, Pusat Perubatan Universiti Malaya, Kuala Lumpur. Kajian ini dijalankan dari bulan Julai 2020 sehingga Disember 2020. Subjek-subjek kajian telah diberi soal selidik yang merangkumi profil sociodemografi, maklumat klinikal, *Fatigue Symptom Inventory (FSI), Hospital Anxiety and Depression Scale (HADS)* dan *Demoralisation Scale.* Subjek-subjek kajian juga ditemuramah berkaitan dengan keletihan dengan menggunakan *Proposed ICD-10 criteria for Cancer-related Fatigue* (temu ramah dijalankan berdasarkan *Diagnostic Interview Guide for Cancer- related Fatigue*). Ujian secara *chi-square*, *Spearman's correlation* dan regresi logistik telah digunakan untuk mengkaji keletihan berkaitan dengan kanser dan faktor-faktor lain yang berkaitan dengannya.

Keputusan: Umur purata subjek-subjek kajian adalah 63.3 ± 10.29 tahun. Majoriti subjek dalam kajian ini adalah wanita (*n*=102, 68.0%), golongan Cina (*n*=74, 49.3%) dan telah

berkahwin (*n*=135, 90.0%). Kebanyakan pesakit menghidap kanser padu (*n*=149, 99.3%) dan kanser payu dara adalah jenis kanser yang paling banyak dihidapi oleh pesakit kita (*n*=50, 33.3%). Kebanyakan pesakit ini menghidapi kanser tahap IV (*n*=68, 45.3%), dan telah menerima diagnosis kanser dalam tempoh masa satu hingga lima tahun (*n*=105, 70.0%). Seramai 58.7% subjek kajian ini mempunyai keletihan berkaitan dengan kanser. Di kalangan pesakit yang mempunyai keletihan berkaitan dengan kanser, seramai 97.7% pesakit mempunyai *clinically meaningful fatigue* (*p*<0.001), 17.0% pesakit mempunyai simptom kegelisahan (*p*=0.009), 34.1% pesakit melaporkan simptom kemurungan (*p*<0.001) dan 28.4% pesakit mempunyai tahap demoralisasi yang tinggi (*p*=0.001). Semua skala penilaian yang digunakan dalam kajian ini mempunyai korelasi yang ketara antara sama lain (*p*<0.001). Skor *ICD-10* berkorelasi positif dengan *Total Disruption Index of FSI* (*r*=0.761, *p*<0.001) dan *FSI composite* (*r*= 0.751, *p*<0.001). Keletihan berkaitan dengan kanser juga berkorelasi positif dengan kegelisahan (*r*= 0.454, *p*<0.001), kemurungan (*r*= 0.544, *p*<0.001) dan demoralisasi (*r*= 0.461, *p*<0.001). Tahap kanser mempunyai hubungan yang ketara dengan keletihan berkaitan dengan kanser (*p*=0.021). Tiada hubungan yang ketara ditemui di antara keletihan berkaitan dengan kanser dengan faktor-faktor sociodemografi dan klinikal yang lain. Selain daripada itu, tahap kanser, kegelisahan, kemurungan dan demoralisasi merupakan peramal untuk keletihan berkaitan dengan kanser.

Kesimpulan: Seramai 58.7% pesakit kanser kami mempunyai keletihan berkaitan dengan kanser. Tahap kanser mempunyai hubungan yang ketara dengan keletihan berkaitan dengan kanser. Korelasi positif ditemui di antara keletihan berkaitan dengan kanser dengan kemurungan, kegelisahan dan demoralisasi. Penilaian mengenai keletihan berkaitan dengan kanser dan faktor-faktor psikologi yang berkaitan dengannya seharusnya dijalankan di kalangan pesakit-pesakit kanser kita.

Kata-kata kunci: *Keletihan berkaitan dengan kanser, kelaziman, kemurungan, kegelisahan, demoralisasi*

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ATP	Adenosine triphosphate
BFI	Brief Fatigue Inventory
BMI	Body mass index
CRF	Cancer-related fatigue
DS	Demoralisation Scale
FACT-F	Functional Assessment of Cancer-Therapy- Fatigue Subscale
FSI	Fatigue Symptom Inventory
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale – Depression subscale
HDI	Human Development Index
HPV	Human Papilloma Virus
IBM	International Business Machines Corporation
ICD-10	International Classification of Diseases, Tenth Revision
MINI	Mini International Neuropsychiatric Interview
MREC	Medical Research Ethics Committee
NCCN	National Comprehensive Cancer Network
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
UMMC	University Malaya Medical Centre
VAF	Visual Analogue Scale
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

Cancer is one of the major contributing cause for morbidity and mortality worldwide (Ferlay et al., 2015; Fidler et al., 2018; Organisation, 2000; The Lancet, 2018). The prevalence of cancer is on the rise worldwide, and the disease burden is expected to increase (Fidler et al., 2018). According to the GLOBOCAN 2018 published by the International Agency for Research on Cancer, there were total of 18.1 million people diagnosed with cancer in 2018 across 185 countries worldwide. Furthermore, approximately 9.6 million deaths have occurred due to malignancy, making it the second leading cause of death worldwide (The Lancet, 2018; World Health Organisation, 2020). World Health Organisation has reported that about one in six deaths has occurred as a result of malignancy.

Being diagnosed with malignancy is deemed as an overwhelming and traumatic experience for many patients. On top of the stress and worry after receiving the diagnosis of malignancy, patients also need to cope with the stresses brought about by the physical symptoms such as physical disability, neuropathy, sleep disturbances and fatigue (Adler et al., 2008). Although many patients experienced the aforementioned symptoms due to the disease itself, the cancer-related symptoms could be related to the cancer treatment (C. S. Cleeland, 2007; Charles S. Cleeland et al., 2003). The disease- and treatment-related symptom clusters might be due to the action of pro-inflammatory cytokines on central and peripheral nervous system as evidenced in both animal models and clinical studies. All these factors play a role in emotional distress among cancer patients.

It is evidenced that patients diagnosed with cancer not only suffered physically, but a great proportion of them also experienced significant amount of psychological distress (Barre et al., 2018; Kadan-Lottick et al., 2005). Studies have shown that cancer

patients are at greater risk of developing mental health problems such as depression and anxiety (Carlsen et al., 2005; Hegel et al., 2006; Spiegel & Giese-Davis, 2003)

Apart from emotional distress, fatigue is known to be one of the most prevalent symptoms reported by patients with cancer (Banipal et al., 2017; Barsevick et al., 2008). It has been observed in patients with different types of cancer (Cella et al., 2001; Maarten Hofman et al., 2007) Cancer-related fatigue is defined as a "persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning" (National Comprehensive Cancer Network, 2003). It could be perceived in the form of physical, emotional or cognitive fatigue (Barsevick et al., 2008). Cancer-related fatigue is different from the characteristic fatigue experienced by most people due to the usual daily life. It does not correspond to the level of exertion by patients, and does not relieved by rest (Morrow et al., 2005).

Cancer patients perceived cancer-related fatigue subjectively during their treatment and some experienced it for months to years after the completion of their treatment. Therefore, before labelling the fatigue as cancer-related, thorough assessment should be done. One has to rule out other possible causes of fatigue such as haematological or endocrine cause, psychological problems such as depression or sleep disturbances (Bower et al., 2014). Due to the significant functional impairment as well as its negative impact on the quality of life, cancer patients often describe cancer-related fatigue as the most distressing symptom.

With the advancement of treatment modalities for various types of cancer, the life expectancy of cancer patients is noted to be increased. As a result, the burden related to cancer-related fatigue is also on the rise (Banipal et al., 2017; Loge et al., 2000). Loge, Abrahamsen, Ekeberg and Kaasa (2000) had described the impact of cancer-related fatigue on cancer treatment, be it the timing or completion of treatment regime. This could

be explained by fatigue being a dose-limiting adverse effect, or its impact on patients' treatment adherence.

Increasing number of clinicians and researchers have recognised the significance of cancer-related fatigue in the recent years. In 1998, cancer-related fatigue was accepted as a valid clinical diagnosis in the International Classification of Diseases, Tenth Revision (Maarten Hofman et al., 2007). National Institutes of Health and the National Comprehensive Cancer Network (NCCN) had published clinical practice guidelines for the management of cancer-related fatigue in year 2000 (National Comprehensive Cancer Network, 2003).

As cancer-related fatigue has received more attention in the recent years, several methods have been demonstrated to measure fatigue among cancer patients (Hann et al., 2000). Fatigue Symptom Inventory (FSI) is among the validated scale developed to measure the intensity, duration of fatigue and total perceived interference to daily life (Hann et al., 1998). Till date, there is no study on the cancer-related fatigue among patients diagnosed with cancer in our local setting. Our study intended to look at the prevalence of cancer-related fatigue among our local population using the proposed ICD-10 criteria for cancer-related fatigue.

CHAPTER 2: LITERATURE REVIEW

2.1 Cancer and Disease Burden

Cancer is a major health issue worldwide. World Health Organisation estimated that more deaths have occurred as a result of cancer compared to cerebrovascular accident or coronary artery disease (World Health Organisation, 2011). According to International Agency for Research on Cancer, WHO (2020), there were approximately 19.3 million new cases of cancer and 9.96 million deaths in 2020. Every one in five men and one in six women would be diagnosed with cancer, whereas cancer-related death occurs in every one in eight men and one in ten women (The Lancet, 2018).

The disease burden is expected to increase. It is predicted that by year 2040, the number of new cases of cancer would have a leap to 30.2 million, with the cancer-related deaths increased to 16.3 million (International Agency for Research on Cancer, 2020). The rise of cancer incidence is the result of population growth and aging, and increasing human development, in terms of economic, societal and lifestyle changes. (Fidler et al., 2018; The Lancet, 2018).

According to World Health Organisation (2020), lung cancer is reported to be the most commonly diagnosed cancer, followed by breast cancer, prostate cancer and colorectal cancer. Lung cancer is also ranked highest for cancer death, followed by colorectal cancer and stomach cancer. It is estimated that 70% of the cancer-related deaths occur in low-income and middle-income countries, out of which 58.3% of the mortality occurred in Asia (World Health Organisation, 2020b; World Health Organisation, 2020a). Countries with low and medium Human Development Index (HDI) are expected to have 80%-100% increase in cancer incidence from year 2008 to 2030 (Fidler et al., 2018).

Globocan has reported that Malaysia has total of 48639 new cancer cases in year 2020 across total population of 32.4 million, with 29530 cancer-related deaths. Across both sexes, breast cancer ranked the top followed by colorectal cancer and lung cancer. Lung cancer has resulted in the highest number of cancer death, followed by breast cancer and liver cancer (International Agency for Research on Cancer, 2020).

Cancer in Malaysia is alarming as the incidence is expected to increase due to aging population (National Cancer Institute, 2019). The high prevalence of smoking among Malaysia population will further worsen the situation as tobacco use is a significant contributing factor to cancer death. Almost half of the male population in Malaysia are smokers, and more than 90% of the male lung cancer patients reported significant smoking history (Rajadurai et al., 2020). Malignancy of respiratory tract has contributed 2.4% of total death in Malaysia (Department of Statistic Malaysia, 2020).

Despite advances in cancer treatment, cancer treatment is less effective in reducing mortality as compared to other non-communicable diseases. Lifestyle and environmental modifications serve as the mainstay to improve disease burden. Several potentially modifiable risk factors have been described by few studies. Tobacco use, alcohol use, low fruit and vegetable intake were the commonest risk factors identified globally that contribute to cancer-related death. Slight discrepancy noted in high income countries where overweight and obesity overtake the fruit and vegetable intake as the third leading risk factor of cancer death (Danaei et al., 2005; World Health Organisation, 2000).

Infection is another strong modifiable risk factor for cancer. In 2018, there were approximately 2.2 million new cancer cases reported to be infection-related. Helicobacter pylori is found to be the leading pathogen, followed by Human Papilloma virus (HPV), Hepatitis B virus and Hepatitis C virus (de Martel et al., 2020). Infection-related cancer incidence was reported to be highest in eastern Asia and sub-Saharan Africa (Bray et al.,

2018). Helicobacter pylori being the most important infectious cause of cancer globally, its successful screening and treatment help to combat the infection and reduce the incidence of stomach cancer to certain extent. HPV, Hepatitis B and C virus are highly linked to cervical cancer and liver cancer respectively. Vaccination towards HPV and Hepatitis B virus is effective in preventing the new cancer cases every year (International Agency for Research on Cancer, 2018; Plummer et al., 2016).

Cancer burden can be reduced by modification of risk factors and cancer prevention programmes. Lifestyle modifications such as tobacco cessation, balanced diet, moderate alcohol consumption and physical activity are recommended by various organisations. Vaccination is another prevention strategy carried out worldwide including Malaysia. Mandatory vaccination programme towards HPV and Hepatitis B virus has been implemented in Malaysia as a strategy to reduce occurrence of cervical cancer and liver cancer respectively. Screening and early diagnosis are essential steps for early detection and early treatment to improve quality of life on cancer patients (American Cancer Society, 2012; World Health Organisation, 2020).

2.2 Cancer-related Fatigue

2.2.1 Concept of Cancer-related Fatigue

Fatigue being the commonest symptom experienced by patients diagnosed with cancer (AD & CA, 2001), it was distressing and has debilitating effect on the quality of life of the patients as well as their family. Cancer-related fatigue is perceived subjectively by cancer patients as sustained exhaustion both physically and mentally, as a result of disease or treatment-related, and is hardly alleviated by rest (Narayanan & Koshy, 2009). The prevalence rate was reported to be as high as 96% among patients receiving treatment (Wagner & Cella, 2004).

Cancer-related fatigue has multiple dimensions and various contributing factors. Till date, little have we known about the mechanism underneath, despite various studies have been conducted over the past twenty years to examine the pathophysiology (HB, 2001). Many researchers have tried to identify the possible contributing factors of cancer-related fatigue from different aspects. The different dimensions identified included direct effect of cancer burden, treatment-related, pre-existing medical illness, chronic physical symptoms and psychosocial aspects (Wagner & Cella, 2004; Wang, 2008).

Previous literatures have reported that there were few different hypotheses postulated for cancer-related fatigue. Anaemia was one of the frequently studied mechanism. Other than that, abnormality of adenosine triphosphate (ATP) metabolism, dysregulation of serotonin, dysregulation of pro-inflammatory cytokines, vagal afferent activation, disruption of hypothalamic-pituitary-adrenal axis and circadian rhythm were also reviewed (Morrow et al., 2002; Ryan et al., 2007).

Being multifactorial, researchers have great difficulties to determine the exact causation of cancer-related fatigue. National Comprehensive Cancer Network (NCCN) has published a list of the contributing and associated factors related to fatigue. The disease itself, anemia, treatment modalities which include chemotherapy, radiotherapy, immunotherapy and bone marrow transplant were among the causes identified for cancer-related fatigue. Other factors such as psychological distress, medical comorbidities, pain, trouble sleeping, cardiac deconditioning and so on were reported to be the significant associated factors (Wang, 2008).

There were variations of incidence rate of fatigue observed in different group of cancer patients. For instance, among patients with lung cancer undergoing treatment, the prevalence rate was reported to be range from 37% to 78%. As high as 91% of patients with breast cancer have reported fatigue, whereas the fatigue rate for patients with prostate

cancer could be as low as 15% (Maarten Hofman et al., 2007). In another study conducted among cancer patients receiving chemotherapy or radiotherapy in outpatient setting, more than 80% of them experienced certain degrees of fatigue (Hickok, Morrow, et al., 2005). Similar result was seen in a study among breast cancer patients undergoing radiotherapy. 84% of them reported fatigue, followed by other symptoms such as pain and nausea (M. Hofman et al., 2005).

Cancer-related fatigue has been observed among cancer patients throughout the course of their malignancy. It could present prior to the diagnosis, while undergoing treatment, or even persisted for years after completion of cancer treatment (Curran et al., 2004). A study conducted among 763 breast cancer survivors has shown that approximately 35% of patients still experiencing fatigue 1-5 years and 5-10 years after completing treatment (Bower et al., 2006).

Cancer-related fatigue not only affect the patients physically, it also has great impact on the psychosocial, occupational and economical aspect of the patients (Gupta et al., 2007). Curt et al. has examined impact of cancer-related fatigue among 397 cancer patients. More than 90% of the study participants reported that they were forced to have an 'abnormal' life or change of routine as a result of fatigue (Curt et al., 2000). Some reported that fatigue has greater negative impact in their life as compared to cancer-related pain (Wagner & Cella, 2004). Cancer patients have difficulty to return to work as a result of fatigue, causing them to face more financial burden (Islam et al., 2014). The economic burden not only affecting the patients, it also involved the family members or caregivers. Their job was affected as some of them need to cut down the working hours in order to take care of cancer patients. Some of them even have to give up their job to provide care.

Psychological impact was also observed in fatigued patients. Depression and anxiety were frequently found to be correlated with cancer-related fatigue (Brown &

Kroenke, 2009). The daily living or self-care of patients might be affected, and there might be interference with the cancer treatment as a negative consequences of emotional disturbance, which might shorten the survival times. A study among lung cancer patients has reported improvement in psychological distress after improvement in fatigue. Hence intervention targeted at fatigue might be useful in managing the emotional symptoms (Tchekmedyian et al., 2003).

2.2.2 Distinguishing Fatigue and Depression

Clinicians often have difficulty in differentiating fatigue and depression among cancer patients in clinical practice due to their overlapping symptoms. Strong association has been demonstrated between the two. Fatigue was said to precede clinical depression, that depression arose as a result of chronic stress and exhaustion. On the other hand, some said that fatigue could occur within the context of depression or worsened because of depressed mood. Furthermore, both fatigue and depression can be attributed to a similar aetiology (Paul B Jacobsen, Kristine A Donovan, 2003).

Fatigue was described as a multidimensional concept, consisted of physical, emotional and cognitive domains. Physical symptoms such as lack of energy and reduction in activity were described in physical domain. Emotional domain consisted of stress, anxiety and sadness. Impairment of attention and concentration was included in cognitive domain. All these symptoms were found to correspond to depressive symptoms. For instance, somatic symptoms and loss of energy described in depression correspond to physical domain of fatigue. Depressed mood, lack of pleasure or anhedonia, psychomotor agitation in the context of depression correspond to emotional domain of fatigue. Cognitive symptoms and sleep disturbance were similar in both context (Reuter & Härter, 2004).

By comparing the symptoms of each domains using this concept, it was evident that symptoms of fatigue corresponded to those of depression. Symptoms of fatigue could be described as a subset of depression, as psychological symptoms which were more distinct for depression were further described in the broader concept of depression. In terms of cognition, depressed individual tends to have pessimistic thoughts about self, world and future (Pössel & Pittard, 2016). They would self-devaluate, felt hopeless, worthless, and became suicidal when depression worsened. In addition, individual who are depressed were more likely to self-isolate and reduce social interaction with surrounding people, resulting in difficulty in their interpersonal relationship. These psychological symptoms and interpersonal difficulties might jeopardise the cancer treatment.

Due to the overlapping symptoms and mechanism, there was consistent positive correlation observed between cancer-related fatigue and depression (Servaes et al., 2002). The proposed ICD-10 criteria was then developed to improve the evaluation of fatigue (Reuter & Härter, 2004).

2.2.3 Diagnosis and Measurement of Cancer-related Fatigue

Since cancer-related fatigue is commonly experienced by our cancer patients, there is a need for proper measurement. However, being multidimensional in nature, and no consistent findings over literature, the definition and measurement of fatigue has been challenging. There was no specific tool to evaluate fatigue and thus clinicians were facing difficulties in the proper assessment and management. A group of medical personnel, patient advocates and researchers have formed Fatigue Coalition and proposed diagnostic criteria in 1998 (Cella et al., 2001).

According to the proposed International Classification of Diseases-10 (ICD-10) criteria for cancer-related fatigue, the individual needed to experience significant amount of fatigue, which was not proportionate to the daily activity, or there might be reduced energy level or increased rest for at least 2 weeks, along with other related physical symptoms. There were few other conditions needed to be ruled out to ensure a proper case definition of cancer-related fatigue. When fatigue coexist with psychiatry diagnosis such as depression, the clinicians might have difficulty to determine whether fatigue was due to malignancy or psychiatry illness (Wagner & Cella, 2004).

The proposed ICD-10 criteria was tested among 379 cancer patients undergoing treatment by Cella and colleagues (2001). A lower prevalence of fatigue was reported (17%) compared to other literature, possibly due to the more stringent criteria. The diagnostic criteria was further evaluated in 2002 and good evidence of validity and reliability has been demonstrated (Sadler et al., 2002). More persistent, severe and frequent fatigue as well as depressive symptoms were reported by those who fulfilled criteria. On top of that, fatigue also interfered more in their daily living compared to their counterpart. Due to the overlapping symptoms of depression, the diagnostic criteria might be beneficial in recognising fatigued patients who might respond to antidepressant (Paul B Jacobsen, Kristine A Donovan, 2003).

On the other hand, Seyidova-Khoshknabi and team has reviewed various assessment tools of cancer-related fatigue. In the systematic review, total of 40 scales were identified, and 37 of them were multidimensional (Seyidova-Khoshknabi et al., 2011). The assessment tools differ from each other in terms of their psychometric properties, domains, stage and site of cancer. Brief Fatigue Inventory (BFI) and Functional Assessment of Cancer-Therapy- Fatigue Subscale (FACT-F) were among the unidimensional scales identified. BFI was used to assess fatigue severity.

Fatigue Symptom Inventory (FSI) was one of the multidimensional assessment tool developed. It has total of 14 items to measure the intensity, duration and daily pattern of fatigue. It has been translated into Chinese version and both version have been demonstrated to be a valid and reliable instrument to assess fatigue across different groups of cancer patients. FSI has been demonstrated to be sensitive throughout the course of malignancy, and has very good completion rate of 98% (S. Shun et al., 2007; S. C. Shun et al., 2006). This is an important point to note as certain scales with 30 or more items would be challenging for the patients to fill in especially for those with severe fatigue. Therefore, it would be essential for future researchers to evaluate the optimal number of items, domains in an assessment tool, in order to improve the scale completion rate (Seyidova-Khoshknabi et al., 2011).

2.3 Cancer and Psychological Distress

The most unsettling part of being a physician is the time when one need to reveal the diagnosis of cancer to the patient under their care. While years of training and experience prepare them to break the bad news with empathy, it will nevertheless leave an impact on the patient.

Often time, we witness patients receive the news with a varying degree of grief (Hamilton, 2016). Some patients reacted angrily to the diagnosis and renounce the diagnosis. These patients often went around doctor shopping with the hope that the diagnosis made was in error or somehow, they miraculously cure from the disease. On the other hand, some patient reacted negatively to the diagnosis and stay in denial. They refuse to acknowledge the diagnosis and try to live their life as normal as the possibly could. Moreover, some will start bargaining and no less, turn to alternative therapy as they struggle to accept the fact. There will also be patients who fall into depression upon

hearing the diagnosis. All the mentioned stages of grieving will very often prolong the duration between diagnosis and initiation of treatment, which leads to poorer outcome. Therefore, it is very important for a physician to be well equipped with necessary clinical skill to recognized psychological distress in cancer patient. A prompt referral will lead to proper evaluation and adequate support for the patient.

Regrettably, clinician often underestimates the psychological impact of cancer on their patients. There is especially true for certain cancer whereby the prognosis is excellent, or state of the art treatment is readily available. However, in a study by C Lavelle et al., they had debunked that belief. The study found that the level of distress in cancer patient have no association with the cancer type. Thus, focus and psychological support should be readily available to patient whom are diagnosed with cancer, regardless of the type, prognosis and stages of their disease (C Lavelle, M F Ismail, K Doherty, A Bowler, M M Mohammad, 2017).

In a study by Birgitte Goldschmidt Mertz et al., it was found that 77% of newly diagnosed breast cancer patients reported to be suffering from psychological distress. This provide an insight that on a given oncology clinic, up to two third of the newly diagnosed patient will need some form of psychological support by the healthcare personnel. It will do patient a disservice if such service is not made available to them (Mertz et al., 2012).

While onset of psychological distress is common, it does not necessarily confine only to the beginning of the diagnosis. Repeatedly, we failed to pick up psychological stress among patient who is undergoing treatment or whom had completed a course of therapy. In the study by Elizabeth et al., it is noted that there is an overlapping acute and chronic psychosocial distress experienced by cancer patient, post operatively. It could surface as soon as immediate post-operative period. Therefore, on-going assessment for

psychological distress should also be done for patient under treatment, as they are as vulnerable psychologically as those who are newly diagnosed (Ercolano, 2017).

2.4 Depression in Patients with Cancer

Depression is one of the common psychological impact experienced by cancer patient. This adverse emotion is not only felt by the patient themselves but also vibrated to their caregiver. Often time, they are under recognized and under diagnosed. This is not surprising due the sheer number of oncology patient in each clinic sessions. On top of that, the wide spectrum and stages of depression, which could present as inconsequential as normal sadness to a variety of mood disturbances, makes the recognition challenging.

In a study by Ng et al., the pooled prevalence of depression in cancer patients was 10.8% (Guan et al., 2011). Separately, Mary Jane Massie et al., insinuated that the prevalence of depression in cancer patient could range from 0% to 58%, based on more than 100 studies. The cancer site and stage of the illness were associated with varying degree of depression. For instances, cancer such as oropharyngeal (22%–57%), pancreatic (33%–50%), breast (1.5%–46%), and lung (11%–44%) cancers, were among cancer with high prevalence of depression. On the other hand, colon (13%–25%), gynaecological cancer (12%–23%), and lymphoma (8%–19%), reported a slightly lower prevalence of depression among the patients (Massie, 2004). Therefore, close attention of patient psychological needs is crucial as part of their disease management.

Nonetheless, there are many confounding factors that contribute directly and indirectly to onset of depression in cancer patient. There is a local systemic review that look into the papers of the prevalence and associated factors of depression in breast cancer survivor. The team led by Zuraida Z. et al. understood the high prevalence of depression among cancer patients. Therefore, in their papers they set forth to look at the multiple

variables that could lead to the onset of depression. It is an extensive paper which delve into 32 high impacts papers. In their conclusion, they summarized that breast cancer survivors whom were at risk for depression were generally contributed by several factors such as low socio-demographic, illness with poor prognostication, sedentary lifestyles, ongoing treatment, i.e. chemotherapy and lack of psychological support i.e. widowed, divorced or unmarried (Zainal et al., 2013). Therefore, it is important for practicing clinicians to offer psych-oncology care on top of their regular treatment.

This finding was further supported by a local study by Ng et al., whereby breast cancer patients at the University Malaya Medical Centre were enrolled into the study (Ng et al., 2015). The patients were assessed at baseline, 6-month and 12-months period. They found that this cohort of patients had rather low levels of depression and anxiety, and high quality of life at the time of diagnosis. They also did not notice any changes to the level of depression at 6 months and 1 year. This could be explained by the patient's global health status and good social support. The data indicated that the perceived social support remained high throughout the 12-months period of study. Therefore, we could conclude that external factors play an important role in minimizing the risk of depression in oncology patients.

It is important to recognized depression early and identify the protective factor as it will have an important impact on patient outcome. In a meta-analysis by Pinquart and Duberstein, they established a finding whereby depression is associated with higher risk for mortality in cancer patients, either new or ongoing treatment. This is especially so in patient with shorter time intervals and in older cohort (M. Pinquart, 2010). Therefore, we hope by recognizing and treating depression in a timely manner, we could alter the outcome of our cancer patient.

2.5 Anxiety in Patients with Cancer

From a patient perspective, being diagnosed with cancer will throw a spanner in their work literally. It is usually a life changing events that could change a person outlook utterly. It not uncommon to see radical changes in one personality. The diagnosis can even negatively impact their relationship with colleagues, friends and family.

Being face with uncertainty and fear of the unknown, many patients will undoubtedly feel anxious about the fate that befall them. The study by G G Gan et al. demonstrated the high prevalence of anxiety in patient newly diagnosed with cancer. It was noted that up to thirty-three percent of patients undergoing treatment were suffering from anxiety. It was found that those who showed anxiety symptoms were more often female who are still undergoing treatment (Gan et al., 2019). Thus, it is important to identify the symptoms among the vulnerable group so that successful treatment can be achieved.

Furthermore, some studies found that anxiety could be more prevailing in cancer patient even more so than depression. In a study by Ng et al., they noted that 50.2%, 51.6% and 40.3% of patients had perceived high level of distress at baseline, 6 months and 1 year after diagnosis. However, as the anxiety score reduced, so did the reported distress level. This was not visible in patient with depression, as even with improved depressive scores, there was no positive correlation with level of distress reported by patient. Therefore, the paper concluded that in comparison with depression, anxiety has a more profound contribution to the feeling of distress in breast cancer (Ng et al., 2017).

Nevertheless, not everything is sad and gloomy for cancer patient. In a study by Leong Abdullah et al., patients who were diagnosed with head and neck cancer within a year were recruited. This cohort was then followed up for the period of 6 months. The study concluded that there were reduction in depression and anxiety within a year of

cancer diagnosis (Leong Abdullah et al., 2015). This illustrated perfectly that as patient goes along the journey of recovery, some do feel less anxious compared to when they first started off. Therefore, it is of paramount important that proper explanation was given to patient as they undergone treatment. It is also worthwhile to continuously provide encouragement and support to the patient. Having a better understanding of their condition and shared decision making in treatment will make them feel better about the whole experience.

There are several interventions which could be deployed to reduce anxiety among cancer patients. A study conducted by Helena et al. looked at efficacy of support group intervention among the cancer patients. They recruited newly diagnosed primary breast cancer patient into an intervention and control group. In the intervention arm, patients would have group sessions with their oncologist about their condition and questions from fellow participants were freely shared and discussed. They were also being attended by psychologist who trained them on coping strategies. In addition, they also gained access to support team like social worker, who, generously shared community resources information, such as being on the sick-list, insurances and economic aid which they can tap into. Patients also being exposed to the importance of food and nutrition by their nutritionist. The intervention group also had relaxation training, physical activities like Qigong, mental visualisation and non-verbal communication (art and liberating dance therapy) provided to them. The team also arranged social activities to make their day more vibrant by arranging visits to places like museum, restaurant and even a concert. This enabled them to hang out with individual of similar situation. Plus, it also enabled them to escape the trouble and burden at home. Meanwhile, the control group just received standard routine follow up. Not surprisingly, at the end of the study the support group intervention reported a lowered anxiety over time. Therefore, this study showed that

cancer patients should be cared for in a multidisciplinary approach (Björneklett et al., 2012).

2.6 Demoralisation in Patients with Cancer

There is increasing attention to demoralisation among cancer patients by the hospice and oncology team. Being a relatively new concept, demoralisation has been recognised as a relevant clinical condition to be assessed and treated (Fang et al., 2014). Before demoralisation was officially proposed, demoralisation was described as a complex psychological state of discouragement, poor coping, hopelessness, helplessness and low self-esteem by Engel and Frank respectively (Bovero et al., 2019).

The concept of demoralisation was officially proposed in 2001. Kissane and colleagues described demoralisation as distress or mental state of lower morale, which occurred as a consequence to adverse life events which could affect patient's integrity and quality of life. For instance, patients demoralise after suffering from chronic medical illness (Kissane et al., 2004; Robinson et al., 2015).

Demoralization is often seen in the same light as depression. However, this cannot be further away from the truth. While both can coexist at the same time in a cancer patient, there are fine distinctions between these two conditions.

As with depression, demoralization can also present in multitude of form like mild loss of confident, dishearten, losing hope and despair. In its worse form, severely demoralized patient will loss the purpose and meaning of life. As we readily know, once a patient loses their hope, their body will follow soon. In a nutshell, the loss of desire to live will hasted their departure.

Recognition of this concepts is important, as demoralization, like any diseases, is a treatable condition. Robinson et al. proposed a simple concept to differentiate depression and demoralization. They can be distinguished as depression core features are loss of pleasure and interest in the present moment. Meanwhile demoralization core features are a loss of hope and meaning. In addition, patients also suffer a loss of anticipatory pleasure rather than general anhedonia (Robinson et al., 2015).

Meanwhile, J. Ignatius and R. De La Garza defined demoralization as a mental state of low morale and poor coping which encompasses; pessimism, helplessness and hopelessness. Eventually this leads to loss of meaning and purpose in life (Ignatius & De La Garza, 2019).

In the same study, they found that despite depression and demoralization being distinct, there is a strong positive correlation between depression and high demoralization. So, it proves that these conditions often coexist hand in hand. Yet, there is also instances where patient reported low depression but high demoralization symptoms. Predictably, the research team postulate that this population tends to respond poorly to antidepressant, and they respond best to centred psychotherapies and symptom burden alleviation. In short, we should review our diagnosis if a patient responded poorly to antidepressant, to avoid overlooking the diagnosis of demoralization.

The importance of detecting demoralization and treating it cannot be overstated. The number of cancer patient contemplating suicide as a permanent solution to their problem is astounding (Daniel C. McFarland, Leah Walsh, Stephanie Napolitano, Jody Morita, 2019). Fortunately, in terms of absolute number, it is not as alarming. Nonetheless, demoralization is identified as one of the contributing factors. Therefore, we should be mindful if we come across demoralized cancer patient.

In short, cancer-related fatigue, depression, anxiety and demoralization are prevalent among patients diagnosed with cancer. It is important to study their relationship and the screening should be made part of our routine assessment in daily clinical practice due to their detrimental effect on the quality of life of cancer patients. The conceptual framework of this study was described in Figure 2.1.

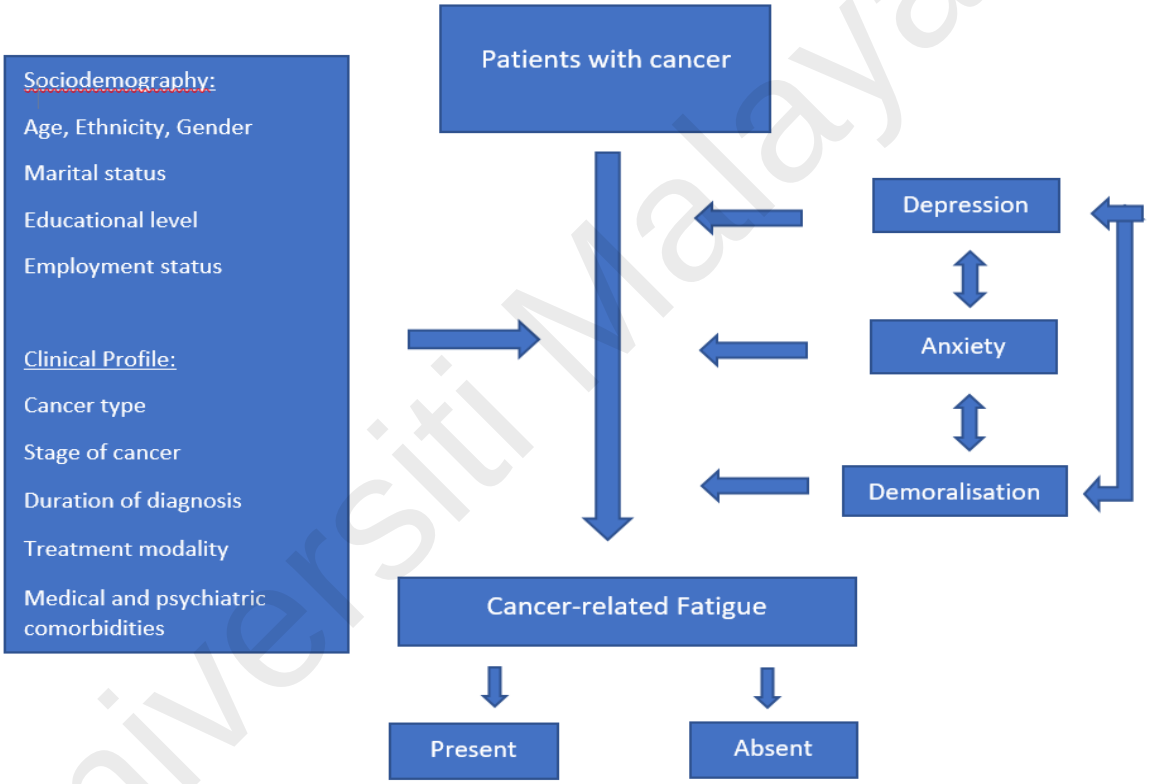


Figure 2.1: Conceptual Framework

CHAPTER 3: RATIONAL, OBJECTIVES AND RESEARCH HYPOTHESIS

3.1 Rationale of the Study

Cancer-related fatigue is well-known to be a virtually universal symptom among patients with advanced cancer. Unfortunately, cancer-related fatigue remains under-recognized, under-evaluated and under-treated. The routine assessment of cancer-related fatigue is rarely practiced in many settings, and there is no proper recommended treatment in existing guideline.

To date, there is no local study regarding cancer-related fatigue among cancer patients. Proper study needs to be conducted to investigate further regarding cancer-related fatigue and its rightful management. By appropriate assessment and better recognition of cancer-related fatigue, the therapeutic alliances between patient and physician would be improved.

By early identification of cancer-related fatigue and others associated factors, it will aid the clinician to deal with cancer patients more holistically. By doing so, it will also help in preventing severe complication such as suicide action among them and other psychological comorbidities like anxiety and depression. Eventually, it will promote patient with cancer to improve their daily activities thus afterward more opportunities to benefits promising enhanced quality of life.

3.2 Objectives of the Study

The study objectives are as follow:

1. To determine the prevalence of cancer-related fatigue (CRF) among patients who had been diagnosed with cancer.

2. To examine the sociodemographic risk factors that associated with cancer-related fatigue.
3. To determine the clinical associated factors of cancer-related fatigue among cancer patients, such as status of the illness, type of cancer and stages, treatment modalities, any psychological comorbidities related to cancer such as anxiety, depression and demoralisation.
4. To determine the correlation between cancer-related fatigue and depression, anxiety and demoralization.

3.3 Research Hypothesis

1. Both sociodemographic and disease-related variables are associated with cancer-related fatigue.
2. Cancer-related fatigue is positively associated with depression, anxiety and demoralisation.
3. Cancer-related fatigue is positively correlated with depression, anxiety and demoralisation.

CHAPTER 4: METHODOLOGY

4.1 Study Design and Sample

The study is a cross-sectional study conducted from July 2020 until Dec 2020 in Clinical Oncology Clinic, University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. All outpatients who had been diagnosed to have cancer, confirmed with the histopathological result, whom are enrolled in follow up by Clinical Oncology Clinic, and eligible for the study are invited.

4.2 Sample Size Calculation

The sample size was calculated using a formula proposed by Daniel (1999). It is estimated that approximately 94.8% of cancer patients who are undergoing cancer treatments experience fatigue (Hwang et al., 2016).

$$n = \frac{Z^2 P (1-P)}{d^2}$$

where n: sample size

Z: Z statistic for a level of confidence, 1.96

P: Estimated prevalence of cancer-related fatigue (95%)

d: Desired precision set at 0.04

Hence, n = 3.8416 x 0.95(1-0.95)/0.0016

= 0.182476/0.0016

= 114

Therefore, the minimum sample size required is 150 subjects, inclusive the additional 30% of possible missing data.

4.3 Selection Criteria

4.3.1 Inclusion Criteria

1. Subjects who are diagnosed with any type of cancer and receiving treatment in Clinical Oncology Unit, UMMC.
2. Subjects who are capable of understanding and reading Malay or English.
3. Subjects who are above the age of 18.
4. Subjects who gave consent with regard to participation of this study.
5. Subjects who do not have major/ acute psychiatric disorder.

4.3.2 Exclusion Criteria

1. Subjects who have severe psychiatric illness or psychosis.
2. Subjects with acute medical illness and unstable.

4.4 Assessment Tools

4.4.1 Sociodemographic and Clinical Profile Questionnaire

Electronic questionnaire was used to gather sociodemographic data and clinical profile of cancer patients such as age, gender, ethnicity, marital status, educational level, employment status, diagnosis, stage of cancer, comorbid medical illness and psychiatry illness.

4.4.2 Proposed ICD-10 criteria for Cancer-related Fatigue

Fatigue was assessed using the proposed ICD-10 criteria for cancer-related fatigue. The criteria was first proposed in 1998 by Cella et al. and subsequently accepted in International Statistical Classification of Diseases and Related Health Problems (10^{th} revision) (ICD-10) (Cella et al., 2001). A structured diagnostic interview guide was also developed to help with the assessment.

There were 4 parts (A, B, C and D) in the proposed criteria. One has to fulfill all 4 criteria in order to be diagnosed as cancer-related fatigue. Criteria A contains 11 items. The first question asking about the presence of significant fatigue, diminished energy or increased need to rest, which was out of proportion to the recent change of activity level. The remaining 10 questions enquired about the common fatigue-related manifestations. In order to fulfill Criteria A, at least 6 or more symptoms need to be present for every day or nearly every day for at least a 2-week period in the past month prior to assessment, and the first item must be included.

The next 3 parts were asked to rule out non-CRF. There must be significant distress and functional impairment as a result of the aforementioned symptoms in Criteria A. In addition, the symptoms must be cancer-related or cancer treatment-related, and not due to psychiatric comorbidities.

The proposed criteria for fatigue has been validated in 2005 via comparison with other scales such as Visual Analogue Scale (VAF) and Functional Assessment of Cancer Therapy Fatigue (FACT-F) (Van Belle et al., 2005). It was reported to have very good internal consistency, with alpha coefficient of 0.82. The criteria has been translated and validated in other country like Taiwan. The Chinese version was shown to be a reliable tool with good internal consistency (Cronbach's alpha of 0.84) (Yeh et al., 2011). Due to

its good psychometric properties, the criteria was recommended to be used to identify fatigued patients.

4.4.3 Fatigue Symptom Inventory (FSI)

Fatigue Symptom Inventory (FSI) was first introduced in 1998 (Hann et al., 1998). It is a commonly used tool to assess fatigue among patients diagnosed with cancer. The psychometric properties of FSI was originally assessed in a sample of women receiving treatment and completed treatment for breast cancer, and those without cancer. It was proven to be a valid and reliable assessment scale among patients with breast cancer and general population (Dittner et al., 2004). FSI was further validated to assess fatigue in various types of malignancy (Hann et al., 2000). A systematic review of FSI psychometric properties strongly suggest researchers to use FSI in their studies due to current extensive evidence (Donovan & Jacobsen, 2011).

FSI is a self-report assessment scale consisted of 14 items. It assesses different dimensions of fatigue namely fatigue severity, frequency, perceived interference associated with fatigue and daily pattern of fatigue in the past week.

Items 1 to 4 measures the severity of fatigue in a Likert scale range from 0 (not at all fatigued) to 10 (as fatigues as I could be). Participants would score their fatigue level based on most fatigue (FSI most), least fatigue (FSI least), on average (FSI average) and fatigue right now. FSI composite is calculated based on the average of the 3 severity items (FSI most, least and average). FSI composite has high internal consistency (alpha = 0.84). Cut-off value of ≥3 for FSI composite is used to determine clinically meaningful fatigue (Donovan et al., 2008).

Items 5 to 11 measure the perceived interference due to fatigue on a Likert scale range from 0 (no interference) to 10 (extreme interference). The interference items

measure the degree to which in the past week, fatigue interfered with general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relation with other, enjoyment with life and mood. The scores of these 7 items can be summed up to get the Total Disruption Index. The total score can also be averaged to get the interference scale (FSI interference). The higher the score, the more interference of fatigue with life.

Item 12 and 13 measure number of days in the past week that patient felt fatigue (0-7 days) and how much on average patient felt fatigue in a day (0 = none of the day, 10 = entire day). The last item is qualitative and measures the daily pattern of fatigue.

4.4.4 Hospital Anxiety and Depression Scale (HADS)

HADS is a self-rated scale that has been extensively used for screening for depression and anxiety in our clinical practice. It was first introduced by Zigmond and Snaith in 1983 (Zigmond & Snaith, 1983). It consisted of 2 subscales, namely Depression and Anxiety, with 7 items in each subscale. For each item, there are 4 points range from 0 to 3 (total score range of 0 to 42). Respondents need to score which point best describes how they have been feeling in the past week. The two subscales are summed up separately to come to a total score of depression and anxiety. Score of 0 – 7 indicates normal result, 8 – 10 indicates borderline case, whereas 11 - 21 indicates clinical case of depression or anxiety (Michopoulos et al., 2008). The Malay version of HADS has been validated among a group of cancer patients in local setting (Lua PL, 2012). It has good reliability and validity to be used as a screening tool for anxiety and depression among cancer patients.

4.4.5 Demoralisation Scale (DS)

Demoralisation Scale (DS) is a self-rated scale first introduced in 2004 to assess demoralization and help with the management in palliative care (Kissane et al., 2004). It was tested among 100 patients with advanced cancer in Australia to assess their existential distress for the past 2 weeks. It composed of 24 items and a 5-point Likert scale was used for each item for respondents to denote how much they agree for each item. For each response, it represents frequency of occurrence, with the range from 0 (never), 1 (seldom), 2 (sometimes), 3 (often) to 4 (all the time).

Out of 24 items, 5 items were reversely scored (item 1, 6, 12, 17 and 19). For these items, score 0 represents all the time, score 1 indicates often, score 2 represents sometimes, score 3 represents seldom and score 4 indicates never. The score of each item is summed up to get the total score of demoralization, which can range from 0 to a maximum of 96.

There were five different factors identified in the factor analysis, namely loss of meaning in life (5 items), dysphoria (5 items), disheartenment (6 items), helplessness (4 items) and lastly sense of failure (4 items). An individual was categorized to be highly demoralized by using the cut-off value of 30 (Kissane et al., 2004).

DS is proven to be a valid and reliable assessment tool to measure extent of demoralization and has been translated and validated in many countries (Deng et al., 2017; Grassi et al., 2017; Rudilla et al., 2016). Different factor structures were used in different types of sample population. For instance, among cancer patients at advanced stage (Mehnert et al., 2011; Mullane et al., 2009), patients with and without cancer in palliative setting (Rudilla et al., 2016) and patients with different stages of cancer (Costantini et al., 2013).

The English version of DS has been recently translated into Malay language (DS-M) and validated among cancer patients in our local setting (Chin HL, Ng CG, 2017). DS-M has 24 items, with 5-point Likert Scale used for each item. The options of frequency of occurence for each item and scoring system were similar to the original English version. However, DS-M applied 4-factor structures, as compared to original 5-factor structures. The 4th factor (helplessness) was absent in the study. DS-M has good internal consistency, with Cronbach's alpha of 0.95. The subscales have Cronbach's alpha of 0.81 to 0.92. DS-M used the cut-off value of 23 to differentiate high and low demoralization (Chin HL, Ng CG, 2017).

DS-M has good psychometric properties and was recommended for screening of demoralization among patients with cancer in Malaysia. In the present study, cut off value of 23 was used to determine both high and low demoralization groups.

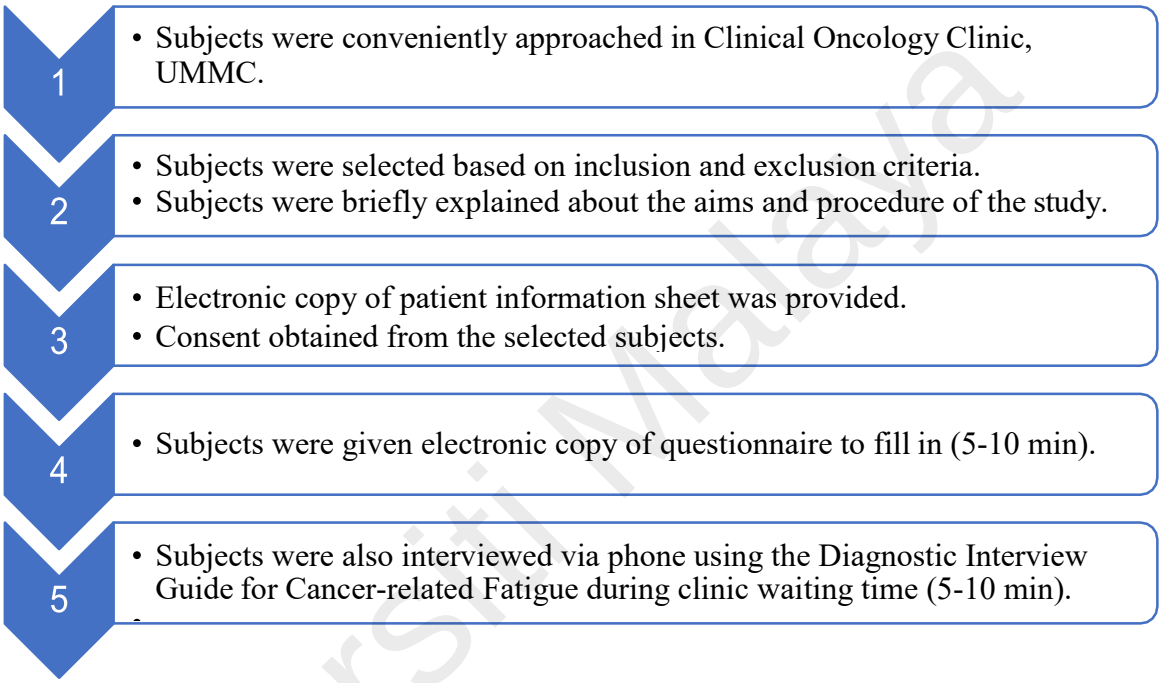
4.5 Data Collection

Participants were recruited from Clinical Oncology Clinic in University Malaya Medical Centre (UMMC) using convenience sampling. They were approached and explained on the objectives and procedure of the study. Participants' confidentiality and rights were emphasized. Patients who fulfilled the inclusion and exclusion criteria of the study and agreed to join the study would be selected.

As the study was conducted amidst Covid-19 pandemic, steps were taken to reduce the contact with patients. All information was provided in the electronic form and patients were interviewed via phone. Electronic copy of patient information sheet and consent were provided for patients to fully understand the study. Participants who have consented for the study would be given an electronic copy of the questionnaire. They would be briefly explained on how to answer the self-assessment scales. The estimated

time taken to fill in the questionnaire was about 5 to 10 minutes. Participants would also be interviewed via phone to assess fatigue using the Diagnostic Interview Guide for Cancer-related Fatigue during clinic waiting time.

Flowchart of the study procedure:



4.6 Statistical Analysis

The data collected were analysed using IBM SPSS statistics version 24. Descriptive statistics and frequencies were generated to describe the sociodemographic data, clinical profile of cancer patients, the scoring of proposed ICD-10 criteria for cancer-related fatigue, FSI, HADS and DS. Spearman's correlation analysis was also used to study the correlation between ICD-10 criteria, FSI (FSI composite and Total Disruption Index), HADS and DS. To compare groups with and without cancer-related fatigue and its associated factors, the following tests were used: independent *T*-test for age, Pearson's chi-square test of independence and Fisher's exact test were used to study the association

and significance of other independent variables. Simple logistic regression was conducted to assess the predictive values of the independent variables.

4.7 Ethical Approval

The study protocol was reviewed by Medical Research Ethics Committee of University Malaya Medical Centre (MREC, UMMC) and approved on 13 July 2020. The MREC ID no given was 202069-8727.

The data collection was started after approval was granted by Medical Research Ethics Committee. The subjects were explained on the objectives of the study and study procedure. Informed consent was obtained before commencement of the study. Patient Information Sheet was provided to participants to ensure that they have understood the study. Participants' confidentiality and their rights to withdraw anytime from the study were emphasized. They were also advised to seek help from psychiatry team if they were noted to have psychological distress.

CHAPTER 5: RESULTS

5.1 Patients

There was a total of 150 cancer outpatients recruited in this study. The mean age of the study participants was 63.3 ± 10.29 years old. Majority of the subjects were more than 65 years old, followed by age group of younger than 60 years old. The remaining 28% of them were in the range of 60 to 65 years old. Majority of the recruited participants were Chinese, followed by Malay population and Indian population. The recruited subjects were predominantly female and married.

For educational level, half of the study population received secondary education, whereas approximately one third of them received tertiary education. Half of the participants were retiree. One third of them were unemployed whereas 15.3% of them were still fully employed at the time of study. Out of 150 study participants, 58.7% of them were diagnosed to have cancer-related fatigue. Detailed sociodemographic characteristics of the study participants are as shown in Table 5.1.

Table 5.1: Sociodemographic data of patients diagnosed with cancer.

Variable(s)	Study population (*N*=150) *n* (%)
Age (in years)	
< 60	43 (28.7)
60-65	42 (28.0)
> 65	65 (43.3)
Ethnicities	
Malay	62 (41.3)
Chinese	74 (49.3)
Indian	14 (9.4)
Gender	
Male	48 (32.0)
Female	102 (68.0)
Marital status	
Married	135 (90.0)
Single	12 (8.0)
Divorced / Widowed	3 (2.0)

Educational level	
None	4 (2.7)
Primary	24 (16.0)
Secondary	77 (51.3)
Tertiary	45 (30.0)
Employment status	
Employed	23 (15.3)
Retiree	78 (52.0)
Unemployed	49 (32.7)
Cancer-related fatigue	
Yes	88 (58.7)
No	62 (41.3)

A vast majority of our patients were diagnosed with solid tumours, with breast cancer being the commonest. Most of our patients were at Stage IV, having had the diagnosis of malignancy between one to five years. Majority of them received chemotherapy or radiotherapy or combination therapy for treatment, with only one fifth of them received other types of treatment. Nearly half of the patients have no known medical illness, with the remaining of them reported to have Diabetes Mellitus, Hypertension and other illnesses. Only 2.7% of the study population have pre-existing psychiatry illness. Table 5.2 further describes the clinical profile of patients diagnosed with cancer in this study.

Table 5.2: Clinical profile of patients diagnosed with cancer.

Variable(s)	**n (%)**
Cancer type	
Breast	50 (33.3)
Gastrointestinal	40 (26.7)
Genitourinary	20 (13.3)
Others	40 (26.7)
Stages of cancer	
I	15 (10.0)
II	31 (20.7)
III	36 (24.0)
IV	68 (45.3)
Duration of diagnosis	
<1 year	18 (12.0)
1 year to 5 years	105 (70.0)
>5 years	27 (18.0)

Treatment modality	
Chemotherapy	39 (26.0)
Radiotherapy	8 (5.3)
Chemotherapy and Radiotherapy	44 (29.4)
Chemotherapy/Radiotherapy and others	30 (20.0)
Others	29 (19.3)
Medical illness	
Diabetes	35 (23.3)
Hypertension	44 (29.3)
Others	4 (2.7)
No	67 (44.7)
Psychiatry illness	
Yes	4 (2.7)
No	146 (97.3)

5.2 Assessment scales

All study participants were assessed using four different types of psychiatric- and oncology-related assessment scales namely the Proposed ICD-10 criteria for Cancer-related Fatigue, FSI, HADS and DS. The participants were categorised based on the respective cut-off values. Demoralization scale has the highest scored range whilst FSI composite scored the least (Table 5.3).

Using the Proposed ICD-10 criteria for Cancer-related Fatigue, participants were categorised into groups of having cancer-related fatigue (≥6 scores) and no cancer-related fatigue (scored <6). The mean score of ICD-10 was 4.8 (SD=3.18). More than half of the study population were having cancer-related fatigue.

For FSI, FSI composite was used to assess fatigue severity among cancer patients. 78.7% of the study populations who scored at least 3 or more were classified as having clinically meaningful fatigue. The mean score was 3.4 (SD=2.16).

Other domains in FSI such as frequency, the perceived interference with daily life and pattern of fatigue were studied as well. For frequency of fatigue in the past week, it has a mean score of 3.4 (SD=2.36), with the range of 0-7. Frequency of fatigue in a day has a mean score of 3.9 (SD=2.36), with the range of 0-10. Total disruption index was used to measure the perceived interference. It ranged from 0-38, with a mean score of

15.1 (SD=9.13). The higher the total disruption index, the more interference of fatigue with patients' daily living. With regards to the daily pattern of fatigue, 66.7% patients reported no consistent pattern, followed by 16% of them reported fatigue more in the evening (data not shown in table).

HADS was used as a screening tool for anxiety and depression among our study population. They were categorised into 3 groups based on different cut-off values. For anxiety subscale (HADS-A), 10% of the patients were having borderline case (score of 8-10) whereas 1.3% of them were having clinical anxiety case (score ≥ 11). 88.7% of those who scored less than 8 were classified as normal. HADS-A has a mean score of 3.0, with interquartile range of 4.00.

The mean score of HADS-D was 5.0 (SD=3.39). 5.3% of the study population were classified as clinically depressed (score ≥ 11) whereas 17.3% of them were having borderline case (score of 8-10). Majority of patients have no depression.

Less than 20% of the study population were highly demoralised (score ≥23) whereas most of them were having low demoralisation level. DS has a median score of 11.0, with interquartile range of 12.00.

Table 5.3: ICD-10, FSI, HADS and DS scores among patients with cancer (*N*=150).

	***n* (%)**	**Range**	**Mean**	**SD**
ICD-10		0-11	4.8	3.18
<6	62 (41.3)			
≥6	88 (58.7)			
FSI (FSI composite)		0-9	3.4	2.16
<3	32 (21.3)			
≥3	118 (78.7)			

HADS- Anxiety*		0-15	3.0	4.00
0-7	133 (88.7)			
8-10	15 (10.0)			
11-21	2 (1.3)			
HADS- Depression		0-17	5.0	3.39
0-7	116 (77.3)			
8-10	26 (17.3)			
11-21	8 (5.3)			
DS*		0-66	11.0	12.00
<23	121 (80.7)			
≥23	29 (19.3)			

Note: *Abbreviation:* ICD-10= Proposed ICD-10 criteria for cancer-related fatigue; FSI = Fatigue Symptom Inventory; HADS = Hospital Anxiety and Depression Scale; DS = Demoralisation Scale; SD = Standard deviation.
*Presented as median and interquartile range.

5.3 Correlation between ICD-10, FSI, HADS and DS

The strength of correlation between the different types of scales used in this study is shown in Table 5.4. We found that all the scales were significantly correlated to each other (p<0.001) with the strongest correlation coefficient noted between FSI composite and ICD-10 (r=0.751) (Figure 5.1).

Table 5.4: Spearman's correlation (*r*) between ICD-10, FSI, HADS and DS.

Scale	Correlation coefficient, *r*				
	ICD-10	**FSI composite**	**HADS-A**	**HADS-D**	**DS**
ICD-10	1.00	0.751*	0.454*	0.544*	0.461*
FSI composite		1.00	0.595*	0.635*	0.589*
HADS-A			1.00	0.527*	0.644*
HADS-D				1.00	0.683*
DS					1.00

Note: *Statistically significant (p<0.001). *Abbreviation:* ICD-10 = Proposed ICD-10 criteria for cancer-related fatigue; FSI = Fatigue Symptom Inventory; HADS = Hospital Anxiety and Depression Scale; DS = Demoralisation Scale.

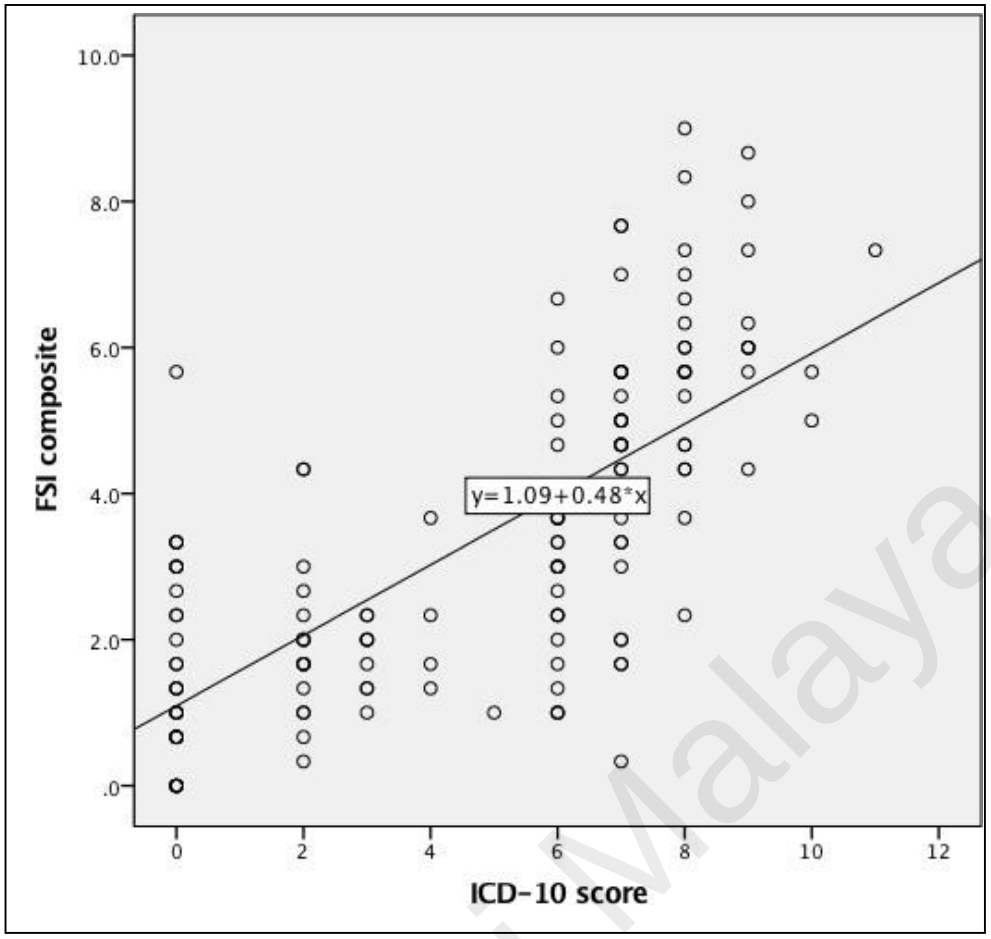


Figure 5.1: Scatterplot showing significant positive correlation between FSI composite scores (Item 1-3) and ICD-10 scoring for cancer-related fatigue (*r*= 0.751, *p*<0.001).

Additionally, there was also a strong positive correlation between totaldisruption index (FSI scoring of item 5-11) and ICD-10 scoring system (r=0.761, p<0.001) (Figure 5.2).

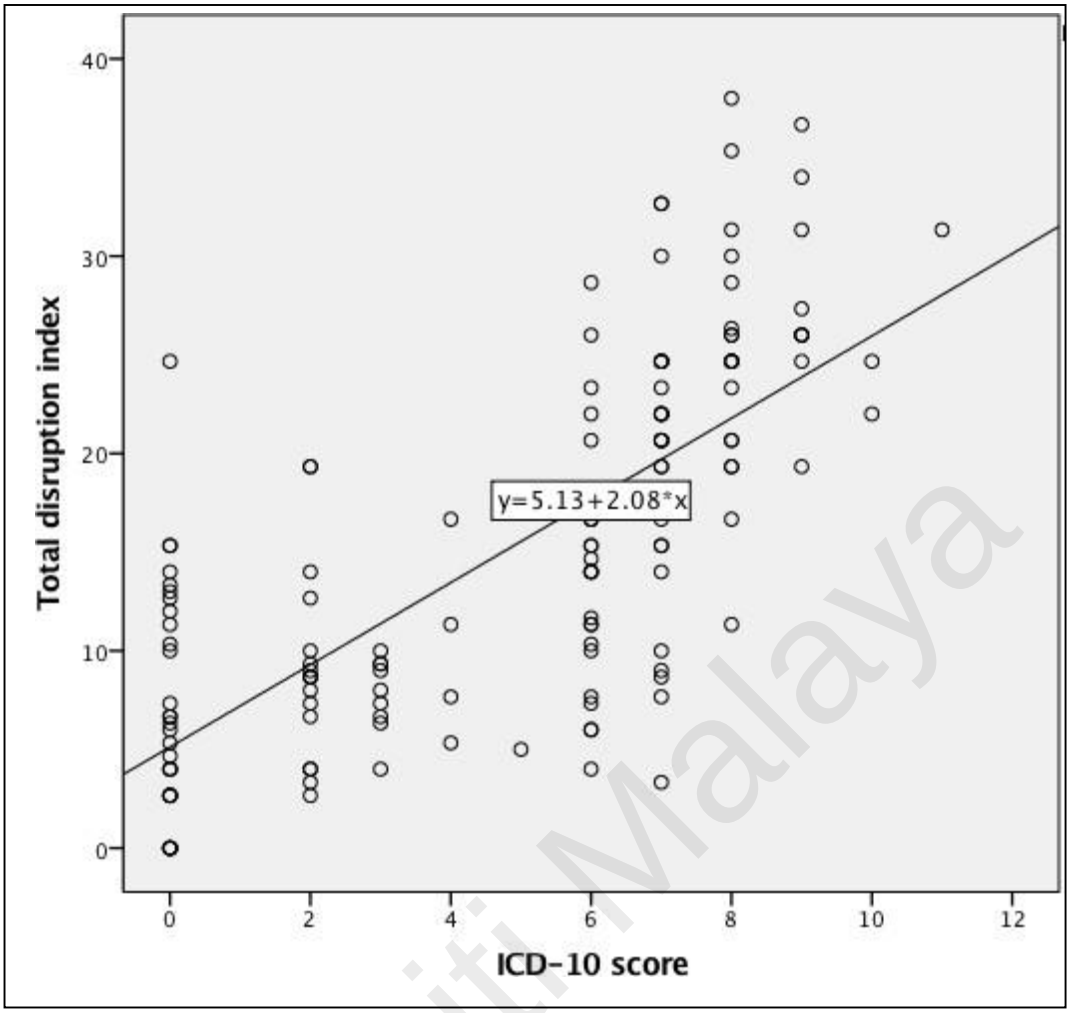


Figure 5.2: Scatterplot showing significant positive correlation between total disruption index and ICD-10 scoring (r=0.761, p<0.001)

5.4 Associated factors of cancer-related fatigue among patients diagnosed with cancer.

Our study identified the stages of cancer as the sole contributing factor to cancer-related fatigue among patients diagnosed with cancer (p=0.021) (Table 5.5).

Univariate analysis of the ICD-10 score with sociodemographic characteristics of the study population did not demonstrate any significant association. Patients older than 60 years old were more likely to experience cancer-related fatigue compared to the younger age group. Patients of Malay and Chinese ethnicity were more likely to be fatigued compared to Indian population. There were not much differences seen for the

proportion of patients experiencing cancer-related fatigue in terms of gender, marital status, educational level and employment status.

With regards to clinical profile of cancer patients, the staging of cancer was demonstrated to be significantly associated with cancer-related fatigue (p=0.021). Patients with advanced stage of cancer were found to have higher occurrence of cancer-related fatigue. Interestingly, patients who were newly diagnosed with cancer within a year have higher proportion of cancer-related fatigue compared to those diagnosed more than a year. However, the association of duration of diagnosis with fatigue was not statistically significant.

In terms of treatment modality, patients who received radiotherapy or combination therapy of chemotherapy and radiotherapy were more likely to be fatigued. However, no significant association identified between treatment modality and cancer- related fatigue in our study. The presence of medical illness, psychiatry comorbidities and types of cancer did not affect the experience of fatigue among our study population.

In addition, univariate analysis of the assessment scales showed significant association between ICD-10 scoring with FSI, HADS and DS. For patients who screened to be having clinically meaningful fatigue (FSI composite score ≥3), most of them were diagnosed to have cancer-related fatigue. A vast majority of those who scored <3 did not have cancer-related fatigue (p<0.001).

For HADS, the association of both subscales with ICD-10 scoring was statistically significant (p=0.009 for anxiety subscale and p<0.001 for depression subscale). Out of 88 patients who have cancer-related fatigue, 17% of them reported anxiety symptoms. On the other hand, only 2 out of 62 patients without fatigue presented with anxiety symptoms. For depression subscale, 34% of 88 fatigued patients reported depressive symptoms

whereas for the non-fatigued group, only 6.5% of them reported depressive symptoms.

Demoralisation Scale also found to be associated with ICD-10 scoring (p=0.001). Among those with high demoralisation level, 86.2% of them were having cancer-related fatigue. For patients with low demoralisation, 52.1% of them were fatigued.

Table 5.5: Univariate analysis of the associated factors to cancer-related fatigue.

Variable(s)	Cancer-related fatigue *n* (%)	No cancer-related fatigue *n* (%)	*p*-value
Sociodemography			
Age (in years)[a]	63.9 (9.10)	62.4 (11.80)	0.385
Age group (in years)[b]			0.238
<60	21 (48.8)	22 (51.2)	
60-65	28 (66.7)	14 (33.3)	
>65	39 (60.0)	26 (40.0)	
Ethnicities[b]			0.179
Malay	37 (59.7)	25 (40.3)	
Chinese	46 (62.2)	28 (37.8)	
Indian	5 (35.7)	9 (64.3)	
Gender[b]			0.313
Male	31 (64.6)	17 (35.4)	
Female	57 (55.9)	45 (44.1)	
Marital status[b]			0.320
Married	81 (60.0)	54 (40.0)	
Single	7 (46.7)	8 (53.3)	
Educational level[b]			0.628
Primary and below	18 (64.3)	10 (35.7)	
Secondary	46 (59.7)	31 (40.3)	
Tertiary	24 (53.3)	21 (46.7)	
Employment status[b]			0.546
Employed	12 (52.2)	11 (47.8)	
Retiree	49 (62.8)	29 (37.2)	
Unemployed	27 (55.1)	22 (44.9)	
Clinical Profile			
Cancer type[b]			0.283
Breast	25 (50.0)	25 (50.0)	
Gastrointestinal	24 (60.0)	16 (40.0)	
Genitourinary	11 (55.0)	9 (45.0)	
Others	28 (70.0)	12 (30.0)	
Stages of cancer[b]			0.021*
I	5 (33.3)	10 (66.7)	
II and III	36 (53.7)	31 (46.3)	
IV	47 (69.1)	21 (30.9)	

Duration of diagnosis[b]			0.083
<1 year	14 (77.8)	4 (22.2)	
1 year to 5 years	62 (59.0)	43 (41.0)	
>5 years	12 (44.4)	15 (55.6)	
Treatment modality[b]			0.248
Chemotherapy	21 (53.8)	18 (46.2)	
Radiotherapy	7 (87.5)	1 (12.5)	
Chemotherapy & Radiotherapy	29 (65.9)	15 (34.1)	
Chemotherapy/Radiotherapy & others	17 (56.7)	13 (43.3)	
Others	14 (48.3)	15 (51.7)	
Presence of medical illness[b]			0.218
Yes	45 (54.2)	38 (45.8)	
No	43 (64.2)	24 (35.8)	
Presence of psychiatric illness[c]			0.549
Yes	2 (50.0)	2 (50.0)	
No	86 (58.9)	60 (41.1)	
Assessment scales			
FSI[b]			<0.001*
<3	2 (6.3)	30 (93.8)	
≥3	86 (72.9)	32 (27.1)	
HADS – Anxiety[c]			0.009*
<8	73 (54.9)	60 (45.1)	
≥8	15 (88.2)	2 (11.8)	
HADS – Depression[c]			<0.001*
<8	58 (50.0)	58 (50.0)	
≥8	30 (88.2)	4 (11.8)	
DS[b]			0.001*
<23	63 (52.1)	58 (47.9)	
≥23	25 (86.2)	4 (13.8)	

Note: [a]Independent *t*-test (described in mean ± standard deviation), [b]Pearson chi-square test of independence, [c]Fisher's exact test. *Abbreviation:* FSI = Fatigue Symptom Inventory; HADS = Hospital Anxiety and Depression Scale; DS = Demoralisation Scale **Statistically significant.*

5.5 Regression analysis of the associated factors of cancer-related fatigue among patients with cancer.

Simple logistic regression was conducted to assess the predictive power of independent clinical factor and assessment scales to the occurrence of cancer-related fatigue. Stages of cancer, HADS (both anxiety and depression subscale) and DS were shown to be significantly associated with the presence of cancer-related fatigue in our study population (Table 5.6).

Table 5.6: Logistic regression analysis of the associated factors to cancer-related fatigue.

Variable(s)	OR (95% CI)	*p*-value
Clinical Profile		
Stages of cancer		0.026*
I	0.22 (0.07, 0.74)	
II and III	0.52 (0.26, 1.05)	
IV	1.00 (Ref.)	
Assessment scales		
HADS – Anxiety		0.019*
<8	0.16 (0.04, 0.74)	
≥8	1.00 (Ref.)	
HADS – Depression		<0.001*
<8	0.13 (0.04, 0.40)	
≥8	1.00 (Ref.)	
DS		0.002*
<23	1.00 (Ref.)	
≥23	5.75 (1.89, 17.53)	

Note: *Abbreviation:* HADS = Hospital Anxiety and Depression Scale; DS = Demoralization Scale.
**Statistically significant.*

CHAPTER 6: DISCUSSION

6.1 Overview of the Study

This study is an observational cross sectional study carried out in Oncology Clinic in University Malaya Medical Centre (UMMC) from the time period of July 2020 until December 2020. This study intended to study the prevalence of cancer-related fatigue among patients diagnosed with cancer. The associations between cancer-related fatigue and sociodemographic variables, clinical profile of cancer patients were explored. Moreover, the correlations between cancer-related fatigue, depression and anxiety, and demoralisation were examined.

Our study identified the stages of cancer as the sole contributing factor to cancer-related fatigue among patients diagnosed with cancer. There was no significant association between cancer-related fatigue and sociodemographic or other clinical characteristic variables. On the other hand, the scoring of Proposed ICD-10 criteria for cancer-related fatigue was significantly correlated to Fatigue Symptom Inventory, Hospital Anxiety and Depression Scale, and Demoralisation Scale. The strongest correlation coefficient was noted between ICD-10 scoring and Fatigue Symptom Inventory (composite score). In addition, there was also a strong positive correlation between ICD-10 scoring and total disruption index in Fatigue Symptom Inventory.

Other than that, stages of cancer, depression, anxiety and demoralisation independently predict the presence of cancer-related fatigue in our study population.

6.2 Overview of the Participants

There was a total of one hundred and fifty study participants recruited in this study. The mean age of the study participants was 63.3 ± 10.29 years old. Majority of the study population being Chinese (49.3%) followed by Malay population which constituted 41.3% of the recruited subjects. Female preponderance among the study population (68.0%). Nearly all the study participants were married (90.0%) and received education (97.3%). Half of them received secondary education and one third of them have received tertiary education. Among the study subjects, only 15.3% of them were still working whereas one third of them were unemployed. Half of the study population have retired at the time of assessment.

A vast majority of our patients were diagnosed with solid tumour, with breast cancer being the commonest (33.3%). Most of our patients were at Stage IV (45.3%), having had the diagnosis of malignancy between one to five years (70.0%). Majority of them received chemotherapy and/or radiotherapy for their cancer treatment, with only one fifth of them received solely other types of treatment modality. Out of the one hundred and fifty study participants, three-fifth of them have other medical illnesses such as Diabetes Mellitus and Hypertension. Only a small proportion of them (2.7%) have pre-existing psychiatry illness.

Other relevant clinical parameters including cancer status (recent diagnosis, remission or recurrent), physical symptoms and medical complications were not collected. This is further discussed in Section 7.1 (page 57).

6.3 Cancer-related Fatigue Among Patients with Cancer

Fatigue is one of the most debilitating symptom experienced by our cancer patients, characterised by feeling weak or tired, or having low energy. It often interferes with the quality of life of cancer patients and result in significant functional impairment

in our patients (Morow et al., 2005). In our study, 79.3% of the study population have experienced fatigue, however only 58.7% of the study population fulfilled the diagnostic criteria for cancer-related fatigue.

The prevalence rate of cancer-related fatigue reported in previous literatures range from 30% to 90% during the treatment course (Maarten Hofman et al., 2007). There were great variations of prevalence rate being reported, possibly due to the lack of standardised diagnostic criteria and screening tools used in different studies (Yeh et al., 2011). In some studies, the recruited patients reported any degree of fatigue irrespective of its impact of functioning.

In our study, we used the proposed ICD-10 criteria which is more stringent which required significant numbers of fatigue-related symptoms and significant functional impairment to reach the diagnosis. On top of that, fatigue must be associated with cancer or treatment, and it is not due to the consequence of any comorbid psychiatry disorder. This could explain why the prevalence of cancer-related fatigue in our study might not be as high as previous studies.

A national survey by Fatigue coalition which was carried out among 379 cancer patients receiving chemotherapy and/or radiotherapy reported presence of fatigue in 75% of patients. Fatigue was found to be the main symptom affecting their quality of life, followed by other symptoms such as nausea, pain and emotional distress like depression (Curt et al., 2000). Another study reported fatigue to be present in 58% of their study population, with fatigue being the most significant factor affecting their life compared to other cancer-related symptoms (Stone, Richardson, et al., 2000).

Cella et al conducted a study among cancer patients receiving treatment in year 2001. Out of 379 patients, 37% of them had experienced fatigue in the past 2 weeks prior to the study, but only 17% of them were diagnosed to have cancer-related fatigue using the ICD-10 criteria (Cella et al., 2001). Another study by Sadler et al reported similar

prevalence rate of 21% (Sadler et al., 2002). More recent study in Taiwan reported a higher prevalence rate of 49.8% (Yeh et al., 2011).

Other studies using other unidimensional scales such as Brief Fatigue Inventory to assess fatigue severity have reported higher prevalence rate. A study done in Eastern China revealed a prevalence rate of cancer-related fatigue of 52% among cancer patients (Tian et al., 2016). In India, the prevalence rate of fatigue among cancer patients receiving treatment was as high as 80% (Banipal et al., 2017).

The mean score of ICD scoring for our present study is 4.8 (SD = 3.18). Among our study population, the A1 criteria of proposed ICD-10 criteria was the most frequently reported symptom, "Significant fatigue, diminished energy or increased need to rest, disproportionate to any recent change in activity level", irrespective of whether they were diagnosed to have cancer-related fatigue. "Generalised weakness or limb heaviness" was the next-in-line symptom reported frequently by our patients (72.7%), followed by symptom of "insomnia or hypersomnia" which was observed in 56% of our study population.

Previous studies have described muscle weakness and reduction in physical activity among cancer patients. The reduction in the daily activity over a period of time would gradually result in the decreased tolerance of usual daily activity and worsen the fatigue experienced by cancer patients (Vestergaard et al., 2009). Exercise was proven to be beneficial in alleviating the clinical fatigue and improve on the emotional distress among cancer patients during treatment (Manzullo & Escalante, 2002; National Comprehensive Cancer Network, 2003).

The management of sleep disturbance related to fatigue is often challenging. Sleep disturbance being a common symptom in malignancy, has been studied in various studies. A healthy sleep hygiene including both stimulus control and sleep restriction during

daytime helps to improve fatigue (Berger et al., 2002). Sleep hygiene training, stress management and cognitive behavioural therapy also offer some benefits in managing sleep disturbance (Given et al., 2004; Simeit et al., 2004).

Since fatigue is a multidimensional symptom that has great impact on quality of life of cancer patients, Fatigue Symptom Inventory was used in our study to assess different aspects of fatigue in our study population. By using this scale, we were able to assess the fatigue severity, frequency, perceived interference to different aspects of quality of life, and lastly the daily pattern of fatigue (Hann et al., 2000).

The fatigue severity was assessed using the FSI composite score. The present study identified 78.7% of our study population of having clinically meaningful fatigue based on FSI composite score of ≥3. The mean score for FSI composite was 3.4 (SD = 2.16). Our study also reported the mean Total Disruption Index to be 15.1 (SD = 9.13), with the mean Interference Scale of 3.2 (SD = 1.30). The result was in line with the finding in other studies. A study in United States has reported mean FSI composite of 2.51 (SD = 1.84) (Donovan et al., 2008). Another study by Brown et al. has shown a mean FSI composite of 5.5 (SD = 2.07) and mean Interference Scale of 4.7 (SD = 2.37) (Brown et al., 2011).

6.4 Depression Among Patients with Cancer

In our study, 22.6% of our cancer patients presented with depressive symptoms based on the screening using HADS, out of which 5.3% of them were identified as clinically depressed, whereas 17.3% of them were borderline case for depression. Our results were similar to other studies on depression among patients diagnosed with cancer. Twelve prevalence studies that screened for depressive symptoms among cancer patients

using HADS reported a range of 7% to 21% for probable cases of depression. Higher rate was reported for borderline cases of depression (Pirl, 2004).

In general, the prevalence of depression ranged from 10% to 25% (Popoola & Adewuya, 2012; Qiu et al., 2012). A systematic review of Asian studies on depression among cancer patients reported prevalence varied from 12.5% to 39% (Zainal et al., 2013). More recent study in Jordan reported 30.2% of cancer patients experiencing depressive symptoms (Alquraan et al., 2020). 11% of Iranian women with breast cancer reported to suffer from severe depression (Isfahani et al., 2020).

The prevalence of depression among cancer patients varies as a result of differences in sociodemographic data, psychosocial factors, illness and treatment-related factors, types of assessment be it diagnostic interview or self-report, and the inclusion criteria used (Zainal et al., 2013).

6.5 Anxiety Among Patients with Cancer

Anxiety symptoms often coexist with depression among patients diagnosed with cancer. It is not uncommon and can interfere with the cancer treatment. 11.3% of our study populations reported anxiety symptoms. However, 10% of them reported to be borderline cases, and only 1.3% of them were having clinical symptomatic anxiety. The cancer patients experiencing anxiety symptoms range from 0.9% to 49% in a meta-analysis (Strong et al., 2007). Like depression, multiple factors contributing to the variation in the prevalence of anxiety among cancer patients. The sociodemographic data, clinical characteristics of patients and psychosocial factors were among the factors studied (Linden et al., 2012; Nikbakhsh et al., 2014; Tsaras et al., 2018). The prevalence also varied between the types of assessment used.

A study conducted among inpatients in a general hospital in Singapore identified 9.5% of the study population to be suffering from Generalised Anxiety Disorder using MINI International Neuropsychiatric Interview (Shian Ming et al., 2014). On the other hand, a prevalence study screened for depression and anxiety among Chinese cancer patients using HADS. The prevalence of depression (66.72%) was much higher compared to anxiety (6.49%)(Hong & Tian, 2014). Using similar assessment tool as present study, another 2 studies conducted in Taiwan and Hong Kong identified higher prevalence of anxiety, 11.8% (Chen et al., 2000) and 21.1% respectively (So et al., 2010).

The lower prevalence of anxiety in our study could be explained by the higher educational level among participants recruited in this study. Higher educational level was shown to be protective against anxiety and depression (Bjelland et al., 2008; Khalil et al., 2016).

6.6 Demoralisation Among Patients with Cancer

Our study recognised 19.3% of the participants with high demoralisation or clinically relevant demoralisation using Demoralisation Scale- Malay version. Our result is similar to a systematic review on demoralization syndrome among patients with malignancy in all stages, which showed prevalence rate varying from 13% to 18% (Robinson et al., 2015). However, advanced clinical stage of malignancy can result in a rise of prevalence rate as high as 52.5% (Julião et al., 2016). A recent study on demoralisation among terminally ill cancer patients demonstrated 22.6% of study population being highly demoralised (Bovero et al., 2019). The reported prevalence was relatively higher compared to other studies among patients with advanced malignancy in Ireland (14%) and Germany (15.7%) (Lichtenthal et al., 2009). The difference could be

explained by the association with clinical staging of malignancy, as well as the cultural difference in regards to cancer-related events (Bovero et al., 2019).

In addition, the variation in prevalence could be a result of different cut-off points used in different studies. The original Demoralisation Scale used the median of 30 as the cut-off value (Kissane et al., 2004). Other values used in different studies could be range from 20 (Mullane et al., 2009) to 43 (Deng et al., 2017; Fang et al., 2014).

6.7 Cancer-related fatigue and other Associated Factors

6.7.1 Sociodemographic Factors

The present study did not find any significant association between cancer-related fatigue and sociodemographic factors. Age, gender, ethnicity, educational level, employment status and marital status were among the sociodemographic variables tested in this study.

The findings on association of cancer-related fatigue and age were mixed. Some studies suggested that younger cancer patients experienced more fatigue compared to their older counterparts (Banthia et al., 2009; Kim et al., 2008; Spichiger et al., 2012). Younger patients may have more burden or demand in terms of occupation and younger children, which result in more pronounced fatigue (Cimprich et al., 2002). Cancer-related fatigue also deemed more burdensome by younger patients as they have more age-related expectancies. Unlike the older patients, younger ones have not experienced fatigue in the process of aging. They did not anticipate serious illness at a young age and found themselves harder to adjust with the illness (Banthia et al., 2009). Experience of fatigue is subjective and varies based on different life experiences and expectations and hence may vary according to age (Visser et al., 2000).

On the other hand, few studies did not find significant association between fatigue and age. Gender, marital status and educational level were also not associated with cancer-related fatigue (Goldstein et al., 2012; Schultz et al., 2011; Tian et al., 2016). In contrary, there were significant association reported in 10 cancer clinical trials between female gender and greater fatigue (Pater et al., 1997), possibly due to the gender difference in terms of perception and report of symptoms. Present study found age to be unrelated to fatigue, which is consistent to the result of more recent literatures.

Employment status was not associated with fatigue in most studies. However, Kim et al. identified more severe fatigue among employed cancer patients, possibly due to more job-related commitment (Kim et al., 2008). In our study, no significant association was reported between employment status and fatigue.

Educational level was identified to be a significant associated factor for fatigue in some studies. Patients with tertiary education reported fatigue of moderate to severe intensity more frequently compared to those with lower educational level (Mao et al., 2018). In contrast, no significant association was found in our study.

6.7.2 Clinical Profile

The present study identified stages of cancer to be the sole contributing factor to cancer-related fatigue. This finding is in accordance with several studies in Western countries which described the association of clinical staging with fatigue (Banthia et al., 2009; Goldstein et al., 2012; Hwang et al., 2003; Schultz et al., 2011). Advanced clinical stage was reported to be positively associated with cancer-related fatigue (Huang et al., 2010; Tian et al., 2016).

Other clinical characteristic variables in the current study were not associated with fatigue. The variables studied included type of cancer, duration of diagnosis, treatment modalities, presence of medical or psychiatry illness.

Type of cancer was reported to be associated with severity of fatigue. In a study comparing pattern of fatigue among patients with prostate, lung, head and neck carcinoma, those with prostate cancer experienced the least severe fatigue compared to other cancer types (Hickok, Roscoe, et al., 2005). This finding is supported by a study describing patients with genitourinary cancer to have lesser fatigue which improve over time (Yennu et al., 2012). However, the present study reported type of cancer to be unrelated to cancer-related fatigue, similar to a recent study in India (Banipal et al., 2017).

Since fatigue is a common presentation of patients receiving chemotherapy or radiotherapy, many studies have identified strong association between treatment modalities and cancer-related fatigue. However, the association is not consistent across studies. Chemotherapy was reported to be linked to more severe fatigue and disruption, compared to radiotherapy (Banipal et al., 2017; Bower et al., 2000; Donovan et al., 2004). Patients received combination therapy of chemotherapy and radiotherapy also experienced more intense fatigue compared to those with monotherapy (Bower et al., 2006). In the contrary, Kim et al. (2008), Goldstein et al. (2012) and Tian et al. (2016) reported that cancer-related fatigue was unrelated to the treatment received irrespective of the types. This finding is similar to our present study.

Duration of diagnosis was not significantly associated with fatigue in the present study. This finding is consistent with the result in previous studies (Bower et al., 2006; Rüffer et al., 2003). Fatigue was still reported among a portion of patients who have completed treatment more than 5 years (Cella et al., 2001). This may suggest that cancer-related fatigue could persist for long period of time even after completion of treatment.

The concomitant medical illness was associated with fatigue in few studies. Bower et al. (2016) described heart disease to have significant association, whereas Hypertension was found to be marginally significant. Interestingly, gastrointestinal diseases such as gastric ulcer, along with symptoms such as appetite loss or bowel changes, were associated with fatigue (Kim et al., 2008). The complications of gastrointestinal diseases such as anaemia, might explain the contribution to fatigue.

6.7.3 Psychological Comorbidities

6.7.3.1 Depression

The present study identified depression to be significantly associated with cancer-related fatigue ($p<0.001$). Depression was moderately correlated with fatigue, with correlation coefficient of 0.544 ($p<0.001$). This finding was consistent with the systematic review of 59 studies regarding the association of cancer-related fatigue with depression and anxiety (Brown & Kroenke, 2009). Brown et al. had concluded that depression was consistently associated with cancer-related fatigue, with the correlation coefficient ranging from 0.16 to 0.84. Across 51 studies, after weighted for sample size, the average correlation coefficient was reported to be 0.56, with 95% CI of 0.54 to 0.58. The coefficient of determination (r^2) suggested that fatigue shared 31% of its variance with depression which is comparable to my study which showed 28.2% of its variance with depression (Appendix I). Among three studies reporting the association of fatigue and depression using odds ratio, the weighted average odds ratio was 1.16 (Brown & Kroenke, 2009).

The variation across studies could be possibly explained by the various assessment scales used in different studies. Hospital Anxiety and Depression Scales (HADS) was the most frequently used scale to assess depression (Brown & Kroenke, 2009). The depression subscale of HADS could be at advantage to identify clinical depression from

fatigue as it did not include any physical symptoms that might overlap with the measurement of fatigue (Fillion et al., 2003; Fossa et al., 2003). However, item 8 of HADS-D stating "I feel as if I am slowed down" was excluded from the correlation analysis in 5 studies as it might be interpreted as having fatigue. Yet, the association between fatigue and depression was still found to be significant (Stone, Hardy, et al., 2000).

Many have postulated that fatigue and depression shared the same mechanism due to its consistent correlation shown in various studies. The relationship of fatigue and depression is complicated. Few causal relationships have been discussed. Fatigue could be a cause of depression or vice versa, or both could be result of another etiology or underlying disease (Weitzner, 2003). Some suggested that fatigue and depression could be a manifestation of medication-induced neurotoxicity (Kim et al., 2008).

On the other hand, some studies suggested that fatigue and depression were two distinct conditions among cancer patients. However, no definitive evidence to support the interdependence of the two symptoms (Wang, 2008). The clustering symptom of fatigue and depression was frequently reported (Bower et al., 2006). Future research involving intervention to improve independent variables associated with cancer-related fatigue might be beneficial to study the interrelationship. For instance, one can analyse the effect on fatigue after treatment of cancer-related depression. In the contrary, improvement of fatigue also contributed to improved depression and anxiety (Tchekmedyian et al., 2003).

6.7.3.2 Anxiety

Significant association was found between cancer-related fatigue and anxiety in the present study (p=0.009). Anxiety was positively correlated to fatigue, with correlation coefficient of 0.454 (p<0.001). Our finding was in accordance to current literature. In a systematic review across 35 studies reporting the association between fatigue and anxiety,

the correlation coefficient ranged from 0.16 to 0.73. The weighted average of correlation coefficient was reported to be 0.46 (95% CI of 0.43, 0.49). The coefficient of determination (r^2) suggested that fatigue shared 23% of its variance with anxiety, which is comparable to my study which showed 16% of its variance with anxiety (Appendix J). The average association between fatigue and anxiety using odds ratio in 2 studies was 1.19 (Brown & Kroenke, 2009).

Anxiety was shown to be consistently associated with fatigue among cancer patients, although the correlation was lower than fatigue with depression. Few studies have reported association of fatigue specific to anxiety itself, rather than as a cluster of symptom with depression. The premorbid anxious personality trait was found to be associated with fatigue, and its impact on the development of fatigue and psychological distress has been studied (Byar et al., 2006; Fossa et al., 2003; Geiser et al., 2007).

6.7.3.3 Demoralisation

Demoralisation was found to be significantly associated with cancer-related fatigue in our study (p=0.001). It has positive correlation with fatigue with coefficient correlation of 0.461 (p<0.001). Out of 88 patients diagnosed with cancer-related fatigue, 28% of them were highly demoralised. On the other hand, only 6% of non-fatigued patients were highly demoralised. To date, there is no literature studied on the association of demoralisation and fatigue among cancer patients. Demoralisation is usually related to depression, anxiety, poorer quality of life (Robinson et al., 2015) and impaired physical symptoms (Vehling & Mehnert, 2014). More importantly, demoralised patients also associated with higher suicidal risk than depression (Fang et al., 2014; Robinson et al., 2016). Hence, it would be beneficial for physicians to screen for demoralisation and assess suicidal risk among fatigued cancer patients.

6.8 Predictive Factors of Cancer-related Fatigue

Our present study identified staging of cancer to be significant predictor of cancer-related fatigue. Similar result was reported in a study among fatigued breast cancer survivors which identified cancer staging as one of the important predictors for fatigue (Banthia et al., 2009). This could be possibly explained by patients with advanced cancer suffered from more disease burden compared to the earlier stage. Patients at terminal stage also less likely to return to their energy level at premorbid state after receiving cancer treatment.

Other than clinical variable, psychological symptoms including depression and anxiety also significantly predict the occurrence of cancer-related fatigue among our study population (p=0.019 for anxiety, p<0.001 for depression). The finding is in accordance with previous literatures which identified depression and anxiety as the predictors for cancer-related fatigue (Banthia et al., 2009; Bower et al., 2000; Brown & Kroenke, 2009; Haghighat et al., 2003).

In addition, demoralisation also predicts cancer-related fatigue independently in our study population. Patients who are highly demoralised have increased odds by 5.75 of having cancer-related fatigue as compared to the group with lower demoralisation score. The study findings highlight the significance of psychological symptoms in relation to cancer-related fatigue, and hence should be screened for and managed accordingly.

CHAPTER 7: LIMITATION, STRENGTH AND RECOMMENDATION

7.1 Limitations of the Study

The study has a few limitations. Firstly, there might be selection bias as convenient sampling was used while selecting participants. Only patients that willing to join would be recruited in the study. Patients with more severe fatigue or depressed might not have volunteered in the study, causing underrepresented of fatigued patients. There was also overrepresented of patients of certain cancer stage.

Secondly, the study was a cross sectional study. We were unable to draw any conclusion to the causal relationship between the dependent and independent variables. Being a retrospective study, there was a risk of recall bias while answering the questionnaire. The assessment was mostly self-reported and no collateral history obtained from family member which might improve the precision of the scores. Furthermore, in the crowded clinic setting, participants might be waiting for their turn for doctor consultation or clinic procedure anxiously. There might be risk of response bias as they answered the questionnaire without understanding in depth.

In addition, the study was conducted only in a single centre in Oncology Clinic, University Malaya Medical Centre. Being strategically located in the capital of Malaysia, the patients that presented to UMMC might be of those with better educational background. The sociodemographic profiles and the response to the questionnaire might be distinct from other centres in other parts of Malaysia. Thus, the generalisability of present study findings might be limited.

The relatively small sample size of the study also limited the power of the study. There were other associated factors which were significantly correlated to cancer-related fatigue such as cancer status, pain and insomnia. However, those factors were not included in our study due to the constraint of various resources.

7.2 Strengths of the Study

There was no local study assessing cancer-related fatigue among patients with cancer in Malaysia. Our study has examined the prevalence of cancer-related fatigue and its associated factors. Being one of the commonest symptoms experienced by cancer patients, cancer-related fatigue has great impact on their quality of life. Our study result would be helpful to highlight the importance of fatigue assessment in the daily clinical practice.

Instead of using unidimensional self-rated tools for assessment of fatigue, the participants were interviewed by the principal investigator using Diagnostic Interview Guide for Cancer-related Fatigue. The Proposed ICD-10 criteria for cancer-related fatigue is a good multidimensional tool with good internal consistency to assess fatigue among cancer patients.

7.3 Recommendations

The sampling method could be improved to reduce selection bias. Probability sampling methods such as stratified sampling method could be employed in the future study.

Future researchers could conduct longitudinal studies to assess cancer-related fatigue and the correlates at different phases, namely pre-, during, and post-treatment. With this, the causal relationship of the variables and independent predictors could be identified. The prospective study also minimise the risk of recall bias.

The power of the future studies could be increased by increasing the sample size. By doing so, the systemic error would be reduced and thereby improve the accuracy of the assessment tools.

In addition, the future studies could be conducted in different centres across regions in Malaysia, taking into account the disparity of socio-cultural background of Malaysian populations. The generalisability of the study would be improved by conducting a multi-centre study.

Moreover, future studies could include other possibly modifiable associated factors with cancer-related fatigue of different dimensions. For instance, cancer status; physical symptoms like pain and insomnia (Mao et al., 2018); haematological markers such as low Haemoglobin and low Sodium level (Hwang et al., 2003), high white cell count; low physical activity and high BMI (LH et al., 2011). Psychosocial variables such as perceived support and coping skills could also be included.

CHAPTER 8: CONCLUSION

Cancer-related fatigue is a highly prevalent symptom experienced by majority of cancer patients. The present study has identified a high prevalence of cancer-related fatigue (58.7%) among patients diagnosed with cancer. Staging of cancer was positively associated with cancer-related fatigue. Depression, anxiety and demoralisation also among the important correlates associated with cancer-related fatigue.

The high prevalence of cancer-related fatigue among our cancer patients and its association with mental health problem is alarming to our oncology team and mental health practitioners. Given its great negative impact on the quality of life of our cancer patients, fatigue should be prioritised and routinely screened for during our daily clinical practice. Further studies to identify possibly modifiable contributing factors would be helpful in the management of cancer-related fatigue. Given its multidimensional profile, fatigue should be managed bio-psycho-socially.

Psychiatry comorbidities should also be assessed and treated promptly as it could worsen the clinical condition and impede the cancer treatment.

CHAPTER 9: REFERENCES

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